

# Changing perspectives regarding late-life dementia

Majid Fotuhi, Vladimir Hachinski and Peter J. Whitehouse

**Abstract** | Individuals over 80 years of age represent the most rapidly growing segment of the population, and late-life dementia has become a major public health concern worldwide. Development of effective preventive and treatment strategies for late-life dementia relies on a deep understanding of all the processes involved. In the centuries since the Greek philosopher Pythagoras described the inevitable loss of higher cognitive functions with advanced age, various theories regarding the potential culprits have dominated the field, ranging from demonic possession, through ‘hardening of blood vessels’, to Alzheimer disease (AD). Recent studies suggest that atrophy in the cortex and hippocampus—now considered to be the best determinant of cognitive decline with aging—results from a combination of AD pathology, inflammation, Lewy bodies, and vascular lesions. A specific constellation of genetic and environmental factors (including apolipoprotein E genotype, obesity, diabetes, hypertension, head trauma, systemic illnesses, and obstructive sleep apnea) contributes to late-life brain atrophy and dementia in each individual. Only a small percentage of people beyond the age of 80 years have ‘pure AD’ or ‘pure vascular dementia’. These concepts, formulated as the dynamic polygon hypothesis, have major implications for clinical trials, as any given drug might not be ideal for all elderly people with dementia.

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## Introduction

Memory loss, dementia, and Alzheimer disease (AD) are major public health concerns worldwide. In recent years, AD has become almost synonymous with late-life dementia. 100 years ago, however, senile dementia (mostly attributed to ‘hardening of the blood vessels’) was considered to be the dominant etiology for cognitive impairment in elderly individuals over the age of 80 years. 1,000 years ago, demonic possession was blamed for the same set of dementia symptoms. Clearly, scientists in each era have tried to untangle the complex etiology of late-life dementia, and still no specific effective remedy has emerged.

In this critical Review of the dementia literature, we trace the development of various dominant concepts and theories and outline a set of key discoveries that have brought us to our current state of knowledge in this field. We focus on the most recent studies, which suggest that cognitive impairment among the oldest old results from a dynamic complex of genetic and environmental factors. We discuss the implications of these developments for the design of future clinical trials and summarize some of the key questions that we must answer in the coming years. For example, is late-life dementia an extension of AD pathology, or is it qualitatively and quantitatively different from early-onset AD? Also, what are the best and most specific biomarkers and imaging techniques to detect presymptomatic cognitive impairment and

to monitor the rate of clinical progression in elderly individuals with dementia?

## Evolution of concepts

### Greco-Roman period to 1907

Cognitive decline with aging was described by Western philosophers and clinicians as early as the 7<sup>th</sup> century BC.<sup>1</sup> The Greek philosopher Pythagoras observed that the pattern of development of new skills early in life reverses toward the end of life. ‘Normal’ regression of mental faculties, according to Pythagoras, would begin in one’s 60s and, by one’s 80s, would lead to the “imbecility of infancy”. These concepts persisted until the Early Renaissance period, when patients with dementia were treated as witches. In the 18<sup>th</sup> century, ‘senile dementia’ was recognized as a distinct condition from normal aging, and patients with this condition were shown to have smaller brains, on average, than their cognitively healthy counterparts.<sup>2</sup> In the 1890s, Alois Alzheimer and Otto Binswanger extensively described and emphasized the critical roles of atherosclerosis and stroke in the development of brain atrophy and senile dementia.<sup>2</sup>

### 1907–1997

Alois Alzheimer’s findings of plaques and tangles during the autopsy evaluation of a young patient with progressive confusion and hallucination were published in 1907 as a case report entitled “About a peculiar disease of the cerebral cortex”. In 1910, Emil Kraepelin, in part for political purposes in the context of rivalry between two

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## Competing interests

The authors declare no competing interests.

## Key points

- Over the past 27 centuries, the perception of cognitive impairment with aging has changed from a normal inevitable part of aging to being mostly attributable to Alzheimer disease (AD)
- Alois Alzheimer was one of the first clinician–scientists to describe the importance of vascular pathology and to de-emphasize the role of amyloid plaques in brain atrophy and late-life dementia
- Clinicopathological studies have consistently shown that individuals over 80 years of age generally have ‘mixed’ pathologies (infarcts, plaques, tangles, Lewy bodies and inflammation) rather than ‘pure AD’
- The size of the cortex and hippocampus—more than AD or any other single pathological finding—correlates with the degrees of cognitive decline and dementia in elderly individuals
- Appreciating the link between midlife risk factors and late-life size of the cortex and hippocampus has serious implications for disease diagnosis, patient management, and interpretation of research findings
- The dynamic polygon hypothesis provides a new framework for thinking about aging and dementia that departs from the linear model proposed by the amyloid cascade hypothesis

major academic institutions in Europe, included this case report in his leading textbook of psychiatry and used the term ‘Alzheimer’s disease’.<sup>1</sup> Alzheimer himself did not consider amyloid to be the primary cause of senile dementia, and he wrote, “plaques are not the cause of senile dementia, but only an accompanying feature of senile involution of the central nervous system.”<sup>23</sup>

For much of the early 20<sup>th</sup> century, AD was considered to be a rare condition that affected young people with presenile dementia. By contrast, ‘hardening of the blood vessels’ was considered to be the main pathology for cognitive decline in the last decades of life. In the 1940s and 1950s, a group of psychiatrists, including David Rothschild, promoted the idea that late-life dementia was a consequence of society’s choice to isolate elderly individuals and deprive them of meaningful interactions with friends and relatives.<sup>4</sup> David Wilson wrote, “loneliness, lack of responsibility, and a feeling of not being wanted all increase the restricted view of life, which in turn leads to restricted blood flow.”<sup>25</sup> In 1974, the increasing realization that strokes can be the primary etiology for brain atrophy and confusion in older patients led to the formulation of the ‘multi-infarct dementia’ diagnosis.<sup>6</sup>

A gradual shift of focus from vascular issues to AD pathology began with reported findings of extensive amyloid plaque loads in the brains of elderly people with dementia.<sup>7</sup> The discovery of mutations in the genes encoding  $\gamma$ -secretase and amyloid precursor protein in familial forms of early-onset AD put amyloid at the center of the pathological processes of dementia, and the amyloid cascade hypothesis attracted substantial attention.<sup>8</sup> This hypothesis proposes that aggregation of amyloid- $\beta$  (A $\beta$ ) protein in the cortex (which begins as toxic dimers and oligomers that later turn into diffuse and then fibrillar ‘insoluble plaques’) triggers oxidative injury and synaptic loss; these, in turn, bring about hyperphosphorylation of tau protein, which leads to

formation of tangles, triggering widespread neuronal dysfunction and dementia.<sup>9,10</sup> Interest in this hypothesis grew rapidly, and the term senile dementia was soon changed to ‘senile dementia of Alzheimer’s type’ and, eventually, simply to ‘Alzheimer disease’.

With increasing interest in plaques and tangles and with the hope of finding a ‘cure’ for late-life dementia, experts in neurology and psychiatry convened and established a set of criteria for a clinical diagnosis of AD.<sup>11,12</sup> In parallel, minimal microscopic criteria were established for a postmortem histological diagnosis of AD. The Khachaturian criteria, reflecting the opinion of a panel of experts who met in 1984, attempted to standardize the pathological diagnosis of AD on the basis of density of senile plaques (both neuritic and diffuse) found in cortical areas.<sup>13</sup> Higher densities of plaques were required for a positive AD diagnosis as the age of the individuals increased from <50 years, through 50–75 years, to >75 years.<sup>13</sup> In 1991, the CERAD (Consortium to Establish a Registry for AD) criteria were established to provide further specificity for an AD diagnosis. Under these criteria, densities of neuritic (not diffuse) plaques above a defined normal value were assigned to three categories, A, B and C, with category C representing the highest plaque density.<sup>14</sup> CERAD used an age-related plaque score, and the diagnostic categories also incorporated clinical information.

The CERAD criteria fulfilled an important need for confirmation of an AD diagnosis in research and clinical centers around the world. However, this widely used classification had two important limitations. First, the pathological distinctions were based on the brains of 142 patients with dementia (average age 76 years) compared with those of only eight much younger ‘control’ individuals (average age 65 years). If the authors had selected patients and controls in their 80s, their cut-off criteria could have been quite different. Second, the quantity and distribution of neurofibrillary tangles—a prominent feature of AD—were not taken into account. These limitations resulted in a great deal of disagreement, even among neuropathologists viewing the same pathological specimens.<sup>15</sup>

The Braak and Braak criteria (stages I–VI), which were based on distribution and progression of neurofibrillary tangles (not plaques) from limbic areas to frontal lobes, showed a close correlation between stages of dementia and the severity of pathological findings.<sup>16</sup> The National Institute on Aging–Reagan criteria, which were introduced in 1997, incorporated information about the severity of the burden of both plaques and tangles along with clinical information regarding dementia, and removed the criteria for age.<sup>17</sup> AD pathology was highly likely to be the underlying cause of dementia if both frequent neuritic plaques (CERAD category C) and widespread neurofibrillary tangles (Braak stage V and VI) were present.

Clinical and pathological consensus guidelines were also proposed for other forms of dementia, such as

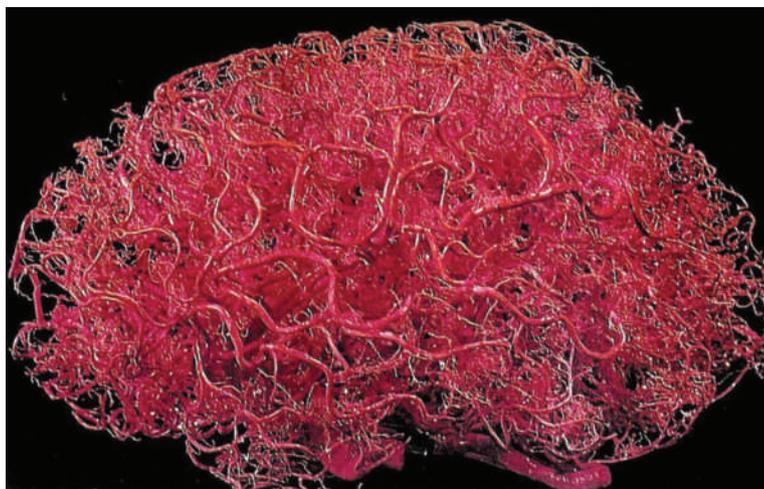
dementia with Lewy bodies, vascular dementia, and normal pressure hydrocephalus.<sup>18–21</sup> The possibility that cerebral amyloid angiopathy could contribute to dementia through mechanisms other than parenchymal AD pathology was also recognized.<sup>22</sup> A major challenge acknowledged by the consensus guidelines was the determination of boundaries between normal aging and dementia among elderly individuals (especially those beyond the age of 80 years), as those without considerable cognitive decline often had some degree of pathology in their brains.<sup>15,23</sup> Reflecting these challenges, one study showed that the frequency of diagnosed cases of dementia in the same patient population of 1,879 men and women over 65 years of age varied by an order of magnitude (from 3.1% to 29.1%), depending on the clinical criteria used.<sup>24</sup>

### 1997–2007

The description of a clinical stage called mild cognitive impairment (MCI) defined a major turning point in dealing with the challenge of dichotomization of patients into normal or dementia categories.<sup>25</sup> Initially, the proposed diagnostic criteria for MCI required significant, objectively measured memory loss that was corroborated by the patient's family. Further progress in refining the definition of MCI came with the recognition that some elderly individuals can have a nonamnestic presentation that leads to vascular or other forms of dementia.<sup>26</sup> Pathology, imaging and cerebrospinal fluid studies all pointed to MCI as a transitional stage along the trajectory of cognitive decline—a stage that could be targeted for intervention in patients with a high likelihood of developing dementia within 2–3 years.

Despite these new developments, the main focus remained on AD. Throughout the 1990s, a consensus had taken shape among clinicians and researchers in the field that plaques and tangles eventually cause AD, and that AD is the predominant cause of dementia among the elderly.<sup>9</sup> A major assumption that was made in hundreds of published studies, and which prevailed until recently, was that most patients had either vascular dementia or AD, but not both.

The Nun Study in 1997 reignited interest in the importance of adequate blood supply to the brain (Figure 1) and the role of vascular disease and stroke in late-life dementia.<sup>27,28</sup> Examination of the brains of elderly nuns revealed a distinct dissociation between the load of AD plaques and tangles and the degree of cognitive impairment that was evident before their deaths. It became clear from the Nun Study that lacunar strokes magnified the effects of any given load of AD pathology, and vice versa. A large, multicenter, longitudinal study in England and Wales published in 2001 also showed that most patients with late-onset dementia had a mixture of cerebrovascular and AD-type lesions.<sup>29</sup> Patients who had either mild subclinical (silent) AD pathology or mild subclinical cerebrovascular disease seemed to remain free of dementia for a longer period of time than those who had a combination of these two pathologies.<sup>23,27,28,30</sup>



**Figure 1** | High density of blood vessels in the brain. To reveal the density of cerebral blood vessels, the brain was injected with a plastic emulsion and the parenchymal tissue was dissolved. As this specimen illustrates, the brain is a highly vascular organ. Thus, vascular risk factors that impede adequate cerebral flow can substantially impair all aspects of cognitive function with aging. Permission obtained from Wolters Kluwer Health © Zlokovic, B. V. & Apuzzo, M. L. J. Strategies to circumvent vascular barriers of the central nervous system. *Neurosurgery* 43(4), 877–878 (1998).

### Box 1 | Factors associated with cognitive function late in life

The summary below is semiquantitative; performing a quantitative meta-analysis for these associations remains challenging owing to marked heterogeneity in selection of participants for longitudinal and interventional studies, and the wide range of outcome measures selected in individual reports.<sup>28,30,32,33,49,52,53,58,60,65,67,71,78,79,83–86,89,92,112,114–118</sup>

#### Factors associated with better cognitive function with aging

- Strong associations: education, walking (physical activity)
- Moderate association: leisure activities
- Mild associations: alcohol (one or two glasses per day), challenging occupation, eating fish, eating fruit and vegetables

#### Factors associated with worse cognitive function with aging

- Strong associations: apolipoprotein E  $\epsilon$ 4 genotype, silent or large strokes, midlife hypertension, obesity
- Moderate associations: depression, diabetes, excessive alcohol use, high homocysteine levels, high midlife cholesterol levels, obstructive sleep apnea
- Mild associations: chronic stress, head trauma, impaired insulin response, low folate and vitamin B<sub>12</sub> levels, smoking

Numerous other clinical, pathological and radiological findings have confirmed a close link between vascular risk factors, the development of strokes (ranging from microscopic to large), and late-onset cognitive decline (Box 1).<sup>28,31,32</sup> Some longitudinal epidemiological studies that monitored participants from midlife to late life revealed that a combination of risk factors could increase the likelihood of dementia more than 16-fold.<sup>33</sup> As vascular lesions could range from a few microscopic infarcts or mild white matter changes to large strokes and marked atrophy (with varying contribution to cognitive decline),

**Box 2 | Neuropathological findings in individuals aged >80 years**

Crystal *et al.* (2000)<sup>38</sup>

- Many patients >80 years with dementia do not meet pathological criteria for Alzheimer disease (AD), dementia with Lewy bodies (DLB) or frontotemporal dementia
- Incidence of non-AD pathology progressively increases beyond 70 years of age, approaching 50% in nonagenarians

White *et al.* (2005)<sup>36</sup>

- Japanese American men—especially those diagnosed with AD—showed considerable discrepancies between clinical diagnosis and pathological findings
- Late-life cognitive impairment and dementia often involve a combination of AD, microvascular lesions, cortical Lewy bodies, hippocampal sclerosis, and diffuse atrophy and/or neuronal loss

Schneider *et al.* (2007)<sup>41</sup>

- Patients with multiple pathologies were three times more likely to exhibit dementia than were those with only one pathology
- Mixed brain pathologies accounted for most dementia cases in patients aged >80 years

Sonnen *et al.* (2007)<sup>45</sup>

- Independent correlates of dementia include Braak stage V or VI, more than two infarcts, and Lewy bodies
- Interventions to reduce infarct risk might prevent or delay dementia onset

Haroutunian *et al.* (2008)<sup>46</sup>

- Individuals aged >80 years show different neuropathological features of dementia from septuagenarians
- Infarcts, DLB, hippocampal sclerosis, or factors yet to be identified, might contribute to dementia in people aged >80 years

Sawa *et al.* (2009)<sup>42</sup>

- Neocortical and hippocampal atrophy was a better predictor of dementia than was AD pathology
- Therapeutic interventions targeting AD pathology might be effective for septuagenarians but not octagenarians or nonagenarians

White (2009)<sup>43</sup>

- Certain lesion combinations, such as AD plus infarcts, were more closely associated with dementia than were individual pathological lesions
- Infarcts were the dominant finding in many cases, perhaps because the participants were elderly men

Schneider *et al.* (2009)<sup>44</sup>

- Odds ratios of clinically probable AD increase significantly when different neuropathological lesions are combined
- Most elderly people with clinically diagnosed AD exhibit mixed pathologies

Erten-Lyons *et al.* (2009)<sup>47</sup>

- Large hippocampal and total brain volume allows elderly people to remain cognitively healthy despite a high AD pathology burden

absence of any vascular risk factors (as a way of excluding individuals with coexisting vascular lesions), the number of cases previously diagnosed with AD dropped by more than 50%.<sup>34</sup> In parallel, examination of brains of patients with late-onset dementia revealed that the link between plaques and tangles and symptoms of clinical dementia was strong in patients younger than 75 years and poor for those older than 90 years.<sup>35,36</sup> Thus, skepticism grew over the simplistic view that the common form of late-life dementia among the oldest old is primarily attributable to the accumulation of plaques and tangles in the brain.<sup>35–40</sup>

**2007 to the present day**

An important study from 2007 confirmed that the load of AD plaques and tangles in elderly individuals with dementia could be similar to that found in cognitively healthy individuals without dementia (30% and 24.2%, respectively), and that the brains of patients with dementia often had a combination of AD lesions, vascular pathology and Lewy bodies.<sup>41</sup> A subsequent study from the same group, along with several other reports, showed that the presence of multiple pathologies significantly increases the likelihood of conversion from cognitively normal to MCI, and from MCI to dementia (Box 2, Supplementary Table 1 online).<sup>36,38,42–47</sup> The odds ratio for a clinically probable AD diagnosis was 4.7 in the presence of AD pathology alone, but it increased to 16.2 in the presence of a combination of AD pathology, infarcts and Lewy bodies.<sup>44</sup> Another study showed that AD lesions fully account for dementia among the ‘young old’ (60–80 years) but not among the oldest old (beyond 90 years).<sup>46</sup> In the Honolulu–Asia Aging Study, only 18.6% of elderly patients with a clinical diagnosis of dementia had pure AD pathology.<sup>43</sup> These and other independent clinicopathological studies concluded that late-life dementia reflects the convergence of several different pathological processes on the brain areas that are important for memory and higher cognitive function; that is, the cortex and hippocampus.<sup>48</sup>

Two studies reported in 2009 have highlighted the size of the cortex and hippocampus as the main determinants of late-life dementia. Erten-Lyons and colleagues analyzed the brains of 36 individuals (12 with normal cognitive function and 24 with a diagnosis of AD before death), all of whom met the standard pathological criteria for AD (Braak stage V or VI, and moderate to frequent neuritic plaques according to the CERAD criteria). Larger cortical and hippocampal volumes were associated with preserved cognition, even in the presence of a high burden of AD lesions.<sup>47</sup> Another clinicopathological study showed that the load of neuritic plaques in the hippocampus rises with each decade of life beyond the age of 70 years in individuals without dementia, but decreases in those with dementia.<sup>42</sup> The degree of atrophy in the cortex and hippocampus remained the most consistent correlate of dementia in the last decades of life.

no consensus could be reached for a widely accepted diagnosis of vascular dementia.<sup>20</sup>

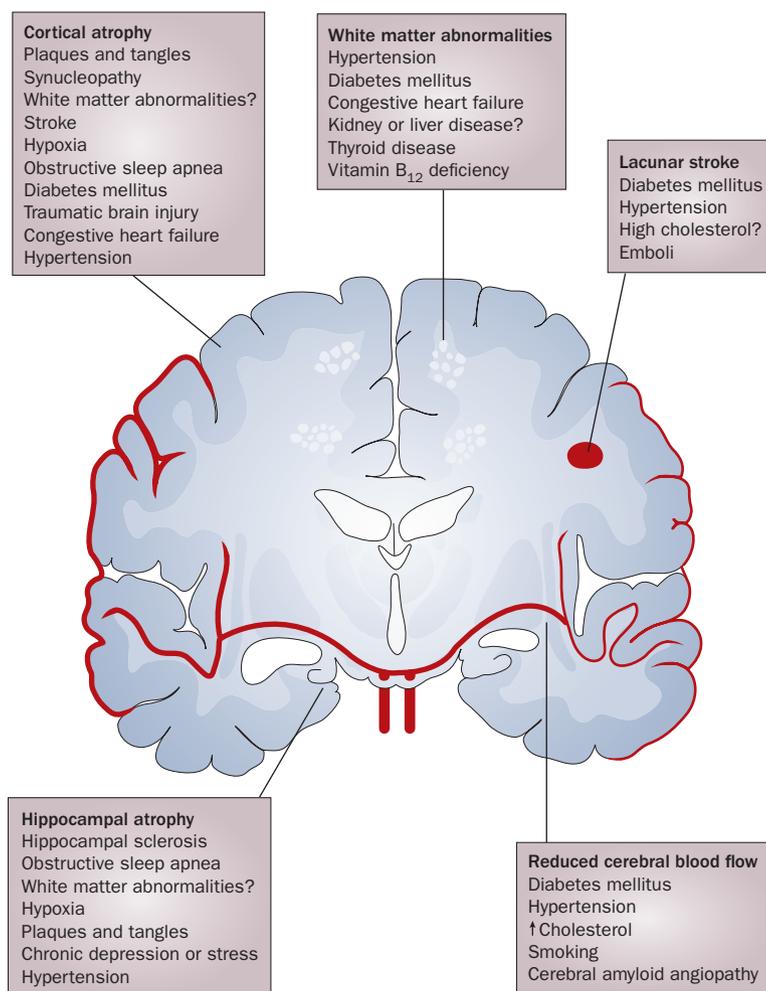
With the realization that even small vascular lesions have profound effects on the brain and can substantially modify the link between AD pathology and dementia, some researchers began to question the accuracy of AD diagnoses in population studies.<sup>34</sup> In a retrospective analysis, when ‘pure AD’ was defined as dementia in the

With the goal of finding effective strategies for prevention and treatment of cognitive impairment with aging, new avenues of research are now focusing on all the pathological and physiological processes that can potentially affect the cortex and hippocampus.<sup>47</sup> Some midlife risk factors are associated with marked late-life dementia and with a smaller cortex and hippocampus.<sup>33</sup> Extensive research is now underway to elucidate the mechanisms through which midlife factors might modulate the likelihood of dementia in the last decades of life (Box 1), and to establish how vascular conditions might interact with each other and with neurodegenerative processes such as AD.<sup>49</sup>

### The dynamic polygon hypothesis

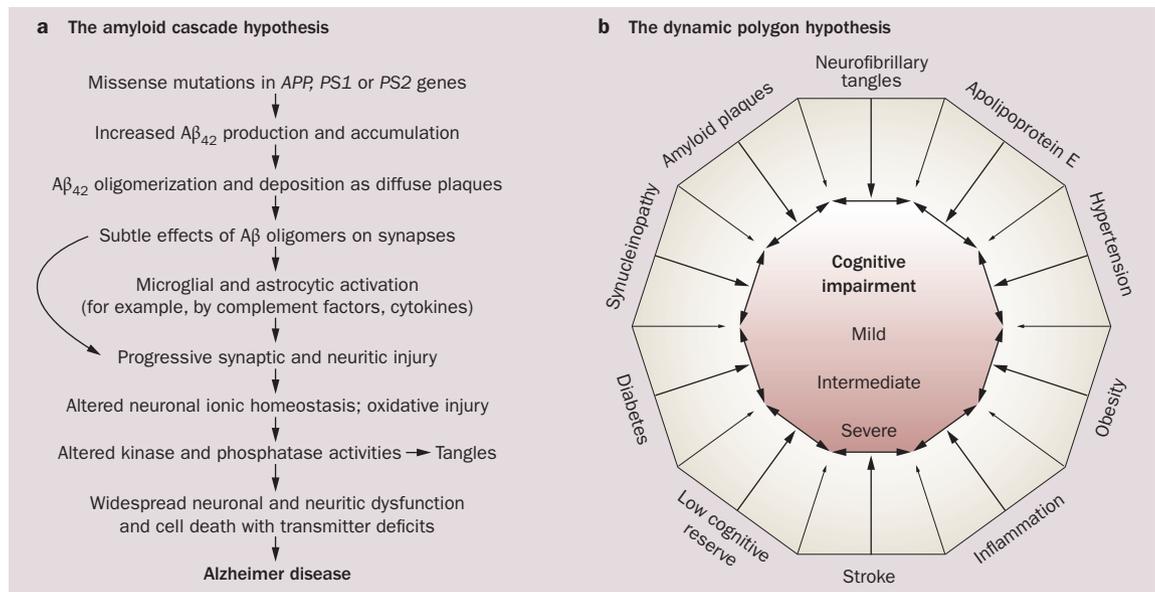
Late-life dementia, in contrast to early-onset AD, can reflect damage to the brain by a wide range of vascular and nonvascular factors (Figure 2). To varying degrees, obesity, hypertension, diabetes, atrial fibrillation, high cholesterol, congestive heart failure, inflammatory conditions (such as lupus), obstructive sleep apnea (OSA), education, exercise, chronic stress, and depression can all alter brain architecture transiently or permanently at the cellular or macroscopic level (Figure 3).<sup>50–61</sup> This broad view, integrating brain function, cardiovascular function, neuroplasticity, and eventual development of cognitive impairment in late life, highlights a dynamic interaction between genetically determined, non-modifiable pathological processes, and processes that are potentially reversible (for example, environmental exposures). This model, which we have termed the ‘dynamic polygon hypothesis,’ departs from a primary focus on plaques and tangles (Figure 3). For example, small-vessel disease and AD pathology are both linked to loss of neurons in the CA1 area of the hippocampus.<sup>62</sup> In turn, high blood pressure, diabetes, obesity, smoking, and sedentary lifestyle are prominent triggers for small-vessel disease and might, therefore, influence the ultimate size of the hippocampus. Moreover, an individual vascular factor such as obesity could have nonlinear and heterogeneous consequences that affect the brain through numerous mediators, including hypertension, infarcts and white matter changes, as well as increased sympathetic activity, interleukins, neurotrophins, growth factors, adipocytokines, adipose-derived leptin, and satiety factors (see below).<sup>63</sup>

Hypertension—a prominent feature of obesity—is likely to lead to atrophy in the cortex and hippocampus through vascular lesions; that is, atherosclerosis, white matter changes, or infarcts.<sup>64</sup> OSA, another condition that is commonly associated with obesity, probably causes marked cortical atrophy through chronic nocturnal cerebral hypoxia over a period of several decades.<sup>65</sup> The severity of cortical atrophy in patients with OSA approaches 18% in the frontal lobes, hippocampus, parahippocampal gyri, parietal cortex, and cingulate cortex—many of the same cortical areas that are known to be affected by AD pathology.<sup>66</sup>



**Figure 2** | Factors that could cause brain atrophy and cognitive impairment. Blood vessels are shown in red. Cortical and hippocampal volumes correlate well with the degree of cognitive decline and dementia. Some processes lead directly to atrophy in these structures, whereas others contribute to white matter abnormalities and strokes (cortical or subcortical, small or large), and might indirectly hasten volume loss in the cortex and hippocampus. Further investigations will be required to ascertain the relative contributions of the various processes—especially those indicated by question marks—to brain atrophy and cognitive impairment.

Midlife obesity might lower the threshold for late-life dementia through mechanisms other than hypertension and/or hypoxic-induced brain atrophy due to OSA.<sup>67</sup> In a study that controlled for high blood pressure, myocardial infarction and strokes, these factors did not fully explain the strong association between midlife excessive abdominal fat accumulation and cognitive decline 30 years later.<sup>67</sup> Other potential mediators include insulin resistance, insulin-like growth factor, inflammation, ghrelin, leptin, or other as yet unidentified hormones.<sup>68–70</sup> High insulin levels could suppress the insulin-degrading enzyme and lead to higher levels of A $\beta$  oligomers, as well as reduce A $\beta$  clearance and increase tau hyperphosphorylation.<sup>69,70</sup> In the setting of metabolic syndrome or diabetes, obesity can heighten



**Figure 3** | Models to account for late-life cognitive impairment. **a** | According to the amyloid cascade hypothesis, a chain of processes that begins with plaques, which in turn cause the formation of tangles, leads to synaptic loss and dementia. In this model, no distinction is made between early-onset and late-life dementia. **b** | According to the dynamic polygon hypothesis, early-onset dementia results from toxicity associated with aggregation of plaques and tangles (although not necessarily in a linear fashion). Late-life dementia, on the other hand, is considered to be a more complex disease: a set of pathological processes that affect the size of the cortex and hippocampus (for example, tauopathy, inflammation, synucleinopathy, amyloid aggregation, and strokes) is interlinked with positive or negative consequences of environmental exposures (for example, education, exercise, leisure activities, or obesity). In this model, plaques and tangles are two components among a larger set of factors that modulate synaptic density and the size of the cortex and hippocampus, and eventually determine the level of cognitive agility or frailty toward the end of life. More studies are needed to establish which model best fits the existing data in this field. Abbreviations:  $A\beta$ , amyloid- $\beta$ ; *APP*, amyloid precursor protein; *PS*, presenilin.

levels of inflammatory processes in the brain and, either independently or in conjunction with degenerative processes, modulate the size of the cortex and hippocampus.<sup>58,71</sup> The obesity–dementia link, therefore, illustrates how various vascular and nonvascular processes might interact in a dynamic and complex network of factors encompassing both genes and environment.

The apolipoprotein E  $\epsilon 4$  (*APOE*  $\epsilon 4$ ) genotype, a major genetic susceptibility factor for AD, increases the risk of dementia between twofold and 12-fold.<sup>72</sup> The presence of *APOE*  $\epsilon 4$  lowers the efficiency of cellular repair mechanisms, reduces the clearance of plaques and tangles in the brain, and decreases gray matter volume.<sup>73,74</sup> The impact of *APOE*  $\epsilon 4$  on the brain is not limited to plaques and tangles, however, as the Apo-E4 protein can interact with and directly modify the severity of vascular conditions such as hypercholesterolemia. Apo-E4 has also been shown to directly interact with the LDL cholesterol receptor.<sup>75</sup>

Other forms of Apo-E might also have roles in both AD and non-AD processes. The *APOE*  $\epsilon 2$  genotype is believed to exert neuroprotective effects through a lowering of levels of  $A\beta$  in the brain. A recent study, however, showed that elderly individuals beyond the age of 90 years who possess *APOE*  $\epsilon 2$  tend to remain cognitively intact even in the presence of a high burden of plaques and tangles, suggesting involvement of non-AD-related

neuroprotective mechanisms against dementia.<sup>76</sup> Thus, presence of the *APOE*  $\epsilon 4$  or *APOE*  $\epsilon 2$  allele might alter the course of cognitive decline with aging through changes in levels of both AD and vascular injury, as well as through modifications in compensatory repair mechanisms that deal with both types of pathology.

In contrast to early-onset AD, which cannot be modified with any known interventions, late-life dementia might be preventable. Some preliminary—and still controversial—findings indicate that a number of protective factors, including exercise, education, participating in brain-stimulating activity, having a cognitively challenging occupation, eating an antioxidant-rich diet, and consuming fish or omega-3 fatty acid supplements, are associated with improved cognitive function and a reduced risk of late-life dementia (Box 1).<sup>30</sup> These factors are believed to increase synaptic density in the brain (that is, create stronger cognitive reserve), perhaps in part through angiogenesis and in part through increasing levels of brain-derived neurotrophic factor (BDNF).<sup>77,78</sup> In animals, exercise selectively increases BDNF gene expression in the hippocampus and reduces the load of amyloid plaques throughout the brain.<sup>79,80</sup>

Results from studies of neuroplasticity in the adult animal brain are beginning to be replicated in humans. Sensitive MRI measurements reveal that the size of the

human cortex and hippocampus can expand significantly with exercise or intense brain stimulation. In a placebo-controlled study, healthy elderly people who participated in a walking program 3 days per week for 6 months experienced a 3% increase in cortical brain volume in their frontal lobes, as determined by MRI findings before and after the exercise program.<sup>81,82</sup> In medical students preparing for their national certification examinations, intensive brain stimulation over a period of 3 months was shown to increase the volume of the cortex and hippocampus.<sup>83</sup> These observations might partly account for resistance to injury triggered by AD pathology, which is observed in individuals with high levels of fitness and cognitive reserve; these individuals could have optimal cerebral blood flow in their brains and a relatively high density of synapses in their cortex and hippocampus.<sup>84,85</sup>

In summary, the primary focus on AD pathology to account for late-life dementia is being superseded by a focus on understanding potentially modifiable processes.<sup>86</sup> According to the dynamic polygon hypothesis, a balance of positive and negative environmental factors, together with a balance of positive and negative genetic factors, seems to affect the brain throughout early life and midlife to determine the degree of cognitive agility or impairment in late life (Box 1, Figure 2).<sup>84,85</sup> These factors increase or decrease cerebral blood flow, oxidative stress, inflammation, insulin-signaling components, size and frequency of infarcts, and concentrations of growth factors, cortisol or other hormones.

Preliminary reports suggest that the load of amyloid plaques, which is determined to some extent by genetic background, can potentially be altered by environmental factors such as exercise, traumatic brain injury or diet.<sup>80,87–89</sup> In animal studies, consumption of apple juice or curcumin seemed to lower amyloid levels.<sup>90,91</sup> Thus, like the degree of microvascular disease in the brain, amyloid levels might depend on lifestyle choices. These observations have provided a strong impetus to establish the profile of risk factors for dementia in late life and to initiate early preventive strategies in individuals with a high likelihood of developing cognitive decline with aging.<sup>92</sup> These preventive strategies would aim to modify both vascular and AD pathology in the brain through changes in lifestyle and use of disease-modifying drugs.

## Future prospects

### Ongoing trials

Over the past two decades, important refinements in defining the pathophysiology of dementia have paved the way for developing effective preventive and treatment strategies. In particular, our understanding of the factors that could cause brain atrophy in late life has expanded substantially over the past 2–3 years. New imaging techniques, such as PET scans using <sup>11</sup>C-labeled Pittsburgh compound B (PIB) have unveiled the distribution of amyloid in the brain in patients with or without dementia.<sup>93</sup> Studies are now in progress that correlate

PIB imaging data with cerebrospinal fluid findings.<sup>94</sup> Standard MRI techniques have enabled us to establish that hippocampal volume is an excellent predictor of further deterioration in patients with MCI and dementia.<sup>95,96</sup> New MRI techniques, such as diffusion tensor imaging, are beginning to reveal the degree and relevance of white matter changes with aging.<sup>97</sup>

More than 100 clinical trials of approaches to prevent and treat patients with varying degrees of cognitive impairment are currently underway.<sup>98,99</sup> Drugs being tested include immune-related medications (for example, immunoglobulin or vaccines), inhibitors of amyloid and tau, and nerve growth factor-like agents.<sup>99,100</sup> Despite the fact that an initial active immunization trial to reduce levels of amyloid in patients with dementia was stopped owing to encephalitic complications, and the preliminary (and incomplete) results were disappointing, passive immunization clinical trials are still in progress.<sup>101,102</sup> Research is also underway to detect 'cognitively normal' individuals at risk of late-life dementia at the pre-symptomatic stage, and to determine the ideal disease-modifying medications for these individuals.<sup>60</sup> Treatment of vascular risk factors is associated with a reduced rate of cognitive decline, and preventive strategies in this area are starting to move from ideas and suggestions to real-life recommendations for clinical practice.<sup>92</sup> The ultimate goal is to determine early-life or midlife interventions, such as factors that enhance cognitive reserve and synaptic density, that would enable people to remain cognitively intact in their 80s and 90s, even if they develop a high load of AD pathology in their brains (Figure 3b).

### Remaining questions

Serial PIB and MRI studies in normal individuals and those with MCI or AD demonstrate a clear dissociation between the annual rate of amyloid deposition and the rate of brain atrophy and neurodegeneration, consistent with previous observations that progression of clinical symptoms in dementia is not coupled to amyloid deposition.<sup>103,104</sup> Consequently, is amyloid still a valid target for the treatment of elderly individuals with late-life dementia and, if so, should research focus on the natural compensatory mechanisms that confront amyloid, on amyloid itself, or on both?<sup>105</sup> Alternatively, should the focus shift toward the dissolution of tau aggregates, given that the density of neurofibrillary tangles correlates more closely with the degree of cognitive impairment than does amyloid pathology?<sup>39</sup>

Strong evidence in support of the amyloid cascade hypothesis links toxic soluble amyloid dimers and oligomers to AD.<sup>106</sup> However, attempts to demonstrate a cascade process from amyloid aggregation to tangle-related neuronal dysfunction have been disappointing, and no convincing causal link has been established between plaques and tangles.<sup>102</sup> These findings have called the amyloid cascade into question, and investigators must now consider how, and indeed whether, this hypothesis should be tested further.<sup>102,107–111</sup>

A body of literature—albeit controversial—suggests that anti-inflammatory and antioxidant medications can lead to better cognitive function and a lower risk of cognitive impairment with aging.<sup>112</sup> Future studies should address whether inflammation is a common denominator in AD, dementia with Lewy bodies, white matter changes and infarcts, and whether late-life dementia is a primary neuroinflammatory condition that is aggravated by other coexisting pathologies.

Another important issue to address is the relationship—if any—between late-life dementia and early-onset AD. Is the common form of late-life dementia simply an extension of early-onset AD, or is it a separate condition, perhaps triggered by genes and proteins that have yet to be discovered?<sup>40,46</sup> Atrophy in the cortex and hippocampus correlates better with the severity and progression of late-life dementia than do white matter changes, infarcts, plaques, tangles or Lewy bodies.<sup>47</sup> The pathogenetic basis of this atrophy is currently unclear: could it result from processes other than strokes, AD, inflammation, and Lewy body pathology? Given the large number of clinicopathological studies that point to the presence of multiple classes of pathology in brains of the oldest old (with or without dementia), a case could be made for re-evaluating the diagnostic criteria for AD in patients beyond the age of 80 years.

Numerous midlife risk factors have been associated with late-life dementia, ranging from early-life education, smoking, choice of hobbies and head trauma, to the presence of medical conditions such as obesity (Box 1). The pathophysiological mechanisms that underlie these associations, and the factors that are most relevant for identifying targets for early intervention, remain to be determined. Future research should also focus on which biomarkers are the best candidates for detecting presymptomatic patients who are at risk of late-life dementia.

Given that a number of environmental risk factors have been implicated in late-life dementia, and considering that rates of obesity and hypertension are rising at a rapid rate among children, efforts to prevent dementia should perhaps start early in life. Numerous studies have examined a possible role for omega-3 fatty acids in reducing the risk of dementia, but the results obtained to date have been heterogeneous.<sup>89</sup> One explanation for the marked variation in findings from dozens of studies in this field—and perhaps the explanation for the failure of most clinical trials in patients with AD—could be the selection and monitoring of participants with various brain pathologies, all of whom were diagnosed with AD. Given the observed heterogeneity of the pathological process in patients with cognitive decline, candidates for clinical trials should perhaps be selected more rigorously, and be subdivided into groups with primary AD, primary vascular pathology, or primary mixed pathology.

The last question is one of terminology. Some researchers consider the word ‘dementia’ to be obsolete and derogatory.<sup>113</sup> Should we replace this diagnostic

terminology with a more respectful label such as ‘cognitive impairment’? The progressive deterioration in cognitive function might be labeled on a scale ranging from MCI, which already has its own established criteria, through intermediate cognitive impairment (patients who have developed difficulty in performing instrumental activities of daily living such as shopping), to severe cognitive impairment (patients who have developed difficulties performing their basic activities of daily living such as managing personal hygiene).

## Conclusions

The dominant conceptual views of late-life memory loss and confusion have shifted considerably throughout history. These symptoms were considered ‘normal’ as early as 700 BC, as signs of being ‘possessed by evil’ in the early Renaissance period, as evidence of ‘hardening of blood vessels’ throughout most of the 20<sup>th</sup> century, and as manifestations of AD since the 1990s. Clinicopathological studies conducted over the past few years agree that most individuals with cognitive impairment over the age of 80 years have a mixture of several coexisting abnormalities, and only a small proportion have pure pathology (for example, dementia with Lewy bodies, AD, or hippocampal sclerosis) in their brains. Technological advances in brain imaging, along with advances in the field of neuroscience, have opened up new possibilities for studying the brain with aging, and have provided an opportunity for researchers to ask more-definitive questions. An enormous amount of progress has been made, but more research is required before specific recommendations to prevent late-life dementia can be formulated.

Alois Alzheimer was one of the first scientists to extensively describe the importance of vascular lesions in brain atrophy in late-life dementia (and to de-emphasize the relevance of amyloid plaques). It is noteworthy that a century later, reduction of vascular risk factors (along with improvement of physical and cognitive fitness) remains the most reasonable recommendation that we can offer to members of the public who strive toward better brain health and successful aging.<sup>28,33,92,114,115</sup>

### Review criteria

MEDLINE was searched for articles published in English from January 1980 to August 2009, with the following keywords: “dementia”, “cognitive impairment”, “memory”, “Alzheimer disease”, “amyloid hypothesis”, “aging” and “clinicopathologic”. Abstracts were reviewed, and papers with a focus on the link between clinical manifestation of cognitive decline and diagnostic criteria for dementia, as well as those with an emphasis on historical development of concepts in the field of dementia, were further analyzed in detail. In addition, the reference sections of these articles, along with relevant chapters in standard neuropathology textbooks, were consulted.

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**Supplementary information**

Supplementary information is linked to the online version of the paper at [www.nature.com/nrneuro](http://www.nature.com/nrneuro)