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Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy in Dementias

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Abstract

This article reviews recent studies of magnetic resonance imaging and magnetic resonance spectroscopy in dementia, including Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, idiopathic Parkinson's disease, Huntington's disease, and vascular dementia. Magnetic resonance imaging and magnetic resonance spectroscopy can detect structural alteration and biochemical abnormalities in the brain of demented subjects and may help in the differential diagnosis and early detection of affected individuals, monitoring disease progression, and evaluation of therapeutic effect.

Major causes of dementia include Alzheimer's disease (AD) and vascular dementia and less commonly frontotemporal dementia, dementia with Lewy bodies, idiopathic Parkinson's disease, and Huntington's disease.^{1–6} Consensus clinical criteria have been proposed and applied for diagnosis of different dementias, but according to pathologic findings, the sensitivity and specificity of these criteria are variable (34%–97%).⁷ Even histopathologic examination cannot definitely determine the underlying cause of dementia for individual subjects owing to a high frequency of mixed pathology in the brain of demented patients.⁸ Identification of specific diagnostic markers for each dementia is mandatory for early detection of the disease, improving patient management, and evaluation of therapeutic response and disease progression, but this goal remains elusive.^{9,10} In vivo structural changes of demented brains have been studied using magnetic resonance imaging (MRI) with increasing frequency.^{11–13} Magnetic resonance imaging can provide detailed anatomic information in multiple imaging sections with excellent tissue contrast and spatial resolution. There is no ionized radiation with the MRI technique, which makes it the modality of choice for repeated measurements in longitudinal studies. Improved MRI pulse sequences now provide information concerning tissue characteristics, water diffusion, and perfusion in addition to anatomic structures. Furthermore, cerebral metabolites can be measured in vivo using magnetic resonance spectroscopy (MRS) during the same examination.¹⁴ Changes in different metabolites reflect underlying brain pathology in dementia.^{15–17} There are several published reviews of MRI^{11–13} and MRS^{15–18} relevant mainly to AD; the goal of this article is to review thoroughly recent advances of MRI and MRS in not only AD but also other neurodegenerative dementias and vascular dementia.

MAGNETIC RESONANCE IMAGING OF ALZHEIMER'S DISEASE

Many studies have used MRI to measure structural changes of the brain in dementia. Studies on AD before 1995 were summarized in three review articles by Wahlund,¹¹ Xanthakos et al,¹² and Smith.¹³ Most MRI studies found global brain atrophy or focal atrophy of cortical gray matter, temporal lobe, and hippocampus that was often associated with enlargement of the ventricular and sulcal cerebrospinal fluid (CSF) spaces.^{11–13} Furthermore, temporal lobe and hippocampal atrophy correlated to some extent with decreased scores on the Mini-Mental State Examination (MMSE).^{11,12} Focal atrophy was also reported in the amygdala, thalamus, and corpus callosum,^{11,12} although these findings were controversial.^{11,12} Magnetic resonance imaging of patients with AD detected increased amounts of white-matter signal hyperintensities (WMSHs) in the periventricular and deep white-matter regions.^{11–13} However, the relationship between periventricular WMSH and MMSE scores remained unclear.^{11,12} Since 1995, more than 100 additional MRI studies of AD were published that focused increasingly on early detection and longitudinal study in patients with AD. This review summarizes findings on recent MRI studies of AD in the following categories: (1) global and focal changes, (2) longitudinal changes, and (3) neuroimaging changes studied by T₂ relaxometry, diffusion MRI, and perfusion MRI (Table 1). In addition to MRI of AD and other dementias, this review also includes MRI studies on subjects with mild cognitive impairment who are not demented but are considered to have a high risk for developing dementia.

WHOLE BRAIN MEASUREMENTS

Alzheimer's disease is characterized by neurofibrillary tangles and neuritic plaques that ultimately cause neuron loss in the limbic system and cerebral cortex.²⁰ Diffuse gray-matter atrophy was consistently found in the frontal, temporal, and parietal lobes^{21–24} and limbic system²⁵ of patients with AD, presumably reflecting neuron loss in these regions. Similar to previous studies, there were no substantial changes in the white matter,^{21,22} implying that global cerebral atrophy in AD is prominently owing to reduced cortical gray matter. However, Brunetti et al²⁶ found significant volume losses of both gray and white matter in 16 patients with probable AD, which were more evident in early-onset subjects. There was substantial enlargement of the ventricular system in patients with AD, but changes in sulcal CSF spaces were controversial.^{21,22} Using segmentation and a three-dimensional rendering technique, Kidron et al²¹ demonstrated that large temporal and parietal ventricular CSF spaces and small temporal gray matter could discriminate 32 patients with probable AD from 20 healthy elderly subjects with 92% accuracy. Concerning the relation of gray matter with neuropsychological functions, Stout et al²⁵ showed on 52 patients with probable AD that increasing dementia severity was associated with reduced gray-matter volumes. The relationship between gray matter and memory function tests was inconclusive.^{27,28}

Recently, head circumference and intracranial area and volume of patients with AD have been evaluated.^{29–33} Schofield et al²⁹ found that a smaller head circumference was associated with a higher risk of AD, and Graves et al³⁰ reported that patients with AD with a smaller head circumference either had the disease longer or it progressed more rapidly. Schofield et al³¹ demonstrated that there was a positive correlation between the intracranial area measured on computed tomography and the age at onset of AD in women. These findings support the hypothesis that a large brain size provides a greater cerebral reserve against the effect of AD. However, in a study of 85 patients with AD, Jenkins et al³² showed that there was no difference in intracranial volume between AD and normal controls, nor was there a correlation between intracranial volume and age at symptom onset. The discrepancy is most likely owing to different approaches for measurement of brain size: intracranial area or head circumference at one section versus intracranial volume from multiple sections. The relationship between intracranial volume and specific neuropsychological functions was inconclusive.^{33,34}

The relationship between general brain atrophy and apolipoprotein E (apo E) $\epsilon 4$ alleles was recently studied by Yasuda et al,³⁵ who found that there was a positive correlation between normalized whole-brain volume and the number of apo E $\epsilon 4$ alleles in 178 patients with late-onset sporadic AD. Patients carrying two apo E $\epsilon 4$ alleles had the least brain atrophy when compared with those carrying no or one apo E $\epsilon 4$ allele, indicating that cognitive dysfunction progresses before severe brain atrophy develops in patients carrying the apo E $\epsilon 4$ allele.³⁵

HIPPOCAMPUS

In AD, medial temporal lobe structures, including the hippocampus,^{36–53} parahippocampal gyrus,^{38,41,45,46,52} and amygdala,^{39,44–46,54} have been widely evaluated by quantitative MRI. Linear measurement of the width of temporal horns³⁶ and rating of perihippocampal CSF spaces³⁷ and hippocampus^{48,51–53,55} showed hippocampal atrophy in large cohorts of patients with AD. Although linear measurements and rating are less time consuming and easier to perform than volume measurements,⁵³ they lack important information about the regional extent of volume losses. In addition, histopathologic studies showed that there was a strong correlation between MRI-determined hippocampal volumes and neuronal counts in the brain of patients with AD.⁵⁶ Therefore, many researchers evaluated hippocampal changes with volumetric MRI^{38–47} using similar anatomic guidelines in most studies. Significant hippocampal atrophy in AD was consistently found in the literature; the range of volume reduction was reported to be 19% to 40%.^{41,42,44,46,47} Volume reduction of the hippocampus has been reported to be most severe in the head portion.⁴⁵ A significant association between hippocampal volumes and dementia scores, MMSE or Clinical Dementia Rating (CDR), has been demonstrated by many researchers.^{39,42,44,45} In an MRI-based volumetric study of 94 patients with probable AD, Jack et al⁴⁵ demonstrated that hippocampal atrophy was associated with cognitive impairment. This is consistent with previous evidence that the hippocampus is involved in memory in both man and experimental animals.⁵⁷ Many researchers disclosed a significant correlation between hippocampal atrophy and poor performance of specific memory function in AD.^{26–28,34,37,38,46,47,58–60} For example, Petersen et al⁵⁸ evaluated a group of 94 patients with AD and found that the volumes of the left hippocampi were correlated with delayed-recall verbal tasks, and the volumes of the right hippocampi were correlated with delayed-recall nonverbal memory performance; none of them were correlated with immediate-recall memory functions.

Several studies demonstrated that the presence of the apo E $\epsilon 4$ allele was associated with smaller hippocampi in AD^{62–64} or in nondemented elderly subjects carrying the apo E $\epsilon 4$ allele.^{65–68} Studying 58 patients with early AD and 34 elderly controls, Lehtovirta et al⁶⁹ found that patients carrying two apo E $\epsilon 4$ alleles had the most severe volume loss in the hippocampus when compared with those carrying no or one apo E $\epsilon 4$ allele. In a volumetric MRI study of 28 right-handed patients with AD and 30 normal subjects, Geroldi et al⁷⁰ demonstrated that the right hippocampus was larger than the left in controls, and this asymmetry was progressively reduced with an increasing number of apo E $\epsilon 4$ alleles in AD. However, the absence of a relationship between apo E $\epsilon 4$ allele variants and hippocampal size⁷¹ or medial temporal lobe⁷² was also noted. Jack et al⁷¹ did not find hippocampal volume differences on the basis of the apo E genotype in 62 patients with probable AD or in 125 elderly controls. Similarly, Barber et al⁷² found that the apo E $\epsilon 4$ allele did not determine medial temporal lobe atrophy or WMSH severity in a cohort of 25 patients with AD, 24 with vascular dementia, and 22 with dementia with Lewy bodies. The authors suggested that although the genotype may modify the risk for acquiring dementia, the number of apo E $\epsilon 4$ alleles did not influence pathologic process thereafter.⁷² Recently, neuroimaging of AD in relation to the apo E $\epsilon 4$ allele was reviewed by Lehtovirta et al.⁷³

PARAHIPPOCAMPAL GYRUS AND AMYGDALA

In addition to the hippocampus, postmortem studies showed that the parahippocampal gyrus and amygdala also had AD pathology.⁷⁴ Volume losses in parahippocampal gyrus^{37,41,45–47,58} and amygdala^{34,39,44–46,55} were consistently identified in AD, even in the early stage of the disease.^{39,41,44–46} Compared with normal elderly, the atrophy of parahippocampal gyrus in AD was in the range of 15% to 20%, smaller than the 30% to 40% loss of amygdala volume.^{45,46} A negative correlation between the number of apo E ϵ 4 alleles and the volume of amygdala has been demonstrated in AD.⁶⁹ Regarding the ability to discriminate AD from normal aging, most studies showed that the volumes of hippocampi could achieve accurate differentiation better than those of the amygdala,^{39,45} anterior temporal lobe,⁴⁰ and parahippocampal gyrus.^{45,47} A correlation between neuropsychological tests and parahippocampal gyrus or amygdala volumes was not consistent in the literature.^{34,38,41,47,58} Petersen et al⁵⁸ showed that there was disproportionate shrinkage of the left parahippocampal gyrus compared with the right parahippocampal gyrus, and this difference in volume reduction correlated with naming performance. The authors suggested that it was probably owing to the fact that the left parahippocampal gyrus receives most connections from the left temporal neocortex, subserving the linguistic function of naming in the left hemisphere.⁵⁸ Mori et al⁶¹ found that volumes of the amygdala and subiculum, not hippocampal volumes, correlated with memory performance, suggesting that changes in perihippocampal structures further increased the severity of memory impairment caused by hippocampal atrophy in AD.⁶¹ However, other researchers did not find similar results.^{34,38,47} Actually, it is not easy to identify boundaries between the hippocampal proper, subiculum, amygdala, and parahippocampal gyrus based solely on MRI, and there are no universal criteria for measurement of these small structures, which may be the key factor that accounts for controversial results in the literature.

ENTORHINAL CORTEX

Pathologic studies of AD showed that neuronal loss and deposition of neurofibrillary tangles were most severe in the entorhinal cortex, occurring in the beginning stage of AD, earlier than their appearance in the subdivisions of hippocampal formation.^{75–78} The volume of entorhinal cortex is thus expected to be a sensitive parameter for identifying the early stage of AD. Several studies emphasized changes in the entorhinal cortex of patients with AD^{41,42,79–81} and demonstrated a volume reduction in the range between 38% and 61% compared with normal subjects. The ability to discriminate AD from normal aging by entorhinal cortex volumes was comparable to or better than hippocampal volumes^{42,79–82} and usually better than the volumes of the perirhinal or temporopolar cortex.⁷⁹ Juottonen et al⁴² suggested that hippocampal voluming was more feasible for daily practice than entorhinal cortex voluming owing to easy tracing of the hippocampal boundary. Similarly, Xu et al⁸¹ demonstrated in 30 patients with AD, 30 subjects with mild cognitive impairment, and 30 elderly controls that MRI volumes of the hippocampus and entorhinal cortex had approximately equivalent ability of intergroup discrimination and suggested that measurement of the hippocampus was preferable because entorhinal cortex boundaries might be obscured by anatomic ambiguity and image artifacts. In contrast, after validating MRI measurements of the entorhinal cortex in 16 patients with necropsy-confirmed AD, Bobinski et al⁸⁰ studied another 8 patients with mild AD with a mean MMSE score of 27 and reported that entorhinal cortex measurements had advantages over the hippocampus in differentiating mild AD from normal elderly. Furthermore, following 79 subjects with mild memory difficulty for 3 years, Killiany et al⁸² found that baseline MRI measures of the entorhinal cortex, not the hippocampus, were useful to predict who will convert to AD during the longitudinal study. Entorhinal cortex volumetry seems to have the potential for early detection and risk prediction of AD; however, anatomic

ambiguity makes delineation of this small structure difficult, and measurement variations may hinder its application in clinical practice.

In a study of 28 patients with mild to moderately severe AD, Geroldi et al⁶² disclosed that an increasing dose of apo E ϵ 4 alleles was associated with more atrophy in the entorhinal cortex, hippocampus, and anterior temporal lobe and less atrophy in the frontal lobe. Similarly, Juottonen et al⁸³ reported that patients with AD with the apo E ϵ 4 allele had significantly greater volume losses in the entorhinal cortex (−45%) than those without the apo E ϵ 4 allele (−27%). A significant correlation between entorhinal cortex volumes and MMSE scores has been noted.⁷⁹

CORPUS CALLOSUM

Many researchers reported regional atrophy of the corpus callosum, which might reflect a topographic cerebral volume reduction in AD.^{84–88} All of these studies consistently identified a reduction of total volume of corpus callosum, but the results of regional changes were controversial. For example, Lyoo et al⁸⁴ identified significantly smaller posterior midbody, isthmus, and splenium of the corpus callosum compared with elderly controls; Pantel et al⁸⁵ found that decreased regional volume of the corpus callosum was most severe in the rostral body and midbody; and Hampel et al⁸⁷ reported that there were regional volume losses in the rostrum and splenium, relatively sparing the body. A correlation of regional atrophy of the corpus callosum with specific neuropsychological functions has been shown in many studies,^{84,85,87} indicating that interhemispheric cortico-cortical disconnection may contribute to dementia syndrome in patients with AD. A correlation between the total corpus callosum area and white-matter lesions has been demonstrated by Vermersch et al,⁸⁹ suggesting that primary white-matter degeneration may contribute to corpus callosum atrophy. Teipel et al⁸⁸ studied further the relationship between regional corpus callosum atrophy and white-matter lesions but did not identify a significant correlation. All of the controversial results concerning regional atrophy of the corpus callosum is most likely owing to different criteria for patient recruitment and various definitions for subdivision of the corpus callosum.^{84–89}

LONGITUDINAL STUDIES

Recently, many researchers have focused on longitudinal studies of AD, measuring global^{90–96} or focal cerebral changes.^{96–100} General brain atrophy in terms of loss of total brain volume determined by serial MRI was in the range of 1% to 2.8% per year for AD, significantly larger than the rate of 0.05% to 0.41% per year for elderly controls.^{91–94} Using the boundary shift technique, which directly compares two sequential MRIs, Rossor et al⁹⁰ and Fox et al^{91,92} demonstrated that there was no overlap between the rate of brain atrophy in AD and normal aging. A significant correlation between the rates of general brain atrophy and cognitive decline in AD has been noted.⁹⁵

In a 2-year follow-up study, Jack et al⁹⁶ found that patients with AD had more severe hippocampal atrophy (−3.98% vs −1.55% per year) and temporal horn enlargement (+14.16% vs +6.15% per year) than age- and gender-matched elderly controls. In a 3-year longitudinal study of seven at-risk members in a familial AD pedigree, Fox et al⁹⁷ showed that the three subjects who became symptomatic during the follow-up period had faster hippocampal volume reduction at the rate of 5% to 10% per year, compared with less than 4% per year in normal controls and those who remained asymptomatic. Recently, Jack et al¹⁰⁰ performed a 3-year longitudinal MRI study of hippocampal volumes in 58 controls, 43 patients with mild cognitive impairment, and 28 patients with AD. They found that the annualized rate of hippocampal atrophy was most severe in patients with AD (−3.5%–1.8%), less in those with mild cognitive impairment (−3.0%–1.6%), and least in controls (−1.9%–1.1%).¹⁰⁰ However, studying

hippocampal changes with volumetric MRI in 27 patients with AD and 8 control subjects over a period of 3 years, Laakso et al⁹⁹ found that there was only a nonsignificant trend toward accelerated volume loss in AD (−2.3%–15.6%) compared with controls (−2.2%–5.8%). Additionally, Kaye et al⁹⁸ performed a 42-month longitudinal study in 30 nondemented elderly subjects and found (1) accelerated atrophy in the temporal lobe, instead of the hippocampus, of 12 subjects who became demented during the study and (2) that both the initial volumes of the hippocampus and temporal lobe were smaller in these 12 subjects than in those who remained nondemented. These findings suggest that it is the superimposition of increasing loss of the temporal association cortex on a critically atrophic hippocampus that led to the emergence of clinical dementia.⁹⁸ Although there are many promising reports, clinical evaluation of disease progression or therapeutic effect in AD with longitudinal hippocampal volumetry will be possible only after a totally automated measurement is developed and validated; otherwise, every manual intervention will introduce bias and cause variation, even larger than the volume changes owing to the AD process.

The relationship between the apo E ϵ 4 allele and the rate of brain atrophy was studied in 81 patients with dementia by Wahlund et al,¹⁰¹ who found that apo E ϵ 4 allele carriers had a significantly larger increase in ventricular volume (+12.7% per year) as compared with noncarriers (+6.4% per year) after an average 16-month period of follow-up. Additionally, Yamaguchi et al¹⁰² measured the progression of hippocampal atrophy as the percentage change of interuncal distance per year in 24 patients with probable AD and found that there was a trend to increasing rates of hippocampal atrophy as a function of the apo E ϵ 4 allele dose.

WHITE MATTER

Many reports concluded that there was increased WMSH on T₂-weighted images of patients with AD.^{22,24,103–106} In a comparative histopathologic study, Scheltens et al¹⁰⁴ found that the denudation of the ventricular ependyma, gliosis, and loss of myelinated axons were more severe in AD than in normal aging, and the presence of WMSH correlated with the loss of myelinated axons in the deep white matter and the denudation of the ventricular lining. Investigating WMSH seen on T₂-weighted images with positron emission tomography (PET) in 16 patients with AD, Yamaji et al¹⁰⁵ demonstrated that there were ischemic changes with fairly compensated oxygen metabolism in the regions with WMSH. Many studies found that AD had significantly increased WMSH in the periventricular region.^{103,106} For example, Fazekas et al¹⁰⁶ studied 30 patients with probable AD and 60 age- and sex-matched controls and found that AD had significantly more frequent and more severe periventricular WMSHs than controls even when matched for cerebrovascular risk factors. However, Smith et al¹⁰⁷ demonstrated in 33 individuals meeting the pathologic criteria of AD that demented patients did not have a more severe rating of periventricular WMSHs than nondemented patients. They also found that reduced white-matter volume was associated with low MMSE scores, but periventricular WMSHs were not related to the severity of dementia. On the other hand, a negative correlation of WMSH volumes with MMSE scores has been reported by Stout et al.²⁵

The relationship between the apo E ϵ 4 allele and WMSHs was explored in several studies.^{71,108–112} Most of these studies were conducted in large cohorts of patients and did not show a significant association of WMSHs with the apo E ϵ 4 allele.^{108–111} Investigating 55 patients with AD and 66 age- and sex-matched controls, Sawada et al¹¹¹ found that the apo E ϵ 4 genotype was not associated with the presence or the degree of WMSHs in AD; instead, aging and femininity were significant risk factors for WMSHs. However, the study by Bronge et al¹¹² showed that patients with AD carrying two apo E ϵ 4 alleles had more extensive WMSHs in the deep white matter than those carrying no or one apo E ϵ 4 allele. Conflicting results of

WMSH studies in AD are most likely owing to different measurement methods (e.g., number, rating, or volume of WMSHs) and patient selection (e.g., diagnosis of AD by clinical or pathologic criteria, consideration of cerebrovascular risk factors or not). Clinical significance of WMSHs in AD cannot be determined based on the findings of MRI studies to date; further assessments with more strict and universal criteria are necessary for drawing a conclusion.

T₂ RELAXOMETRY

Prolongation of hippocampal T₂ relaxation time (+30 msec)^{19,113} and a correlation between T₂ prolongation and clinical severity have been reported in AD.¹⁹ However, recent studies in much larger cohorts showed that there was only mild prolongation of T₂ relaxation time (+5–6 msec) in the hippocampi.^{114,115} In a study of 54 patients with probable AD with a mean MMSE score of 22, Laakso et al¹¹⁴ demonstrated that there was a substantial intergroup overlap of hippocampal T₂ relaxation time, suggesting that T₂ relaxometry did not help in diagnosing mild AD. In patients with AD, T₂ prolongation in the white matter of the temporal and parietal lobes and thalamus was in the same range as that in elderly controls.¹¹⁴ T₂ relaxation time of the hippocampus correlated with MMSE scores¹¹⁴ but not with hippocampal volumes.¹¹⁵

DIFFUSION MAGNETIC RESONANCE IMAGING

Recently, MRI was used to investigate changes in water diffusion in the hippocampus and cerebral white matter of patients with AD.^{116–119} Hanyu et al¹¹⁷ found that there was a significant increase in the apparent diffusion coefficient in apparently normal periventricular white matter in patients with AD, suggesting a disruption of the axon-myelin sheath complex. They also demonstrated that there was a significantly increased apparent diffusion coefficient and a decreased index of diffusion anisotropy in the temporal stem of 18 patients with mild and moderate AD, indicating that reduced fiber density owing to disruption and loss of axonal membranes or myelin occurs early in the AD process.¹¹⁶ These authors did not find significant changes in diffusion parameters of the hippocampus.¹¹⁶ Sandson et al¹¹⁸ studied diffusion-weighted MRI in 10 patients with AD and found that they had diminished anisotropy in the occipital white matter and increased apparent diffusion coefficient in the hippocampus as compared with 11 control subjects. The correlation of diffusion measures with the severity of dementia was controversial.^{116,118} The usefulness of diffusion MRI in the clinical evaluation of AD remained undetermined.

PERFUSION MAGNETIC RESONANCE IMAGING

Positron emission tomography and single photon emission computed tomography (SPECT) detect metabolism and perfusion abnormalities in the bilateral temporoparietal cortex in patients with AD.¹²⁰ Recently, many researchers investigated the usefulness of perfusion MRI for detecting hemodynamic changes in AD patients; both dynamic susceptibility contrast MRI^{121–126} and arterial spin-labeled MRI^{127,128} have been evaluated. All of the dynamic susceptibility contrast MRI studies showed a reduction of cerebral blood volume in the bilateral temporoparietal regions,^{121–126} consistent with the regional changes detected by PET¹⁰⁴ or SPECT.^{125–127} The reduction of cerebral blood volume measured by perfusion MRI was in the range of 15% to 20% for temporoparietal regions and 8.5% to 12% for sensorimotor regions.^{122,126} Using echo-planar imaging and signal targeting with alternating radio-frequency technique, Sandson et al¹²⁸ demonstrated that there was focal hypoperfusion in the posterior temporoparieto-occipital region in 7 of 11 patients with AD, and the parieto-occipital hypoperfusion correlated with dementia severity. Similarly, applying spin-labeled MRI in 18 patients with probable AD, Alsop et al¹²⁷ found that there were cerebral blood flow decreases in the temporal, parietal frontal, and posterior cingulate cortices and that the decreases in the posterior parietal and posterior cingulate cortices correlated with reduced MMSE scores. These

reports indicate that perfusion MRI is a promising alternative to radionuclide techniques for investigation of hemodynamic changes in AD.

MILD COGNITIVE IMPAIRMENT

Neuropsychological studies have shown that 50% to 75% of the elderly with mild cognitive impairment were at increased risk for developing of AD.^{129,130} Detection of cerebral changes in mild cognitive impairment using MRI has been reported recently.^{47,81,131,132} Compared with normal controls, significant atrophy was identified in the hippocampus^{47,131,132} and entorhinal cortex⁸¹ of patients with mild cognitive impairment but not in the parahippocampal gyrus, fusiform gyri, and temporal gyri.^{47,131} patients with mild cognitive impairment had less severe hippocampal atrophy (−12%–14%) than those with AD (−22%–23%)^{47,82} and fewer entorhinal cortex volume losses (−21%) than those with AD (−38%).⁸¹ Longitudinal volumetric MRI studies in mild cognitive impairment have been performed by Jack et al.^{100,132} Their results showed that hippocampal atrophy in mild cognitive impairment was somewhat predictive of subsequent conversion to AD,¹³² and the controls and patients with mild cognitive impairment who declined cognitively during a 3-year follow-up had significantly accelerated hippocampal atrophy than those who remained stable.¹⁰⁰

MAGNETIC RESONANCE IMAGING OF FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia is an important and frequent cause of non-AD degenerative dementia, especially that of presenile onset. In 1994, the Lund and Manchester Groups¹³³ proposed census clinical and pathologic criteria for frontotemporal dementia. Extensive loss of pyramidal neurons in the frontotemporal cortex, severe gliosis within the gray and white matter, and presence of Pick's bodies are the most common histologic findings, which are not seen in AD.^{133–135} Many MRI studies demonstrated significant atrophy of the frontal and temporal lobes,^{136–141} with lateral asymmetry of volume loss in more than 50% of patients with frontotemporal dementia.^{138,139} Evaluating cortical atrophy in 18 patients with frontotemporal dementia and 18 patients with AD, Kitagaki et al¹³⁸ disclosed that both the patients with frontotemporal dementia and AD had significant atrophy in most cortical regions, but the subjects with frontotemporal dementia had more severe volume loss in the medial frontal and anterior temporal lobes than the subjects with AD. A differential pattern of lobar atrophy between frontotemporal dementia and AD was also found by Fukui and Kertesz¹⁴²: patients with frontotemporal dementia had a significantly smaller right frontal lobe, whereas patients with AD showed smaller parietal lobes bilaterally.

In addition to frontotemporal atrophy, atrophy of the hippocampus,^{136,143,144} entorhinal cortex,^{110,143,145} and corpus callosum¹⁴⁶ and enlargement of Sylvius' fissure¹⁴⁰ have been reported in patients with frontotemporal dementia. In vivo atrophy of the hippocampus identified by MRI was consistent with histopathologic findings in frontotemporal dementia.¹³⁴ In a volumetric MRI study of 12 patients with frontotemporal dementia and 30 patients with AD, Frisoni et al¹⁴³ demonstrated that hippocampal atrophy was less severe in frontotemporal dementia (−16%–21%) than in AD (−28%–32%), and entorhinal cortex atrophy was similar in both groups (−27%–28%). Furthermore, Laakso et al¹⁴⁵ disclosed that there was a different pattern of hippocampal atrophy between patients with AD and those with frontotemporal dementia: atrophy of the hippocampus was diffuse in the patients with AD and localized predominantly in the anterior hippocampus in those with frontotemporal dementia. They also demonstrated that the amount and pattern of entorhinal cortex atrophy were virtually equal in both groups.¹⁴⁵ Evaluating the corpus callosum and pericallosal CSF space in terms of the percentage of midsagittal cerebral area, Kaufer et al¹⁴⁶ concluded that there was a much smaller genu in patients with frontotemporal dementia compared with those with AD, although there was no difference in the total area of the corpus callosum. Furthermore, they demonstrated

a region-specific increase in the anterior pericallosal CSF space that distinguished frontotemporal dementia from AD, reflecting selective degenerative changes in the midline frontal and anterior cingulate regions in patients with frontotemporal dementia.¹⁴⁶ Kitagaki et al¹⁴⁷ showed that patients with frontotemporal dementia had more WMSHs in the frontal lobe compared with controls and those with AD. The authors suggested that astrocytic gliosis and mild demyelination were most likely the causes of white-matter lesions in frontotemporal dementia.¹⁴⁷ In summary, compared with patients with AD, those with frontotemporal dementia have more severe atrophy in the frontal lobe, have less in the hippocampus, and are similar in the entorhinal cortex and in the total corpus callosum area and have more WMSHs in the frontal lobe (see Table 1).

The relationship between volumetric MRI and cognitive functions in frontotemporal dementia was seldom addressed. A significant correlation has been found between dementia severity and enlargement of the anterior pericallosal CSF space¹⁴⁶ or atrophy of the hippocampus and entorhinal cortex.¹⁴³

MAGNETIC RESONANCE IMAGING OF DEMENTIA WITH LEWY BODIES

Dementia with Lewy bodies is a large category of age-related non-AD dementia beginning to be recognized in neuropsychiatric clinics.^{5,148,149} Although universal criteria have not been validated, consensus guidelines for clinical and pathologic diagnosis of dementia with Lewy bodies were established in 1996.¹⁵⁰ Recently, pathologic studies revealed a consistent pattern of vulnerability to Lewy body formation across subcortical, paralimbic, and neocortical structures that was not related to the amount of AD changes, indicating that dementia with Lewy bodies is a distinct pathology rather than a variant of AD.^{151,152}

Based on in vivo cerebral MRI studies, patients with dementia with Lewy bodies have various morphologic changes, including global brain volume loss¹⁵³ and regional atrophy in the frontal lobe,^{154–156} temporal lobe,^{154,155,157,158} hippocampus,^{145,147,153,156,159} amygdala,^{153,155,158} and parahippocampal gyrus.^{156,160} Volume losses in the hippocampus, amygdala, and parahippocampal gyrus reflect the underlying accumulation of neurofibrillary tangles and loss of neuronal cells in the medial temporal structures of patients with dementia with Lewy bodies.^{159,160} Differences in the severity of regional atrophy between AD and dementia with Lewy bodies have been investigated using volumetry,^{153,155,158} cross-sectional area,¹⁶⁰ or visual rating.^{157,162} Most studies reported that patients with dementia with Lewy bodies had less severe atrophy than those with AD in temporal lobe structures^{153,156–158,160,162} and similar losses in the total brain volume (see Table 1).^{153,158} For example, studying volumetric MRI in 27 patients with dementia with Lewy bodies, 25 with AD, and 24 with vascular dementia, Barber et al¹⁵⁸ found that patients with dementia with Lewy bodies had significantly larger temporal lobe, hippocampus, and amygdala volumes than those with AD, and there was no significant volumetric difference between dementia with Lewy bodies and vascular dementia. Recently, Barber et al¹⁶³ reported that the severity and prevalence of periventricular and deep WMSHs were similar in patients with dementia with Lewy bodies and those with AD. Atrophy of frontal cortex and hippocampus has been reported to correlate with the severity of clinical dementia in dementia with Lewy bodies.¹⁵⁶

MAGNETIC RESONANCE IMAGING OF IDIOPATHIC PARKINSON'S DISEASE

About 40% to 70% of patients with idiopathic Parkinson's disease are demented, the percentage increasing with age.¹⁶⁴ Typical dementia in idiopathic Parkinson's disease is a form of subcortical dementia resulting from dopaminergic insufficiency.¹⁶⁵ Postmortem studies identified increased iron content in the substantia nigra^{166–168} and basal ganglia¹⁶⁹ of patients with idiopathic Parkinson's disease when compared with age-matched controls. Signal attenuation on T₂-weighted images in the substantia nigra, selectively the pars compacta, was

identified in many MRI studies.^{166,170–174} Abnormal signal hypointensities and atrophy owing to iron deposition and iron-induced cytotoxic reaction result in smudging of the posterior border of the substantia nigra toward the red nucleus and narrowing of the width of the pars compacta.^{175–177} Magnetic resonance imaging consistently demonstrated a high iron level in the substantia nigra, based on the increasing effect of iron on the transverse relaxation rate.^{166,171–173} The ferritin level was found to be increased in early-onset idiopathic Parkinson's disease and, in contrast, significantly decreased in late-onset idiopathic Parkinson's disease after 60 years of age.¹⁶⁶ However, the results concerning the clinical specificity of signal changes in the substantia nigra were inconclusive: both the absence^{171,172} and presence¹⁷³ of correlation between decreased T₂ relaxation time and disease duration or severity have been reported.

Signal changes in the basal ganglia based on MRI studies are more complicated. Most researchers reported T₂ hypointensities in the basal ganglia in subjects with idiopathic Parkinson's disease,^{166,169,170,172} but others demonstrated abnormal T₂ hyperintensities¹⁷¹ or found no difference from the control group.¹⁷⁶ Abnormal putaminal hypointensities seem to be more frequently found in patients with atypical parkinsonism with poor levodopa response than in those with idiopathic Parkinson's disease,^{170,178,179} and T₂ prolongation with hyperintensities in the putamina and globus pallidi tends to occur in patients with idiopathic Parkinson's disease with a disease duration of more than 10 years.¹⁷¹ Specifically, Ryvlin et al¹⁷¹ showed that there was a positive correlation between putaminal T₂ relaxation time and disease duration in 45 patients with levodopa-responsive idiopathic Parkinson's disease. However, a limited value of T₂ relaxation time in discrimination of idiopathic Parkinson's disease from normal controls owing to considerable overlap between groups was noted.¹⁷⁹

Several MRI studies of idiopathic Parkinson's disease showed volume reduction in the caudate, putaminal and thalamic nuclei,¹⁸⁰ medial temporal lobe,¹⁵⁴ and hippocampus,¹⁸¹ consistent with histopathologic findings.¹⁸² In contrast, Schulz et al¹⁸³ found that the mean volumes of the caudate nucleus, putamen, brain stem, and cerebellum were normal in 11 patients with idiopathic Parkinson's disease. Because the number of patients in the study was so small and the measurement guidelines were different, a conclusion of volumetric MRI changes in idiopathic Parkinson's disease cannot be obtained at present.

MAGNETIC RESONANCE IMAGING OF HUNTINGTON'S DISEASE

Huntington's disease is a rare neurodegenerative disease of middle and late adulthood with autosomal dominant transmission, characterized by dementia and movement disorders.^{2,3,6} The clinical features result from dysfunction of the frontostriatal circuits, caused by neostriatal gliosis and neuron loss.^{6,184} Atrophy of the basal ganglia in patients with Huntington's disease was consistently identified on MRI using linear measurements,^{185–188} volumetric studies,^{187–193} or visual rating.¹⁹⁴ Patients with Huntington's disease have a larger bicaudate ratio^{187–189} and bifrontal ratio¹⁸⁹ than control subjects, reflecting caudate atrophy and ventricular enlargement, respectively. The increase in the bicaudate ratio was around 30%^{188,189}; a strong correlation between the bicaudate ratio and caudate volume in Huntington's disease has been confirmed.¹⁸⁹ Volumetric MRI studies identified atrophy in the caudate nucleus,^{187–193} putamen,^{186,187,189–192} and thalamus.^{187,190,191,193} Most researchers found a large overlap in caudate volumes between patients with Huntington's disease and controls, and putamen volumes were a better group discriminator.^{188,192} In a volumetric MRI study of 15 patients with mild Huntington's disease, Harris et al¹⁹² showed that putamen atrophy (–50.1%) exceeded caudate changes (–27.7%), and volumetric measurement of the putamen was a more sensitive indicator of brain abnormalities in patients with mild Huntington's disease than measures of caudate atrophy. Measuring the caudate volumes of 13

patients who had Huntington's disease for less than 4 years and 16 patients who had Huntington's disease for more than 7 years, Aylward et al¹⁸⁹ disclosed that the volume changes were -34.1% compared with controls for those with shorter duration and -53.4% for those with longer duration. In a longitudinal MRI study of 23 patients with Huntington's disease with a mean symptom duration of 7 years, Aylward et al¹⁹⁵ demonstrated that there was (1) volume reduction over a relatively short period of time (mean imaging interval, 21 months) in the caudate (-9.5%), putamen (-6.0%), and globus pallidus (-1.8%) and (2) a greater rate of atrophy in patients with earlier symptom onset than in those with later onset. The above findings indicate that putamen atrophy occurs first and faster in Huntington's disease than in caudate atrophy, and caudate atrophy is more prominent in the late stage of the disease.^{189,192,195}

Atrophy of basal ganglia structures also appears in presymptomatic subjects who are positive for Huntington's disease gene mutation.¹⁹⁶⁻¹⁹⁸ Aylward et al¹⁹⁶ were the first group reporting volume reduction in the caudate (-30.9%), globus pallidus (-29.3%), and putamen (-25.7%) in presymptomatic at-risk subjects before Huntington's disease was clinically diagnosed. Recently, in a larger cohort of patients, Harris et al¹⁹⁸ showed that there was a dramatic reduction of putamen volume (-50%) and less caudate atrophy in gene mutation-positive subjects who were within 6 years of the estimated age of Huntington's disease onset. These data suggest that putamen volume measured with MRI is a preferable marker of pre-clinical Huntington's disease.¹⁹⁸ In addition to basal ganglia, atrophy in the frontal lobe,^{187,190,191,194} temporal lobe,^{187,190} and medial temporal lobe¹⁹³ was also noted in subjects with Huntington's disease. Evaluating the frontal lobe in 10 patients with mild and 10 patients with moderate Huntington's disease, Aylward et al¹⁹⁴ demonstrated that atrophy of the frontal lobe (-17%) was characteristic only of the late stage of Huntington's disease, and the volume reduction was mainly owing to white-matter atrophy (-28%).

A correlation between caudate atrophy and memory impairment^{186,191} or decreased cognitive scores^{188,190} has been reported in Huntington's disease. A significant correlation between putamen volumes and various neuropsychological functions was shown in several studies.^{188,190,192} Frontal atrophy was consistently found to correlate with cognitive^{190,194} or memory¹⁹² impairment in Huntington's disease.

Other than volume loss in the neostriatum, signal changes on MRI owing to iron and ferritin deposition in the brain of patients with Huntington's disease were also noted.^{169,199-201} Abnormal signal hyperintensities in the basal ganglia on T₂-weighted images were frequently identified in the rigid form of Huntington's disease^{199,201}; in contrast, abnormal signal hypointensities in the basal ganglia were more common in hyperkinetic Huntington's disease.²⁰¹ But Kido et al²⁰⁰ did not find signal abnormalities in 12 patients with Huntington's disease using high-field MRI. In a postmortem MRI study of 6 patients with Huntington's disease and 10 controls, Chen et al¹⁶⁹ disclosed that there was a tremendously large amount of iron (+200%) and ferritin (+500%) in the putamen associated with unexpected T₂ prolongation, and the increase of iron and ferritin in the globus pallidus was less severe and associated with mild T₂ shortening. In addition to iron and ferritin accumulation, the authors suggested that there were other underlying causes for signal changes in the basal ganglia of patients with Huntington's disease.¹⁶⁹

MAGNETIC RESONANCE IMAGING OF VASCULAR DEMENTIA

Cerebrovascular disease is a common cause of dementia, secondary only to AD.²⁰² Vascular dementia is increasingly diagnosed as a disease category where dementia and impaired neuropsychiatric functions are the result of cerebral ischemic insults. However, there are no universal diagnostic criteria for vascular dementia. Most studies of vascular dementia were based on one or more of the proposed diagnostic guidelines.²⁰³⁻²⁰⁶ Histopathologic data

indicated that 20% to 50% of patients clinically diagnosed with vascular dementia were found at autopsy to have coexistent AD pathology.²⁰⁷ These situations make it difficult to compare and analyze various neuroimaging results of vascular dementia in the literature. The following sections summarize the most consistent MRI findings in vascular dementia, especially vascular dementia with small, deep infarcts (lacunar infarcts) in the subcortical nuclei or white-matter pathways owing to small-vessel disease.²⁰⁸

Quantitative MRI of vascular dementia consistently identified general brain atrophy^{209,210} and loss of cortical gray matter.²¹⁰ Enlargement of the ventricular CSF spaces was always noted, either by rating scales^{211–213} or voluming methods.^{209,213} The volume of sulcal CSF spaces seemed to be similar to that of normal elderly.^{209,214} Atrophy of the hippocampus or hippocampo-amygdala complex²¹⁰ was also found in vascular dementia, either owing to coexistent AD pathology or ischemic injury.²¹⁵ General atrophy of the cerebellum²¹⁰ and shrinkage of the corpus callosum,^{209,216} which was consistent with autopsy findings,²¹⁷ have been reported in MRI studies of vascular dementia (see Table 1). Comparison of quantitative MRI between vascular dementia and AD was seldom discussed, and the results were inconclusive.^{214,218} A correlation between measurements of cerebral structures and performance of neuropsychological tests remained unclear.^{211–213}

The relationship of white-matter lesions to vascular dementia and its effects on cognitive functions have been studied extensively.^{173,175,213,218–227} Compared with normal subjects, an increased load of abnormal WMSHs on T₂-weighted images was identified consistently in vascular dementia, either by rating^{163,212,213,219–223} or quantitative measurements.^{209,224} In a neuropathologic study including 22 patients with vascular dementia and 20 with AD, Erkinjuntti et al²¹⁹ found that, in addition to infarcts, there was diffuse vacuolization of white matter, arteriosclerotic changes, widening of perivascular spaces, and myelin loss in vascular dementia, whereas white-matter changes in AD could not be related to infarction. They concluded that pathologic changes in small blood vessels were associated with white-matter changes and had a distinct role in the genesis of vascular dementia.²¹⁹ Several studies demonstrated that cortical metabolic dysfunction^{223,224} and disturbed cerebral perfusion^{223,225} correlated significantly with subcortical white-matter lesions in vascular dementia. However, the relationship of white-matter abnormalities to cerebrovascular risk factors remained undetermined: some researchers identified a positive association,^{220,228} whereas others did not.²²¹ Generally speaking, there are widespread abnormalities in both the deep and periventricular white matter of patients with vascular dementia.^{163,211,213,220,221} In a comparative MRI study of 25 patients with vascular dementia, 28 with AD, and 27 with dementia with Lewy bodies, Barber et al¹⁶³ found that the abnormalities in the deep white-matter region and basal ganglia were much more severe in vascular dementia than in AD and dementia with Lewy bodies, and the severity of periventricular lesions was similar among groups. Studying 31 patients with vascular dementia and 27 with probable AD, Schmidt²¹³ showed that patients with vascular dementia had more white-matter lesions in both the deep and periventricular regions than patients with AD. The association between white-matter lesions and severity of dementia in vascular dementia has been demonstrated in many studies.^{218,220–222} Several studies showed a correlation between the severity of lacunar infarcts and neurologic dysfunction,^{208,229} especially the number, but not the volume, of lacunes.²²⁹

Recently, the magnetization transfer ratio and diffusion MRI have been applied to evaluate WMSHs in vascular dementia.^{224,227} Using the magnetization transfer ratio as a measure of compromised white-matter integrity in a group of 15 patients with vascular dementia, Tanabe et al²²⁷ demonstrated that the magnetization transfer ratio of periventricular white matter, not that of deep white matter, was lower in patients with vascular dementia than in normal elderly, indicating that pathologic changes were more severe in the periventricular region of vascular

dementia. Applying diffusion-weighted MRI in 30 patients with vascular dementia, Choi et al.²²⁶ showed that small foci of abnormal signal intensity on diffusion images, consistent with recent infarcts, occurred commonly in vascular dementia, even in patients without a recent deterioration of clinical symptoms. The regional differences in diffusion abnormality in WMSHs between vascular dementia and AD have been evaluated by Hanyu et al.¹¹⁹ They found that the diffusion restricted perpendicular to the direction of nerve fibers was more severe in the frontal white matter in patients with vascular dementia and more severe in the parieto-occipital white matter in patients with AD.¹¹⁹ These data suggest that diffusion MRI provides the potential to examine the pathophysiology underlying vascular dementia and also to discriminate vascular dementia from AD with white-matter abnormalities.

MAGNETIC RESONANCE SPECTROSCOPY OF ALZHEIMER'S DISEASE

Based on essentially the same principle of MRI, in vivo proton MRS can determine the amount of cerebral metabolites, including *N*-acetylaspartate (NAA), choline-containing compounds (Cho), creatine-phosphocreatine (Cr), and myoinositol (MI).^{14,230} *N*-acetylaspartate is a key molecule involving the metabolism of aspartate^{231,232} and excitatory dipeptide *N*-acetylaspartylglutamate,²³³ synthesis of lipid,²³⁴ and regulation of cellular osmosis.²³² *N*-acetylaspartate is present in the neurons, neuroglial precursors, and immature oligodendrocytes and is absent in mature glial cells.²³⁴ Although the exact role of NAA in the human brain remains unknown, it has been shown that the intensity of NAA correlates with neuronal density and viability in the adult brain.²³⁵ *N*-acetylaspartate levels have also been shown to reversibly change in multiple sclerosis,^{236,237} epilepsy,²³⁸ and amyotrophic lateral sclerosis.²³⁹ These changes have been thought to reflect alterations of neuronal oxidative metabolism. *N*-acetylaspartate is regarded as a neuron marker and has been extensively studied in AD^{214, 240–262} The intensity of Cho in cerebral proton MRS has major contributions from phosphocholine and glycerophosphocholine and some from free choline, acetylcholine, and phosphatidylcholine, a major constituent of the cell membrane.¹⁴ Choline involves the synthesis of both the cell membrane and the neurotransmitter.^{14,15} Decreased cortical acetylcholine prior to the loss of cholinergic cells and increased catabolism of membrane phospholipid have been confirmed in AD.^{263,264} Phosphocreatine serves as a reserve for high-energy phosphates in the cytosol of neurons and reflects high-energy metabolism in the brain.¹⁴ Magnetic resonance spectroscopy-detectable Cr reflects the sum of phosphocreatine and free Cr. Myoinositol can be identified in the cerebral proton MRS using short echo time sequences.^{14,230} The function of MI in the human brain is not clear but may be a storage form of the inositol diphosphate messenger system.²⁶⁵ However, there is no evidence to link changes of MI with changes of inositol diphosphate. At present, MI is considered to be a tentative glial marker and to represent the gliosis severity in AD (see Table 2).^{15,265}

Basically, there are two different techniques available for acquisition of cerebral proton MRS: single-voxel spectroscopy²⁶⁶ and MRS imaging.^{267–269} These two techniques are comparable in terms of sensitivity per unit volume and unit acquisition time. Single-voxel spectroscopy detects the signal from a single region during one measurement, whereas MRS imaging, using additional phase-encoding pulses, obtains the signal from multiple regions at the same time and provides the information of spatial distribution of major cerebral metabolites. Both single-voxel^{43,241–251} and spectroscopic imaging^{214,252–257} techniques have been applied for evaluation of cerebral metabolite changes in AD. Changes of cerebral metabolites have been expressed in terms of semiquantitative ratios such as NAA/Cr, NAA/Cho, Cho/Cr, and MI/Cr^{43,214,242,243,245,246,252–255,258,270} and absolute concentrations.^{240–242, 244–246,250–252,254,257,271} Metabolite ratios are easy to calculate; however, they mix the information of different metabolites together, which sometimes reduces the ability to clarify the changes of individual metabolites. In contrast, absolute quantification has the potential to provide more specific information on each metabolite. But calculation of absolute

concentration of cerebral metabolites is a process of sophisticated analysis; the lack of a standard reference system and the absence of an exact relaxation value of each metabolite make its application more difficult.

Reduction of NAA concentration or the ratio between NAA intensity and other metabolites was consistently found in the frontal lobe,²⁵³ parietal lobe,^{242,244,245,253} temporal lobe,^{43,241,253} centrum semiovale,^{246,255,257} mesial cortex,²⁵⁷ and hippocampus²⁵² of patients with AD. Compared with elderly controls, patients with AD had an 8% to 50% decrease in NAA concentration,^{241,242,244–246,251,252,257,272} a 5% to 40% decrease in the NAA/Cr ratio,^{43,214,241,242,246,252–255,258,270} and a 4% to 43% decrease in the NAA/Cho ratio.^{43,214,246,252,254,255,258} The wide range of NAA changes was most likely owing to different patient recruitment, MRS techniques, acquisition parameters, and regions of interest. In vitro studies also confirmed a reduction of NAA concentration in the extraction of the brains of patients with AD.^{248,251,261,262} In a spectroscopic imaging study of 12 patients with AD and 17 elderly controls, Schuff et al²⁵² found that the NAA/Cr and NAA/Cho ratios were reduced in the hippocampus, in addition to the 15% to 16% decrease in NAA concentration. This study also demonstrated that the hippocampal NAA concentration, together with hippocampal volume, differentiated between patients with AD and normal controls better than either measure alone.²⁵² Schuff et al²⁵² and MacKay et al²⁵⁴ also showed that NAA losses were independent of cerebral atrophy in AD. It is most likely owing to the fact that structure changes are the result of coexistent neuron loss and gliosis, whereas NAA intensity measures changes in neuronal density and metabolic stages. Recently, studying metabolite ratios in the medial temporal lobe, which is affected early in AD, and the primary motor and sensory cortex (central region), which is affected late in the disease, Jessen et al²⁷³ found that the ratio between the NAA/Cr_{medial temporal lobe} and the NAA/Cr_{central region} was significantly reduced in AD, correlating with MMSE scores, whereas the ratio between the Cho/Cr_{medial temporal lobe} and the Cho/Cr_{central region} did not. Show a Significant difference between groups. The authors suggested that the severity of AD can be monitored by the relative reduction of NAA/Cr in the medial temporal lobe in comparison with an intraindividual unaffected central region.²⁷³ It has been shown that there was correlation of cortical NAA intensity with AD pathology, including senile plaques and neurofibrillary tangles^{248,262} and cognitive tests, such as MMSE^{241,242,248,262} and CDR²⁴⁰ scores.

The changes in occipital NAA levels are controversial. Miller et al²⁴³ and Moats et al,²⁴⁴ using single-voxel MRS and a short echo time, identified reduced NAA intensity in the occipital lobe of patients with AD. However, Tedeschi et al,²⁵³ using the spectroscopic imaging technique and a long echo time, and Kantarci et al,²⁷⁴ using the single-voxel method and a long echo time, did not find significant changes in occipital NAA levels. Since occipital lobe is not the major cortical region affected by AD, the potential NAA changes may not be large enough to be consistently detected by MRS.

In contrast with gray matter, where most MRS studies showed NAA losses in different locations of the brain of patients with AD,^{214,241,243–245,250,254,255,258,261} cerebral white matter had conflicting results of NAA changes. Many studies reported that there was reduced NAA intensity in the white matter of AD,^{214,241,243,255,256,258} less severe as compared with the NAA reductions in gray matter.^{241,243} Constans et al²⁵⁶ demonstrated a reduction of NAA intensity in WMSH in patients with AD. However, several studies did not identify significant NAA changes in the white matter in patients with AD.^{244,250,253,254,261} Since white matter is thought to be secondarily or retrogradely affected by AD pathology in gray matter, it is reasonable to identify fewer changes in NAA intensity and to have variable results in different patient groups. Most studies did not find a correlation between neuropsychiatric tests and white-matter NAA.

In vivo proton MRS studies of AD showed controversial results with regard to Cho and Cr intensities.^{214,240–246,250–258} Many studies did not find significant changes in Cho and Cr in AD, either their concentrations^{43,240,241,244,245,251} or the ratios.^{43,243} However, Jessen et al²⁷³ found a significant decrease in the Cho/Cr ratio in the medial temporal lobe of patients with AD. In contrast, using the spectroscopic imaging technique, Weiner's group^{254–256} consistently showed that there was an increase in Cho/Cr of the posterior parietal gray matter, reflecting effects owing to membrane degradation.²⁵⁵ Similarly, using single-voxel spectroscopy, Rose et al²⁴² and Kantarci et al²⁷⁴ also identified increased Cho/Cr in the parietal lobe and posterior cingulate gyrus, respectively. Furthermore, Schuff et al²⁵⁷ showed that there were increased Cho and Cr concentrations in the WMSHs of 28 patients with AD compared with 22 elderly controls. There was no correlation of Cho, Cr, or their ratio with neuropsychiatric tests.^{43,246,252,273}

Pathologically, neuron loss was associated with glial hypertrophy or gliosis in AD.^{272,275} In vivo proton MRS of AD consistently disclosed that there was increased MI, a glial marker, in the frontal lobe,^{240,241} parietal lobe,^{242,244} temporal lobe,²³⁵ and temporoparietal lobe.^{234,236} Again, changes in MI of the occipital lobe were controversial.^{244,245,274} Compared with elderly controls, the range of MI increases in AD was between 8% and 33%^{240–242, 244,245,271} and that of the MI/Cr ratio was between 11% and 58%.^{240,242,243,246,258, 274} Moats et al²⁴⁴ studied 10 patients with probable AD using a short echo time of 30 msec and identified an increase in MI intensity in both the gray matter (+19%) and white matter (+17%) of the parieto-occipital lobe. Owing to the coexistence of decreased NAA and increased MI in AD, the ratio between NAA and MI is expected to improve the classification between AD and normal controls. Using NAA/MI as the classification parameter, Parnetti et al²⁴¹ could correctly discriminate 13 patients with AD from 7 elderly controls. It has been shown that MI intensity correlated with CDR scores²⁴⁰ and the NAA/MI ratio with MMSE scores²⁴² in AD. Recently, studying metabolite ratios in 21 patients with mild cognitive impairment, 21 patients with probable AD, and 63 elderly controls, Kantarci et al²⁷⁴ demonstrated that patients with AD had significantly lower NAA/Cr in the left superior temporal lobe and higher Cho/Cr and MI/Cr in the posterior cingulate gyrus compared with controls, whereas patients with mild cognitive impairment only had significantly elevated MI/Cr in the posterior cingulate gyrus compared with controls. These findings suggest that an increase in MI/Cr is an initial MRS change in AD progression, and decreased NAA/Cr and increased Cho/Cr occur later in the disease course.²⁷⁴ Magnetic resonance spectroscopy of age-associated memory impairment has been studied by Parnetti et al,⁴³ who found that both NAA decreases and MI increases occurred in age-associated memory impairment but was less severe than the changes in AD.

There is a paucity of longitudinal proton MRS studies related to AD. Rose et al²⁴² reported that cerebral NAA was stable in a group of 36 elderly controls during a follow-up period of 260 days, implying that proton MRS could be used to monitor the progress of AD. Doraiswamy et al²⁷⁶ studied metabolite ratios in 12 patients with probable AD during 1 year follow-up and found that there was a positive correlation between baseline NAA/Cr and MMSE scores and an inverse correlation between baseline MI/NAA and MMSE scores. Satlin et al²⁷⁷ found that Cho decreased in 10 patients with AD after treatment with xanomeline, an MI selective cholinergic agonist, raising the possibility of monitoring therapeutic response with proton MRS in AD.

Proton MRS has often been used because proton has high sensitivity and proton MRS can be performed with conventional head coils in clinical MR scanners. However, phosphorus MRS has also been applied for AD research owing to its ability to provide additional information on the cellular energy state and brain lipids.^{14,16} The following metabolites can be detected using in vivo phosphorus MRS: phosphomonoesters (PMEs); inorganic orthophosphate (Pi); phosphodiesteres (PDEs); phosphocreatine (PCr); α , β , and γ phosphates of nucleotide

adenosine triphosphate (ATP); and α and β phosphates of nucleotide adenosine diphosphates (ADP).^{14,16} Changes of PME (soluble membrane precursors) and PDE (membrane degradation products) reflect the biophysical states of membrane phospholipid, whereas Pi, PCr, and ATP are key metabolites involving energy metabolism.¹⁶ Most in vivo and in vitro phosphorus MRS studies showed that PME and PDE were elevated in AD,^{259,278–286} implying accelerated membrane turnover. Furthermore, in a comparative study using phosphorus MRS and histopathologic examination, Pettegrew et al²⁷⁹ showed that PME intensity correlated inversely with the density of senile plaques in AD. However, other studies did not find significant changes in these membrane phospholipids.^{287–291} Most phosphorus MRS studies did not find changes in ATP, Pi, or PCr,^{282,287–289} but decreased PCr/Pi was reported in several.^{284,290,292} Smith et al²⁹⁰ found that the PCr/Pi ratio was reduced in the frontal lobes, correlating with CDR scores in a group of 17 patients with AD. Similarly, in an in vivo phosphorus MRS study of the frontal and temporoparietal regions of 17 patients with probable AD, Brown et al²⁹² showed that there was a significant decrease in PCr/Pi compared with 17 elderly controls and 10 patients with multiple subcortical infarct dementia. Generally, phosphorus MRS is not practical for the clinical study of AD owing to the disadvantages of limited availability, low magnetic sensitivity, and poor spatial resolution.

MAGNETIC RESONANCE SPECTROSCOPY OF OTHER NEURODEGENERATIVE DEMENTIAS

Magnetic resonance spectroscopy has been used to study neurodegenerative dementias other than AD, including frontotemporal dementia,²⁴⁰ Parkinson's disease,^{293–311} Huntington's disease,^{310,312–317} and age-associated memory impairment,⁴³ a disorder of the elderly presenting with selective memory deficits in the absence of other intellectual difficulties.

MAGNETIC RESONANCE SPECTROSCOPY OF FRONTOTEMPORAL DEMENTIA

Performing proton MRS of the midfrontal and temporoparietal gray matter in 14 patients with frontotemporal dementia, 12 with probable AD, and 11 control subjects, Ernst et al²⁴⁰ found that there was a 28% decrease in NAA concentration, a 16% decrease in glutamine plus glutamate, and a 19% increase in MI concentration in the frontal lobe of patients with frontotemporal dementia compared with elderly controls, indicating neuronal loss and gliosis. Furthermore, three patients with frontotemporal dementia had a lactate peak in their frontal spectra.²³⁹ The authors also demonstrated that the magnitude of MI elevation was larger in frontotemporal dementia (+16%) than in AD (+8%), and 92% of patients with frontotemporal dementia were correctly differentiated from AD using MRS data alone (see Table 2).²³⁹

MAGNETIC RESONANCE SPECTROSCOPY OF PARKINSON'S DISEASE

The results of proton MRS^{294–304,308–311} or phosphorus MRS^{305,310} in patients with Parkinson's disease were controversial. Many researchers disclosed a significant reduction of ratios between NAA and other metabolites in the temporoparietal cortex,^{294,297} substantia nigra and basal ganglia,²⁹⁵ striatum,^{296–298} or occipital lobe.²⁹⁹ In non-demented patients with Parkinson's disease, for example, Hu et al²⁹⁴ demonstrated that there was a significant temporoparietal cortex reduction in NAA/Cr ratios using multivoxel proton MRS. Studying single-voxel proton MRS in 15 patients with Parkinson's disease with unilateral symptoms, Choe et al²⁹⁵ found a reduced NAA/Cr ratio in the substantia nigra and lentiform nucleus ipsilateral to the symptomatic side as compared with the contralateral side. In a multicenter MRS study of 151 patients with Parkinson's disease and 97 age-matched controls, Holshouser et al²⁹⁶ showed that there was a significant reduction in the striatal NAA/Cho ratio in patients not being treated. Similarly, Ellis et al³⁰⁷ found a significant reduction in putaminal NAA/

Cho ratios contralateral to the most affected side in 9 drug-naïve patients with idiopathic Parkinson's disease but not the 7 levodopa-treated patients. However, an absence of significant differences in metabolite profiles between patients with Parkinson's disease and elderly normals was also frequently reported, either in terms of metabolite ratios^{299–303,308,309} or concentrations.^{304,310,311} Interestingly, Bowen et al,²⁹⁹ using single-voxel proton MRS, demonstrated increased occipital lactate/NAA ratio in 14 patients with Parkinson's disease, with the greatest increase (threefold) in a subgroup of 4 patients with dementia. This finding supported the hypothesis that Parkinson's disease is a systemic disease characterized by an impairment of oxidative energy metabolism.²⁹⁹ Furthermore, performing a phosphorus MRS and fluorodeoxyglucose-positron emission tomography (FDG-PET) study in 10 nondemented patients with Parkinson's disease, Hu et al³⁰⁵ disclosed that there was a significantly increased Pi/ β -ATP ratio and reduced glucose metabolism in bilateral temporoparietal cortices, suggesting that both glycolytic and oxidative pathways were impaired. However, Hoang et al³¹⁰ did not find abnormalities owing to energy failure using quantitative phosphorus MRS in idiopathic Parkinson's disease. Published MRS findings in Parkinson's disease were extremely variable, suggesting that there is no dramatic difference from normal,³¹⁰ or proton MRS in the current state may not be sensitive enough to provide markers of neurodegeneration in idiopathic Parkinson's disease.³¹¹

MAGNETIC RESONANCE SPECTROGRAPHY OF HUNTINGTON'S DISEASE

Proton MRS of Huntington's disease found reduced NAA and increased lactate and glutamine-glutamate in the striatum, occipital cortex, and frontal cortex.^{312–317} Jenkins et al³¹³ demonstrated that lactate concentrations were increased in the occipital cortex and NAA concentrations were decreased and Cho and lactate concentrations were increased in the basal ganglia in a group of 18 patients with Huntington's disease compared with 12 normal controls. Furthermore, Koroshetz et al³¹⁴ demonstrated that medical treatment resulted in decreased cortical lactate in 18 patients with Huntington's disease, which reversed following withdrawal of the therapy. All of these findings support the hypothesis that disturbed cerebral energy metabolism contributes to the pathogenesis of Huntington's disease. However, studying quantitative proton-decoupled phosphorus MRS and proton MRS in 15 patients with DNA-proven, symptomatic Huntington's disease, Hoang et al³¹⁰ found no lactate and no change in the concentrations of ATP, PCr, and Cr in the gray and white matter compared with 20 age-matched controls; only a reduced Cr and an increased MI and glucose were found in the basal ganglia of patients with Huntington's disease. A correlation of duration of symptoms with reduced NAA or lactate concentrations³¹⁵ has been reported.

Another important metabolite change was elevated glutamine-glutamate in the striatum of patients with Huntington's disease, which has been demonstrated in several small cohort studies.^{312,316,317} For example, Taylor-Robinson et al,³¹⁷ using single-voxel proton MRS, demonstrated a significant elevation of glutamine-glutamate/Cr ratio in the striatum but not in the temporo-occipital cortex of 5 patients with early Huntington's disease, whereas the asymptomatic gene carrier had no significant change as compared with controls.³¹⁷ These findings have been evoked to support the glutamate excitotoxic theory of neuronal degeneration in Huntington's disease.^{312,317} However, the glutamate signal observed by MRS is almost certainly from intracellular glutamate. Extracellular glutamate, which exerts neurotoxicity, is probably present in too low a concentration to be detected by MRS.

MAGNETIC RESONANCE SPECTROSCOPY OF VASCULAR DEMENTIA

In addition to neurodegenerative dementias, MRS studies in patients with vascular dementia have been reported recently.^{214,247,256,318–320} Most studies had a small number of subjects but consistently identified a reduced NAA/Cr or NAA/Cho ratio in patients with vascular

dementia compared with controls and regional metabolite differences between vascular dementia and AD (see Table 2). Studying 8 patients with vascular dementia, 9 with AD, and 11 normal subjects with spectroscopic imaging and a long echo time of 272 msec, Mackay et al²¹⁴ showed that patients with vascular dementia had significantly lower NAA/Cr in the frontal white matter and significantly lower NAA/Cho and higher Cho/Cr in the parietal gray matter than normal subjects, and patients with AD had even lower NAA/Cho in the parietal lobe than those with vascular dementia. These findings suggest that there was a regional difference in disease distribution between vascular dementia and AD: more involvement in the frontal lobe of vascular dementia and more in the parietal region of AD.²¹⁴ In a single-voxel proton MRS study of 8 patients with vascular dementia and 10 with AD, Kattapong et al²⁴⁷ found that patients with vascular dementia had significantly lower NAA/Cr and NAA/Cho ratios in the subcortical white matter when compared with patients with AD, implying more severe axonal injury in the subcortical region of vascular dementia. Performing T₂-weighted MRI and spectroscopic imaging on 8 patients with vascular dementia and 11 with AD, Constans et al²⁵⁶ found that patients with vascular dementia had significantly higher Cho and lower Cr levels in WMSHs than in normal-appearing white matter, whereas patients with AD had reduced NAA and elevated Cr levels in the regions of WMSH. The authors concluded that regional metabolite variations and the presence of WMSHs are important covariates that must be considered in the analysis of MRS data.²⁵⁶

Using single-voxel proton MRS to study cerebral biochemicals in 12 patients with advanced cerebrovascular disease and 5 subjects without MRI evidence of cerebrovascular disease, Kario et al³¹⁸ identified a significant reduction of the NAA/Cr ratio in the deep white-matter area of patients with advanced cerebrovascular disease. Furthermore, two patients with vascular dementia in this study showed clinical improvement with marked increases in the NAA/Cr ratio and MMSE scores after 1-week treatment with a potent selective thrombin inhibitor.³¹⁸ Changes in cerebral metabolites before and after treatment with fasudil hydrochloride, an intracellular calcium antagonist, have been evaluated by Kamei et al using phosphorus MRS.³²⁰ They found reduced PME and PDE intensities and elevated ATP intensities before treatment, and these changes disappeared after treatment in 2 patients with vascular dementia.³²⁰ These findings imply that MRS may be helpful in monitoring the therapeutic effects in vascular dementia; however, comprehensive studies with a large cohort of subjects are necessary to validate its clinical usefulness.

CONCLUSION

In addition to the anatomic information and volumetric data obtained by in vivo MRI, advanced MRI and MRS techniques have the ability to measure specific changes in tissue characteristics of demented brains, such as T₂ relaxation, water diffusion, blood volume, blood flow, and metabolite contents. Furthermore, comparative studies using histopathologic examinations or other neuroimaging modalities, such as SPECT and PET, provided the pathophysiologic basis of structural and biochemical changes observed on MRI and MRS, which, in turn, helps to interpret the neuroimaging data of individual subjects. Many MRI and MRS studies showed promising results regarding discrimination between different dementias, detection of demented patients in the early stage or in the presymptomatic stage, follow-up of disease progression, and evaluation of cerebral condition before and after treatment. Taken together, recent advancement in MRI and MRS and extensive application of these techniques in the field of dementia research certainly increase our knowledge of dementia diseases and hopefully improve the management of demented patients.

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Table 1
Summary of Main Magnetic Resonance Imaging Observations across Diagnostic Categories

	AD	FTD	VD	IPD	DLB	HD
Gray matter	↓ (Frontal, temporal, parietal)	↓ (Asymmetry in frontal, temporal)	↓ (Total)			↓ (Frontal, late stage)
White matter	↓ or ↑		↑ (>AD)			
Ventricular CSF	↑ or –					
Sulcal CSF	↓ (Diffuse)	↓ (< AD, mainly in anterior part)	↓ (<AD)	↓ or –	↓ (<AD, = VD)	
Hippocampus		↓ (=AD)				
Entorhinal cortex	↓					
Amygdala	↓				↓ (<AD)	
Corpus callosum	↓ (Total area)	↓ (Total area, mainly in anterior part)	↓ (Total area)			
White-matter T ₂ hyper intensities	↑	↑ (> AD in frontal)	↑ (>AD and DLB in deep white matter)		↑ (= AD)	
Cerebellum			↓	↓ or –		
Substantia nigra				↓ or – (T ₂ hypointensity)		
Putamen				↓ or –		↓ (Early stage)
Caudate nucleus				↓ or –		↓ (& Last; stage)

AD = Alzheimer's disease; FTD = frontotemporal dementia; VD = vascular dementia; IPD = idiopathic Parkinson's disease; DLB = dementia with Lewy bodies; HD = Huntington's disease; ↓, ↑, or – = decreases, increases, or no change in the volume when compared with controls; <, >, or = = less severe, more severe, or similar when compared with specific dementia; CSF = cerebrospinal fluid.

Table 2
Summary of Main Magnetic Resonance Spectroscopy Findings across Diagnostic Categories

	AD	FTD	VD	IPD	HD
<i>N</i> -acetylaspartate					
Hippocampus	↓ (Independent of atrophy)				
Gray matter	↓ (Early in temporal, late in frontoparietal)	↓ (Frontal)	↓ (Parietal, < AD)	↓ or –	
White matter	↓ or –		↓ (Frontal)		
Choline	↑ or –		↑ (Parietal, white-matter T ₂ -weighted hyperintensities)		
Myoinositol	↑ (Temporal, frontal, parietal; earlier than NAA changes)	↑ (Frontal, > AD)			
Glutamine-glutamate		↓ (Frontal)			↑ (Striatum)
Lactate					↑ (Frontal, occipital, basal ganglia)

AD = Alzheimer's disease; FTD = frontotemporal dementia; VD = vascular dementia; IPD = idiopathic Parkinson's disease; HD = Huntington's disease; ↓, ↑, or – = decreases, increases, or no change in the volume when compared with controls; <, >, or = less severe, more severe, or similar when compared with specific dementia, NAA = *N*-acetylaspartate.