

Reduced Cerebral Grey Matter Observed in Alcoholics Using Magnetic Resonance Imaging

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Twenty-eight chronic alcoholics and 36 age- and sex-matched non-alcoholic controls were examined with magnetic resonance imaging and brain morphometric analyses. Results confirmed large increases in subarachnoid cerebrospinal fluid (CSF) volume and mild ventricular enlargement in the alcoholics and revealed associated volume reductions of localized cortical and subcortical cerebral structures. Volume losses in the diencephalon, the caudate nucleus, dorsolateral frontal and parietal cortex, and mesial temporal lobe structures were the most prominent. Significant correlations between increments in cortical and ventricular CSF and decrements in the volume of cortical and subcortical grey matter were noted. Although there was little evidence for relationships between performance on neuropsychological tests and volume of grey matter structures, significant correlations between some cognitive measures and subcortical and cortical fluid volumes were found. The parallels between this pattern of affected structures and recent neuropathological findings are discussed.

Key Words: MRI, Alcoholism, Cerebral Atrophy.

PREVIOUS NEURORADIOLOGICAL comparisons of chronic alcoholics and nonalcoholic controls have consistently demonstrated cerebrospinal (CSF) increases in the brains of the alcoholics, especially in the subarachnoid spaces.¹⁻¹⁰ These changes would seem to support neuropathological reports of reduced brain weight and brain volume in alcoholics¹¹⁻¹³ and perhaps even the general notion that ethanol is a neurotoxic agent affecting a number of brain regions important for higher cognitive functions.¹⁴⁻¹⁷ However, this interpretation of these neuroradiological findings has been challenged by reports that these increases in CSF are at least partially reversible with prolonged abstinence¹⁸⁻²² and may actually reflect a transitory brain overhydration during detoxification.²³⁻²⁶ In

addition, the failure, in some instances, of these increases in CSF to be consistently and highly correlated with neuropsychological deficits after the effect of age has been removed has raised further doubts concerning the permanent pathological implications of the observed CSF increments.^{1,2,5}

With the development of quantitative (morphometric) techniques for evaluating the volume of grey matter structures seen on magnetic resonance (MR) images, it is now possible to ascertain more precisely the implications of the CSF increases in alcoholics' CT scans and pneumoencephalograms. In an initial study, Jernigan et al.²⁷ compared CSF increases and grey matter reductions in eight alcoholics with Korsakoff's Syndrome, 12 age-matched nonamnesic alcoholics, and 13 age-matched nonalcoholic controls. Both alcoholic groups had significant cortical and subcortical grey matter losses in association with CSF increases, but these changes were more extensive in the amnesic alcoholics. While grey matter reductions in the diencephalon and superior fronto-parietal cortices characterized alcoholism per se, the Korsakoff patients were distinguished by unusual volume losses in the anterior diencephalon, mesial temporal, and orbitofrontal regions. Since recent neuropathological reports^{14-16,28-30} have noted abnormalities in cortical, diencephalic, basal forebrain, and hippocampal structures of alcoholics, these volume decrements on MR may actually be in vivo indices of significant cellular changes in grey matter.

In the present study, the findings of Jernigan et al.²⁷ are extended to a larger and younger population of nonamnesic alcoholics who have been administered an extensive neuropsychological examination. Besides a detailed evaluation of the relationship between CSF increases and specific grey matter losses and white matter signal hyperintensities, correlations between cognitive losses and various MR indices are also assessed. It was anticipated that the greater resolution of MR combined with morphometric techniques would result in higher brain-behavior correlations than usually reported in previous CT scan studies. Furthermore, increments in sulcal and ventricular CSF were expected to be correlated with volume reductions in association cortices and subcortical nuclei, respectively. If both of these predictions were realized, they would strengthen the notion that the CSF increments noted in neuroradiological reports of alcoholics do indeed reflect significant changes in various grey matter structures.

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MATERIALS AND METHODS

Subjects

Twenty-eight alcoholic males (mean age = 49.5 years, SD = 9.9) were subjects in this study. These patients had undergone detoxification prior to admission to the San Diego Department of Veterans Affairs Medical Center's Alcohol Treatment Program (ATP), a 28-day program for alcoholism counseling and treatment. Using the Alcohol Research Center Intake Interview,³¹ data on drinking and medical histories were obtained from each patient and at least one resource person, such as a close friend or family member, and the diagnosis of alcohol abuse or dependence was documented using DSM-III³² criteria. Individuals were excluded from this study if they had a history of overt liver (e.g., cirrhosis, jaundice), metabolic (e.g., diabetes), vascular (e.g., coronary artery disease), or neurologic (e.g., head injury, encephalitis, epilepsy) disorders. Patients with a history of drug abuse or of major psychiatric illness (e.g., schizophrenia, PTSD, bipolar affective disorder) predating the onset of alcoholism were also screened from the study. The alcoholics' years of alcohol abuse and their mean daily consumption of ethanol for the 3-month period prior to admission to the ATP are shown in Table 1. Ten of the older alcoholic patients in the present study were also subjects in the previous report comparing MRI indices of alcoholics with and without Korsakoff's Syndrome.³³

All 28 alcoholics were administered a neuropsychological examination comprised primarily of tests known to be affected in recently detoxified patients.³⁴ The Vocabulary test (WAIS-R), Trails A and B, Digit Symbol (WAIS), and Visual Search Test³⁵ were administered within 48 hr of

admission. The booklet form of the Category Test,³⁶ the Stroop Color & Word Test,³⁷ the Rey Auditory Verbal Learning Test (RAVLT),³⁸ and Story Recall (Story 1 of the Logical Memory test from the Wechsler Memory Scale-Revised³⁹) were administered 3 to 4 weeks following admission. For Story Recall, the number of correctly recalled ideas on the first test trial, trials to reach a predetermined learning criterion, and the number of correctly recalled ideas after a 30-min delay were recorded.

The 36 nonalcoholic male controls (mean age = 48.0 years, SD = 10.1) were recruited from the community by newspaper advertisements. All of these control subjects were screened for a history of alcohol abuse, alcoholism, drug abuse, and the same medical and psychiatric disorders described for the alcoholic subjects. Thirteen of the older nonalcoholic controls also participated in Jernigan et al.'s³³ previous MRI study of alcoholic Korsakoff's Syndrome. Of the 36 nonalcoholic controls, 15 were administered the same neuropsychological examination as the alcoholics.

Table 1 shows the mean age, education, drinking histories (i.e., years of alcoholism, mean daily consumption for the 3-month period prior to admission), and neuropsychological test scores for the 28 alcoholics and 15 controls who were administered psychological tests. Since the two groups' difference in education was significant ($p < 0.05$), analyses of covariance controlling for education were used to compare their performances on the neuropsychological tests. As expected, the alcoholics were impaired on most of the test scores, and thus, appeared similar on the basis of their cognitive deficits, as well as their drinking history, to patients reported in other neuropsychological and neuroradiological studies.^{1,34,40-43}

Table 1. Mean Age, Education, Drinking Variables, and Neuropsychological Test Scores for Alcoholic (N = 28) and Nonalcoholic Control (N = 15) Subjects

	Alcoholics	Controls	p*
Age (years)	49.5 (9.9)	50.4 (10.0)	NS
Education (years)	13.9 (1.9)	15.1 (1.6)	<0.05
Years of alcoholism	12.0 (8.8)		
Daily ethanol consumption in 3-months prior to admission (mean number of drinks per day)	14.9 (10.0)	0.4 (0.9)†	<0.01
Vocabulary (WAIS-R scaled score)	9.8 (2.0)	12.1 (1.9)	<0.01
Trails A (seconds)	31.8 (10.3)	25.0 (6.4)	<0.06
Trails B (seconds)	107.6 (48.1)	66.9 (22.6)	<0.01
Digit symbol (WAIS scaled score)	9.0 (2.3)	11.6 (3.0)	<0.01
Visual search (seconds)	164.3 (95.1)	126.2 (48.9)	NS
Category Test (total errors)	64.0 (27.3)‡	35.6 (17.6)	<0.01
Stroop Test (Card 3: number correct)	33.3 (8.1)‡	40.9 (7.7)	<0.02
Story Recall—immediate (number correct: trial 1)	12.4 (4.2)	15.7 (2.8)	<0.02
Story Recall—trials-to-criterion	2.1 (1.1)	1.4 (0.5)	NS
Story Recall—delayed (number correct)	15.5 (2.8)	16.5 (3.1)	NS
RAVLT—immediate recall (number correct: trial 1)	5.6 (1.5)	7.7 (2.2)	<0.01
RAVLT—immediate recall (total correct: trials 1-5)	43.0 (8.6)	49.7 (8.8)	<0.06
RAVLT—delayed recall (number correct)	9.0 (2.6)	9.8 (3.2)	NS

* Age, education, and daily ethanol consumption were assessed with two-tail t-tests; neuropsychological test scores with analysis of covariance controlling for education differences.

† Daily ethanol consumption for the 3 months prior to the interview was available for only 13 of the 15 nonalcoholic controls.

‡ The Category Test and Stroop Test were administered to only 27 alcoholics because one subject was colorblind.

Imaging Protocol

MR was performed with a 1.5-T super-conducting magnet (Signa; General Electric, Milwaukee), at the UCSD/AMI Magnetic Resonance Institute. A standard protocol was used for the acquisition of MR brain images, and the images were analyzed in the Brain Image Analysis Laboratory of the Department of Psychiatry, UCSD. Proton-density weighted (PDW) and T₂-weighted (T₂W) images (Fig. 1) were obtained simultaneously for each section, using an asymmetrical, multiple-echo sequence (TR = 2000 msec, TE = 25, 70 msec) to obtain images of the entire brain in the axial plane. Section thickness was 5 mm with a 2.5 mm gap between successive sections in all instances. A 256 × 256 matrix and 24 cm field of view were used. No sedation was administered for the examinations. For the following discussion of image analysis, the term pixel will be used to refer to a single picture element (or signal value) from the image matrix. The term voxel will be used to refer to the corresponding 3-dimensional volume from which the signal value for a pixel is taken.

Image Analysis

The visual identification of specific structures in MR images is possible because of the tissue contrast between the grey matter structures and the surrounding white matter or CSF. However, measurements of volumes of cerebral structures must overcome several problems. First, because of partial-voluming of grey matter with white matter, or CSF (or all three) at the edges of structures, sharply defined edges are not always present. This allows considerable scope for variability in subjective determinations of such boundaries when, for example, tracing methods are used, leading to measurement unreliability in the computed volumes.

Visual determination of specific cortical structures on MRI presents additional challenges and depends upon the presence of visible gross morphologic features relative to which the boundaries of the cortical regions can be defined. Standard regional divisions for the cortex are based to a large extent on cortical gyral patterns, but the accurate localization of particular gyri or sulci, throughout a series of images, is often impossible. Furthermore, some boundaries, such as that between posterior temporal and inferior parietal cortex, are not clearly defined in gross morphological terms. Also, even when attempts are made to

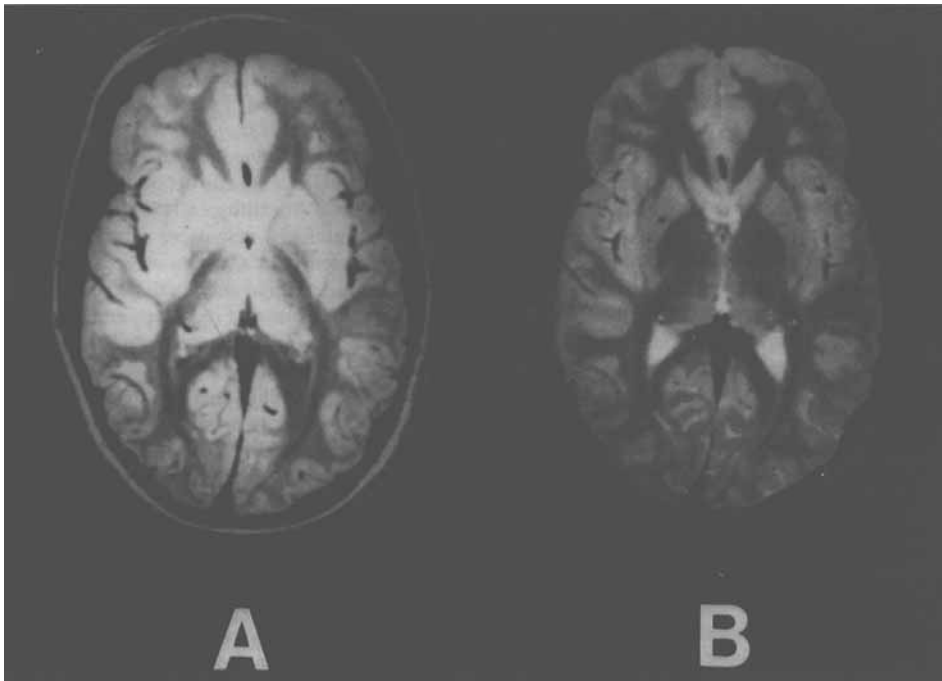


Fig. 1. Representative images from the standard protocol. A, Axial section, SE 2000/25 (PDW in text). B, Axial section, SE 2000/70 (T₂W in text). Sections are 5 mm thick, matrix 256 × 256, with 2.5 mm gaps between images. A field of view of 24 cm was used.

standardize head positioning, rotation of the head (relative to the imaging plane) occurs in all three planes. This is especially true with unsedated subjects who must be sufficiently comfortable in position to avoid movement during the imaging session. Careful inspection indicates that relatively small rotations substantially change the appearance of brain structures in the image plane, further complicating their visual identification. Thus, manually tracing the structures in the sections where they are best visualized often leads to inaccurate volume and asymmetry assessments. The techniques described below are designed to address these difficulties.

To facilitate and standardize the determination of structural edges, our method involves a semi-automated classification of all pixels in the images on the basis of their signal characteristics on the two original image matrices for each section. A detailed description of the basic image analysis method has been reported.⁴⁴ Only a brief summary is provided here: Each axial image is first digitally filtered to reduce the signal drift across the image due to magnetic field and gradient inhomogeneities. Information in the two images for each axial section is then combined to best distinguish the different tissues in the image. For each section imaged, a computed matrix is produced. In this matrix, voxels are classified as most resembling (in signal strength) grey matter, white matter, CSF, or signal hyperintensities (tissue abnormalities). The full series of axial images is analyzed, beginning at the bottom of the cerebellar hemispheres and extending through the vertex.

Further manipulations to derive the specific structural measures for the present study were then made using these "pixel-classified" images. Trained operators, blind to any subject characteristics, used a stylus-controlled cursor on the displayed images to manually separate infratentorial from supratentorial areas, left from right hemispheres, and the cortical from subcortical regions of the supratentorial cranium. Thus, separate estimates of the four classes of pixels were made for these areas.

Definition of Subcortical Structures

To delineate subcortical structures, the operators circumscribed pixels classified as subcortical grey matter that were visually determined to be in caudate nuclei, lenticular nuclei, and diencephalic grey matter structures (including mammillary bodies, other hypothalamic grey, septal nuclei, and thalamus). They did not trace the edges of the structures (since the pixel classification defined the transition from grey to surround-

ing white matter), but defined polygons that included all grey matter pixels within the structures, and excluded those grey matter pixels associated with other structures. In some cases, when the subcortical nuclei were contiguous with other areas classified as grey but clearly not in the structures, boundaries were manually constructed using the filmed images as a guide.

Definition of Cortical Regions

To define anatomically consistent cortical regions, a method was adopted for making subdivisions of the supratentorial cranium relative to the centromedial structural midline and two consistently identifiable points: the most anterior midline point in the genu and the most posterior midline point in the splenium of the corpus callosum. By calculating rotation angles using these landmarks, it was possible to perform a 3-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 which resulted in highly consistent placement of regional boundaries relative to gross anatomical landmarks.

The two corpus callosum points were considered to lie in the true midsagittal plane. The orientation of this plane was then determined by computing a regression line through a series of visually-selected brainstem midline points on different sections. The division of the cerebrum was based on two major planes (see Fig. 2): an *axial plane*, which is perpendicular in orientation to the midsagittal plane and passes through the two corpus callosum points, and a *coronal plane*, which is defined as perpendicular to the first plane and which passes through the midpoint between the two corpus callosum points. By computing new coordinates for each voxel relative to these planes, each is assigned to one of four zones: one, inferior to the axial plane and anterior to the coronal plane (IA); a second, inferior to the axial plane and posterior to the coronal plane (IP); a third, superior to the axial plane and anterior to the coronal plane (SA); and a fourth, superior to the axial plane and posterior to the coronal plane (SP). Again, these defined planes are independent of the image plane, as a 3-dimensional rotation is first applied based on the positions of the landmarks described above. Anterior temporal, orbito-frontal, and some dorsolateral and mesial frontal cortex lie in the inferior anterior zone. Posterior temporal and inferior occipital cortex fall in the inferior posterior zone. Most of the remaining parts of the frontal lobe fall into the superior anterior zone, and the superior posterior zone

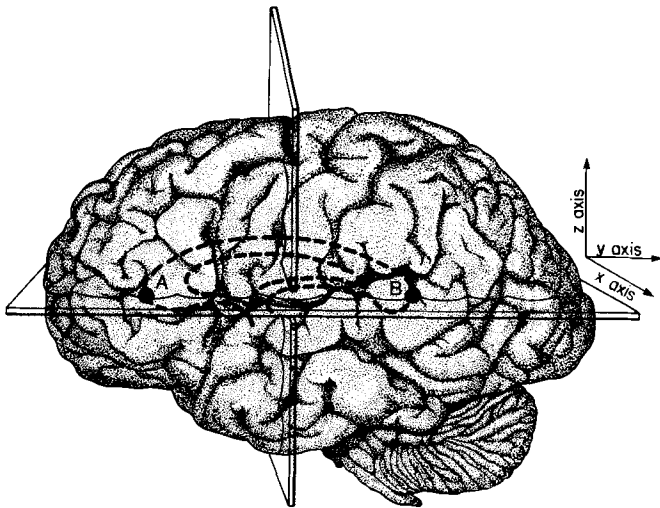


Fig. 2. Cerebral regions are defined as follows: Points A and B in the corpus callosum, shown above, are the most anterior midline point in the genu, and the most posterior midline point in the splenium, respectively. An axial plane passing through these two points is defined, as shown, perpendicular to the midsagittal plane. A coronal plane is defined perpendicular to the axial plane and passing through the midpoint between points A and B. Thus four cerebral zones are defined: inferior anterior, inferior posterior, superior anterior, and superior posterior. Anterior temporal, orbitofrontal, and some dorsolateral and mesial frontal cortex lie in the inferior anterior zone. Posterior temporal and inferior occipital cortex fall in the inferior posterior zone. Most of the remaining parts of the frontal lobe fall into the superior anterior zone, and the superior posterior zone contains primarily parietal and superior occipital cortex.

contains primarily parietal and a small portion of the superior occipital cortex.

To further separate mesial from peripheral cortical regions, an ellipsoid volume was defined within the supratentorial cranial vault. This volume constitutes 30% of the supratentorial volume and has cardinal dimensions proportional to those of the supratentorial vault (i.e., the z-axis extent of the ellipsoid is proportional to the maximum z-axis extent of the supratentorial cranium, the y-axis extent of the ellipsoid to the maximum y-axis extent, and the x-axis to the maximum x-axis extent). The ellipsoid is centered slightly behind, but in the same axial plane as, the origin of the coordinate system described above, at a point 60% of the distance from the genu to the splenium reference point along the line connecting them. The size and center point of the volume were chosen empirically so as to isolate as well as possible the medial cortical surfaces of the limbic lobe,⁴⁵ while excluding the more lateral neocortical surfaces. The area designated as mesial with this method is shown in green in Fig. 3. It consistently includes the most posterior parts of the orbital frontal lobe, the amygdala, the hippocampus and most of the parahippocampal gyrus, the insula, and most of the cingulate gyrus. The ellipsoid defines mesial and peripheral zones within each of the four original cerebral zones described above. A summary of the cortical structures falling into each of the resulting eight zones is given in Table 2.

The fully processed images are illustrated in Fig. 3. The images shown are the actual color-coded digital images produced for one of the subjects. The different pixel classes are color coded as follows: Diencephalic areas are purple, caudate nuclei are blue, and lenticular nuclei are magenta. Within the subcortical white matter there are some voxels with signal values that fall not within the criterion range for white, but within the range of grey matter values (i.e., they demonstrate lengthened T_2 relative to other white matter voxels). These voxels have been coded separately and are shown in Fig. 3 in yellow. The red line running through each section indicates the position of the coronal dividing plane. This plane consistently intersects the amygdala and falls between the column of the fornix and the mammillothalamic tract (See Fig. 3). At the level of the mammillary bodies it consistently divides them from the more anterior hypothalamic grey areas. Because this plane passes through the dience-

phalic grey matter regions and divides the anterior hypothalamic and septal structures (lying anteriorly) from the bulk of the thalamus (lying posteriorly), the corresponding anterior and posterior diencephalic areas were examined separately. It should be noted that areas within the lenticular nucleus containing significant iron deposits, particularly in globus pallidus, do not meet the signal criteria for grey matter and are thus not included in this region. Fluid and white matter are shown in red and black, respectively; however, subcortical and cortical fluid are measured separately.

Volume of the supratentorial cranium was estimated by summing supratentorial voxels (including CSF, hyperintensities, and grey and white matter) over all sections. The subcortical and cortical CSF voxels were summed over all sections separately to estimate the ventricular and cortical sulcal volumes. The grey matter voxels within each of the subcortical structures and the cortical grey matter voxels within each of the eight cerebral zones were summed separately. Eight regional volumes were also computed by summing all supratentorial voxels (including CSF, hyperintensities, and grey and white matter) within each region. All subcortical measures and both CSF measures were expressed as proportions of the supratentorial cranial volume, and all cortical grey matter measures as proportions of their respective regional volumes. Finally, an index of signal alterations in the white matter was constructed by summing voxels within the subcortical white matter regions having signal characteristics meeting criteria for "grey matter" or for "signal hyperintensities", i.e., they had longer T_2 values. This measure was also expressed as a proportion of the supratentorial cranial volume. It should be mentioned that while all subjects show some voxels in the subcortical white matter with longer T_2 , the number of such voxels has been shown to increase significantly with age²⁷ and the presence of dementia.⁴⁶

Statistical Analysis

Because there are well-established age changes in most, if not all, of these measures, it is advisable to remove age effects before estimating the group effects. In our previous articles we, and others, have pointed out that removing age effects from the full sample (including alcoholics) tends to remove part of the "alcoholism" effect, because older alcoholics (with longer drinking histories) usually have more atrophy, which is incorrectly attributed to "aging." The approach we have used avoids this problem, and provides an accurate means of removing variance associated with normal aging even when examining alcoholic patients in whom age and years of alcoholism are usually confounded. This method also facilitates comparison of the extent of damage to different structures by placing the measures on a standard scale.

These measures were converted to age-corrected z-scores using formulae derived from control data in 55 normal volunteers ranging from 30 to 79 years of age.²⁷ These values, by definition, have an expected mean of 0 and a standard deviation of 1 in the controls. The group means presented here are the averages of these z-scores.

The computation of age-adjusted scores is described in greater detail in earlier reports.^{9,10,27,46} These values take advantage of the fact that we have examined a larger group of controls and estimated the changes with aging of both mean and standard deviation of each measure. On the basis of this information we have then expressed each subject's value in terms of its deviation from the mean of his normal age-peers in the standard deviation units observed at his age. The coefficients used to compute the age-adjusted scores are given in the Appendix. To ensure that the full control sample was not in some way unrepresentative of the alcoholic sample, we directly compare the values in the alcoholics with the present sample of controls, carefully matched to the alcoholics by age and gender. Differences between the means of the z-scores for the alcoholic patients and those of their age- and sex-matched controls were significance tested with Student's t tests. Degree of correlation between measures was estimated with the Pearson Product-Moment coefficient.

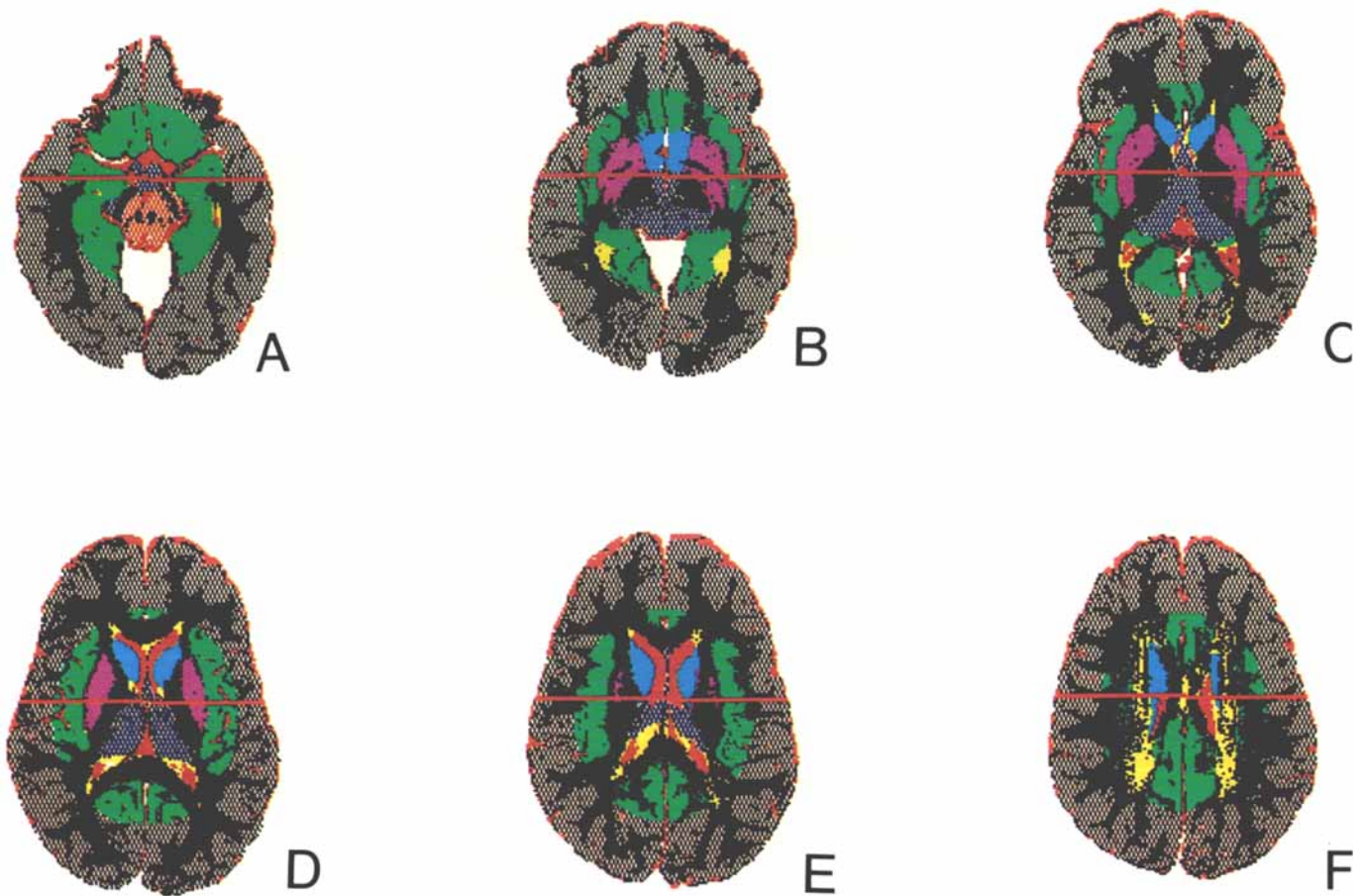


Fig. 3. Representative, fully-processed images. Pixels are classified and zones have been manually designated. The grey matter pixels have been color-coded to display the zone designations: peripheral cortex = grey, mesial cortex = green, caudate = blue, lenticular nucleus = magenta, diencephalon = purple. CSF and white matter pixels in all zones are displayed here in red and black, respectively; however, these pixels are coded separately by zone so that regional measures may be computed. The yellow pixels within the subcortical zone are white matter having the signal characteristics of grey matter. A-C, Sections completely classified as inferior to dividing plane. D-F, Sections completely classified as superior to dividing plane. For both inferior and superior zones, the red line shown within the sections indicates the position of the coronal dividing plane. The ellipsoid volume defining the mesial cortex has cardinal dimensions proportional to those of the supratentorial cranium and occupies 30% of its volume.

RESULTS

The group comparisons on the CSF measures are summarized in Table 3. The increase in CSF on the cortical surface in the alcoholic patients is highly significant ($p < 0.001$). The group difference in ventricular size is also significant but less dramatic ($p < 0.05$). The results for grey matter measures and the index of white matter abnormality are provided in Table 4. The overall volumes of both cortical ($p < 0.02$) and subcortical ($p < 0.01$) grey matter are significantly reduced in the alcoholic patients. The caudate and diencephalic measures show significant volume reduction in the alcoholics ($p < 0.01$ and 0.05 , respectively), and the reduction in the lenticular nucleus approaches significance ($p < 0.10$). The regional cortical measures suggest that significant volume reductions are present in mesial temporal structures (mesial IP), dorso-lateral frontal cortex (peripheral SA), and parieto-occipital cortex (peripheral SP).

For purposes of comparison, the raw summed voxels for the measures, and these sums expressed as percents, either of total supratentorial cranial volume, or regional

cranial volume (for the cortical measures) are given in Table 5 for each group.

To examine the relationship between the CSF increases and the statistically significant grey matter decreases, correlations of these measures were estimated separately for the two groups. The results for the controls are given in Table 6. Since all measures have been corrected for normal aging effects (based on data from 55 normal subjects aged 30 to 80 years),²⁷ any association due to normal aging has been removed. Thus, as expected, there is little evidence of any association between the CSF and grey matter measures for the control subjects. None of the 16 correlations is statistically significant. However, for the alcoholic subjects (Table 7) highly significant correlations are present between the cortical CSF measure and the two superior cortical grey matter measures (Peripheral SA and Peripheral SP). More modest associations are observed between cortical CSF and the subcortical grey matter volumes. In contrast, ventricular CSF is associated with all subcortical grey matter volumes, as well as with the parieto-occipital cortical volume (Peripheral SP).

Table 2. Summary of Cortical Structures within Each Cerebral Region

Peripheral cortex	
Inferior anterior	
Frontal cortex including most of the orbitofrontal cortex and the inferior mesial frontal cortex (excluding most of the cingulate).	
The cortex of the temporal pole (excluding the uncus).	
Inferior posterior	
Most of the lateral surface of the temporal lobe (excluding the temporal pole).	
The inferior occipital lobe.	
Superior anterior	
Frontal cortex including most of the dorsolateral frontal cortex and the superior mesial frontal cortex (excluding most of the cingulate).	
The frontal operculum.	
Superior posterior	
Most of the parietal lobe.	
The superior occipital lobe.	
Mesial cortex	
Inferior anterior	
The mesial parts of the orbitofrontal cortex.	
Most of the inferior cingulate.	
The anterior insula below the frontal operculum.	
The uncus and part of the amygdala.	
Inferior posterior	
Part of the amygdala.	
The hippocampal formation and parahippocampal gyrus.	
The posterior insula below the parietal operculum.	
Superior anterior	
Anterior insula at the level of the frontal operculum.	
Anterior cingulate above the genu of the corpus callosum.	
Superior posterior	
Posterior insula at the level of the parietal operculum.	
Posterior cingulate above the splenium of the corpus callosum.	

Table 3. Comparisons of Alcoholic Patients and Controls on CSF Measures

	Mean age-adjusted z-scores (SD)		t	p
	Controls	Alcoholics		
Ventricles	0.1 (1.3)	1.0 (1.7)	2.38	0.020
Cortical sulci	-0.3 (1.0)	1.7 (1.7)	6.05	0.000

Table 4. Comparisons of Alcoholic Patients and Controls on Cerebral Structure Volumes and White Matter Index

	Mean age-adjusted z-scores (SD)		t	p
	Controls	Alcoholics		
Overall subcortical grey	0.1 (1.0)	-0.7 (1.1)	2.91	0.005
Caudate	0.1 (0.9)	-0.6 (0.8)	3.45	0.001
Lenticular	0.1 (1.1)	-0.4 (1.1)	1.77	0.082
Diencephalic	-0.1 (1.2)	-0.9 (1.5)	2.15	0.036
Anterior	-0.2 (1.0)	-0.5 (0.7)	1.63	0.108
Posterior	-0.1 (1.2)	-0.7 (1.4)	1.73	0.088
Overall cortical grey	0.0 (1.0)	-0.6 (0.9)	2.51	0.015
Peripheral cortex				
Inferior anterior	0.1 (1.0)	-0.3 (0.9)	1.45	0.151
Inferior posterior	-0.2 (1.1)	-0.6 (0.9)	1.61	0.112
Superior anterior	0.2 (1.0)	-0.4 (0.9)	2.61	0.011
Superior posterior	0.1 (1.0)	-0.7 (1.0)	2.95	0.004
Mesial cortex				
Inferior anterior	-0.1 (1.0)	-0.5 (0.9)	1.83	0.073
Inferior posterior	-0.2 (0.9)	-0.7 (0.6)	2.36	0.022
Superior anterior	0.0 (0.9)	0.1 (0.9)	0.45	0.652
Superior posterior	0.0 (0.9)	0.1 (0.9)	0.34	0.736
White matter index	0.1 (0.5)	0.5 (0.8)	2.50	0.015

To assess the degree of relationship between the 28 alcoholics' cognitive deficits and MRI abnormalities, Pearson correlation coefficients were computed. Table 8 shows the results for the cognitive measures and the cortical (sulcal) and subcortical (ventricular) fluid volumes. For

the ventricular fluid volumes, six (46%) of the 13 correlations attained statistical significance. Trails A and B, Digit Symbol, the Stroop Test, and the acquisition scores on the RAVLT showed the closest relationships with this fluid index. For the sulcal fluid volumes, three (23%) (Trails A and B, the Stroop Test) of the 13 correlations proved significant. All significant correlations were in the predicted direction (i.e., greater fluid volumes with poorer cognitive performances).

Correlations between nine measures of grey matter volume (i.e., those attaining statistical significance in Table 4 plus anterior and posterior diencephalon measures) and the 13 cognitive indices (total of 117 correlations) yielded only five (4.3%) significant relationships. Of the five, only one was in the expected direction (i.e., lower volume associated with poorer test performance); the other four significant correlations were in the opposite direction (i.e., lower volumes associated with superior test performances). Thus, there was no evidence of any overall tendency for the grey matter volume measures to be associated with neuropsychological test performance. Correlations between the index of white matter abnormality and the 13 test scores failed to yield a single significant relationship.

Similar correlational analyses were conducted for the 15 nonalcoholic control subjects. Since these subjects were carefully screened, and age variation was removed from the brain measures, no correlation between the normal test performances and (normal) brain volumes were expected. The results were consistent with this prediction. For the ventricular and sulcal fluid measures, only two (8%) of 26 correlations were significant ($p \leq 0.05$). While six (5.1%) of the 117 correlations between cortical and subcortical grey matter volumes and test scores were significant, only one of the six was in the predicted direction. Five (38%) of the 13 correlations between white matter abnormalities and test scores proved to be significant, with four of the five in the predicted direction.

DISCUSSION

The results of the present study confirm that the often-reported CSF increases in chronic alcoholics are accompanied by volume reductions in specific cerebral grey matter structures. In an earlier study of amnesic alcoholics using the same methods,³³ volume reductions of frontoparietal cortex and diencephalic structures were observed. In the present larger, and somewhat younger, sample, further reductions could be detected in the caudate nucleus and mesial temporal lobe structures. The reduced volume of the mesial temporal grey matter is consistent with both animal¹⁷ and human¹⁶ neuropathological reports of cell loss in limbic structures. Also, the observed reductions in superior frontal and parietal regions are consistent with recent reports of reduced number and size of superior frontal neurons in the cortices of alcoholics' brains.²⁹

Volume reductions in subcortical structures have not

Table 5. Means of Volumes (Sums of Designated Voxels) and Percents for Brain Structural Measures

	Controls		Alcoholics	
	Volume (SD)	Percent (SD)	Volume (SD)	Percent (SD)
CSF measures				
Ventricles	3704 (1456)	1.8 (0.7)	4743 (2099)	2.3 (0.9)
Cortical sulci	17396 (5202)	8.6 (2.5)	27779 (8909)	13.7 (4.4)
Overall subcortical grey	5903 (792)	2.9 (0.4)	5440 (882)	2.7 (0.4)
Caudate	1830 (233)	0.91 (0.12)	1667 (244)	0.82 (0.10)
Lenticular	1967 (376)	0.98 (0.17)	1834 (359)	0.90 (0.17)
Diencephalic	2107 (354)	1.05 (0.16)	1938 (426)	0.95 (0.20)
Anterior	346 (141)	0.17 (0.07)	293 (100)	0.14 (0.05)
Posterior	1761 (304)	0.88 (0.15)	1645 (379)	0.81 (0.18)
Overall cortical grey	86425 (10658)	43.10 (4.59)	82095 (10886)	40.27 (4.28)
Peripheral cortex				
Inferior anterior	10023 (1805)	52.58 (5.39)	9989 (1958)	50.42 (5.10)
Inferior posterior	16484 (3362)	49.66 (7.84)	16314 (3683)	46.48 (6.93)
Superior anterior	17524 (2974)	47.87 (6.57)	15813 (2631)	43.70 (5.81)
Superior posterior	24724 (3654)	47.10 (6.24)	22508 (4430)	42.45 (6.43)
Mesial cortex				
Inferior anterior	4584 (713)	41.78 (5.44)	4561 (628)	39.31 (4.24)
Inferior posterior	5179 (761)	32.72 (4.19)	5012 (696)	30.29 (2.98)
Superior anterior	3037 (502)	23.63 (3.28)	3068 (552)	23.95 (3.55)
Superior posterior	4870 (729)	25.22 (2.96)	4829 (716)	25.34 (2.78)
White matter index	3468 (1297)	1.73 (0.58)	4095 (1688)	1.99 (0.75)

Table 6. Correlations between Nonalcoholic Controls' (N = 36) CSF and Grey Matter Measures

	Cortical CSF		Ventricular CSF	
	r	p	r	p
Overall subcortical grey	-0.055	0.752	-0.234	0.169
Caudate nucleus	-0.055	0.751	-0.282	0.095
Diencephalic grey	-0.059	0.734	-0.158	0.357
Lenticular nucleus	0.010	0.955	-0.152	0.375
Overall cortical grey	0.097	0.572	-0.047	0.787
Mesial IP grey (Mesial temporal)	-0.178	0.300	-0.115	0.504
Peripheral SA grey (Dorsolateral frontal)	-0.010	0.952	-0.120	0.485
Peripheral SP grey (Parieto-occipital)	0.107	0.533	0.026	0.882

Table 7. Correlations between Alcoholics' (N = 28) CSF Measures and Grey Matter Measures

	Cortical CSF		Ventricular CSF	
	r	p	r	p
Overall subcortical grey	-0.478	0.010	-0.599	0.001
Caudate nucleus	-0.334	0.083	-0.420	0.026
Diencephalic grey	-0.382	0.045	-0.508	0.006
Lenticular nucleus	-0.481	0.010	-0.577	0.001
Overall cortical grey	-0.658	0.000	-0.566	0.002
Mesial IP grey (Mesial temporal)	-0.155	0.430	-0.288	0.138
Peripheral SA grey (Dorsolateral frontal)	-0.611	0.001	-0.348	0.070
Peripheral SP grey (Parieto-occipital)	-0.678	0.000	-0.504	0.006

been reported previously in neuroradiological studies of chronic alcoholics, although some studies have found reduced CT scan density measures in the thalamus and basal ganglia.^{5,47,48} Harper's⁴⁹ neuropathological report did note shrinkage of the mammillary bodies, frequent periventricular hemorrhages, some necrosis in brainstem structures, and the general pathological signs of Wernicke's encephalopathy in apparently non-amnesic alcoholics. Bowden³⁰ has recently reviewed a number of other

Table 8. Correlations between Alcoholics' (N = 28) Ventricular and Sulcal Fluid Volumes and Neuropsychological Performance

	Cortical CSF		Ventricular CSF	
	r	p	r	p
Vocabulary	-0.239	0.110	-0.001	0.499
Trails A	0.315	0.051	0.325	0.046
Trails B	0.321	0.048	0.463	0.007
Digit symbol	-0.191	0.166	-0.344	0.037
Visual search	0.242	0.107	0.224	0.126
Category Test	-0.159	0.214	-0.025	0.451
Stroop Test	-0.510	0.003	-0.383	0.024
Story Recall (trial 1)	0.249	0.100	0.216	0.135
Story Recall (trials-to-criterion)	-0.030	0.439	-0.144	0.232
Story Recall (delayed recall)	-0.026	0.448	0.029	0.442
RAVLT (trial 1)	-0.253	0.097	-0.430	0.011
RAVLT (trials 1-5)	-0.240	0.109	-0.386	0.021
RAVLT (delayed recall)	-0.139	0.240	-0.154	0.217

pathological studies further demonstrating the existence of significant subcortical abnormalities in chronic alcoholics. Thus, although it is often difficult to delineate the neuropathological basis of subtle neuroradiological changes, the present findings are at least consistent with microscopic neuropathological reports of widespread subcortical grey matter losses.

With regard to the etiology of these cortical and subcortical volume changes, two possibilities seem worth considering. One, the losses are directly related to the neurotoxic effects of ethanol, an interpretation supported by animal studies.¹⁷ Two, the decrements in cortical and subcortical volumes may be the consequence of the mild, but numerous, bouts of malnutrition which plague chronic alcoholics. Bowden³⁰ has concluded from a review of the neuropathological literature that such a nutritionally-based Wernicke's encephalopathy⁵⁰ may be present in a large percentage of alcoholics but that the severe neurologic (e.g., ophthalmoplegia, peripheral neuropathy) and cog-

nitive (e.g., anterograde and retrograde amnesia) symptoms associated with this pathology may not be evident until some threshold of cerebral damage has been exceeded. Certainly the finding that the non-amnesic alcoholics in this study have a pattern of subcortical and cortical changes not too dissimilar to that noted in alcoholics with Korsakoff's Syndrome³³ is consistent with Bowden's proposal. However, since alcoholic Korsakoff patients have significantly more volume loss in the anterior diencephalon (hypothalamic grey, septum) and orbital frontal regions,³³ the possibility that some acute event, resulting in damage to specific cortical-subcortical structures, may be responsible for the neurological and neuropsychological differences between these two groups of alcoholics cannot be dismissed.⁵¹

The numerous moderate-to-high correlations between increased CSF and decreased grey matter volumes suggest that these measures do reflect in part significant neuropathological changes within the brains of alcoholics. They also lend support to the notion that, within alcoholics, loss of parenchymal constituents from brainstem nuclei contribute to ventricular enlargement, and losses from cortex contribute to sulcal widening. The lack of correlation between the grey matter volume in the mesial IP region (mesial temporal structures) and cortical CSF increments may simply be due to a restriction of the range of mesial IP volume values. In fact, the variance for the mesial IP measure in the alcoholics is significantly reduced relative to that in the controls (Bartlett test for homogeneity of group variances, Chi-square = 4.8, $p < 0.03$), and only four of the 28 alcoholics have z-scores greater than zero. Also, atrophy of these structures is likely to contribute to ventricular as well as cortical CSF spaces because of their proximity to the temporal horns of the ventricular system.

The analyses aimed at assessing the relationships between MR-derived indices and neuropsychological performance in alcoholics yielded mixed results. The finding that CSF indices correlate with some neuropsychological measures indicates that volume loss, especially in the periventricular areas, contributes significantly to cognitive impairment in this population. However, grey matter volumes of individual structures showed little association with test scores. Several factors may be related to this result. First, it is probably the case that much of the variability present in the CSF volumes of the alcoholics is due to the amount of tissue loss in surrounding structures, whereas relatively little of this variability is due to pre-existing individual differences. However, for any given grey matter structure, most of the variability in size is probably due to normal variation, and little of the variability is indicative of the relatively subtle volume loss from that particular structure. In addition, since most neuropsychological tests used in the present study tap the function of multiple brain systems, high correlations between the test scores and damage to any single structure should

perhaps not be expected. Finally, using MRI and the present methods, the accuracy and reliability of CSF indices are somewhat higher than for measurements of grey matter volumes.

It is of some interest that although the noted reductions in alcoholics' subcortical grey matter are commensurate with the degree of their ventricular enlargement, their cortical grey matter losses are less striking than their CSF increases. This finding suggests that other factors serve to increase cortical CSF in alcoholic patients. As Harper et al.¹² have suggested, white matter degeneration probably also contributes to the volume loss reflected in increased CSF. Temporary overhydration may also affect the volume of the CSF spaces.²³⁻²⁶ One important question that arises is whether the reduction in CSF that has been observed in abstaining alcoholics is accompanied by volume increases in grey matter structures,¹⁸⁻²² or whether such reductions are entirely due to other factors associated with detoxification and abstinence. Our ongoing longitudinal studies of the sample of alcoholics examined here may provide an answer to this question.

In summary, the present MR findings suggest that alcoholics detoxified for 4 to 5 weeks exhibit a number of brain changes. Besides increments in both sulcal and ventricular CSF, alcoholics may show a significant reduction in the volume of a number of subcortical grey matter structures and cortical regions. Consistent with recent neuropathological reports, these changes involve reductions in the volume of the caudate nuclei, diencephalon, superior frontal and parietal cortex, and mesial temporal lobe structures. While CSF volumes and some neuropsychological performances were correlated, there was little evidence of significant relationships between cognition and grey matter volumes. It is possible that a number of artifacts and confounding factors that plague both behavioral and MR grey matter measures may have contributed to this lack of brain-behavior correlations.

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APPENDIX

Formulae For Calculation of Age-Adjusted Scores

Fluid Measures:

adjusted ventricular fluid proportion =
 $(\text{ventricular fluid proportion} - 0.018453885 +$
 $(.000175934 \times \text{aged}))/0.0048)$

adjusted cortical fluid proportion =
 $(\text{cortical fluid proportion} - 0.096338739 +$
 $(.000938685 \times \text{aged}))/0.024)$ where aged = age - 52
 (mean of control sample) and proportions are sums
 of voxels/supratentorial voxels

Grey Matter Measures:

adjusted subcortical grey proportion =
 $(\text{subcortical grey proportion} - (0.033940 - 0.000100$
 $\times \text{age}))/0.003239)$

adjusted lenticular proportion =
 $(\text{lenticular proportion} - (0.010899 - 0.000025 \times$
 $\text{age}))/0.00150)$

adjusted diencephalic proportion =
 $(\text{diencephalic proportion} - (0.011012 - 0.000007 \times$
 $\text{age}))/0.00132)$

adjusted caudate proportion =
 $(\text{caudate proportion} - (0.011025 - 0.000042 \times \text{age}))/$
 $0.00121)$

adjusted anterior diencephalic proportion =
 $(\text{anterior diencephalic proportion} - (0.002589 -$
 $0.000016 \times \text{age}))/0.00068)$

adjusted posterior diencephalic proportion =
 $(\text{posterior diencephalic proportion} - (0.008423 +$
 $0.0000099 \times \text{age}))/0.00127)$

adjusted cortical grey proportion =
 $(\text{cortical grey proportion} - (0.497016 - 0.001391 \times$
 $\text{age}))/0.04405)$ where proportions are sums of voxels/
 supratentorial voxels

adjusted ipm cortical grey proportion =
 $(\text{ipm cortical grey proportion} - (0.410926 - 0.001537$
 $\times \text{age}))/0.04919)$

adjusted spl cortical grey proportion =
 $(\text{spl cortical grey proportion} - (0.542298 - 0.001552$
 $\times \text{age}))/0.05890)$

adjusted ial cortical grey proportion =
 $(\text{ial cortical grey proportion} - (0.597499 - 0.001574$
 $\times \text{age}))/0.05494)$

adjusted ipl cortical grey proportion =
 $(\text{ipl cortical grey proportion} - (0.595156 - 0.001821$
 $\times \text{age}))/0.06978)$

adjusted sal cortical grey proportion =
 $(\text{sal cortical grey proportion} - (0.546727 - 0.001667$
 $\times \text{age}))/0.06177)$

adjusted iam cortical grey proportion =
 $(\text{iam cortical grey proportion} - (0.479964 - 0.001187$
 $\times \text{age}))/0.05163)$

adjusted sam cortical grey proportion =
 $(\text{sam cortical grey proportion} - (0.253183 -$
 $0.000346 \times \text{age}))/0.03644)$

adjusted spm cortical grey proportion =
 $(\text{spm cortical grey proportion} - (0.281200 -$
 $0.000628 \times \text{age}))/0.02936)$

where i = inferior s = superior

a = anterior p = posterior

l = lateral m = mesial

and proportions are sums of voxels/regional cra-
 nial voxels

White Matter Index:

adjusted subcortical abnormal white proportion =
 $(\text{subcortical abnormal white proportion} - ((0.050352$
 $- 0.001723 \times \text{age}) + (0.000020 \times \text{age} \times \text{age}))/$
 $0.01004)$

where proportion is sum of voxels/supratentorial
 voxels