Cognitive aging and Alzheimer’s disease

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Cognitive aging and clinically probable Alzheimer’s disease can be discriminated by means of clinical and neuropsychological testing, and structural and functional imaging techniques. Research at the level of cognitive brain systems and at the molecular level provides exciting new insights into the relation between aging and neurodegeneration. The advances at the clinical and at the basic research levels are necessary if we wish to meet the formidable challenge that the increasing prevalence of Alzheimer’s disease poses to the medical community.

Among the neurodegenerative diseases, clinically probable Alzheimer’s disease (AD) has the highest prevalence, estimated at 1.450/100 000.¹ Between 65 and 69 years of age, its prevalence is estimated at 1.53%.² From the age of 60 onwards up to 80 years of age, incidence and prevalence of AD increases exponentially with age, doubling every five years.³ Between the age of 80 and 85 the prevalence is as high as 25%–30% of the population.⁴ The distinction between this highly prevalent disorder and normal aging will be the focus of this review. Given the demographic evolution, AD will pose a challenge over the decades to come all over the world. The distinction between normal aging and AD is one first step if we want to combat this disease efficiently.

This review draws a new face of AD: a treatable disorder that evolves insidiously over many years and that can be diagnosed at an early stage by means of positive diagnostic features. This contrasts with a more traditional view of AD as an exclusion diagnosis of an untreatable disorder associated with impairment of basic activities of daily living.

We will adopt an evidence based approach (table 1). On several occasions positive likelihood ratios will be used. This permits the combination of sensitivity and specificity into one value (table 1). Positive likelihood ratios between 2 and 5 imply small (but sometimes important) shifts between pre-test and post-test probabilities and values between 5 and 10 moderate shifts. Values above 10 imply conclusive changes to the pre-test probability.

### DISCRIMINATING NORMAL AGING FROM PROBABLE AD

The distinction between age related cognitive decline and probable AD has important clinical implications. Probable AD is a treatable disorder⁵ while no evidence exists at the moment that medical treatment is beneficial for age related cognitive decline. Counselling about diagnosis and prognosis also differs between cognitive aging and probable AD. The transition from normal aging to probable AD, however, is not categorical. Mild cognitive impairment (MCI) refers to this transition zone from normal aging to probable AD.⁶

#### Clinical features

**Cognitive aging**

Only a minority of aged people maintain their peak cognitive performance level during senescence. They experience successful aging.¹¹ In most healthy people above the age of 50, episodic memory (table 2) declines with respect to the person’s prior performance.¹² Age related episodic memory decline typically affects free recall more than recognition (familiarity judgment).¹³ Other cognitive changes associated with normal aging are a decrease in cognitive processing speed and executive functions (table 2). Typically, cognitive aging does not affect cognition globally but leaves specific cognitive domains intact, for example, familiarity judgement. In this review, we refer to this pattern of age related cognitive changes as cognitive aging.

On its own a subjective memory complaint does not increase the risk of developing probable AD.¹⁷ In a hierarchical regression model, subjective memory complaints were explained significantly more by mood than by actual memory performance on cognitive tests.¹⁸ When a patient presents with a subjective memory complaint, two key questions are: “Have your relatives...

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**Table 1** Evidence based medicine terminology

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Specificity = d/(b+d); sensitivity = a/(a+c); positive likelihood ratio = sensitivity/ (1 – specificity); positive predictive value = a/(a+b); negative predictive value = d/(c+d).

**Abbreviations:** AD, Alzheimer’s disease; MCI, mild cognitive impairment; MMSE, mini-mental state examination; IADL, instrumental activities of daily living; PET, positron emission tomography; MRI, magnetic resonance imaging; CT, computed tomography; LTP, long term potentiation; CREB, cAMP response element binding protein; PKA, protein kinase A; APP, amyloid precursor protein; KPI, kunitz protease inhibitor; AVF, animal verbal fluency.
friends or colleagues noticed any change?’, and ‘‘Does the cognitive change impact on the way you carry out daily activities (professional, leisure, finances, shopping, car driving, etc)?’’ A positive answer increases the likelihood that the patient suffers from an objective cognitive deficit, possibly related to degenerative disease, rather than a subjective perception of age related memory decline.

A diagnosis of age related memory decline requires exclusion of alternative explanations, such as vascular brain lesions, obstructive sleep apnea syndrome, depression, chronic obstructive pulmonary disease, diabetes mellitus, or cardiac failure. The drug list must be systematically reviewed for drugs that are used commonly in the elderly population and that exert minor or major cognitive side effects, such as benzodiazepines used during the day, tricyclic antidepressants, opioid derivatives, and centrally active antihistaminergic drugs.

Mild cognitive impairment

The distinction between cognitive aging and a pathological deficit may be subtle. A standardised systematic neuropsychological assessment may be necessary to distinguish between cognitive aging and a pathological deficit. A prospective longitudinal study of the diagnostic accuracy of neuropsychological tests in patients referred for memory loss determined which neuropsychological tests discriminated best between patients who developed probable AD and those who remained non-demented over a two year follow up period. Classic neuropsychological episodic memory tests, which require the learning and recalling of lists of words, elements of a story, or series of abstract visual designs, had a positive likelihood ratio of about 12, corresponding to a moderate to large change from pre-test to post-test probability (table 1).

Could we increase the diagnostic value by doing repeat examination at, for example, one year intervals and carrying out within subject comparisons? There are two caveats. The standard error of the difference between the initial and the repeat test is the square root of two times higher than the standard error of the test itself. Secondly, repeat assessments in normal controls suffer from a comparatively high within subject variance from one test to another. Specific norms of longitudinal change are necessary for each of the tests to discover if a person’s change falls within a normal range. Despite these caveats, if repeat neuropsychological assessment with a one year interval shows significant deterioration in a patient classified as MCI or, on the other hand, improvement or stabilisation, this is clinically valuable information regarding the risk of conversion to probable AD. If a pathological memory deficit is present, if there is no alternative explanations (medication, comorbidity, depression), then the patient suffers from concomitant diseases that may contribute to the cognitive deficits, the patient falls under the category of clinically possible AD.

Episodic memory impairment is a cornerstone of the diagnosis of probable AD (table 2). Typical episodic memory complaints are: I have to re-read previous passages in books more frequently than before, I have difficulty in remembering where I keep things, I have problems organizing my daily activities (professional, leisure, finances, shopping, car driving, etc), and I have problems knowing what I had to do. A positive answer increases the likelihood that the patient suffers from a pathological episodic memory deficit (table 2). The drug list must be systematically reviewed for drugs that are used commonly in the elderly population and that exert minor or major cognitive side effects, such as benzodiazepines used during the day, tricyclic antidepressants, opioid derivatives, and centrally active antihistaminergic drugs.

Clinically probable AD

A diagnosis of probable AD requires the presence of an acquired and progressive episodic memory deficit (table 2) combined with impairment in at least one other cognitive domain and associated with a significant impact on instrumental activities of daily living (NINCDS-ADRDA or DSM-IV criteria). The cognitive deficits should not occur exclusively during the course of a delirium. If the patient suffers from concomitant diseases that may contribute to the cognitive deficits, the patient falls under the category of clinically possible AD.

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Brain pathology

Cognitive aging

In rat hippocampus and prefrontal cortex stereological postmortem studies have not provided clear proof of age related neuronal loss. In humans, the number and length of dendritic segments in specific layers of dorsolateral prefrontal cortex decreases with age, together with a decrease in dendritic spine and synaptic density. In the non-demented elderly population, the entorhinal cortex and the basal forebrain (fig 1) display diffuse plaques as well as neurofibrillary tangles or pre-tangle tau pathology. It is possible that these lesions also contribute to cognitive aging.

Clinically probable AD

Neurodegenerative diseases are characterised by the progressive loss of neurons with a high neuroanatomical selectivity at the initial stages. This neuroanatomical selectivity determines the clinical manifestations. The earliest changes in AD are in the entorhinal cortex (fig 1), a structure that lies just laterally to the hippocampus and provides input to the

Key point

Criteria for a diagnosis of clinically probable Alzheimer’s disease are the presence of an episodic memory deficit in combination with impairment of at least one other cognitive domain. Frequently affected domains at an early stage are executive functions and word finding. There must be a significant impact on activities of daily living and no alternative explanations (delirium, medication, comorbidity, depression).
This explains why episodic memory deficits play such a prominent part in the definition of AD. From the entorhinal cortex, disease spreads to the hippocampus and subsequently to the inferotemporal and lateral temporal cortex and other neocortical association areas. This explains the impairment of other cognitive domains apart from episodic memory. This hierarchical spread of AD has been divided into six stages by Braak and Braak. According to this proposal, the topography and intensity of the Alzheimer lesions parallels different stages in the clinical evolution.

Several criteria have been put forward for a pathological diagnosis of definite AD, with varying emphasis on the presence of neuritic plaques or neurofibrillary tangles (fig 2). Neuritic plaques (fig 2A) consist of the extracellular deposition of congophilic, amyloid material that can be immunostained with antibodies against Ab42 and also with antibodies against paired helical filament τ (PHF τ). Neuritic plaques must be distinguished from diffuse plaques, which only stain for Ab42 and are present in the aging brain from the age of 40 onwards.

Neurofibrillary tangles (fig 2B) represent intracellular paired helical filaments of hyperphosphorylated protein. They can be visualised with silver and thioflavin S staining and with immunostaining for PHFτ. Neurofibrillary tangles are nearly always present in the entorhinal cortex above the age of 75.

Brains from patients with probable AD also show vascular lesions, such as cerebral amyloid angiopathy and cerebral endothelial degeneration. The additional presence of lacunar infarcts in the basal ganglia, the thalamus, or the white matter in neuropathologically definite AD brains significantly increases the probability that the disease expressed itself clinically, with an odds ratio of 21.

The neuropathological distinction between brains of patients that suffered from probable AD during their lifetime and brains of cognitively normal people is less clear cut than originally proposed. In people who do not show pathological cognitive deficits during life, neuritic plaques and neurofibrillary tangles may be present in sufficient quantity to warrant a neuropathological diagnosis of definite AD.

In the Medical Research Council cognitive function and aging (MRC-CFAS) study, a prospective community based necropsy study, diffuse and neuritic amyloid plaques as well as neurofibrillary tangles were present in a significant percentage of cognitively intact elderly people in numbers and with a distribution sufficient to warrant a pathological diagnosis of definite AD. Multiple regression analysis with dementia status as outcome measure and the degree and distribution of tangles and plaques as explanatory variables misclassified one in four non-demented controls as demented.

Neurochemically, AD is associated with neuronal loss in the nucleus basalis of Meynert leading to cholinergic depletion. According to the cholinergic theory, this depletion underlies the episodic memory and attentional deficits. This influential theory has driven the development of cholinesterase inhibitors as a treatment for probable AD. In mild to moderate disease stages (MMSE 10 to 24 of 30), cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) favourably affect cognition, activities of daily living, and behavioural symptoms. The difference between patients receiving active treatment or receiving placebo is sufficiently large to be detectable by means of semi-structured interviews of patients and caregivers by clinicians blinded for the treatment (such as the clinician interview based impression of change).

Mild cognitive impairment

Necropsy studies in MCI so far have mostly shown pathological features consistent with the diagnosis of early stage AD, corresponding to Braak and Braak stages 3 to 4 (limbic stages).

Neurochemically, no cholinergic depletion was found in neocortex or in the hippocampal formation in patients who died with a diagnosis of MCI or early probable AD. This has cast doubt on the validity of the cholinergic theory at an early disease stage. In a recent necropsy study of the nucleus basalis, the important source of cholinergic innervation for the cortex, Mesulam et al compared a group of five MCI patients and seven age matched controls: the cholinergic neurons of the nucleus basalis showed significantly more tangles and pre-tangles than the age matched controls. This suggests that cholinergic depletion does have a role at the pre-dementia stage in structures that are most sensitive to the disease process.

Key point

Several sets of consensus criteria exist for a diagnosis of pathologically definite AD. Neuritic plaques and neurofibrillary tangles are the hallmarks of AD but also occur in normal aging. Prospective double blind studies that correlate the clinical diagnosis with pathological diagnosis show that brain necropsy findings do not always accurately predict who was demented or cognitively normal during lifetime.
Key point
Pathological findings support the notion that MCI is a transition zone between normal aging and AD.

In vivo structural and functional imaging
Cognitive aging

Recent technical advances permit the investigation of age related brain changes in humans during lifetime. In a large cross sectional structural magnetic resonance imaging (MRI) study of 465 normal adult human brains, medial temporal structures such as the hippocampus or the entorhinal cortex did not show measurable diminution of volume. This corresponds to recent stereological findings in rat brains that did not show age related neuronal loss in the hippocampus.

A second in vivo brain imaging technique, positron emission tomography (PET), permits the measurement of regional brain glucose metabolism ([18F]fluorodeoxyglucose (FDG) PET) as well as the integrity of neurotransmitter systems. Aging is associated with a decline in glucose metabolism in specific brain regions, such as the anterior cingulate and perisylvian cortex and with changes in neurotransmitter systems, such as a decrease in D2 dopamine receptors and presynaptic dopamine transporters. Given the projections of the dopaminergic system to prefrontal cortex (fig 1), this dopaminergic decrease may be related to the decrease in mental flexibility that occurs with aging.

A different methodology, functional MRI (fMRI), permits the measurement of brain activation related to motor, sensory, or cognitive processes. Most studies of age related changes in cognitive brain systems have relied on cross sectional comparisons between comparatively small numbers of younger and elderly subjects. Potential confounders in functional imaging studies of aging are between subject differences in task performance and the adoption of task solving strategies that differ from those used by the young subjects. Some of the general principles of age related reorganisation are:

1. Loss of inter-hemispheric gradients. For instance, in younger subjects the left prefrontal cortex is more active during encoding and the right prefrontal cortex during retrieval. In older subjects this hemispheric encoding/retrieval asymmetry is much less pronounced.

2. Context dependency of age related changes. A given region may be less active when two specific conditions are compared but may be normally activated in a contrast between two other conditions. The dynamic nature of the age related changes differs fundamentally from the context independent changes studied with structural MRI.

3. Loss of cognitive specificity of activity patterns. For instance, while the processing of location and facial identity follows a dorsal and a ventral processing stream, respectively, in the younger group, this distinction is less clear in older subjects. This loss of specificity could be considered as a reversal of the functional differentiation during the developmental stage.

Key point
Cognitive aging is not merely associated with decreases in brain activations but also with activity increases and functional reorganisation.

Clinically probable AD

Only in 1%-5% of patients who are clinically suspected to suffer from probable AD and have no clinical indication of an alternative cause does computed tomography (CT) disclose an alternative cause, such as a tumour, silent large vessel stroke, or subdural haematoma. As the detection of neoplasms or subdural haematoma significantly changes diagnosis and treatment, one brain scan in the routine initial evaluation of patients with dementia is appropriate.

MRI allows for accurate volumetric measurements of medial temporal structures, such as the hippocampus. As medial temporal neuronal loss is an important feature of AD, MRI can be used to corroborate the positive diagnosis of...
probable AD (for review see Scheltens et al38), and not only as a tool to exclude alternative explanations (fig 3 A and B). In early stage AD (MMSE>21) the percentage of patients with a normalised total hippocampal volume below the 50th centile compared with normal controls was 97%. Fifty eight per cent was situated below the 5th centile.74 Visual ratings of medial temporal lobe atrophy in probable AD and healthy controls reach a sensitivity of 81% and a specificity of 67%75,76 (fig 3 C, D, E, F). Hippocampal volume correlates with disease stage, as measured with MMSE or neuropathology.75 Hippocampal atrophy does not differentiate AD from other types of dementia.75 In one longitudinal three year study, the mean annualised rate of hippocampal atrophy was 1.73% in stable controls and 3.5% in patients with probable AD.77 A potential application lies in the use of hippocampal atrophy as a surrogate marker in therapeutic trials.77

A second MRI investigation in the diagnosis of AD is the evaluation of the vascular burden. The presence of lacunar infarcts on MRI by no means excludes a diagnosis of probable AD.78 When the vascular lesions are extensive, for example, encompassing more than one fourth of the white matter, or strategically localised, for example, in the dorsomedial thalamus, the patient may be classified as clinically probable vascular dementia according to the NINDS-AIREN criteria74 rather than probable AD under the condition that the patient also has clinical signs of neurological lateralisation and a stepwise progressive disease course.74 A prospective community based necropsy study in 80 patients with an MMSE below 24 showed that the specificity of the NINDS-AIREN criteria was 95% with a sensitivity of only 43%.79

While structural MRI studies have focused on hippocampal changes, FDG PET principally provides an image of the involvement of neocortical association areas. The characteristic FDG PET pattern in probable AD is a decline of FDG uptake in posterior cingulate, temporoparietal, and lateral frontal association cortex (fig 4). This decline correlates with dementia severity.78 In patients with mild probable AD (MMSE above 23) compared with non-demented controls the sensitivity was 84% at a specificity of 93%.42 Among 128 patients with cognitive decline who underwent an FDG PET during lifetime as well as postmortem neuropathological diagnosis, sensitivity of FDG PET for the diagnosis of AD compared with other forms of dementia was 94% and specificity 73%.78 Single photon emission computed tomography (SPECT) may also show characteristic patterns of perfusion changes that distinguish AD from normal controls. A neuropathologically verified series of 80 AD patients, 24 non-AD dementia patients, and 14 controls showed a sensitivity of 89% with a specificity of only 60%. The positive predictive value of SPECT for the discrimination between AD and normal controls was 81% and the negative predictive value 74%.77

Functional MRI studies comparing probable AD with age matched controls showed higher activity in prefrontal cortex during episodic and semantic memory in early stage AD.74 The activity increases correlated positively with performance, suggesting that they represent compensatory mechanisms.76 Activity levels in the hippocampus during episodic memory tasks are decreased in AD.73

**Mild cognitive impairment**

A structural quantitative hippocampal volumetry study in 80 MCI patients showed that according to a lifetable analysis, probable AD free survival differed significantly between MCI patients with volumes above the 50th centile (n = 13), between the 50th and the 1st percentile (n = 54), and those lower than the 1st percentile (n = 13). In the first group 75% of patients did not convert to probable AD after a five year period while in the second group this number was 25%.79

**Cellular biology**

Cognitive aging

In mouse models of aging the age related decline in spatial memory is associated with a reduction of long term potentiation (LTP), a neurophysiological mechanism for episodic memory.83 Specifically, the late phase of LTP is affected. This late phase is mediated by cAMP and protein kinase A (PKA) and is associated with RNA and protein synthesis (for review see Nguyen and Woo84) (fig 5). This pathway can be activated by an increased Ca influx (fig 5A) or by activation of guanine nucleotide binding regulatory protein (G protein) (fig 5B). This induces cytosolic cAMP,

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**Key point**

Hippocampal volumes differ significantly between elderly people and patients who have probable AD or who are going to develop probable AD. There is however a pronounced degree of overlap in volumes so that predictions at the individual level are difficult.
which leads in its turn to activation of calcium/calmodulin dependent kinase IV or protein kinase A (PKA), which then translocates to the nucleus and phosphorylates cAMP response element binding protein (CREB), phosphoCREB in turn activates gene transcription necessary for memory and neuronal plasticity. Expression of CREB and coactivators of CREB as well as CREB DNA binding activity decrease significantly with aging. These age related molecular changes in cognitive brain systems differ between brain regions. Advancing age results in the reduction of cAMP/PKA signalling in hippocampus where the opposite can be shown for prefrontal cortex. This neuroanatomical specificity has its consequences for the development of therapeutic agents for age related memory decline. Activation of cAMP/PKA through phosphodiesterase inhibitors or dopamine 5 receptor agonists may be beneficial for hippocampus dependent age related memory impairment while agents that increase PKA activity impair prefrontal cortical function in aged rats and monkeys with prefrontal cortical deficits.

Clinically probable AD
Trisomy 21, mutations of the amyloid precursor protein (APP) gene and of presenilin 1 and 2 lead to AD. In these familial disorders Aβ 42 is increased because the total production of Aβ, the ratio of Aβ 42 over Aβ 40, or its fibrilligenetic propensity are increased. The Aβ 40–42 is proteolytically released from a larger amyloid precursor protein (APP) by two sequential cleavages (fig 6).

- A first cleavage occurs in the extracellular domain and is exerted by β secretase, identified as BACE1, an aspartic protease.
- The second cleavage is an intramembraneous cleavage by the γ-secretase complex. This cleavage requires at least three other members (aph 1, pen 2, and nicastrin) in addition to the proteolytic active presenilins.

According to the amyloid cascade hypothesis, the neurotoxic Aβ 42 is the culprit of both sporadic and familial AD. Aβ is a highly hydrophobic peptide that can aggregate into oligomers, protofibrils, and eventually can precipitate in the characterising amyloid plaques. The amyloid cascade hypothesis provides several potential targets for drug development, such as β-secretase inhibitors or active immunisation against amyloid plaques.

Excitotoxicity refers to the damage evoked by over-stimulation of the glutamatergic N-methyl D-aspartate (NMDA) receptors. This over-excitation provides a rationale for treating probable AD patients by means of memantine, a reversible competitive NMDA receptor antagonist. Memantine has verified efficacy in patients with probable AD and an MMSE between 3 and 14. The effect size, measured by means of cognitive scales, is somewhat smaller than that reported with cholinesterase inhibitors in mild to moderate AD patients.

AGING AS A RISK FACTOR FOR NEURODEGENERATIVE DISEASE
The strongest risk factor for probable AD is age. Over our lifespan the consequences of noxious events accumulate and may progressively affect the brain and increase the risk of

Key point
Morphometry of the hippocampus does not show clear age related neuronal loss in the hippocampus. At the molecular level, however, pathways that underlie memory consolidation undergo age related changes that may account for cognitive aging patterns.

Key point
The molecular pathway that gives rise to amyloid deposition is known in reasonable detail and offers multiple potential targets for drug treatment.
neurodegenerative disease (indirect consequence of aging). Alternatively, the aging process by itself may be associated with changes that increase the risk of AD (direct effect of aging).

**Indirect consequences of aging**

Epidemiological studies provide evidence for an association between probable AD and mid-life hypertension,87–89 diabetes mellitus,89 90 and hyperhomocysteinaemia.91 Clinical stroke is also an important risk factor for the development of AD. In the absence of clinical stroke, the presence of white matter hyperintensities on T2 MRI also increases the risk of dementia.92

**Direct consequences of aging**

Aging and the amyloid cascade hypothesis

In humans, monkeys, and transgenic mice, Aβ levels increase with age.93 Logically, this could happen through three major mechanisms:

1. Increased production of Aβ and hence, of Aβ 42
2. Increased ratios of Aβ 42 over Aβ 40
3. Reduced clearance of Aβ 42

**Increased production of total Aβ or Aβ 42.**

Total APP mRNA or protein brain levels do not increase with age94 but there is a significant relative increase in mRNA for two APP isoforms as a result of alternative splicing (kunitz protease inhibitor (KPI) harbouring APP751 and 770).95 These KPI containing APP isoforms comparatively increase the production of Aβ.96 Activity of β-secretase, a necessary enzymatic step in the production of Aβ (fig 6), also increases with age in the cortices of both humans and monkeys because of age related post-translational changes.97

**Reduced Aβ clearance**

Neprilysin and insulin degrading enzyme (IDE) are two important Aβ degrading enzymes.97 98 The age related changes in these enzymes differ between regions and no clear picture has emerged until now. A genetic polymorphism of apolipoprotein E(e4–e4 and e4–e3) is associated with an earlier onset of the AD in a dose dependent manner.35 Apolipoprotein E binds to the VLDL related protein receptor and also to amyloid plaques. One possible explanation for the association between AD and the apolipoprotein E polymorphism is that the e4 polymorphism is associated with a reduced clearance of Aβ 42.

Not only does Aβ 42 increase with age,99 the toxicity of Aβ may also augment with age.100 The gradual load of toxic Aβ species can further induce tauopathy, inflammatory changes, and oxidative stress, events that are already setting off...
in normal aged brains and could intensify Aβ-induced pathology.

CONCLUSION

The discrimination between cognitive aging and probable AD has important implications for treatment and also fundamentally changes the information provided to the patient and the caregiver concerning diagnosis and prognosis. In our experience, coping by the patient or the caregiver may significantly improve with early clarification of the nature of the disease that underlies cognitive and behavioural changes. At a moderate to severe disease stage clinical tests of cognitive functioning may suffice together with brain imaging and blood examination to establish the diagnosis. In early probable AD or in MCI, neuropsychological assessment, hippocampal MRI volumetry, and FDG PET have confirmed positive diagnostic value. They may provide a means to diagnose neurodegenerative diseases before massive and irreversible neuronal loss has taken place. These tools may have an important role in the development of treatment aimed at prolonging neuronal survival. Given the association between AD and aging, delaying the onset of probable AD would significantly reduce its overall prevalence.

MULTIPLE CHOICE QUESTIONS (TRUE(T)/FALSE (F); answers at end of references)

1. Neuropathological examination alone is the gold standard for the diagnosis of AD.
2. Normal aging is not associated with hippocampal atrophy, in contrast with probable AD.
3. Initial assessment of a patient with a pathological memory deficit requires, among other tests, structural brain imaging, and determination of vitamin B12 and TSH.
4. A modern diagnosis of probable AD relies on technical investigations.
5. The animal verbal fluency test has confirmed diagnostic accuracy for the discrimination between normal aging and probable AD.
6. Hippocampal atrophy allows for the distinction between different dementia subtypes.
7. Aging inevitably leads to AD.
8. Mid-life hypertension is a risk factor for cognitive decline in later life stages.

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