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Title
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Permalink
https://escholarship.org/uc/item/7zt66819

Journal
JAMA Psychiatry, 52(9)

ISSN
2168-622X

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Publication Date
1995-09-01

DOI
10.1001/archpsyc.1995.03950210041009

Peer reviewed

Magnetic Resonance Imaging and Mood Disorders

Localization of White Matter and Other Subcortical Abnormalities

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Background: Recent reports in the literature document an association between focal white matter abnormalities in bipolar as well as unipolar mood disorder. The importance of this finding and other associated anatomic differences is uncertain.

Methods: We examined the volume of abnormal white matter and other brain volumes using quantitative magnetic resonance imaging analysis. We explored the relationship of these variables with diagnosis, cognitive function, and clinical variables in 36 patients with bipolar disorder, 30 patients with unipolar disorder, and 26 control subjects who were free from significant medical and neurologic illness.

Results: Younger patients with bipolar disorder (but not similarly aged patients with unipolar disorder or controls) have an increased volume of abnormal white matter. Data also indicate that the total volume of abnormal white matter may be associated with increased cognitive impairment, increased rate of psychiatric illness in the family, and onset after adolescence.

Conclusion: Patients with bipolar disorder demonstrate a pattern of subcortical brain morphologic abnormalities and cognitive impairment.

(Arch Gen Psychiatry. 1995;52:747-755)

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SUBCORTICAL WHITE matter abnormalities may be associated with primary and secondary psychiatric disorders. For example, a relationship between one white matter disease (multiple sclerosis) and depression or mania has been recognized in clinical and epidemiologic studies.[1-3] Moreover, our group,[4,5] Swayze et al,[6] Figiel et al,[7] and Aylward et al[8] have all reported a higher rate of white matter signal hyperintensity in patients with bipolar (BP) disorder than in age-matched control subjects. Patients with depression may also have a higher rate of white matter lesions.[9-14]

To our knowledge, this is the first study in which quantitative magnetic resonance imaging (MRI) analysis was used to compare patients with BP disorder (n=36), patients with unipolar (UP) disorder (n=30), and control subjects (n=26). The purpose of this study was to extend our clinical MRI findings in patients with BP disorder through the use of quantitative image analysis and to include comparison groups of patients with major depressive mood disorder and healthy control subjects. Based on our previous finding of increased prevalence of areas of signal hyperintensity in patients with BP disorder, we predicted an increased volume of abnormal white matter (AWM) in patients

with BP disorder compared with age-matched control subjects and patients with UP disorder. Second, prior studies suggest that the abnormalities associated with BP disorder will be located in frontal (cortical or subcortical) and possibly thalamic[15-17] areas. Groups were compared with regard to the volumes of the following cortical and subcortical gray matter structures: caudate, lenticular nucleus, anterior diencephalon, and cortical gray matter, as well as cortical and subcortical fluid. Third, pilot data led us to hypothesize that subcortical cognitive impairment would be associated with an increased volume of AWM.[5]

RESULTS

PRESENCE AND VOLUME OF WHITE MATTER ABNORMALITIES

Across all subjects, the number of areas of signal hyperintensity was significantly correlated with the quantitative volume of

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SUBJECTS AND METHODS

SUBJECTS

Healthy control subjects, who themselves and whose first-degree relatives were free of current or past psychiatric diagnoses, as well as patients with UP or BP mood disorder, were recruited through advertisement or physician referral to the University of California at San Diego Mental Health Clinical Research Center, La Jolla. All subjects were screened before the study with use of identical mechanisms, including a structured telephone interview, a standardized psychiatric interview (Schedule for Affective Disorders and Schizophrenia[18] or Structured Clinical Interview for DSM-III-R[19]), a physical examination, and laboratory evaluation. Psychiatric interviews were conducted by a trained psychiatry research fellow, psychologist, psychiatric research nurse, or master's level psychology graduate. All medical histories and physical examinations were performed by a psychiatry research fellow. Final diagnoses were made during a weekly consensus conference of all diagnosticians at the Mental Health Clinical Research Center; final application of inclusion and exclusion criteria was made by one of us (R.M.D.). All patients with BP disorder met criteria for BP disorder with at least one full manic episode according to DSM-III-R.[20] Information regarding psychiatric disorders in first-degree relatives was gathered from each study participant. All but three patients with BP disorder were outpatients at the time of study. Study participants were told that they might undergo urine toxicology screening as part of the study; this test was administered where clinically indicated to determine reliability.

Medical and neurologic exclusion criteria included any medication known to affect brain volume (eg, steroids), age over 55 years, substantial substance dependence (5 years' duration at any time or meeting criteria for dependence in the 5 years preceding the study), history of intravenous drug abuse, or severe head injury with loss of consciousness lasting more than 5 minutes or with subsequent neurologic sequelae. In addition, subjects who had used amphetamine, cocaine, or methylphenidate more than 10 times were also excluded. Subjects with a medical history of hypertension, seizures, hypoxia, migraine headaches, neurodevelopmental disorders, learning disorders, and other central nervous system disorders that would affect anatomy were excluded.

Two patients with BP disorder who were initially admitted into the study were excluded on the basis of MRI abnormalities: one had an arachnoid cyst and the other had almost total agenesis of the corpus callosum. A single control subject was excluded from the study when MRI assessment revealed a ventricular volume more than 7 SDs larger than normal and blinded clinical evaluation of neuropsychological test results suggested severe cognitive impairment. Eighteen of the subjects with BP disorder and seven of the controls were part of an earlier published study that addressed the clinical assessment of focal abnormalities in MRI scans of patients with BP disorder.[5] All subjects analyzed herein were included in a report on the importance of visually identified focal areas of signal hyperintensity in patients with BP disorder.[21]

As will be explained in the "Results" section, a second control group was selected from the database of the imaging laboratory and matched with the patients with BP disorder on the basis of AWM volume. These controls were generated from a number of studies at the University of California at San Diego and were judged to be medically and psychiatrically healthy before evaluation, but screening and selection criteria were not identical to the entrance criteria of this study. This group was used only for analysis regarding the distribution of AWM.

The data for this study came from 26 control subjects, 36 patients with BP, and 30 patients with UP. Demographic data are shown in **Table 1**. At the time of the study, the mean ($\pm$SD) score on the 17-item Hamilton Rating Scale for Depression was 12.5 ± 4.9 for patients with UP disorder, 9.2 ± 6.5 for patients with BP disorder, and 0.6 ± 0.8 for controls. Twenty-two of the 30 patients with UP disorder and six of the 36 patients with BP disorder met criteria for major depression at the time of study entry, while seven patients with BP disorder met criteria for hypomania or mild mania. Data on additional diagnoses and medications for each group can be found in **Table 2** and **Table 3**.

MAGNETIC RESONANCE IMAGING

All subjects underwent MRI with a 1.5-T imager (General Electric, Milwaukee, Wis) according to a standard protocol. Data for quantitative analysis were derived solely from the full axial series (echo time, 25, 70 milliseconds; repetition time, 2000 milliseconds; 5 mm thick; 2.5-mm gap). Partial sagittal series and a full coronal series (used in clinical analyses) were obtained but not used in the quantitative analysis.

All images were blindly rated by a single senior neuroradiologist (J.H.). The instructions to the rater were to identify and localize any and all abnormalities. Areas of signal hyperintensity were defined as areas of increased signal intensity present on the early and late echo images. Ten subjects underwent scanning on two occasions; the results of all ratings were identical on both occasions.

All images were analyzed quantitatively according to previously described methods[22] by a trained operator who did not know the diagnosis of the subject. Briefly, each pixel was classified on the basis of its signal values in both original images (echo time, 25 milliseconds; echo time, 70 milliseconds) as most resembling cerebrospinal fluid (CSF), gray matter, white matter, or signal hyperintensity (tissue abnormality). This was accomplished in two steps: First, two new linear combinations of the pixel values were computed to optimize tissue contrast (CSF/brain, gray matter/white matter). Second, classification criteria that were adjusted separately for each section were applied to these computed values. The full series of axial images was analyzed, beginning at the bottom of the cerebellar hemispheres and extending through the vertex.

Consistently identifiable landmark points and structural boundaries were designated on the pixel-classified images by trained image analysts, as described below. The processed image data were then transformed spatially so that all locations within the brain images could be identified relative to a common anatomic coordinate system. Cerebral regions were then defined relative to this coordinate scheme (ie, stereotactically).

Definition of Subcortical Gray Matter Structures

The operator circumscribed pixels classified as gray matter that were visually identified as caudate nuclei, lenticular nuclei, and diencephalic gray matter structures. A division of anterior from posterior diencephalic structures was made based on a stereotactic coronal dividing plane. The anterior diencephalon was composed of mamillary bodies, hypothalamic gray matter, and septal nuclei. The posterior diencephalon comprised the thalamus. The operators did not trace the edges of the structures but defined polygons that included all gray matter pixels within the structures and excluded those gray matter pixels associated with other structures. In some cases, when the subcortical nuclei were contiguous with other areas classified as gray matter but clearly not in the structures, boundaries were manually constructed with use of the filmed images as a guide. Estimates of the volumes of the subcortical structures were made by summing the designated gray matter pixels across all sections.

Definition of Regions
Within the Cerebral Hemispheres

To define anatomically consistent regions, a method was adopted for making subdivisions of the cerebrum relative to the centromedial structural midline and two consistently identifiable (operator-designated) points: the most anterior midline point in the genu and the most posterior midline point in the splenium of the corpus callosum. By calculating estimated rotation angles with use of these landmarks, it was possible to perform a three-dimensional rotation of the images, thus correcting each individual's image data for rotation out of the optimal imaging plane. Regions could then be constructed that resulted in highly consistent placement of regional boundaries relative to gross anatomic landmark (ie, stereotactically).

The division of the cerebrum was based on two major planes: an axial plane, which was perpendicular in orientation to the midsagittal plane and passed through the two corpus callosum points, and a coronal plane, which was defined as perpendicular to the first plane and which passed through the midpoint between the two corpus callosum points. By computing new coordinates for the center point of each voxel relative to these planes, each voxel was assigned to one of four zones: (1) inferior to the axial plane and anterior to the coronal plane; (2) inferior to the axial plane and posterior to the coronal plane; (3) superior to the axial plane and anterior to the coronal plane; and (4) superior to the axial plane and posterior to the coronal plane. Anterior temporal, orbitofrontal, and some dorsolateral and mesial frontal cortex are in the inferior zone. Posterior temporal and inferior occipital cortex are in the inferior posterior zone. Most of the remaining parts of the frontal lobe are in the superior anterior zone, and the superior posterior zone contains primarily parietal and a small portion of the superior occipital cortex.

Measures of White Matter Abnormalities

A global index of signal alterations in the white matter was constructed by summing voxels within the subcortical white matter having signal characteristics meeting criteria for "gray matter" or for areas of "signal hyperintensity," ie, they had longer T_2 relaxation times. These were classified as AWM. Regional measures of signal alteration in the white matter were also computed by summing these voxels separately within each of the eight cerebral regions defined above.

Other Structural and Regional Volumes

The volume of the supratentorial cranium was estimated by summing all supratentorial voxels (including CSF, areas of hyperintensity, and gray and white matter). Eight regional volumes were also computed by summing all supratentorial voxels (including CSF, areas of hyperintensity, and gray and white matter) within each region.

Reliability coefficients (Pearson's r) are available for the following measures from a study of 10 images: cerebral volume (.99), ventricular CSF (.99), cortical CSF (.99), cortical gray matter (.88), caudate (.93), diencephalon (.87), and lenticular nuclei (.73). At the time that interoperator reliability was determined, AWM as expressed herein was not being measured; therefore, reliability coefficients for this measurement are unavailable. Any lack of reliability (noise) in this measurement should serve to decrease group differences, unless it reflects a true (systematic) difference between groups. A discussion of the reliability and validity of this method, as well as factors affecting the outcome of volume measurements, has been published previously.[22]

NEUROPSYCHOLOGICAL ASSESSMENT

All subjects were administered a standard battery of tests for the assessment of attention, learning, memory, and verbal fluency. Performance on tests relevant to the hypothesis that AWM is associated with a pattern of subcortical cognitive impairment are presented, specifically Trails B,[23] letter and category fluency,[24] and learning and memory (the California Verbal Learning Test).[25] A listing of the complete battery is presented in **Table 4**.[26-29]

STATISTICAL ANALYSIS

Analysis of variance (ANOVA) was used to assess the a priori hypothesis that the volume of AWM in patients with BP disorder would be greater than that in patients with UP disorder or controls. Multivariate analysis of variance (MANOVA) was used to explore group volumes on regional white matter differences and other brain structural measurements. When Hotelling's T statistic was significant in the MANOVA, univariate comparisons were performed. Bonferroni's correction for number of comparisons was computed for AWM regional analysis and gray matter structural analyses. Student's-Neuman-Keuls test of significance was used to test for differences between individual groups on post hoc testing. Nonparametric Mann-Whitney U comparisons were used to test differences between groups formed on the basis of AWM volume. Clinical and neuropsychological comparisons across groups were not corrected for the number of comparisons. Pearson's Product-Moment Correlation Coefficients were used to assess the relationship between age at onset and volume of AWM and between lithium use and cognitive impairment.

Table 1. Demographic Characteristics of Subject Groups

	Control Group (n=26)	Bipolar Group (n=36)	Unipolar Group (n=30)	F	P	Post Hoc Tests (Student's-Newman-Keuls)
Mean (SD) age, y	39.1 (9.4)	36.6 (10.8)	38.6 (10.6)	0.54	.5	...
Mean (SD) education, y	16.0 (2.2)	15.0 (2.2)	15.0 (1.8)	2.09	.1	...
Sex, No. (%)						
M	15 (58)	24 (67)	9 (30)	4.98	.01	Bipolar vs unipolar group;
F	11 (42)	12 (33)	21 (70)			control group vs unipolar group
Handedness, No. (%)						
R	23 (88)	33 (92)	26 (87)	0.21	.8	...
L	3 (12)	3 (8)	4 (13)			

Table 2. Additional Diagnoses of Patients With Bipolar and Unipolar Disorders*

Diagnosis	No. of Patients With Bipolar Disorder With Diagnosis	No. of Patients With Unipolar Disorder With Diagnosis
Dysthymia	1	10
Panic disorder with/without agoraphobia	1	6
Agoraphobia without panic	0	1
Bulimia nervosa†	1	1
Somatoform pain disorder	0	1
Social phobia/simple phobia	0	6
Alcohol abuse*	1	1
Cannabis abuse*	1	0
Sedative abuse*	0	1

*No control subject met criteria for any Axis I disorder.
†In remission.

Table 3. Medication Status of Control Subjects and Patients With Bipolar and Unipolar Disorders

Medication(s)*	No. of Patients With Bipolar Disorder Taking Medication(s)	No. of Patients With Unipolar Disorder Taking Medication(s)
Lithium	22	1
Anticonvulsants/calcium channel blockers	4	0
Antidepressants	5	12
Antipsychotics	6	0
Thyroid	6	1
Anticholinergics	2	0

*Ten patients with bipolar disorder, 17 patients with unipolar disorder, and all controls were receiving no medications. Patients may have been taking more than one medication.

AWM (Pearson's r=.38, $P<.001$). The ANOVA demonstrated a significant difference between groups for the AWM (F[2, 89]=5.5; $P<.006$), with post hoc tests indicating that the volume of AWM for patients with BP disorder were significantly higher than those for patients with UP disorder or controls (mean AWM volume for patients with BP disorder, 3279±1187 voxels; mean AWM volume for patients with UP disorder, 2803±1147 voxels; and mean AWM volume for controls, 2656±684 voxels). (The relationship between BP disorder and control groups remained significant with use of a nonparametric analysis [Mann-Whitney U, $Z=-3.1$; $P<.002$].) An example of the AWM distribution in one patient with BP is shown in **Figure 1**.

The MANOVA for eight white matter regions yielded a significant main effect for group (F[16, 162]=2.08; $P<.01$); univariate ANOVA (**Table 5**) indicated that significant differences between groups were present for right (F=6.35, $P<.003$) and left (F=7.84, $P<.001$) superior anterior, right (F=7.38, $P<.001$) and left (F=5.44, $P<.006$) inferior anterior, and right superior posterior (F=3.85, $P<.02$) regions. Bonferroni's correction for number of comparisons requires a significance level of $P<.006$ for a result to be considered significant. With use of this conservative assessment, significant differences exist in superior and inferior right and left anterior regions. With use of post hoc Student's-Neuman-Keuls tests, patients with BP disorder had significantly higher AWM vol-

umes than did controls in all four anterior regions and had higher volumes than patients with UP disorder in both superior anterior regions. Patients with UP disorder, although not manifesting an overall increase in volume of AWM, had a larger AWM volume in the right inferior anterior region compared with controls. However, the group×region interaction did not reach significance. When regional white matter abnormalities were analyzed covarying for regional cerebrum size (to correct for any differences in regional cranial volume), the pattern of differences was unchanged.

SPECIFICITY OF PATTERN OF WHITE MATTER ABNORMALITIES

Although the pattern of white matter abnormalities appeared to be different between patients and controls, it is possible that this difference resulted from measurement imprecision or nonspecific factors influencing the distribution of white matter abnormalities (eg, vascular supply). To address the question regarding the specificity of the AWM pattern in patients with BP disorder, a second group of controls was selected from the database of the neuroimaging laboratory based on a previously established age function for the AWM volume.[22] By design, the mean volume of AWM in this control group was very close to that of the patients with BP disorder. The mean age of the second ("older") control group (n=25) was 51.0±6.6 years (15 years older than the patients with BP disorder to whom they were matched for

Table 4. Performance on Cognitive Tests by Volume of White Matter Abnormality in Patients With Bipolar Disorder*

	Low Volume (n=9)†	High Volume (n=25)	P
Age, y	35.8 (11.0)	36.9 (10.9)	...
Education, y	15.6 (1.1)	14.9 (2.5)	...
Trails B (time)	59.0 (14.7)	80.2 (27.1)	.02
Letter fluency	44.1 (9.2)	36.5 (10.1)	.05
Category fluency	53.8 (9.2)	46.1 (9.8)	.04
CVLT List 1-5, total	56.6 (8.2)	49.0 (8.8)	.03
CVLT List B, total	7.7 (1.7)	6.0 (1.7)	.03
List A, Short Delay, free recall	13.0 (2.0)	10.3 (2.9)	.02
List A, Short Delay, cued recall	13.1 (2.3)	10.8 (2.6)	.03
List A, Long Delay, free recall	12.9 (2.6)	10.6 (3.1)	.06
List A, Long Delay, cued recall	13.6 (2.4)	11.3 (3.0)	.06
Discriminability	−0.3 (0.7)	−0.4 (0.6)	...
Semantic cluster	2.7 (0.9)	1.8 (0.9)	.02
Serial cluster	1.2 (0.7)	2.6 (1.4)	.005

*Values are mean (SD) Wilcoxon Mann-Whitney U values.
†Data were missing for two patients and thus are not included. Data from the following tests are not presented: Mattis Dementia Rating Scale,[26] Wechsler Memory Scale–Revised,[27] Logical Memory, Visual Reproduction, Wisconsin Card Sort Test,[28] and Wechsler Adult Intelligence Scale–Revised subtests[29]: Information, Digit Span, Vocabulary, Arithmetic, and Block Design. CVLT indicates California Verbal Learning Test.

Figure 1. *Segmented magnetic resonance imaging scan showing the distribution of abnormal white matter in a single patient with bipolar disorder. Dark areas represent pixels defined by quantitative image analysis as abnormal white matter.*

AWM volume). As shown in **Figure 2**, the older controls showed elevations compared with younger controls in every region tested. When the Bonferroni correction was applied, however, only the two superior anterior and two posterior inferior regions were significantly different. In contrast, patients with BP disorder demonstrated increases in all frontal regions and no posterior region compared with the younger controls. Nevertheless, the group×region interaction did not reach significance.

The regional pattern suggested that the distribution of AWM in patients with BP disorder may be relatively more frontal than in the healthy older subjects matched for the volume of AWM. Post hoc tests were therefore conducted by comparing groups based on the ratio of anterior AWM volume to total AWM (ie, the proportion of total AWM that is anterior). As a first step to assess whether differences in distribution could be related to differences in total or regional cerebral volume, groups were compared with regard to anterior, posterior, and total cerebral volume and the ratio of anterior to total cerebrum. There were no significant group differences in any of these volumes between groups. The ratio of the frontal to total cerebral volume also did not differ between groups. Given that there were no differences in these relationships, groups were compared with regard to the ratio of frontal to total cerebral AWM. Expressed in percent, the groups differed statistically as follows: patients with BP disorder, 26.3%±5.7%; patients with UP disorder, 23.3%±3.8%; elderly controls, 25.5%±3.5%; and younger controls, 22.8%±4.0% (ANOVA: F=4.035, P<.009). Post hoc tests (Student's-Neuman-Keuls) showed that patients with BP disorder had a significantly more anterior distribution of AWM than did younger controls and patients with UP disor-
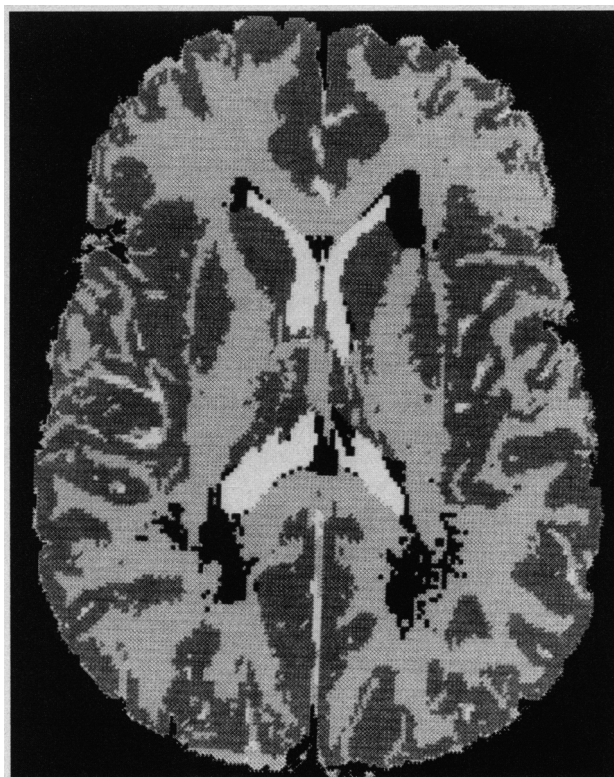
der. Older controls were intermediate in the anterior distribution of AWM and did not differ significantly from any other group.

RELATIONSHIP BETWEEN CLINICAL VARIABLES AND VOLUME OF AWM

To explore the relationship of AWM to clinical variables, we divided subjects into groups with high and low volumes of AWM based on the mean of the control subjects. Earlier data on focal signal abnormalities[21] had suggested that AWM in both patients with UP disorder and those with BP disorder was associated with a trend toward an increased rate of familial psychiatric illness. Twelve controls were in the high group (AWM volume, 3154±491 voxels) and 14 were in the low group (AWM volume, 2059±319 voxels); 27 patients with BP disorder were in the high group (AWM volume, 3748±942 voxels) and nine were in the low group (AWM volume, 2247±182 voxels); 17 patients with UP disorder were in the high group (AWM volume, 3517±1033 voxels) and 13 were in the low group (AWM volume, 1869±305 voxels). Nonparametric Mann-Whitney U Wilcoxon rank-sum tests were used for comparison of groups with high vs low AWM volume. Because of the number of comparisons, positive post hoc results must be considered highly preliminary. While there was no difference in age within groups between high- and low-volume control or BP groups (control: low volume, 40.2±9.0 years; high volume, 37.8±10.2 years; BP group: low volume,

**Table 5. Multivariate Analysis of Variance* and Univariate Analysis of Variance†
of the Volume of White Matter Abnormalities by Subcortical Region‡**

Region (Side)	Control Group (n=26)	Bipolar Group (n=36)	Unipolar Group (n=30)	F (df=2, 89)†	P
Superior anterior (R)	249.46 (93.56)	372.31 (180.61)	280.77 (137.11)	6.35	.003
Superior anterior (L)	266.08 (118.05)	404.42 (209.52)	264.00 (144.30)	7.84	<.001
Inferior anterior (R)	49.92 (25.84)	74.39 (33.26)	69.10 (29.25)	7.38	.001
Inferior anterior (L)	49.96 (29.56)	77.25 (47.21)	65.47 (24.81)	5.44	.006
Superior posterior (R)	717.77 (234.63)	884.14 (279.76)	730.57 (285.18)	3.85	.02
Superior posterior (L)	718.42 (212.95)	865.69 (257.46)	787.33 (304.57)	2.41	.10
Inferior posterior (R)	231.54 (111.48)	325.14 (168.74)	295.50 (230.02)	2.10	.13
Inferior posterior (L)	281.92 (109.42)	355.19 (190.82)	310.47 (171.02)	1.56	.22

*For the multivariate analysis of variance, F (16, 162)=2.08, P<.01.
†Univariate analysis of variance.
‡Values are mean (SD) voxels of abnormal white matter.

35.8 ± 11.0 years; high volume, 36.9 ± 10.9 years), patients with UP disorder in the high-volume group were significantly older than those in the low-volume group (32.8 ± 9.7 vs 43.0 ± 9.2 years). In patients with BP disorder and patients with UP disorder, patients in the high AWM volume group had more family members with psychiatric disorders than did patients in the low AWM volume group (BP group: low volume, 0.3 ± 0.5; high volume, 1.7 ± 2.3; $P<.05$; UP group: low volume, 0.8 ± 0.6; high volume, 1.6 ± 1.4). Patients with BP disorder who were receiving lithium showed a nonsignificant trend toward classification in the high AWM volume group (20% in the low-volume group vs 50% in the high-volume group were receiving lithium; $P<.07$). Although this result might suggest that lithium is associated with the presence of AWM, 22% of patients with BP disorder not receiving any medication were also found to have a high volume of AWM. Also in support of this finding is that patients with BP disorder not receiving lithium had more AWM than did control subjects (patients with BP disorder not receiving lithium [n=20]: AWM volume, 3390 ± 1236 voxels; control subjects [n=26]: AWM volume, 2565 ± 684 voxels; $P<.006$).

Because age at the time of study is a significant confounding factor for the presence of AWM[30] (and patients with UP disorder with a higher volume of AWM were significantly older at the time of study), an analysis of covariance (ANCOVA) contrasting high and low AWM volume groups with regard to age at onset, covarying for age at the time of study, was performed. In the patients with BP disorder, but not in those with UP disorder, controlling for age at the time of study revealed a significant partial correlation between age at onset and volume of AWM (in patients with BP disorder, partial $r=.405$; $P<.008$; in those with UP disorder, partial $r=-.194$; $P<.16$). This finding suggests that increased volume of AWM is associated with later age at onset of BP disorder in the age range sampled.

Cerebrovascular risk factors are highly correlated with the incidence of areas of focal white matter signal hyperintensity.[30] Data on cigarette smoking revealed a significant relationship between smoking and AWM volume in patients with UP disorder ($r=.6$, $P<.001$) but not in those with BP disorder or control subjects. Data on
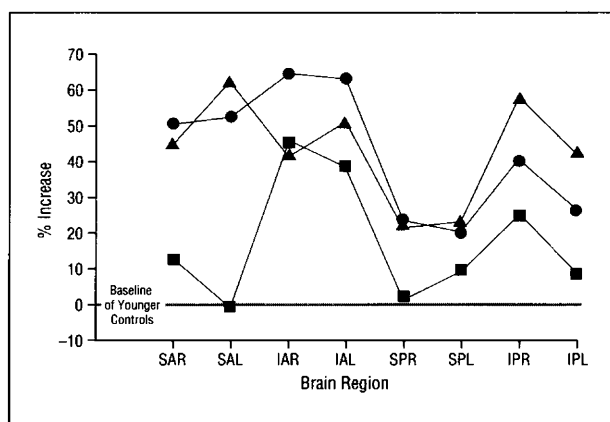

Figure 2. The distribution of abnormal white matter in patients with bipolar disorder (circles, n=36), patients with unipolar disorder (squares, n=30), and older controls (triangles, n=25) expressed as a percentage increase over the mean of the younger control group. SAR indicates superior anterior right; SAL, superior anterior left; IAR, inferior anterior right; IAL, inferior anterior left; SPR, superior posterior right; SPL, superior posterior left; IPR, inferior posterior right; and IPL, inferior posterior left.

smoking duration and amount were available for only a subset of the latter groups (75%). In all groups, the majority had never smoked, and the distribution was skewed (mean pack-years of smoking: patients with BP disorder, 9.9 ± 22.7; patients with UP disorder, 6.8 ± 14.3; control subjects, 9.7 ± 20.1).

NEUROPSYCHOLOGICAL CORRELATES OF AWM

Our earlier study[5] had suggested that the presence of focal white matter abnormalities on MRI scans in patients with BP disorder was associated with psychomotor slowing, decreased verbal fluency, and impaired free recall on a test of word list learning. We therefore compared high and low AWM volume groups within diagnoses on tests of these functions (Table 4). Data from two patients with BP disorder are missing owing to failure to complete the testing battery. Groups were compared with use of a nonparametric (Mann-Whitney U Wilcoxon rank-sum) test owing to small group size in the low AWM volume BP group. While patients with BP disorder with a high vol-

Table 6. Multivariate Ananysis of Variance* and Univariate Analysis of Variance† of the Volume of Major Brain Regions‡

Region	Control Group (n=26)	Bipolar Group (n=36)	Unipolar Group (n=30)	F (df=2, 89)†	P
Cerebral volume	193 525.65 (15 901.37)	197 055.61 (15 374.84)	192 060.67 (19 334.80)	0.77	.47
Cortical fluid	15 523.02 (4927.41)	14 510.87 (5466.07)	17 632.82 (5372.94)	2.91	.06
Subcortical fluid	2610.51 (1028.06)	3065.55 (1284.46)	2944.06 (1148.69)	1.17	.32
Caudate nucleus	1806.35 (243.73)	1808.81 (259.72)	1719.17 (245.10)	1.26	.29
Anterior diencephalon	357.77 (111.87)	385.94 (136.89)	355.80 (126.24)	0.58	.56
Posterior diencephalon	1716.85 (293.02)	1904.81 (343.06)	1570.77 (345.89)	8.46	<.001
Lenticular nucleus	1922.77 (299.85)	2030.17 (364.55)	1873.17 (430.86)	1.55	.22
Cortical gray matter	85 494.87 (12 355.46)	89 504.48 (9875.74)	84 691.76 (9631.95)	1.98	.14

For the multivariate analysis of variance, F (16, 162)=1.79, P<.037.
†Univariate analysis of variance.
‡Values are mean (SD) voxels. In pairwise comparisons, values for the bipolar group were greater than those for controls and the unipolar group and values for the unipolar group were greater than those for controls.

ume of AWM demonstrated significantly more impairment on nine of the 12 scores, with a trend in the same direction on two more, such differences were not found within either control or UP groups. While the pattern of differences is of interest, actual differences between groups were modest and would not be statistically significant if corrected for the number of comparisons performed. In patients with BP disorder, there were no differences between groups on mean Hamilton Depression Rating Scale[31] scores.

Because there was a nonsignificantly higher rate of lithium-treated patients with BP disorder in the high AWM volume group, we performed an ANCOVA to assess the contribution of lithium treatment to cognitive performance (lithium levels were unavailable). The confound between lithium treatment, BP diagnosis, and high AWM volume made the ANCOVA a conservative estimate of non–lithium-related impairment in cognitive function. Specifically, response to lithium therapy and poor cognitive performance could be epiphenomena of a single process. The following variables remained significantly correlated with volume of AWM: Trails B time (r=.411, P<.01), category fluency (r=−.369, P<.02); California Verbal Learning Test List 1 to 5 total (r=.341, P<.03), and List A Short Delay Cued Recall ($r1$=−.360, P<.02). Trends for a relationship remained in Letter Fluency (r=−.257, P<.07) and Long Delay Cued Recall (r=.223, P<.10). Thus, the deficits in the high AWM volume group do not appear to be attributable to lithium treatment. Because of the conservative nature of this analysis, results that are significant at a trend level are presented herein.

ASSOCIATED STRUCTURAL ABNORMALITIES

Because mood disorders have been associated with cortical and subcortical abnormalities, we evaluated measures of supratentorial cranial volume, cortical gray matter volume, cortical and subcortical fluid volume, caudate and lenticular nucleus volume, and anterior and posterior (thalamic) diencephalic volume (**Table 6**).

Our first approach was to assess the relationship between these structural variables and our three diagnostic groups using MANOVA; there was a significant group effect (F[16, 162]=1.79; P<.04). Using ANOVA, we then assessed which of the variables were contributing to this

group difference. The only difference between groups was in the volume of the thalamus (posterior diencephalon) (F=8.46, P<.0004), which is significant even with application of Bonferroni's correction for multiple comparisons. Post hoc tests demonstrated a significantly larger thalamus in patients with BP disorder compared with those with UP disorder and controls and a smaller thalamus in the patients with UP disorder compared with those with BP disorder and controls. An increased volume of AWM in the patients with BP and UP disorders was correlated with increased ventricular volume (patients with BP disorder: r=.353, P<.05; patients with UP disorder, r=.581, P<.01).

COMMENT

INCREASED VOLUME OF WHITE MATTER ABNORMALITIES

To our knowledge, this is the first study to use quantitative MRI to compare patients with BP or UP mood disorder and control subjects and to include behavioral (cognitive and clinical) correlates. The major finding was that patients with BP disorder demonstrated a higher volume of AWM than either control subjects or patients with UP disorder. The volume of quantitatively assessed AWM was highly correlated with the number of visually identified areas of focal signal hyperintensity. In addition, for both patients and control subjects, AWM could be identified in locations without visually identified lesions. The quantitative methods appear to delineate a more extensive and diffuse white matter process than that suggested by the small, highly localized areas of signal hyperintensity seen visually. The exact neuropathologic correlates ($\geq$1) of AWM are unknown. That subcortical areas of signal hyperintensity may be related to AWM is suggested (but not proved) by the correlation of AWM volume with the presence of areas of signal hyperintensity. In addition, an earlier report[22] demonstrated a relationship between age and pixels classified as areas of hyperintensity in control subjects. It is possible that the neuropathologic underpinnings of this finding (AWM) are multiple and that they may vary with the location in the brain where AWM is found. Patients with BP disorder with an increased volume of AWM were, on aver-

age, more likely to have had a later age at onset than those with low volumes of AWM and to demonstrate a pattern of cognitive impairment suggestive of subcortical dysfunction compared with that of patients with less AWM.

Early research suggested that white matter abnormalities may be related to primary mood disorders.[32] In addition, computed tomographic studies suggest that x-ray attenuation values (the extent to which x-rays fail to be transmitted through a structure) are abnormal in the white matter of patients with BP disorder.[33,34] Moreover, possible state-related change in T_1 relaxation times (suggesting differences in the local proton environment or chemical structure of white matter) have been reported in patients with BP disorder.[35,36] Most recently, as noted previously, there is increasing evidence of white matter abnormalities in patients with UP disorder.[9-14] Our failure to find this relationship is puzzling. However, the exclusion criteria of this study included many risk factors for signal hyperintensities, including hypertension. None of the above studies excluded subjects with hypertension. The age range of the subjects in the present study was relatively limited and did not sample older unipolar subjects.

DISTRIBUTION OF WHITE MATTER ABNORMALITIES

Compared with young controls and similarly aged patients with UP mood disorder, subjects with BP may have had a relatively frontal distribution of AWM. Compared with older controls who are matched for total volume of AWM, our test of the specificity of the frontal pattern was not entirely conclusive. A higher percentage of AWM is found within the frontal lobe in subjects with BP than in any other group, but this difference is not statistically different from the older controls. The fact that one regional pattern is not unique to subjects with BP is not surprising, as even in secondary mood disorders there is not a one-to-one correspondence between lesion location and mood disturbance.

CLINICAL AND NEUROPSYCHOLOGICAL SIGNIFICANCE OF WHITE MATTER ABNORMALITIES

In our study, patients with BP and UP who had higher volumes of AWM had a higher rate of psychiatric disorders among relatives (based on patient-provided history), and subjects with BP in this group had a later age at onset. On first pass, the relationships between AWM, later age at onset, and positive family history in the subjects with BP appears to contrast with the results of Taylor and Abrams,[37] who demonstrated a relationship between younger age at onset and family loading for mood disorder. The majority of our patients, however, would be defined as having "early onset" based on the study of Taylor and Abrams,[37] and only seven (19%) of our subjects had onset after age 29 years, the age cutoff used by Taylor and Abrams to define early vs late onset.

We failed to find a relationship between most clinical variables and structural variables, possibly reflecting the limited sample size, experimental noise, or hetero-

geneity of the causes of mood disorders. Factors such as treatment effectiveness, duration of illness, medication compliance, and patient symptom reporting bias greatly influence the type of clinical phenomenologic profile of each subject.

The relationship between volume of AWM and impairment on tests of fluency, psychomotor speed, and free recall suggests that this particular structural brain abnormality itself (or a close correlate) mediates trait-related cognitive impairment. Furthermore, the nature of the cognitive impairment seen in the patients with BP disorder is similar to that reported by Junque et al[38] in a study of nonpsychiatric elderly patients with white matter abnormalities seen on MRI scans. The further increase in the incidence of white matter disease with aging may explain why older patients with BP exhibit more cognitive impairment than do age-matched patients with UP disorder, controls, and younger patients with BP disorder.[39]

The presence of white matter signal abnormalities does not necessarily define a group of patients with BP disorder who have "secondary" BP mood disorder. Within the limits of our rather extensive clinical assessment, no patient had a known cause for his or her mood disorder.

OTHER STRUCTURAL ABNORMALITIES ASSOCIATED WITH MOOD DISORDER

Exploratory analysis suggested that the volume of the thalamus was increased in the BP group and decreased in the UP group compared with controls and each other. Like Schlegel and Kretzschmar,[40] we did not find an increase in ventricular fluid volume, as reported by some other investigators,[6,41,42] nor did we find a ventricular size and sex interaction, as reported by Andreasen et al.[43] It is possible that the nature of our patient sample, which included patients with relatively few hospitalizations, a low rate of psychosis, and little substance abuse, is relevant to this outcome, as it is not unreasonable to predict that patients with the most severe symptoms may have the most severe structural anomalies. Finally, these data do not allow conclusions to be drawn regarding the relationship of a particular mood state to structural abnormalities, as these subjects were primarily outpatients and not severely ill. Our earlier report suggests, however, that white matter abnormalities detected on MRI are stable over time.[5] The comorbidity demonstrated in the lifetime diagnoses of the subjects reflects the comorbidity in the general population affected with mood disorders. Results should be interpreted with knowledge of the presence of these comorbid diagnoses, which may themselves or in combination with mood disorder be associated with brain structural changes. Because toxicology screening procedures were not routinely performed, our assessment of substance abuse/dependence reflects information based on patient report and past medical records. One patient was excluded owing to agenesis of the corpus callosum. This finding in a patient with BP disorder is intriguing because it is a relatively rare abnormality hypothesized by Swayze et al[44] to be etiologically related to the development of schizophrenia.

It is conceivable that some of the white matter ab-

normalities seen in the patients with BP disorder are not a reflection of aging or injury but rather anomalous myelination. The latter process continues throughout adolescence.[45,46] The findings of an absence of volume loss in our patients with BP disorder, combined with increased AWM volume and thalamic volume (similar to thalamic volume found in late adolescent controls[47]), may support the hypothesis that a subset of BP mood disorder results from anomalous neurodevelopment.

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