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Alzheimer Disease and Subcortical Ischemic Vascular Dementia: Evaluation by Combining MR Imaging Segmentation and H-1 MR Spectroscopic Imaging¹

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Abstract

Purpose—To determine the association between H-1 magnetic resonance (MR) spectroscopic imaging and MR imaging differences in subjects with Alzheimer disease (AD) or subcortical ischemic vascular dementia (SIVD) versus control subjects and if both studies combined enable discrimination of AD from control subjects better than either study alone.

Materials and Methods—Measures were obtained in nine AD, eight SIVD, and 11 control subjects with MR imaging segmentation software.

Results—Statistically significantly lower *N*-acetylaspartate/choline-containing metabolites (Cho) and higher Cho/creatine-containing metabolites in posterior mesial gray matter in AD versus control subjects were independent of MR imaging differences. Combined measures allowed correct classification of AD and control subjects, but none of the MR measures allowed accurate discrimination between AD and SIVD subjects.

Conclusion—Between-group differences in tissue-type contributions to H-1 MR spectroscopic imaging voxels must be accounted for when reporting H-1 MR spectroscopic imaging data in AD, SIVD, and control subjects. Combined studies allowed more accurate discrimination between AD and control subjects than either study alone.

Index terms

Brain, ischemia, 10.781; Brain, metabolism, 10.12145; Dementia, 10.83; Magnetic resonance (MR), spectroscopy, 10.12145

ALZHEIMER disease (AD) and subcortical ischemic vascular dementia (SIVD) are associated with measures of cerebral atrophy such as brain volume loss (1,2), ventricular and sulcal dilatation (1,3-7), and reduced volume of the hippocampus (8-10) and corpus callosum (11,12). The results of magnetic resonance (MR) imaging volumetric studies suggest that volume loss in

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patients with AD is due to the loss of gray matter (2,13) rather than white matter. Also, others report a higher frequency of abnormal signal intensity of white matter (ie, abnormal white matter signal [AWMS]), such as is seen with leukoaraiosis, in patients with AD and SIVD compared with the signal intensity of white matter in control subjects (14–16). In SIVD, it has been hypothesized that loss or damage to subcortical tissues results in a subcortical-cortical disconnection (17). In both AD and SIVD, atrophy may be due to loss of neurons or glial cells, or both.

Hydrogen-1 MR spectroscopic imaging of tissue samples in vitro (18,19) and in vivo (20–24) demonstrates differences in brain metabolites between patients with AD and elderly control subjects. Lower levels of the amino acid, *N*-acetylaspartate (NAA), which is found only in neurons and their processes, were reported in patients with AD (20–24); this finding suggests loss or damage to neurons or axons. Higher levels of choline-containing metabolites (Cho) (23,24) and *myo*-inositol (22) were also observed in patients with AD. We have observed metabolite differences with H-1 MR spectroscopic imaging in patients with SIVD versus elderly control subjects (25). Because the extent of atrophy, and the amount of abnormal white matter, is different in disease groups compared with that in control subjects (1–7,11,12,14–16), differences in H-1 MR spectroscopic imaging metabolites (ie, NAA, Cho, and *myo*-inositol) may be the result of between-group differences in gray matter, white matter, WMSH, or cerebrospinal fluid (CSF).

We studied the relationship between the MR imaging and H-1 MR spectroscopic imaging changes in patients with AD and SIVD and elderly control subjects. Our goals were (a) to replicate previous reports of MR imaging segmentation differences (1–7) in patients with AD and SIVD compared with that of control subjects, (b) to determine if observed differences in H-1 MR spectroscopic imaging metabolites in patients with AD and SIVD were associated with, or independent of, MR imaging changes, and (c) to determine which study, MR imaging or H-1 MR spectroscopic imaging, enables better discrimination between patients with AD and control subjects and if MR imaging and H-1 MR spectroscopic imaging together discriminate better than either study alone.

Materials and Methods

Study Population

Nine patients (four men, five women; age range, 59–82 years; mean, 71 years $\pm$ 6) met the criteria for probable AD as established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. SIVD was diagnosed in eight patients (three men, five women; age range, 51–80 years; mean age, 73 years $\pm$ 9) by using the criteria of Chui et al (26). Patients with cortical strokes were excluded. Eleven elderly control subjects (seven men, four women; age range, 61–80 years; mean age, 69 years $\pm$ 6) were studied. The spectroscopic imaging data from these 28 subjects were used in previous studies (23–25). The mean mini-mental state examination (MMSE) (24) score for eight of the nine AD subjects was 13 ± 8.0 ; for the eight SIVD subjects, 19 ± 7.0 ; and for the 11 control subjects, 30 ± 0.4 . All subjects were screened for (a) major neurologic illnesses, such as cortical stroke, head injury with loss of consciousness, seizure disorder, and Parkinson disease; (b) alcohol or drug abuse; and (c) major psychiatric illness, such as bipolar disorder or psychosis. All subjects or their guardians provided informed consent, and all procedures were approved by the University of California, San Francisco, Committee on Human Research.

MR Imaging

All MR studies were performed on a whole-body, 2-T MR imaging–MR spectroscopic system (Philips Medical Systems, Shelton, Conn) as previously described (24). Nineteen to 23 transverse MR sections of 5.1-mm thickness and 0.5-mm intersection gap (repetition time msec/echo time msec = 3,000/30, 80) were obtained parallel to the canthomeatal line to image the entire brain from cerebellum to vertex. Immediately after MR imaging, a 17-mm-thick, point-resolved spatially localized spectroscopic (PRESS) volume of interest (VOI) was selected for two-dimensional H-1 MR spectroscopic imaging (2,000/272) immediately superior to the lateral ventricles as seen on the midsagittal MR image. Because of the different shape of the ventricles in the subjects, the PRESS VOI included a small fraction of the ventricle in some of the subjects. The PRESS VOI always corresponded in position, thickness, and angulation to three MR imaging sections (24). The anteroposterior and left-to-right dimensions (approximately 100 × 80 mm, respectively) of the PRESS VOI were adjusted on axial MR imaging sections for every subject according to brain size. The position and angulation of a typical VOI are depicted in Figure 1a and 1b. This PRESS VOI is referred to as a “supraventricular” VOI. The H-1 MR spectroscopic imaging parameters (field of view of 180 × 180 mm, number of phase-encoding steps of 16 × 16) resulted in a nominal in-plane resolution of 11 mm, and a nominal MR spectroscopic imaging volume element (voxel) size of approximately 2.2 mL before zero-filling. The total H-1 MR spectroscopic imaging acquisition time was 34 minutes. The complete examination with MR imaging and H-1 MR spectroscopic imaging took less than 2 hours.

MR Spectroscopic Imaging Data Processing

The MR spectroscopic imaging data were analyzed by using custom spectroscopic imaging display software (28), as previously described in detail (24). The MR spectral dimension was zero-filled to 1,024 points. Both spatial dimensions were zero-filled to 32 points. For display purposes only, spectroscopic images were further zero-filled to 64 points in each spatial dimension. A 1-Hz exponential line broadening was applied in the time domain. For both spatial domains, a mild Gaussian multiplication was used that corresponded to a broadening of approximately 1 mm and resulted in a final effective voxel size of less than 3 mL, including the effects of the spatial response function. After Fourier transformation in spectral and spatial dimensions, two-dimensional MR spectroscopic images were created by means of integration over selected regions of the magnitude spectra. For selection of the voxels to be analyzed, the spatially correlated, summed MR image (composed of three transverse T2-weighted MR imaging sections) was used exclusively. Spectra were extracted from nine voxels within the preselected VOI outlined on the summed MR image. The typical location and size of the analyzed voxels are indicated on the transverse summed MR image shown in Figure 1b. We were careful to select only voxels that were at least one nominal voxel size away from the PRESS volume boundaries to avoid chemical shift–dependent variations in signal intensity. Three voxels were selected from the midline of the brain (one from the anterior mesial cortex, one from the posterior mesial cortex, and one from an intermediate region); these voxels were selected to include as much gray matter and as little white matter as possible. Six lateral voxels were selected, two each in the anterior, medial, and posterior regions; these voxels were selected to include as much white matter as possible while avoiding large sulci.

MR Imaging Segmentation

Proton-density–weighted (the 30-msec echo) and T2-weighted (the 80-msec echo) images were used for computer-assisted segmentation analysis. Brain tissue, ventricular CSF, and sulcal CSF volumes were obtained for all subjects. The tissue versus CSF segmentation was performed on sequential sections beginning with the lowest axial section on which the frontal, temporal, and occipital lobes appeared contiguously (the superior aspect of the temporal lobes)

and ending at the last apical section to contain both 50% or more tissue (as opposed to CSF) and clear sulcal and gyrate anatomic features. The resultant volume is referred to as the “superior” brain volume. The brain inferior to this was not segmented owing to technical difficulties in the accurate stripping of the skull in this region. Stripping of the skull was accomplished by using a modification of the algorithm developed by Lim and Pfefferbaum (29). The resultant image, which was used for all remaining analyses, was limited to the boundaries of the intracranial vault. This was followed by estimation and removal of radio-frequency field inhomogeneity by means of digital filtering with a 33×33 averaging kernel that was passed over the brain region separately for the T2- and proton-density- weighted images, generating an image of the low frequency inhomogeneity. Each image was then normalized to its low-frequency image, which thereby removed the low-frequency contribution.

The inhomogeneity-corrected images were then processed by a trained operator (V.D.S.) blind to the identity of the subject. On a section-by-section basis, the operator selected the threshold subtraction images (ie, the difference image between the T2-and proton-density-weighted images) to specify conservative CSF and non-CSF samples. The conservative CSF and non-CSF samples were then used as training sets for a discriminant analysis (30) that used both the proton-density- and the T2-weighted pixel intensities to classify each pixel as either CSF or non-CSF. The operator then separated ventricular from sulcal CSF by delineating the anatomic boundaries of the ventricular system on each section. Ventricular and sulcal CSF volumes aggregated over all analyzed sections were computed as a percentage of total intracranial vault volume from those sections to correct for variation in head size.

A further, more detailed segmentation of the five MR imaging sections immediately superior to the lateral ventricles (corresponding to the spectroscopic PRESS volume) was performed in 24 of the 28 cases (the images of three AD patients and one SIVD patient contained artifact [chiefly movement] and were of insufficient quality for the more sensitive gray matter versus white matter discrimination). This volume is referred to as the “supraventricular” brain volume and yielded measures of gray matter, white matter, sulcal CSF, ventricular CSF, and AWMS that included regions of white matter with high signal intensity and regions of white matter pallor.

The procedure for gray matter versus white matter discrimination was accomplished in a manner similar to the CSF versus non-CSF discrimination in all respects except that the initial section-by-section thresholding specified conservative white matter and gray matter samples on the addition image (ie, the sum of the proton-density- and T2-weighted images). Pixels that were classified by the discriminant analysis as gray matter but which must be white matter according to anatomic location were changed manually to the classification of AWMS. The white matter and gray matter volumes aggregated over the analyzed sections were computed as a percentage of total volume of the intracranial vault on those sections. Interoperator reliability with this segmentation method was assessed on a previous sample of 25 alcoholic patients and control subjects. The between-operator correlations for percentage ventricular CSF, percentage sulcal CSF, percentage white matter, percentage AWMS, and percentage grey matter were .99, .99, .82, .87, and .66, respectively. Results of segmentation with use of a single MR imaging section superior to the lateral ventricles in a representative subject are displayed in Figure 1c.

MR Imaging Segmentation of MR Spectroscopic Imaging Voxels

MR imaging and MR spectroscopic coregistration was achieved through the following steps:

1. A spatial response function was computed that, when applied to the segmented MR imaging data, produced a data set with the same spatial resolution as that of the H-1 MR spectroscopic imaging data.
2. The location of the PRESS volume on the segmented MR data set was determined, and the PRESS location was computed separately for each metabolite to account for metabolite-specific chemical shift offset. The locations of the spatially shifted PRESS volumes are shown in Figure 1a and 1b. The PRESS volume for NAA was shifted 3.0 mm anteriorly, superiorly, and to the left relative to the center of the middle MR imaging section. The creatine-containing metabolite (Cr) volume was shifted 3.7 mm posteriorly, inferiorly, and to the right relative to the center of the middle MR image section. The Cho volume was shifted 5.0 mm posteriorly, inferiorly, and to the right relative to the center of the middle MR image section. This caused an 8-mm shift between the NAA-and Cho-defined PRESS volumes in each direction. Because of the chemical shift– dependent profiles of the radio-frequency pulses used for PRESS volume selection, the MR signal was estimated to be at full strength for all metabolites in the inner 68% (by area) of the PRESS volume and at zero outside the PRESS volume. Between the inner area and the PRESS boundary, signal was estimated to decrease linearly. A matrix representing the phase-encoded signal attenuated by the PRESS volume selection was then computed for each metabolite for application to the MR data.
3. Composite, or “columnar,” MR images for each tissue type were generated, representing the percentage of that tissue type contained in the column of MR data corresponding to the metabolite-defined PRESS volume. Intensity on the image represented the fraction of gray matter, white matter, CSF, or AWMS present at each pixel location in the H-1 MR spectroscopic imaging field of view and took into account a linear drop-off at the boundaries of the PRESS in the z (out-of-plane) axis. MR sections located in the center of the PRESS volume, therefore, contributed more signal than did the sections at the edges. A columnar image for gray matter, which corresponds to the PRESS volume for Cho, is displayed in Figure 1d.
4. The spatial response function was adjusted for the PRESS volume and centered on each selected voxel. This spatial response function was specific to both metabolite and voxel. The adjusted spatial response function, multiplied on an element-by-element basis with the columnar data, produced a value for spectroscopic imaging signal contributed by each tissue type, for each voxel and each metabolite.

Statistical Analyses

A priori hypotheses were formulated to test previously reported MR imaging segmentation differences in AD patients compared with control subjects. These hypotheses were variously tested by linear regression, analysis of variance (ANOVA), analysis of covariance (ANCOVA), or logistic regression, as appropriate, by using the SPLUS environment for data analysis (Statistical Sciences, Seattle, Wash). Because of the small sample size, some of the hypotheses, including most hypotheses related to SIVD, were prespecified to be exploratory in nature, since it was anticipated there would be insufficient power to test all hypotheses while correcting for multiple comparisons. MR imaging segmentation was performed on a subset of previously reported subjects who underwent H-1 MR spectroscopic imaging (24,23). To test whether the H-1 MR spectroscopic imaging metabolite differences were statistically significant between groups in this sub-sample, repeated-measures multivariate ANOVA was used to test the hypotheses of lower NAA/Cho, lower NAA/Cr, and higher Cho/Cr between AD patients and control subjects across all nine voxels (with measures repeated across voxels). Similarly, repeated-measures ANOVA was used to test the hypothesis that NAA/Cr was lower in SIVD patients than in control subjects across all nine voxels, and to test whether NAA/Cr was lower

in frontal white matter in SIVD patients than in control subjects. Finally, multivariate ANOVA was used to test whether NAA/Cho was lower and Cho/Cr higher in AD patients than in control subjects in posterior mesial gray matter. We then tested the hypothesis that these differences would still be statistically significant after adjusting for between-group differences in tissue type.

The same analyses described in the preceding paragraph were repeated, with the addition of covariates for percentage supraventricular gray matter, percentage supraventricular white matter, percentage supraventricular sulcal CSF and supraventricular ventricular CSF, and percentage AWMS. These analyses were performed by using the BMDP Program 5V (BMDP, Los Angeles, Calif).

We used linear discriminant analysis (31) to assess if each of our most sensitive MR measures (percentage ventricular CSF or posterior mesial gray matter NAA/Cho) enabled discrimination between disease groups and to determine if MR imaging and MR spectroscopic imaging measures together enabled better discrimination than either MR imaging or MR spectroscopic imaging measure alone. Analyses were performed by using the BMDP Program 7M. They were performed separately for each measure and for each pair of disease groups (AD patients vs control subjects, AD patients vs SIVD patients, SIVD patients vs control subjects). When only one measure is used in each analysis, as was done in this study, linear discriminant analysis can be performed very simply with the following steps: (a) Compute u and v , the respective sample means of the measure in each of the two disease groups, and (b) assign each individual to a disease group according to whether the individual's observed measure falls above or below $(u + v)/2$. Because the usual classification probabilities computed with linear discriminant analysis tend to be higher for the data set on which they were computed than for future data sets, jackknifed classification probabilities (automatically computed by the BMDP Program 7M) were used to assess performance. Jack-knifed classifications were computed as follows: We took each individual one at a time, omitted an individual's data, applied steps *a* and *b* to calculate $(u + v)/2$ for the remaining data, then classified the omitted individual according to whether its observation was above or below $(u + v)/2$.

Results

MR Imaging Segmentation

The initial segmentation analysis discriminated between brain tissue and sulcal and ventricular CSF in the superior brain. The mean values (expressed as a percentage of intracranial volume) for each group are displayed in Table 1. By using ANCOVA, no significant covariant effect was observed for age. By using ANOVA, percentage ventricular CSF and percentage sulcal CSF were significantly higher in AD patients than in control subjects, whereas percentage brain tissue was significantly lower. Similar differences in ventricular and sulcal CSF and brain tissue were observed in SIVD patients compared with control subjects. No statistically significant differences were observed between the AD and SIVD groups. A significant negative correlation between MMSE score and percentage CSF (sulcal plus ventricular) was observed in the SIVD group ($P = .03$) but not in the AD group ($P = .4$) by using linear regression.

Segmentation of the five MR imaging sections superior to the lateral ventricles yielded five measures: supraventricular sulcal CSF, supraventricular ventricular CSF, supraventricular gray matter, supraventricular white matter, and AWMS. The mean values (expressed as a percentage of intracranial volume for those five MR imaging sections) for each group are shown in Table 2. Percentage supraventricular gray matter was significantly lower in AD patients vs control subjects ($P = .001$), whereas percentage supraventricular white matter was unchanged between the groups. Similar differences were observed between SIVD patients and control subjects. No tissue-type differences were observed between AD and SIVD patients. These results suggest

that volume loss in the supraventricular brain in AD and SIVD patients was due to a loss of gray matter. Neither percentage supraventricular gray matter nor percentage supraventricular white matter correlated with MMSE score in either patient group. Percentage AWMS in the supraventricular volume was significantly greater in SIVD patients than in control subjects ($P < .05$). Supraventricular AWMS was predicted to be greater in SIVD patients than in AD patients and greater in AD patients than in control subjects. When tested by using ANOVA with linear contrast, this trend was statistically significant ($P = .014$). Differences in supraventricular ventricular CSF (30%) and supraventricular sulcal CSF (100%) between AD patients and control subjects were of a magnitude similar to that of differences observed over the entire “superior” brain; however, these differences were not statistically significant because of greater variation.

Analysis of H-1 MR Spectroscopic Imaging Data

Lower NAA/Cho ($P = .012$) and higher Cho/Cr ($P = .005$) were observed over all nine voxels in AD patients than in control subjects. Regional metabolite differences were also found. Lower NAA/Cho ($P = .002$) and higher Cho/Cr ($P = .002$) were observed in the mesial posterior gray matter in AD patients than in control subjects. Lower NAA/Cr was found in the frontal white matter of SIVD patients than in control subjects ($P = .008$). The H-1 MR spectroscopic imaging data are presented in Table 3.

Effects of Tissue Types on H-1 MR Spectroscopic Imaging Data

MR imaging segmentation analysis was applied to the H-1 MR spectroscopic imaging voxels used in the preceding analysis. Because of chemical shift offsets of the PRESS volume, calculation of the point spread function for each voxel resulted in a Cho-defined voxel, a Cr-defined voxel, and an NAA-defined voxel. Measures of percentage supraventricular gray matter, percentage supraventricular white matter, percentage supraventricular sulcal CSF, percentage supraventricular ventricular CSF, and percentage AWMS were obtained for all three metabolite-defined voxels in each region of interest (all nine voxels, frontal white matter, and posterior mesial gray matter). These data are displayed in Table 4.

Comparison of percentage tissue type between metabolite-defined voxels across all subjects by using repeated-measures ANOVA (data not shown) indicated significant differences in the following regions: (a) across all nine voxels: percentage gray matter ($P < .001$), percentage white matter ($P < .001$), percentage CSF ($P < .001$); (b) in frontal white matter: percentage gray matter ($P < .001$), percentage white matter ($P = .001$), percentage AWMS ($P < .001$); (c) in posterior mesial gray matter: percentage gray matter ($P < .001$), percentage white matter ($P < .001$). These results suggest that out-of-plane spatial shifts of the PRESS volumes for chemically shifted metabolites have a statistically significant effect on tissue contributions to H-1 MR spectroscopic imaging metabolite-defined voxels.

Tissue-type differences in a given metabolite-defined voxel between groups were investigated by using repeated-measures ANOVA followed by individual Student *t* tests. Significant differences in percentage gray matter and percentage CSF in NAA-, Cho-, and Cr-defined voxels were observed between AD patients and control subjects and between SIVD patients and control subjects across all nine voxels. In frontal white matter, statistically significant differences in percentage gray matter and percentage CSF were observed between AD patients and control subjects and between SIVD patients and control subjects. When percentage white matter and percentage AWMS were summed; however, no statistically significant differences were seen between the groups. This suggested that the white matter findings were due to a reclassification of white matter as AWMS in the AD and SIVD groups. In posterior mesial gray matter, lower percentage gray matter was seen in both the AD and SIVD groups than in control subjects. These results are shown in Table 4.

Because our H-1 MR spectroscopic imaging data are presented as metabolite ratios, we next calculated ratios of tissue types (analogous to ratios of metabolites) for metabolite-defined voxels in each of the three regions under consideration and compared these between groups. Across all nine voxels, only the ratio of percentage gray matter_{NAA}/percentage gray matter_{Cr} in SIVD patients was significantly different from that of control subjects ($P = .03$). In frontal white matter, again, percentage gray matter_{NAA}/percentage gray matter_{Cr} was significantly different in SIVD patients versus control subjects ($P = .02$). This is consistent with the finding of statistically significant differences in percentage supraventricular gray matter between SIVD patients and control subjects. This result raised the possibility that differences in percentage gray matter in NAA- and Cr-defined voxels in the frontal white matter in SIVD versus control subjects were responsible for the observed between-group difference in NAA/Cr in this region. In posterior mesial gray matter, percentage AWMS_{Cho}/percentage AWMS_{Cr} was significantly different in AD patients compared with that in control subjects ($P = .02$). Consequently, differences in percentage AWMS in Cho- and Cr-defined voxels in posterior mesial gray matter in AD patients versus control subjects could be responsible for the observed between-group difference in Cho/Cr in this region.

To test whether lower NAA/Cho or higher Cho/Cr in the posterior mesial gray matter of AD patients versus control subjects was due to differences in tissue types, we performed an ANCOVA by using the covariates percentage gray matter, percentage white matter, percentage CSF, and percentage AWMS for each metabolite. Lower NAA/Cho in posterior mesial gray matter remained significant at $P = .02$, and Cho/Cr in posterior mesial gray matter remained significant at $P = .05$; these findings suggested that these between-group metabolite differences were independent of tissue-type differences in this region.

To test whether lower NAA/Cr in the frontal white matter of SIVD patients versus control subjects was due to differences in tissue types, we performed a repeated-measures ANCOVA by using the covariates percentage gray matter, percentage white matter, percentage CSF, and percentage AWMS, with separate covariant values entered for each of the two voxels in the frontal white matter. NAA/Cr was not statistically significantly different between groups. This finding suggested that the observed metabolite differences were affected by tissue-type differences in the frontal white matter; however, the small sample size and large number of covariates (twice that of the posterior mesial gray matter analysis) reduced the power of this test to enable detection of between-group differences, possibly resulting in a type II error. When only percentage gray matter (ie, the measure that was significantly different between groups) was used as a covariate, frontal white matter NAA/Cr remained statistically significantly lower suggesting that NAA/Cr differences observed between SIVD patients and control subjects were independent of gray matter differences between groups.

Classification

To determine the power of MR imaging measures, H-1 MR spectroscopic imaging measures, or a combination of the two, to enable correct classification of AD patients and control subjects, we performed a linear discriminant analysis by using percentage ventricular CSF and posterior mesial gray matter NAA/Cho. Ventricular CSF was chosen because many investigators have reported it to be reduced in patients with AD compared with control subjects (1,3–7). Posterior mesial gray matter NAA/Cho was chosen because in our prior analyses it demonstrated the greatest statistically significant difference between groups (23,24). The analysis was performed on 11 control subjects, six AD patients, and seven SIVD patients. The results of this analysis are given in Table 5. Percentage ventricular CSF enabled correct identification of 10 (91%) of 11 control subjects and four (67%) of six AD patients for a combined correct classification percentage of 82% (Fig 2a). Jackknifed analysis reduced this classification to 77%. Posterior mesial gray matter NAA/Cho enabled correct identification of eight (73%) of 11 control

subjects and six (100%) of six AD patients for a combined correct classification percentage of 82% (Fig 2b). Jackknifed analysis resulted in an equivalent classification percentage of 82%. The ratio of percentage ventricular CSF and NAA/Cho enabled correct identification of 11 (100%) of 11 control subjects and six (100%) of six AD patients for a combined correct classification percentage of 100% (Fig 2c). With the jackknifed classification, two control subjects were misidentified for a total of 88% correct classification. When SIVD patients were compared with control subjects, the combined MR imaging and H-1 MR spectroscopic imaging measure enabled correct classification of 100% of the control subjects and 100% of the SIVD patients, whereas the correct classification with use of percentage ventricular CSF was better (94%) for this sample pair than was the H-1 MR spectroscopic imaging measure (72%). Correct classification for SIVD versus AD patients was poor, with posterior mesial gray matter NAA/Cho providing the best correct classification (77%). These results suggest that H-1 MR spectroscopic imaging combined with MR imaging has greater classification power than either study alone. They also suggest that the ventricular dilatation observed in AD and SIVD patients and the metabolite differences observed in the posterior mesial gray matter are independent of each other.

Discussion

By using MR imaging segmentation, we found statistically significant differences in tissue types between AD patients and control subjects and between SIVD patients and control subjects. Application of MR imaging segmentation techniques to H-1 MR spectroscopic imaging data revealed that NAA/Cho and Cho/Cr differences in the posterior mesial gray matter in AD patients compared with that in control subjects were not due to differences in tissue type in the VOIs. A third major finding of this study was that, in AD patients and control subjects, H-1 MR spectroscopic imaging combined with MR imaging had greater classification power than either study alone.

MR Imaging Segmentation

Our results of MR imaging segmentation confirmed previous reports of enlarged ventricles (1,3–7) and loss of gray matter (2,13) in AD patients compared with that in control subjects. Contrary to previous findings (6), ventricular CSF was not increased to a greater degree than sulcal CSF in our AD patients. In SIVD patients, we observed increases in ventricular and sulcal volume similar to those observed in AD patients. Segmentation analysis of the supraventricular volume studied with H-1 MR spectroscopic imaging revealed lower supraventricular gray matter and higher AWMS in SIVD patients compared with that in control subjects. Although the higher proportion of AWMS is consistent with previous reports (14, 16) and pathogenetic hypotheses of SIVD, the finding of lower gray matter in this group, with relative sparing of white matter, is inconsistent with theories that suggest that SIVD is primarily a subcortical disease with relative sparing of cortical gray matter (17). No segmentation measure was different between the AD and SIVD groups.

Effects of Tissue Types on the Analysis of H-1 MR Spectroscopic Imaging Data

Differences in H-1 MR spectroscopic imaging metabolites between AD patients and control subjects were found across all nine voxels in the supraventricular brain (lower NAA/Cho, higher Cho/Cr) and in the posterior mesial gray matter (lower NAA/Cho, higher Cho/Cr). Lower NAA/Cr was found in the frontal white matter of SIVD patients compared with that in control subjects. A comparison of tissue-type contribution to H-1 MR spectroscopic imaging voxels across all subjects showed that statistically significant tissue-type differences were found between metabolite-defined voxels owing to the out-of-plane spatial shifts of the PRESS volumes for chemically shifted metabolites. For example, percentage gray matter was lower in NAA-defined voxels compared with Cho-defined voxels in the posterior mesial gray matter.

This indicated that, when H-1 MR spectroscopic imaging metabolite ratios were calculated, the numerator and denominator reflected different tissue types.

Statistically significant tissue-type differences were also observed between groups for a given metabolite-defined voxel (Table 4). For example, the CSF contribution to the NAA-defined voxels in frontal white matter was lower in AD and SIVD patients than in control subjects. This suggests that, if absolute metabolite measurements (rather than ratios) were used for between-group comparisons, any observed metabolite differences could be due to tissue-type differences between groups.

When tissue-type ratios of metabolite-defined voxels were compared between groups, most between-group differences disappeared. Two statistically significant tissue ratio differences that might explain metabolite ratio differences remained: percentage gray matter_{NAA}/percentage gray matter_{Cr} in frontal white matter in SIVD patients versus control subjects ($P = .02$) and percentage AWMS_{Cho}/percentage AWMS_{Cr} in posterior mesial gray matter in AD patients versus control subjects ($P = .02$).

The above findings suggested that both metabolite ratios and absolute metabolite measurements are affected by between-group tissue-type differences. A covariant analysis of tissue-type differences and metabolite ratios in AD patients and control subjects indicated that lower NAA/Cho and higher Cho/Cr in posterior mesial gray matter were not due to between-group differences in AWMS. A similar analysis in frontal white matter in SIVD patients suggested that lower frontal white matter NAA/Cr may reflect tissue-type differences between SIVD patients and control subjects. However, the larger number of covariates in this analysis, compared with the number of covariates in the posterior mesial gray matter analysis, resulted in very low power; thus, conclusions were difficult to make. When only percentage gray matter was used as a covariate, NAA/Cr differences between SIVD patients and control subjects remained statistically significant.

Implications for Interpretation of MR Spectroscopic Imaging Studies

The results of the combination H-1 MR spectroscopic imaging and MR imaging analysis have several important implications for MR spectroscopic imaging studies. First, the results of many reports indicate differences in the MR spectra of brain, or other tissues, between control subjects and disease groups. The diseases in question frequently are associated with anatomic alternations that are detectable with MR imaging. In most cases, it has not been determined whether the MR spectroscopic imaging findings are closely associated with (or caused by, or dependent on) the anatomic changes detected with MR imaging. Statistical analysis (by multivariate ANCOVA or other techniques) of MR spectroscopic imaging and MR imaging data is necessary to determine the relationship between these measures.

Second, the results of our combination MR spectroscopic imaging and MR imaging analysis demonstrated that the tissue composition (ie, gray matter, white matter, etc) of a region giving rise to NAA signal was significantly different from the composition of the region giving rise to Cho or Cr signal. These differences are due to the out-of-plane spatial extent of the chemical shift offset that occurs whenever section selection is used for spatial localization (eg, image-selected in vivo spectroscopy, stimulated-echo acquisition mode, PRESS). Chemical shift offset is determined in part by gradient strength, with steeper gradients reducing the offset. Therefore, tissue-type differences revealed by tissue segmentation may be an important variable in the interpretation of MR spectroscopic imaging studies. This is especially important because the metabolite composition of gray matter and white matter is different (32,33) and because disease may alter metabolite concentrations in each tissue type.

Finally, these results also have important practical implications for the use of MR imaging and MR spectroscopic imaging together. If the MR spectroscopic imaging results were very closely associated with (and not independent of) the MR imaging findings, then there would be no reason to perform an MR spectroscopic imaging study. Alternatively (eg, the current results in the AD patients), if the MR spectroscopic imaging data are independent of the MR imaging findings, these measures may be used together for greater diagnostic sensitivity and specificity.

Classification

MR imaging segmentation measures of percentage ventricular size and H-1 MR spectroscopic imaging measures of posterior mesial gray matter NAA/Cho allowed discrimination essentially equally well between AD patients and control subjects (77% and 82%, respectively, according to jackknife analyses). A combination of these two measures resulted in 88% correct classification of AD patients and control subjects after applying jackknife analysis. This suggests that H-1 MR spectroscopic imaging combined with MR imaging has a greater ability to facilitate discrimination of AD patients from control subjects than does H-1 MR spectroscopic imaging or MR imaging alone. The latter is also true for discrimination between control subjects and SIVD patients. The power of MR measures to allow discrimination between AD and SIVD patients, however, is poor. It should be noted though that the number of subjects in this analysis was small and that this analysis was not intended as an a priori test of discrimination power of the two measures. Future studies with larger numbers of subjects will test the predictive power of MR imaging and MR spectroscopic imaging measures.

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Abbreviations

AD	Alzheimer disease
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AWMS	abnormal white matter signal
Cho	choline-containing metabolites
Cr	creatine-containing metabolites
CSF	cerebrospinal fluid
MMSE	mini-mental state examination
NAA	<i>N</i> -acetylaspartate
PRESS	point-resolved spatially localized spectroscopy
SIVD	subcortical ischemic vascular dementia
VOI	volume of interest

Figure 1.

(a) Sagittal MR image shows outlines of NAA- (blue), Cr- (yellow), and Cho- (red) defined PRESS volumes. (b) Axial T2-weighted MR image shows NAA- (blue), Cr- (yellow), and Cho- (red) defined PRESS volumes, plus the positions of the nine individual MR spectroscopic imaging voxels extracted for MR spectroscopic imaging data analysis. (c) Segmented axial MR image section from the supraventricular brain, with gray matter in green, white matter in white, AWMS in pink, and CSF in blue. (d) "Columnar" image for the Cho-defined PRESS volume, with the scale showing the weighting of each pixel for contribution from gray matter (%GM).

Figure 2. Scatter plots show (a) percentage ventricular CSF, (b) NAA/Cho ratios, and (c) percentage ventricular CSF/(NAA/Cho) for control subjects and AD and SIVD patients.

Table 1**Whole-Brain Segmentation Analysis**

Volume	Control Subjects (n = 11)	AD Patients (n = 9)	SIVD Patients (n = 8)
Sulcal CSF	14 ± 2	18 ± 4 [*]	17 ± 3 ^{*†}
Ventricular CSF	4 ± 1	7 ± 3 [*]	7 ± 1 ^{†‡}
Brain tissue	83 ± 3	76 ± 5 [‡]	75 ± 3 ^{†‡}

Note.—Values are expressed as a percentage of total “superior” intracranial volume and are presented as the mean ± standard deviation.

^{*} $P < .01$ between patient and control groups with ANOVA.

[†] Exploratory analysis was not corrected for multiple comparisons.

[‡] $P < .001$ between patient and control groups with ANOVA.

Table 2
Supraventricular Brain Segmentation Analysis

Volume	Control Subjects (<i>n</i> = 11)	AD Patients (<i>n</i> = 6)	SIVD Patients (<i>n</i> = 7)
Gray matter	36 ± 3	29 ± 2 [*]	29 ± 3 ^{*†}
White matter	43 ± 3	42 ± 4	42 ± 4
Sulcal CSF	15 ± 4	20 ± 6	18 ± 3
Ventricular CSF	2 ± 2	4 ± 3	4 ± 2
AWMS	4 ± 2	5 ± 3	8 ± 3 ^{†‡}

Note.—Values are expressed as a percentage of supraventricular intracranial volume and are presented as the mean ± standard deviation.

^{*} *P* < .001 between patient and control groups with ANOVA.

[†] Exploratory analysis was not corrected for multiple comparisons.

[‡] *P* < .05 between patient and control groups with ANOVA.

Table 3
H-1 MR Spectroscopic Metabolite Ratios

Volume	Control Subjects (<i>n</i> = 11)	AD Patients (<i>n</i> = 6)	SIVD Patients (<i>n</i> = 7)
All nine voxels			
NAA/Cho	2.4 ± 0.4	1.9 ± 0.3 [*]	2.0 ± 0.3
NAA/Cr	3.0 ± 0.4	2.9 ± 0.3	2.7 ± 0.4
Cho/Cr	1.4 ± 0.1	1.6 ± 0.1 [†]	1.4 ± 0.3
Frontal white matter			
NAA/Cho	1.9 ± 0.3	1.8 ± 0.6	1.7 ± 0.3
NAA/Cr	3.1 ± 0.3	3.2 ± 0.7	2.5 ± 0.5 [†]
Cho/Cr	1.7 ± 0.2	1.9 ± 0.5	1.6 ± 0.6
Posterior gray matter			
NAA/Cho	3.3 ± 1.0	1.8 ± 0.3 [†]	2.4 ± 0.6
NAA/Cr	2.4 ± 0.3	2.1 ± 0.6	2.4 ± 0.7
Cho/Cr	0.8 ± 0.2	1.2 ± 0.3 [†]	1.0 ± 0.3

Note.—Data are presented as the mean ± standard deviation.

^{*} *P* < .05 between patient and control groups with repeated-measures multivariate ANOVA or multivariate ANOVA.

[†] *P* < .01 between patient and control groups with repeated-measures multivariate ANOVA or multivariate ANOVA.

Table 4

Segmentation of H-1 MR Spectroscopic Voxels

Volume	Cho				Cr				NAA			
	Control Subjects	AD Patients	SIVD Patients		Control Subjects	AD Patients	SIVD Patients		Control Subjects	AD Patients	SIVD Patients	
All nine voxels												
Gray matter	33 ± 19	29 ± 16 [*]	28 ± 16 [†]		33 ± 21	28 ± 16 [*]	27 ± 17 [†]		30 ± 23	25 ± 17 [†]	23 ± 19 [†]	
White matter	50 ± 27	47 ± 24	48 ± 23		50 ± 27	47 ± 23	47 ± 22		47 ± 25	44 ± 21	43 ± 20	
CSF	11 ± 16	17 ± 18 [†]	16 ± 17 [†]		11 ± 16	16 ± 18 [†]	15 ± 16 [†]		9 ± 13	16 ± 17 [†]	13 ± 14 [*]	
AWMS	5 ± 10	7 ± 13	8 ± 14		6 ± 11	8 ± 14	10 ± 15		13 ± 16	15 ± 18	21 ± 24	
White matter + AWMS	55 ± 32	54 ± 28	56 ± 29		57 ± 32	55 ± 28	57 ± 29		60 ± 33	59 ± 29	64 ± 30	
Frontal white matter												
Gray matter	24 ± 9	18 ± 6	17 ± 7		22 ± 10	17 ± 6	16 ± 7		15 ± 12	13 ± 8	7 ± 5	
White matter	72 ± 10	68 ± 13	60 ± 15 [§]		73 ± 10	69 ± 12 [#]	58 ± 15 [§]		71 ± 12	62 ± 11 ^{†//}	45 ± 22 [§]	
CSF	1 ± 5	8 ± 11 [†]	8 ± 6 [†]		1 ± 4	7 ± 9 [†]	7 ± 6 [†]		1 ± 3	9 ± 9 [§]	5 ± 7 [†]	
AWMS	3 ± 3	5 ± 5	15 ± 15		5 ± 4	7 ± 6	20 ± 17		13 ± 9	16 ± 15	43 ± 23	
White matter + AWMS	75 ± 10	74 ± 13	74 ± 9		78 ± 11	76 ± 12	77 ± 8		84 ± 13	78 ± 13 ^{//}	88 ± 6	
Posterior gray matter												
Gray matter	54 ± 11	43 ± 11 [†]	42 ± 15 [*]		56 ± 12	44 ± 11 [†]	43 ± 16 [*]		64 ± 12	48 ± 13 [†]	49 ± 17 [†]	
White matter	17 ± 9	23 ± 10	26 ± 16		16 ± 9	23 ± 10	25 ± 16		11 ± 10	20 ± 9	19 ± 14	
CSF	29 ± 14	33 ± 18	32 ± 16		29 ± 14	33 ± 17	32 ± 17		26 ± 11	31 ± 15	34 ± 16	
AWMS	0 ± 0	1 ± 2	0 ± 1		0 ± 1	1 ± 2	0 ± 1		-1 ± 3	0 ± 4	-1 ± 2	
White matter + AWMS	17 ± 9	24 ± 11	26 ± 17		16 ± 9	23 ± 11	25 ± 17		11 ± 12	20 ± 13	18 ± 15	

Note.—Values are expressed as a percentage of the region of interest and are presented as the mean ± standard deviation.

* $P < .10$ between patient and control groups with repeated-measures ANOVA followed by individual Student t tests.

† $P < .05$ between patient and control groups with repeated-measures ANOVA followed by individual Student t tests.

$P < .001$ between patient and control groups with repeated-measures ANOVA followed by individual Student t tests.

§ $P < .01$ between patient and control groups with repeated-measures ANOVA followed by individual Student t tests.

// $P < .01$ between patient and control groups with repeated-measures ANOVA followed by individual Student t tests.

// $P < .10$ between AD and SIVD patient groups with repeated-measures ANOVA followed by individual Student t tests.

$P < .05$ between AD and SIVD patient groups with repeated-measures ANOVA followed by individual Student t tests.

Table 5
Classification Analysis for MR Imaging and MR Spectroscopic Measures

A: Control Subjects versus AD Patients				
Measure	Control Subjects	AD Patients	Studies Combined	Jackknife Analysis
Gray matter NAA/Cho	8 (73)	6 (100)	14 (82)	14 (82)
Percentage ventricular CSF	10 (91)	4 (67)	14 (82)	13 (76)
Percentage ventricular CSF/(NAA/Cho)	11 (100)	6 (100)	17 (100)	15 (88)
B: Control Subjects versus SIVD Patients				
Measure	Control Subjects	SIVD Patients	Studies Combined	Jackknife Analysis
Gray matter NAA/Cho	7 (64)	6 (86)	13 (72)	13 (72)
Percentage ventricular CSF	10 (91)	7 (100)	17 (94)	13 (76)
Percentage ventricular CSF/(NAA/Cho)	11 (100)	7 (100)	18 (100)	18 (100)
C: AD versus SIVD Patients				
Measure	AD Patients	SIVD Patients	Studies Combined	Jackknife Analysis
Gray matter NAA/Cho	5 (83)	5 (71)	10 (77)	10 (77)
Percentage ventricular CSF	3 (50)	3 (43)	6 (46)	3 (23)
Percentage ventricular CSF/(NAA/Cho)	3 (50)	5 (71)	8 (62)	7 (54)

Note.—The analysis was performed in 11 control subjects, six AD patients, and seven SIVD patients. Data are presented as numbers of patients. Numbers in parentheses are percentages.