Axonal Injury and Membrane Alterations in Alzheimer's Disease Suggested by In Vivo Proton Magnetic Resonance Spectroscopic Imaging

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We used spin-echo magnetic resonance imaging and proton magnetic resonance spectroscopic imaging in 8 patients with probable Alzheimer's disease and in 10 age-matched elderly control subjects to assess the effects of Alzheimer's disease on the brain. On magnetic resonance images the patients showed significant ventricular enlargements relative to the control subjects. We measured the distribution and relative signal intensities of N-acetylaspartate (a putative neuronal marker), of choline residues representing lipid metabolites, and of creatine-containing metabolites in a large section of the centrum semiovale containing white and mesial gray matter. Throughout the white matter of the patients with Alzheimer's disease compared to elderly control subjects, N-acetylaspartate was decreased relative to choline (N-acetylaspartate-choline ratio) and creatine-containing metabolites (N-acetylaspartate-creatine ratio) with no changes in the choline-creatine ratio. The N-acetylaspartate-choline ratio was lower and choline-creatine higher in the mesial gray matter of AD patients relative to elderly controls. The posterior section of the centrum semiovale in the patients showed increased choline-creatine and choline-N-acetylaspartate ratios with the N-acetylaspartate-creatine ratio unchanged between the patients and control subjects. These spectroscopic findings give suggestive evidence of diffuse axonal injury and membrane alterations in gray and white matter of the centrum semiovale in patients with Alzheimer's disease.

white matter in vivo. A secondary goal was to determine if potential metabolite alterations in the brains of AD patients are observable in the presence or absence of atrophy estimated from standard spin-echo MRIs.

Materials and Methods

Subjects

All subjects were screened for (a) major medical illnesses, such as hypertension, heart disease, hypothyroidism, and diabetes; (b) major neurological illnesses, such as stroke, head injury with loss of consciousness, seizure disorder, and Parkinson's disease; (c) alcohol or drug abuse; and (d) major psychiatric illness, such as major depression or psychosis. Nineteen elderly subjects participated successfully in the MRSI study. They included 8 AD patients (5 men, 5 women; mean age, 72 ± 8 years; range, 59-82 years) (of 14 AD patients who initially enrolled in the study 5 were unable to complete a combined MRI and \(^1\)H MRSI study and 1 did not meet the selection criteria). All 8 AD patients met the National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association (NINCDS-ADRD A) criteria for probable AD. Two AD patients were receiving thyroid replacement treatment. One AD patient had a history of hypertension but was normotensive without medication. This same patient was taking bupropion for depression. The mean Mini-Mental State Examination (MMSE) score (10) for 6 of the 8 AD patients was 13 ± 11, with a range of 0 to 28. One patient with mild probable AD had a MMSE score of 28; this patient's diagnosis was based on a gradual, well-documented decline in psychosocial functioning. Two patients were too impaired to complete the test. The MMSE yielded a global impairment score. In addition, a neurocognitive status examination (NCSE) screening test was used to assess cognitive functioning in five major ability areas (language, construction, memory, calculation, and reasoning) \[11, 12\]. NCSE scores were obtained from 5 of 8 patients with probable AD, with a mean value of 5 ± 2, that is, while 3 AD patients were unable to complete the NCSE, 5 scored impaired on an average of 5 of the 10 subtests.

Ten healthy elderly subjects (6 men, 4 women; mean age, 70 ± 6 years; range, 60-80 years) served as comparably aged controls. Control subjects were screened as above. One control subject was receiving thyroid replacement therapy; otherwise all elderly control subjects were free of medical, neurological, and psychiatric illnesses. All elderly control subjects scored higher than 28 on the MMSE (mean score, 29 ± 0.7) and in the normal range on all subtests of the NCSE.

Subjects were sedated with 5 to 10 mg of diazepam orally or 1 to 2 mg of lorazepam sublingually for the MR examination when necessary. Lorazepam was the preferred agent because of its rapid onset when given sublingually and its shorter half-life of action. Heart rate and oxygen tension (\(P_O_2\)) were monitored using a pulse oximeter. To control for normal aging effects, the spectroscopic data were also compared to data from 6 young and healthy subjects (4 men, 2 women; mean age, 32 ± 10 years) who were examined as part of a different study (unpublished results, 1993).

Magnetic Resonance

Data Acquisition. All MR studies were performed on a whole-body 2T MRI/MRS system (Philips Medical Systems, Shelton, CT). The procedures for MRI and \(^1\)H MRSI were the same as those previously described \[13\] except for the following modifications: The sections for transverse MRI were angulated along the canthomeatal line. Nineteen to 23 contiguous sections of 5.1-mm thickness and 0.5-mm section gap (TR 3000/TF 30/80 msec) were obtained to cover the entire brain from the cerebellum to the vertex. MRIs were evaluated by a board-certified neuroradiologist (D. N.) who was blinded to each subject's diagnosis. Ventricular atrophy and sulcal atrophy were each rated as absent, mild, moderate, or severe. White matter signal hyperintensities (WMHs) were rated on a 0 to 4 scale, previously published \[14\]. After MRI, a 17-mm-thick volume of interest (VOI), corresponding in location and thickness to three MRI sections, was selected for \(^1\)H MRSI from the angulated transverse images. Figure 1A shows a midline sagittal MRI of a normal volunteer with the angulated transverse MRSI region. The VOI was generally chosen to include the most cranial aspect of the corpus callosum and the two superior cranial MRI sections. The anterior-posterior and left-right dimensions of the MRSI VOI were adjusted for every subject according to brain size (typically about 100 x 80 mm, respectively). The position and angulation of a typical VOI are depicted in Figure 1. The parameters selected here for \(^1\)H MRSI resulted in a nominal in-plane resolution of 11 mm, and a nominal MRSI volume element (voxel) size of approximately 2.2 cm^3^.

Total MRSI acquisition time was 34 minutes. The entire MRI and MRSI examination took less than 2 hours.

Data Processing. The MRSI data and transverse MRIs were analyzed using home-written spectroscopic imaging display software \[15\]. The MRSI spectral dimension was zero-filled to 1,024 points. Both spatial dimensions were zero-filled to 32 points so that 32 spectra were obtained along each of the spatial dimensions across the field of view. For display purposes only, spectroscopic images were further zero-filled to 64 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, corresponding to a broadening of approximately 1 mm and resulting in a final effective voxel size of approximately 2.5 cm^3^.

After Fourier transformation in spectral and spatial dimensions, two-dimensional MRSIs were created by integration over selected regions of the magnitude spectra. For selection of the voxels to be analyzed, the spatially correlated summed MRI (composed of three thin MRI sections) was used exclusively. Spectra were extracted from nine voxels within the preselected VOI outlined on the MRI. The typical location and size of the analyzed voxels are indicated on the transverse summed MRSI shown in Figure 1B. Voxels were selected in the following way: three voxels from the midline area of the brain (one from anterior mesial cortex, one from posterior mesial cortex, and one from an intermediate region), and three lateral voxels from each hemisphere in the frontal, anterior-parietal, and posterior-parietal regions. The three midline voxels were selected so they contained as much gray matter as possible, avoiding white matter tissue. The six lateral voxels were selected so they contained a maximum of white matter tissue (appearing dark on the T2-weighted MRI), avoiding large sulci and any focal WMHS if present in the VOI.

The nine extracted magnitude spectra were then transferred to a workstation equipped with NMRi software (New Methods Research, Syracuse, NY) for automated line-fitting and peak area determination. Following manual setting of the baseline midway through the noise, three gaussian peaks
Fig 1. The sagittal magnetic resonance image (MRI) (TR 450/TE 30) (A) shows typical caudocranial placement and angulation of the volume of interest (VOI) in the suprasylvatic region of the brain used for $^1$H magnetic resonance spectroscopic imaging (MRSI). The summed MRI (TR 3000/TE 80) of three transverse sections through the head (B) corresponds in thickness and caudocranial position to the VOI used for $^1$H MRSI. The large rectangle indicates a typical position of the VOI inside the cerebrum. The nine small squares inside the VOI indicate nominal size (determined from field of view and number of phase encoding steps) and typical positions of the $^1$H volume elements (voxels) from which spectra were analyzed. Three voxels were placed in the mesial cortex, and three each in both hemispheres of the centrum semiovale, containing primarily white matter tissue.

were fitted to the three major resonances in the spectra, originating from choline-containing metabolites (Cho), from the sum of creatine and phosphocreatine (Cr), and from N-acetyl groups, predominantly NAA. The peaks were fitted with gaussian rather than lorentzian lines because they are due to multiple compounds and spectral residuals after line-fitting were smaller with fitting gaussian line shapes. Peak areas were derived from the NMR1 software in arbitrary units; no intensity standard was included in the studies. Since absolute peak areas are affected by possible long-term spectrometer instabilities and atrophy in the analyzed voxel, peak area ratios (NAA/Cho, NAA/Cr, and Cho/Cr) were used for primary data analysis.

Statistical Analysis
The hypothesis of reduced NAA in gray matter was tested by using average data from the three mesial cortex spectra, while metabolites in white matter were analyzed using average data from the six bilateral volumes. The Wilcoxon signed rank test was used to determine differences in metabolite measures. Given that a preliminary analysis of 5 of the AD patients showed an increase of the Cho/Cr ratio in the posterior-parietal brain [16], we analyzed data from this brain region in a post hoc manner using a $t$ test. All values are expressed as a mean ± 1 standard deviation (SD), and $p < 0.05$ was considered statistically significant.

Results
Figure 2 shows the results of combined MRI and MRSI examinations of a healthy elderly control subject and an AD patient. Comparing the spectroscopic images of the AD patient with those from the control subject (Fig 2A), a general reduction of NAA relative to the sum of Cho and Cr can be noted in the AD patient. This is also reflected in the stacked plot of spectra obtained from a row of voxels through the posterior-parietal brain of each subject, displayed in Figure 2B.

To test for NAA reductions in cortical and bilateral voxels of AD brains, average metabolite ratios from

Fig 2. Results of combined magnetic resonance imaging (MRI) and $^1$H magnetic resonance spectroscopic imaging (MRSI) examinations of an elderly control subject and a patient with Alzheimer's disease (AD). (A) Summed MRIs through the centrum semiovale superimposed with the volume of interest (VOI) (blue rectangle) and the field of view (red rectangle) used, and spectroscopic images reconstructed from the N-acetylaspartate (NAA) resonance and the sum of choline-containing (Cho) and creatine-containing (Cr) metabolite resonances (superimposed with a high-pass-filtered MRI in red). The pseudocolor scale to the right of the spectroscopic images ranges from red (highest signal intensity) to black (lowest signal intensity). Images are displayed after zero-filling to 64 points along the two axes. (B) Stacked plots of spectra obtained from the data sets shown in (A) from one row of voxels in the posterior-parietal brain region at the position of the arrow on the MRIs. Twelve to 14 individual spectra are typically obtained in a left-right direction through the VOI, out of 32 voxels across the field of view.
the three mesial voxels containing primarily gray matter and from the six lateral voxels containing mostly white matter were compared between the 8 AD subjects and 10 control subjects. The results together with the corresponding ratios from 6 young control subjects, which are included for comparison, are listed in Table 1. Overall, the differences of metabolite ratios derived from cortical and bilateral spectra were more pronounced in control subjects than in AD patients. More specifically, in white matter voxels the mean NAA/Cho ratio was lower in AD patients (1.9 ± 0.2) than in elderly control subjects (2.3 ± 0.4; p = 0.05, Wilcoxon). The white matter NAA/Cr ratio was also lower in AD patients (2.9 ± 0.2) than in control subjects (3.5 ± 0.2; p = 0.04, Wilcoxon). There was no difference in the mean white matter Cho/Cr ratio between AD patients (1.6 ± 0.2) and control subjects (1.5 ± 0.3). This suggests that reduced white matter NAA is responsible for the observed metabolite ratio differences. Analysis of mesial gray matter metabolite ratios found the mean NAA/Cho ratio to be lower in AD patients (1.7 ± 0.1) compared to control subjects (2.2 ± 0.6; p = 0.04, Wilcoxon), while the mean gray matter NAA/Cr ratio was not different in AD patients (2.6 ± 0.5) and control subjects (2.5 ± 0.4). The mean Cho/Cr ratio in the gray matter of AD patients (1.6 ± 0.3) was significantly higher than control values (1.3 ± 0.2; p = 0.05, Wilcoxon). These findings suggest that an elevation of Cho in AD is responsible for the mesial gray matter metabolite differences. No sex-related differences of metabolite ratios within groups and no differences of metabolite ratios between elderly and young control subjects were found.

Our preliminary finding of increased Cho/Cr in the posterior mesial gray matter volume of AD patients [16] and metabolite changes in the adjacent lateral white matter volumes of the posterior-parietal area were further examined using t-tests. The results for AD patients and elderly control subjects are given in Table 2 (for comparison, ratios from young control subjects are also included). The largest differences were observed in the posterior mesial gray matter voxel of AD patients and elderly control subjects. The mean NAA/Cho ratio from this voxel in AD patients was 34% lower than that in control subjects (p = 0.005). Cho/Cr in this same voxel was 37% higher in AD than in control subjects (p = 0.0002). NAA/Cr was not reduced, suggesting that increased Cho is primarily responsible for the observed differences in metabolite ratios in the posterior gray matter. In the adja-

### Table 1. Mean $^1$H Metabolite Ratios Obtained from the Centrum Semiovale

<table>
<thead>
<tr>
<th></th>
<th>NAA/Cho</th>
<th>NAA/Cr</th>
<th>Cho/Cr</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cortical</td>
<td>Bilateral</td>
<td>Cortical</td>
</tr>
<tr>
<td>AD</td>
<td>1.7 ± 0.1</td>
<td>1.9 ± 0.2</td>
<td>2.6 ± 0.5</td>
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<tr>
<td>P (Wilcoxon)</td>
<td>0.04</td>
<td>0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Elderly</td>
<td>2.2 ± 0.6</td>
<td>2.3 ± 0.4</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>Young</td>
<td>2.3 ± 0.5</td>
<td>2.2 ± 0.3</td>
<td>2.8 ± 0.1</td>
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</table>

Values are averaged from three spectra of the mesial cortex and six spectra of the bilateral white matter. The groups are AD patients (n = 8), elderly control subjects (n = 10), and young control subjects (n = 6). The data are means ± standard deviations.

AD = Alzheimer's disease; NAA = N-acetylaspartate; Cho = choline-containing metabolites; Cr = creatine-containing metabolites; NS = not significant.

### Table 2. Mean $^1$H Metabolite Ratios Obtained from the Posterior-Parietal Brain Region

<table>
<thead>
<tr>
<th></th>
<th>NAA/Cho</th>
<th>NAA/Cr</th>
<th>Cho/Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cortical</td>
<td>Bilateral</td>
<td>Cortical</td>
</tr>
<tr>
<td>AD</td>
<td>1.9 ± 0.4</td>
<td>2.1 ± 0.4</td>
<td>2.3 ± 0.5</td>
</tr>
<tr>
<td>P (t test)</td>
<td>0.005</td>
<td>0.03</td>
<td>NS</td>
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<tr>
<td>Elderly</td>
<td>2.9 ± 0.8</td>
<td>2.7 ± 0.4</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>P (t test)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Young</td>
<td>3.0 ± 0.5</td>
<td>2.6 ± 0.2</td>
<td>2.5 ± 0.2</td>
</tr>
</tbody>
</table>

Values are from the mesial cortical spectrum and averaged from two spectra of bilateral white matter. The groups are AD patients (n = 8), elderly control subjects (n = 10), and young control subjects (n = 6). The data are means ± standard deviations.

AD = Alzheimer's disease; NAA = N-acetylaspartate; Cho = choline-containing metabolites; Cr = creatine-containing metabolites; NS = not significant.
cent lateral voxels representing primarily white matter, alterations of metabolite ratios in AD patients relative to elderly control subjects were less pronounced than in the posterior cortex (NAA/Cho decrease: 22%, p = 0.05; Cho/Cr increase: 25%, p = 0.05). Again, metabolite ratios from elderly and young control subjects were not different. NAA/Cho ratios obtained from the spectra of posterior gray matter of AD patients and elderly control subjects are shown in the scatter plot of Figure 3.

Comparison of metabolite ratios from voxels of other brain regions revealed no significant group-by-location differences.

On MRIs, all patients with probable AD had ventricular enlargements with an average grade of 1.9 (±1.0) on a 0 to 3 scale. This compared to only 2 of the 10 elderly control subjects displaying mild (grade 1) ventricular enlargements. The difference in ventricular widening between both groups was significant (p = 0.0015). Sulcal widening was prevalent in both groups; the AD group, however, had a slightly higher average grade (1.8 ± 1.0 vs 1.2 ± 0.8 on a 0–3 scale). There were no correlations between MRI estimates of atrophy and any of the metabolite measures.

Discussion

Analysis of tissue-specific 1H MRSI spectra from the supraventricular brain of AD patients relative to elderly control subjects revealed (1) significantly lower NAA/Cr and NAA/Cho ratios in the white matter in the absence of changes in the Cho/Cr ratio, and (2) a significantly lower NAA/Cho ratio in the gray matter in the presence of a significantly higher gray matter Cho/Cr ratio. Gray-white matter signal differences in the supraventricular brain were less pronounced in AD brains than in elderly control brains. In the posterior-parietal region of AD brains compared to age-matched control brains, Cho was higher relative to both NAA and Cr. No differences of metabolite resonances between the brains of elderly and young control subjects were detected, suggesting that the metabolic alterations in the brains of AD patients were likely due to the effects of the AD process on the brain. Standard spin-echo MRI revealed a significantly higher incidence and degree of ventricular dilatation in AD patients than in elderly control subjects. These MRI abnormalities were not correlated to any of the metabolic measures, and the metabolite changes were observed throughout regions that showed no obvious abnormalities on MRIs other than atrophy. Therefore, MRS measures provide metabolic information for the assessment of AD in addition to the structural information obtained by MRI.

Results of the tissue-specific analysis (white and gray matter voxels analyzed separately) imply lower NAA in the white matter of the CSO of AD patients relative to elderly control subjects, while metabolite ratio changes in mesial gray matter may be due to reduced NAA and/or increased Cho. (When metabolite ratios were averaged over all nine voxels, the mean NAA/Cho ratio was the only one significantly lower in the AD than in the elderly control sample (p = 0.02).) Lower NAA would be in keeping with MR findings of other research groups who reported NAA signal losses in AD brain using mostly single-volume MRSI localization techniques [6, 17–19]. NAA signal loss suggests neuron loss when it is observed in gray matter and loss of or damage to axonal structures when it is observed in the white matter. A higher Cho signal in AD brains is consistent with the membrane alterations previously postulated from the studies of AD brain extracts [20–23] and with the abnormal lipid composition in cell membranes reported recently [24]. Therefore, our findings derived from measurements of metabolite ratios give suggestive evidence in vivo for diffuse axonal injury and membrane alterations in the AD brain while cortical neuron loss was not clearly identified in the mesial cortex. The determination of absolute metabolite concentrations from MRSI spectra [25] together with MRI tissue segmentation developed in this laboratory will help to answer without ambiguity the questions of which metabolites are altered in AD and to what extent.

The observed signal differences between groups may be due to differences in metabolite concentrations and/or metabolite relaxation times (T1 and T2) between groups. The spectroscopic measurement of relaxation times with MRSI was not performed in any of these patients because of the prohibitively long examination times required for such measurements. Estimates of T1 relaxation times of metabolites in 4 AD patients and 10 age-matched elderly control subjects.
from spectra obtained at two different scan repetition times revealed no T1 differences between the two groups [6]. Recently, the T2 relaxation time for NAA in a single frontal volume of AD patients (containing a mixture of white and gray matter) was found to be significantly longer relative to that for control subjects [26]. Assuming that the relaxation time for NAA is not regionally different, this suggests that the true NAA level in the supraventricular region of the AD brain observed in this study may be overestimated. Cho and Cr T2 relaxation times in the frontal lobe were not different between groups [26], suggesting that changes in the amount of choline-containing metabolites are responsible for our findings.

The posterior-parietal brain region (primarily posterior-parietal cortex) showed the greatest decrease of NAA/Cho (34%, \( p = 0.005 \)) and the greatest increase of Cho/Cr (37%, \( p = 0.0002 \)) in brains of AD patients relative to elderly control subjects. This region coincides roughly with a region that has a high amount of plaque and neurofibrillary tangle deposition with neurodegeneration in AD brains [27]. The Cho resonance in \(^1\text{H} \text{MRS} \) taken at 272 msec echo time contains contribution from several choline-containing metabolites [28]. These are primarily lipid metabolites such as glycerophosphocholine (GPC) and phosphocholine. Very low amounts of acetylcholine and free choline also contribute to this resonance [28]. Thus, the in vivo observed higher Cho/Cr ratio in AD patients compared to elderly control subjects suggests higher lipid components. This is in concordance with biochemical [22, 23] and MRS [20] findings of increased GPC in extracts of frontal, primary auditory, and parietal cortices of AD brains. The authors of these studies interpreted their results to reflect membrane degradation effects due to increased phospholipid turnover [22, 23] and/or decreased GPC degradation [20] in AD. Furthermore, our Cho findings are consistent with recent reports of defective membrane lipid compositions associated with membrane bilayer destabilization as determined from postmortem measurements of the critical temperature of membranes in regions of the AD brain that are subject to neurodegeneration [24]. These reports [20, 22–24] are unified by an “autocannibalism” theory [21] in which acetylcholine-deficient neurons try to survive by breaking down cell membranes to satisfy their need for choline. Our in vivo \(^1\text{H} \text{MRS} \) findings may support this theory.

Significantly reduced NAA ratios throughout white matter suggest involvement of axons in the white matter in the AD process, which to the best of our knowledge has not been observed previously in in vitro MRS examinations of AD brain tissues. An additional explanation for metabolite signal changes in the white matter may be that, due to the limited spatial resolution of the MRS measures (effective voxel size was approximately 2.5 cm\(^3 \)) and due to the spatial extent of the SI point spread function (see e.g., [9]), signal from voxels placed in white matter are “contaminated” by signal from adjacent gray matter tissue. Similarly, signal from voxels placed in mesial gray matter tissue are likely “contaminated” by white matter signal from adjacent voxels; this may also mask the findings specific to gray matter. The fact, however, that gray-white differences were easily measured should diminish the concern of completely artifactual white matter signal alterations.

According to postmortem studies of AD brain extracts, decreased NAA and increased choline-containing metabolites are associated with AD [23]. Huntington’s disease, another neurodegenerative disease, shows no measurable NAA decrease in vitro, and Down’s syndrome, characterized by amyloid deposition and neurofibrillary tangles, similar to AD, also shows no NAA decreases or Cho alterations in vitro. Thus, the in vivo MR findings in the brains of AD patients may be characteristic for AD [23].

MRI estimates of cerebral atrophy revealed a highly significant widening of ventricular tissue between AD patients and age-matched control subjects. Ventricular widening, however, was not correlated with our relative NAA or Cho measures, suggesting that these measures are not related to or that they do not describe the same neuropathological phenomena; instead, they must reflect changes other than a generalized cerebral tissue loss (atrophy) such as neuronal loss, gliosis, or membrane abnormalities. Alternatively, the relative small variance of the estimates of atrophy in our patient cohort may not provide enough power to detect a correlation even if there were one.

Recently, increased myo-inositol was found in parietal and occipital cortical regions of AD patients with impairments similar to those of our patient population [6]. The authors suggested that the findings of increased myo-inositol in the presence of decreased NAA may have diagnostic value. They used a single-volume localization technique which allowed them to measure \(^1\text{H} \text{m} \) metabolites with an echo time of 30 msec. The experimental conditions for the \(^1\text{H} \text{MRS} \) data acquisitions described here were different (e.g., TE 272 msec) and not optimal for observation of myo-inositol. However, according to Miller and colleagues [6], increased myo-inositol can be linked to our findings of altered phospholipid metabolites via the polyphosphoinositol second messenger cascade.

We conclude that AD, but not normal aging, is associated with alterations of \(^1\text{H} \text{m} \) metabolites in the supraventricular region of the brain, which may suggest widespread axonal damage and lipid abnormalities, and with a local membrane defect in the posterior-parietal brain region. The application of \(^1\text{H} \text{MRS} \) was particularly useful in this clinical study because it allowed evaluation of multiple regions (gray vs white matter, poste-
terior vs anterior brain) in a large section of the brain that showed no discernible abnormalities other than atrophy on standard spin-echo MRIs. Furthermore, $^1$H MRSI allowed detection of metabolic alterations in supraventricular regions of the AD brain which, at the onset of this study, were not expected to be affected by the AD process.

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References

Fairfax, CA: The Northern California Neurobehavioral Group, 1983

Meyerhoff et al: MR Spectroscopy of Alzheimer's Disease 47