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Magnetic resonance imaging of Alzheimer's disease

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Abstract A modern challenge for neuroimaging techniques is to contribute to the early diagnosis of neurodegenerative diseases, such as Alzheimer's disease (AD). Early diagnosis includes recognition of pre-demented conditions, such as mild cognitive impairment (MCI) or having a high risk of developing AD. The role of neuroimaging therefore extends beyond its traditional role of excluding other conditions such as neurosurgical lesions. In addition, early diagnosis would allow early treatment using currently available therapies or new therapies in the future. Structural imaging can detect and follow the time course of subtle brain atrophy as a surrogate marker for pathological processes. New MR techniques and image analysis software can detect subtle brain microstructural, perfusion or metabolic changes that provide new tools to study the pathological processes and detect pre-demented conditions. This review focuses on markers of macro- and microstructural, perfusion, diffusion and metabolic MR imaging and spectroscopy in AD.

Keywords Alzheimer's disease · MRI · Volumetry · Diffusion · Perfusion · Spectroscopy

Introduction

Alzheimer's disease and neurodegenerative dementias are growing health problems, since populations are constantly aging. The diagnosis of neurodegenerative diseases is therefore a challenge for modern neuroimaging techniques that extends them beyond their traditional role of excluding other conditions such as neurosurgical lesions. In addition, early diagnosis would allow early treatment using currently available therapies, such as cholinesterase inhibitors that improve or stabilize cognition more efficiently when administered in the early stages of the disease, or using new therapies in the future. Early diagnosis includes recognition of the pre-demented conditions, such as the identification of people with mild cognitive impairment (MCI) or with a high risk of developing AD.

The hallmark of Alzheimer's disease is the presence of extracellular deposits of β-amyloid plaques, intraneuronal neurofibrillary tangles (NFT) and neuropil threads (paired helical filaments containing abnormally phosphorylated

tau protein). Histological studies have shown that the progression of neurofibrillary changes in Alzheimer's disease follows a specific pattern in the brain [1, 2]. Lesion deposition begins in the entorhinal area, then the hippocampal formation, and extends sequentially toward the temporal neocortex, multimodal associative temporal areas, and other neocortical areas. Therefore, lesion burden and neuronal loss are higher in the medial temporal lobe (MTL) than in other brain regions [1, 2].

CT in Alzheimer's disease

Computed tomography (CT) is mainly used to rule out surgical causes of dementia. To obtain the best data, the CT scan should be performed using thin slices parallel to the long axis of the hippocampus. Helical acquisitions allow coronal reconstruction perpendicular to the long axis of the hippocampus and therefore a better visualization of medial temporal lobe atrophy. CT shows an enlargement of cerebrospinal fluid spaces, lateral ventricles, particularly the temporal horn of the lateral ventricle, and cortical sulci. CT studies showed that the rate of brain atrophy is larger than the annual rate observed in normal aging [3] and that the hippocampal fissure is wider than in age-matched non-demented people [4]. CT is less efficient than MR in identifying early positive signs of neurodegenerative dementias, i.e., medial temporal lobe atrophy in Alzheimer's disease. Therefore, MR is preferred over CT whenever possible.

MRI in Alzheimer's disease

Brain atrophy in Alzheimer's disease

MR acquisitions that are useful in Alzheimer's disease include high resolution T_1-weighted images perpendicular to the long axis of the hippocampus to evaluate medial temporal lobe atrophy (Figs. 1 and 2), axial or coronal T_2-weighted or FLAIR images to evaluate cerebrovascular pathology and white matter hyperintensities, and axial gradient echo T_2-weighted images to detect microbleeds in vascular dementia.

Rapid evolution of MTL atrophy on successive MR examinations is a highly evocative feature of AD (Fig. 3). For more than a decade, researchers have documented MTL atrophy using MRI morphometry. In the early 1990s, MRI replaced CT as a preferred method for the detection and quantification of brain atrophy. Initially, MRI measurements were performed in the MTL, including the hippocampus and the amygdala, then the entorhinal cortex using region-of-interest (ROI) methods. A few early studies used linear measurements [5]. This method is easy and quick, but provides an indirect estimate of MTL volumes. When rigorously applied, it can give a reliable estimate of hippocampal atrophy [6]. MR volumetry is theoretically the best method to assess atrophy when the intra- and inter-rater reliability has been thoroughly evaluated. MR volumetry is time consuming, requiring the manual outline of the ROI on each slice (Fig. 1); visual assessment of MTL atrophy was proposed as an alternative to volumetry [7, 8]. Visual assessment of MTL atrophy is easily applicable in clinical practice, but is subjective, highly observer dependent and does not provide a true quantitative assessment of the volumes. Therefore, most studies interested in MTL structures included MR volumetry [9]. New areas of research include the development of dedicated software for MR volumetry and computer-assisted diagnosis of AD.

The volume of the hippocampus is significantly reduced in Alzheimer's disease compared to control subjects, by 30–40% in moderate [5, 9–11], 20–30% in mild (MMS greater than 20) [12–18] and about 10–12% in early Alzheimer's disease (MMSE about 27) [19]. Measurements of the entorhinal cortex are more difficult because

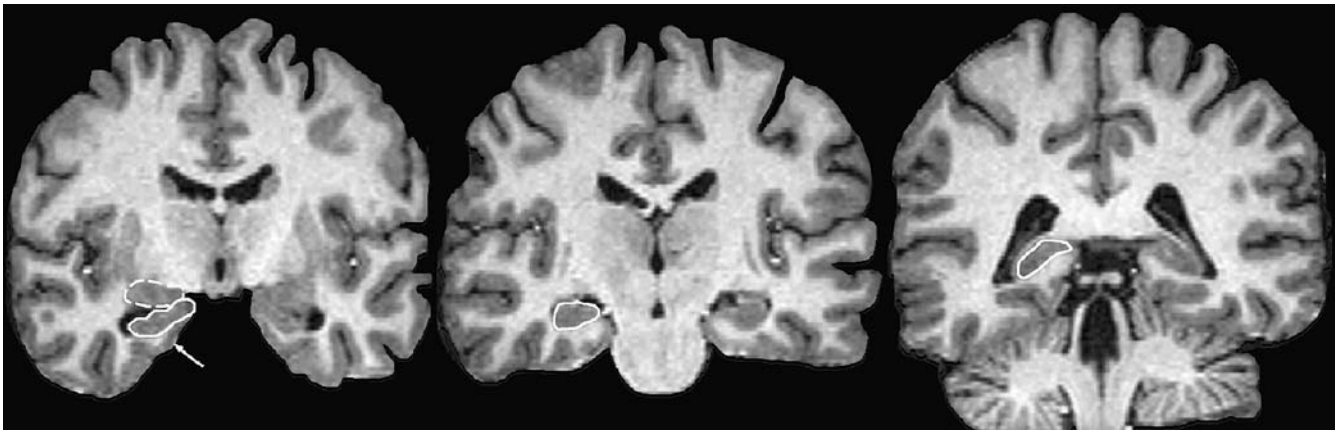

Fig. 1 MR anatomy of the medial temporal lobe. Oblique coronal slices perpendicular to the long axis of the hippocampus passing at the level of the head (*left*), the body (*middle*) and the tail of the hippocampus (*right*). The contours of the hippocampus (*solid line*) and the amygdala (dashed line) are shown. The *arrow* points to the entorhinal cortex

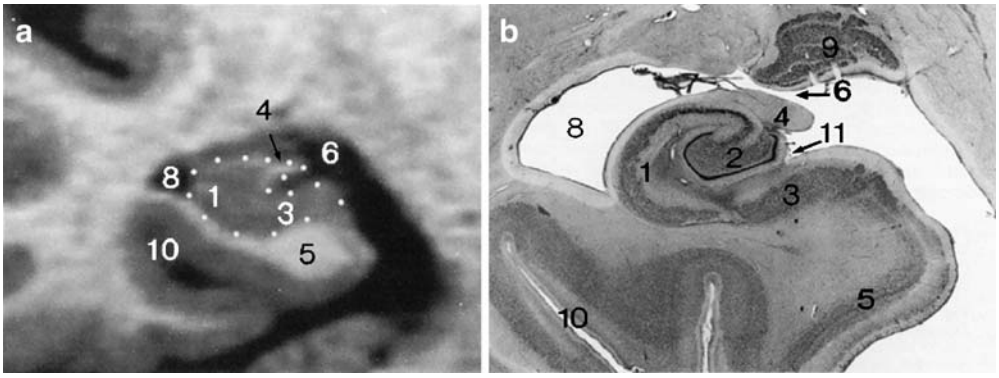

Fig. 2 Histological MR comparison of the hippocampus. **a** Coronal MR slice passing at the level of the body of the hippocampus. The hippocampal formation is outlined using *white dots*. **b** Corresponding histological slice (courtesy of Michel Baulac): (1) Ammon's horn, (2) dentate gyrus, (3) subiculum, (4) fimbria, (5) parahippocampal gyrus, (6) transverse fissure, (7) choroids plexus, (8) temporal horn, (9) lateral geniculate body, (10) collateral sulcus, and (11) hippocampal sulcus

the anatomical boundaries of the structure are not as easy to determine. According to models of disease progression in AD [2], atrophy of the entorhinal cortex should be more severe than hippocampal atrophy in early stages of Alzheimer's disease. This was confirmed in some studies, which reported higher atrophy of the entorhinal cortex than the hippocampus in early AD [19]. Some studies indicated that entorhinal cortex measurements have a higher sensitivity to differentiate AD patients from control subjects [19–23], whereas other studies did not [24–26]. Overall, the sensitivity and specificity of hippocampal and entorhinal cortex measurements to distinguish patients from age-matched control subjects are in the range of 80–100% and 80–95%, respectively.

Aside from ROI approaches, computerized morphometry methods have gained great interest because they allow whole brain analysis and do not depend on the examiner's abilities. Voxel-based morphometry (VBM) has become a tool of predilection to study the anatomical differences between two populations [27]. VBM is an automatic whole brain method that compares signal intensity voxel by voxel. VBM has been widely used to compare AD populations to healthy elderly subjects [28–31]. Using VBM, several studies have reported differences in the grey matter between controls and mild to moderate AD in the posterior and temporal areas (Fig. 4) [28–35]. Patients with early onset (age ≤65 years) showed greater neocortical atrophy at the temporoparietal junction than patients with late onset [36]. VBM may be more accurate than hippocampal volumetry to detect medial temporal lobe atrophy in Alzheimer's disease, but this needs to be confirmed in larger series [37, 38].

Several imaging methods have been developed to follow disease progression and understand the effects of disease in AD. Earlier studies used serial manual measurements of the hippocampus [39]. More recent studies have used specific software that normalizes brain structures into a common reference space, allowing statistical comparisons and group difference mapping [40, 41]. Some software also match cortical features across individuals, by warping one brain surface onto another [42, 43]. Iterative principal component analysis by considering voxel intensity pairs from co-registered MR images has also been successfully used to map sequential volume changes [44]. Atlas-based automatic segmentation of the hippocampus has been reported [45]. Overall, the annual rate of hippocampal atrophy in AD was calculated at 2.2% [46] to 3.6–5.9% [20, 39, 47] compared to 0.24% [46] to 1.4–1.73% [39, 47] in age-

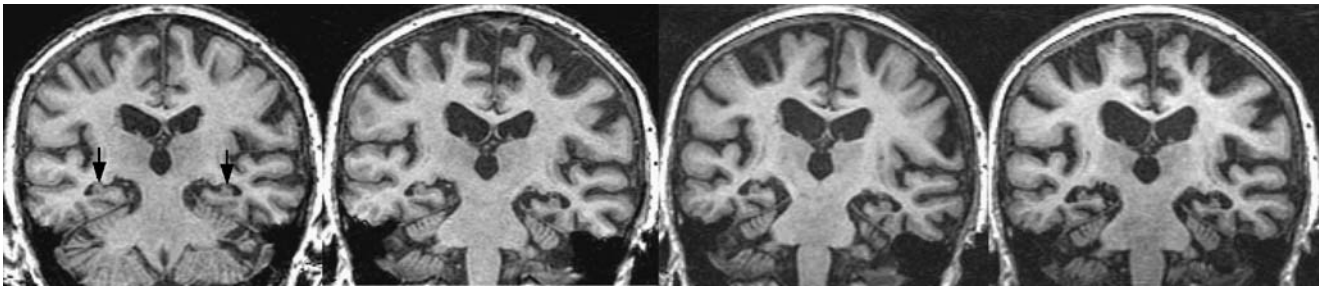

Fig. 3 Progression of hippocampal atrophy in Alzheimer's disease. From *left* to *right*, the yearly examination of the same subject is shown. Increasing hippocampal and parahippocampal atrophy is observed over time as well as ventricular enlargement and widening of cortical sulci. The *arrows* point to the hippocampus

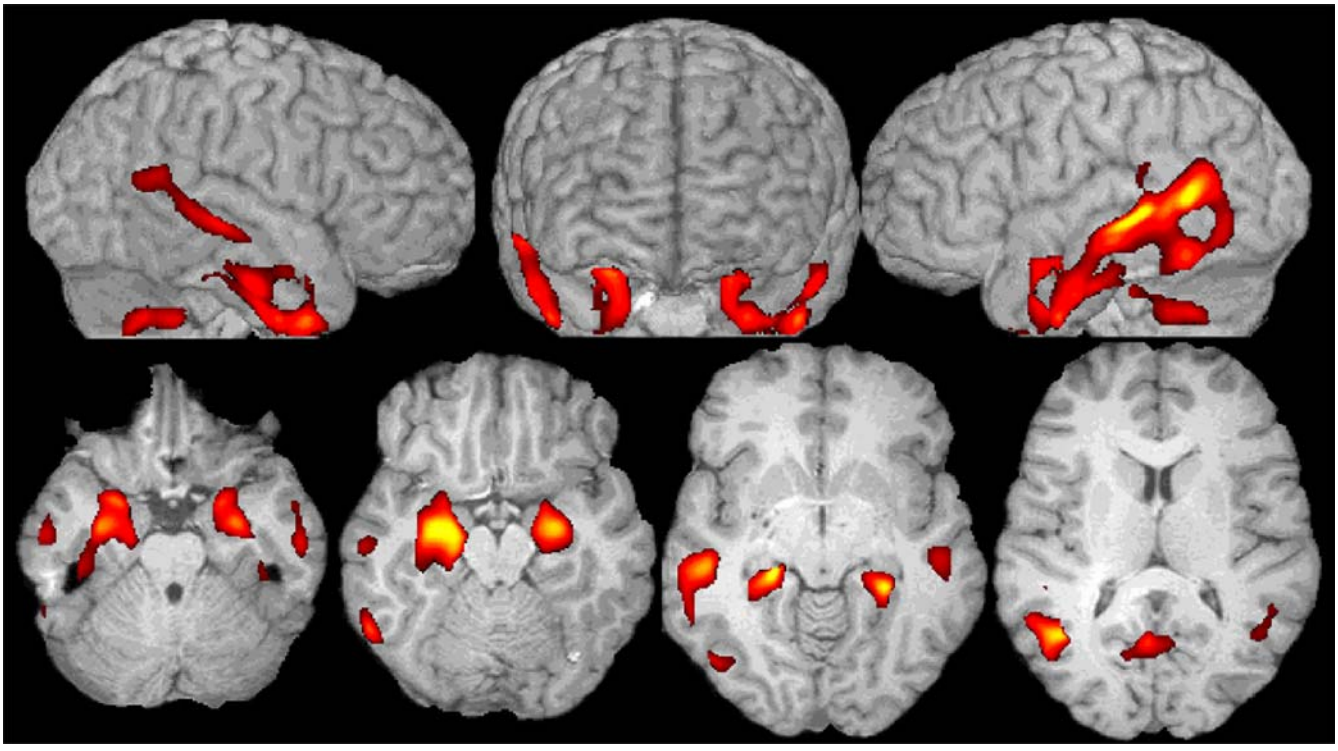

Fig. 4 VBM comparison of patients with Alzheimer's disease and age-matched control subjects. Maps of significantly lower grey matter density in 15 patients with Alzheimer's disease (MMSE =20.9±3.7) compared to 15 age-matched control subjects. Maps are superimposed on a three-dimensional surface rendering (*upper row*) and on axial slices of a brain template (lower row). Clusters were significant at $P<0.05$ corrected for multiple comparisons. Grey matter density was decreased in the medial temporal lobe structures, the lateral temporal and inferior parietal areas, the posterior cingulum, and the cerebellum

matched control subjects. The annual rate of entorhinal cortex atrophy in AD was about 7 to 8% [20, 47, 48]. Dynamic maps of disease progression in AD show a spreading wave of grey matter loss extending from limbic to frontal cortices, whereas the sensorimotor cortex is relatively spared [43], in agreement with postmortem observations [1, 2].

Basal forebrain atrophy in Alzheimer's disease

Degeneration of cholinergic neurons in the basal forebrain, including the nucleus basalis of Meynert, is another feature of AD [49, 50]. The cholinergic deficit partially contributes to the cognitive deficits observed in AD and is the basis for the use of cholinesterase inhibitors. Atrophy of the substantia innominata was observed in AD patients and was more pronounced in patients who responded to cholinesterase inhibitors [51, 52].

Brain atrophy in patients with risk factors of Alzheimer's disease

In line with histological findings, MR studies have shown that MTL atrophy was present before subjects developed the first symptoms. Longitudinal studies of subjects with a family history of Alzheimer's disease [46, 53–55], carriers of apolipoprotein E4 (apo E4) [56, 57] and normal elderly subjects [47, 58] have detected MTL atrophy in subjects who developed Alzheimer's disease. In subjects who developed dementia during the study, the hippocampal volume at entry was smaller than in subjects who did not develop dementia. The annual rate of atrophy was either similar for the two groups [58] or higher in subjects with familial risk factors who became demented (1.5% per year in demented and 0.2% in non-demented subjects) [46, 53, 54] or in carriers of apo E4 (2.86% in apo E4+ and 0.85% in apo E4– subjects) [59]. Similarly, the rate of temporal atrophy was higher in normal subjects who converted to dementia during the follow-up [47, 58]. The annual rate of hippocampal atrophy was increased in presymptomatic subjects and to a greater extent when the first cognitive symptoms have occurred [46].

Medial temporal lobe atrophy in mild cognitive impairment

MCI defines a state of cognition where the deficiency is greater than expected for subjects of the same age and socio-cultural background, but not severe enough for

dementia. The concept of MCI is not grounded on a causal mechanism and encompasses a heterogeneous population of patients, including those with other degenerative or vascular diseases, and with attention deficits such as those observed in metabolic or iatrogenic disorders, depression or anxiety. Although all patients with MCI do not develop Alzheimer's disease, they present an increased risk of progression to dementia [60–63]. A fundamental question is thus to determine whether the diagnosis of Alzheimer's disease can be made at this stage. This is particularly important in the selection of patients that can benefit from future treatment.

Given the pattern of progression of histological lesions in Alzheimer's disease, the medial temporal lobe, and particularly the hippocampus, is the structure where early lesions are expected in MCI patients who will develop Alzheimer's disease. Early studies have shown abnormalities in hippocampal volumes in patients with mild cognitive impairment [64, 65]. A 10 to 20% reduction in hippocampal volume was reported in MCI patients [21, 26, 65–72]. Using VBM, reduced grey matter density was observed in the medial temporal lobe and the posterior association cortex of MCI patients [73–75]. Moreover, greater grey matter loss was observed in the medial, inferior and middle temporal areas, posterior cingulate, and precuneus in MCI patients who developed Alzheimer's disease relative to non-converters [74] (Fig. 5). In AD patients, the hippocampal region's atrophy observed in MCI patients extends to the neighboring temporal association neocortex.

Longitudinal MRI studies using an individual's first scan as the reference have shown that MTL volumes can predict which MCI subject will develop AD. Atrophy of the hippocampus [67] and the entorhinal cortex [68, 76, 77], as well as an increased rate of atrophy [47, 78, 79], measured using MRI, were associated with an increased risk of

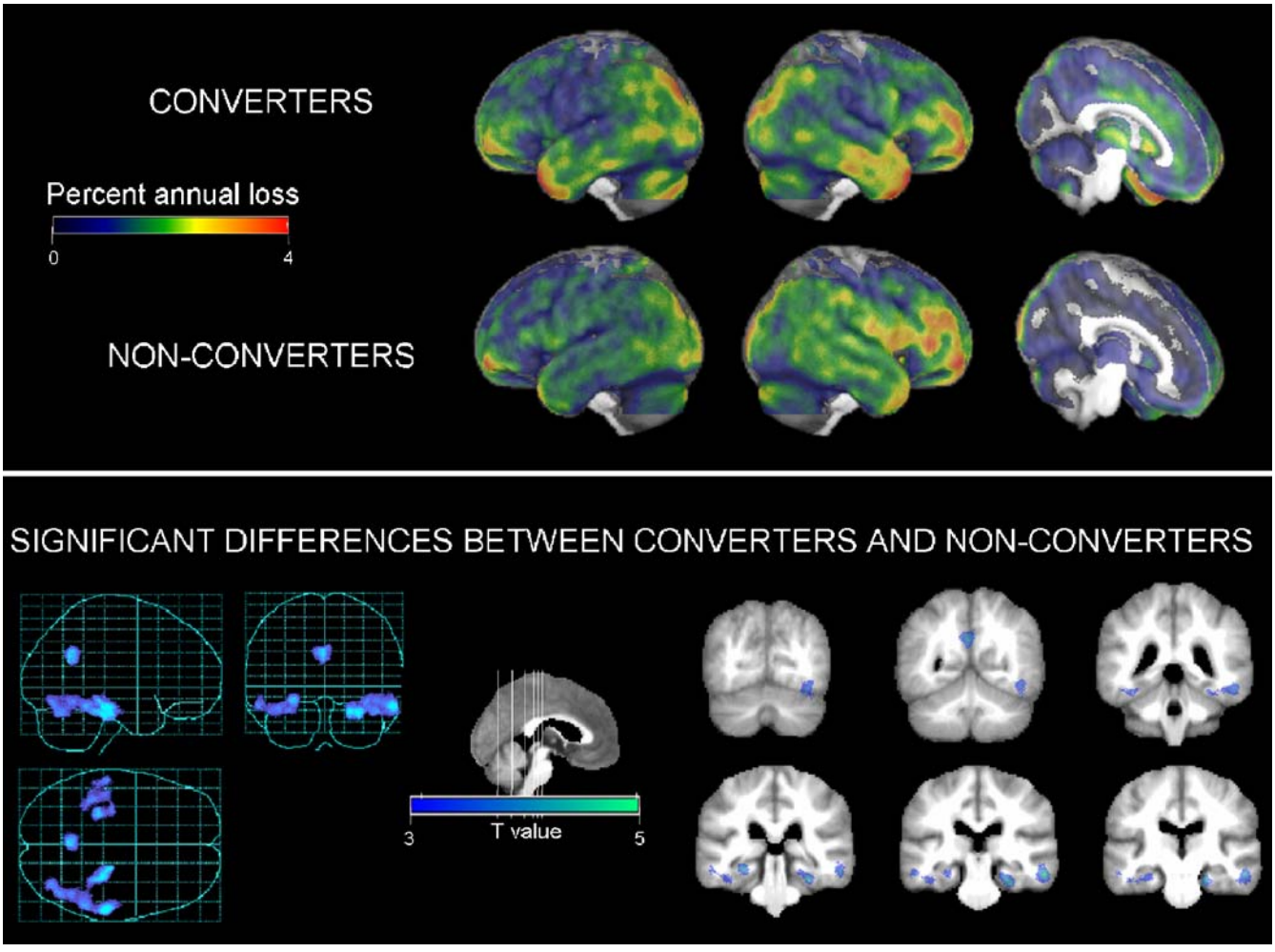

Fig. 5 VBM differences in MCI patients who developed Alzheimer's disease compared to non-converters. *Top*: surface rendering of the maps of percent annual gray-matter loss in converters and in non-converters (from left, right, and medial viewpoints). *Bottom*: significant clusters of greater grey-matter loss in converters relative to non-converters as projected onto the 'glass-brain' representation of SPM (*left*) and onto coronal sections of a whole-brain template (*right*) (courtesy of Gaël Chetelat, Ph.D.)

Alzheimer's disease. Similar results were obtained using visual scaling [80]. The annual rate of hippocampal atrophy was higher in MCI patients whose cognitive impairment increases over time (3.69%) compared to stable patients (2.55%) and control subjects (1.73%) [78]. Measurements of the volume of the entorhinal cortex, the superior temporal sulcus and the anterior cingulate cortex differentiate control subjects from patients with AD, as well as 93% of MCI patients who will develop AD, and 85% of MCI patients who will not develop AD [68]. However, the goal is not to define structural predictive factors of Alzheimer's disease, but to diagnose patients with a pre-demented stage of Alzheimer's disease among MCI patients. Recently, a longitudinal study of 205 aged subjects and MCI patients followed over 5.5 to 8.5 years has shown that MR volumetric measurements of the hippocampus were able to help predict the conversion of MCI patients to AD [61]. In this study, the best predictive model was obtained when genetic susceptibility factors, specific memory tests, and volumetric measurements of the hippocampus were combined. A large multi-site longitudinal MRI and FDG-PET study, the Alzheimer's Disease Neuroimaging Initiative (ADNI http://www.ADNI-info.org), has recently started to develop improved imaging methods to measure longitudinal changes of the brain in normal aging, during the transition to early Alzheimer's disease, and in Alzheimer's disease patients [81].

It should be noted that MTL structures decrease in size with normal aging, mainly the hippocampal formations [39, 47, 53, 58, 82, 83], as well as the temporal cortex [83] and temporal gray matter [82]. However, atrophy in MCI patients is more marked than in normal aging.

Medial temporal lobe atrophy in patients with other degenerative diseases

MTL atrophy has been reported in other dementias, such as Parkinson's disease (with or without dementia) [84, 85], dementia with Lewy bodies [86, 87] and vascular dementia [88]. MTL atrophy is more severe in Alzheimer's disease than in these diseases, however. The rate of progression of MTL atrophy over time is also higher in patients with Lewy body dementia and vascular dementia than in aged-matched controls [89]. Therefore, MTL atrophy is apparently not specific for Alzheimer's disease. Other neurodegenerative diseases are associated with atrophy in other brain regions that depends on the type of neurodegenerative process. This suggests that whole brain analysis of the profiles of grey matter loss has better potential to differentiate neurodegenerative dementias [34, 90, 91].

Correlations between structural lesions and neuro-psychological deficits

Early CT studies have reported correlations between performances in global measurements of cognitive functions, such as the MMSE [92] or the Mattis Dementia Rating Scale, and global measurements of atrophy such as ventricular enlargement [3].

A deficit in recent memory is generally predominant at the early stage of Alzheimer's disease [93, 94]. Classically, this deficit relates to lesions of medial temporal lobe structures that are affected early in AD [1, 2, 95]. Several studies have confirmed that volumes of MTL structures, and particularly the hippocampus, were correlated with memory performances [20, 84, 96–101]. Correlations were also reported with the entorhinal cortex [20, 47].

The correlation between MTL structures was specific to memory performances [96, 97, 102], in line with the specific role of the MTL structures in early memory impairment observed in the disease. Overall, the correlation was higher for delayed than for immediate memory tasks [96, 97]. Performances at verbal memory tests correlated best with left MTL volumes, whereas performances at non-verbal memory tests correlated best with right medial temporal lobe volumes [98–100]. This specificity indicates that hippocampal atrophy does not correlate with global indices of cognitive impairment, but is specifically associated with memory function deficits. Memory scores were less correlated with volumes of the para-hippocampal gyrus or the temporal lobe [99, 100]. As already mentioned, these structures are more difficult to measure and therefore correlations may be more difficult to determine. Indeed, a recent study reported that the Delayed List Verbal Recall test correlated significantly with atrophy rates of the entorhinal cortex [20].

Other studies have reported correlations between non-memory tests and various brain regions. Anterior and inferior structures of the left temporal lobe were related to semantic memory deficits, as suggested by the difference in patterns of atrophy between semantic dementia (predominance in the left infero-anterior temporal regions) and Alzheimer's disease (symmetric temporal atrophy without antero-posterior gradient) [103]. Impaired naming difficulties correlated with grey matter atrophy in the left anterior-lateral temporal and anterior cingulate regions [33]. A selective correlation between performances at verbal fluency tests and the frontal lobe volumes was observed, in line with the role of the frontal lobe in the generation of verbal and non-verbal material, whereas this correlation was not observed with MTL structures [104].

In contrast to ROI studies, VBM or other whole brain techniques allow the correlation of neuropsychological variables and grey matter loss in the entire brain. Indeed, significant positive correlations were observed among the MMSE scores and temporal, posterior cingulate gyri, and precuneus regions in AD patients [31, 90], as well as

hippocampal atrophy and enlargement of the temporal horn of the lateral ventricle [105].

White matter pathology in Alzheimer's disease

Vascular lesions can occur in AD. Vascular risk factors such as hypertension, hypercholesterolemia, and apolipoprotein E4 allele may predispose to AD [106, 107]. Changes in the endothelium and amyloid angiopathy have been described in AD [108]. Over 60% of patients with Alzheimer's disease present white matter lesions [109]. The clinical differentiation of vascular dementia from Alzheimer's disease with cerebrovascular disease can therefore be difficult [110]. Vascular lesions are milder in AD as compared with vascular dementias, however. The recognition of white matter and other vascular lesions in AD is important, since vascular pathology can lower the threshold for dementia or increase its severity [111–113]. Vascular lesions may represent a target for treatment.

Other MRI techniques

Beside MR morphometry, several more recent imaging techniques have shown a potential to detect early abnormalities in AD that may be useful in the clinical diagnosis of dementias. These techniques include perfusion, diffusion, spectroscopy and microscopy.

– Perfusion MRI
  Perfusion MRI techniques can assess cerebral perfusion (cerebral blood volume and cerebral blood flow).

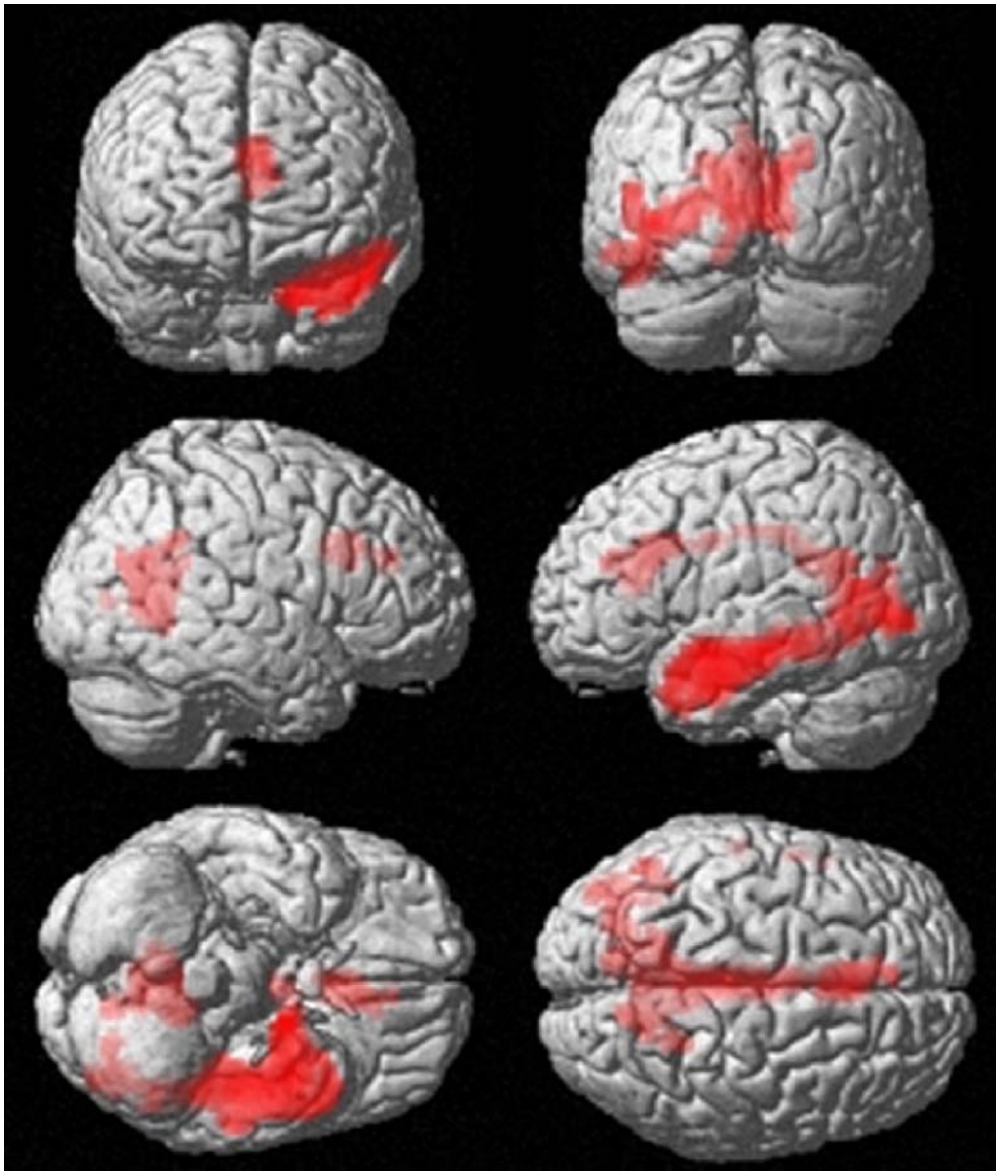

Fig. 6 Voxel based-DTI comparison of patients with Alzheimer's disease and age-matched control subjects. Maps of significantly higher FA in ten patients with Alzheimer's disease (MMSE =24.0±3.5) compared to ten age-matched control subjects (MMSE =28.0± 1.6). Maps are superimposed on a three dimensional surface rendering of a template brain (upper left: anterior view; upper right: posterior view, middle: lateral views, lower left: inferior view, lower right: superior view). Clusters were significant at $P<0.05$ corrected for multiple comparisons. FA was decreased in frontal, parietal and temporal structures and the cerebellum

They therefore have the potential to depict functional deficiencies in a way similar to HMPAO SPECT [114–116]. Techniques using radiotracers have consistently shown a reduction in cerebral blood flow in patients with AD, in the temporo-parietal association areas, the posterior cingulate cortex, and, to a lesser extent, in frontal association areas with relative sparing of the primary motor and sensory areas [114–118].

Cerebral perfusion can be assessed using contrast-enhanced techniques that require the injection of a paramagnetic contrast agent. In Alzheimer's disease, reduced perfusion was reported in parietal areas using contrast-enhanced perfusion imaging [119]. Arterial spin labeling (ASL) techniques use electromagnetic labeling of water in the blood to acquire images sensitive to flow without any external contrast agents [120]. Initially limited to the acquisition of a few slices only, recent technical advances have allowed the acquisition of multiple slices [121] and absolute quantification [122]. In Alzheimer's disease, cerebral perfusion assessed using ASL techniques was altered in the parietal, temporal and cingulate regions, similar to those seen in HMPAO SPECT [119, 123–125]. Perfusion in posterior parietal and cingulate areas correlated with neuropsychological performances such as memory scores [123] or the MMSE [124]. By the assessment of cerebral blood flow in AD with spin labeling techniques, MRI has the potential to assist in the diagnosis of neurodegenerative dementias.

– Diffusion imaging

Diffusion-weighted imaging (DWI) is sensitive to the random motion of water molecules in the brain. Measures of water diffusivity from DWI provide an estimate of the microstructural integrity of the brain parenchyma. Diffusion tensor imaging (DTI) can also detect the directionality of molecular diffusion in the white matter and allows the demonstration of fiber tracts in vivo in humans [126–128]. The directionality dependence of diffusion is called anisotropy and is measured using indices such as fractional anisotropy (FA) [129].

Increased diffusivity has been reported in the temporal lobe [130, 131] and the posterior white matter [132] of patients with Alzheimer's disease, as well as MCI subjects [133, 134]. Increased diffusivity can reflect a change in the ultrastructural organization of brain tissue or represent an index of neuronal atrophy. In contrast, brain anisotropy was decreased in several white matter regions including the corpus callosum, the cingulum, the superior longitudinal fasciculus [135–138] or the area of the perforant pathway [139], reflecting a change in the white matter bundles connecting the brain areas affected in AD (Fig. 6). In MCI subjects, higher baseline hippocampal diffusivity was associated with a greater risk of progression to AD [140]. Similarly to voxel-based morphometry, voxel-based comparison of anisotropy maps showed reduced FA in posterior brain regions [141]. DTI abnormalities showed some correlation with measures of cognitive performances. Left hippocampal volumes were associated with poor verbal memory performance, particularly when associated with high diffusivity values [133]. Performance in the delayed verbal recall test correlated significantly with posterior cingulate bundle anisotropy and diffusivity [136]. Although the neurobiological abnormalities that result in abnormal DTI are not completely understood, DTI is a useful tool for the in vivo detection of microstructural abnormalities in AD. Improvements in diffusion techniques should further enhance the information that can be derived from DTI.

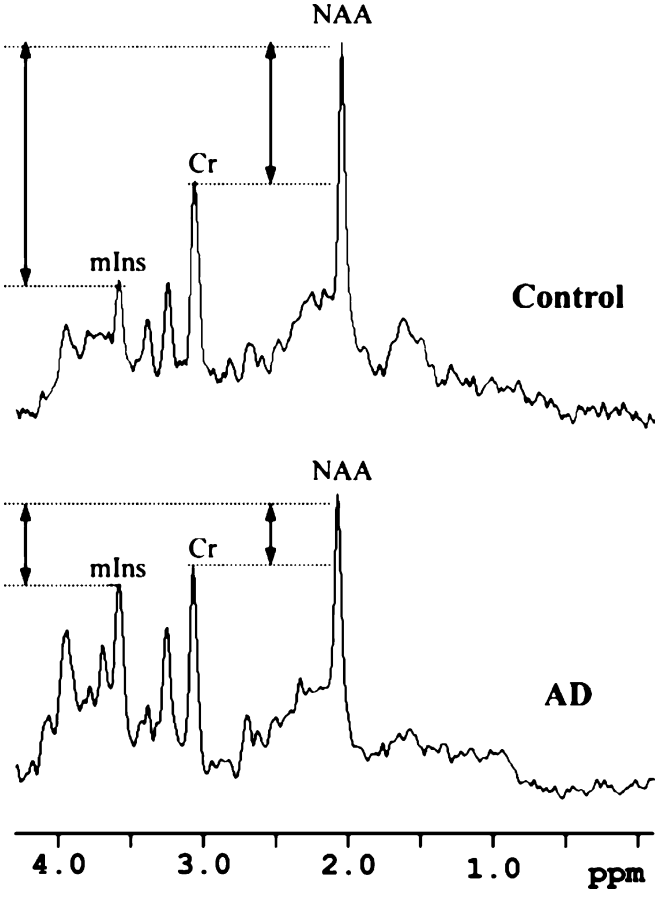

Fig. 7 *^{1}H MR spectra comparison of a patient with Alzheimer's disease and age-matched subject*. MR spectra obtained using single voxel spectroscopy with short echo time (30 ms) from the posterior cingulate in an age-matched control subject (*top*) and in a patient with Alzheimer's disease (*bottom*). NAA/Cr ratio is lower in the patient with AD than in the control subject, and mIns/Cr ratio is higher in the AD patient than in the control subject (courtesy of Kejal Kantarci, M.D.)

In Alzheimer's disease, white matter abnormalities had already been reported in the corpus callosum using measurements on T_1-weighted images [142, 143]. Atrophy predominated in the posterior part of the structure, whereas the anterior part was atrophic in fronto-temporal dementia.

– Magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (^{1}H MRS) provides information about the levels of metabolites in the brain. Metabolite levels are sensitive to different in vivo pathological processes at the molecular or cellular level; consequently, they can provide both qualitative and quantitative information about the degenerative process. Different metabolites provide information about different processes; for example, *N*-acetylaspartate (NAA) is believed to be a marker for neuronal number and health; choline-containing compounds (Cho) are markers of demyelination and cell proliferation; *myo*-inositol (mIns) is thought to be a marker for osmotic stress or astrogliosis; lactate is frequently associated with the presence of pathology.

In most AD studies, the metabolite levels are reported as their ratios over the sum of creatine and phosphocreatine (Cr). Cr is used as a concentration reference, since its concentration is regarded as being relatively stable. Two methods are generally used to obtain information about the levels of metabolites in the brain: chemical shift imaging (CSI is also referred to as spectroscopic imaging) and single voxel spectroscopy. CSI can provide information about the spatial distributions of metabolite levels from multiple slices simultaneously (3D-CSI), with the drawback of providing information mostly about NAA, Cho and Cr, especially when run at a long echo time, and with problems with implementation of efficient water suppression. There is usually not enough signal to quantify the concentration of mIns or other *J*-coupled metabolites. The metabolite levels cannot be obtained from the entire brain due to the problems with magnetic field homogeneity when optimizing large volumes of interest and with lipid artifact signals when the borders of the VOI are too close to the skull. The

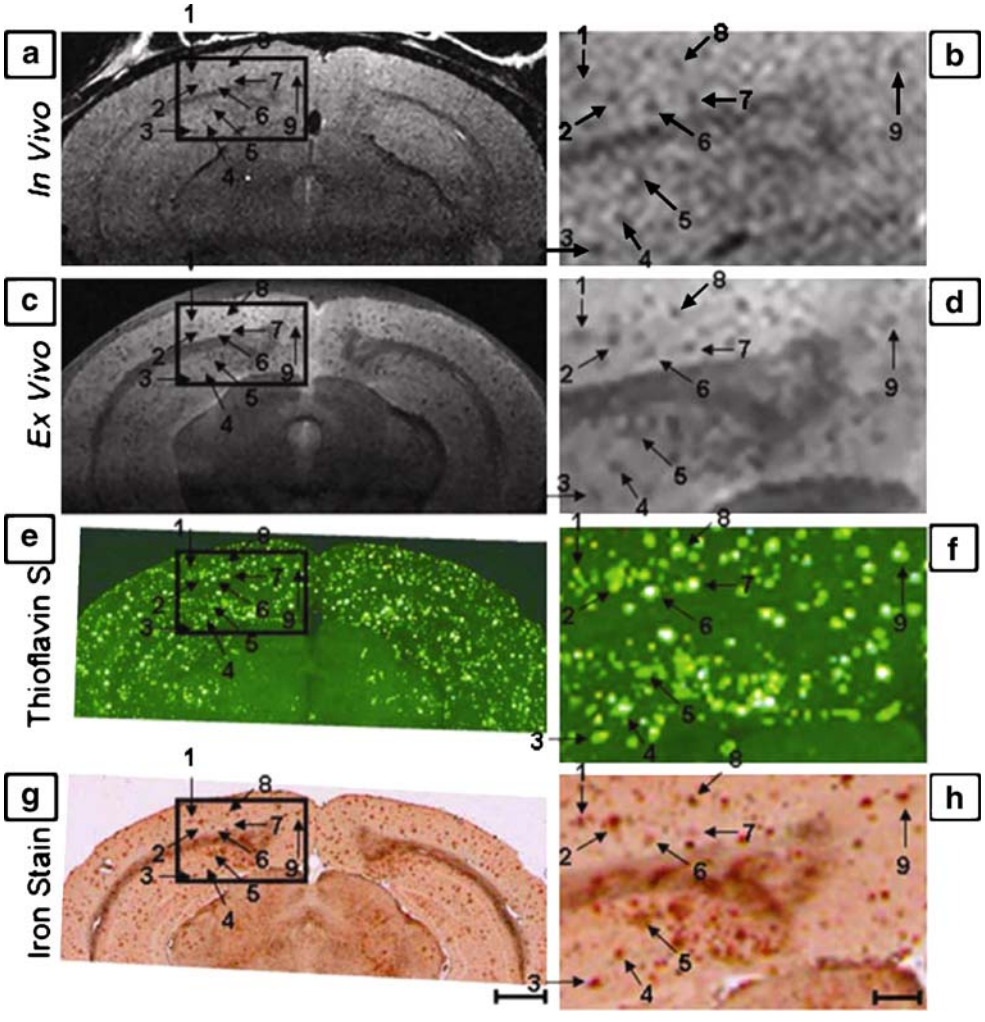

Fig. 8 MR microscopy Four-way correlation in a 24-month-old AD mouse. In vivo MR microscopy (**a**, **b**), ex vivo MR microscopy (**c**, **d**), thioflavin-S-stained (**e**, **f**), and iron-stained (**g**, **h**) images have been precisely spatially registered over a circumscribed area of the cortex, indicated by the *box*. The *boxes* in the *right column* represent 3× magnified portions of the adjacent parent image in the *left column*. The *numbered arrows* indicate individual plaques visualized in each of the four different image types (reprinted with permission from [174], copyright 2005 by the Society for Neuroscience)

single voxel spectroscopy run at shorter echo times allows a good quantification of *J*-coupled metabolites such as mIns, but the information is coming from one spatial location in the brain. In AD, both spectroscopy methods have been used.

The proton spectrum is drastically different in AD patients from normal subjects with reduced NAA/Cr and with elevated mIns/Cr [144] (Fig. 7). The ratios of NAA/Cr, NAA/Cho and NAA/mIns are consistently decreased [145–149]. A larger decrease in the NAA level has been reported in the temporal lobe tissue in patients with AD compared with controls than in the rest of the brain, which showed a seemingly uniform decrease [150]. The decrease in NAA ratios accelerates with the disease progression [151], and changes in NAA concentration are detectable early in the progression of the disease [152]. Cognitive dysfunction of demented subjects was significantly correlated with a reduction of NAA in some studies [153], but not in others [149]. Note that in healthy elderly people NAA does not change significantly with further aging [154] and that those individuals with a higher white matter Cho/Cr ratio were shown to have a higher risk of developing dementia or AD within 4 years [155]. The raised mIns/Cr levels allow for the distinction between AD patients and cognitively normal elderly subjects. The mIns levels were raised uniformly throughout the brain [150]. Elevated levels of mIns were also observed in frontotemporal lobar degeneration (FTLB) [156] and mild cognitive impairment (MCI) patients [157]. NAA/mIns ratios distinguished clinically diagnosed patients with AD from cognitively normal elderly with a sensitivity of 83% and specificity of 98% in one cohort [146], and a sensitivity of 82% and specificity of 80% in another [158]. There are conflicting reports about Cho levels in AD. Some studies identified elevated Cho levels [156], and others did not [150, 159]. Decreased levels of glutamate + glutamine (Glx) have been reported using single voxel spectroscopy [160, 161]. In spite of the fact that lactate was found in a significant portion of elderly persons [162] and was observed in the CSF in Alzheimer's disease [163], no studies have reported increased brain tissue lactate levels in Alzheimer's disease.

– MR microscopy

Amyloid plaques in patients with AD range in size from 2 to 200 μm. The direct imaging of plaques requires very high spatial resolution. Although scintigraphic markers (such as the "Pittsburgh-B" compound) have been developed that can visualize the plaque burden with positron emission tomography (PET) in living Alzheimer's patients [164–166], individual plaques are beyond the resolution of PET. Very high field magnets (≥7 T) allow very high spatial resolution and therefore MR microscopy. Individual plaques were first evidenced at 7 T using a gradient echo T_2-weighted sequence and a spatial resolution of 40 μm cubic isovoxel size [167]. Plaques appeared as dark round spots, probably because they contain metals such as iron. This finding was not replicated in another study that reported the dark spots to be vascular structures [168]. Later studies in ex-vivo transgenic mouse brain specimens confirmed that plaques could be imaged at 7 T [169–172] (Fig. 8). These methods are not yet applicable to human studies as the imaging time was greater than 10 h. Recently, the imaging time was reduced to 1 h-1 h 30 m using optimized sequences at 9.4 T, and images were obtained for the first time in a transgenic mouse in vivo [173, 174]. Scanning time is thus approaching a reasonable time for in vivo human studies. Additionally, the amyloid plaques have been detected in mice with ^{19}F MRI using a ^{19}F-containing amyloidophilic probe [175]. The images were obtained in 2 h with virtually zero background noise since ^{19}F is absent in living beings. The used resolution did not allow the detection of the individual plaques in vivo.

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