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Index terms:
Alzheimer disease, 13.83
Brain, CT, 13.12111
Brain, function
Brain, MR, 13.121411, 13.121412, 13.121416, 13.12144, 13.12145
Brain, radionuclide studies, 13.12162, 13.12163
State of the Art

Published online before print
10.1148/radiol.2262011600
Radiology 2003; 226:315–336

Abbreviations:
AD = Alzheimer disease
FDG = fluorodeoxyglucose
MCI = mild cognitive impairment
MMSE = Mini-Mental State Examination
NAA = *N*-acetylaspartate

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Neuroimaging and Early Diagnosis of Alzheimer Disease: A Look to the Future[1]

Alzheimer disease (AD), a progressive neurodegenerative disorder, is the most common cause of dementia in the elderly. Current consensus statements have emphasized the need for early recognition and the fact that a diagnosis of AD can be made with high accuracy by using clinical, neuropsychologic, and imaging assessments. Magnetic resonance (MR) or computed tomographic (CT) imaging is recommended for the routine evaluation of AD. Coronal MR images can be useful to document or quantify atrophy of the hippocampus and entorhinal cortex, both of which occur early in the disease process. Both volumetric and subtraction MR techniques can be used to quantify and monitor dementia progression and rates of regional atrophy. MR measures are also increasingly being used to monitor treatment effects in clinical trials of cognitive enhancers and antidementia agents. Positron emission tomography (PET) and single photon emission CT offer value in the differential diagnosis of AD from other cortical and subcortical dementias and may also offer prognostic value. In addition, PET studies have demonstrated that subtle abnormalities may be apparent in the prodromal stages of AD and in subjects who carry susceptibility genes. PET ligands are in late-stage development for demonstration of amyloid plaques, and human studies have already begun. Functional MR–based memory challenge tests are in development as well.

Alzheimer disease (AD) is a progressive neurodegenerative disorder associated with disruption of neuronal function and gradual deterioration in cognition, function, and behavior (1). It is the most common cause of dementia in the elderly and affects approximately 2–4 million individuals in the United States and more than 30 million worldwide. Age is a strong risk factor, with the disease affecting approximately 8% of individuals over the age of 65 years and 30% over the age of 85 years in developed countries. The progression of AD is gradual, and the average patient lives 8–10 years after onset of symptoms. Thus, with the growth of the older population in developed nations, the prevalence of AD is expected to triple over the next 50 years (2). Female-to-male prevalence is 70%, likely related to increased life expectancy in women. The annual cost of the disease in the United States alone, including medical, long-term, and home care, as well as loss in productivity, is currently estimated at $100 billion (3). Not only is the financial burden substantial, but the psychologic and emotional burden on patients and their families is even greater.

With the recent availability of several effective pharmaceutical agents for treatment of AD symptoms, along with several new agents undergoing clinical trials, we are entering a new age in the treatment of AD. Current consensus statements have emphasized the need for early recognition; thus, there is an urgent need to develop sensitive markers that may serve as adjuncts to current clinical and neuropsychologic tests to facilitate detection and/or monitoring of early brain changes suggestive of AD. Such markers may also facilitate early-intervention studies to prevent or slow disease progression.

Conventional structural neuroimaging, such as computed tomography (CT) or magnetic resonance (MR), has long played a supportive role in the diagnosis of memory disorders and is recommended for the routine evaluation of AD. However, because structural changes may not be detected at visual inspection until late in the course of the disease, more contemporary structural imaging techniques, such as serial volumetric imaging and voxel compression subtraction, have emphasized a quantitative approach capable of

aiding in detection of subtle changes not readily apparent on routine images obtained at a single time point. Likewise, functional imaging modalities that demonstrate physiologic changes in the brain, including positron emission tomography (PET), single photon emission CT (SPECT), and functional MR imaging, also have the potential to enable identification of more subtle pathologic changes earlier during the disease course and, therefore, may have equal or greater potential in comparison with structural imaging modalities such as CT and conventional MR imaging.

This article will address the evolving role of contemporary neuroimaging in the evaluation of memory disorders, particularly AD. The intent is to focus primarily on AD; therefore, discussion of other causes of dementia is presented, in less detail, for the purpose of differential diagnosis. We will begin by briefly describing the current understanding of the neuropathology and genetics of AD, because these will have a direct bearing on diagnosis and treatment. Second, we will discuss pathologic and clinical diagnosis of memory disorders, followed by a description of the current role of structural neuroimaging evaluation. Third, we will give the reader perspective on the potential role of functional imaging in the broader scheme of clinical diagnosis and conventional imaging. Last, we will address what future steps are required for the implementation of advanced imaging techniques as useful diagnostic tools for work-up in the patient with dementia.

PATHOLOGY AND ETIOLOGY

Over the past 2 decades, rapid advances have occurred in our molecular genetic and cell biologic understanding of the pathogenesis of AD. Pathologically, AD is characterized by damage to the large cortical neurons subserving cognition, initially in the temporal lobes and later in the remaining neocortex and association areas. Damage is believed to occur owing to mechanisms outside the neuron, as well as inside the neuron, and is characterized by the appearance of extracellular senile (amyloid) plaques and intracellular neurofibrillary tangles (4) (Fig 1). Much work over the past 2 decades has focused on these two pathologic components of the disease, with application of molecular genetic, biochemical, and morphologic techniques to study them in great detail (5).

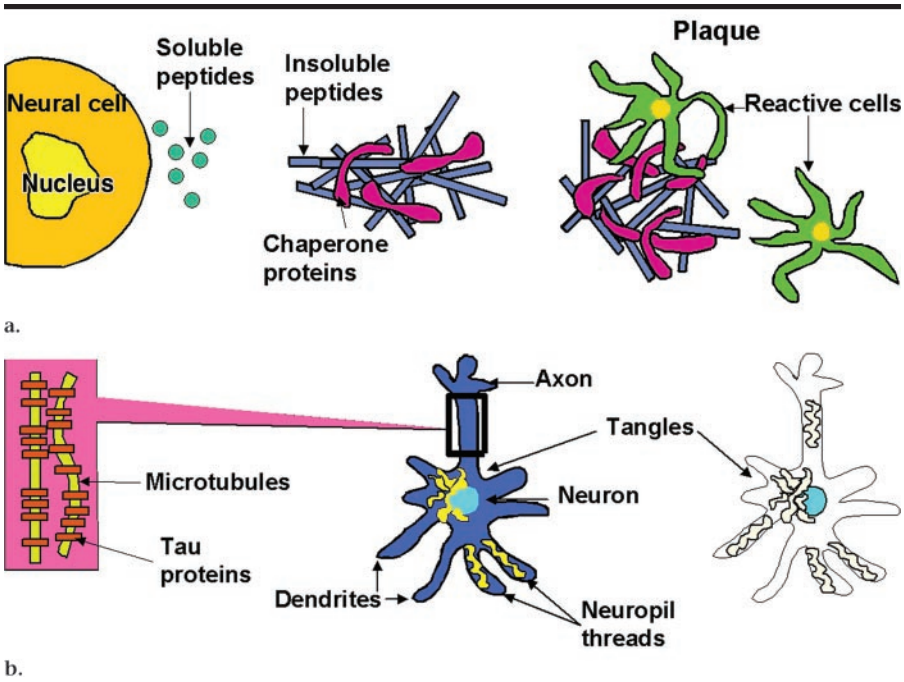


Figure 1. Two theories of how damage occurs in AD. **(a)** From outside the cell, amyloid β peptides secreted by brain cells are normally soluble, and any excess is cleared away. When these peptides become insoluble, however, they collect in the space between cells. Amyloid fibrils are "herded" together by chaperone proteins. The large plaques that form then damage brain cells and attract reactive cells, microglia and astrocytes, which cause further damage. **(b)** From inside the cell, tau proteins, which normally stabilize microtubules in brain cells, undergo abnormal chemical changes and assemble into spirals called paired helical filaments, thus creating tangles that disrupt cell functions and lead to cell death. (Images courtesy of Dr John Trojanowski and Dr Virginia M. Y. Lee, University of Pennsylvania Medical Center, Philadelphia.)

Senile Plaques

All patients with AD develop neuritic plaques, which are extracellular aggregations of amyloid protein intimately associated with dystrophic axons and dendrites (neurites), activated microglia, and reactive astrocytes. Aggregations of amyloid protein that lack altered neurites and glia are known as diffuse plaques and may be found in normal aging, as well as in degenerative diseases other than AD. The primary component of these plaques is the amyloid β protein. This protein is characteristic of AD and structurally distinct from the amyloid-forming proteins found in systemic amyloidosis.

Release of amyloid β protein results from abnormal cleavage of the amyloid precursor protein, a glycoprotein found in high concentrations in the cell membrane of virtually all mammalian cells but in especially high concentrations in neuronal cell membranes. The enzymes responsible for normal and abnormal cleavage of amyloid precursor protein (α, β, γ secretases) have been described and targeted for drug therapy. Amyloid precursor protein is normally secreted by both brain and nonbrain cells into extracellular fluids throughout life. Increased production of amyloid β protein leads to precipitation, aggregation, and progressive deposition in the form of plaques. Plaque buildup is thought to incite an inflammatory and/or oxidative response, leading to progressive disruption of neuronal function and injury in the hippocampal complex and cerebral cortex (6).

Recent evidence suggests that genetic alterations underlying familial AD result in increased production of amyloid β protein (Table 1). Mutations in the gene for amyloid precursor protein, leading to abnormal cleavage, are located on chromosome 21 and are present in patients with the rare early-onset familial form of the disease. Cloning of these mutations has lead to increased production of amyloid β protein in cell cultures, and plasma levels of amyloid β protein are elevated in some mutation carriers, even presymptomatically. Mutations of the presenilin 1, or *PS-1,* and presenilin 2, or *PS-2,* genes, on chromosomes 1 and 14 respectively, are also associated with the early-onset familial form of AD. Moreover, postmortem studies in patients with tri-

TABLE 1
Genetic Factors Predisposing to AD: Relationship to Amyloid-β Phenotype

Chromosome	Gene Defect	Age of Onset (y)	Amyloid-β Phenotype
21	*β APP* mutations	50	Production of total amyloid-β peptides or of amyloid-β 42 peptides
19	Apolipoprotein ϵ4 polymorphism	≥60	Density of amyloid-β plaques and vascular deposits
14	*PS-1* mutations	40s and 50s	Production of amyloid-β 42 peptides
1	*PS-2* mutations	50s	Production of amyloid-β 42 peptides

Note.—Adapted, with permission, from reference 5.

somy 21 (Down syndrome) and in those who carry susceptibility genes for AD have shown that amyloid β protein accumulation in the cortex is an early invariant event in AD pathology, sometimes occurring decades before symptoms become apparent (5). Given this evidence, current thinking suggests that AD may represent not a single disease entity but rather a syndrome resulting from different genetic determinants that lead to a common phenotype with amyloid deposition and neuronal degeneration in specific brain regions (6).

Neurofibrillary Tangles

Neurofibrillary tangles consist of intraneuronal bundles of paired helical filaments composed of an abnormal microtubule-associated protein known as tau. Virtually all brains of AD patients contain neurofibrillary tangles. Unlike the gene for amyloid precursor protein, however, there is no evidence of defects in the gene encoding for tau in patients with familial forms of AD. In fact, neurofibrillary tangles, consisting of similar forms of modified tau protein, are detected in other etiologically distinct diseases such as subacute sclerosing panencephalitis, Hallervorden-Spatz disease, Parkinson dementia complex, and dementia pugilistica. Despite the lack of a direct etiologic connection, the results of numerous studies have demonstrated elevated levels of tau protein in the cerebrospinal fluid of patients with AD, compared with those levels in age-matched control subjects.

At present, the molecular and etiologic relationship between plaques and tangles is not fully understood. The bulk of current data suggests that these two lesions might be formed independently of each other. In fact, the distribution and density of both diffuse and neuritic senile plaques have not been consistently shown to correlate with the presence or severity of dementia (7), whereas the total density of neurofibrillary tangles does (8,9). Indeed, some elderly individuals without dementia have as much plaque deposition as have those with severe dementia. However, the neuritic variety of plaque associated with dystrophic axons and dendrites and reactive glial cells appears to be a more specific feature of AD than is the neurofibrillary tangle. Furthermore, results of a number of in vitro and in vivo studies have shown amyloid β protein to be directly toxic to neurons, leading to phosphorylation of tau protein, the principal component of neurofibrillary tangles (10).

Pathologic Progression

The insidious onset and gradual progression of symptoms in patients with AD are thought to parallel the progression of AD-related brain destruction from entorhinal cortex to hippocampus to neocortex (11). In typical cases, there initially is isolated impairment of learning and short-term memory, without alteration in other domains of cognition or consciousness. This is followed by changes in long-term memory, personality, orientation, and executive function. After cognitive losses, there are behavioral problems (eg, hallucinations, delusions). Finally, there is deterioration of language, visuospatial skills, and, eventually, motor function, which leads to loss of activities of daily living.

Three stages in the gradual evolution of plaque deposition have been described (11). Stage A is characterized by deposition in the basal temporal neocortex, or entorhinal cortex. There then is extension through the hippocampal formation in stage B, eventually leading to deposits in virtually all cortical areas, including the highly myelinated primary areas of the neocortex in stage C.

There are reported to be six stages in the evolution of neurofibrillary tangles (11). Stage I is defined by the appearance of neurofibrillary tangle–bearing neurons in the transentorhinal region, with progression to the entorhinal region and hippocampal formation in stage II. These stages represent the presymptomatic phase of the disease. Further progression leads to stages III and IV, which are characterized by severe involvement of the entorhinal region, amygdala, and hippocampal formation. This involvement leads to interruption of the limbic loop, which is responsible for data transfer back and forth between the neocortex and the hippocampal formation. In addition, there is also involvement of many subcortical nuclei with diffuse projections to the cortex, among them the cholinergic system of the basal forebrain, including the nucleus basalis of Meynert. Patients with disease at these stages may present with symptoms of mild cognitive impairment (MCI) or prodromal AD, although symptoms may be masked by a high cognitive-reserve capacity. In stage V, there is extension to all major regions of the cerebral cortex, from association areas into primary areas. In stage VI, even the primary sensory areas are severely involved, although the motor area continues to be relatively spared. Stages V and VI are generally characterized by severe dementia.

PATHOLOGIC DIAGNOSIS

AD is characterized pathologically by reductions in the number of large cortical neurons in temporal and frontal cortex and by the appearance of senile (amyloid) plaques and neurofibrillary tangles (4). In living subjects, only a provisional diagnosis of possible or probable AD may be made, by using clinical, laboratory, and imaging evidence. Definitive diagnosis of AD is made by means of pathologic examination of tissue derived from autopsy or brain biopsy. For this reason, criteria have been created to standardize the pathologic diagnosis.

In the past, the two most extensively used pathologic criteria have been the National Institute on Aging consensus criteria (1) and the Consortium to Establish a Registry for Alzheimer's Disease, or CERAD, criteria (12). The National Institute on Aging criteria are based on subject age and clinical history, taking into account the number of senile plaques per high-power microscopy field and the presence of neurofibrillary tangles in specific regions of the neocortex, hippocampus, and subcortical gray matter. The

CERAD criteria use only the presence and density of neuritic senile plaques in the neocortex for establishment of the diagnosis of AD. The density is classified as "sparse," "moderate," or "severe" and is then combined with the age of the subject to yield an age-related plaque score. The plaque score is integrated with clinical information for the diagnosis of "definite," "probable," or "possible" AD.

More recently, the National Institute on Aging–Reagan Institute criteria, based on the number of both plaques and tangles in the neocortex and the limbic and paralimbic regions, were introduced (13,14). These criteria essentially combined the CERAD criteria, which are based on plaque frequency, and the staging criteria of Braak and Braak (15), which are based on neurofibrillary tangle distribution and frequency. The possibility of coexisting pathologic conditions other than AD is also recognized.

Unfortunately, because these criteria place varying degrees of dependence on the number and type of senile plaques and neurofibrillary tangles in various sections of the brain, as well as on the presence of a clinical history of dementia, the same diagnosis may not be rendered at autopsy in a given patient (16). In a recent study (17), however, a good correlation was shown between the National Institute on Aging–Reagan Institute criteria and the previous two criteria. The National Institute on Aging–Reagan Institute criteria offer the possibility of better diagnostic refinement because of the recognition that dementia in the elderly may arise from more than one disorder. In dementia with Lewy bodies, for example, there may be considerable clinical and pathologic overlap with AD.

CLINICAL DIAGNOSIS

The accuracy of a clinical diagnosis of AD depends on the stage of disease and the clinical setting. In an academic memory-disorders clinic setting, the diagnostic accuracy can exceed 90% (18–20), while accuracy may be substantially lower in the general community setting where there is less consistency and reliance on established diagnostic criteria. In this section, we will briefly review the clinical criteria for diagnosing AD and other common dementias of old age. We will also present current treatment options.

Diagnostic Criteria

AD.—Clinical criteria used for a provisional diagnosis consist of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria (21) (Fig 2) for possible or probable AD or the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria (22) for dementia of the Alzheimer type. Probable AD can be categorized as mild (early), moderate (middle), or severe (late) dementia. Clinical work-up includes a detailed history from the patient and/or an informant, a general physical and mental status examination, neurologic assess-

I. Criteria for the clinical diagnosis of PROBABLE Alzheimer disease
- dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed with neuropsychologic tests
- deficits in two or more areas of cognition
- progressive worsening of memory and other cognitive functions
- no disturbance of consciousness
- onset between ages 40 and 90, most often after age 65
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

II. The diagnosis of PROBABLE Alzheimer disease is supported by:
- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perceptions (agnosia)
- impaired activities of daily living and altered patterns of behavior
- family history of similar disorders, particularly if confirmed neuropathologically; and laboratory results of:
  - — normal lumbar puncture as evaluated by standard techniques
  - — normal pattern or non-specific changes in EEG, such as increased slow-wave activity
  - — evidence of cerebral atrophy on CT with progression documented with serial observation

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer disease, after exclusion of causes of dementia other than Alzheimer disease, include:
- plateaus in the course of progression of the illness
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder
- seizures in advanced disease
- CT normal for age

IV. Features that make the diagnosis of PROBABLE Alzheimer disease uncertain or unlikely include:
- sudden, apoplectic onset
- focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness
- seizures or gait disturbances at the onset or very early in the course of the illness

Figure 2. NINCDS/ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association) criteria (21) for probable AD. *EEG* = electroencephalogram.

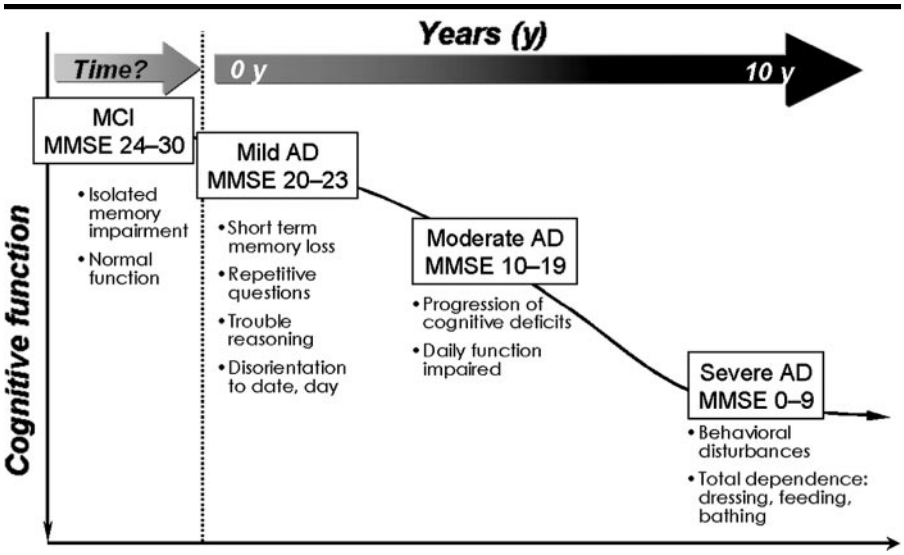


Figure 3. Over the clinical course of AD, patients will demonstrate progressive declines in functional ability that correlate with MMSE scores. In the preclinical phase, also called MCI, patients with MMSE score greater than 23 will demonstrate minimal impairment—generally, mild memory loss—while functioning normally and independently. The typical length of the MCI phase remains undetermined. Onset of mild AD is indicated by MMSE score of 20–23; these patients exhibit gradual alterations in cognition, function, behavior, and mood. Forgetfulness and repetitive questions are hallmarks; daily function begins to become impaired. In moderate AD (MMSE score of 10–19), cognitive impairments progressively deteriorate and now include short-term memory loss (eg, difficulty in recalling recent conversations, forgetting to keep appointments, inability to remember recent events). Patients begin to have trouble with verbal fluency; specifically, increasing difficulty in remembering the correct word. Severe stage is reached when MMSE scores decline to less than 10. At this point, patients exhibit behavioral changes that include agitation, delusion, aggression, wandering, and hallucination. Sleep patterns are altered, and the patient eventually becomes completely dependent on others for dressing, feeding, and bathing. The clinical progression from onset of mild AD to onset of severe AD, although variable, is about 10 years.

ment, and objective tests such as the Mini-Mental State Examination (MMSE) to help assess cognitive dysfunction. In addition, tests are also available to quantify activities of daily living, behavioral dysfunction, and caregiver stress. Staging instruments such as the Clinical Dementia Rating Scale and the Global Deterioration Scale are frequently used in academic settings.

Laboratory evaluation is performed to exclude medical diseases that may cause dementia (eg, hypothyroidism, vitamin B_{12} deficiency). Cerebrospinal fluid assays of amyloid β-42 and tau protein have been shown to have high sensitivity (~80%) and moderate specificity for the diagnosis of AD but are not widely used in routine practice. Other tests such as plasma assays of amyloid, cerebrospinal assays of neurotransmitter metabolites, and urine-based assays of neural thread protein have not been widely accepted as providing diagnostic value. Genetic testing is discussed elsewhere in this article.

Although variants with atypical manifestations have been described, the diagnosis of AD requires memory impairment as the most prominent manifestation, with a deficit in one or more cognitive domains, including language, orientation, or executive functioning (ie, planning, organizing, abstracting). The course of the disease is variable but is characterized by gradual onset with progressive decline in memory, with initial sparing of sensory and motor function. The memory impairment may initially manifest itself as a deficit in learning or recall of new information, followed by loss of remote memory. Behavioral and psychologic disturbances (depression, delusions, wandering, paranoia, anxiety, sleep changes) also develop in virtually 100% of patients over the course of the disease (Fig 3). Differentiation from dementia associated with depression (pseudodementia) may be difficult.

AD is characterized by cholinergic deficits. There are currently three cholinesterase inhibitors in wide use as treatments of choice. Such treatments improve or stabilize cognition, and some evidence suggests that early initiation of therapy may delay institutionalization (23). Many patients are also treated "off label" with vitamin E, ginkgo biloba, and psychotropic drugs.

Differential diagnosis with other forms of dementia.—In developed countries, AD accounts for approximately 50%–70% of all cases of dementia in the elderly. Diagnostic criteria require that AD be distinguished from other causes of dementia such as vascular dementia, frontotemporal dementia, dementia with Lewy bodies, normal-pressure hydrocephalus, depression-related cognitive impairment, and intracranial mass.

Vascular dementia, which accounts for about 15% of all dementias in the United States, can be distinguished from AD by its more sudden onset and association with vascular risk factors. Vascular dementia is characterized by a stepwise course with periods of stability followed by sudden decline in cognitive function. Patients may experience focal neurologic deficits after a sudden decline, such as slurred speech or sensorimotor dysfunction. Clinical criteria for diagnosis of probable vascular dementia were created in 1993 and are known as the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (Fig 4) (24). The term vascular dementia is preferred over multiinfarct dementia, because the former is an acknowledgment of the many vascular causes that can contribute to dementia. Control of vascular risk factors is the treatment of choice. Cholinesterase inhibitors are also increasingly being used to treat vascular dementia.

Frontotemporal dementia comprises a group of dementias (eg, Pick disease) and accounts for approximately 5%–10% of cases of dementia. Frontotemporal dementia is clinically characterized by behavioral and language disturbances that may precede or overshadow memory deficits. There currently is no treatment for this condition.

Normal-pressure hydrocephalus is characterized by a classic triad of gait disturbance (25), dementia, and incontinence. There is evidence that ventricular shunting in a select group of these patients may improve symptoms, provided either pronounced gait difficulty or the full triad are present; however, there is little effect in patients in whom dementia is the first or primary symptom (26,27).

Dementia with Lewy bodies is being diagnosed more frequently; study results have demonstrated that it is responsible for approximately 25% of dementias. The clinical manifestation may be similar to

that of AD or the dementia associated with Parkinson disease. Patients typically present with one of three symptom complexes: detailed visual hallucinations, Parkinson-like symptoms, or alterations in alertness and attention (3). Pathologically, the disease is characterized by the presence of Lewy bodies in various regions of the hippocampal complex, subcortical nuclei, and neocortex, with a variable number of diffuse amyloid plaques; however, the neurites (axons and dendrites) and neurofibrillary tangles seen in AD are not seen in this disease. In 1996, consensus criteria were developed for the diagnosis of probable dementia with Lewy bodies (28) (Fig 5). Cholinesterase inhibitors are currently the treatment of choice for this condition.

MCI.—Increasing evidence now suggests that the early pathogenic process of AD is protracted and may extend over decades (29). This preclinical stage of AD appears to be separated into two stages: an extended "latent period," where there may be no observable symptoms of the disease, followed by a shorter "prodromal phase," where mild symptoms are observed but preclude a clinical diagnosis. The prodromal phase is characterized by progressive isolated memory deficit, a condition now increasingly being termed in research settings as MCI. In contrast to MCI, patients with mild AD have more prominent deficits in one or more other cognitive domains (eg, language, executive function), as well as in daily functioning, and their memory deficits are usually also more pronounced.

Results of neuropsychologic studies of early AD have demonstrated that specific patterns of recent memory impairment help distinguish between early-stage AD, normal aging, and other dementing conditions (30). Based on these and other data, research criteria have been developed for identification of patients with MCI ("prodromal AD"), and such criteria are currently being used for selecting patients for ongoing-intervention trials (31). Specifically, MCI is characterized by a prominent and relatively isolated impairment in so-called secondary memory, or memory for information after short delays. Patients with MCI may also have impairments of working memory. This deficit in patients with MCI is believed to be to caused by impaired acquisition or consolidation of new information into permanent memory stores, presumably related to damage to the medial temporal lobe and/or specific prefrontal–temporal lobe circuits (Fig 6).

I. Criteria for the clinical diagnosis of PROBABLE vascular dementia include all of the following:
- Dementia defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferably established by clinical examination and documented with neuropsychologic testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.
  - — Exclusion criteria: cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.
- Cerebrovascular disease, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant CVD by brain imaging (CT or MR) including multiple large-vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as multiple basal ganglia and white matter lacunes or extensive periventricular white matter lesions, or combinations thereof.
- A relationship between the above two disorders, manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

II. Clinical features consistent with the diagnosis of PROBABLE vascular dementia include the following:
- Early presence of a gait disturbance (small-step gait or marche à petits pas, or magnetic, apraxic-ataxic or parkinsonian gait)
- history of unsteadiness and frequent, unprovoked falls
- early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease
- pseudobulbar palsy
- personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III. Features that make the diagnosis of vascular dementia uncertain or unlikely include:
- early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain images
- absence of focal neurologic signs, other than cognitive disturbance
- absence of cerebrovascular lesions at brain CT or MR.

Figure 4. NINDS-AIREN (National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences) criteria (24) for probable vascular dementia. *ACA* = anterior cerebral artery, *CVD* = cerebrovascular disease, *PCA* = posterior cerebral artery.

I. The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of fronto-subcortical skills and visuospatial ability may be especially prominent.

II. Two of the following core features are essential for a diagnosis of PROBABLE DLB:
- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations that are typically well formed and detailed
- Spontaneous motor features of parkinsonism

III. Features supportive of the diagnosis are
- Repeated falls
- Syncope
- Transient loss of consciousness
- Neuroleptic sensitivity
- Systematized delusions
- Hallucinations in other modalities

IV. A diagnosis of DLB is less likely in the presence of
- Stroke disease, evident as focal neurologic signs or on brain images
- Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

Figure 5. Proposed criteria of McKeith et al (28) for probable dementia with Lewy bodies *(DLB)*.

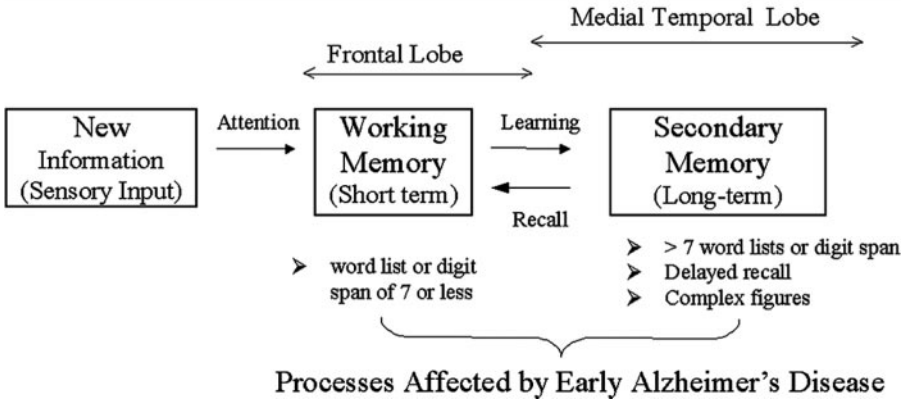


Figure 6. Model of neural deficits in early AD. Neural connections associated with normal memory function involve frontal and temporal lobes. Somatosensory, visual, and auditory information proceed from primary and association cortex to prefrontal cortex, located in the posterior frontal lobe. This region plays a major role in executive function (ie, organizing and directing attention), as well as in working memory, acting as a "mental scratchpad" for short-term information needed to perform a task, such as dialing a phone number. Part of this information may be consolidated, branching to the medial temporal lobe region via the entorhinal cortex (medial temporal lobe) and into the hippocampal complex. Projections from the hippocampal complex can transfer long-term information back to prefrontal cortex. This back-and-forth pathway between prefrontal cortex and medial temporal lobes is known as the limbic loop and is considered important for emotional stability, learning and memory function, and regulation of autonomic and endocrine functions. It is precisely these areas that are particularly susceptible to the pathologic changes of AD (11). (Adapted, with permission, from reference 32.)

There is still some controversy about the definition of MCI. Some experts believe that MCI simply reflects a very mild form of AD and that virtually all patients with MCI may have pathologic changes of AD (33). Others believe that patients with MCI represent a more heterogenous group, with some proportion of subjects staying stable or even "reversing" back to normal and with some patients progressing to develop additional deficits and meeting criteria for AD.

Although the definition of MCI has differed somewhat from study to study, there are now several longitudinal investigations in subjects with MCI. Peterson (34) has followed up MCI subjects and demonstrated that, on average, approximately 40% of carefully characterized subjects with MCI will progress to meet criteria for AD over a 4-year period. At present, there is no reliable test to predict which subjects will convert or progress, although all of the aforementioned risk factors may play a role. Symptoms of forgetfulness can be ambiguous and easily confused with the benign forms of memory change associated with normal aging (35) (Fig 7). Thus, there is an urgent need to develop sensitive markers that may serve as adjuncts to current clinical and neuropsychologic tests to facilitate detection and/or monitoring of early brain changes suggestive of AD. Such markers may also facilitate early intervention studies to prevent or slow further neuronal loss.

The criteria for identification and classification of subjects with MCI are evolving. Current criteria for identifying subjects with MCI for secondary prevention trials of AD usually depend on one or more of the following factors: *(a)* impaired memory performance on a normalized objective verbal memory delayed-recall test (eg, word list or paragraph); *(b)* recent history of symptomatic worsening in memory, supported by an informant; *(c)* normal or near-normal performance on global cognitive tests (eg, MMSE score > 24), as well as on an activities of daily living scale; *(d)* global rating of 0.5 (questionable dementia) on the Clinical Dementia Rating Scale, with a score of at least 0.5 on the memory scale; *(e)* absence of other factors that may better explain memory loss; and *(f)* presence of other risk factors such as family history, older age, and presence of the apolipoprotein $\epsilon 4$ allele. While these criteria may seem relatively easy to apply, questions still remain with regard to which of these criteria to use, which memory test(s) to use, what cutoffs to apply to de-

termine impairment, and how to deal with fluctuations in performance.

Genetic Testing

Genetic testing can be performed by using numerous markers (Table 1), many of which facilitate a diagnosis of early-onset dementia. Mutations of the *PS-1, PS-2,* and amyloid precursor protein genes on chromosomes 1, 14, and 21, respectively, are associated with early onset of the familial—and extremely rare—form of AD. The only useful marker for the more common late-onset (sporadic form) dementia is the apolipoprotein ϵ allele on chromosome 19. Results of genetic studies have shown that the ϵ4 allele is associated with a high incidence of AD, whereas the ϵ2 allele may be a protective factor. The ϵ3 allele is thought to represent no increased or decreased risk (36). Because the ϵ4 allele is more prevalent in patients with AD, it may be useful for differential diagnosis in patients with memory disorders. However, it is currently not recommended as a predictor of prognosis in asymptomatic subjects. The ϵ4 allele is found in about 30% of healthy subjects and is absent in approximately 30%–40% of patients with AD (37).

ROLE OF STRUCTURAL NEUROIMAGING

Conventional CT and MR Imaging

Conventional CT and MR imaging are used routinely in the work-up of patients with dementia; however, because of their low sensitivity and specificity for the diagnosis of AD, they are primarily used as an adjunct to help assess the degree of atrophy and rule out other causes of dementia such as normal-pressure hydrocephalus, vascular dementia, or intracranial mass. Currently, there is no reason to support CT over MR in the evaluation of patients with dementia, except in cases where MR is contraindicated or not readily available or affordable.

Standard MR pulse sequences at most centers consist of nonenhanced transverse spin-echo T1-weighted imaging to help assess the presence and degree of generalized (eg, AD) or focal (eg, cerebellar degenerative diseases, Pick disease, AD) atrophy (38,39). Transverse dual-echo long-repetition-time imaging, including proton-density and/or fluid-attenuated inversion-recovery and T2-weighted imaging, is also used in the assessment for periventricular and subcortical white matter hyperintensities; cortical or deep gray matter lacunar infarcts (vascular dementia); and peri-aqueductal, cerebellar, or dorsal thalamic changes (eg, alcohol-related dementia) (40). At centers where fast spin-echo rather than conventional spin-echo imaging is used, T2*-weighted or gradient-echo imaging may be needed to help assess the degree of iron deposition (eg, parkinsonian disorders) (41). T1-weighted and T2-weighted sequences may also be used to help assess for the presence of ventricular dilatation or intracranial mass. Thin-section (≤3-mm-thick) coronal T1-weighted images obtained in a plane orthogonal to the long axis of the hippocampus are useful for assessment of the degree of medial temporal lobe and hippocampal atrophy.

AD.—Medial temporal lobe atrophy, particularly of the amygdala, hippocampus, and parahippocampal gyrus, can be seen with higher frequency on structural images in patients with AD (42,43). Early investigators used CT to assess cortical, cerebellar, and hippocampal atrophy on transverse images; however, the addition of the coronal imaging plane with MR provided better qualitative assessments of the hippocampal region (Fig 8). Studies in which T1-weighted MR imaging was used in evaluation of the anterior hippocampus have been particularly useful. Data from a study (44) with 222 subjects (controls and patients with various forms of dementia) in which a visual rating scale was used to assess temporal lobe atrophy suggest that sensitivities and specificities in the area of 85% may be obtained for patients with AD.

Normal-pressure hydrocephalus.—Normal-pressure hydrocephalus, an idiopathic form of communicating hydrocephalus,

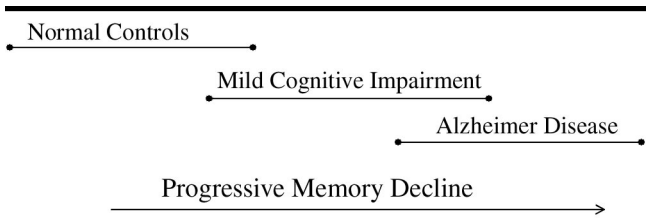


Figure 7. Conceptual continuum of memory decline in early AD. Diagram demonstrates overlap between healthy control subjects and patients with MCI and between patients with mild AD and those with MCI.

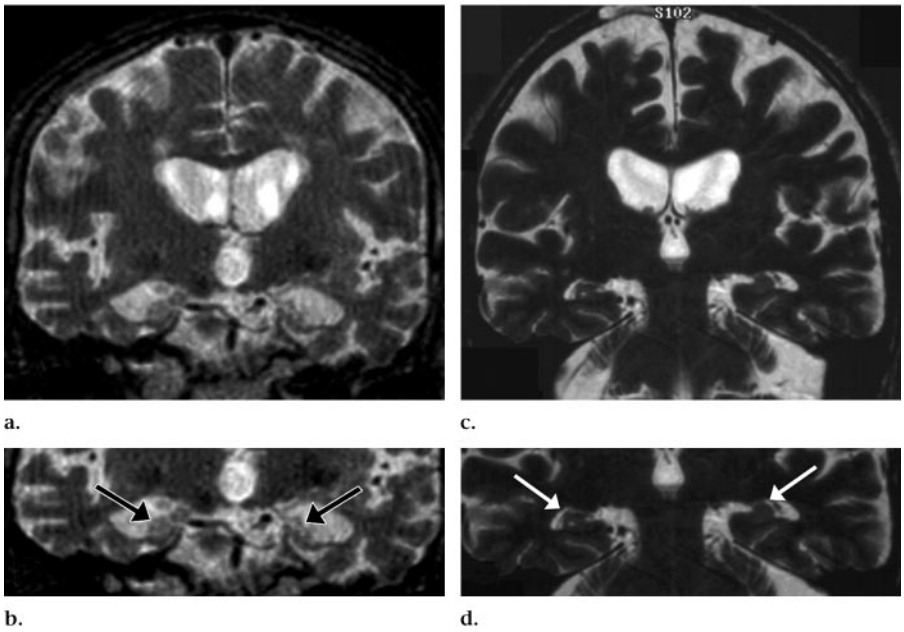


Figure 8. Coronal T2-weighted fast spin-echo MR images (repetition time msec/echo time msec, 2,700/80) in **(a, b)** a patient with AD and **(c, d)** an age-matched control subject. **(a, b)** The patient with AD has severe bilateral hippocampal atrophy (arrows). Compare this with **(c, d)** normal hippocampus (arrows) in the control subject. Note that **b** is a close-up of **a**, and **d** is a close-up of **c.** (Images courtesy of Daniel P. Barboriak, MD, Duke University Medical Center, Durham, NC.)

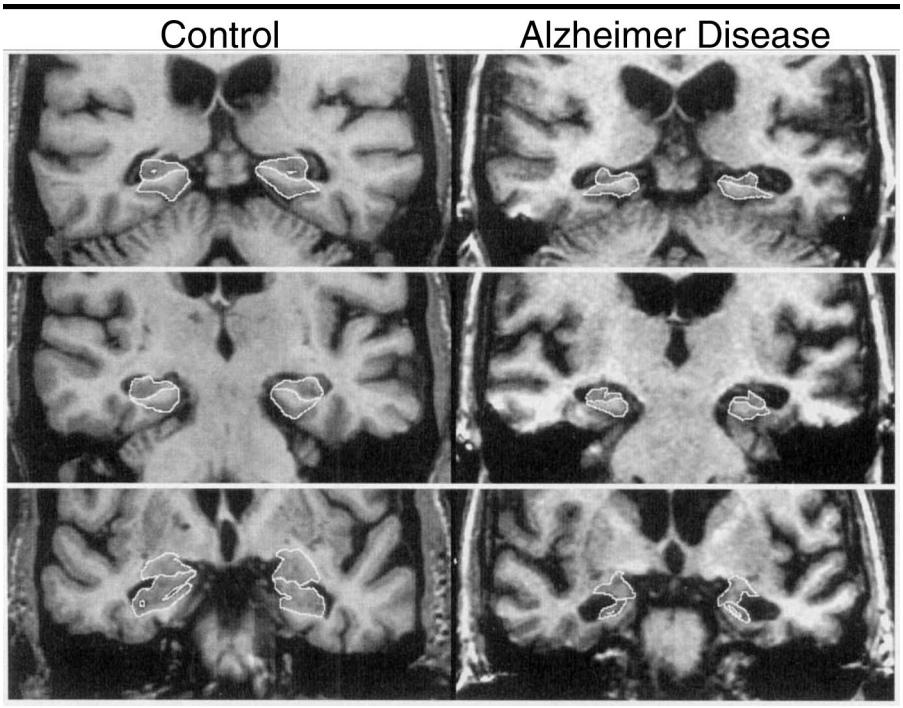


Figure 9. Coronal T1-weighted MR images demonstrate tracings of the hippocampus and parahippocampal gyrus in a 75-year-old female control subject (left) and 73-year-old woman with AD (right). Outlines of the amygdala and hippocampus are indicated in the bottom images.

is characterized by holoventricular enlargement out of proportion to sulcal enlargement. These findings are in contrast to the findings of generalized atrophy, where the degree of sulcal and ventricular prominence are concordant. Radionuclide cisternography, demonstrating activity within the ventricular system at 24 hours, has been used to help diagnose normal-pressure hydrocephalus and determine which patients are more likely to respond to shunting (45). MR imaging can also be useful in this regard. MR images may show the presence of high signal intensity in the periventricular and subcortical white matter on T2-weighted, proton-density, or fluid-attenuated inversion-recovery images; this high signal intensity has been thought to represent transependymal edema. These abnormalities may, however, represent small-vessel ischemic changes, reflecting the relationship between normal-pressure hydrocephalus and decreased blood flow in the periventricular white matter (46). The presence of a prominent flow void in the cerebral aqueduct has been shown to correlate well with a positive response to shunting (47). More recently, a number of groups have demonstrated increased aqueductal cerebrospinal fluid flow, as measured with quantitative cine phase-contrast MR imaging, as a good predictor of response to shunting (48,49).

Despite the existence of consistent imaging findings, it should be noted that the diagnosis of normal-pressure hydrocephalus is made primarily on the basis of clinical findings. Without a prior suspected clinical diagnosis, it is unlikely the diagnosis will be made on the basis of imaging results alone.

Vascular dementia.—Vascular dementia, or multiinfarct dementia, is often characterized by multiple areas of high signal intensity on T2-weighted, proton-density, or fluid-attenuated inversion-recovery MR images. The high signal intensity may be in white matter, basal ganglia, and/or thalamus. Focal infarcts or lacunae in strategic locations can also be associated with vascular dementia. Clinical onset of cognitive deficits is characterized by a stepwise decline, as opposed to the more continuous decline in AD. Periods of abrupt decline may be followed by stable periods. Patients typically have cerebrovascular risk factors, including male sex, smoking, hypertension, and/or diabetes. Clinical characteristics such as abrupt onset of symptoms of memory impairment, emotional lability, somatic complaints, and focal neurologic deficits, along with a history of stroke or transient ischemic attacks, often guide the clinician in making a diagnosis of vascular dementia.

Modern diagnostic criteria emphasize the importance of imaging to support a clinical diagnosis (24). This diagnosis cannot be made on the basis of imaging findings alone, as white matter hyperintensities or lacunae on MR images do not necessarily always lead to dementia or notable cognitive impairment. Although study results have associated cognitive impairment with MR hyperintensities, the nature and strength of these associations have varied from one study to another (44,50–52). This variability may be due in part to the confounding effects of high cognitive reserve or education level, which may mask a neurocognitive decline. The volume of white matter lesions does, however, correlate with the presence of cerebrovascular risk factors (53). Patients with AD may also have abundant white matter lesions, and there is often overlap between vascular dementia and AD, a so-called mixed dementia. Thus, the presence of white matter lesions on T2-weighted MR images should not be used to exclude a diagnosis of AD (3). Likewise, several strategically placed infarcts may be sufficient to cause symptoms of vascular dementia and should not be viewed as unimportant.

Quantitative Imaging of Atrophy

Quantitative measures of generalized cerebral atrophy were developed for both CT and MR imaging in an attempt to identify pathologic atrophy in early dementia, as distinguished from the atrophy of "normal" aging. Such approaches included linear and volumetric CT measurements of ventricles and subarachnoid spaces and MR imaging measurements of cerebrospinal fluid and gray and white matter volumes (54–56). Unfortunately, age-related atrophy in individuals without dementia also occurs, causing substantial overlap between the two groups and limiting the diagnostic utility of such measurements. Subsequent work focused on the medial temporal lobes, given that the pathologic substrate of AD is known to affect the hippocampus and anatomically related areas such as the entorhinal cortex at the earliest stages of the disease. Authors of early studies with CT who focused on this region applied a linear approach to measure medial temporal lobe atrophy (57,58) and a stereological approach to measure hippocampal volume (59). However, because of the small size and uneven shape of the hippocampus, as well as considerations of section thickness, the transverse CT approach turned out not to be well suited for volumetric assessment.

Quantitative hippocampal volume analysis with MR imaging turned out to be better than that with CT, given the superior soft-tissue contrast capabilities of MR, the lack of beam-hardening artifacts, and the multiplanar capability. Initial techniques used linear and area measurements. Subsequent techniques have used semiautomated computer algorithms to calculate hippocampal volumes. Authors of a number of initial studies describing MR-based volume measurements reported extremely high sensitivity in distinguishing patients with AD from elderly control subjects; however, many of these studies were flawed by imaging methods that were not state of the art, by variations in neuroanatomic boundary criteria, and by small and highly selected samples, which made extrapolation to diagnosis of AD in a general setting problematic (60). The most widely used volumetric technique is the semiautomated tracing-thresholding method, where a threshold is used to outline the high-contrast portions of the anatomic boundary and an interactive manual trace is used to outline the low-contrast portions (61). Using the tracing-thresholding method, Jack et al (62) reported a sensitivity of 82% and a specificity of 80% in discriminating patients with AD from control subjects in a study of 220 individuals (Fig 9).

Difficulties with single measurements of generalized and regional atrophy include the large overlap in volume measurements between control and AD populations. Serial measurements may be more specific than single measurements for detecting differences between patients with AD and control subjects, as serial measurements are less affected by overlap between populations. Several groups have evaluated dementia populations by using serial volume measurements in various memory-specific brain regions, including the medial temporal lobes. Rates of hippocampal atrophy have correlated with cognitive status at baseline and with change in cognitive status over time. Jack et al (63) studied 22 subjects with probable AD and 22 age- and sex-matched control subjects. The annualized rate of hippocampal atrophy and temporal horn enlargement was approximately two times greater in patients with probable AD. More recently, in a study with 129 patients grouped according to probable AD, MCI, or age-matched control, Jack et al (64) showed that rates of hippocampal atrophy lie along a continuum from patients with AD to those with MCI to age-matched control subjects. Within the control and MCI groups, subjects who subsequently showed a decline had a significantly greater rate of atrophy than did those whose condition remained clinically stable.

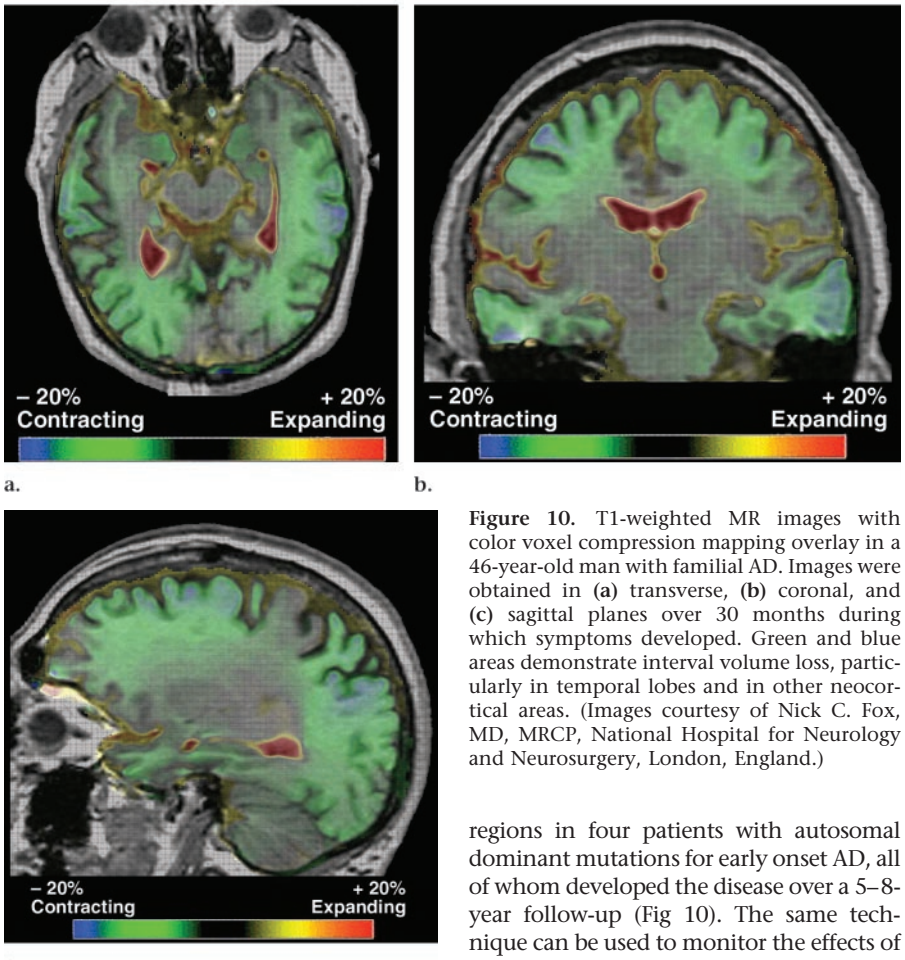


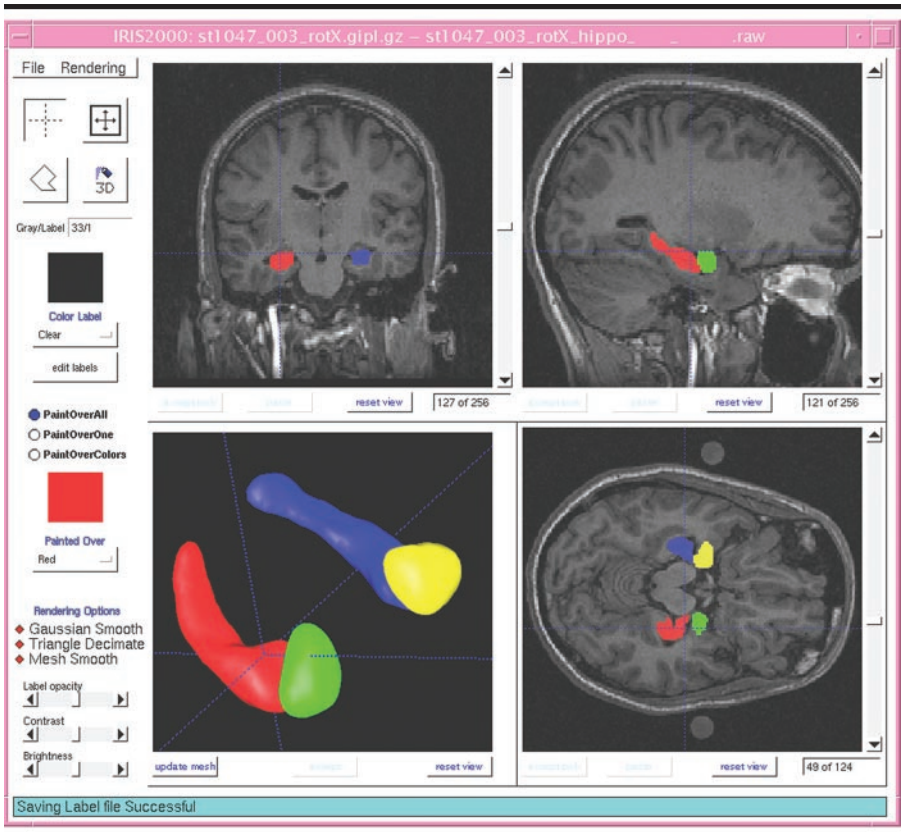
Figure 10. T1-weighted MR images with color voxel compression mapping overlay in a 46-year-old man with familial AD. Images were obtained in **(a)** transverse, **(b)** coronal, and **(c)** sagittal planes over 30 months during which symptoms developed. Green and blue areas demonstrate interval volume loss, particularly in temporal lobes and in other neocortical areas. (Images courtesy of Nick C. Fox, MD, MRCP, National Hospital for Neurology and Neurosurgery, London, England.)

The potential of serial volume measurements to aid in prediction of a subsequent development of AD and evaluation of the efficacy of therapeutic regimens in at-risk populations, particularly those with MCI (65,66), has been evaluated. Fox et al (67) used a voxel compression subtraction technique to assess serial volume changes in individual subjects. The technique uses scaling, interpolation, and a rigid body registration method to first bring the later and earlier images into subvoxel alignment. A nonlinear registration algorithm using a compressible viscous fluid model is then applied to track local cerebral losses and deformations, which are presented in the form of a color overlay map on the baseline anatomic image. Fox et al (67) recently reported use of voxel compression mapping to show progressive regional atrophy involving the temporoparietal cortex and medial temporal and posterior cingulate regions in four patients with autosomal dominant mutations for early onset AD, all of whom developed the disease over a 5–8-year follow-up (Fig 10). The same technique can be used to monitor the effects of therapeutic regimens in slowing the rate of brain atrophy. It has been estimated that detection of a 20% reduction in atrophy rate would require approximately 200 patients and 200 control subjects in a 1-year placebo-controlled drug trial (68).

Despite its promise, the lack of availability of a completely automated method for segmenting small and irregular structures such as the hippocampus, as well as the time-consuming and labor-intensive nature of the current methods, limits widespread use of serial volume measurements in clinical practice at this time. Techniques for automated segmentation of structures such as the hippocampus are in development (69) and await more extensive testing before they can be used in routine clinical settings (Fig 11).

ROLE OF FUNCTIONAL NEUROIMAGING

Conventional structural neuroimaging with CT or MR is recommended in the routine evaluation of patients with memory disorders, to exclude treatable causes such as normal-pressure hydrocephalus



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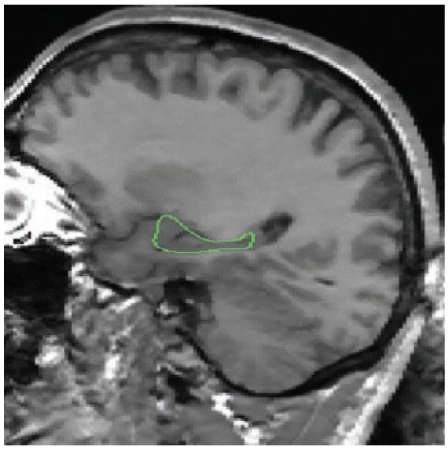

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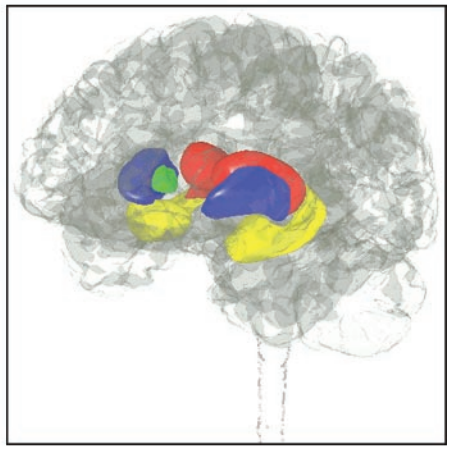


c.

Figure 11. Three-dimensional model–based segmentation. Screenshot demonstrates elastic model–based segmentation of limbic structures, including amygdalae (green and yellow) and hippocampi (blue and red). **(a)** Segmentation is shown in three-dimensional surface rendering (bottom left) and two-dimensional overlay on T1-weighted MR images in three orthogonal planes (top left and right, bottom right). **(b)** Sagittal T1-weighted MR image demonstrates outline of hippocampus in green. **(c)** Hippocampus (yellow) and neighboring brain structures (blue, green, and red) are shown on three-dimensional volume rendering of the brain. (Images courtesy of Guido Gerig, PhD, University of North Carolina, Chapel Hill.)

or intracranial mass. Functional imaging modalities, including SPECT and PET, also offer value in the differential diagnosis of dementia, particularly in distinguishing AD from vascular dementia, frontotemporal dementia, dementia with Lewy bodies, and depression. Moreover, because structural changes occur late in the course of the disease, functional imaging modalities, including SPECT, PET, and functional MR imaging techniques, may have greater potential in identifying more subtle pathologic changes earlier during the disease course.

SPECT Imaging

Cerebral SPECT, which is based on brain uptake of a technetium 99m–based lipid-soluble radionuclide such as ethyl cysteinate dimer or hexamethylpropylene amine oxime, is a widely available technique for evaluation of brain perfusion with a rotating gamma camera. Although the technique does not yield absolute values for cerebral blood flow, it does yield semiquantitative or relative values for comparison within and between patients when normalization by cerebellar activity is used (70).

Patients with AD have typically demonstrated a relative paucity of activity in the temporoparietal regions, compared with the activity in control subjects. Results of several studies have also shown that the magnitude of the perfusion abnormality correlates with the severity of cognitive impairment (71). In a prospective study with histologic confirmation of over 200 dementia cases and 119 control cases (72), the technique was reported to enable differentiation of patients with AD from healthy control subjects with a high degree of sensitivity and specificity (89% and 80%, respectively). Moreover, the accuracy of a clinical diagnosis of AD is improved with the aid of this technique, especially in mild cases of dementia, or "possible AD." In a study with histologic confirmation in 70 patients with dementia and 85 control subjects (73), a positive SPECT scan increased the pretest probability from 84% to 92% in patients with a clinical diagnosis of "probable AD" and from 67% to 84% in patients with "possible AD." A negative SPECT scan decreased the probability from 84% to 70% in patients with "probable AD" and from 67% to 52% in patients with "possible AD."

SPECT imaging also aids in the differential diagnosis of patients with dementia. Numerous studies have been performed in patients with various forms of dementia, including AD, frontotemporal dementia, and vascular dementia, with demonstration of unique uptake patterns. The presence of a frontal or anterior perfusion deficit has been associated with frontotemporal dementia and not with AD. In one study (74) in which a simple decision rule based on discriminant analysis of SPECT data was applied, 20 patients with probable AD and 20 with probable frontotemporal dementia were evaluated. One hundred percent of

patients with frontotemporal dementia and 90% of patients with AD were correctly classified. In another study (75) with 16 patients with frontotemporal dementia, 71 patients with other forms of dementia, and 28 control subjects, an anterior-to-posterior ratio was successfully used to classify patients with frontotemporal dementia from those with other forms of dementia and from control subjects with a sensitivity of 87.5% and a specificity of 78.6%. The effect of different SPECT uptake patterns at baseline on modification of the differential diagnosis was evaluated in a study (76) with 363 patients followed up for a median of 3 years. Patients were classified into disease groups on the basis of clinical criteria. A bilateral posterior perfusion abnormality was associated with AD, whereas a bilateral anterior abnormality was associated with frontotemporal dementia. A patchy uptake pattern significantly increased the odds of a patient having vascular dementia.

It has been suggested that dementia with Lewy bodies may demonstrate occipital hypoperfusion, differentiating it from AD (77). Recently, Lobotesis et al (78) studied 23 subjects with a clinical diagnosis of dementia with Lewy bodies that had been based on consensus criteria. SPECT measures of occipital and medial temporal perfusion enabled correct classification of 69% of all subjects, with 65% sensitivity and 87% specificity for dementia with Lewy bodies versus AD and controls.

Thus, results of numerous studies to date have demonstrated that SPECT imaging offers additional diagnostic value in the work-up of patients with dementia. The question remains as to the cost-effectiveness of this additional diagnostic value at this time. McMahon et al (79) recently examined this question by utilizing a decision model designed to calculate quality-adjusted life-years that accrue to hypothetical cohorts of patients at the time of presentation to an AD center. This model depended on the sensitivity and specificity of the standard diagnostic work-up, the effectiveness of current treatments, and the severity of disease. The authors concluded that addition of SPECT imaging to the diagnostic regimen was not cost-effective given currently available therapies (79).

The use of a temporoparietal hypoperfusion pattern on SPECT images to help predict the clinical onset of AD in at-risk populations has not been extensively studied. One study (80) in which 36 patients with MCI were followed up for 3 years failed to show a correlation between the presence of a SPECT abnormality at baseline examination and subsequent cognitive decline in MMSE score. The investigators in that study used visual inspection alone for evaluation of SPECT scans. Authors of another study (81), using a quantitative singular-value decomposition analysis of SPECT images in patients with MCI, demonstrated regional decreases in uptake in the medial temporal lobe and cingulate regions that were most prominent among patients with MCI who subsequently converted to AD over the 1- to 2-year follow-up. The same group (82) also demonstrated reduced perfusion in the hippocampal complex in asymptomatic subjects with the *PS-1* gene mutation, as compared with that in control subjects and in the anterior and posterior cingulate gyrus, posterior parietal lobe, and anterior frontal lobe regions. The authors suggested that a distributed brain network pertaining to memory might be selectively affected in the earliest stages of the disease.

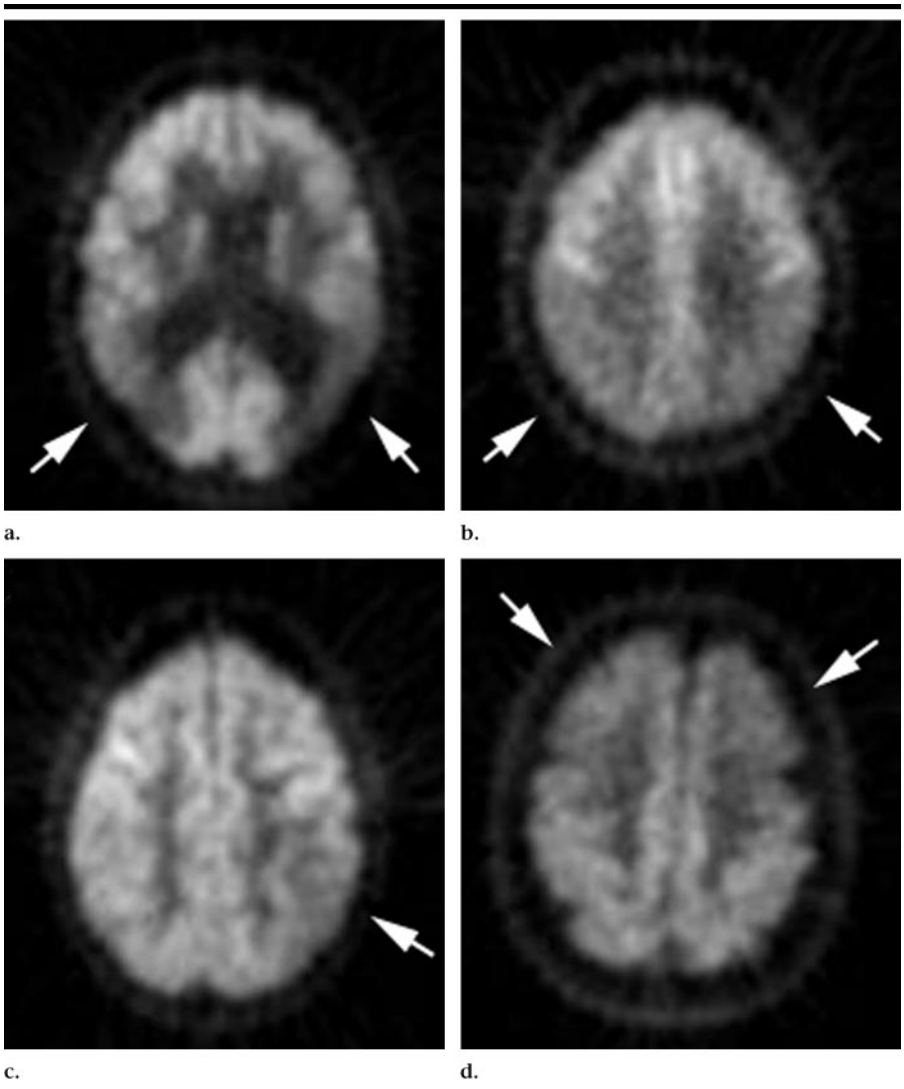


Figure 12. FDG PET images demonstrate typical findings in **(a–c)** three patients with AD and **(d)** one patient with frontotemporal dementia. **(a)** Note bilateral parieto-occipital hypometabolism (arrows) in a 77-year-old woman with AD. **(b)** Bilateral parietal hypometabolism (arrows) is also noted in a 62-year-old woman with AD. **(c)** Changes may be asymmetric, as demonstrated in a 53-year-old woman with AD, with the metabolic defect (arrow) primarily on the left. **(d)** As shown in a patient with frontotemporal dementia, PET may help differentiate frontotemporal dementia from AD by demonstrating metabolic deficits (arrows) in the frontal and anterior temporal lobes (not shown).

PET Imaging

PET has been used to study the brain's metabolic uptake of fluorine 18 (^{18}F)-labeled fluorodeoxyglucose (FDG) and blood

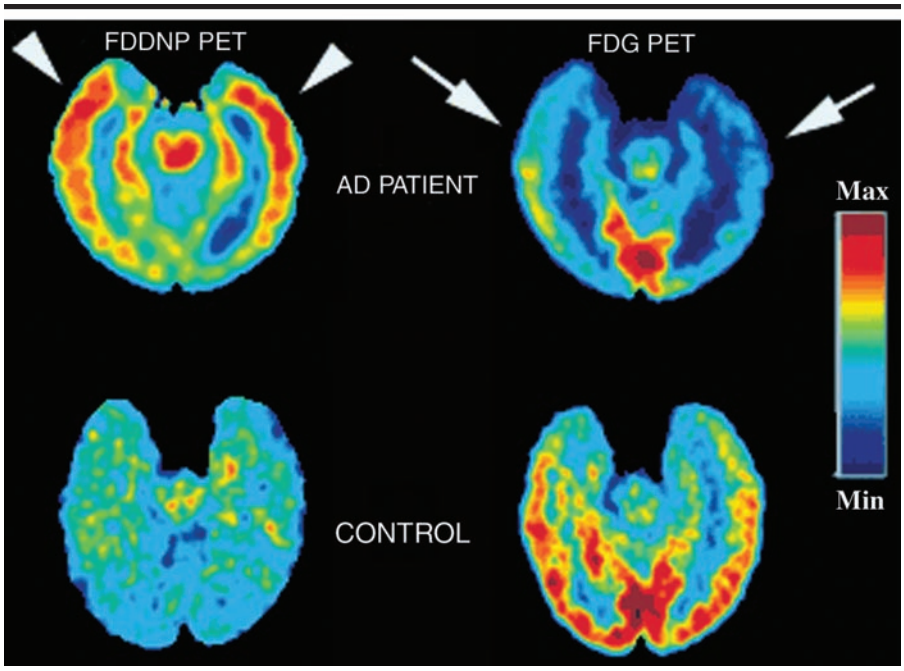


Figure 13. PET images comparing temporal lobe uptake of [^{18}F]FDDNP (see text), an amyloid-binding radiotracer, and FDG, a marker of glucose metabolism, in a patient with AD (left) and a control subject (right). Note increased uptake and retention of [^{18}F]FDDNP (arrowheads) in temporal lobes of the patient with AD, compared with those in control subject. The patient with AD still demonstrates typical findings of decreased temporal (arrows) and parietal (not shown) FDG uptake.

flow in patients with dementia. PET has been performed at baseline, as well as during the performance of various cognitive tasks. Baseline PET studies have been successful in enabling differentiation of AD from other forms of dementia on the basis of the pattern of FDG uptake. Specifically, deficits in temporoparietal metabolism are typically seen in patients with AD and not in patients with other forms of dementia or in age-matched control subjects (Fig 12a, 12b). Asymmetry of the metabolic deficits is not uncommon (Fig 12c). There typically is sparing of the basal ganglia, thalamus, cerebellum, and primary sensorimotor cortex (83). The magnitude of these deficits correlates well with the degree of cognitive impairment.

The ability to differentiate AD from frontotemporal dementia, depression, vascular dementia, and dementia with Lewy bodies was demonstrated in a blinded evaluation of PET studies (84). The frontotemporal dementias demonstrate decreased FDG uptake in the frontal, anterior temporal, and medial temporal cortices (Fig 12d). Patients with depression demonstrate a normal scan easily distinguishable from the pattern on scans in patients with AD. Patients with vascular dementia usually demonstrate patchy defects in central white matter and cortical regions. Dementia with Lewy bodies demonstrates a bilateral temporoparietal deficit similar to that seen in AD, but the deficit also involves the occipital lobes and cerebellum, areas typically spared in AD (85).

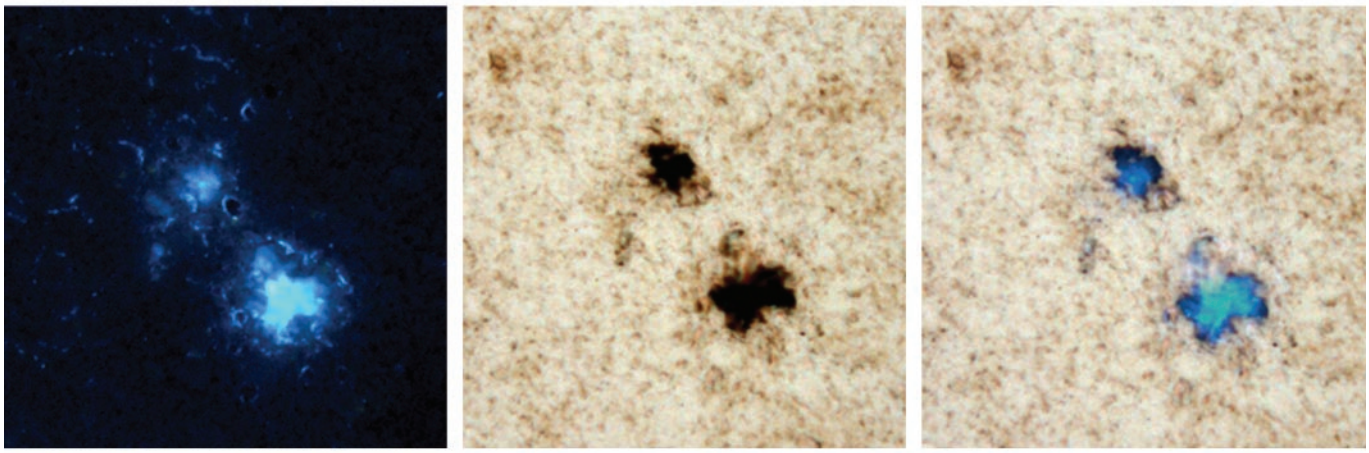
Several investigators have demonstrated that FDG PET offers diagnostic value even in mild or very mild stages of AD, although sensitivity and specificity are greater in moderate to severe cases. In a study (84) with 129 cognitively impaired patients, the overall sensitivity for detecting temporoparietal hypometabolism in patients with probable AD was 94%. In patients with mild disease, the sensitivity was 87%, whereas in patients with moderate to severe disease, the sensitivity was 96%. In another study (86) with 23 patients with isolated mild memory impairment or MCI in whom a diagnosis of probable AD could not be made at the time the initial PET scan was obtained, eight patients subsequently progressed to AD over a 3.3-year follow-up. All patients demonstrated changes similar to those on scans in patients with probable AD; these changes, although less apparent, were still statistically significant.

Recent studies in asymptomatic at-risk populations have demonstrated abnormal temporoparietal uptake patterns at PET, including in asymptomatic members of families in which a familial form of early-onset AD is found (86). Furthermore, asymptomatic subjects with the apolipoprotein ϵ4 allele, a genetic risk factor for the more common late-onset form of AD, have significantly lower temporoparietal metabolic activity than those without the allele (87).

The prognostic value of PET for predicting cognitive decline has also been evaluated. Drzezga et al (89) performed FDG PET in 15 patients with MCI at the time of protocol entry and at 1-year follow-up. In six of these patients, MCI progressed to a diagnosis of probable AD at 1 year; all six patients showed greater metabolic reduction in the posterior association cortex on the initial PET scan, compared with that on PET scans in those in whom the condition did not convert. These patients also showed a progressive metabolic reduction in the frontal association cortex over the 1-year follow-up.

Perhaps the most compelling evidence to date for the prognostic value of FDG PET for prediction of cognitive decline is provided by a recent multinational consortium study (90) conducted at eight academic institutions, with autopsy data in 138 of 284 patients evaluated for symptoms of dementia. Mean age was 66 years and mean MMSE score was 24, with a mean follow-up of 3.2 years (range, 2.0–9.4 years). All scans were interpreted as positive or negative on the basis of visual assessment of the metabolic distributions. In the group with longitudinal clinical follow-up (n = 146), progressive dementia was predicted with a high degree of sensitivity (93%) and moderate specificity (73%). Among the group with a pathologic diagnosis (n = 138), PET enabled correct identification of the presence of AD with similar sensitivity (94%) and specificity (73%). Because accurate diagnosis is most clinically relevant early in the course of the disease, a subset of patients with pathologic confirmation who were documented to have questionable or mild dementia at the time of the initial PET scan were analyzed separately. The overall sensitivity (95%) and specificity (71%) of PET in this group were similar.

In a number of blood flow and glucose metabolism PET activation studies obtained during the performance of memory tasks, decreased responses have been demonstrated in the brains of patients with AD, compared with responses in corresponding regions in control subjects (91–94). These data suggest there may be



a. b. c.

Figure 14. Transgenic mouse model of AD (tg2576). **(a)** Section from entorhinal cortex demonstrates in vivo labeling of amyloid plaques. Fluorescent labeling of plaques is seen after intravenous injection of *(trans,trans)*-1-bromo-2,5-bis-(3-hydroxycarbonyl-4-hydroxy)styrylbenzene, or BSB, an amyloid β binding agent that crosses the blood-brain barrier. (Original magnification, ×400.) **(b)** The same section was also immunostained with amyloid β–specific antiserum 2332, as demonstrated in this light microscopy image. (Original magnification, ×400.) **(c)** Digital overlay of **a** and **b** reveals high specificity of BSB plaque labeling. (Original magnification, ×400.) (Adapted and reprinted, with permission, from reference 100.)

disease-related functional failure in these regions. In a number of other studies, additional areas of activation outside those seen in control subjects have been demonstrated during performance of the same task, indicating compensatory recruitment of additional brain regions and functional reallocation of brain resources (95–97).

The majority of PET studies in the memory impairment population have used FDG as a radiolabeled tracer. Most recently, a new radiolabeled tracer, known as 2-(1-{6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2naphthyl}ethylidene)malononitrile, or [^{18}F]FDDNP, has been developed. This tracer is reported (98) to target the amyloid β senile plaques and neurofibrillary tangles in AD. An initial study in an 82-year-old woman with pathologically proved AD showed longer tracer retention times in the hippocampus, which corresponded to pathologically confirmed areas of plaque and tangle deposition seen at postmortem examination (98). In a subsequent study with the same tracer (99), nine patients with AD and seven control subjects demonstrated greater accumulation and slower clearance of the probe in brain areas worst affected by plaque and tangle deposition. Retention time of the tracer in brain regions known to be affected by AD is correlated with lower memory performance scores and is significantly greater in patients with AD than in control subjects (Fig 13). Additional ligands are in the preclinical development phase (100) (Fig 14).

MR Perfusion Imaging

Dynamic susceptibility-contrast MR perfusion imaging, a method that uses rapid T2*-weighted imaging of the brain during intravenous injection of a bolus of paramagnetic contrast material, is another functional technique that has been used to study patients with dementia. This technique enables measurement of several hemodynamic parameters, including relative cerebral blood volume, flow, and transit time (101,102). Unlike PET perfusion imaging, MR perfusion imaging takes less time to perform (about 1 minute), involves no radiation exposure, and is readily available on any MR unit capable of echo-planar imaging.

Because this technique is relatively new, only a few studies have been performed in patients with dementia. Nevertheless, it has been shown that MR perfusion measurements of cerebral blood volume closely parallel changes in cerebral metabolic rate of glucose consumption as determined with PET in patients with dementia and may be a lower cost alternative to PET (103). Harris et al (104,105) originally reported a 17% average reduction in temporoparietal cerebral blood volume, with 88.5% accuracy for correct categorization of 13 patients with AD and 13 control subjects. Maas et al (106) examined 16 patients with probable AD and 16 control subjects and found the technique to be 81% sensitive and 88% specific. More recently, the sensitivity and specificity of MR perfusion imaging have been shown to be superior to those of cerebral SPECT, with sensitivities in the 87%–95% range for patients with mild or moderate AD and specificities of 88%–95% in control subjects (104,107). To our knowledge, studies have yet to be performed in patients with various forms of dementia, patients with MCI, and presymptomatic patients at genetic risk for future development of AD.

Functional MR Imaging

Functional MR imaging has proved to be a powerful research technique to aid in identifying regions of brain activated by particular stimuli and tasks. With this technique, regional brain activity is measured on the basis of local changes in deoxyhemoglobin concentration in response to various stimuli and tasks (109). In brief, rapid T2*-sensitive imaging, usually gradient-echo echo-planar imaging, is performed during presentation of a stimulus or performance of a specific task and during rest periods. A voxel-by-voxel statistical comparison is then performed with images obtained during the stimulus/task periods versus those obtained during the rest periods, creating a statistical-activation map that can be "thresholded" and presented as a color overlay on anatomic T1-weighted images. Because functional MR imaging does not use ionizing radiation, it can be applied repeatedly in the same patients without risk. Although not currently used in the routine work-up of patients with memory disorders, the technique offers considerable potential in early identification

TABLE 2
Functional MR Imaging Studies of AD

Study and Year	Sample	Task	Findings	Comments
Bookheimer et al (117), 2000	16 Apolipoprotein ε4-positive and 14 apolipoprotein ε4-negative subjects	Auditory, learning and recalling unrelated word pairs	Greater extent and intensity of activation in apolipoprotein ε4-positive group in left frontal, temporal, and parietal lobes; greater number of regions activated in left hemisphere correlated with greater cognitive decline at 2 y	Supports compensatory-recruitment hypotheses; only one memory load condition; no direct monitoring of subject responses
Small et al (118), 2000	4 Control subjects, 12 patients with MCI, 4 patients with mild AD	Visual, faces: sex discrimination	In comparison with controls, AD group and $\frac{1}{3}$ of MCI group showed diminished activation throughout hippocampal formation; other $\frac{2}{3}$ of MCI group showed decrease only in subiculum	Restricted to hippocampal formation and subregions; refutes compensatory-recruitment hypothesis with regard to hippocampus
Johnson et al (119), 2000	16 Control subjects, 8 patients with mild AD	Auditory, word pairs (category example) with semantic decision	In AD group, greater atrophy associated with greater activation in left inferior frontal gyrus	Supports compensatory-recruitment hypothesis
Thulborn et al (120), 2000	10 Control subjects, 18 patients with AD	Visual saccade	Reversal of hemispheric dominance (from right to left) in intraparietal sulcus region in AD group	Supports compensatory-recruitment hypothesis
Saykin et al (121), 1999	Control subjects, patients with mild AD	Auditory, word pair with semantic or phonologic decision	Additional activation in right prefrontal cortex and inferior and middle temporal gyri in AD group, compared with control group	Supports compensatory-recruitment hypothesis
Corkin et al (122), 1997	9 Control subjects, 9 patients with mild AD	Visual, novel picture encoding and recognition	Equal activation in prefrontal cortex during encoding but weak and diffuse or no activation during retrieval in AD group despite equal performance	Does not support compensatory-recruitment hypothesis
Smith et al (123), 1999	14 high-risk (family history, apolipoprotein ε4 carrier) and 12 low-risk subjects	Visual, letter fluency and object naming	Decreased activation in high-risk group relative to that in low-risk group in middle and posterior inferior temporal regions	Does not support compensatory-recruitment hypothesis; did not monitor performance

of patients with prodromal dementia. We will first discuss functional MR imaging studies of normal memory. This will be followed by discussion of studies in patients with memory impairment.

Functional MR imaging activation patterns during various memory tasks have been studied in healthy volunteers. Two main groups of structures involved in working memory and secondary memory include the prefrontal cortex and the medial temporal lobe. Hence, these regions have been the focus of prior functional MR imaging studies of normal memory. In prior functional MR imaging studies (109–114), the prefrontal cortex has consistently been found to be involved in learning and recall. In these studies, specific regions or hemispheres have been localized on the basis of the cognitive paradigm used. Activation in the prefrontal cortex is greater with increasing memory loads (109) and is more pronounced during initial, as opposed to repeated, attempts at learning (113). Increased activation during learning is associated with more successful subsequent recall (113,114).

Authors of functional MR imaging studies have also documented the role of the medial temporal lobe in learning and recall. The medial temporal lobe structures most often implicated in these studies are the hippocampus and the parahippocampal cortex (115). Another area in the medial temporal lobe, the fusiform gyrus (lateral temporo-occipital cortex), is involved in the processing of faces (116).

There have been a number of recent functional MR imaging studies related to early AD, the results of which are summarized in Table 2. In the majority of these studies, diminished intensity and/or extent of activation has been demonstrated in the frontal and temporal regions in patients with AD, as compared with those in control subjects, when performance has been controlled for. Studies in which "at-risk" populations were examined have shown mixed results with increased (117) or decreased (123,124) activation in the at-risk group, as compared with activation in a control group. Authors of the studies in which increased activation was seen in the AD or at-risk groups explain their findings in terms of a compensatory-recruitment hypothesis, in which greater cognitive effort is required to perform the same task as compared with that required by a control group (Fig 15). This hypothesis presumes there is enough healthy neural tissue present to accommodate the task. In the

presence of substantial neuronal loss, as may be seen when clinical manifestations of memory loss are present, decreases in activation may result (117). Such decreases may be seen only in tasks that make sufficiently high demands to exceed the subject's compensatory reserve.

In summary, results of previous functional MR imaging studies of cognitively impaired or at-risk patients have shown increases or decreases in the intensity and extent of activation, as compared with findings in control groups. The discrepancies between increased or decreased activation may have to do with either differing task demands or different levels of compensatory reserve. Studies in which results supported or refuted the compensatory hypothesis have not used tasks with varied levels of difficulty in the same subjects; therefore, it is difficult to assess whether task difficulty met or was exceeded by cognitive reserve. Depending on the level of task difficulty and the patient population, varying degrees of activation have been seen. Moreover, many of these studies did not distinguish between compensatory reserve—that is, increased activation in regions known to activate in control subjects—and compensatory recruitment—namely, additional regions of activation outside those regions known to activate in control subjects (117).

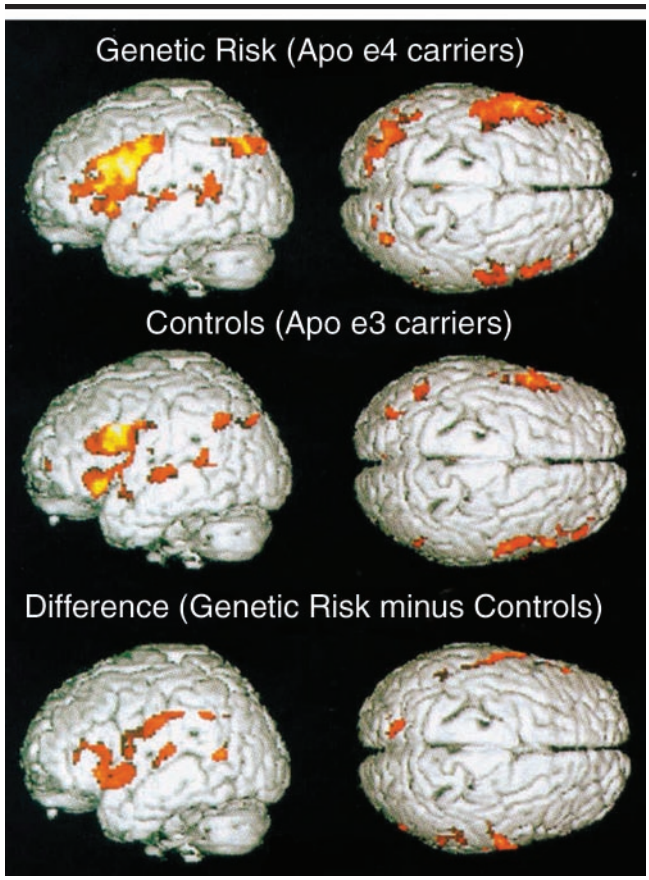


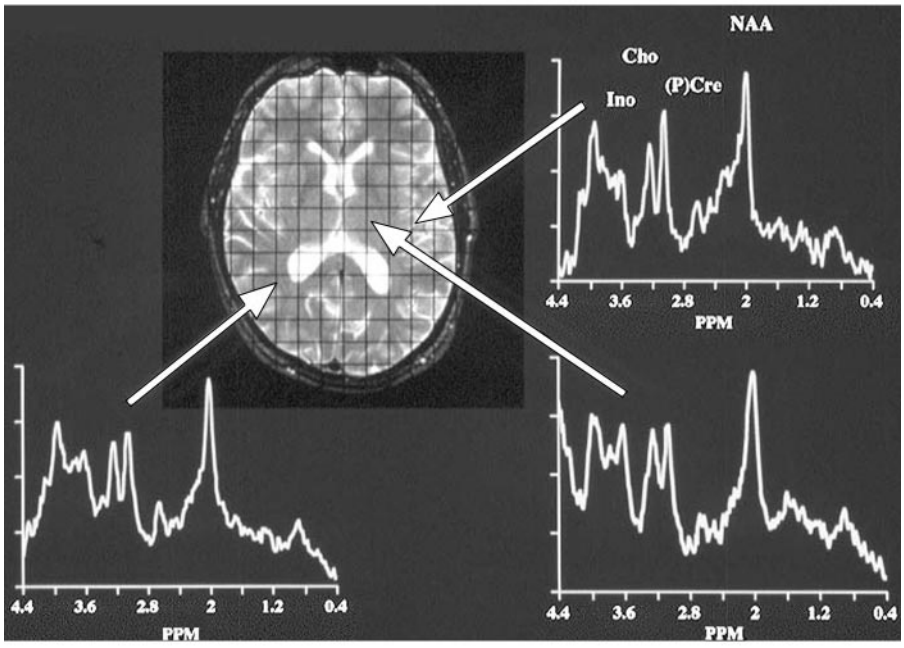
Figure 15. Brain activation maps obtained during memory-activation task in patients at genetic risk for AD (carriers of apolipoprotein *[Apo]* ϵ4 allele) compared with control subjects (apolipoprotein ϵ3 carriers). Three-dimensional renditions of the brain surface are shown in gray, and colored areas indicate regions of significantly increased MR signal intensity during performance of memory task as compared with that during resting periods. Activation is seen in temporal and frontal regions in both groups; however, both the extent and intensity of activation are greater among the genetic risk group, which suggests compensatory brain function. (Adapted and reprinted, with permission, from reference 117.)

MR Spectroscopy

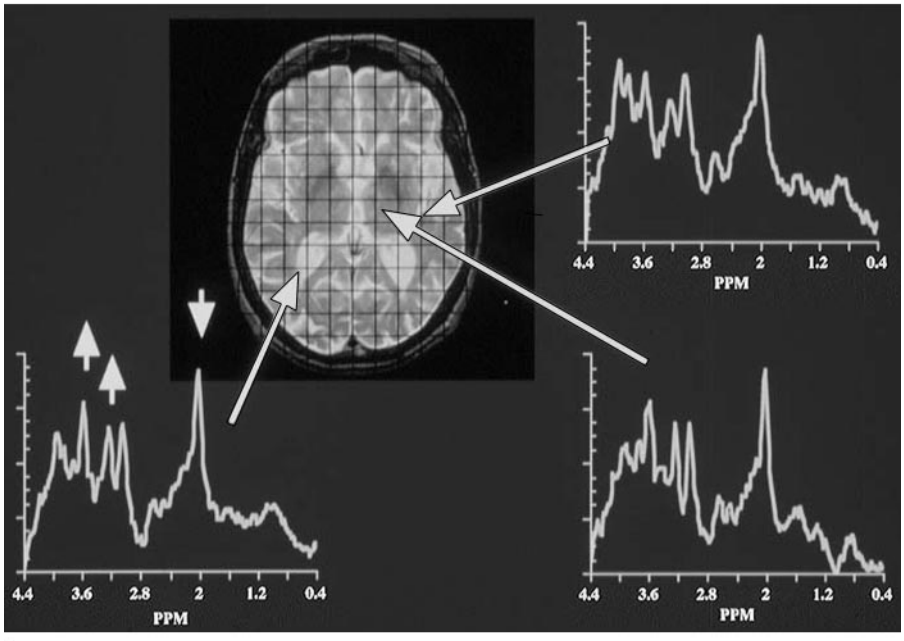
Proton MR spectroscopy is an application of MR that allows noninvasive assessment of a number of local metabolite levels in brain tissue (125). Proton MR spectroscopy allows in vivo assessment of *N*-acetylaspartate (NAA), glutamine and glutamate, γ-aminobutyric acid, *myo*-inositol, glycine, mobile choline moieties, creatine and phosphocreatine, lipids, and lactate. NAA is present primarily in neurons within the central nervous system but not in glial cells or other nonneuronal tissue. Although the exact metabolism of NAA remains unclear, NAA is generally thought to represent a marker of neuronal function (125,126). The NAA level is decreased in cases of neuronal loss or damage yet may return to normal levels during recovery. Elevated *myo*-inositol levels may mark gliosis, membrane dysfunction, and/or cytoskeletal abnormalities. Elevated choline levels may reflect cellular proliferation, as in neoplasia, or myelin breakdown. Most studies in the dementia population have used a single-voxel approach (125); however, multivoxel spectroscopic imaging techniques, known as chemical shift imaging, are also available (127).

In several in vitro studies (128–131) on postmortem brains, decreases in NAA levels have been demonstrated in patients with AD, as compared with levels in controls. Moreover, there has been a positive correlation between the magnitude of NAA decreases and the severity of neuropathologic findings (eg, counts of amyloid plaques and neurofibrillary tangles) (128,131). Similarly, in vivo studies (132–135) have also demonstrated decreases in NAA in patients with AD in both the temporal and parietal lobes. In some studies (136,137), higher choline levels have been demonstrated in the brains of patients with AD; however, these results have been inconsistent. *myo*-Inositol levels have been shown to be elevated in most studies (134,138–142), although *myo*-inositol levels may be confounded by a number of other coexisting disease processes (143–146) (Fig 16).

Metabolite levels have correlated with cognitive scores and dementia severity (138), and several groups have suggested that metabolite levels may be used as a diagnostic tool to help differentiate patients with AD from those with other forms of dementia and age-matched control subjects. Shonk et al (139) determined that changes in the *myo*-inositol–to-NAA ratio would help distinguish patients with AD from control subjects with a sensitivity of 83% and a specificity of 98% and that changes in the *myo*-inositol–to–creatine and phosphocreatine ratio would help distinguish patients with AD from elderly patients with other



a.



b.

Figure 16. Multivoxel MR spectroscopic imaging in **(a)** a 62-year-old healthy volunteer and **(b)** an 80-year-old patient with AD. Sample spectra are shown from right temporal lobe (bottom left), left insula (top right) and left thalamus (bottom right). Note the increase in *myo*-inositol *(Ino)* and choline *(Cho)* levels and the decrease in NAA level (short arrows in **b**) in the right temporal lobe of the patient with AD, compared with those levels in the healthy volunteer, suggesting the presence of gliosis, increased membrane turnover, and neuronal loss in AD. *(P)Cre* = creatine and phosphocreatine. (Images courtesy of H. Cecil Charles, PhD, Duke University Medical Center, Durham, NC.)

forms of dementia, with a sensitivity of 82% and a specificity of 64%. However, lack of specificity in distinguishing AD from other forms of dementia causes MR spectroscopy to remain a research tool and only an adjunct to clinical evaluation at this time.

With regard to patients at risk for AD, the results of one study (140) have shown NAA and *myo*-inositol metabolite levels in patients with MCI to be between those of cognitively normal subjects and patients with AD. Patients who are positive for the apolipoprotein ϵ4 allele tend to demonstrate similar findings prior to the onset of dementia or notable anatomic changes (unpublished data, 2002). Longitudinal evaluation may play an important role in determining prognosis and evaluating treatment in such at-risk groups of patients. Also, MR spectroscopic measures have been shown to be predictors of cognitive scores at 1-year follow-up (147). In addition, at least two controlled studies have used MR spectroscopy to monitor treatment effects in AD. Decreases in the choline-to–creatine and phosphocreatine ratio have been demonstrated in response to xanomeline, a muscarinic agonist; and decreases in the *myo*-inositol–to-NAA ratio have been seen in response to donepezil, a cholinesterase inhibitor (148,149). Doraiswamy et al (125) recently published a comprehensive review of the role of MR spectroscopy in dementia drug development and have also reviewed all the central nervous system drug trials in which MR spectroscopic results were used as an outcome measure. They concluded that MR spectroscopic measures of NAA, when combined with hippocampal volumetry, could provide highly useful surrogate markers of AD progression in trials of neuroprotective agents.

Diffusion-weighted MR Imaging

Diffusion-weighted MR imaging is a technique that is sensitive to the microscopic motion of water molecules in tissue. Its primary applications have been in the evaluation of acute cerebral ischemia. The technique has also been applied to the study of patients with AD (150–152). Most recently, Kantarci et al (153) studied various brain regions including the medial temporal lobes in a group of 19 patients with MCI, 21 with AD, and 55 age-matched control subjects. They used an index of mean diffusibility: the apparent diffusion coefficient. Confirming and expanding on the results of previous work, Kantarci et al demonstrated statistically significant differences in mean diffusibility between the AD group and the control group in a number of brain regions, most notably the hippocampus, and in temporal, cingulate, and parietal white matter. Although statistically significant differences were found only for the hippocampus, values in the MCI group were between those in the AD group and the control group for all re-

gions studied. The authors postulated that pathologic destruction of cell membranes, with subsequent loss of myelin and axonal processes due to wallerian degeneration, lessens the restriction of water diffusion in the hippocampus and afferent white matter tracts. Such pathologic changes are manifested by an increased apparent diffusion coefficient in these regions. The value of diffusion-weighted MR imaging as a diagnostic tool is still in question, however. Kantarci et al found that at a fixed specificity of 80%, the sensitivity was only 57% for distinguishing patients with AD from control subjects by using the hippocampal apparent diffusion coefficient.

Diffusion tensor MR imaging is a more advanced application of diffusion-weighted imaging; diffusion tensor imaging enables measurement of the directionality or asymmetry of microscopic water movement in tissue (154). Such asymmetric diffusion, known as anisotropy, is seen in normal white matter, owing to the integrity of white matter tracts that preferentially allows diffusion of water parallel, rather than perpendicular, to the tracts. Primary applications of this technique are in the evaluation of cerebral white matter tracts (155). Recently, the technique has been applied in human studies of AD (156). So far, results demonstrate a statistically significant reduction in white matter integrity throughout the brain, with relative sparing of the motor tracts, reflecting the known pathologic and clinical findings in AD.

PREDICTION AND EARLY DIAGNOSIS: THE FUTURE

For differential diagnosis in the patient with dementia, during the middle or late stages of the disease the current clinical criteria have a high sensitivity and specificity for determination of AD. Thus, the future role of imaging in patients with dementia at these stages will likely remain to help exclude other causes of dementia. The American Academy of Neurology Quality Standards Subcommittee recently published evidence-based practice parameters for the diagnosis, management, and early detection of dementia (157–159). Current imaging recommendations for the initial evaluation of patients with dementia include nonenhanced CT or MR imaging; however, because of insufficient data on validity, no other imaging procedure is recommended in these guidelines. The subcommittee recommended further research to determine the utility of other neuroimaging modalities in the work-up of the patient with dementia (157).

PET is currently used primarily as an adjunct to clinical diagnosis, especially in differentiating AD from vascular dementia and other focal dementias such as frontal lobe dementia. Given the growing evidence, PET will likely come to the forefront both as a diagnostic tool and as a prognostic tool. This will be especially true if amyloid imaging becomes standardized and widely available. Reimbursement issues remain a problem with PET, and it is hoped scientific advances will be recognized by third-party payers.

For determination of preclinical or early-stage disease, imaging will play an increasingly greater role in the future, especially as new agents to delay the onset of dementia become available. As clinical trial results confirm the efficacy of new therapeutic agents and as combination therapies are used, earlier and more accurate diagnoses will become more crucial. The at-risk patient with MCI may also be considered for treatment options that might alter the rate of progression to dementia. No specific neuroimaging protocol is recommended in this group at present (159), although more sensitive functional imaging techniques, as well as subtraction MR imaging, seem to be logical candidates. FDG PET has demonstrated the highest prognostic utility for providing a diagnosis of AD 2–3 years before the full dementia-related symptoms manifest (160). The role of SPECT in this regard remains less promising. Further longitudinal studies must be developed to examine the predictive power of these functional techniques in order to determine which patients will ultimately develop AD. Most likely, the answer will be a battery of tests that combine functional and structural imaging with clinical, genetic, and other laboratory data (161).

The major goals in treating AD currently are to recognize the disease early in order to initiate appropriate therapy and delay functional and cognitive losses. In addition, as powerful antiamyloid therapies are developed, there will be a need to monitor brain changes and treatment efficacy at the earliest stages of the disease, perhaps even in prodromal patients. It is hoped that the widespread availability of newer MR and PET markers will supplement the strengths of the currently available structural and functional imaging techniques in helping to achieve these goals.

Acknowledgments: The authors thank Haris Sair, BS, and Sarah Hart, BS, for their assistance in preparing tables and figures, and Christine Hulette, MD, for consultation on neuropathologic criteria.

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