Structural Magnetic Resonance Imaging in Established and Prodromal Alzheimer Disease: A Review

Monika Atiya, MD, Bradley T. Hyman, MD, PhD, Marilyn S. Albert, PhD, and Ronald Killiany, PhD

Alzheimer disease (AD), the most common form of dementia among the elderly,[1] is currently diagnosed on the basis of clinical criteria that have been in use for many years.[2] When these criteria are applied in tertiary care settings by experienced clinicians, the accuracy of diagnosis in comparison to autopsy findings is 80% to 90%.[3–6] In primary care settings, the accuracy of diagnosis is considerably lower. Thus, there remains a great need for a definitive test for AD. In addition, there is increasing optimism that medications will be developed that are truly effective at preventing or slowing down the progression of symptoms. Therefore, there is increasing interest in determining whether there are surrogate markers for AD that can be used, either for diagnosis or for measuring disease progression. One potential surrogate marker is magnetic resonance imaging (MRI). This report will give an overview of structural MRI findings in patients with mild to moderate AD, as well as those in the prodromal stage of disease, and will compare the imaging findings to what is known about the pathology of AD that is presumed to underlie the MRI measures. Both cross-sectional and longitudinal studies will be described. The latter are particularly relevant to the potential for using MRI measures as a surrogate marker for progression of disease in clinical trials.

PATHOLOGY OF AD

The major microscopic changes in AD are neuritic or senile plaques and neurofibrillary tangles, which are associated with widespread neuronal loss and synapse loss.[7] These pathologic changes are now known to display a specific topographic distribution and appear to follow a predictable sequence during the disease course.

Patterns of Hierarchical Vulnerability in AD

First described by Brun and Gustafson and later by many other authors, degeneration does not occur uniformly in AD.[8–12] Rather, there is a pattern of hierarchical vulnerability to neurofibrillary tangles, senile plaques, and atrophy. Medial temporal lobe structures are the most severely affected, and neurofibrillary tangles are reported to first appear specifically in the entorhinal cortex, CA1 and subiculum of the hippocampus, the amygdala, and strongly related structures such as the nucleus basalis of Meynert.[13–6] The distribution of the neurofibrillary tangles correlates well with atrophy[17] and appears to map well onto neuronal systems, with the memory-related system being impaired first in early stages of AD.[10]

As the disease spreads, limbic isocortical regions, that are anatomically closely related to the medial temporal lobe, such as the posterior parahippocampal gyrus, the cingulate, the temporal pole, and the orbitofrontal cortex, as well as the insula become affected.[13,14,18,19]

Next, high-order association cortices, including most of the lateral temporal lobe, and to a slightly lesser extent, the dorsolateral frontal lobe and parietal lobes are affected, whereas primary motor and sensory cortices, subcortical structures, and the cerebellum are involved latest.[14]

Although senile plaques do not display the same distribution as the tangles, they also seem to have a hierarchic pattern of vulnerability.[7] They are reported to first appear in areas of the neocortex, such as lateral temporal, posterior orbitofrontal, and insular neocortex, whereas areas of the medial temporal lobe tend to be less affected. In prodromal AD plaques are present in the neocortex.[20–22] In advanced stages of the disease, plaques are found throughout the cortex and in many subcortical areas as well.[18,19]

It has long been recognized, however, that the plaques and tangles that are the hallmark of AD are also found in the brains of some normal elderly individuals, but in lesser concentrations. In addition, it has been shown that these changes occur in the same hierarchical distribution that is seen in AD, with the major difference being quantitative: only neuroana-

tomical areas at the peak of the hierarchy pyramid are affected, and the number of lesions, even in those areas, is modest compared with the number observed in AD.[13,18,23]

One implication of this observation is that these brain areas are affected prior to the onset of clinical symptoms. If so, with increasing time, more lesions would be expected in the first areas, and as the disease spreads, ultimately reaching an extent where threshold for clinical detection is crossed. This model of neural system dysfunction predicts that initial lesions in medial temporal lobe structures lead to a predominant and relatively isolated clinical syndrome of memory impairment. Later a dementia syndrome occurs with greater impairment of executive function and judgment, reflecting involvement of additional neural systems such as paralimbic cortical areas and higher-order association cortices.

In assessing whether MRI measures can serve as a surrogate marker of AD, either for diagnosis or for disease progression, one would expect the MRI alterations to parallel, at least to some degree, the neuropathology pattern of the disease.[24] The following is therefore presented from that perspective.

MRI MEASURES OF ATROPHY IN AD

A variety of MRI measures have been used to discriminate AD patients from controls and from other patient groups. In addition, MRI measures have been used to assess the course of disease in AD patients. These measures include: (1) volumes of specific brain regions, (2) volumes of entire lobes, and (3) whole brain measures. Each of these is reviewed below and is summarized in Table 1.

MRI Measures of Regions of Interest (ROI)

One of the most widely applied volumetric methods consists of manually outlining specific anatomic structures, known as ROI. This is generally performed on consecutive MRI slices, most often coronal T1-weighted MRI sections. After carefully outlining the ROI, the volume is obtained automatically by having the computer add up the number of voxels (i.e., volume units) identified as being within the ROI.

Choice of MRI Regions of Interest to Measure

At any point in time, the area of a given region can be measured and the average size of that region can be compared across groups. Four factors are generally considered in deciding which brain regions are most likely to be informative if measured in a cross-sectional MRI-based anatomic study. First, if the comparison group is controls, a critical factor would be to choose regions that have relatively small degrees of variability from person-to-person among controls, so that individuals with some atrophy would stand out from the background of interindividual noise.

A second factor pertains to the ability of the imaging system to accurately capture anatomic detail. For example,

basal portions of the temporal lobe are more susceptible to MRI artifacts than many other areas, and it is important to take such artifacts into account when determining how to acquire the data and how to measure regions in this area.

Third, the details of the boundaries used for defining a ROI are critical. Specific techniques that optimize measurements so that they are reproducible in an individual and across individuals are important. For example, there is great variability in secondary sulci, and even in the primary sulci in some regions of the brain; manual measurements of anatomic regions using these variable sulcal patterns would be extremely difficult.

Finally, how large a difference might be expected is a critical component, both in carrying out the study and in planning it. Ideally, the brain regions should have been examined by quantitative or semiquantitative means in postmortem neuropathological studies, to provide an appropriate quantitative framework for the anatomic measurements on MRI scans.

Thus, one would ideally choose areas that are as nearly uniform across patients as possible, with minimum artifact, whose borders can be reliably and reproducibly measured, and in which there is an expectation of a relatively large change in AD but not in normal aging or other comparison groups of interest.

As shown in the review below, some limbic structures, although neuropathologically as equally affected as the hippocampus, would appear to be disadvantageous to measure due to great interindividual variability in size and structure and difficulties in discerning borders on MRI. Similarly, among high-order association cortices, there is variability in the sulcal pattern of many cortical regions, such as the dorsolateral frontal cortex, the inferior temporal lobe, and substantial right-left differences in the angular gyrus, and other parts of the inferior parietal lobule. By contrast, the superior temporal sulcus region, which is a high-order association cortical region, is relatively uniform across patients and has readily measured boundaries. These principles are useful to keep in mind when comparing studies because the observation of a statistically significant difference between, for example, AD patients and control individuals, depends both on the biology of AD (the degree of atrophy) and the degree of biologic variability and measurement variability in that structure in controls.

Medial Temporal Lobe and Related Regions
Hippocampus

Pathologic changes in the hippocampus in AD are so characteristic that AD has sometimes been referred to as "hippocampal dementia."[25] There are pronounced changes, including neurofibrillary tangles, neuronal loss, and neuritic plaques in the CA1/subiculum subregion, early in the disease course, and macroscopic neuropathological evaluation reveals hippocampal atrophy.[9,14,18,19,26,27] These pathologic findings are consistent with the critical role the hippocampus plays in nor-

mal memory function[28] and with the fact that memory deficits are the earliest sign of disease in most patients with AD.[29]

Reductions of MRI hippocampal volumes have been consistently reported, ranging from 15% to 22% in mild AD patients, to 40% in groups with more impaired AD patients.[30–35] In most studies, the discrimination of AD patients from controls ranges from 92% to 88%.[32,33,36–38] The hippocampal volumes of very mild AD cases are also significantly different from controls, although to a lesser extent, but adding information about the shape of the hippocampus improves discrimination.[39]

Although these findings confirm that major differences in the volume of the hippocampus can be observed in mild AD patients, hippocampal atrophy does not appear to be useful as a single diagnostic marker for AD. This is because most studies demonstrate overlap between AD patients and controls. Only two studies reported that measures of hippocampal volume showed no overlap between the groups, but both had a small sample size[30,31] and the former included severe AD patients. In addition, as discussed below, hippocampal atrophy is also not specific for AD but can be found in other dementias as well.[40–45]

Hippocampal volumetric measures have been validated by demonstrating a correlation between MRI volumes and pathologic assessment.[45–47] In addition, measures of the hippocampus have been shown to correlate with memory test performance in AD patients, demonstrating the functional significance of these changes in volume.[46–51]

The foregoing findings are particularly consistent, as studies have varied in sample size, degree of dementia, as well as in methods of measurement. Different scanners (from 0.5–1.5T) and various MR acquisition techniques have been used, for example, slice thickness has ranged from 1.5 to 1.6 mm to 5 mm.[30,31,33–37,52,53] Moreover, several studies did not use contiguous slices.[31,34,52] The axis of the coronal plane has varied as well; coronal images have been obtained perpendicular to the long axis of the hippocampus,[32,33,36,37,53] perpendicular to the orbitomeatal line,[52] to the sylvian fissure,[31] and to the anteroposterior commissure plane.[30,54,55] Normalization procedures to adjust for overall differences in brain size have also varied, from the use of the lenticular nucleus,[30] the intracranial area, and total intracranial volume. Similarly, boundaries of the hippocampal formation have been based on measuring the structure on only one slice,[30,34] to 5 or 6 slices,[31,56] to including its extensions from the end of the amygdala to the fornix (CA1-4, hippocampus proper, dentate and subiculum).[32,33,35–37,55,57]

Entorhinal Cortex

While many of the early pathologic reports mentioned above did not focus on the entorhinal cortex (a portion of the anterior parahippocampal gyrus), more recently it has become evident that this brain region, which contains major afferents to the hippocampus, undergoes profound neuronal loss in the early phase of AD[14,27,57] and displays significant volume loss.[27] Depletion of neurons in the perforant pathway, which includes the entorhinal cortex, is thought to isolate the hippocampus from neocortical association areas and contribute to the memory impairment seen in AD.[9,10,58]

With increased understanding of the importance of entorhinal neuronal loss in early AD, measures of the entorhinal cortex have recently been examined in mild AD patients. These MRI investigations have uniformly reported that the entorhinal cortex is substantially decreased in mild AD patients, demonstrating 22% to 39% volume loss.[17,38,54,56,59–61] This is also true for studies that have measured the anterior parahippocampal gyrus, which includes the entorhinal cortex.[57,62]

The findings of these studies are striking in that, as with the hippocampus, methods of measurement have varied widely. Some investigators have used a surface area measurement,[17] some have used 3 slices,[59] some 5 or 6 slices,[56] and others have attempted to measure the entire structure.[38,54,61,63] It is important to note that several groups have argued that the measure using the total volume of the entorhinal cortex, which is the one most frequently used,[63] is less reliable than the measure of the hippocampus.[54,64] It should be noted that investigators who have used only 3 slices have reported a high level of reliability.[59] The foregoing differences in methodology and sample characteristics might account for the differences in the discrimination accuracy for AD patients and controls, ranging between 83% and 98%.[17,38,56,60,61,64]

Parahippocampal Gyrus

Pathologic studies have also reported that the parahippocampal gyrus (PHG) is affected early in the disease process.[14,19]

Measurements of the entire parahippocampal gyrus on MRI show a significant volume decrease in AD compared with controls, although the hippocampus appears to be more affected.[31,33,52] A recent study measuring the hippocampus and parahippocampus, along with other medial temporal lobe structures, showed these two regions to be among the most affected in mild- to moderate-AD patients. None of the two measures alone was able to discriminate subjects with a higher than 85% accuracy.[55] The reported volume reductions ranged from 23.6% to 37.7% in mild- to moderate-AD patients.[31,52] However, measurements of the entire PHG were found to show more anatomic variability than the hippocampal ones, thus being less reliable.[33,55]

Amygdala

The amygdala, which has interconnections with hippocampal formation and parahippocampal gyrus, is also known to show degenerative changes during the course of AD.[65,66] Advanced AD patients demonstrate volume reductions of

TABLE 1. Cross-Sectional MRI Studies in AD

Author	Sample Characteristics		Scan and ROI Procedures	Structure	% Change	$p \leq$ Value
Bobinski et al. 1999	Control	8	2 mm	Hippocampus body	12	0.05
	AD	8	coronal	Entorhinal cortex surface area	27	0.005
	MMSE	27	manual	Superior temporal gyrus	na	ns
	Age	80				
Callen et al. 2001	Control	40	1.3 mm	Limbic structures	na	0.0005
	AD	40	coronal, axial +	Anterior cingulate gyrus	na	ns
	MMSE	20	sagittal			
	Age	69	manual			
Csernansky et al. 2000	Control	18	1.0 mm	Hippocampus		
	AD	18	3D	Volume	na	0.0005
	MMSE	25	manual +	Shape	na	0.0005
	Age	74	automated			
Cuenod et al. 1993	Control	6	5 mm	Hippocampus	20	ns
	AD	11	coronal + saggital	Amygdala	33	0.0005
	MMSE	21	manual	Temporal lobe	15	0.05
	Age	77		Corpus callosum	18	0.05
				Ventricular CSF	23	ns
				Sylvian fissue	35	0.005
Foundas et al. 1997	Control	8	1.25 mm	Hippocampus	na	0.0005
	AD	8	coronal	Parietal cortex	na	0.05
	MMSE	17	manual +	Insula	na	0.005
	Age	76	automated	Striate cortex	na	ns
Ikeda et al. 1994	Control	8	5 mm	Hippocampus	29	0.005
	AD	14	coronal	Parahippocampus gyrus	24	0.05
	MMSE	18	manual	Temporal lobe	26	0.005
	Age	67				
Jack et al. 1992	Control	22	4 mm	Hippocampus	na	0.005
	AD	20	coronal	Anterior temporal lobe	na	0.005
	MMSE	n.a.	manual			
	Age	73				
Jack et al. 1997	Control	126	1.6 mm	Hippocampus	na	0.005
	AD	94	coronal	Amygdala	na	0.005
	MMSE	18	manual	Parahippocampus gyrus	na	0.005
	Age	74				
Juottonen et al. 1998	Control	32	2 mm	Entorhinal cortex	40	0.0005
	AD	30	coronal	Perirhinal cortes	27	0.0005
	MMSE	21	manual	Temporal lobe cortex	17	0.0005
	Age	70				
Juottonen et al. 1999	Control	32	2 mm	Hippocampus	35	0.005
	AD	30	coronal	Entorhinal cortex	40	0.005
	MMSE	21	manual			
	Age	70				
Kesslak et al. 1991	Control	7	5 mm	Hippocampus	49	0.05
	AD	8	coronal	Parahippocampus gyrus	38	0.05
	MMSE	21	manual	Striate cortex	11	ns
	Age	72				
Kidron et al. 1997	Control	20	2.6 mm	Hippocampus	21	0.05
	AD	32	coronal	Temporal lobe gray matter	16	0.005
	MMSE	19	manual +	Parietal lobe gray matter	10	0.05
	Age	69	automated	Temporal lobe CSF	56	0.005
				Parietal lobe CSF	80	0.005
Killiany et al. 1993	Control	7	1.5 mm	Hippocampus	na	0.005
	AD	8	coronal	Amygdala	na	ns
	MMSE	23	manual	Temporal lobe	na	0.005
	Age	72		Basal forebrain	na	ns
				Temp horn	na	0.005

TABLE 1. Continued

Author	Sample Characteristics		Scan and ROI Procedures	Structure	% Change	$p \leq$ Value
Krasuski et al. 1998	Control	21	5 mm	Hippocampus	19	0.005
	AD	13	coronal	Amygdala	33	0.005
	MMSE	24	manual	Ant parahippocampal gyrus	18	0.005
	Age	71		Post parahippocampus gyrus	20	0.05
Laakso et al. 1995	Control	16	1.5–1.8 mm	Hippocampus	38	0.0005
	AD	32	coronal	Amygdala	18	ns
	MMSE	22	manual	Frontal lobe	14	ns
	Age	69				
Laakso et al. 1998	Control	42	1.5–2.0 mm	Hippocampus		
	AD	55	coronal	Volume	na	0.0005
	MMSE	22	manual	Area	na	0.05
	Age	70				
Lehericy et al. 1994	Control	8	5 mm	Hippocampus	30	0.05
	AD	13	coronal	Amygdala	27	0.05
	MMSE	20	manual +	Amygdala + hippocampus	34	0.05
	Age	72	automated	Caudate nucleus	13	0.05
				Ventricular CSF	25	ns
Murphy et al. 1993	Control	18	6 mm, 7 mm	Temporal lobe	na	0.005
	AD	19	coronal + axial	Whole brain	na	0.005
	MMSE	16	manual +	Subcort nuclei	na	ns
	Age	68	automated	Ventricular CSF	na	0.005
				Sulcal CSF	na	ns
Ohnishi et al. 2001	Control	92	1.23 mm	Hippocampal gray matter	na	0.005
	AD	26	sagittal	Entorhinal cortex gray matter	na	0.005
	MMSE	21	automated	Parahippocampus gray matter	na	0.005
	Age	72		Whole brain gray matter	na	0.005
Salat et al. 2001	Control	26	4 mm	Prefrontal cortex	na	0.05
	AD	26	coronal	Inferior prefrontal cortex	na	0.05
	MMSE	17	manual	Prefronal gray matter	na	0.05
	Age	70		Prefrontal white matter	na	ns
Seab et al. 1988	Control	7	5 mm	Hippocampus	40	0.0005
	AD	10	coronal	Whole brain	8	0.05
	MMSE	16	manual	Ventricular CSF	46	0.05
	Age	70		Sulcal CSF	19	0.05
Tanabe et al. 1997	Control	17	3 mm	Whole brain	6	0.0005
	AD	21	axial	Cortical gray matter	10	0.0005
	MMSE	21	automated	Subcortical gray matter	na	ns
	Age	72		White matter	na	ns
				White matter hyperintensities	8	0.005
				Ventrical CSF	78	0.0005
				Sulcal SCF	17	0.005

AD, Alzheimer disease; MMSE, Mini-Mental State Examination; Ant, anterior; Post, posterior; CSF, cerebrospinal fluid; na, not available; ns, not significant.
Technique: 1 = slice thickness; 2 = orientation (ie, coronal); 3 = tracing method.

about 45%.[66] However, in mildly demented patients, the amygdaloid nuclei show fewer neurofibrillary tangles than either the hippocampus or entorhinal cortex.[18,19] In addition, the subnuclei of the amygdala vary in the degree to which they are affected, with the magnocellular region of the basolateral complex being most affected.[66] Interestingly, the affected subnuclei are connected to several limbic structures, such as the entorhinal cortex, subiculum, and hippocampus,[67] as well as to

the nucleus basalis of Meynert,[68] the dorsomedial thalamic nucleus,[69] and frontal, temporal and insular cortex.[70]

It is therefore, perhaps, not surprising that quantitative MRI findings of the amygdala in AD have been inconsistent. Some studies have reported statistically significant differences between AD patients and controls,[33,53,55,57,71] but others have not.[35,36] Studies comparing the amygdala with other brain regions have also varied in outcome. Some studies have reported

that using both the amygdala and the hippocampus yields 94% correct classification between AD patients and controls,[57] whereas other studies have found that combinations of other brain regions, such as the hippocampus and temporal horn, are more discriminating.[55] In addition, a number of studies have reported that hippocampal volumetry is superior to the amygdala as a single discriminating measure between AD patients and controls.[33,36,55] One explanation for these differences pertains to the difficulty in measuring the anterior part of the amygdaloid complex and reliably separating the posterior part from the hippocampus, resulting in interoperator variability and differences across studies.[33,35,36,70] To date, it has not been possible to reliably distinguish subdivisions of the amygdala on MRI.[33,71]

Basal Forebrain

The nucleus basalis of Meynert of the basal forebrain has also been shown to be affected in AD.[72,73] Neuronal loss in this brain region is, in fact, the basis of the cholinergic therapies that are available today. The only two studies that have measured the basal forebrain on MRI showed a volume decrease of about 22% in mild- to-moderate AD patients compared with controls.[35,55] This difference in volume was not significant in the study with a modest sample size,[35] but it reached significance in a larger, more recent, study.[55]

Cingulate

Histopathologic changes have been reported in the cingulate, although to a somewhat lesser extent than in other areas of medial temporal lobe.[15] The posterior portion of the cingulate appears to be part of the memory system, based on its interconnections with the hippocampus, entorhinal cortex, and parahippocampal gyrus,[74] as well as on behavioral studies in animals. The caudal portion of the anterior cingulate is also thought to be involved in executive function abilities[75] and executive function is another cognitive area impaired in mild AD patients.[76]

Only two MRI studies to date have measured volumes of the cingulate in mild- or moderate-AD patients.[55,59] One study demonstrated that the caudal portion of the anterior cingulate, together with the entorhinal cortex and the banks of superior temporal sulcus, discriminated mild AD patients from controls with an accuracy of 100%.[59] It was noted that the volume loss in the caudal portion of the anterior cingulate was highly asymmetric; thus, the measure employed subtracted the volume in the right hemisphere from that on the left. In a second study, the posterior cingulate was significantly reduced in moderate AD patients, displaying a reduction of 20%, comparable to the amygdala (21%) and parahippocampal gyrus (21%). The caudal portion of the anterior cingulate did not differ between the groups.[55] These negative findings might be related to the fact that asymmetry was not taken into account.

Temporal Neocortex

The temporal neocortex is one of the first association areas involved in AD;[14] thus, MRI studies have also focused on measures of the whole or of parts of the temporal lobe. Two studies that measured the whole temporal lobe reported a significant difference between controls and patients,[35,52,77] the latter demonstrating a 26.1% reduction in AD. Likewise, the area of the temporal lobe measured on one slice was significantly reduced in AD patients.[71] Measures of the anterior parts of the temporal lobe, such as the anterior temporal lobe or temporopolar cortex, have also displayed a significant decrease in volume in AD.[32] Volume reduction was reported to be 17%, with a discrimination accuracy of 76%.[38] The anterior temporal lobe is, however, reported to be less discriminating than the hippocampus.[32]

Other measures of temporal neocortex, such as the banks of superior temporal sulcus (measured on one slice), have also been shown to be significantly decreased in mild AD patients. Together with the entorhinal cortex and the caudal portion of anterior cingulate, this superior temporal measure showed an accuracy of discrimination between AD patients and controls of 100%.[59] Measures of the temporal horn of the ventricles, which reflects atrophy of adjacent temporal structures, have also been reported to differentiate AD patients from controls.[35] The volume of the middle/inferior temporal gyrus and the superior temporal gyrus appears to be more variable. In one study, this measure was reported to be reduced by 10% in mild- to moderate-AD patients compared with controls, with a classification accuracy of 78%,[62] but the identical measure in a study with a smaller sample size found no significant differences.[17]

Combination of ROIs Within the Medial Temporal Lobe

The pathologic staging scheme of Braak and Braak defines AD stages III to IV, in which many medial temporal regions, including parts of the thalamus, are affected.[14] A recent MRI study measured many of these brain regions, including the parahippocampal cortex, the hippocampus, the amygdala and anterior parahippocampal gyrus, the basal forebrain, anterior thalamus, septal area, mamillary bodies, fornix, hypothalamus, cingulate, and orbitofrontal cortex. They demonstrated significant atrophy of all the components, except the anterior cingulate, in mild- to moderate-AD.[55] In addition, this study demonstrated that certain structures, such as the hippocampus, parahippocampal gyrus, amygdala/anterior parahippocampus, posterior cingulate, and the septal area, were involved to a greater degree than the other regions measured. However, no single measure achieved a discrimination accuracy >90%, although the patients were mildly to moderately impaired. Two combination measures, one including the hippocampus and the posterior cingulate and the other consisting of the septal area and the amygdala/anterior parahippocampus,

discriminated the groups with an accuracy of 90% and 93%, respectively.

Other Brain Regions

Pathologically, Braak stages V and VI are characterized by the spread of plaques and tangles to widespread areas of the association neocortices. This includes the parietal and the frontal lobes.[14]

Frontal Lobe and Parietal Lobe Measures

The volume of the frontal lobe is reported to be significantly reduced in one hemisphere only (the left) in mildly impaired patients.[36] However, a study in which severe AD patients were included found a significant volume decrease in the frontal lobe.[78] A more recent study demonstrated volume loss of the inferior prefrontal cortex in mild- to severe-AD patients.[79] Several studies have reported a significant decrease in the area or volume of the corpus callosum in AD (measured on one slice).[71,80,81] Only two studies have evaluated parietal lobe volumes in AD patients, reporting volume differences between AD patients and controls.[82,83]

Ventricular Size

Gross pathologic examination in moderate and advanced stages of AD reveals cortical atrophy and ventricular enlargement, as well as reduced brain weight.[84,85]

MRI measures of cerebrospinal fluid (CSF) volume are significantly increased in mild to moderate AD compared with controls,[43,61,71,77,86-88] as are moderate-AD patients compared with controls.[53] Moreover, adding CSF volume data to measures of the hippocampus and entorhinal cortex in a logistic regression model improves the sensitivity and specificity of discriminating AD patients from controls.[61]

Noncontributory ROIs

Volumes or areas of subcortical nuclei, such as the lenticulate nucleus, the caudate, and the striatum, do not appear to be significantly reduced in AD patients compared with controls.[30,31,53,77] Likewise, measures of the total volume of the thalamus,[77] the cerebellum and pons,[80] as well as striate cortex[83] are not significantly different in AD patients from controls.

Summary

In summary, structural MRI in mild to moderate AD, seem to confirm the pattern described in pathologic studies, with changes being most pronounced in medial temporal lobe regions, but also found beyond it, namely, in temporal neocortical association areas and in structures containing connecting fibers to the medial temporal lobe.

Whole Brain Measures

Recently, in addition to measuring specific ROIs, whole brain measures of atrophy have been examined in AD patients.

These measures have used automated techniques, such as statistical parametric mapping, for quantifying the whole brain. Statistical parametric mapping, using a technique known as voxel-based morphometry, is a method in which the image of the whole brain is normalized to fit into a standardized three-dimensional space and smoothed by applying a Gaussian smoothing filter. Thus, each voxel also contains the average data concentration from around the voxel. The brain is then segmented into tissue classes (gray matter, white matter, and CSF). Group average maps can then be generated and voxel-based comparisons can be made.[89]

One recent cross-sectional study found a reduction of gray matter volume in the hippocampus and entorhinal cortex bilaterally in mild- to moderate-AD patients.[90] Another study that mapped gray matter density with statistical parametric mapping techniques reported gray matter reduction affecting (in decreasing order) medial temporal structures, the cingulate gyrus, the precuneus, and the temporoparietal association and perisylvian neocortex.[91]

Measures of global atrophy, such as mean cerebral brain volume, have also been shown to be significantly reduced in mildly demented patients.[77] Using tissue segmentation techniques, which quantify the amount of different tissues types (i.e., gray matter, white matter, and CSF) according to intensity-based features, a significant decrease in total brain tissue and cortical gray matter was found in AD patients compared with controls; there was no difference in the volume of white matter.[87] However, another study applying the same technique found significant declines in the volume of both gray matter and white matter in mild- to moderate-AD patients compared with controls.[61] Likewise, significantly more white matter signal hyperintensities have been reported in AD patients.[87,92]

Specificity of Discrimination

Surrogate markers that are useful for discrimination should not only be able to distinguish AD patients from normal controls but also from other patient groups.[93] MRI studies that have examined this issue with respect to AD underline the importance of combinations of regions that differentiate groups of individuals, rather than the use of a single ROI in the differential diagnosis of dementia.

Dementia With Lewy Bodies

Dementia with Lewy bodies (DLB) refers to cases in which Lewy bodies are present, most often in combination with AD pathology.[94] Pathologic studies have demonstrated that neuronal counts of medial temporal lobe number are higher in DLB patients than in AD.[95,96] However, the distribution of Lewy bodies in several regions (including subcortical and medial temporal lobe areas) appears to be similar in DLB patients with or without concomitant AD.[97] In addition, accumulation of Lewy bodies does not appear to correlate with the number of neurofibrillary tangles or neuritic plaques.

TABLE 2. Longitudinal Studies with Serial MRI

Author	Sample Characteristics		Techinique	Rate of Atrophy Per Year		
				Structure	% Change	*p* Value
Fox et al. 1996	Control	38	1.5 mm	Hippocampus		
	At risk	7	Coronal	Control	1	
	Converted	3	Manual	At risk	5–10	0.05
	MMSE	29				
	Age	45				
	Scan interval	3 years				
Fox et al. 1997	Control	19	1.5 mm	Brain tissue		
	AD	9	Coronal	Control	0.24	
	MMSE	19	Automated	AD	2.8	0.0005
	Age	54	(BSI)			
	Scan interval	400 days				
Fox et al. 1999a	Control	26	1.5 mm	Brain atrophy		
	At risk	28	Coronal	Control	0.2	
	Converted	5	Automated	At risk	0.5	0.0005
	MMSE	29	(BSI)			
	Age	58				
	Scan interval	1 year				
Fox et al. 1999b	Control	15	1.5 mm	Brain atrophy		
	AD	29	Coronal	Control	0.4	
	MMSE	21	BSI	AD	2.4	0.005
	Age	58				
	Scan interval	2 years				
Fox et al. 2000	Control	18	1.5 mm	Brain atrophy		
	AD	18	Coronal	Control	0.4	
	MMSE	20	BSI	AD	2.4	0.05
	Age	65				
	Scan interval	1 year				
Fox et al. 2001	Control	20	1.5 mm	Brain atrophy		
	At risk	4	Coronal	Control	0.2	
	Converted	4	Automated	At risk	1.0	
	MMSE	29	(VBM)	AD	2.2	0.0005
	Age	43				
	AD	20				
	MMSE	22				
	Age	53				
	Scan interval	5–8 years				
Jack et al. 1998	Control	24	1.6 mm	Hippocampus		
	AD	24	Coronal	Control	1.6	
	MMSE	29	Manual	AD	4	0.005
	Age	81		Temporal Horn		
				Control	6	
	Scan interval	1 year		AD	15	0.005
Jack et al. 2000	Control	129	1.6 mm	Hippocampus		
	MCI	43	Coronal	Control	1.9	
	MMSE	26	Manual	MCI	3.0	
	Age	78		AD	3.5	
	AD	28				
	MMSE	22				
	Age	74				
	Scan interval	3 years				

TABLE 2. Continued

Author	Sample Characteristics		Techinique	Rate of Atrophy Per Year		
				Structure	% Change	*p* Value
Kaye et al. 1997	Control	18	4.0	Hippocampus		
	MCI	12	Coronal	Control	2	
	MMSE	27	Manual	AD	2	ns
	Age	90		Parahippocampal gyrus		
				Control	2	
	Scan interval	44 months		AD	3	ns
				Temporal lobe		
				Control	0	
				AD	1.3	0.05
Laakso et al. 2000	Control	8	2.0 mm	Hippocampus		
	AD	24	Coronal	Control	2.9	
	MMSE	22	Manual	AD	8.3	ns
	Age	69				
	Scan interval	3 years				
Scahill et al. 2002	Control	8	1.5 mm	No rate of atrophy for single structure but pattern of atrophy (see text)		
	At risk	4	Coronal			
	MMSE	29	Automated			
	Age	43	(VBM)			
	Control	12				
	AD	22				
	MMSE	19				
	Age	60				
	Scan interval	447 days				
Teipel et al. 2002	Control	10	2.0 mm	Corpus callosum		
	AD	21	Sagittal	Control	0.9	
	MMSE	17	Manual	AD	7.7	0.05
	Age	69		Splenium		
				Control	1.5	
	Scan interval	18 months		AD	12	0.05
				Rostrum		
				Control	0.6	
				AD	7.3	0.05

AD, Alzheimer disease; MCI, subjects with cognitive complaints, mostly memory, but not necessarily fulfilling the Petersen criteria for MCI (Petersen et al., 1999); MMSE, Mini-Mental State Examination; BSI, Brain Boundary Shift Integral; VBM, voxel-based morphometry.

In line with these findings, MRI studies have shown less atrophy of medial temporal lobe structures in DLB patients than AD patients.[98] However, correct discrimination of DLB from AD based on hippocampal volume was only possible in 72% of cases,[98] which most likely reflects the fact that AD and DLB are coexistent in most patients.

Frontotemporal Dementia

Frontotemporal dementia (FTD) refers pathologically to a constellation of findings that includes the changes seen in classic Pick's disease as well as the pathologic entity first described as dementia lacking histopathology.[100,101] Gross pathology usually shows significant frontal and/or temporal lobe atrophy, but the distribution and severity are not specific for a particular neurodegenerative disorder. Microscopic findings include neuronal loss and gliosis; in some cases, tau-positive and ubiquitin-positive inclusions are seen in addition.[102] Hippocampal involvement varies considerably.[103,104]

MRI studies of FTD patients have shown temporal atrophy with an anteroposterior gradient, compared with a more even distribution of atrophy in AD.[44] In a subtype of FTD, known as semantic dementia, asymmetric temporal lobe atrophy has been reported, in addition to an anteroposterior gradient of atrophy.[44] Volumetric measures of the hippocampus and entorhinal cortex have demonstrated significant atrophy in FTD patients with a mild to severe range of impairment.[40,42]

Vascular Dementia

Contrary to these quite consistent findings in DLB and FTD, results in vascular dementia are discrepant. While two

TABLE 3. Cross-Sectional MRI Studies with Comparisons Including MCI

Author	Sample Characteristics		Scan and ROI Procedures		Structure	% Change	$p \leq$ Value
Convit et al. 1993	Control	18	4 mm coronal manual	Control vs MCI:	Hippocampus	12	0.05
	MCI	17		Control vs AD:	Hippocampus	na	0.05
	MMSE	28			Parahippocampus gyrus	na	0.05
	Age	74			Fusiform gyrus	na	0.05
					Middle & inferior temporal gyri	na	0.05
	AD	15			Superior temporal gyrus	na	0.05
	MMSE	17			Cerebral spinal fluid	na	0.05
	Age	71					
Convit et al. 1997	Control	27	4 mm coronal manual	Control vs MCI:	Hippocampus	14	0.05
	MCI	22		Control vs AD:	Hippocampus	22	0.05
	MMSE	28			Parahippocampal gyrus	15	0.05
	Age	74			Fusiform gyrus	23	0.05
	AD	27			Middle & inferior gyri	15	0.05
	MMSE	18			Superior temporal gyrus	11	0.05
	Age	72			Cerebral spinal fluid	19	0.05
				MCI vs AD:			
					Hippocampus	10	ns
					Parahippocampus gyrus	11	0.05
					Fusiform gyrus	23	0.05
					Middle & inferior temporal gyri	9	ns
					Superior temporal gyrus	9	ns
					Cerebral spinal fluid	13	ns
De Santi et al. 2001	Control	11	1.3 mm & 4 mm coronal manual + automated	Control vs MCI:	Hippocampus	15	0.05
	MCI	15		Control vs AD:	Hippocampus	19	0.05
	MMSE	29			Ant parahippocampal gyrus	na	ns
	Age	75			Post parahippocampal gyrus	na	ns
					Superior temporal gyrus	10	0.05
	AD	12			Middle & inferior gyri	10	0.05
	MMSE	20			Fusiform gyrus	na	ns
	Age	76					
				MCI vs AD:	Middle & inferior temporal gyri	8	0.05
De Toledo-Morrell 2000	Control	34	5 mm coronal manual	Control vs MCI:	Hippocampus	9	0.05
					Entorhinal cortex	18	0.05
	MCI	28		Control vs. AD:	Hippocampus	25	0.05
	MMSE	27			Entorhinal cortex	32	0.05
	Age	69					
	AD	16		MCI vs AD:	Hippocampus	16	0.05
	MMSE	27			Entorhinal cortex	14	ns
	Age	71					
Du et al. 2001	Control	40	1.4 mm coronal manual + automated	Control vs MCI*:	Hippocampus	11	0.05
		36			Entorhinal cortex	13	0.05
	MCI	26			Cortical gray matter	na	0.05
	MMSE	75			White matter hyperintensities	na	0.05
	Age				Ventricular cerebrospinal fluid	na	0.05

studies have demonstrated that volumes of the hippocampus or other measures of the medial temporal lobe are significantly different in vascular dementia from AD patients,[43,105] others have not.[41] This may result from the fact that AD pathology frequently coexists with vascular components as well as the difficulty in diagnosing vascular dementia. Another factor may be the location and size of the infarcts in the specific patients selected for study; for example, if the infarcts encroach

TABLE 3. Continued

Author	Sample Characteristics		Scan and ROI Procedures		Structure	% Change	$p \leq$ Value
	AD	29		Control vs AD:	Hippocampus	27	0.05
	MMSE	18			Entorhinal cortex	39	0.05
	Age	76			Cortical gray matter	na	0.05
					Subcortical gray matter	na	ns
					White matter	na	0.05
					White matter hyperintensities	na	0.05
					Ventricular cerebrospinal fluid	na	0.05
					Sulcal cerebrospinal fluid	na	0.05
				MCI* vs AD:	Hippocampus	na	0.05
					Entorhinal cortex	na	0.05
					White matter	na	0.05
Xu et al. 2000	Control	30	1.6 mm coronal manual	Control vs MCI:	Hippocampus	na	0.005
					Entorhinal cortex	na	0.05
	MCI	30					
	MMSE	26		Control vs AD:	Hippocampus	na	0.005
	Age	78			Entorhinal cortex	na	0.005
				MCI vs AD:	Hippocampus	na	0.005
	AD	30			Enthorhinal cortex	na	0.005
	MMSE	21					
	Age	79					

AD, Alzheimer disease; MCI, subjects with cognitive complaints, mostly memory, but not necessarily fulfilling the Petersen criteria for MCI (Petersen et al., 1999); MMSE, Mini-Mental State Examination; Ant, anterior; Post, posterior; na, not available.

on the hippocampus, then the volume of the hippocampus would be unlikely to discriminate patients with vascular dementia from those with AD. In this context, it should be noted that at least one of the studies cited above stated that there were no large or strategic infarcts found in the temporal lobe that might explain the atrophy observed.[41] Thus, further MRI studies in patients with vascular disease who come to autopsy are needed to elucidate this issue.

Longitudinal MRI Measures in AD

There are few longitudinal studies of AD, in comparison to the large number of cross-sectional studies cited above (Table 2). Those longitudinal MRI studies that have focused on ROI measures of regions in the medial temporal lobe have demonstrated that hippocampal atrophy increases over time as AD patients become more impaired.[106-108] The annual rate of hippocampal volume loss is reported to be 2 to 3 times greater in mild AD patients than in controls, ranging from 45 to 8% per year.[107,108] A similar atrophy rate has been found in subjects with AD caused by mutation of one of the dominant AD genes.[109] The volume of the temporal lobe and the temporal horn has also been found to display significantly different rates in AD patients compared with controls.[106,107] Contrary to these findings, Kaye et al.[106] reported comparable annual rates of hippocampal atrophy in mild AD patients and controls; it is

noteworthy that these findings were derived from a sample of the oldest old (subjects older than 85 years).

Longitudinal MRI studies of whole brain atrophy have also been performed, primarily based on a method employing the boundary shift integral.[110-113] More recently, the same research group has also used a method known as voxel-compression mapping, which incorporates nonlinear scaling.[114] Both methods have been used to estimate change in atrophy over time by superimposing MRI scans, obtained at two points in time, on one another.

A significantly greater rate of brain atrophy has been reported in patients with mild- to moderate-AD versus controls (2.4%/year vs 0.4%/year), some of whom had a mutation in one of the dominant AD genes.[110-115] Using voxel compression, Scahill et al.[116] showed the progression of regional atrophy in AD. In the medial temporal lobe, increased rates of hippocampal atrophy were found in mild AD, with a shift toward lateral temporal and inferior temporal regions in moderately impaired patients. In addition, increased posterior cingulate atrophy was seen in mild AD. Increased rates of medial parietal lobe atrophy were present at all stages, whereas the frontal lobe was primarily involved later in the course of disease.

To date, the sample sizes of these studies have been small. Some have argued that the spatial normalization required by these and other whole brain methods limits the exact

volume determination, but others argue that automated measurements may be more accurate in the evaluation of longitudinal change than manually drawn ROIs.

MRI MEASURES OF ATROPHY IN PRODROMAL AD

It is increasingly recognized that AD has a long prodromal phase. The term mild cognitive impairment (MCI) is now widely used to refer to nondemented individuals with a memory complaint (corroborated by an informant), along with evidence of impaired memory function but preserved general cognition and activities of daily living[117] Individuals who meet criteria for MCI are at higher risk of being diagnosed with AD over time, with a reported rate of conversion of 12% to 15% per year compared with 1% to 2% per year in controls.[117,118] MCI can result from differing causes and clinical symptoms;[119] thus, MCI of the Alzheimer type will be the focus of this review and summarized in Tables 3 and 4.

Structural MRI studies measuring medial temporal lobe structures and global atrophy in prodromal AD addressed the question of whether there are measurable changes in MCI and whether they are predictive of subsequent diagnosis of AD (i.e., conversion to AD). The findings will be discussed in the following sections.

Medial Temporal Lobe and Related Structures

Hippocampus

Clinicopathologic studies in subjects similar to those with MCI have revealed neurofibrillary tangles and senile plaques in the hippocampus.[21,22] Cross-sectional MRI studies, comparing MCI subjects with controls and with mild AD patients, have demonstrated significant differences in the hippocampus, with volume reductions from 9.2% to 15% in subjects similar to those meeting criteria for MCI.[56,61,62,120] A single measure of the hippocampus discriminated the groups from one another with only a modest degree of accuracy, ranging between 60% to 76%.[60,61,64,120]

Some groups have also reported that a decrease in hippocampal volume is associated with subsequent progression to dementia in nondemented individuals with memory problems.[106,120,121] However, several groups have found that hippocampal volumes do not discriminate individuals who develop dementia within a few years from those who do not.[56,60,122] Increasing atrophy has been shown to be associated with increasing severity of symptoms reflecting the clinical stage of the patients,[123] suggesting that some of the differences between these studies may be related to the degree of impairment of the subjects.

Moreover, in asymptomatic individuals with an autosomal dominant mutation in the APP gene (know to cause early onset AD), decrease in hippocampal volume has been shown to precede onset of clinical symptoms by 1 to 2 years[109,114] and clinical diagnosis of dementia by 4 to 5 years.[114]

Entorhinal Cortex

As mentioned above, the entorhinal cortex demonstrates considerable neuronal loss in nondemented individuals with memory problems, with up to 60% neuronal loss in layer II of the entorhinal cortex.[57,124] Layer II gives rise to the perforant pathway, the major excitatory afferent to the hippocampus

In line with these findings, MRI studies have shown entorhinal cortex volume reductions in nondemented individuals with memory problems (between 13% and 17.9%) that were significantly different from that seen in AD patients or controls.[56,59,61,64] The entorhinal cortex has also been shown to be a good predictor of conversion to AD.[56,59,122]

Most studies have found that a measure of the entorhinal cortex alone shows only a modest ability to distinguish MCI patients from controls (i.e., 56% to 75%).[56,61,64] Although one recent study could distinguish between normals and individuals with prodromal AD with 84% accuracy, this measure could not be used to differentiate nondemented individuals with memory problems who would not progress to AD over several years from those who would.[60] To our knowledge, there have been no longitudinal MRI studies in the entorhinal cortex in prodromal AD.

Entorhinal Cortex Versus Hippocampus

There has been inconsistency with regard to which measures are best for discriminating individuals in the prodromal stage of AD. Comparing the entorhinal cortex to the hippocampus, some groups reported that the entorhinal cortex showed better discrimination ability,[56,60] whereas others have found it to be less or equivalent to that of the hippocampus.[61,64] Several groups have argued that a measure of the total volume of the entorhinal cortex, which is the one most frequently used,[63] is less reliable than the measure of the hippocampus.[54,64] A measure of the entorhinal cortex based on only 3 slices appears to have greater reliability.[59,60]

Parahippocampal Gyrus

Cross-sectional studies have demonstrated no significant difference in PHG volume between MCI subjects and controls.[62,86] There are only a few studies evaluating parahippocampal gyrus volume in prodromal AD. Kaye et al.[106] found no difference in the PHG volume at baseline between normal controls and individuals who subsequently converted to AD, whereas others have found the volume of the PHG predictive of subsequent conversion to AD.[48] The only longitudinal examination of the PHG to date reported no difference in progression rates among normal, very old controls and a group with "preclinical dementia."[106]

Temporal Neocortex

The volume of the temporal lobe, when added to hippocampal volume, leads to a classification accuracy of 80% in predicting which nondemented individuals with memory prob-

TABLE 4. Cross-Sectional MRI Studies Predicting Conversion to AD

Author	Sample Characteristics		Scan and ROI Procedures		Structure	% Change	$p \leq$ Value
Convit et al. 2000	Control	26	4 mm coronal manual	Decliners vs nondecliners:	Hippocampus * parahippocampus gyrus	7	ns
					Fusiform gyrus	14	0.05
	MCI	20			Middle & inferior temporal gyrus	9	0.05
	MMSE	28			Superior temporal gyrus	3	ns
	Age	75			Cerebral spinal fluid	29	0.05
	Decliners	14					
Dickerson et al. 2001	Control	34	5 mm coronal manual	Control vs MCI:	Hippocampus	na	0.05
					Entorhinal cortex	na	0.05
	MCI	28					
	MMSE	27		Control vs AD:	Hippocampus	na	0.05
	Age	69			Entorhinal cortex	na	0.05
	AD	16		MCI: vs AD:	Hippocampus	na	0.05
	MMSE	27			Entorhinal cortex	na	ns
	Age	71					
				Decliners vs	Hippocampus		ns
	Decliners	12		nondecliners:	Entorhinal cortex	na	ns
Janowsky et al. 1996	Control	60	5 mm sagittal manual	Control vs MCI*:	Corpus callosum	na	ns
					Cerebellum	na	ns
	MCI*	20			Pons	na	ns
	MMSE	27					
	Age	88		Control vs AD:	Corpus callosum	na	0.005
					Cerebellum	na	ns
	AD	39			Pons	na	ns
	MMSE	17					
	Age	72					
Killiany et al. 2000	Control	24	1.5 mm coronal manual	Control vs nondecliners:	Entorhinal cortex	33	0.00005
					Superior temporal sulcus	11	0.05
	MCI	79					
	MMSE	29		Control vs decliners:	Entorhinal cortex	36	0.0005
	Age	72			Superior temporal sulcus	24	0.005
					Anterior cingulate	52	0.05
	AD	16					
	MMSE	25		Control vs AD:		na	
	Age	68					
	Decliners	19					
Killiany et al. 2002	Control	28	1.5 mm coronal manual	Control vs nondecliners:	Hippocampus	7	0.05
					Entorhinal cortex	30	0.0005
	MCI	94					
	MMSE	29		Control vs decliners:	Hippocampus	9	0.05
	Age	72			Entorhinal cortex	37	0.0005
	AD	16		Control vs AD:	Hippocampus	16	0.05
	MMSE	24			Entorhinal cortex	40	0.0005
	Age	70					
				Decliner vs	Hippocampus	2	0.005
	Decliners	22		nondecliner:	Entorhinal cortex	10	0.05
				Decliner vs AD:	Hippocampus	8	0.05
					Entorhinal cortex	37	0.0005

TABLE 4. Continued

Author	Sample Characteristics		Scan and ROI Procedures	Structure		% Change	$p \leq$ Value
Visser et al. 1999	Control	14	5 mm, 1 mm gap coronal	Control vs MCI:	Hippocampus	na	na
					Parahippocampus gyrus	na	na
	MCI	13	manual		Temporal lobe	na	na
	MMSE	23					
	Age	79		Control vs AD:	Parahippocampus gyrus	12	0.05
	AD	7		Nondecliners vs decliners:	Parahippocampus gyrus	12	0.05
	MMSE	17					
	Age	80					

AD, Alzheimer disease; MCI, subjects with cognitive complaints, mostly memory, but not necessarily fulfilling the Petersen criteria for MCI (Petersen et al., 1999); MMSE, Mini-Mental State Examination; Decliners, subjects who decline to AD at clinical follow-up (includes MCI and/or Controls at baseline); Nondecliners, subjects who are MCI at baseline and show no change at clinical follow-up.

*Cognitively normal at baseline; MCI at clinical follow-up.

lems will develop AD over time.[106] The addition of the middle and inferior temporal gyrus volume to the volume of the hippocampus increases accuracy of prediction as well.[120] Likewise, the volume of the banks of superior temporal sulcus, together with the caudal portion of the anterior cingulate and the entorhinal cortex, increased the prediction of those who will convert to 93%.[59]

However, one study with a small sample size found no difference in lateral temporal lobe volume between converters and normals.[48] Similarly, the rate of temporal lobe volume loss differed significantly between controls and converters.[106] In a cross-sectional comparison among groups, measures of the fusiform gyrus or middle and inferior temporal gyrus added to the discrimination ability of the hippocampus.[62,86]

Cingulate

As mentioned above, there is pathologic evidence of early involvement of the cingulate. Using structural MRI measures, areas of the cingulate gyrus, such as its posterior portion and the caudal portion of its anterior part, have been shown to improve the accuracy of identifying those individuals who will convert to AD over time.[59,114] findings are consistent with a number of PET and SPECT studies of prodromal AD.[125-127]

Amygdala

There are, to our knowledge, no published studies examining the amygdala in prodromal AD.

Whole Brain Measures of Atrophy in Prodromal AD

Cross-sectional studies of whole brain atrophy have shown no significant difference between MCI subjects compared with controls.[86] However, a cross-sectional study, in which cerebral gray matter was segmented and ventricular CSF spaces were evaluated, demonstrated significant differences between MCI subjects and controls.[61] Likewise, MCI patients destined to be diagnosed with AD over time displayed 29.2% larger CSF spaces at baseline than nonconverters.[120]

Longitudinal studies using the brain boundary shift integral or voxel-compression mapping have shown an increased rate of whole brain atrophy among asymptomatic individuals with an autosomal dominant mutation of the APP gene compared with controls.[111-114] Likewise, increased hippocampal atrophy and lateral ventricle size have been shown in such presymptomatic early-onset AD individuals.[116] To date, this research group has focused on these familial early onset-cases of AD and have not, to our knowledge, published data pertaining to older individuals at risk for AD.

Influence of ApoE Genotype on MRI Measures of Atrophy

The E4 allele of the APOE gene is a well-known risk factor for late-onset AD.[128-132] However the E4 allele does not invariably cause the disease, and its specificity and sensitivity as a diagnostic marker are low.[133] Although the E4 allele is found 3 to 4 times more often in late-onset AD than controls,[134,135] it adds only 5% to 10% confidence to the diagnosis if AD when used in conjunction with a conventional diagnostic workup.[133]

The primary effect of the E4 allele is to lower the age of onset in a dose-dependent fashion.[128-132] There is an association of E4 with increased pathologic change in AD, such as amyloid deposition[136] and neurofibrillary tangle formation, although the findings concerning NFT have been somewhat controversial.[135,137–139]

Structural MRI studies have focused on the association of the APOE-4 allele and the volume of medial temporal lobe structures, with inconsistent findings. The most recent study, with the largest AD sample size so far, included 46 patients in

each of 3 groups (E3/3, E3/4, and E4/4) and, most importantly, matched the groups with regard to variables likely to affect brain volume, such as age, gender, disease duration, disease severity, and education (mean age 69.5 years). The authors demonstrated a dose-dependent relationship between the presence of an E4 allele and hippocampal and amygdala atrophy.[140] Other studies have shown increased hippocampal atrophy, of up to 40%, in AD patients with an E4 allele in a slightly younger population (subjects younger than 70 years).[141–143] However, another large study with an older population (mean age 75 years) reported no association between E4 status and hippocampal volume.[144] Of note is the fact that APoE-4 has been reported to exert its maximal effect before age 70, decreasing in penetrance with advancing age.[132]

Similarly discrepant are the results for the entorhinal cortex, which has been less often examined in conjunction with ApoE-4. Some studies have reported a 43% to 45% reduction of entorhinal cortex volume in E4-positive AD patients, compared with 205 to 27% in E4 noncarriers.[143,145] However, other studies have not replicated these findings.[146] Likewise, a recent study reported no significant difference in entorhinal cortex volume between controls and prodromal AD based on ApoE4 status.[60]

Recently, two groups reported a region-specific effect of E4 in AD patients in that they found not only smaller volumes of medial temporal lobe structures, but also larger whole brain or frontal lobe volumes in E4 carriers.[140,143,147]

The rate of hippocampal atrophy has not been found to differ in AD patients based on the E4 allele,[107,108] which is in accordance with some investigators who report that ApoE-4 does not influence the rate of clinical progression.[148] Nondemented E4 carriers have, however, been shown to display a steeper rate of hippocampal atrophy than noncarriers.[149]

Influence of ApoE-4 on the hemispheric asymmetry of the hippocampus has been another area of investigation. A reversal of asymmetry has been reported, changing from the right to left hippocampus in noncarriers to left to right in E4 homozygotes.[146,150] Again, other groups have not replicated these findings.[144,149]

It is likely that some of the reasons for the variation in results described above pertain to differences in age and gender of the study population, and the relation of these factors to the influence of the APOE-4 allele. Differences in sample size are also relevant. Future well-powered studies, adjusting for age and gender, are needed to clarify the significance of ApoE on MRI measures. In addition, much remains to be learned about the function of ApoE4 and how it exerts its effect, permitting these factors to be included in analyses.

CONCLUSION

Structural MRI abnormalities seem to reflect the ongoing pathology in AD as suggested by histopathology, with the entorhinal cortex and hippocampus being affected first and to a greater extent than other areas of the medial temporal lobe. Eventually, temporal neocortical association areas are affected. However, the exact temporal evolution of pathology beyond the above-mentioned structures is less well examined with MRI; data on structural alterations of the parietal and frontal neocortex are scarce.

Although there is wide agreement that statistically significant differences exist between prodromal or mild AD and controls for a number of measures, none of the measures alone is sufficient to be used as a diagnostic test. For example, individuals with prodromal AD seem to display measurable atrophy in the entorhinal cortex and hippocampus, and atrophy of these structures have predictive ability for who will progress to AD. Disagreement remains, however, concerning which measures are best. Nonetheless, studies show that combining ROI measures considerably increases the accuracy of discrimination. Likewise, studies focusing on specificity suggest that a combined pattern of atrophy may be more helpful than reliance on a single measure.

The few longitudinal studies that exist have shown that changes in medial temporal structures progress with advancing disease and thus might be useful in monitoring response to treatment. However, more longitudinal studies are needed to evaluate the sequence and pattern of atrophy and to compare different methods with one another. Specifically, manual measures of ROIs have not been compared with whole brain measures in the same individuals. Moreover, automated methods for identifying regions of interest are under development,[151] and these will also need to be competitively compared with other measurement techniques. The most important task therefore is to compare the different approaches to determine which is the most sensitive and thus can serve as the best potential surrogate marker for progression of disease.

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