ACADEMIC PRESS

Available online at www.sciencedirect.com

SCIENCE DIRECT®

NeuroImage

NeuroImage 18 (2003) 525–541

www.elsevier.com/locate/ynimg

Review

Early diagnosis of Alzheimer's disease: contribution of structural neuroimaging

Gaël Chetelat[a] and Jean-Claude Baron[b,*]

[a] *INSERM E0218, University of Caen, France*
[b] *Department of Neurology, University of Cambridge, Cambridge, UK*

Received 20 May 2002; revised 6 August 2002; accepted 18 September 2002

Abstract

To accurately predict the development of Alzheimer's disease (AD) at its predementia stage would be a major breakthrough from both therapeutic and research standpoints. In this review, our focus is on markers obtained with structural imaging—especially magnetic resonance imaging (MRI)—and on studies of subjects at risk of developing AD. Among the latter, amnestic mild cognitive impairment (MCI) is currently the most commonly accepted reference, and therefore is specially targeted in this review. MCI refers to patients with significant but isolated memory impairment relative to subjects of identical age. Consistent with established histopathological data, structural imaging studies comparing patients with early probable AD to healthy aged subjects have shown that the most specific and sensitive features of AD at this stage are hippocampal and entorhinal cortex atrophy, especially when combined with a reduced volume of the temporal neocortex. MCI patients have significant hippocampal atrophy when compared to aged normal controls. When comparing patients with probable AD to MCI subjects, hippocampal region atrophy significantly extends to the neighboring temporal association neocortex. However, only longitudinal studies of MCI subjects are suited to assess (in a retrospective way) the predictive value of initial atrophy measurements for progression to AD. Few such studies have been published so far and for the most they were based on small samples. Furthermore, the comparison among studies is clouded by differences in both populations studied and MRI methodology used. Nevertheless, comparing the initial MRI data of at-risk subjects who convert to AD at follow-up to those of nonconverters suggests that a reduced association temporal neocortex volume combined with hippocampal or anterior cingulate cortex atrophy may be the best predictor of progression to AD. These data, although still preliminary, are consistent with postmortem studies describing the hierarchical progression of *tau* lesions in normal aging and early stages of AD, such that damage to the medial temporal lobe and association cortex would account for the memory and nonmemory cognitive impairments, respectively, the combination of which is required to operationally define probable AD. Future research in this field should capitalize on thorough methodology for brain structure delineation, and combine atrophy measurements to cognitive and/or functional imaging data.
© 2003 Elsevier Science (USA). All rights reserved.

Definition of terms

Dementia: deficits in two or more areas of cognition, sufficient to interefere significantly in social and occupational functioning (DSMIV; American Psychiatric Association, 1994).

AD: patients with clinically probable AD according NINCDS-ADRDA (McKhann et al., 1984) or DSMIV (American Psychiatric Association, 1994) criteria.

Mild AD: Patients with probable AD at a mild stage of global cognitive impairment as assessed by MMSE >20 and/or a CDR score <1.

Accuracy: Although when referring to predicting the development of a disease the term accuracy should formally pertain to proven diagnosis (postmortem, biopsy, or genetics), this formality has thus far not applied to MCI. Thus, for the sake of clarity and as currently used in the MCI literature, the term accuracy will refer here to the agreement between structural imaging markers and present or final clinical diagnosis (calculated as *accuracy = number of well classified subjects/total number of subjects*).

* Corresponding author. University of Cambridge, Department of Neurology, Box 83, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK. Fax: +44-1223-217909.

E-mail address: jcb54@cam.ac.uk (J.-C. Baron).

1053-8119/03/$ – see front matter © 2003 Elsevier Science (USA). All rights reserved.
PII: S1053-8119(02)00026-5

Introduction

In this review, "early diagnosis" will refer to one's ability to diagnose Alzheimer's disease (AD)[1] at a very early stage, before symptoms and clinical signs have reached the stage at which a diagnosis of clinically probable AD can be made according to currently recommended criteria. In a patient with cognitive complaint, early diagnosis therefore entails first detecting whether the subject's cognitive status is part of normal or abnormal aging, and in the latter case, whether or not this is the forerunner of AD (or some other degenerative disease). The goal of research in this area is therefore to develop highly specific and sensitive tools capable of identifying as early as possible among at-risk subjects those who will eventually progress to AD. Our goal with this review concerns early recognition of but not screening for AD, which would imply searching for all prevalent cases of AD in the general population regardless of symptoms or severity, and distinguish, among the demented subjects, the AD cases from the other pathologies. When assessing a demented subject, structural imaging is the most powerful investigation for excluding other pathology, such as tumor, hydrocephalus, and multiple vascular lesions (Scheltens et al., 1999; Frisoni et al., 2001), and is recommended practice (Knopman et al., 2001). However, it is not our aim to review here the contribution of neuroimaging in distinguishing AD from other causes of dementia, and the interested reader is referred to specific reviews of this topic (Frisoni, 2001; Scheltens et al., 2002, for example). Our focus here is the use of structural imaging in identifying, among individuals with isolated memory impairment, those who have abnormal aging, and among them, those who will progress to AD.

We will therefore first review the main methods used to extract information from structural brain imaging, secondly provide evidence-based data on the added value of structural neuroimaging in assessing subjects at risk for developing AD, and finally suggest avenues for future research. Before going into this, however, a brief account of some aspects basic to understanding of the topic of this review will be given.

Relevance of an early diagnosis

AD affects a considerable and increasing part of the population. Despite the lack of disease-modifying treatment at present, discovering sensitive and specific markers of early AD would be a major breakthrough as it would allow us—once this treatment is available—to slow or perhaps even arrest the degenerative process before dementia develops. Furthermore, current symptomatic treatments, such as acetylcholine esterase inhibitors, may be more efficient when administered in the early stages of AD. However, early diagnosis remains difficult to achieve, and currently the clinical diagnosis of AD comes relatively late into the disease. The difficulties lie for the most part in the similarities between cognitive impairment due to normal aging processes and initial manifestations of AD.

The diagnosis of clinically probable AD can currently be made in living subjects only once the stage of dementia has been reached. It is based on a number of criteria as defined by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann et al., 1984) (see below), but can only be confirmed by postmortem histopathology. While the clinical signs of AD are well established, the early symptomatic and predementia stage remains to be better defined.

Relevance of structural imaging

Patients with significant cognitive impairment but who do not meet criteria for dementia are at increased risk for developing AD (see below), and a number of approaches can be considered in order to achieve an early diagnosis. Although screening neuropsychological tests are necessary to recognize and monitor these at-risk subjects, there is no perfectly accurate cognitive marker of early AD identified to date (Chen et al., 2000). Moreover, cognitive performances depend not only on age and education but also on mood and attention at the time of testing, and thus lack wide generalizability. Likewise, the concentration of *tau* protein and amyloid Aβ42 in the cerebro-spinal fluid (CSF) appears to have some diagnostic value in probable AD, but it is an invasive procedure and its value for predicting AD has received only little attention thus far (Boss, 2000). Whether used alone or in combination with tests such as neuropsychological assessment (Laakso et al., 2000), other approaches such as neuroimaging should therefore be considered. Indeed, neuropathological studies show that brain degeneration occurs very early in the course of the disease, even before the first clinical signs, and predominates in certain areas, chiefly the medial temporal lobe (MTL) (see below). Thus, neuroimaging, which comprises structural (i.e., mainly CT and MRI) and also functional neuroimaging (i.e., mainly PET, SPECT, and fMRI), may enable us to visualize these early brain changes in the living subject. In

[1] Abbreviations used: AACD, age-associated cognitive decline; AAMI, age-associated memory impairment; ACMI, age-consistent memory impairment; AD, Alzheimer's disease; ARCD, age-related cognitive decline; BSF, benign senescent forgetfulness; CDR, Clinical Dementia Rating; CT, computed tomography; GDS, Global Deterioration Scale; HAS, healthy aged subjects; Hcp, hippocampus; LLF, late-life forgetfulness; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MSF, malignant senescent forgetfulness; NFT, neurofibrillary tangles; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; PET, positron emission tomography; ROI, regions of interest; SPECT, single-photon emission tomography.

what follows, we will focus on structural brain imaging because, as compared to functional imaging, it is a relatively simple, quick, and cheaper technique which is easily accessible in clinical practice.

Relevance of studies on at-risk subjects

Since it is currently impossible to foretell which subjects in the aged population will develop AD, one approach would be to prospectively collect longitudinal data on a sample of the population and retrospectively analyze the initial characteristics of those who eventually convert. However, since AD affects 6 to 8% of the overall population over 65 years of age, very large numbers of subjects would need to be followed in order to have a large enough sample of converters for valid statistical analysis. While this type of study undoubtedly has its advantages, it would be cumbersome and costly to implement a large-scale study involving neuroimaging. It seems therefore more pertinent to recruit subjects with a higher risk of developing AD (i.e., at-risk subjects). Apart from cognitive decline per se, the main currently recognized risk factors for AD are as follows:

—age: the prevalence of AD doubles every 5 years from age 60 on (Small et al., 1997);

—a family history of AD, which increases the risk of developing AD two- to fivefold (van Duijn and Hofman, 1992);

—the E4 allele of apolipoprotein E (Corder et al., 1993): risk for AD increases from 20 to 90% with increasing numbers of APOE-epsilon 4 alleles in families with late onset AD.

Cognitive decline also significantly increases the risk of developing AD. Some longitudinal studies show that up to 72% of subjects with cognitive decline develop clinically probable AD within 4 years (de Leon et al., 1993) (see Table 3). This review will focus on this last kind of subjects, who also form the bulk of patients consulting in a memory clinic for questionable AD. In the literature, this category of patients has been referred according to a host of acronyms, all referring to individuals "who cannot be classified as normal or demented but who are cognitively (usually memory) impaired," as defined by the American Academy of Neurology (Petersen et al., 2001). This transitional stage of cognitive impairment between normal aging and AD is widely referred to as "mild cognitive impairment" (MCI) in the recent literature.

Defining MCI at large

Apart from MCI, more than 20 different names have been used in the literature to define cognitively impaired but nondemented subjects, including "age-associated cognitive decline," "age-associated memory impairment," "age-consistent memory impairment," "age-related cognitive decline," "benign senescent forgetfulness," and "late-life forgetfulness." Their multiplicity reflects fundamental difficulties in differentiating physiological from pathological aging and establishing operational criteria for the study of these populations. These classifications actually refer to criteria and concepts that vary among authors and often even within a given term (see, for example, Ritchie and Touchon, 2000, for a review). One consequence of this confusing situation is that highly inconsistent values both for the incidence of such populations and for their annual rate of conversion to AD have been reported (see, for example, Table 3, and for review, Petersen et al., 2001a; Ritchie and Touchon, 2000; Celsis, 2000). This marked variability reflects not only definition problems but also selection biases, e.g., subjects selected by press ads vs. patients from specialized clinics or retirement homes (Daly et al., 2000), as well as variability in the neuropsychological tests used to define cognitive impairment (Koivisto et al., 1995). The broad characteristics for the main classifications of patients with cognitive impairments will be discussed now. Crook et al. (1986) suggested that subjects over 50 reporting memory impairment and whose performances in standard tests of secondary memory were beyond one standard deviation (SD) lower than young subjects be designated as age-associated memory impairment. However, AAMI defines normal aging and was not intended to diagnose pathological processes (Crook, 1989). Widely criticized (Bamford and Caine, 1988; Blackford and La Rue, 1989; Smith et al., 1991; O'Brien and Levy, 1992; Caine, 1993; Koivisto et al., 1995; Hanninen and Soininen, 1997; Nielsen et al., 1998), this ill-defined and overinclusive concept was progressively replaced by other classifications based on more appropriate criteria, notably, using age-matched norms (Blackford and La Rue, 1989). Some classifications suggested subsequently, such as the AACD (Levy, 1994) or the age-related cognitive decline (ARCD) included in the DSM-IV (American Psychiatric Association, 1994), consider mild impairment in multiple cognitive domains.

In its currently recommended definition, MCI denotes individuals with isolated progressive memory impairment (Petersen et al., 1999). Flicker et al. (1991) have documented that the risk of developing AD is higher in MCI than in the overall population, and introduced the notion of underlying pathological process, suggesting that MCI represents "the clinical manifestation of incipient Alzheimer's disease." MCI is considered to better represent the clinical manifestation of incipient AD than other, overinclusive, terms (Petersen et al., 2001), and therefore is currently the most widely accepted entity. Nevertheless, even MCI has been defined by various criteria, and apart from the now recommended criteria, i.e., isolated memory impairment (Jack et al., 1999), previous definitions have included impairment in any area of cognitive function (Smith et al., 1996) and abnormal global assessment scales (Convit et al., 1993; Daly et al., 2000). Widely used global assessment scales are the Clinical Dementia Rating (CDR) and the Global Deterioration Scale (GDS) (Flicker et al., 1991; de

Leon et al., 1993; Convit et al., 1993; Convit et al., 1997; Jack et al., 1999; Killiany et al., 2000; Petersen et al., 2001a). A score of 0.5 on the CDR and/or 3 on the GDS are widely used as cutoffs. However, when used in isolation, these subjective global scales result in populations that may, and often do, differ among studies and comprise very heterogeneous states, including mild dementia (Petersen et al., 1999, 2000; Morris et al., 2001). Thus, although these global scales are helpful as complementary tools, they are not reproducible and reliable enough to be used alone, and additional, more objective, inclusion and exclusion criteria should be resorted to, especially neuropsychological tests of episodic memory and other cognitive processes. Petersen et al. (1999) propose the following criteria for the diagnosis of MCI: (i) memory complaint; (ii) normal activities of daily living; (iii) normal general cognitive function; (iv) abnormal memory for age; and (v) no dementia. This current definition of "amnestic" MCI is better suited to represent the clinical manifestation of incipient AD, and is recommended when specifically assessing the predementia stage of AD (Petersen et al., 2001a).

Defining normality

Apart from the selection of appropriate at-risk patients, another important but largely unsolved issue regarding the early diagnosis of AD concerns the selection of appropriate controls and what defines "normal aging," the main concern being of course to exclude incipient AD (Sliwinski et al., 1996). Indeed, a decline in episodic memory with advancing age is considered normal, though it may relate to the hippocampal region *tau* pathology which is constantly observed in aged people (Braak and Braak, 1996; Delacourte et al., 1999; see below). Although amnestic MCI is defined operationally by a performance in episodic memory below the 1.5 SD limit of normal aged controls, it is clear that including normals with episodic memory within the normal range does not protect against the risk of some of these subjects progressing to MCI, and ultimately to AD, during follow-up. This likely explains at least in part the consistent overlap in individual hippocampal volumes between "normal" aged subjects and MCI or mild AD subjects (de Leon, 1999). The implications of this problem for statistically valid estimates of diagnostic accuracy are beyond the scope of this review, but the interested reader can refer to, e.g., Sliwinski et al. (1996).

Emphasis on the medial temporal lobe

Histopathological studies in AD have shown that neurofibrillary tangles (NFT) and *tau* protein deposits develop first, and remain most severe in, the hippocampal region (Braak et al., 1993). Consistent with the findings of Vermersch et al. (1995), Morrison and Hof (1997), and Braak and Braak (1996), Delacourte et al. (1999), studying subjects ranging from normal to severely demented, proposed that the spread of neurofibrillary degeneration may be hierarchized according to 10 stages. The perirhinal cortex (*stage 1*) and subsequently the entorhinal cortex and Hcp (*stages 2 and 3*) are first affected. Subsequently, the rest of the temporal cortex is involved (*stages 4–6*), followed by association areas (*stage 7*) and finally the entire cortex (*stages 8 to 10*). These authors also found a relationship between pathological stage and roughly assessed premortem cognitive status, with stages 1 to 3 corresponding to an unaltered cognitive state. Concordant with Price (1997), neurofibrillary degeneration was found at least in the Hcp in 100% of subjects over 75 years of age. While some subjects showed no cognitive alteration until stage 6, most exhibited slight cognitive deficits such as isolated memory deficits (CDR = 0.5) between stages 4 and 6, i.e., when most of the temporal cortex was involved. From stage 7 onward, when lesions extended to the polymodal association areas, almost all subjects were demented.

The distribution of neurofibrillary degeneration therefore widely straddles different clinical conditions such as apparent normality, not demented but cognitively impaired, and early stage of AD. However, these pathological stages only take NFT distribution, but not density, into consideration. As such, they are qualitative only and thus potentially misleading. For instance, Price et al. (1997) reported that during the stage when lesions are mainly limited to the MTL, NFT density increases across the above three clinical conditions. Nevertheless, the overlap of individual density measures was still considerable, and very early stages of AD may be better correlated with neuronal loss (Gomez-Isla et al., 1996). Overall, the question as to whether asymptomatic subjects with NFTs in the medial temporal cortex are at a preclinical stage of AD, and whether the degenerative process has any predictive value, remains unanswered to this day.

On a clinical standpoint, the fact that the MTL may be the target of both normal aging and early stages of AD points to the importance of this brain area in the study of at-risk subjects. It is reassuring in that regard that postmortem studies have shown that, both in AD and in nondemented subjects, neuron loss and neurofibrillary lesions are linked to a smaller volume of the Hcp (Bobinski et al., 2000; 1996; de la Monte, 1989). Moreover, loss and atrophy of layer II entorhinal cortex neurons was also recently evidenced in elderly people with MCI relative to those with no cognitive impairment (Kordower et al., 2001). Finally, the now well recognized key role of the MTL in episodic memory, (see, for example, Squire and Zola-Morgan, 1991; Eichenbaum et al., 1996), the most severely and earliest affected cognitive process in AD, further justifies focusing on this brain area in the study of early AD. Nevertheless, as will be seen below, considerable interest has recently emerged in the study of the neocortex and other nonhippocampal areas in MCI.

I. Methodological considerations

Three different types of studies involving structural imaging in early AD can be distinguished. First, if there exist structural magnetic resonance imaging (MRI) indices able to predict the development of AD in at-risk subjects, then in a first approximation such indices would be expected to remain prominently abnormal at later stages of the disease. Therefore, studies that compare healthy aged subjects (HAS) and AD patients should be considered a first but necessary step in the quest for early markers. Our review therefore will start with studies that use structural measures to efficiently classify HAS and AD. However, only studies that dealt with mild AD, as defined by MMSE >20 and/or CDR <1, will be considered here, as they are expected to inform us specifically on early markers. A second type of study compares at-risk subjects with HAS. Although these studies do give a better characterization of the ill-defined population of at-risk subjects, only some of the latter will develop AD, so that the predictive value of potential early markers cannot be assessed without follow-up. Ultimately, therefore, only longitudinal studies on at-risk subjects reporting outcome can provide reliable information on whether there exist detectable structural changes before probable AD can be diagnosed. This third type of study will therefore be given particular emphasis hereafter. Before presenting the results from these studies, certain methodological aspects of atrophy assessment with structural imaging will be addressed.

Delineating regions of interest (ROI)

For reasons already noted, most studies have focused on the hippocampal region. This is a particularly complex area that is made of several distinct structures, most of which are small and with boundaries that are ill-defined in anatomical atlases and often difficult to delineate on a CT or MRI films. This is particularly true for the entorhinal and perirhinal cortices, which partly explains why they have been relatively rarely assessed, although they are the first to be affected by neurofibrillary degeneration in AD. When these components of the hippocampal region have been studied, either their anatomical borderlines have been poorly respected or they were merged in a single ROI referred to with imprecise terms such as "parahippocampal gyrus," "hippocampal formation," "MTL," or both, making it all the more difficult to compare different studies. A major technical reason that causes differences between volumetry results for the hippocampal region is the difficulties in delineating the borders of structures along the axis of the hippocampus, and the often arbitrary rules used by the investigators.

The article by Insausti et al. (1998) addressed in detail the issue of the study of the rhinal area with MRI. They precisely described the cytoarchitectonic limits of the temporo-polar, entorhinal, and perirhinal cortex from the postmortem morphological and cytoarchitectonic analysis of 49 brains. They then set up a step-by-step procedure to define the borders of the entorhinal and perirhinal cortices on anatomic MRI according to visible indices such as the morphology of the sulci and neighboring elements. Although widely used today, this is an extremely long and tedious procedure, which has been shown to be only imperfectly reproducible (Xu et al., 2000). Bobinski et al. (1999) also developed a ROI method to sample the entorhinal cortex based on postmortem validation, and this technique has been used in other papers by the same group with some success (De Santi et al., 2001).

Recently, a method for the in vivo volumetric measurement of the human hippocampus with high neuroanatomical accuracy has also been proposed. These tracing guidelines aim to sample the entire hippocampal formation using its true anatomical definition based on the morphological description given by Duvernoy (1988) (Pantel et al., 2000). Although excellent reliability, sensitivity, and specificity were reported for this method, it remains a time-consuming procedure as well as the need for extensive training of its utilization. Automated methods have recently appeared to both reduce the workload and improve the reproducibility for hippocampus volumetry (Goshe et al., 2001), but they now require wide validation.

Because of all these problems, assessing atrophy in the medial temporal region has often been based on visual, linear, or surface measurements rather than on actual volumetry. These methods will be reviewed now.

Methods for assessing atrophy of the medial temporal lobe

Only a brief overview will be given here; for further detail about these methods and their limitations as applied to the study of early AD, the reader is referred to the recent reviews of Frisoni (2001) and Scheltens et al. (2002).

Visual inspection

A qualitative assessment of CSF accumulation in the fissures of the perihippocampal region has been used in some studies (see, for example, de Leon et al., 1993), using a 4 point scale (0 = no hippocampal atrophy; 1 = questionable; 2 = mild; 3 = moderate to severe). One to three contiguous sections through the temporal lobes, at an infra-orbital-meatal angulation of 20 to 25° negative to the canthomeatal plane, are usually examined. This so-called "negative-angulation plane" runs almost parallel to the longitudinal axis of the Hcp. The subsequent classification of patients was often binary, "atrophy" being used if at least one hemisphere scored 2 or more. This approach, also used for other brain structures, is quick and definite, which makes the statistical analysis easier, but is eminently subjective, raising issues of sensitivity, validity, and interrater repro-

Table 1
Accuracy of MRI measures in discriminating mild AD from healthy aged subjects (HAS) according to the brain structure

Reference	M	Sample (mildAD/HAS)	Hcp	Amg	AHC	ERh	PHG	TL	FL
A Erkinjuntti et al., 1993	1	34/39	67% (74% (a))			92%		77%	
	2		69% (b)						
Laakso et al., 1995b	4	32/16	88% + Amg+FL: 92%	58%					65% (c)
Maunoury et al., 1996	4	12/15		89%					
Frisoni et al., 1996	2	33/31	89% (d)						61% (c)
Jack et al., 1997	4	79/126	80%	<			< (c)		
Krasuski et al., 1998	4	13[a]/21	< +Amg: 91% +Amg+PHG: 94%	83%		< (c)	< (c, f)		
Killiany et al., 2000	4	16/24				+TL (g): 100%			
Laakso et al., 2000	4	41/34	87%						
Mizuno et al., 2000	4	15/27	69% (h)	88%			64%		
Dickerson et al., 2001	4	16/34	+ERh (i): 86%						
B Killiany et al., 1993	4	7/7	100% (j)						
Cuenod et al., 1993	3	11/6	< (k)	94%				< (c, l)	
	4								
Lehericy et al., 1994	4	13/8	90%	95%	100%				
Pantel et al., 1997	4	7/10			88%			<	<
Bobinski et al., 1999	3	8/8				94% (m)			
	4		81%			+TL: 100%		62% (c, n)	
Hampel et al., 2002	4	9/28			97%				

Note. Percentages correspond to overall accuracy calculated as [number of well-classified HAS + number of well-classified mild AD]/total number of subjects. When not specifically noted in the articles, these percentages were calculated from the data published. Only results concerning mild AD are reported and calculations were made taking only early cases into account. Sections A and B of the Table concern studies with samples respectively larger and smaller than 10 in each group; * sample made of both possible and probable AD subjects ($n = 4$ and 9, respectively). Discriminant accuracy not available but stated in the original article as lower than the one listed here for the same study.

AD, Alzheimer's disease; AHG, amygdalo-hippocampal complex; Amg; amygdala; ERh, entorhinal cortex; FL, frontal lobe; HAS, healthy aged subjects; Hcp, hippocampus; M, method used (1, visual evaluation; 2, linear measurements; 3, area measurements; 4, volumetric measurements; see text for further details); mild AD, probable Alzheimer's disease at early stage; PHG, parahippocampal gyrus; TL, temporal lobe (lateral part): (a) temporal horn; (b) width of the temporal horn + estimation of hippocampal area from hippocampal height and width; (c) ROI included white matter; (d) width of the temporal horn + width of the choroid fissure + hippocampal height; (e) bifrontal index and interhemispheric fissure width; (f) posterior part of parahippocampal gyrus; (g) ERh, studies on three consecutive sections centered at the level of the mammillary bodies; TL, ROI sampled the banks of the superior temporal sulcus; (h) anterior part of the hippocampus; (i) the shoulder of the collateral sulcus has been used as the lateral border of entorhinal cortex, thus not including the entire volume of the structure as described by Insausti et al. (1998); (j) temporal horn of the lateral ventricles + Hcp; (k) at the level of the lateral geniculate body; (l) on the slice passing though the anterior commissure; (m) estimated by adding the landmark length of the ERh along its boundary with the subarachnoid cerebrospinal fluid measured on all slices that spanned from 4 mm posterior to the frontotemporal junction to the anterior margin of the lateral geniculate body, and multiplying by the slice thickness; (n) superior temporal gyrus.

ducibility, such that it usually does not add significant diagnostic information (Frisoni, 2001). Even though fairly accurate in some studies (see, for example, Convit et al., 1993; Wahlund et al., 1999), the method has had poor reliability in others (Victoroff et al., 1994). Finally, the binary classification prevents the comparing of means, establishing individual thresholds, or computing percentages of variation for longitudinal studies.

Linear and surface measurements

Another approach is to obtain as atrophy indices either linear measures for the thickness, height, length, or width between well-identified landmarks, or surface measures of a ROI drawn on a single predetermined section. A well-known example is "the minimum width of the MTL" used by Jobst et al. (1992). Although quick, fairly easy, objective, and usually well reproducible, this approach is but an indirect estimation of the actual volume of the structure. Especially, choosing a section "a priori" implies that changes may not be detected in other planes. Jobst et al.'s minimum width index has, however, been fairly extensively validated against hippocampal volume and when rigorously applied is considered a good approximation of hippocampal atrophy (Meguro et al., 2001).

Volume measurements

The volumetric approach consists in delineating the contours of the structure of interest on every section where it is present. With this direct measurement, the volume of the structure can be computed, which should theoretically be the best way to assess atrophy. However, there is a reproducibility problem with MTL volumetry, particularly for small structures that may be difficult to delineate, with attending poor intra- and interreliability (Whalley et al., 1999). In addition it is a particularly time-consuming method, which requires adequate image resolution and therefore depends more on the characteristics of the scanner and acquisition parameters (such as the thickness of the sections) than the approaches above.

In Tables 1–3 visual inspection, linear measurements,

Table 2
Percentage size difference for different brain structures in at-risk subjects (ARS) relative to healthy aged subjects (HAS) and AD patients in cross sectional MRI studies

Category	Reference	Sample size			M	Structures	ARS vs HAS (%)	AD vs ARS (%)
		ARS	HAS	AD				
AAMI	Soininen et al., 1994	16	16		4	Hcp	−1	
					4	Amg	−5	
	Laakso et al., 1995a	38	34	54	4	Amg	3	−24*
	Parnetti et al., 1996	6	6	6	4	Hcp	−29*	−8
	Laakso et al., 1998	43	42	55	4	Hcp	−2	−32*
					3	Hcp (1)	−18*	−16
ApoE4	Schmidt et al., 1996	22	108		4	Hcp	−7	
					4	PHG (c)	0	
		39	175		2	Hcp (o)	9	
	Tohgi et al., 1997	40	14		3	R Hcp (p)	−15*	
	Reiman et al., 1998	11	22		4	Hcp	−8	
	Moffat et al., 2000	13	13		4	Hcp	NS	
MCI	Convit et al., 1997 (q_1)	27	27	27	4	Hcp	−14*	−10
					4	PHG (c)	−5	−11*
					4	Fusif (c)	0	−23*
					4	TL (c)	−5	−9
	Visser et al., 1999	20	18	7	4	Hcp	−1	−9
					4	PHG (c)	−5	−8
					4	TL	−2	−6
	Jack et al., 2000	43	58	28	4	Hcp	*	*
	Xu et al., 2000	30	30	30	4	Hcp	−12*	−12*
					4	ERh	−21*	−20*
					2	ERh	−10.5	−12*
	de Santi et al., 2001	15	11	12	4	Hcp	−15*	−5
						PHG (c)	−7	−7
						Fusif (c)	−2	−10
						TL (c)	−3	−8*
	Du et al., 2001	36	40	29	4	Hcp	−11*	−19*
						ERh	−13*	−30*
	Wolf et al., 2001	12	17	10	4	Hcp	−13*	−16*
Non demented (r)	Dickerson et al., 2001	28	34	16	4	Hcp	*	*
						ERh (i)	*	NS
PossAD	Ikeda et al., 1994 (q_2)	6	8	8	3	Hcp (s)	−23*	−9
					3	PHG (s, c)	−22*	−2
					3	TL (s, c)	−4	−23*

Note. When not specifically noted in the original article, percentages were calculated from available data whenever possible; if otherwise, no percentage is shown.

* Statistically significant difference between groups (i.e., ARS vs HAS, or ARS vs AD). AAMI, age-associated memory impairment; ApoE4, subjects with at least one e4 allele and cognitively normal (except in Moffat et al., 2000, which also included individuals with MCI); ARS, at-risk subjects; Fusif, fusiform gyrus; MCI, mild cognitive impairment; NS, nonsignificant; PossAD, possible Alzheimer's disease (in the studies listed here, this term refers exclusively to subjects with isolated memory loss); R, right; (o) width of the temporal horn; (p) area of the hippocampus head measured in the plane in which it was largest; (q) prior work by the same group concerning overlapping samples of subjects is not listed in this table (q_1, Convit et al., 1993; q_2, Yamada et al., 1996; q_3, de Leon et al., 1989; q_4, Fox et al., 1996b ; q_5, Fox et al., 1996a); (r) patients with memory complaint, both including patients with objective deficits in memory or in one other area of cognition and patients with no objectively evidenced deficit at all; (s) measurements were made using the coronal image intersecting the anterior part of the pons on the cross-referenced midline sagittal image. See Table 1 for details.

surface measurements, and volume measurements will be noted 1, 2, 3, and 4, respectively.

II. Studies comparing mild AD to HAS

The first volumetric MRI study of AD was published in 1988 (Seab et al., 1988). It disclosed a decrease in Hcp volume averaging 40% in AD patients when compared to healthy aged subjects (HAS), which probably preceded overall brain atrophy. There was no overlap of individual values. Since then, studies have repeatedly found significant atrophy of the hippocampal and parahippocampal formation in AD, ranging from 20 to 52% (Mega et al., 2000, for review), and already present at the first stages of AD (Celsis, 2000; Fox and Rossor, 1999, for reviews). Thus, "CT- and MRI-based measurements of hippocampal atrophy show promise in providing useful diagnostic information for

Table 3
Methodological characteristics of longitudinal MRI studies on at-risk subjects

Reference	Category	Sample	Follow-up (yrs)	Conv	Structures studied	M
de Leon et al., 1993 (q_3)	MCI (t)	32	4	23 (72%)	Hcp (u)	1
Fox et al., 1996c (q_4)	ARS-FAD (v)	7	3	3 (43%)	Hcp	4
Yamada et al., 1996	PossAD	8	5	3 (37%)	Hcp, TL	3
Kaye et al., 1997	Oldest old (w)	30	3.5	12 (40%) (x)	TL, PHG (c), Hcp	4
Swann et al., 1997	HcpA-HAS (y)	5	2	0 (0%)	Hcp	1
Jack et al., 1999	MCI (z)	80	2.7	27 (34%)	Hcp	4
Fox et al., 1999 (q_5)	ARS-FAD (v)	28	3	5 (18%)	Whole brain	
Visser et al., 1999	Minimal dementia (α)	13	3	9 (69%)	Hcp, PHG (c), TL	4
Convit et al., 2000	MCI (t)	20	3.2	12 (60%)	Hcp, PHG, Fusif,	4
	HAS	26		2 (8%)	TL (β), TL (n)	
Killiany et al., 2000 (2002)	Questionable AD (γ)	79	3	19 (24%)	ERh (i), TL (n), Ant Cing, Post Cing, (Hcp)	4
Dickerson et al., 2001	Nondemented(r)	23	3.3	12 (52%)	ERh (i), Hcp	4

Note. Ant Cing, anterior cingulate; Conv, number (rate) of converters; FAD, familial Alzheimer's disease; HcpA, hippocampal atrophy; Post Cing, posterior cingulate; (t) GDS = 3; (u) CT scan was used in this study; (v) HAS having family history of autosomal dominant early-onset AD, that are within 5 years of the historical age at onset of the disease within the family and neither they nor their families had any complaints relating to their cognitive function; (w) HAS older than 83 years; (x) subjects clinically demonstrating deterioration as evidenced by a CDR score $\geq$0.5 or a MMSE score $<$24 on two consecutive semiannual evaluations. At end of follow-up, the current dementia diagnoses of the 12 PreD subjects were probable or possible AD (n = 7 and 5, respectively); (y) HAS having hippocampal atrophy as evaluated by visual rating; (z) see Table 2 for criteria; (α) overall clinical impression of limited and variable impairment in cognitive and social functioning such as difficulty with learning and recalling events, a tendency to misplace possessions, and minor errors in orientation; (β) combined volumetric measurements of middle and inferior temporal gyri; (γ) CDR = 0.5. See Table 1 and 2 for details.

identifying patients with probable AD from normal elderly individuals" (Scheltens, 1999). The editorial by Frisoni (2001) provides a detailed overview of the ability of CT and MRI techniques to help discriminate patients with AD (not restricted to mild cases) from nondemented elderly persons.

Table 1 lists those studies that explicitly noted that mild AD was investigated and that assessed the diagnostic accuracy of volume measurements (thus excluding, for example, the study by DeToledo-Morrell et al., 1997). Significant atrophy of the *hippocampus* has been a constant finding in these studies, ranging in average from 12 to 38% (data not shown). Table 1, which tabulates the accuracy of atrophy measurements in separating mild AD from HAS, shows that Hcp atrophy is only a fair discriminator, with an overall accuracy ranging from 67 to 100%, reflecting substantial overlap between mild AD and HAS. Because of this, linear or volumetric MR or CT measurements are not recommended for routine use in the diagnostic workup of AD at this stage (Knopman et al., 2001).

Concerning the *amygdala*, results have been quite divergent, with accuracy for discriminating mild AD from HAS higher than that of the Hcp according to four studies, but lower in the remaining two studies (see Table 1). However, three out of the four studies that report a higher accuracy of amygdala volume were limited by small sample size (Lehericy et al., 1994; Cuenod et al., 1993) or inadequate selection criteria (Krasuski et al., 1998; see Table 1). The overall accuracy for amygdala atrophy ranged from 58 to 95%, which would suggest that, all in all, amygdala volume is less efficient than Hcp volume to discriminate mild AD from HAS. However, a combination of the amygdala and Hcp volumes was shown to enhance accuracy, consistent with early results suggesting that the volume of the amygdalo-hippocampal complex may be particularly efficient to differentiate mild AD from HAS (Pantel et al., 1997; Lehericy et al., 1994; Hampel et al., 2002).

So far, five studies have assessed the *entorhinal* cortex, but each used suboptimal measuring methods (see Table 1 for details). The results have, however, been encouraging, as they suggest that, consistent with histopathological studies, the entorhinal cortex is overall the most efficient structure to discriminate between mild AD and HAS. Three groups have recently published results of rigorous measurements of the entire volume of the entorhinal cortex, taking its anatomy into consideration when delineating the ROI (Juottonen et al., 1998; 1999; Frisoni et al., 1999; Chan et al., 2001). Although these studies were not limited to mild AD (and thus are not presented in Table 1), they are worth looking at. The entorhinal cortex was the most atrophic structure in the study by Chan et al. (2001), and, in agreement, Juottonen et al. (1998, 1999) showed that the entorhinal volume was more efficient for classifying subjects (with 87% accuracy) than the Hcp, temporo-polar cortex, or perirhinal cortex. In contrast, Frisoni et al. (1999) reported a lesser atrophy and lower accuracy for the entorhinal cortex than for the Hcp (67% vs 85% accuracy, respectively), a discrepancy that they explained partly by difficulties in delineating this structure on the MRI.

According to three studies, the measurement of the entire

parahippocampal gyrus lacks accuracy (Table 1), reinforcing the belief that its components should be assessed separately. In the same way, isolated measurements of the frontal and lateral temporal cortex have systematically been of little accuracy (Table 1). Nevertheless, when added to those of the entorhinal cortex, volume measurements of the *temporal neocortex* may allow a better classification of mild AD patients and HAS, resulting in 100% accuracy in two studies (Killiany et al., 2000; Bobinski et al., 1999). This impressive accuracy would be consistent with histopathological studies, in so far as the entorhinal cortex, being the earliest affected, would increase the sensitivity, while the temporal neocortex, affected later than the entorhinal in AD but more specifically so relative to normal aging, would reinforce specificity (Delacourte et al., 1999). Interuncal distance is not reported in Table 1 because its anatomic meaning is rather vague, as it is assumed to represent atrophy of the Hcp but may also be affected by other neighboring structures. Furthermore, its measurement is poorly reproducible and its diagnostic usefulness has been questioned (see de Leon et al.'s comments in Ishii, 1994). This measurement will therefore not be taken into account in the sections to follow on at-risk subjects.

III. Cross-sectional studies on at-risk subjects

Table 2 lists the percentage change in cerebral structure size in different categories of at risk subjects as compared to HAS and probable AD. The accuracy of atrophy measurements is not listed in this table for it was only assessed in Convit et al. (1997), Xu et al. (2000), Du et al. (2001), and De Santi et al. (2001) (see below) and has but little interest, because of the heterogeneity of the at-risk population. Furthermore, in most of these studies, the AD patients were not exclusively at an early stage of the disease.

Regarding *AAMI,* and when volumetric measurements were used, the Hcp and the amygdala were found to be preserved relative to HAS, whereas they were atrophied in AD as compared to AAMI. Opposite results were found in Laakso et al.'s study (1998) for the Hcp area (see above for problems with measurements), and in Parnetti et al.'s (1996) study but it used a small and possibly more severely affected sample, as the AAMI subjects were older than the HAS.

Regarding *ApoE4 subjects,* three out of four studies report no difference in Hcp volume (nor in parahippocampal volume in one study) between carriers and noncarriers of the ApoE4 allele. The single discrepant study measured Hcp area rather than volume. In a longitudinal study, however, the annual rate of Hcp volume reduction was significantly greater in the ApoE4+ than in the ApoE4- group (2.86% versus 0.85%, respectively; data not shown in the table), contrasting with whole brain atrophy rates, which were not significantly different (Moffat et al., 2000). However, subjects in this ApoE4 study included both normals and patients with mild cognitive decline (Table 2).

Finally, studies on patients with *isolated memory impairment* (broken down as "possible AD," "not demented," or "MCI" in Table 2) all report a significantly lower Hcp volume in these patients as compared to HAS, ranging from 11 to 23%, except for the study by Visser et al. (1999; see below for comments). This contrasts with lateral temporal neocortex volumes, for which a significant difference between patients with cognitive impairments and HAS was never found. Discrepant results were reported for the parahippocampal gyrus, but measurements lacked precision (see Table 2 for details), and only three studies focused specifically on the entorhinal cortex (Xu et al., 2000; Du et al., 2001; Dickerson et al., 2001). Consistent with histological studies (Kordower et al., 2001), results of these studies all showed significantly lower entorhinal cortex volume in MCI than in HAS, the difference being almost twofold that found for the Hcp in Xu et al. (2000), although they were similarly affected in Du et al. (2001). Nevertheless, the volume of the Hcp was found to be more efficient than that of the entorhinal cortex in separating both groups, significantly so in Du et al. (2001) (overall accuracy of 70% versus 66%, respectively), but not significantly so in Xu et al. (2000) (overall accuracy of 72% versus 68%, respectively). According to the latter authors, these results may be due to the anatomical ambiguity of the entorhinal cortex, the presence of artifacts in the MRI data, and the heterogeneous MCI group. Differences in criteria used to select MCI sample as well as to delineate the entorhinal cortex may account for these differences in the results of these two studies (see also below). According to Convit et al. (1997) and De Santi et al. (2001), the Hcp was also more efficient than other temporal lobe structures to separate MCI subjects from HAS (overall accuracy of 73% in both studies). In contrast to the comparison between MCI and HAS, that between MCI and AD yielded less concordant results (Table 2), possibly due to the various degrees of disease severity in the AD samples across studies. Overall, the difference between AD and MCI appears to be less marked than that between MCI and HAS for the Hcp, but more marked for the other temporal lobe structures. The negative findings of Visser et al. (1999) should be considered with caution, as these authors found no significant difference in Hcp atrophy between AD patients and HAS. Some methodological limitations (use of a 0.6 T MR scanner with thick sections and interslice gap) may account for these discrepant results. In both Xu et al. (2001) and Du et al. (2001), the volume of Hcp and entorhinal cortex were both significantly reduced in AD when compared to MCI, more markedly so for the latter structure. Concerning the accuracy of volumetric measurements in separating MCI from AD, these two studies reported a better discrimination using the entorhinal cortex than the Hcp (overall accuracy of 72% versus 70%, respectively, in Xu et al., 2000; and of 74% versus 72%, respectively, in Du et al., 2001). The discrimination power was enhanced by both the parahippocampal and fusiform gyri in the study of Convit et al. (1997) (overall accuracy of 88%), and only by the mid-

Table 4
Longitudinal MRI studies of at-risk subjects, classified according to both the brain structures studied and the study findings, i.e., significant predictive value or nonsignificant predictive value of MRI measures

Structure	Measure	Predictive value	No predictive value
Hcp	Size	De Leon et al., 1993	Swann et al., 1997
		Fox et al., 1996c	Visser et al., 1999
		Jack et al., 1999	Killiany et al., 2002
	RA	Fox et al., 1996c	Yamada et al., 1996
			Kaye et al., 1997
PHG	Volume	Visser et al., 1999	Kaye et al., 1997
	RA		Kaye et al., 1997
TL	Volume	Visser et al., 1999	
	RA	Yamada et al., 1996	
		Kaye et al., 1997	
Combination TL and HCP	Volume	Kaye et al., 1997	
Combination TL and Ant Cingulate	Volume	Killiany et al., 2000	

Note. RA = rate of atrophy; see Tables 1 and 3 for details.

dle/inferior temporal gyri (overall accuracy of 81%) in De Santi et al. (2001). Finally, as reported above for ApoE4 (Moffat et al., 2000, see above), Jack et al. (2000) also found a significantly higher annual rate of Hcp atrophy in MCI subjects than in HAS (3% versus 1.9%, respectively), while the difference between MCI and AD patients was not significant.

Several studies have suggested that the right Hcp may be larger than the left in HAS but not in at-risk subjects (Tohgi et al., 1997; Soininen et al., 1994; see Mega et al., 2000, for review), which may indicate a more severe or rapid atrophy of the right Hcp. However, this is not a constant finding (Reiman et al., 1998; Parnetti et al., 1996; Ikeda et al., 1994; Du et al., 2001), and additional studies are required before these diverging results can be explained.

In sum, AAMI subjects seem to represent a separate entity among the various classifications proposed to define nondemented patients with cognitive impairments, for in contrast with MCI, they do not differ from HAS in terms of medial temporal lobe atrophy, consistent with the view that this category does not differ from normality (see introduction). In contrast, the findings regarding atrophy measurements in patients with isolated memory impairment are consistent with the well-known progression of histopathological lesions in AD, with the hippocampal region (entorhinal cortex, Hcp) being significantly atrophic in patients with memory impairment, and the rest of the temporal lobe (fusiform gyrus, lateral temporal lobe) being progressively involved in AD. However, whether Hcp atrophy in subjects with isolated memory impairment predicts a higher risk of developing AD, or conversely is only related to the presence of memory deficit, can only be addressed by longitudinal studies, which will be reviewed in the next section.

IV. Longitudinal studies on at-risk subjects

De Leon et al. (1989) were the first to publish a small-scale MRI study on MCI subjects with longitudinal follow-up. The results of this preliminary study were confirmed in 1993 on a larger sample and with longer follow-up; therefore, only the results from this second study are presented here. These authors visually assessed the dilatation of the perihippocampal fissure according to a 4-point scale and found that significant dilatation was much more frequent in those MCI subjects who eventually developed AD (converters, 91%) than in those who did not (nonconverters, 11%). The overall accuracy of this measurement in differentiating these two subgroups was 91%. Since these landmark reports, numerous longitudinal investigations on at-risk subjects have appeared in the peer-reviewed literature. Their main methodological characteristics are presented in Table 3 which lists all these studies in chronological order of publication, while Table 4 summarizes their main results. In what follows, we will detail these studies according to the type of design used rather than chronology of publication.

Comparing the initial volume of various brain structures between converters and nonconverters, Visser et al. (1999) reported a significant 12% smaller parahippocampal gyrus in the former. The difference between these two subgroups was not significant for the Hcp (about 11%) nor for the lateral temporal lobe. Accordingly, the parahippocampal gyrus was more efficient than either the Hcp or the lateral temporal lobe to differentiate converters from nonconverters (overall accuracy = 77, 69, and 65%, respectively). In this study, the predictive value of MRI measurements was also compared to that of memory assessment. It was found that although memory scores better predicted conversion (accuracy: 88%), the best prediction was obtained when the memory scores and the volume of the parahippocampal gyrus were combined (accuracy: 96%). Although because of its small sample this study has uncertain reliability, it suggests the potential interest of combining both neuropsychological and MRI measures in the design of longitudinal studies of MCI. Although the same group has recently applied this approach to an heterogeneous sample of patients with minor cognitive impairment of various causes

(Visser et al., 2002), their 1999 study remains the sole of its kind to this date.

Dickerson et al. (2001) compared the initial volumetric measurements for the Hcp and the entorhinal cortex between converters and nonconverters, also including patients without cognitive deterioration at testing (see details in Table 2). Although the measure for the entorhinal cortex was suboptimal (see details in Table 1), the authors found significant between-groups differences only for this structure, being the single significant predictor of conversion with 78% overall accuracy.

In Convit et al. (2000), the converter and nonconverter samples also both included individuals with and without initial cognitive deterioration (see Table 3). These authors found a significant reduction of hippocampus (11%) and fusiform gyrus (14%) volumes, while other temporal lobe structures were not significantly atrophied. When the volumes of all the studied structures were combined, 96% of the subjects were correctly classified as converters or nonconverters.

Swann et al. (1997) adopted a quite different approach. They assessed the outcome of patients classified as with or without Hcp atrophy, regardless of their initial cognitive status, namely HAS, depressed subjects, or AD patients. They found no difference in cognitive decline, mortality, or progression to dementia between subjects with or without Hcp atrophy. However the HAS were quite aged in this study (mean: 81 years) and as the authors commented, the specificity of Hcp atrophy to diagnose AD drops after age 75. The authors suggest that Hcp atrophy in their HAS subjects may simply be due to the normal aging process and be of no predictive value.

Kaye et al. (1997) studied healthy "very aged" subjects (over 85 years). Their results are not directly comparable to other studies since their group of "converters" included subjects who developed either probable or possible AD (defined as isolated memory impairment). In contrast with the parahippocampal gyrus, the Hcp and lateral temporal lobe volumes were significantly smaller in converters than in nonconverters and correctly classified 80% of subjects when combined. Furthermore, the annual rate of Hcp atrophy was identical across both groups (about 2%) while that of the lateral temporal lobe was significantly higher in converters than in nonconverters (1.3% vs 0%). According to the authors, atrophy of the Hcp and parahippocampal gyrus may be a normal aging process due to lesional disruption of the entorhinal cortex, and "it is the superimposition of increasing loss of temporal association cortex upon a critically atrophic hippocampus that results in the emergence of clinical dementia in the oldest old." These interesting results are therefore consistent with the postmortem histopathological data previously detailed.

Yamada et al. (1996) also used an MRI longitudinal approach. As Kaye et al. (1997), these authors also reported a similar annual rate of Hcp atrophy for converters and nonconverters (defined in a more classic way), as opposed to temporal lobe atrophy rate, which was higher in converters than in nonconverters and HAS. These results and their interpretation would be similar to those of Kaye et al. just described.

In five related papers on subjects at risk of developing an autosomal dominant form of AD, Fox et al. also reported annual atrophy rates. In two of these studies (Fox et al., 1996b,c), the authors assessed Hcp volume with the ROI method. They showed that the mean initial Hcp volume of converters was lower than that of nonconverters by about 20%, with no individual overlap, and all converters had a greater Hcp asymmetry than nonconverters. Moreover, the annual rate of Hcp atrophy was greater in converters (mean annual rate: about 5%) when compared to nonconverters. In their two other studies (Fox et al., 1996a, 1999), the annual rate of overall brain atrophy was assessed using positional matching (registration) and digital subtraction of serially acquired MRI scans. Converters ($n = 3$) exhibited a higher global atrophy rate than HAS (respectively about 6% vs 0.3%) and nonconverters (1.5% vs 0.1%), with a 93% discrimination between converters and nonconverters. However, as shown in Table 3, small samples were assessed and the clinical situation was rather peculiar. Following the implementation of regional rather than global atrophy assessment, this technique was recently applied to four at-risk individuals with known autosomal dominant mutations. Evolving atrophy was shown to concern more specifically the medial temporal lobe, as well as the inferior temporal gyrus, parietal lobe, and posterior cingulate gyrus (Fox et al., 2001), and to be statistically significantly greater than in HAS in the hippocampus, precuneus, and anterior frontal cortex (Scahill et al., 2002).

Though of considerable interest, the findings from all the studies described above should be considered with caution, notably because of methodological limitations and differences in the type of recruitment, which may account for some diverging results. More precisely, these limitations can be categorized as follows (see Tables 1, 2, and 3 for details):

—small samples, and especially small number of converters (<10 in Yamada et al., 1996; Fox et al., 1996c, 1999; Swann et al., 1997; Visser et al., 1999);

—heterogeneity in age and cognitive status, both within (with poorly matched groups in Yamada et al., 1996; Swann et al., 1997; Kaye et al., 1997; Convit et al., 2000) and between studies, with subjects being occasionally very aged (Swann et al., 1997; Kaye et al., 1997) or with particularly low memory scores (Swann et al., 1997; Visser et al., 1999);

—use of low-resolution scanners (de Leon et al., 1993; Visser et al., 1999);

—suboptimal methods to assess cerebral structures, e.g., visual (de Leon et al., 1993; Swann et al., 1997), surface-based (Yamada et al., 1996), or volumetric but with suboptimal anatomical accuracy (Kaye et al., 1997; Visser et al., 1999; Dickerson et al., 2001; Convit et al., 2000);

—finally, the use of annual rates of atrophy (Fox et al.,

1999; Scahill et al., 2002) has limited interest for early diagnosis, since at least a 1-year MRI follow-up is required.

Four recent MRI studies from two independent groups stand in contrast to the rest as they did not have any of the above-listed limitations (Jack et al., 1999, 2000; Killiany et al., 2000, 2002). These studies will now be presented in detail. Jack et al. (1999) studied 80 MCI patients with a ROI method that provided a very precise delineation of the Hcp. They found that the Hcp volume was statistically significantly predictive of conversion, the patient group with the most marked Hcp atrophy having the highest rate of conversion (46% vs 15% for the group with no atrophy). Furthermore, the predictive value of Hcp volume was independent from all other variables assessed, most notably memory performance. In 2000, the same team reported that the annual rate of Hcp volume loss was higher in converters than in nonconverters (Jack et al., 2000). Unfortunately, neither the specificity/sensitivity of these measurements to predict conversion nor the volume measurements of other brain regions were reported in either article.

Killiany et al. (2000, 2002) studied subjects who were not consulting for memory impairment but were recruited via the press and followed them for 3 years. The sole selection criterion was a 0.5 score on the CDR, which could be criticized (see introduction). The sample studied appeared less affected than groups in other studies, as demonstrated by a high average MMSE score (29.1) and a low conversion rate (24% in Killiany et al., 2000; and 22% in Killiany et al., 2002, over 3 years). However, the sample studied was large ($n = 79$ and 94, respectively), and the volumes of the entorhinal cortex (though measured with suboptimal ROI; see Table 1), the lateral temporal lobe, and the cingulate gyrus were assessed. The volume of the entorhinal cortex alone as well as combined to that of the superior temporal lobe both significantly differentiated HAS from nonconverters (overall accuracy of 83 and 85%, respectively) and converters (overall accuracy of 84 and 93%, respectively), whereas the volume of the hippocampus did not. Only the combination of the superior temporal lobe and anterior cingulate volumes significantly contributed to discriminate between nonconverters and converters (overall accuracy of 75%), whereas neither the hippocampus nor the entorhinal cortex volumes did. Although in need of independent replication, these results suggest that the anterior cingulate may be affected early on in the disease and that degeneration in this area may be specific to those subjects that will develop AD. The anterior cingulate cortex is highly and reciprocally connected to the entorhinal and prefrontal cortex, among other areas, and may be involved in executive functions, in contrast with the entorhinal cortex and superior temporal lobe, which preferentially serve episodic memory. Thus, the results from this study may be interpreted as follows: as all MCI patients present memory impairment, the volume of the medial temporal regions understandably poorly predicts conversion; conversely, atrophy of the anterior cingulate cortex may be a specific marker for AD and may precede the alteration of executive functions, and consequently accurately predict conversion. This interpretation is consistent with the conclusion of Delacourte et al. (1999), even though the anterior cingulate cortex was not specifically assessed in their postmortem study, that at least two polymodal areas need to be affected by *tau* degeneration in order for the subject to be demented.

Overall, and as shown in Table 4, the studies reviewed above suggest that Hcp atrophy does have a significant predictive value for conversion to AD, but that this predictive value is moderate, presumably because Hcp atrophy is associated with episodic memory impairment whether or not as part of incipient AD. The latter seems to be predicted by an increased rate of temporal neocortex atrophy, and several studies emphasize the combined predictive value of temporal neocortex and Hcp or anterior cingulate volumes, especially as the volumes of polymodal association areas appear to enhance specificity.

The notion is therefore emerging that the early diagnosis of AD with structural imaging will need to rely not only on the MTL, which has sensitivity but poor specificity (as it is targeted by *tau* pathology in normal aging too), but also on other brain areas such as the temporal neocortex and the anterior cingulate, which may exhibit less evident atrophy but confer specificity as they tend to be neuropathologically affected only in clinically probable AD. It remains to be seen whether other structures, such as the corpus callosum (Hensel et al., 2002) may also help in this endeavor.

Conclusions

Quite logically guided by histopathological data on the distribution of neurodegenerative changes at early stages of AD, structural imaging studies have targeted the hippocampal region. However, these histopathological studies have also shown that what differentiates AD from “normal” aging is the involvement of the association neocortex, and this corresponds to the operational criteria for AD which require impairment in memory and at least one other cognitive function. Quite appropriately, this has recently led to MRI studies that have investigated the combined value of hippocampal regions and lateral temporal cortex. Regarding study design, it has now become clear that only longitudinal investigations assessing the predictive value of MRI measures at study entry for subsequent conversion to AD have clinical relevance. These studies tend to suggest that the initial degree of Hcp atrophy, and also the combination of a reduced temporal neocortex and an atrophied Hcp or anterior cingulate cortex, may be the most significant predictors of progression to AD. These findings suggest that patients who later develop AD are affected by a marked and sensitive but poorly specific hippocampal/entorhinal atrophy underlying their memory impairment, in association with a

milder but more specific temporal neocortex/cingulate atrophy, which would predict the imminent development of deficits in other areas of cognition, and thus of dementia.

Suggestions for future research

Based on the above review, it is clear that further prospective studies on larger samples, with sufficient but also same follow-up for all subjects, a detailed analysis of both medial temporal and association neocortex substructures, and incorporating sensitive cognitive tests, are needed to complement these preliminary findings. It will also be of interest to consider in future studies the fraction of MCI patients that convert in a reasonably short interval ("rapid converters"), as being able to identify such subjects at first encounter may have direct bearing on the design of drug trials.

A number of additional methodological requirements should be considered in future studies. First, a rigorous selection of subjects, using well-defined operational criteria, is paramount. It is evident that, at present, the amnestic MCI category, as defined by Petersen et al. (1999, 2000, 2001a), is the most relevant as well as convenient to represent the predementia stage of AD. Secondly, it is important to ensure homogeneity of the groups to be compared in terms of age and cognitive status, or otherwise to incorporate these variables in the statistical analysis. Thirdly, the MRI procedure should not only be the same for all patients but also use high-resolution scanners, implement volume measurements (rather than surface or visual), and pay considerable attention to the issue of anatomical boundaries of the structures (especially regarding the parahippocampal gyrus components). For instance, the Insausti et al. (1998) criteria have been adopted by many authorities when considering the entorhinal and perirhinal cortices, even though implementing them remains considerably difficult, and will in all likelihood remain so in view of the intersubject variability in the relationships between cyto-architectonics and surface sulci.

Some novel imaging techniques are being developed and may prove to be useful in the early diagnosis of AD. First, even if it does not adequately address the issue of predicting conversion to AD at first assessment, the serial MRI mapping approach is of considerable interest in terms of rate of atrophy, and to address the issue of the evolution of the pathological process of AD (Scahill et al., 2002; Fox et al., 2001). Secondly, novel methods to analyze MRI data sets such as voxel-based morphometry (VBM) explore the entire brain without bias (Rombouts et al., 2000; Baron et al., 2001; Matsuda et al., 2002; Chételat et al., 2002) and so would have interesting diagnostic applications, but their reliable use at the single-subject level remains to be implemented. Thirdly, functional neuroimaging with resting state SPECT or PET (Matsuda, 2001) and activation mapping with PET of fMRI (Burggren and Bookheimer, 2002) may prove powerful tools to predict conversion, as they may reveal functional abnormalities that precede atrophy. Finally and foremost, assessing all brain structures in a single study, together with cognitive and functional neuroimaging data and perhaps also of CSF markers, is likely to eventually prove to be the most sensitive and specific approach to the early diagnosis of AD.

References

American Psychiatric Association, 1994. In: DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Am. Psychiatric Assoc. Press, Washington, DC.

Bamford, K.A., Caine, E.D., 1988. Does "benign senescent forgetfulness" exist? Clin. Geriatr. Med. 4, 897–916.

Barker, A., Jones, R., Jennison, C., 1995. A prevalence study of age-associated memory impairment. Br. J Psychiatry 167, 642–648.

Baron, J.C., Chételat, G., Desgranges, B., Perchey, G., Landeau, B., de la Sayette, V., Eustache, F., 2001. *In vivo* mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. NeuroImage 14, 298–308.

Blackford, R.C., La Rue, A., 1989. Criteria for diagnosing age-associated memory impairment: Proposed improvements from the field. Dev. Neuropsychol. 5, 295–306.

Bobinski, M., de Leon, M.J., Convit, A., de Santi, S., Wegiel, J., Tarshish, C.Y., Saint, L.L., Wisniewski, H.M., 1999. MRI of entorhinal cortex in mild Alzheimer's disease. Lancet 353, 38–40.

Bobinski, M., de Leon, M.J., Wegiel, J., Desanti, S., Convit, A., Saint, L.L., Rusinek, H., Wisniewski, H.M., 2000. The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer's disease. Neuroscience 95, 721–725.

Bobinski, M., Wegiel, J., Wisniewski, H.M., Tarnawski, M., Reisberg, B., de Leon, M.J., Miller, D.C., 1996. Neurofibrillary pathology—Correlation with hippocampal formation atrophy in Alzheimer disease. Neurobiol. Aging 17, 909–919.

Boss, M.A., 2000. Diagnostic approaches to Alzheimer's disease. Biochem. Biophys. Acta 1502, 188–200.

Bowen, J., Teri, L., Kukull, W., McCormick, W., McCurry, S. M., Larson, E.B., 1997. Progression to dementia in patients with isolated memory loss. Lancet 5, 763–765.

Bozoki, A., Giordani, B., Heidebrink, J.L., Berent, S., Foster, N.L., 2001. Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. Arch. Neurol. 58, 411–416.

Braak, H., Braak, E., 1996. Evolution of the neuropathology of Alzheimer's disease. Acta Neurol. Scand. Suppl. 165, 3–12.

Braak, H., Braak, E., Bohl, J., 1993. Staging of Alzheimer-related cortical destruction. Eur. Neurol. 33, 403–408.

Burggren, A.C., Bookheimer, S.Y., 2002. Structural and functional neuroimaging in Alzheimer's disease: an update. Curr. Top. Med. Chem. 2, 385–93.

Caine, E.D., 1993. Should aging-associated cognitive decline be included in DSM-IV? J. Neuropsychiatry Clin. Neurosci. 5, 1–5.

Celsis, P., 2000. Age-related cognitive decline, mild cognitive impairment or preclinical Alzheimer's disease? Ann. Med. 32, 6–14.

Chan, D., Fox, N.C., Scahill, R.I., Crum, W.R., Whitwell, J.L., Leschziner, G., Rossor, A.M., Stevens, J.M., Cipolotti, L., Rossor, M.N., 2001. Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. Ann. Neurol. 49, 433–442.

Chen, P., Ratcliff, G., Belle, S.H., Cauley, J.A., DeKosky, S.T., Ganguli, M., 2000. Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. Neurology 55, 1847–1853.

Chetelat, G., Desgranges, B., de la Sayette, V., Vinder, F., Eustache, F., Baron, J.-C., 2002. Mapping gray matter loss with voxel-based mor-

phometry in mild cognitive impairment. NeuroReport 13, 1939–1943.

Convit, A., de Leon, M.J., Golomb, J., George, A.E., Tarshish, C.Y., Bobinski, M., Tsui, W., de Santi, S., Wegiel, J., Wisniewski, H., 1993. Hippocampal atrophy in early Alzheimer's disease: anatomic specificity and validation. Psychiatry Q. 64, 371–387.

Convit, A., de Leon, M.J., Tarshish, C., de Santi, S., Tsui, W., Rusinek, H., George, A., 1997. Specific hippocampal volume reductions in individuals at risk for Alzheimer's disease. Neurobiol. Aging 18, 131–138.

Convit, A., de Asis, J., De Leon, M.J., Tarshish, C.Y., De Santi, S., Rusinek, H., 2000. Atrophy of the medial occipitotemporal, inferior, and middle temporal gyri in non-demented elderly predict decline to Alzheimer's disease. Neurobiol. Aging 21, 19–26.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923.

Coria, F., Gomez, d.C.J., Minguez, L., Rodriguez-Artalejo, F., Claveria, L.E., 1993. Prevalence of age-associated memory impairment and dementia in a rural community. J. Neurol. Neurosurg. Psychiatry 56, 973–976.

Crook, T., Bartus, R.T., Ferris, S.H., Whitehouse, P., Cohen, G.D., Gershon, S., 1986. Age-associated memory Impairment: proposed diagnostic criteria and measures of clinical changes—Report of a National Institute of Mental Health Work Group. Dev. Neuropsychol. 2, 261–276.

Crook, T.H., 1989. Diagnosis and treatment of normal and pathologic memory impairment in later life. Semin. Neurol. 9, 20–30.

Cuenod, C.A., Denys, A., Michot, J.L., Jehenson, P., Forette, F., Kaplan, D., Syrota, A., Boller, F., 1993. Amygdala atrophy in Alzheimer's disease. An in vivo magnetic resonance imaging study. Arch. Neurol. 50, 941–945.

Daly, E., Zaitchik, D., Copeland, M., Schmahmann, J., Gunther, J., Albert, M., 2000. Predicting conversion to Alzheimer disease using standardized clinical information. Arch. Neurol. 57, 675–680.

de la Monte, S.M., 1989. Quantitation of cerebral atrophy in preclinical and end-stage Alzheimer's disease. Ann. Neurol. 25, 450–459.

de Leon, M.J., George, A.E., Stylopoulos, L.A., Smith, G., Miller, D.C., 1987. Early marker for Alzheimer's disease: the atrophic hippocampus. Lancet 2, 672–673.

de Leon, M.J., Golomb, J., George, A.E., Convit, A., Tarshish, C.Y., McRae, T., de Santi, S., Smith, G., Ferris, S.H., Noz, M., 1993. The radiologic prediction of Alzheimer disease: the atrophic hippocampal formation. AJNR Am. J Neuroradiol. 14, 897–906.

De Leon, M.J., Convit, A., de Santi, S., Bobinski, M., 1999. Structural neuroimaging: early diagnosis and staging of Alzheimer's disease, in: Iqbal, K., Winblad, B., Nishimura, T, Takeda, M, Wisniewski, H.M. (Eds.), Alzheimer's Disease and Related Disorders, Vol. 14, Wiley, New York, pp. 105–126.

Delacourte, A., David, J.P., Sergeant, N., Buee, L., Wattez, A., Vermersch, P., Ghozali, F., Fallet-Bianco, C., Pasquier, F., Lebert, F., Petit, H., Di Menza, C., 1999. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 52, 1158–1165.

de Santi, S., de Leon, M.J., Rusinek, H., Convit, A., Tarshish, C.Y., Roche, A., Tsui, W.H., Kandil, E., Boppana, M., Daisley, K., Wang, G.J., Schlyer, D., Fowler, J., 2001. Hippocampal formation glucose metabolism and volume losses in MCI and AD. Neurobiol. Aging 22, 529–539.

Detoledo-Morrell, L., Sullivan, M.P., Morrell, F., Wilson, R.S., Bennett, D.A., Spencer, S., 1997. Alzheimer's disease: in vivo detection of differential vulnerability of brain regions. Neurobiol. Aging 18, 463–468.

Dickerson, B.C., Goncharova, I., Sullivan, M.P., Forchetti, C., Wilson, R.S., Bennett, D.A., Beckett, L. A., Detoledo-Morrell, L., 2001. MRI-derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. Neurobiol. Aging 22, 747–754.

Du, A.T., Schuff, N., Amend, D., Laakso, M.P., Hsu, Y.Y., Jagust, W.J., Yaffe, K., Kramer, J.H., Reed, B., Norman, D., Chui, H.C., Weiner, M.W., 2001. Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 71, 441–447.

Duvernoy, H., 1988. The Human Hippocampus: An Atlas of Applied Anatomy. Springer-Verlag, New York.

Eichenbaum, H., Schoenbaum, G., Young, B., Bunsey, M., 1996. Functional organization of the hippocampal memory system. Proc. Natl. Acad. Sci. USA 93, 13500–13507.

Erkinjuntti, T., Lee, D.H., Gao, F., Steenhuis, R., Eliasziw, M., Fry, R., Merskey, H., Hachinski, V.C., 1993. Temporal lobe atrophy on magnetic resonance imaging in the diagnosis of early Alzheimer's disease. Arch. Neurol. 50, 305–310.

Fabrigoule, C., Lafont, S., Letenneur, L., Rouch, I., Dartigues, J.F., 1996. WAIS similarities subtests performances as predictors of dementia in elderly community residents. Brain Cogn. 30, 323–326.

Flicker, C., Ferris, S.H., Reisberg, B., 1991. Mild cognitive impairment in the elderly: predictors of dementia. Neurology 41, 1006–1009.

Fox, N.C., Rossor, M.N., 1999. Diagnosis of early Alzheimer's disease. Rev. Neurol. 155 (Suppl. 4), S33–S37.

Fox, N.C., Freeborough, P.A., Rossor, M.N., 1996a. Visualisation and quantification of rates of atrophy in Alzheimer's disease. Lancet 348, 94–97.

Fox, N.C., Warrington, E.K., Freeborough, P.A., Hartikainen, P., Kennedy, A.M., Stevens, J.M., Rossor, M.N., 1996b. Presymptomatic hippocampal atrophy in Alzheimer's disease. A longitudinal MRI study. Brain 119, 2001–2007.

Fox, N.C., Warrington, E.K., Stevens, J.M., Rossor, M.N., 1996c. Atrophy of the hippocampal formation in early familial Alzheimer's disease. A longitudinal MRI study of at-risk members of a family with an amyloid precursor protein 717Val-Gly mutation. Ann. N.Y. Acad. Sci. 777, 226–232.

Fox, N.C., Warrington, E.K., Rossor, M.N., 1999. Serial magnetic resonance imaging of cerebral atrophy in preclinical Alzheimer's disease. Lancet 353, 2125.

Fox, N.C., Crum, W.R., Scahill, R.I., Stevens, J.M., Janssen, J.C., Rossor, M.N., 2001. Imaging of onset and progression of Alzheimer's disease with voxel-compression mapping of serial magnetic resonance images. Lancet 358, 201–205.

Frisoni, G.B., Beltramello, A., Weiss, C., Geroldi, C., Bianchetti, A., Trabucchi, M., 1996. Linear measures of atrophy in mild Alzheimer disease. AJNR. Am. J Neuroradiol. 17, 913–923.

Frisoni, G.B., Laakso, M.P., Beltramello, A., Geroldi, C., Bianchetti, A., Soininen, H., Trabucchi, M., 1999. Hippocampal and entorhinal cortex atrophy in frontotemporal dementia and Alzheimer's disease. Neurology 52, 91–100.

Frisoni, G.B., 2001. Structural imaging in the clinical diagnosis of Alzheimer's disease: problems and tools. J. Neurol. Neurosurg. Psychiatry 70, 711–718.

Gomez-Isla, T., Price, J.L., McKeel, D.W., Jr., Morris, J.C., Growdon, J.H., Hyman, B.T., 1996. Profond loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. J. of Neurosci. 16, 4491–4500.

Goshe, K.M., Mortimer, J.A., Smith, C.D., Markesbery, W.R., Snowdoon, D.A., 2001. A technique for measuring hippocampal volumes from MR imaging studies. AJNR Am. J. Neuroradiol. 22, 1686–1689.

Hampel, H., Teipel, S.J., Bayer, W., Alexander, G.E., Schwarz, R., Schapiro, M.B., Rapoport, S.I., Moller, H.J., 2002. Age transformation of combined hippocampus and amygdala volume improves diagnostic accuracy in Alzheimer's disease. J. Neurol. Sci. 194, 15–19.

Hanninen, T., Koivisto, K., Reinikainen, K.J., Helkala, E.L., Soininen, H., Mykkanen, L., Laakso, M., Riekkinen, P.J., 1996. Prevalence of ageing-associated cognitive decline in an elderly population. Age Ageing 25, 201–205.

Hanninen, T., Soininen, H., 1997. Age-associated memory impairment. Normal aging or warning of dementia? Drugs Aging 11, 480–489.

Hensel, A., Wolf, H., Kruggel, F., Riedel-Heller, S.G., Nikolaus, C., Arendt, T., Gertz, H.J., 2002. Morphometry of the corpus callosum in patients with questionable and mild dementia. J. Neurol. Neurosurg. Psychiatry 73, 59–61.

Ikeda, M., Tanabe, H., Nakagawa, Y., Kazui, H., Oi, H., Yamazaki, H., Harada, K., Nishimura, T., 1994. MRI-based quantitative assessment of the hippocampal region in very mild to moderate Alzheimer's disease. Neuroradiology 36, 7–10.

Insausti, R., Juottonen, K., Soininen, H., Insausti, A.M., Partanen, K., Vainio, P., Laakso, M.P., Pitkanen, A., 1998. MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. AJNR Am. J. Neuroradiol. 19, 659–671.

Ishii, K., 1994. Value of interuncal distance measure in diagnosis of Alzheimer disease questioned. AJNR. Am. J. Neuroradiol. 15, 1286–1290.

Jack, C.R., Petersen, R.C., Xu, Y., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Boeve, B.F., Tangalos, E.G., Kokmen, E., 2000. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology 55, 484–489.

Jack, C.R.J., Petersen, R.C., Xu, Y.C., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Boeve, B.F., Waring, S.C., Tangalos, E.G., Kokmen, E., 1999. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 52, 1397–1403.

Jack, C.R.J., Petersen, R.C., Xu, Y.C., Waring, S.C., O'Brien, P.C., Tangalos, E.G., Smith, G.E., Ivnik, R.J., Kokmen, E., 1997. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. Neurology 49, 786–794.

Jobst, K.A., Smith, A.D., Szatmari, M., Molyneux, A., Esiri, M.E., King, E., Smith, A., Jaskowski, A., McDonald, B., Wald, N., 1992. Detection in life of confirmed Alzheimer's disease using a simple measurement of medial temporal lobe atrophy by computed tomography. Lancet 340, 1179–1183.

Juottonen, K., Laakso, M.P., Insausti, R., Lehtovirta, M., Pitkanen, A., Partanen, K., Soininen, H., 1998. Volumes of the entorhinal and perirhinal cortices in Alzheimer's disease. Neurobiol. Aging 19, 15–22.

Juottonen, K., Laakso, M.P., Partanen, K., Soininen, H., 1999. Comparative MR analysis of the entorhinal cortex and hippocampus in diagnosing Alzheimer disease. AJNR. Am. J. Neuroradiol. 20, 139–144.

Kaye, J.A., Swihart, T., Howieson, D., Dame, A., Moore, M.M., Karnos, T., Camicioli, R., Ball, M., Oken, B., Sexton, G., 1997. Volume loss of the hippocampus and temporal lobe in healthy elderly persons destined to develop dementia. Neurology 48, 1297–1304.

Killiany, R.J., Moss, M.B., Albert, M.S., Sandor, T., Tieman, J., Jolesz, F., 1993. Temporal lobe regions on magnetic resonance imaging identify patients with early Alzheimer's disease. Arch. Neurol. 50, 949–954.

Killiany, R.J., Gomez-Isla, T., Moss, M., Kikinis, R., Sandor, T., Jolesz, F., Tanzi, R., Jones, K., Hyman, B.T., Albert, M.S., 2000. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Ann. Neurol. 47, 430–439.

Killiany, R.J., Hyman, B.T., Gomez-Isla, T., Moss, M.B., Kikinis, R., Jolesz, F., Tanzi, R., Jones, K., Albert, M.S., 2002. MRI measures of entorhinal cortex vs hippocampus in preclinical AD. Neurology 58, 1188–1196.

Knopman, D.S., DeKosky, S.T., Cummings, J.L., et al., 2001. Practice parameter: diagnosis of dementia (an evidence-based review). Neurology 56, 1143–53.

Koivisto, K., Reinikainen, K.J., Hanninen, T., Vanhanen, M., Helkala, E.L., Mykkanen, L., Laakso, M., Pyorala, K., Riekkinen, P.J.S., 1995. Prevalence of age-associated memory impairment in a randomly selected population from eastern Finland. Neurology 45, 741–747.

Kordower, J.H., Chu, Y., Stebbins, G.T., DeKosky, S.T., Cochran, E.J., Bennett, D., Mufson, E.J., 2001. Loss and atrophy of layer II entorhinal cortex neurons in elderly people with mild cognitive impairment. Ann. Neurol. 49, 202–213.

Kral, V.A., 1962. Senescent forgetfulness: benign and malignant. J. Can. Med. Assoc. 86, 257–260.

Krasuski, J.S., Alexander, G.E., Horwitz, B., Daly, E.M., Murphy, D.G., Rapoport, S.I., Schapiro, M.B., 1998. Volumes of medial temporal lobe structures in patients with Alzheimer's disease and mild cognitive impairment (and in healthy controls). Biol. Psychiatry 43, 60–68.

Laakso, M.P., Hallikainen, M., Hanninen, T., Partanen, K., Soininen, H., 2000. Diagnosis of Alzheimer's disease: MRI of the hippocampus vs delayed recall. Neuropsychologia 38, 579–584.

Laakso, M.P., Partanen, K., Lehtovirta, M., Hallikainen, M., Hanninen, T., Vainio, P., Riekkinen, P.S., Soininen, H., 1995a. MRI of amygdala fails to diagnose early Alzheimer's disease. NeuroReport 6, 2414–2418.

Laakso, M.P., Soininen, H., Partanen, K., Helkala, E.L., Hartikainen, P., Vainio, P., Hallikainen, M., Hanninen, T., Riekkinen, P.J.S., 1995b. Volumes of hippocampus amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory functions. J. Neural Transm. Park. Dis. Dement. Sect. 9, 73–86.

Laakso, M.P., Soininen, H., Partanen, K., Lehtovirta, M., Hallikainen, M., Hanninen, T., Helkala, E.L., Vainio, P., Riekkinen, P.J.S., 1998. MRI of the hippocampus in Alzheimer's disease: sensitivity, specificity, and analysis of the incorrectly classified subjects. Neurobiol. Aging 19, 23–31.

Lehericy, S., Baulac, M., Chiras, J., Pierot, L., Martin, N., Pillon, B., Deweer, B., Dubois, B., Marsault, C., 1994. Amygdalohippocampal MR volume measurements in the early stages of Alzheimer disease. AJNR Am. J Neuroradiol. 15, 929–937.

Levy, R., 1994. Aging-associated cognitive decline. Working Party of the International Psychogeriatric Association in collaboration with the World Health Organization. Int. Psychogeriatr. 6, 63–68.

Matsuda, H., 2001. Cerebral blood flow and metabolic abnormalities in Alzheimer's disease. Ann. Nucl. Med. 15, 85–92.

Matsuda, H., Kitayama, N., Ohnishi, T., Asada, T., Nakano, S., Sakamoto, S., Imabayashi, E., Katoh, A., 2002. Longitudinal evaluation of both morphologic and functional changes in the same individuals with Alzheimer's disease. J. Nucl. Med. 43, 304–311.

Maunoury, C., Michot, J.L., Caillet, H., Parlato, V., Leroy-Willig, A., Jehenson, P., Syrota, A., Boller, F., 1996. Specificity of temporal amygdala atrophy in Alzheimer's disease: quantitative assessment with magnetic resonance imaging. Dementia 7, 10–14.

McKelvey, R., Bergman, H., Stern, J., Rush, C., Zahirney, G., Chertkow, H., 1999. Lack of prognostic significance of SPECT abnormalities in non-demented elderly subjects with memory loss. Can. J Neurol Sci. 26, 23–28.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34, 939–944.

Mega, M.S., Thompson, P.M., Toga, A.W., Cummings, J.L., 2000. Brain mapping in dementia, in: Mazziotta, J.C., Frackowiak, R.S.J., Toga, A. (Eds.), Brain Mapping: The Disorders, Academic Press, San Diego, pp. 217–239.

Meguro, K., Le Mestric, C., Landeau, B., Desgranges, B., Eustache, F., Baron, J.C., 2001. Relationships between posterior association cortex hypometabolism and hippocampal atrophy in Alzheimer's disease. J. Neurol. Neurosurg. Psychiatr. 71, 315–321.

Mizuno, K., Wakai, M., Takeda, A., Sobue, G., 2000. Medial temporal atrophy and memory impairment in early stage of Alzheimer's disease: an MRI volumetric and memory assessment study. J. Neurol. Sci. 173, 18–24.

Moffat, S.D., Szekely, C.A., Zonderman, A.B., Kabani, N.J., Resnick, S.M., 2000. Longitudinal change in hippocampal volume as a function of apolipoprotein E genotype. Neurology 55, 134–136.

Morris, J.C., Storandt, M., Miller, J.P., McKeel, D.W., Price, J.L., Rubin, E.H., Berg, L., 2001. Mild cognitive impairment represents early-stage Alzheimer disease. Arch. Neurol. 58, 397–405.

Morrison, J.H., Hof, P.R., 1997. Life and death of neurons in the aging brain. Science 278, 412–419.

Nielsen, H., Lolk, A., Kragh-Sorensen, P., 1998. Age-associated memory impairment—Pathological memory decline or normal aging? Scand. J Psychol. 39, 33–37.

O'Brien, J.T., Levy, R., 1992. Age associated memory impairment. Br. Med. J. 304, 5–6.

Pantel, J., Schroder, J., Schad, L.R., Friedlinger, M., Knopp, M.V., Schmitt, R., Geissler, M., Bluml, S., Essig, M., Sauer, H., 1997. Quantitative magnetic resonance imaging and neuropsychological functions in dementia of the Alzheimer type. Psychol. Med. 27, 221–229.

Pantel, J., O'Leary, D.S., Cretsinger, K., Bockholt, H.J., Keefe, H., Magnotta, V.A., Andreasen, N.C., 2001. A new method for the in vivo volumetric measurement of the human hippocampus with high neuroanatomical accuracy. Hippocampus 10, 752–758.

Parnetti, L., Lowenthal, D.T., Presciutti, O., Pelliccioli, G.P., Palumbo, R., Gobbi, G., Chiarini, P., Palumbo, B., Tarducci, R., Senin, U., 1996. IH-MRS, MRI-based hippocampal volumetry, and 99m Tc-HMPAO-SPECT in normal aging, age-associated memory impairment, and probable Alzheimer's disease. J. Am. Geriatr. Soc. 44, 133–138.

Petersen, R.C., Jack, C.R.J., Xu, Y.C., Waring, S.C., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Tangalos, E.G., Boeve, B.F., Kokmen, E., 2000. Memory and MRI-based hippocampal volumes in aging and AD. Neurology 54, 581–587.

Petersen, R.C., Smith, G.E., Ivnik, R.J., Tangalos, E.G., Schaid, D.J., Thibodeau, S.N., Kokmen, E., Waring, S.C., Kurland, L.T., 1995. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. J. Am. Med. Assoc. 273, 1274–1278.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999. Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 56, 303–308.

Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., Ritchie, K., Rossor, M., Thal, L., Winblad, B., 2001a. Current concepts in mild cognitive impairment. Arch. Neurol. 58, 1985–1992.

Petersen, R.C., Stevens, J.C., Ganguli, M., Tangalos, E.G., Cummings, J.L., DeKosky, S.T., 2001b. Practice parameter: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 56, 1133–1142.

Price, J.L., 1997. Diagnostic criteria for Alzheimer's disease. Neurobiol. Aging 18 (Suppl. 4), S67–S71.

Reiman, E.M., Uecker, A., Caselli, R.J., Lewis, S., Bandy, D., de Leon, M.J., de Santi, S., Convit, A., Osborne, D., Weaver, A., Thibodeau, S.N., 1998. Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. Ann. Neurol. 44, 288–291.

Ritchie, K., Artero, S., Touchon, J., 2001. Classification criteria for mild cognitive impairment: a population-based validation study. Neurology 56, 37–42.

Ritchie, K., Touchon, J., 2000. Mild cognitive impairment: conceptual basis and current nosological status. Lancet 355, 225–228.

Rombouts, S.A., Barkhof, F., Witter, M. P., Scheltens, P., 2000. Unbiased whole-brain analysis of gray matter loss in Alzheimer's disease. Neurosci. Lett. 19, 231–233.

Scahill, R.I., Schott, J.M., Stevens, J.M., Rossor, M.N., Fox, N.C., 2002. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. Proc. Natl. Acad. Sci. USA 99, 4703–4707.

Scheltens, P., 1999. Early diagnosis of dementia: neuroimaging. J. Neurol. 246, 16–20.

Scheltens, P., Fox, N., Barkhof, F., De Carli, C., (2002). Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. Lancet Neurol. 1, 13–21.

Schmidt, H., Schmidt, R., Fazekas, F., Semmler, J., Kapeller, P., Reinhart, B., Kostner, G.M., 1996. Apolipoprotein E e4 allele in the normal elderly: neuropsychologic and brain MRI correlates. Clin. Genet. 50, 293–299.

Schroder, J., Kratz, B., Pantel, J., Minnemann, E., Lehr, U., Sauer, H., 1998. Prevalence of mild cognitive impairment in an elderly community sample. J. Neural. Transm. Suppl. 54, 51–59.

Seab, J.P., Jagust, W.J., Wong, S.T., Roos, M.S., Reed, B.R., Budinger, T.F., 1988. Quantitative NMR measurements of hippocampal atrophy in Alzheimer's disease. Magn. Reson. Med. 8, 200–208.

Sliwinski, M., Lipton, R.B., Buschke, H., Stewart, W., 1996. The effects of preclinical dementia on estimates of normal cognitive functioning in aging. J. Gerontol. B. Psychol. Sci. Soc. Sci. 51, 217–225.

Small, G.W., Rabins, P.V., Barry, P.P., Buckholtz, N.S., DeKosky, S.T., , et al., 1997. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. J. Am. Med. Assoc. 278, 1363–1371.

Smith, A.D., Jobst, K.A., 1996. Use of structural imaging to study the progression of Alzheimer's disease. Br. Med. Bull. 52, 575–586.

Smith, G., Ivnik, R.J., Petersen, R.C., Malec, J.F., Kokmen, E., Tangalos, E., 1991. Age-associated memory impairment diagnoses: problems of reliability and concerns for terminology. Psychol. Aging 6, 551–558.

Smith, G.E., Petersen, R.C., Parisi, J.E., Ivnik, R.J., Kokmen, E., Tangalos, E., Waring, S., 1996. Definition, course, and outcome of Mild Cognitive Impairment. Aging Neuropsychol. Cogn. 3, 141–147.

Soininen, H.S., Partanen, K., Pitkanen, A., Vainio, P., Hanninen, T., Hallikainen, M., Koivisto, K., Riekkinen, P.J.S., 1994. Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment: correlation to visual and verbal memory. Neurology 44, 1660–1668.

Squire, L.R., Zola-Morgan, S., 1991. The medial temporal lobe memory system. Science 253, 1380–1386.

Swann, A., O'Brien, J., Ames, D., Schweitzer, I., Desmond, P., Tress, B., 1997. Does hippocampal atrophy on MRI predict cognitive decline? A prospective follow-up study. Int. J Geriatr. Psychiatry 12, 1182–1188.

Tohgi, H., Takahashi, S., Kato, E., Homma, A., Niina, R., Sasaki, K., Yonezawa, H., Sasaki, M., 1997. Reduced size of right hippocampus in 39- to 80-year-old normal subjects carrying the apolipoprotein E epsilon4 allele. Neurosci. Lett. 236, 21–24.

van Duijn, C.M., Hofman, A., 1992. Risk factors for Alzheimer's disease: the EURODEM collaborative re-analysis of case-control studies. Neuroepidemiology 11 (Suppl. 1), 106–113.

Vermersch, P., David, J.P., Frigard, B., Fallet-Bianco, C., Wattez, A., Petit, H., Delacourte, A., 1995. Cortical mapping of Alzheimer pathology in brains of aged non-demented subjects. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 19, 1035–1047.

Victoroff, J., Mack, W.J., Grafton, S.T., Schreiber, S.S., Chui, H.C., 1994. A method to improve interrater reliability of visual inspection of brain MRI scans in dementia. Neurology 44, 2267–2276.

Visser, P.J., Scheltens, P., Verhey, F.R., Schmand, B., Launer, L.J., Jolles, J., Jonker, C., 1999. Medial temporal lobe atrophy and memory dysfunction as predictors for dementia in subjects with mild cognitive impairment. J. Neurol. 246, 477–485.

Visser, P.J., Verhey, F.R., Hofman, PAM, Scheltens, P., Jolles, J., 2002. Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. J. Neurol. Neurosurg. Psychiatry 72, 491–497.

Wahlund, L.O., Julin, P., Lindqvist, J., Scheltens, P., 1999. Visual assessment of medical temporal lobe atrophy in demented and healthy control subjects: correlation with volumetry. Psychiatry Res. 90, 193–199.

Whalley, H.C., Kestelman, J.N., Rimmington, J.E., Kelso, A., Abukmeil, S.S., Best, J.J., Johnstone, E.C., Lawrie, S.M., 1999. Methodological issues in volumetric magnetic resonance imaging of the brain in the Edinburgh High Risk Project. Psychiatry Res. 91, 31–44.

Wolf, H., Grunwald, M., Ecke, G.M., Zedlick, D., Bettin, S., Dannenberg, C., Dietrich, J., Eschrich, K., Arendt, T., Gertz, H.J., 1998. The prognosis of mild cognitive impairment in the elderly. J. Neurol. Transm. Suppl. 54, 31–50.

Wolf, H., Grunwald, M., Kruggel, F., Riedel-Heller, S.G., Angerhofer, S., Hojjatoleslami, A., Hensel, A., Arendt, T., Gertz, H., 2001. Hippocampal volume discriminates between normal cognition: questionable and mild dementia in the elderly. Neurobiol. Aging 22, 177–186.

Xu, Y., Jack, C.R.J., O'Brien, P.C., Kokmen, E., Smith, G.E., Ivnik, R.J., Boeve, B.F., Tangalos, R.G., Petersen, R.C., 2000. Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD. Neurology 54, 1760–1767.

Yamada, N., Tanabe, H., Kazui, H., Ikeda, M., Hashimoto, M., Nakagawa, Y., Wada, Y., Okuda, J.I., 1996. Longitudinal neuropsychological and quantitative MRI assessments in early alzheimer's disease. Alzheimer's Res. 2, 29–36.