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Subcortical Abnormalities Detected in Bipolar Affective Disorder Using Magnetic Resonance Imaging: Clinical and Neuropsychological Significance

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- Magnetic resonance imaging was utilized to determine the nature and rate of subcortical abnormalities in bipolar affective disorder. Nine of 19 bipolar patients and no controls demonstrated subcortical signal hyperintensities on blind evaluation of the images. There was no apparent change in the appearance of the hyperintensities in 7 of 7 subjects with abnormal magnetic resonance images who underwent repeated imaging at 1 year. Bipolar patients with abnormalities had a history of more hospitalizations and appeared more impaired on tests of fluency and recall when compared with bipolar patients without abnormalities or with controls. The possible etiology and significance of signal hyperintensities in bipolar affective disorder is discussed. (Arch Gen Psychiatry. 1990;47:55-59)

Abnormalities in brain structure and function have been observed in some patients with affective disorders. Ventricular enlargement demonstrated using computed tomography has been reported by some investigators in bipolar disorder,16 unipolar depression,68 and mixed affective disorders.8,15 Cerebellar atrophy4,16 and altered x-ray attenuation17,18 were also shown in some patients with bipolar affective disorder. The latter measurements may reflect abnormalities in white matter that are beneath the limits of spatial resolution using computed tomography. In the first study using magnetic resonance imaging (MRI) to look at brain structure in carefully screened bipolar subjects and normal controls, we described the presence of subcortical signal hyperintensities in relatively young bipolar depressives but not in similarly matched control subjects.19 In two later studies using MRI,20,31 subcortical signal abnormalities in older depressed patients were reported. Since such abnormalities have been noted frequently in asymptomatic as well as ill elderly individuals,27-36 the significance of these observations is ambiguous without the inclusion of demographically matched control subjects.

The neuropsychological profiles of depressed patients and of patients with so-called subcortical dementias (eg, Huntington's disease [HD], progressive supranuclear palsy) have both been characterized by psychomotor slowing, lack of initiation (ie, bradyphrenia), and attentional deficits combined with intact language function and praxis.37,38 In a study designed to compare the memory disorders of unipolar and bipolar patients with those of patients with HD (ie, a genetically transmitted, progressive basal ganglia disorder), Wolfe and her colleagues55 found that bipolar patients and patients with HD performed more poorly than did unipolar patients and normal controls on tasks placing maximum demands on retrieval from long-term memory. It is important to emphasize that despite the similarity in cognitive profiles between subcortical dementias and affective disorders, there is no evidence to indicate that the latter disorder demonstrates a similarly progressive course.

Other behavioral studies in bipolar illness,35,36 reporting that the cognitive impairments of depressed patients45-46 may persist when their mood disorders are in remission, also lend support to the possibility of a persistent cognitive syndrome in these patients. In a series of case reports, McCallister and Price41 demonstrated that reversible cognitive deficits associated with depression may be superimposed over an irreversible dementia, and Reding et al42 have reported that more than 50% of a group of elderly patients with a diagnosis of pseudodementia eventually became demented within a 3-year follow-up period. All of these studies suggest that some underlying pathophysiological condition, rather than the state of depression itself, may be responsible for the cognitive deficits reported in some patients with affective disorders.

The present study represents a further assessment of subcortical structural abnormalities in patients with bipolar affective disorder. Twenty bipolar patients and 10 age-matched controls, carefully screened to minimize the presence of confounding historical and medical factors, were examined with MRI and a battery of cognitive tests previously shown to be sensitive to basal ganglia dysfunction. Magnetic resonance imaging was chosen because of its demonstrated sensitivity for detecting small subcortical abnormalities. The inclusion of appropriately matched control subjects provided an opportunity to compare the incidence of any noted abnormalities in the two groups and thereby control for the increased sensitivity of MRI to structural changes. A previous report of a subset of patients included in this study has been published.27

PATIENTS AND METHODS

Patients

Patients with bipolar affective disorder were recruited from the University of California, San Diego, Clinical Mental Health Research Center (MHCRC) clinical inpatient wards, and from outpatient clinics at the San Diego Veterans Administration Medical Center, the University of California, San Diego Medical Center inpatient service, a community mental health center, and community mental health activist groups. Controls were recruited from the normal control pool of the MHCRC. All subjects were willing and able to give informed consent for participation in this study.

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All patients and controls were screened using the following procedures: Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L) interview, history and physical examination, and laboratory examination. All bipolar patients met Research Diagnostic Criteria for bipolar affective disorder, type I; patients were allowed entry without regard to medication status with the exceptions of benzodiazepines or antihypertensives with known central nervous system effects. Because we were interested in exploring persistent structural and cognitive alterations, all patients were studied regardless of mood state if they met entrance criteria, could complete the protocol, and were capable of giving informed consent.

Patients and controls were excluded if they were over 55 years of age, had a history of head injury with loss of consciousness for more than 5 minutes or with any neurological sequelae, had poorly controlled hypertension, or gave a history of alcohol abuse of 5 years' duration or more or for any duration within 5 years of the study. No subject with a history of intravenous drug abuse was included in the study. No subject showed any clinical evidence of tardive dyskinesia. All controls and their first-degree relatives had no history of major psychiatric illness or substance abuse.

Approximately 160 bipolar patients were screened to select the final 29 who met entrance criteria. Major grounds for exclusion were alcoholism, drug abuse, history of head injury, and age. The final study sample comprised 20 bipolar patients (19 men, 1 woman) and 10 controls (all men). Of the bipolar patients studied initially, 8 were taking lithium carbonate alone; 1 was taking lithium carbonate plus desipramine; 1 was taking lithium carbonate, benzotropine, and fluphenazine; 1 was taking lithium carbonate plus a diuretic; 1 was taking lithium carbonate plus mesoridazine; 2 were taking lithium carbonate plus carbamazepine; 1 was taking lithium carbonate plus thiouoxetine; 1 was taking lithium carbonate, perphenazine, and carbamazepine; 1 was taking carbamazepine; and 3 were taking no medication. None of the patients had ever received bilateral electroconvulsive therapy.

One patient, who was the only left-handed subject in the study, had a history of treatment with unilateral electroconvulsive therapy. Control and bipolar subjects used in the final analysis (see “Results” section) did not differ in age or years of education.

Neuropsychological Test Battery

The test battery (Table 1) was part of a larger battery administered at one 2- to 3-hour sitting. Two subjects (one control and one patient) did not complete the California Verbal Learning Test. In these cases, partial test battery results were entered into the analyses. The test battery utilized for this report was designed to evaluate whether impairments in the initiation of retrieval (eg, poor recall and fluency, intact recognition) are evident in bipolar patients and to place such findings in the context of other cognitive performances. Accordingly, indexes of language function, visuospatial capacity, and verbal and figural memory and two tests highly sensitive to cerebral dysfunction in general were all included in the test battery.

Imaging Protocol

All images were obtained on a 1.5-T superconducting magnet (Signa, General Electric, Milwaukee, Wis) at the University of California, San Diego–American Medical International Medical Center Magnetic Resonance Institute. Images were obtained using the standard MRI protocol of the Image Analysis Laboratory of the Department of Psychiatry: proton density and T1-weighted coronal and axial images are obtained using an asymmetrical, multiple-echo sequence (TR 2000, TE 25, 70). T2-weighted sagittal images (TR 600, TE 25) are also collected. All sections are 5 mm thick with a 2.5-mm gap between sections. A 256 x 256 matrix with a 24-cm field of view is used. The 20-section series extends from the apex to the brain stem in the axial plane but does not extend fully through the frontal and occipital poles in the coronal plane. Nine T1-weighted sagittal images are centered at the midsagittal plane and are acquired to visualize medial structures, the corpus callosum, and the brain stem.

A senior neuroradiologist (J.R.H.) blind to group membership and demographic data evaluated all images for structural abnormalities. Particular attention was paid to subcortical regions, with careful notation of all signal hyperintensities. Signal hyperintensities were diagnosed when regions of high signal were present on both the balanced and T1-weighted images. Lesions were defined on both the transaxial and coronal views when locations were within the extent of the partial coronal series. Because high-signal “caps” immediately adjacent to the frontal or occipital horns of the lateral ventricle are normal, hyperintensities in these areas were not considered to represent focal abnormalities. Regions of high signal in the vicinity of slowly flowing vessels were not included if their appearance could be accounted for by the phenomenon of flow enhancement, nor were penetrating cortical vessels or thalamostrate vessels with their linear high-intensity T1 signal considered abnormal.

RESULTS

Ten of the 20 bipolar subjects and none of the controls had abnormal MRI images based on the blind examination. One bipolar subject, excluded from further analysis, demonstrated a previously undiagnosed arachnoid cyst displacing the left temporal lobe posteriorly. The subject groups did not differ significantly in age or education (Table 2). None of the 19 remaining bipolar patients but none of the 10 controls exhibited the presence of subcortical signal hyperintensities involving the white matter (P<.001, Fisher's Exact Test; Figure).

Distribution of Signal Abnormalities

The distribution of signal hyperintensities was varied. Seven of the nine patients had abnormalities involving the frontal lobes. Only two

<table>
<thead>
<tr>
<th>Table 1.—Neuropsychological Test Battery</th>
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</thead>
<tbody>
<tr>
<td><strong>Vocabulary Test</strong></td>
</tr>
<tr>
<td><strong>Confrontation Naming Test</strong></td>
</tr>
<tr>
<td><strong>Controlled Oral Word Association Test</strong></td>
</tr>
<tr>
<td><strong>Judgement of Line Orientation Task</strong></td>
</tr>
<tr>
<td><strong>Embedded Figures Test</strong></td>
</tr>
<tr>
<td><strong>California Verbal Learning Test</strong></td>
</tr>
<tr>
<td><strong>Digit Symbol Substitution</strong></td>
</tr>
<tr>
<td><strong>Trailmaking Test, part B</strong></td>
</tr>
</tbody>
</table>

The proton density–weighted image (left) and T1-weighted image (right) of a 30-year-old bipolar man are displayed. Two regions of signal hyperintensity are demonstrated: anterolateral to the frontal horn of the left lateral ventricle, and in the left subcortical temporoparietal area. In contrast to cerebrospinal fluid and brain, these regions show high signal on both images.
patients had no apparent right-hemisphere hyperintensities at all. Bilateral hemisphere involvement was seen in four patients, unilateral right hemisphere involvement in three, and unilateral left hemisphere involvement in two subjects. All hyperintensities except one in the thalamus were located in subcortical white matter regions. One patient had involvement of the corpus callosum posteriorly; one patient had a lesion directly adjacent to the left caudate nucleus. The number of hyperintensities per patient ranged from 1 to 12. In two patients, both in their 40s, moderate to marked cortical atrophy was noted; both of these individuals had scans demonstrating hyperintensities. One of those patients had diffuse increase in perivascular spaces with resultant linear hyperintensities on $T_1$-weighted but not balanced images. No patient displayed evidence of focal cortical abnormalities.

We recontacted all subjects with abnormalities after 1 year for repeated imaging to examine the persistence of these signal abnormalities. We were able to restudy seven of the nine patients with hyperintensities (one subject refused, one subject had moved). Six of these seven patients were found to have abnormalities that were unchanged on visual examination compared with the previous study. The one individual who appeared to demonstrate no abnormality on repeated scan underwent scanning a third time with contiguous sections, to eliminate the possibility that the abnormality had been missed because of the 2.5-mm gap between sections on the second scan. In this third scan, the hyperintensity was again detected, unchanged compared with the first scan. Thus, no individual studied demonstrated visually evident resolution or worsening of the abnormalities in this short follow-up period. In addition, four patients who underwent repeated scanning were in affective states clinically different from their initial MRI examination. Depressed individuals no longer met Research Diagnostic Criteria for major depression, though some residual symptoms remained; one manic individual now met criteria for major depression; one depressed individual was now in remission).

Thus, these MRI abnormalities are apparently not reversible state markers.

**Clinical Correlates of Signal Hyperintensities**

As shown in Table 2, bipolar patients with lesions had more psychiatric hospitalizations than those without lesions ($P<.05$), although no significant differences were found between the groups with respect to age at onset, duration of illness, or current age. Family history of psychiatric disorder, and history of psychosis, were not associated with the presence of these lesions. Although duration of neuroleptic use did not appear to differ between these groups, this insensitive, retrospective measure does not take into account type of neuroleptic used, dosage, compliance, or exposure to side effects.

<table>
<thead>
<tr>
<th>Table 2. — Description of Clinical Variables in Bipolar Patients and Normal Subjects*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bipolar With Normal MRI</strong></td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Education, y</td>
</tr>
<tr>
<td>Age at onset, y</td>
</tr>
<tr>
<td>Marital status, %</td>
</tr>
<tr>
<td>No. of hospitalizations</td>
</tr>
<tr>
<td>No. with history of psychosis, %</td>
</tr>
<tr>
<td>Neuroleptic use</td>
</tr>
<tr>
<td>Hamilton Rating Scale for Depression</td>
</tr>
</tbody>
</table>

*MRI indicates magnetic resonance imaging. Values are mean ± SD, except for marital status, which is percentage married or divorced at the time of the study. For neuroleptic use, 0 indicates no use at all; 1, used 6 months or less; 2, used more than 6 months but not long-term use; 3, long-term use. 

†$P<.05$ compared with bipolar patients with normal MRI scan. 

‡$P<.10$ compared with bipolar patients with normal MRI scan.

**Table 3. — Summary of Neuropsychological Test Results**

<table>
<thead>
<tr>
<th>Test</th>
<th>Bipolar Patients (n = 19)</th>
<th>Controls (n = 10)</th>
<th>Bipolar MRI− (n = 10)</th>
<th>MRI+ (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>Vocabulary</td>
<td>20.3</td>
<td>21.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Naming test</td>
<td>26.7</td>
<td>24.9</td>
<td>2.2†</td>
<td>27.0</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>40.7</td>
<td>41.5</td>
<td>0.2</td>
<td>46.0</td>
</tr>
<tr>
<td>Visuospatial Line Orientation (No. correct)</td>
<td>17.4</td>
<td>17.8</td>
<td>0.3</td>
<td>18.9</td>
</tr>
<tr>
<td>Embedded Figures (time)</td>
<td>585</td>
<td>487</td>
<td>0.7</td>
<td>484</td>
</tr>
<tr>
<td>Memory measures CVLT Recall; trials I-V T-score</td>
<td>39.4</td>
<td>45.1</td>
<td>1.1</td>
<td>45.1</td>
</tr>
<tr>
<td>CVLT Recognition (discriminability)</td>
<td>93.0</td>
<td>95.7</td>
<td>1.6</td>
<td>92.8</td>
</tr>
<tr>
<td>General measures Trailmaking Test B (s)</td>
<td>84.9</td>
<td>90.7</td>
<td>0.2</td>
<td>77.8</td>
</tr>
<tr>
<td>Digit Symbol (scaled score)</td>
<td>10.8</td>
<td>14.0</td>
<td>3.4§</td>
<td>11.9</td>
</tr>
</tbody>
</table>

*MRI indicates magnetic resonance imaging (plus and minus indicate abnormal and normal, respectively); CVLT, California Verbal Learning Test. One control subject and one bipolar patient (with normal MRI) did not complete the CVLT. Thus, the numbers were reduced for the two CVLT measures in the relevant groups. 

†$P<.05$. 

‡$P<.10$. 

§$P<.01$. 

**Neuropsychological Test Results**

Table 3 gives the performances of the bipolar patients and control subjects on the neuropsychological test battery. Little evidence of a general cognitive impairment was found in the bipolar patients as a group (n = 19) compared with the control group (n = 10). Although a single significant comparison in this context is not substantially above chance expectations, it is of interest that on the Digit Symbol Substitution Test, a measure highly sensitive to cerebral dysfunction in general, the bipolar patients as a group performed significantly worse than the control subjects. In contrast, on the Naming Test, the control subjects actually performed significantly more poorly than the bipolar patients.

Comparisons of the performances of bipolar patients with and without MRI abnormalities did yield significant differences. Patients with abnormalities had significantly lower verbal fluency and Digit Symbol scores than did patients without abnormalities. In addition, the difference between the two bipolar subgroups on the recall measures of the California Verbal Learning Test, and on the Line Orientation task, approached statistical significance.

**COMMENT**

The major finding of this investigation is the unusually high incidence of signal hyperintensities in the brain MRIs of the bipolar patients. These abnormalities appear to be persistent, remaining unchanged for a year in all patients who underwent repeated scanning. Although the significance and histopathological nature of white matter hyperintensities remain controversial, these lesions have been shown in the normal elderly and in patients with a variety of medical and neurological disorders to be strongly associated with ischemic brain disease and various risk factors for atherosclerotic vascular disorders (eg, smoking, hypertension). In younger individuals, Awad et al report that in a study of a large number of clinical scans, no individual without brain disease and under 40 years of age demonstrated these abnormalities. Signal hyperintensities with unique distributions may be indicative...
of disease states such as multiple sclerosis and subacute arteriosclerotic encephalopathy (Binswanger's disease). It seems unlikely that the positive MRI findings for the bipolar patients are attributable either to their age (which was relatively young) or to undiagnosed neurological disorders since our similarly screened and age-matched controls had none.

This study does not establish either the etiology or clinical significance of the bipolar patients' signal hyperintensities. However, three general hypotheses concerning the relationship between bipolar illness and the MRI abnormalities should be considered. (1) The MRI abnormalities precede and predispose to or cause bipolar illness. (2) The MRI abnormalities follow the onset of the bipolar condition and reflect damage associated with treatment or repeated affective episodes. (3) The MRI abnormalities and bipolar illness arise from a common cause but are not directly linked. Finally, in all of these cases it may be possible that the MRI abnormality is a nonspecific finding in neuropsychiatric illnesses.

With regard to the first possibility, the signal hyperintensities could be due to posttraumatic, viral, toxic, or genetic factors or to some combination of these and other factors that also predispose individuals to affective disturbances. It is noteworthy in this regard that Robinson et al and Starkstein et al have reported that patients who develop bipolar illness following brain injury are more likely to have a positive family history of affective illness than are those who manifest depression. These findings suggest that structural lesions may lead to bipolar illness in individuals with a genetic predisposition for affective illness. Although our sample of bipolar patients was limited, the incidence of a positive family history for affective illness was not greater in patients with MRI abnormalities than without.

Second, the possibility that the noted hyperintensities might be associated with treatment or severity of illness demands consideration of a number of factors. For instance, hypotension induced by the α-blocking action of numerous psychotropic drugs may result in ischemic lesions. Also, brain dysfunction (and associated hyperintensities) may be related to frequency of bipolar episodes.

Third, the logical possibility must be considered that the MRI abnormalities and bipolar illness are not directly related to one another in an etiological sense but reflect the effect of some common processes. For example, if bipolar illness results from a diffuse alteration in membrane physiology, as some have hypothesized, it is possible that this could result in detectable MRI hyperintensities through an alteration in protein-water relationships. Consistent with this possibility, Rangel-Guerra et al have reported that altered T2-weighted relaxation times in bipolar patients are normalized after lithium carbonate treatment, while such values in normal controls showed no change with lithium carbonate treatment.

Finally, to address the nonspecificity of these abnormalities, it is possible that the signal hyperintensities will prove to be present in some but not all neuropsychiatric illnesses. They might be similar to decreased rapid eye movement latency, which has been reported in depression, schizophrenia, borderline personality disorder, and obsessive-compulsive disorder, among others. Magnetic resonance imaging studies in other disorders are clearly needed to determine the diagnostic specificity of this abnormality.

In addition to the noted MRI abnormalities, the neuropsychological results provide further evidence of subcortical dysfunction in our bipolar patients. The 9 patients with signal hyperintensities encountered more difficulty with the letter fluency and verbal recall tests than did the 10 patients with no MRI abnormalities. On the other language tests and the verbal recognition task, the two subgroups of bipolar patients performed almost identically. Deficient verbal fluency (Letter Category Test) with normal naming and vocabulary perfor-

This study was supported by Mental Health Clinical Research Center Grant MH 50794, grant MH 42575, and fellowship training grant MH 18598 from the National Institute of Mental Health; by a Veterans Administration research training grant for psychiatrists; and by the San Diego Veterans Administration Research Service.

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