MR Signal Abnormalities in Memory Disorder and Dementia

Brian C. Bowen1
William W. Barker2
David A. Loewenstein3
Jerome Sheldon1
Ranjan Duara1,4

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1 Department of Radiology, University of Miami School of Medicine, and Mount Sinai Medical Center, 4300 Alton Rd., Miami Beach, FL 33140. Address reprint requests to B. C. Bowen, Department of Radiology (R-130), University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33101.

2 Wien Center for Alzheimer’s Disease and Memory Disorders, Mount Sinai Medical Center, Miami Beach, FL 33140.

3 Department of Psychiatry, University of Miami School of Medicine, and Cognitive Neuropsychological Laboratory, Wien Center for Alzheimer’s Disease and Memory Disorders, Mount Sinai Medical Center, Miami Beach, FL 33140.

4 Department of Neurology, University of Miami School of Medicine, and Mount Sinai Medical Center, Miami Beach, FL 33140.

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MR imaging of the brain, performed in 86 normal subjects and 113 patients with objective memory disorder or dementia, demonstrated white- and gray-matter areas of high signal intensity on long TR images (short and long TE). Hyperintensities were analyzed with respect to size (on a scale of 0–3) and location: lesions were periventricular, subcortical, or cortical. The patients with memory disorder and dementia were categorized as having probable/possible Alzheimer disease, a combination of Alzheimer disease and multiinfarct cognitive disorder, or multiinfarct cognitive disorder alone on the basis of clinically determined Hachinski ischemic scores. Significant correlations were found between age and scores for periventricular lesions (r = .40, p < .0005) and subcortical lesions (r = .39, p < .0005) in normal subjects. Correlations were also found between the Hachinski ischemic score and scores for periventricular lesions (r = .21, p < .01), subcortical lesions (r = .27, p < .0002), and cortical lesions (r = .32, p < .0005) in subjects with memory disorder/dementia. Comparing multiinfarct cognitive disorder, Alzheimer disease, and normal groups, the mean scores for periventricular lesions were 12.0 ± 4.6, 7.6 ± 4.8, and 3.4 ± 2.6, while mean scores for subcortical lesions were 10.8 ± 12.2, 4.1 ± 6.4, and 0.8 ± 1.2, respectively. Periventricular lesions were present in 99–100% of patients with Alzheimer disease and multiinfarct cognitive disorder. On the other hand, subcortical lesions, which were identified in 100% of patients with multi­

Thus, scores for both periventricular and subcortical lesions are positively correlated with age and risk factors for cerebrovascular disease and also are significantly increased in the presence of objective memory disorder or dementia. These results imply that in the subject groups considered here, elderly patients with vascular dementia are most likely to have severe white-matter abnormalities on MR scans. The score for subcortical lesions appears to be more helpful than the score for periventricular lesions in distinguishing vascular dementia from Alzheimer disease and normal aging, so that a patient with prominent subcortical white-matter abnormalities is more likely to have a diagnosis of vascular than degenerative dementia.

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MR imaging is known to be sensitive in detecting periventricular and subcortical white-matter lesions, which appear as hyperintense areas of variable configuration and size on long TR spin-echo images. The number and size of these lesions correlate with chronological age and with such risk factors for cerebrovascular disease as hypertension and prior ischemic event [1–3]. There are, however, conflicting reports as to how lesion severity correlates with the clinical diagnosis of dementia [1–5]. It has been suggested that the two main types of dementia, multiinfarct cognitive disorder (MICD) and Alzheimer disease (AD), may be differentiated by the severity of white-matter abnormalities [5]. An analysis based on CT characteristics has demonstrated significantly increased severity of periventricular white-matter abnormalities in MICD compared with AD [6]. Nevertheless, quanti­
eration given to the location of the lesions and clinical diagnosis of dementia, has not as yet been reported.

In this study, the location and size of white- and gray-matter lesions in clinically normal individuals and in those with memory disorder have been examined. The results have been analyzed with respect to the clinical diagnosis (MICD vs AD) in the memory disorder patients, and conclusions have been drawn regarding the contribution of MR to the proper diagnosis of dementia.

**Subjects and Methods**

Patients presenting with memory impairment underwent medical, neurologic, and psychiatric examinations; clinical laboratory tests; and MR examination of the brain. All patients included in this study were found to have objective memory disorders by neuropsychological testing. Patients who were considered to have a primary psychiatric diagnosis, such as depression, or a neurologic diagnosis other than AD or MICD (e.g., Parkinson disease) were excluded from this study. Eighty-six normal volunteers underwent the same evaluation as the patients, except that the psychiatric interview was not done. Patients with memory disorder who were also demented, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM III) [7], were considered separately from those without dementia for certain analyses. Otherwise, the demented and nondemented patients with objective memory disorders were combined and then divided into three groups on the basis of their Hachinski ischemic score [8] (see Fig. 1). Those in the group with the lowest ischemic scores (0–4) were labeled probable or possible AD; patients in the group with the highest ischemic scores (7–14) were labeled MICD [9]. MICD was preferred to multifarct dementia [8, 10] because many patients with objectively determined memory disorders did not fulfill DSM III criteria for dementia. Patients in the group with intermediate Hachinski scores (5 and 6) were labeled mixed disorder (MIX). The degree of cognitive deficit was quantified by the Mini-mental State examination of Folstein et al. [11].

Spin-echo MR images were obtained using a Siemens Magnetom superconducting magnet operating at 0.5, 1.0, or 1.5 T and a 25-cm-diameter RF head coil. Seven- or 10-mm-thick contiguous axial images and contiguous sagittal images with long TRs and short TEs, 1500–3000/25–35 (TR/TE), and long TEs, 1500–3000/80–105, were obtained. Scans were interpreted by a radiologist who had no knowledge of the age, identity, or clinical diagnosis of the subjects.

MR signal abnormalities were identified as areas of increased signal intensity relative to surrounding brain parenchyma on both short and long TE images (Fig. 2) and were scored using the following scheme:

1. Lesions contiguous with the margins of each lateral ventricle were designated periventricular lesions (PVLs). They were arbitrarily assigned to anterior, central, and posterior periventricular regions to indicate lesions located respectively in the regions of frontal horn, body, or trigone/occipital horn of the lateral ventricle. The lesions in each region were given a score (similar to the scheme of Kinkel et al. [12]) of 0–3 based on severity (0 = none; 1 = punctate or thin band [less than 0.5 cm thick]; 2 = thick "cap" or broad band [approximately 0.5–1 cm thick]; 3 = lobular, irregular area [outermargin always greater than 1 cm from the ventricular margin]). Although central PVLs can be confused with the normal appearance of the caudate nucleus on short TE images, the caudate signal intensity decreases relative to the signal produced by PVLs on long TE images (Fig. 2). A total score was obtained by summing the scores for the right and left hemispheres (maximum score, 18).

2. White-matter lesions outside the periventricular domain (i.e., in the corona radiata of the frontal, parietal, temporal, and occipital lobes) and in the centrum semiovale, along with subcortical gray-matter lesions, were designated subcortical lesions (SCLs). MR axial images were assigned to one of four anatomic levels: supraventricular, high ventricular, low ventricular, and infraventricular. For each level, each cerebral hemisphere was divided into anterior, central, and posterior regions. SCLs in each region at each level were given a score of 0–3 (0 = none; 1 = punctate lesion [less than 0.5 cm in maximum diameter]; 2 = nodular lesion [approximately 0.5–1 cm in maximum diameter]; 3 = patchy, irregular lesion area always greater than 1 cm maximum diameter). A total score was obtained by summing the scores of all regions in both right and left hemispheres for the four brain levels.

3. Cortical gray-matter lesions (CLS) were assigned to a location using the same scheme as for SCLs. Each lesion was given a score of 0–3 (none, small, moderate, and large, as for SCLs). A total score was obtained for both hemispheres and four brain levels.

*Lesion* was used to describe all periventricular and subcortical, as well as cortical, hyperintensities. For subjects in whom a perifrontal hyperintensity had an anterior PVL score of 1 or 2, the term lesion (meaning more or less circumscribed pathologic change) may not be correct since such hyperintensities can represent normal variation [13]. Because a spectrum of perifrontal hyperintensities, as well as hyperintensities located at other periventricular sites, were being evaluated, the term lesion was used throughout. Previous authors have used the term lesion similarly [1, 2, 4, 12].

**Statistical Analysis**

PVL, SCL, and CL scores were obtained for each subject. Because these data were not normally distributed, a nonparametric analytic strategy was used. Comparisons between various groups (young normal, elderly normal, AD, MICD, and MIX) were made using the Kruskal-Wallis one-way analysis of variance procedure. Post hoc tests were conducted using Mann-Whitney U tests. The relationship between MR scores and age, Hachinski ischemic score, and the Mini-mental status score of Folstein et al. [11] were examined using Spearman rank-order correlation coefficients.

**Results**

Table 1 gives the mean scores for right and left hemispheres for PVLs, SCLs, and CLs in each subject group. No significant differences were found in the laterality of these lesions in any subject group.
Table 2 gives the mean scores for anterior, central, and posterior regions of PVLs and SCLs in all subjects. It was found that for PVLs, the highest mean scores were in the anterior regions and the lowest mean scores were in the central region; intermediate scores were in the posterior region. For SCLs, no significant differences in mean scores were obtained for anterior, central, and posterior regions.

Table 3 gives the mean SCL scores in all subjects according to the horizontal level of the brain in which they were seen. The high ventricular level had the highest scores, followed by supraventricular and low ventricular levels, which had equal mean scores. The infraventricular level had the lowest mean scores.

In 86 clinically normal individuals between the ages of 23 and 84 (mean age, 53.6 ± 16.6 years), there was a significant increase with age in the average total score for PVLs (r = .40, p < .0005) and for SCLs (r = .39, p < .0005), but not for CLs (r = .02, p < .42) (Figs. 3 and 4). In 113 patients with memory disorders, significant positive correlations were found between Hachinski ischemic scores and PVL scores (r = .21, p < .01), SCL scores (r = .27, p < .002), and CL scores (r = .32, p < .0005). There was no significant correlation between PVL, SCL, or CL scores and Mini-mental State scores in memory disorder/dementia subjects.

The mean PVL and SCL scores for all memory disorder subjects without dementia were not significantly different from those for demented subjects. However, the scores for both demented and non-demented subjects with memory disorder were significantly higher than the corresponding scores for age-matched normal individuals (Table 4). Approximately 90% of elderly normals exhibited PVLs, with the majority of the subjects having scores between 1 and 4 (Fig. 3). In comparison, 99–100% of memory-disordered/demented individuals exhibited PVLs; the majority of these subjects had total scores between 5 and 18. For SCLs, a similar skewing of the score distribution toward higher scores (5–40) for memory-disordered/demented individuals was found (Fig. 4).

When memory-disordered/demented patients were divided into groups on the basis of their clinically determined ischemic score (Fig. 1), the data on white-matter lesions could be presented in another way. Mean PVL scores for probable/possible AD, MIX, and MICD patients, and for age-matched controls were compared (Table 4). The mean SCL score for the MICD group was significantly greater than that for the AD and MIX groups, both of which in turn were significantly greater than that for normals. The mean SCL score for the MICD group was also significantly greater than that for the AD group but not the MIX group. MICD, MIX, and AD groups each had a mean SCL score significantly greater than that of the normal group.

Discussion

The goals in this study were to determine the prevalence and severity of white-matter abnormalities detected by MR in normal individuals and in elderly patients with memory disorders and dementia, and to correlate the MR results with clinical data such as Hachinski ischemic scores, which are routinely used in practice to determine whether a patient's cognitive deficits are due to primarily vascular or degenerative disease. The ischemic score has been used previously to classify patients with dementia in CT [6] and MR studies [5]. The Hachinski ischemic score, though not a simple linear, parametric scale, nevertheless assigns a semiquantitative value to risk factors for cerebrovascular disease [8].

Neuropathologic studies have demonstrated that patients who are diagnosed as having Alzheimer-type dementia on the basis of Hachinski ischemic scores of 4 or less, do have this pathologic diagnosis alone in 80–90% of cases [14, 15]. However, when multifocal dementia is diagnosed on the basis of a Hachinski ischemic score of 7 or greater, this pathologic diagnosis alone is found in approximately 25% of cases; most often, a mixed vascular and degenerative disorder is found [14]. We recognized this weakness in clinical categorization of patients by use of the Hachinski ischemic score, but were forced, because of the lack of an alternative clinical method, to employ this procedure. It is likely that some of the overlap in MR scores between clinical groups in this study may have resulted from this lack of specificity of the Hachinski ischemic scores.

In their study, Fazekas et al. [16] described large, confluent periventricular hyperintensities extending into the deep white matter in multifocal dementia, in contrast to the smooth, halo-like periventricular hyperintensities and small focal deep white-matter hyperintensities seen in AD patients. By grading such lesions, we were able to examine their significance statistically.

Punctate and triangular perifrontal hyperintensities have been reported to be a common finding in normal individuals, secondary to locally decreased myelin content, focal ependymal breakdown ("ependymitis granularis"), and preferential centripetal drainage of interstitial fluid [13]. Perioccipital hyperintensities are also seen occasionally in normal individuals, secondary to focal ependymal breakdown [13, 17]. Pathologic hyperintensities can then represent extension from these "normal" foci, possibly related to primary or secondary vascular abnormalities occurring in the periventricular watershed or "border zones" [18, 19] in elderly normals and patients with memory disorder/dementia (see later discussion of MICD and AD).

In normal subjects, PVLs were a common finding in our study. They occurred in 74% of young normals (41.5 ± 9.9 years) and 89% of elderly normals (70.3 ± 6.1 years), while SCLs were seen in only 6% of young normals and in 39% of elderly normals (Figs. 3 and 4). The increase in the prevalence and severity of lesions with age was similar for PVLs and SCLs.

SCLs occurred most often in the high ventricular level and least frequently in the infraventricular level (Table 3). The predilection for the high ventricular level, which encompasses the bodies of the lateral ventricles and surrounding white matter, may be explained primarily by the vascular anatomy. At this level, the medullary branches of the anterior, middle, and posterior cerebral arteries reach their smallest size and
Fig. 2.—Scoring of white-matter lesions is illustrated on this and the next page.

A and B, 0.5-T MR images, 2000/35/1 (A) and 2000/105/1 (B). Score of anterior periventricular lesion is 1 for each hemisphere (arrows).

C and D, 0.5-T MR images, 2000/35/1 (C) and 2000/80/1 (D). Score of central periventricular lesion is 2 for each hemisphere. Scores of anterior and central subcortical lesions (arrowheads) are 2.

E and F, 0.5-T MR images, 2000/35/1 (E) and 2000/105/1 (F). Scores of anterior periventricular lesions, posterior periventricular lesions, and anterior subcortical lesions (arrows) are 3 for each hemisphere.

G and H, 1.5-T MR images, 2500/28/1 (G) and 2500/84/1 (H). Score of central periventricular lesion is 3.

(Fig. 2 is continued on the opposite page.)
Fig. 2—(continued).

I and J, 1.5-T MR images, 2500/25/1 (I) and 2500/90/1 (J). Left hemisphere scores of high ventricular, central subcortical lesions are 3 (long arrows) and 2 (arrowheads); right hemisphere scores are 2 (arrowheads) and 1 (short arrows).

K and L, 0.5-T axial (K) and sagittal (L) MR images, 2000/35/1. Score of high ventricular/supraventricular, central subcortical lesion is 2 (arrowheads).

M, 1.0-T MR image, 2000/28/1. Scores of low ventricular posterior and central subcortical lesions are 3 (small arrow) and 2 (arrowhead), respectively. Score of right occipital cortical lesion is 3 (large arrow).

N, 1.0-T MR image, 2000/28/1. Score of low ventricular central subcortical lesion is 2 (arrow).

### TABLE 1: Mean Scores of Periventricular, Subcortical, and Cortical Lesions by Hemisphere

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Age (mean ± SD)</th>
<th>Periventricular Lesions</th>
<th>Subcortical Lesions</th>
<th>Cortical Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>All subjects</td>
<td>199</td>
<td></td>
<td>2.8 ± 2.5</td>
<td>2.7 ± 2.5</td>
<td>1.6 ± 3.4</td>
</tr>
<tr>
<td>Young normals</td>
<td>50</td>
<td>41.5 ± 9.9</td>
<td>0.9 ± 0.8</td>
<td>0.9 ± 0.6</td>
<td>0.1 ± 0.5</td>
</tr>
<tr>
<td>Elderly normals</td>
<td>36</td>
<td>70.3 ± 6.1</td>
<td>1.9 ± 1.6</td>
<td>1.5 ± 1.2</td>
<td>0.6 ± 1.1</td>
</tr>
<tr>
<td>Probable and possible Alzheimer disease</td>
<td>87</td>
<td>73.1 ± 8.4</td>
<td>3.8 ± 2.5</td>
<td>3.8 ± 2.4</td>
<td>2.3 ± 3.5</td>
</tr>
<tr>
<td>Mixed disorder</td>
<td>14</td>
<td>72.5 ± 11.2</td>
<td>3.5 ± 2.3</td>
<td>3.6 ± 2.5</td>
<td>2.6 ± 4.7</td>
</tr>
<tr>
<td>Multinfarct cognitive disorder</td>
<td>12</td>
<td>73.4 ± 9.3</td>
<td>6.0 ± 2.2</td>
<td>5.9 ± 2.6</td>
<td>5.7 ± 6.3</td>
</tr>
</tbody>
</table>

Note.—No hemispheric difference was found in any subject group. Lesions were assessed on a scale of 0–3, with 0 reflecting no lesions and 3 being the most severe. Lesions were given separate grades for the anterior, central, and posterior regions of each hemisphere.
TABLE 2: Mean Scores of Periventricular and Subcortical Lesions by Region in All Subjects

<table>
<thead>
<tr>
<th>Region</th>
<th>Periventricular</th>
<th>Subcortical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>2.8 ± 1.6</td>
<td>0.7 ± 2.3</td>
</tr>
<tr>
<td>Central</td>
<td>1.1 ± 1.7</td>
<td>1.5 ± 3.2</td>
</tr>
<tr>
<td>Posterior</td>
<td>2.0 ± 2.2</td>
<td>0.8 ± 2.5</td>
</tr>
</tbody>
</table>

Note.—Lesions were assessed on a scale of 0–3, with 0 reflecting no lesions and 3 being the most severe.

**a-c** Mean scores with different superscripts a–c are significantly different (p < .05 by Mann-Whitney U test).

TABLE 3: Mean Scores of Subcortical Lesions by Horizontal Brain Level

<table>
<thead>
<tr>
<th>Horizontal Brain Level</th>
<th>Lesion Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infra-ventricular</td>
<td>0.1 ± 0.7</td>
</tr>
<tr>
<td>Low ventricular</td>
<td>0.7 ± 2.0</td>
</tr>
<tr>
<td>High ventricular</td>
<td>1.5 ± 2.9</td>
</tr>
<tr>
<td>Supra-ventricular</td>
<td>0.7 ± 2.0</td>
</tr>
</tbody>
</table>

Note.—Lesions were assessed on a scale of 0–3, with 0 reflecting no lesions and 3 being the most severe.

**a-c** Mean scores with different superscripts a–c are significantly different (p < .05 by Mann-Whitney U test).

greatest depth of penetration into the white matter, and the opportunity for ischemic injury is greatest.

PVL and SCL scores for demented or memory-disordered patients were significantly higher than for age-matched normals (Table 4). As seen in Figures 3 and 4, the distributions of patient scores are skewed toward higher values in the memory disorder groups. These results agree with those of Brant-Zawadzki et al. [4], who found a higher prevalence of white-matter lesions in elderly subjects with dementia (non-AD) than in elderly subjects with normal neurologic examinations. At the same time, our results are not necessarily inconsistent with those of Awad et al. [1], who reported no correlation between the severity of white-matter "incidental lesions" and the presence of dementia. Awad et al. did not present a direct comparison between demented patients and age-matched normals, nor did they distinguish between memory disorder and dementia. If patients who had memory disorder but were not demented were included in the normal group in our study, we would also not have discovered a difference in mean PVL and SCL scores between demented and normal subjects. It has been reported that the severity of MR-detected [5] and CT-detected [20] white-matter lesions does not increase with the severity of dementia; our results imply this as well, since we found no correlation between Mini-mental State scores and PVL or SCL scores. We note, however, that our study included only ambulatory outpatients, and thus excluded severely demented, usually bedridden patients.

While the degree of the association between PVLs, SCLs, and CLs and the Hachinski score was small, our results emphasize the association of cerebrovascular risk factors with white-matter and cortical abnormalities. Awad et al. [1] previously indicated a positive correlation between the prevalence/severity of white-matter lesions and the presence of hypertension, as well as a history of previous brain ischemia. Our results show a trend toward a stronger correlation between SCLs and the Hachinski ischemic score than between PVLs and the ischemic score, suggesting that SCLs may be a more reliable indicator of cerebrovascular disease.

We next compared MR results in those patients with a clinical diagnosis of possible/probable AD to those with a diagnosis of MCD (Table 4). The mean PVL score for the MCD group was 1.6 times greater than that for the AD group, and 3.5 times greater than that for elderly controls. The mean SCL score for the MCD group was 2.6 times greater than that for the AD group and 13.5 times greater than that for the elderly controls. While both PVL and SCL scores were higher in MCD than in AD, the SCL score better differentiated between MCD (primary vascular dementia) and AD (primary degenerative dementia). Thus, an MR scan showing bilateral subcortical nodular or confluent areas of prolonged T2 relaxation time in the centrum semiovale and corona radiata tends to favor a clinical diagnosis of vascular dementia over AD.

In pathologic studies of nondemented individuals, Awad et al. [21] found MR-detected, incidental white-matter lesions to
be associated with arteriosclerosis, vascular ectasia, and dilated perivascular spaces (état criblé). According to Braffman et al. [22, 23] and others [24], however, dilated perivascular spaces such as those identified by Awad et al. are isointense relative to CSF, and thus not hyperintense compared with surrounding brain parenchyma on short TE images. The results of Braffman et al. indicate that in elderly patients the majority of lesions that are hyperintense on both short and long TE images represent subtle changes of gliosis and demyelination, possibly due to chronic vascular insufficiency [25] and/or frank infarction [26] in regions supplied by the medullary arteries of the hemispheres. In a pathoanatomic study without MR correlation, Brun and Englund [27] found that most of the 23 patients with multifarct dementia showed cerebral hypertensive angiopathy, and the white matter had multiple asymmetrically distributed, complete infarctions surrounded by a transitional zone of reactive gliosis and loss of tissue components. Thus, patients with diffuse cerebrovascular disease, at risk for multifarct dementia, would be expected to have prominent MR abnormalities in the periventricular watershed zone [18, 19, 28] and in the subcortical white matter. This would be consistent with the MR findings of our study.

The severity of MR-detected white-matter lesions seen in patients with a clinical diagnosis of possible/probable AD was intermediate between the findings in elderly normals and those of MCI patients (Figs. 3 and 4). Therefore, the MR abnormalities associated with primary degenerative disease and with vascular dementia may be different only on quantitative grounds.

Pathologically, changes in the deep white matter in elderly patients with AD have been characterized by symmetrically distributed, partial loss of myelin, axons, and oligodendroglial cells, with mild reactive gliosis and hyaline fibrosis of arterioles and capillaries, yet without complete infarctions and without hypertensive angiopathy [27, 29]. George et al. [20] described white-matter changes as typical pathologically of subcortical vascular disease. Rezek et al. [29] found the periventricular changes in AD patients indistinguishable from those occurring in normal elderly individuals, yet increased in prevalence and extent. Brun and Englund [27] and George et al. [20] also found white-matter changes to be quantitatively increased in AD.

A pathogenetic basis for the increase in deep white-matter changes in AD is uncertain, and some investigators argue that white-matter changes are incidental [1, 20, 21]. Brun and Englund [27] considered the possibility of Wallerian degeneration, secondary to the cortical gray-matter disease occurring in AD, to be unlikely because the severity of white-matter changes did not correlate with the regional or global severity of the cortical disease. Instead, regional cerebral hypoperfusion, secondary to cardiovascular dysfunction and systemic hypotension, in a brain with small-vessel disease was favored as the cause of the deep white-matter changes in AD. In other pathologic studies, vasculopathies associated with AD have been reported, including amyloid angiopathy [30] and, more recently, a denervation microangiopathy [31]. Regardless of origin, if the pathologic white-matter changes in AD cause only an exacerbation of the normal aging process, then MR would show signal abnormalities most prominent in the periventricular (watershed) zone and relatively less prominent in the subcortical white matter. The severity of white-matter abnormalities in a 60-year-old patient with AD would thus be expected to be similar to those of a normal 90-year-old individual.

In this study we were unable to show a high degree of specificity of MR findings for any subject group with memory disorder or dementia. In part, this may have been due to inaccuracies in clinical diagnoses. Nevertheless, the significant differences observed in the mean scores of white-matter lesions in different clinical groups can provide supportive data for a suspected clinical diagnosis. Alternatively, when the
expected severity of MR signal abnormalities for a particular clinical diagnosis is not found, other diagnoses should be entertained.

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