Modifiable factors that alter the size of the hippocampus with ageing

Majid Fotuhi, David Do and Clifford Jack

Abstract | The hippocampus is particularly vulnerable to the neurotoxic effects of obesity, diabetes mellitus, hypertension, hypoxic brain injury, obstructive sleep apnoea, bipolar disorder, clinical depression and head trauma. Patients with these conditions often have smaller hippocampi and experience a greater degree of cognitive decline than individuals without these comorbidities. Moreover, hippocampal atrophy is an established indicator for conversion from the normal ageing process to developing mild cognitive impairment and dementia. As such, an important aim is to ascertain which modifiable factors can have a positive effect on the size of the hippocampus throughout life. Observational studies and preliminary clinical trials have raised the possibility that physical exercise, cognitive stimulation and treatment of general medical conditions can reverse age-related atrophy in the hippocampus, or even expand its size. An emerging concept—the dynamic polygon hypothesis—suggests that treatment of modifiable risk factors can increase the volume or prevent atrophy of the hippocampus. According to this hypothesis, a multidisciplinary approach, which involves strategies to both reduce neurotoxicity and increase neurogenesis, is likely to be successful in delaying the onset of cognitive impairment with ageing. Further research on the constellation of interventions that could be most effective is needed before recommendations can be made for implementing preventive and therapeutic strategies.

Introduction

Large hippocampal size is closely linked with good memory and cognitive function;1 conversely, atrophy of the hippocampus is associated with the development of dementia.2–4 In patients with mild cognitive impairment (MCI), a high rate of decline in hippocampal size strongly heralds conversion to Alzheimer disease (AD).5,6 Accelerated progression of atrophy is also associated with rapid cognitive decline in both MCI and AD.7–10 Given these associations, determination of the exact size of the hippocampus on brain MRI is becoming increasingly important in the prediction and diagnosis of AD.4

Traditionally, hippocampal atrophy was attributed to neurodegeneration caused by AD or, to a lesser degree, by frontotemporal lobar degeneration.11–13 A small hippocampus has also been reported in patients with various neurological conditions, including multiple sclerosis and epilepsy-related hippocampal sclerosis.14–18 Notably, studies from the past 2–3 years suggest that hippocampal atrophy can be modulated by processes other than neurodegeneration. For example, elderly individuals with a large hippocampus can remain free of dementia, even in the presence of substantial AD pathology.19 Elucidation of the factors that have an effect on hippocampal size is, therefore, critical.

This Review focuses on modifiable factors that can reduce or increase the size of the hippocampus throughout life. We first examine evidence for a link between various medical conditions and hippocampal atrophy, and the potential underlying mechanisms that might account for this association. We then review studies that demonstrate the effects of several interventions that can result in a significant increase in hippocampal volume over a period of weeks to months.

Measuring the hippocampus

Hippocampal size can be assessed in a number of different ways. The most common and straightforward approach is simple visual inspection of MRI scans. This approach has proved to be effective in evaluating conditions such as AD.20,21 However, visual assessment of hippocampal size is not as accurate as formal measurement for detecting subtle variations in size. Another limitation of visual ranking is the considerable subjective inter-rater variability. Formal measurement of hippocampal size on MRI scans, using computer-aided software tools, enables manual tracing of the entire three-dimensional boundary of the hippocampus. These tools were introduced in the late 1980s to assess seizure lateralization in patients with epilepsy who would be undergoing surgery.22,23 Manual tracing has been useful for research in many diseases (such as epilepsy and dementia); however, the technique is time-consuming, requires trained operators, and results in tracer-to-tracer variability.24,25 Consequently, when conducting large-scale studies, in which sample sizes might comprise thousands of patients, or when using hippocampal volume measures for clinical purposes, the manual tracing

Competing interests
The authors declare no competing interests.

Improved understanding of the modifiable factors that cause changes in cognitive stimulation, physical exercise and treatment of vascular risk factors. Automated MRI measurements of brain size assist in detecting reductions or atrophy in the hippocampus, which can be key factors in the process of age-related cognitive impairment. These improvements in memory seem to result in measurable increases in hippocampal volume, in addition to changes in the levels of several enzymes and transcription factors, which have been implicated in hippocampal atrophy.

Cognitive stimulation, physical exercise and treatment of vascular risk factors seem to result in measurable increases in hippocampal volume, in addition to improvements in memory. Improved understanding of the modifiable factors that cause changes in hippocampal volume throughout life will assist in the development of clinical trials aimed at preventing age-related cognitive impairment.

### Risk factors for hippocampal atrophy

A diverse range of medical conditions seem to influence the size of the hippocampus with increasing age. Cardiovascular disease (CVD) and vascular risk factors, as well as other common conditions such as clinical depression, anxiety and traumatic brain injury (TBI), have all been linked with a small hippocampus (Box 1).

#### CVD and vascular risk factors

CVD in midlife increases the risk of late-life dementia. CVD has been linked to varying degrees of atrophy in the hippocampus (Figure 1). The marked cognitive decline that occurs in patients following cardiac arrest, or as a result of atrial fibrillation, diabetes mellitus, hypertension, obesity or obstructive sleep apnoea, is partly attributable to hippocampal atrophy. Commonly, more than one vascular risk factor is present in an individual, and these factors can have synergistic effects on the processes involved in normal ageing of the brain. However, a single risk factor can also affect cognitive function through a reduction in the size of the whole brain, and the hippocampus in particular. For example, children with heart failure have a marked reduction in hippocampal volume in the absence of obesity, hypertension and other vascular comorbidities.

#### Obesity

Obesity is associated with a below-average hippocampal size, and with an increased risk of cognitive impairment in late life. Furthermore, a high BMI in midlife is associated with an increased rate of hippocampal atrophy in late life. One study that controlled for confounding variables (age, sex and ethnic group) found that elderly individuals with a BMI >30 and normal cognition had smaller hippocampi compared with those who had a BMI <30. Low total brain volumes are also reported in overweight individuals and in those who have a normal BMI but a large abdominal diameter. Central obesity (waist-to-hip ratio >0.9) seems to be particularly damaging to the brain—a 1 SD increase in the waist-to-hip ratio is associated with a 0.2 SD decrease in hippocampal volume.

#### Diabetes mellitus

The hippocampus seems to be particularly vulnerable to the neurotoxic effects of diabetes mellitus (Box 2). Patients of all ages with diabetes mellitus who have elevated levels of haemoglobin A1c are at high risk of developing cognitive deficits and exhibiting considerable atrophy of the hippocampus. Results from the cohort of individuals involved in the Honolulu–Asia Aging Study showed that elderly people with diabetes mellitus have smaller hippocampi than those without diabetes mellitus. In another study, in which the relative decline in cognitive performance (measured using the Mini-Mental State Examination [MMSE]) of elderly...
patients with diabetes mellitus was compared with that in an age-matched control group without diabetes mellitus, those with diabetes mellitus had increased atrophy of the hippocampus and the whole brain. The MMSE scores in the group with diabetes mellitus were negatively correlated with the amount of hippocampal atrophy, but not with whole-brain atrophy. A cross-sectional study found a similar correlation among obese adolescents: obese teenagers with type 2 diabetes mellitus had smaller hippocampi than did those without diabetes mellitus.

**Hypertension**
The association between chronic, untreated hypertension and hippocampal atrophy in late life is complex. In the Honolulu—Asia Aging Study, patients with hypertension who had never received treatment with antihypertensive agents had significantly smaller hippocampi than those who had received such treatment. However, low diastolic blood pressure in patients treated with antihypertensive agents has also been associated with hippocampal atrophy. In elderly patients with hypertension, a small whole-brain volume and a nonsignificant trend towards reduced hippocampal size has been observed. Further studies are underway to elucidate the effects of high systolic versus high diastolic blood pressures, well-controlled hypertension versus treatment-resistant hypertension, and different antihypertensive medications (such as calcium channel blockers and β-blockers) on the brain during the process of ageing.

**Hypoperfusion injury**
The hippocampus is particularly vulnerable to acute cerebral hypoperfusion. MRI scans of children with a history of mild hypoxic brain injury—who experience minimal cognitive deficits consisting largely of episodic memory loss—exhibit signs of atrophy in the hippocampus alone. Acute cerebral hypoperfusion in patients following cardiac arrest also seems to damage the hippocampus, more so than any other brain region. Investigators from one study reported that the hippocampus was 28% smaller in patients 8–21 days after cardiac arrest than in healthy controls matched for age, sex and body size distribution, and that most cell loss occurred in the CA1 subdivision of the hippocampus. In fact, the hippocampus is the only region of the brain that consistently undergoes atrophy in all patients with anoxia. A recent study suggests that specific segments of the hippocampus might be particularly sensitive to hypoxia: volume reductions were most evident in posterior areas of the hippocampus in a cohort of patients following successful resuscitation after cardiac arrest.

**Elevated homocysteine levels**
Patients with vitamin B₁₂ deficiency have elevated levels of homocysteine, which are associated with a 2.9-fold increased risk of AD and a 5.5-fold increased risk of stroke. In a study of 1,077 individuals without dementia aged from 60–90 years, elevated plasma levels of homocysteine were associated with hippocampal atrophy.

High homocysteine levels seem to correlate closely with both low baseline hippocampal size and a high rate of hippocampal atrophy over a 2-year period.

**Psychiatric disorders**
The relationship between psychiatric disorders and the hippocampus has frequently been investigated, in view of the functional importance of the hippocampus in neural circuits related to mood and cognition. Many studies have examined the effects of clinical depression,

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**Box 2 | Hippocampal atrophy in diabetes mellitus**

The following mechanisms are thought to contribute to hippocampal atrophy in type 2 diabetes mellitus:
- Vascular ischaemic damage
- Neural pathology (amyloid-β plaques and neurofibrillary tangles)
- Hyperinsulinaemia
- Elevated cortisol levels
- Abnormal glycosylation of proteins
- Oxidative stress
- Inflammation

The most important mechanisms are thought to be microvascular ischaemia and elevated cortisol levels.
bipolar affective disorder and post-traumatic stress disorder (PTSD) on the hippocampus, with variable results (Figure 2).67,68

Clinical depression
The severity and duration of clinical depression, and the response of this condition to medical treatment, have all been linked to the size of the hippocampus.67,69–72 In five of 12 small cross-sectional studies included in a meta-analysis, significant differences were observed in hippocampal size between patients with clinical depression and a healthy control group.67 The aggregated data from all 12 studies, which included 351 patients with clinical depression, showed smaller hippocampi in patients than in controls (approximately 8% smaller left hippocampus and 10% smaller right hippocampus).67

Whether clinical depression causes hippocampal atrophy or whether reduced hippocampal tissue volume results in a predisposition to clinical depression is unclear. Although the results of some studies provide evidence for a causative relationship, other studies, by correlating lifelong duration of illness with the amount of atrophy in different patient populations,73 support the predisposition hypothesis. For example, a brain MRI study of children with a family history of clinical depression showed evidence of hippocampal atrophy predating any signs of the illness.74 Two studies of hippocampal volume in patients with a first episode of clinical depression produced conflicting results on whether atrophic changes were present at baseline.75,76 On the basis of the available data, the association between clinical depression and hippocampal atrophy is most likely to be a bidirectional process.

Post-traumatic stress disorder
Overall, the evidence for hippocampal atrophy in patients with PTSD is equivocal. The results from several studies, including one in a population of Vietnam combat veterans, have demonstrated significant hippocampal atrophy in patients with PTSD.77–79 However, after accounting for potential confounding variables (alcoholism, sleep disorders and clinical depression), the association between PTSD and the volume of the hippocampus often loses significance.80–83 By contrast, a robust connection between childhood-onset PTSD and hippocampal size has been identified. Children exposed to emotional, physical and sexual abuse have below-average hippocampal sizes compared with their peers, and this difference persists into adulthood.84

As with clinical depression, whether this association represents a causal relationship is unclear. PTSD tends to occur in individuals with a family history of the disorder, and is triggered after acute stress, but this predisposition for PTSD might be associated with a small hippocampal size. One study found, on average, 10% smaller hippocampi in veterans with PTSD than in those without PTSD. The veterans in this study were each part of a set of monozygotic twins. The non-military twins of veterans with PTSD also had equally small hippocampi.84 The results of this study suggest a weak association, in which small hippocampal size renders a person more vulnerable to traumatic events.

Chronic alcohol abuse
Studies of clinical depression and PTSD are often confounded by the effects of chronic alcohol abuse. Hippocampal volume is, on average, 8% smaller in individuals with chronic alcohol abuse than in the general population, and increased atrophy is seen with a longer duration of abuse.81,85 Adolescents seem to be affected more severely by alcohol abuse than are adults.86
Head trauma

Physical trauma to the head—either repeated minor injuries or a single major injury—can reduce the size of the hippocampus. The selective vulnerability of the hippocampus to head trauma seems to be one of the main reasons for the high prevalence of cognitive impairment and dementia among war veterans and American football players.

Chronic traumatic brain injury

Repeated head trauma of low (often subclinical) magnitude in sports such as boxing, American football, rugby and hockey leads to neurodegenerative changes termed chronic traumatic encephalopathy. A study of 100 individuals who were either professional boxers or martial artists who had competed for an average of 5 years found that 59% had hippocampal atrophy. Chronic traumatic encephalopathy has been associated with development of clinical depression, dementia and alcoholism.

Acute traumatic brain injury

Patients with a history of a single TBI tend to develop dementia earlier than the general population. Atrophic changes generally start to develop between 3 and 7 months after the injury. The changes are persistent, and are associated with cognitive decline, including memory loss. In an experimental model of head trauma, quantitative MRI measurements showed that an acute decrease in the size of the ipsilateral hippocampus at 3 h to 3 days after the event predicted long-term deficits in memory and spatial learning. Neurofibrillary tangles and amyloid-β plaques are seen years after the injury in 28% of cases.

Mechanisms of hippocampal atrophy

CVD and vascular risk factors

The mechanisms through which different vascular risk factors affect the hippocampus, both directly and indirectly, remain an active area of intense research, and most probably involve a combination of the following: microvascular ischaemia; inflammation; abnormal glycosylation of proteins in the brain; alterations to glucose transportation in the brain; impaired amyloid clearance; and high levels of cortisol, insulin, leptin and ghrelin (Box 2 and Figure 3). The neurochemical consequences of obstructive sleep apnoea and clinical depression, which are common comorbid conditions in patients with obesity and diabetes mellitus, might also be important mediators of hippocampal atrophy.

Metabolic syndrome and type 2 diabetes mellitus have both been linked with substantial brain injury over time. The microvascular ischaemia and inflammation associated with both conditions cause damage (both directly and indirectly, via hypertension) to axons throughout the brain and contribute to diffuse white matter disease that, in turn, can lead to hippocampal atrophy. Although type 1 diabetes mellitus has not.

Figure 3 | Pathways leading to hippocampal growth or atrophy. Modifiable factors, such as meditation, cognitive stimulation, exercise and antidepressant treatment, increase neurogenesis, whereas conditions such as traumatic brain injury, obesity, clinical depression and alcoholism both inhibit neurogenesis and cause atrophy. These conditions and therapies mediate hippocampal atrophy or growth, respectively, via a number of common signalling pathways. *An omega-3 fatty acid. Abbreviations: APOE ε4, apolipoprotein E, allele ε4; BDNF, brain-derived neurotrophic factor; CREB-1, CAMP-responsive element-binding protein 1; IGF, insulin-like growth factor; NMDA, N-methyl-D-aspartate; REST, RE-1-silencing transcription factor; TLRs, Toll-like receptors; VEGF, vascular endothelial growth factor.
been associated with atrophy of the hippocampus. Patients with a long history of this condition are at high risk of developing coronary heart disease, renal impairment and stroke, and are, therefore, also at risk of brain atrophy. Interestingly, a prospective study published in 2011 demonstrated that over a period of 2 years, young people (mean age 12.5 years) with type 1 diabetes mellitus who had frequent episodes of hyperglycaemia had a significantly greater decrease in whole-brain grey matter compared with those with good glycaemic control.

In addition to vascular injury and inflammation in both the heart and the brain, diabetes mellitus impairs the feedback mechanism for suppression of the hypothalamic–pituitary–adrenal (HPA) axis. The resulting high levels of cortisol can directly impair glucose transport in hippocampal neurons and lead to N-methyl-D-aspartate (NMDA)-mediated excitotoxic effects. Corticosteroids bind to intracellular and extracellular glucocorticoid and mineralocorticoid receptors in the hippocampus, and chronic elevation of corticosteroid levels induces changes in transcription of genes encoding corticotropin-releasing hormone receptors, manifesting as neurotoxicity, suppression of dendritic arborization, and inhibition of neurogenesis. These effects might occur as a result of downregulation of brain-derived neurotrophic factor (BDNF), which is believed to be an important mediator in the association between exercise, hippocampal growth and improved memory in both animals and humans.

The selective vulnerability of the hippocampus to hypoxia in patients after cardiac arrest might be related, in part, to the high density of NMDA receptor subtypes in this region of the brain. Another mechanism that could result in selective vulnerability of the hippocampus is apoptotic cascades triggered by glucocorticoid receptors: the hippocampus has a large concentration of neurons with glucocorticoid and mineralocorticoid receptors that seem to be particularly sensitive to hypoxia.

Inflammation seems to be a factor in many processes that cause atrophy in the hippocampus and throughout the brain, including neurotoxicity in diabetes mellitus, as well as obesity, clinical depression, systemic lupus erythematosus and epilepsy. Inflammation can also accelerate the neurodegenerative processes leading to dementia.

Alcohol-mediated hippocampal atrophy is incompletely understood, but much attention is focused on its inhibition of neurogenesis by modulation of cAMP-responsive element-binding protein 1 (CREB-1) and RE1-silencing transcription factor (REST, also known as neural-restrictive silencer factor, or NRSF) signalling pathways. Other possible mechanisms include induction of oxidative stress and neuroinflammation.

### Psychiatric disorders
PTSD and clinical depression might cause hippocampal injury and atrophy via the mechanisms described for vascular risk factors. In fact, the widely accepted explanation for a small-sized hippocampus in patients with PTSD and clinical depression involves dysregulation of the HPA axis and subsequent elevation of cortisol and corticotropin-releasing hormone. The downstream effect of HPA axis dysregulation involves downregulation of CREB-1, leading to decreased levels of BDNF and activation of REST, which inhibits neuronal differentiation. Predictably, patients with Cushing syndrome (which is associated with high baseline cortisol levels) also have small hippocampi; however, this feature is reversible with treatment for the primary condition. Results from a 2-year study of patients with AD showed that the elevation in baseline cortisol levels predicted the extent of hippocampal atrophy, suggesting that glucocorticoids are critical mediators of hippocampal atrophy and cognitive decline, even in patients with classic AD pathology.

A host of other stress-related molecules modulate the hippocampal circuitry; however, limited evidence is available for their involvement in hippocampal atrophy. The levels of these molecules—which include vasopressin, dopamine, noradrenaline, orexin, ghrelin and dynorphin—depend on the magnitude and duration of the stressful stimuli.

### Head trauma
Neurons in the hippocampus are more prone to degeneration after TBI than are those in any other cortical or subcortical area. This acute injury could be mediated by a contusion, axonal damage, vascular damage leading to microhaemorrhage, or increased intracranial pressure due to brain swelling. In addition, brain injury (even from a single event) can cause the formation of neurofibrillary tangles and amyloid-β plaques, as observed in neurodegenerative diseases, the role and pathogenesis of these neurohistological findings is unclear. Beyond the immediate damage, TBI leads to a state of oxidative stress in the brain, causing reductions in levels of the proteins Sir2α, creatine kinase U-type, mitochondrial, and other mitochondrial kinases, which in turn can cause cell death and reduced neurogenesis. Sir2α enhances DNA repair and conveys longevity in yeast, and this protein is also thought to mediate homeostasis under challenging conditions.

### Counteracting hippocampal atrophy
In the past 2–3 years, automated high-resolution brain imaging techniques have aided the evaluation of interventions that can potentially increase the size of the hippocampus and reverse the atrophy caused by degenerative, traumatic or cardiovascular aetiologies. The hippocampus possesses a particular capacity for neuroplasticity...
blind people also found that these individuals had significantly larger hippocampi (on average, 8.5% larger) than did age-matched, sighted controls.132 Blind people also made significantly fewer errors on a complex route-learning task compared with the control group. The increased effort associated with learning orientation and navigation skills without the aid of vision might have stimulated hippocampal growth in these individuals.

A cross-sectional study involving taxi drivers reported that individuals with extensive experience of navigating through the streets of London had proportionally larger posterior hippocampi (on average, 8.5% larger) than did age-matched, control group. Taxi drivers had larger posterior hippocampi (P<0.06) and lower anterior hippocampal grey matter volume (P<0.05). Results from initial studies investigating these interventions have been promising (Box 3 and Tables 1–4).115,127

Cognitive stimulation

Brain stimulation with various cognitive interventions has been associated with a reduced risk of developing dementia (Table 1). Individuals without dementia who participate in cognitively engaging leisure activities (such as reading, writing, and crossword puzzles) have reduced rates of both decline in memory and development of AD later in life.130 Neuroplastic changes with cognitive stimulation are not limited to the hippocampus. In fact, engaging in training sessions to perform juggling or mirror-reading can lead to an increase in cortical grey matter volume in the frontal, parietal and temporal lobes of the brain.129,130

Another study examined the correlation between intense cognitive stimulation and size of the temporal lobe and hippocampus in medical students.131 Comparison of the MRI scans showed that the size of the parietal lobe increased during 3 months of intensive study for National Board examinations, and this structural change was maintained during the 3 months after the examination. Surprisingly, the posterior hippocampi, which grew substantially during the 3 months of intensive studying and memorization, continued to grow at the same rate during the subsequent 3 months of light mental work. One possible explanation for this unexpected result is that during the period of intensive studying, increased neurogenesis might have occurred in the hippocampus compared with other regions of the brain, leading to an increased density of neuropil as new neurons formed interconnections both inside and outside the hippocampus.131

Table 1 | Effects of cognitive stimulation and music on hippocampal volume

<table>
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<tr>
<th>Study design and inclusion criteria</th>
<th>Outcome measures and results</th>
<th>Further comments</th>
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<tr>
<td>Maguire et al. (2000)132</td>
<td>MRI–VBM</td>
<td>Number of years of taxi-driving experience correlated with higher posterior hippocampal volume (P&lt;0.06) and lower anterior hippocampal volume (P&lt;0.05)</td>
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<td>(Cross-sectional study; 16 right-handed, male, licensed London taxi drivers with &gt;1.5 years’ experience in the profession (mean 14.3 years), mean age 44 years (range 32–62 years); 50 age-matched controls who did not drive taxis)</td>
<td>No significant difference in total hippocampal volume between taxi drivers and control group Taxi drivers had larger posterior hippocampi (P&lt;0.05) and smaller anterior hippocampi (P&lt;0.05) than controls</td>
<td>Bilateral increase in parietal cortex grey matter volume in medical students (P&lt;0.001)</td>
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<tr>
<td>Draganski et al. (2000)132</td>
<td>MRI–VBM at –3 months, 0 months, and +3 months relative to the examination</td>
<td>Bilateral increase in parietal cortex grey matter volume in medical students (P&lt;0.001)</td>
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<td>(6-month prospective cohort study; 38 medical students studying for their national medical examination, mean age 24 years; 12 physical therapy students (matched controls))</td>
<td>Medical students demonstrated an increase in hippocampal grey matter that became significant toward the third time point (P&lt;0.05 for left and right hippocampi)</td>
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<td>Fortin et al. (2008)132</td>
<td>Performance in a maze task and MRI–VBM</td>
<td>Blind individuals made fewer errors on the complex route-learning task than did sighted individuals (P&lt;0.01)</td>
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<td>(Cross-sectional study; 12 participants with early-onset blindness (age of onset &lt;5 years), mean age 33.8 years; 7 participants with late-onset blindness (age of onset ≥14 years), mean age 39.9 years; 19 sighted, blindfolded, matched controls, mean age 36.0 years)</td>
<td>Participants with either early or late-onset blindness had on average 8.5% larger hippocampi than the control group (hippocampal volume 4,237 mm³ [blind] versus 3,906 mm³ [sighted], P&lt;0.01) No difference in hippocampal grey matter volume and route-learning performance between groups with early-onset and late-onset blindness</td>
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<tr>
<td>Groussard et al. (2010)132</td>
<td>MRI–VBM</td>
<td>None</td>
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<tr>
<td>(Cross-sectional study; 20 right-handed musicians from a music conservatory (average 15.3 years of experience), mean age 22.85 years; 20 controls who were not musicians, mean age 24.55 years)</td>
<td>Musicians had higher grey matter density in the left hippocampal head (no statistical data available)</td>
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<tr>
<td>Woollett et al. (2011)134</td>
<td>MRI–VBM</td>
<td>Baseline hippocampal volume not statistically different between participants who succeeded and those who failed to qualify</td>
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<td>(4-year prospective cohort study; 59 male participants training to become licensed taxi drivers in London (39 eventually qualified, 20 failed), mean age 38 years; 31 controls who were not training to become taxi drivers)</td>
<td>Trainees who qualified: bilaterally increased grey matter in the posterior hippocampi (P&lt;0.05, corrected for multiple comparisons across the whole brain) compared with baseline measurements No significant change in hippocampal size in trainees who did not qualify</td>
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Abbreviation: VBM, voxel-based morphometry.
larger posterior hippocampi than those who did not drive taxis. A recent longitudinal study examined the changes in hippocampal size in adults who were preparing to take the qualifying examination to become a taxi driver in London. No increase in hippocampal size was observed either in individuals who failed to qualify or control participants who were not preparing for the examination; however, after 4 years of training, 30 of 59 individuals who passed the examination demonstrated a significant bilateral increase from baseline in the volume of grey matter in the posterior hippocampus.

Patients with bilateral impairment of the vestibular system often have difficulties with spatial memory and navigation, and exhibit a loss of up to 16.9% of their hippocampal volume compared with age-matched healthy control groups. Activation of the vestibular system enhances memory in humans, although no studies have yet demonstrated that it increases the size of the hippocampus.

Neuroplasticity and an increase in the volume of grey matter are not unique to the hippocampus. Indeed, challenging activities that require intense training and practice can also cause an increase in the volume of cortical areas engaged in performing the specific task. For example, a prospective study showed that healthy volunteers who learned how to juggle showed a bilateral increase in the size of their cortex in the midtemporal areas. Other studies have documented changes in the cerebellar vermis in basketball players; in the parietal lobes in mathematicians; in Broca’s area in symphony orchestra musicians; and in the sensorimotor cortex in ballet dancers. A prospective study showed that novice golfers had an increase in sensorimotor cortical areas after 40 h of training. The structural changes in the brain could be the result of axonal remodelling, synaptogenesis, gliogenesis, neurogenesis, an increase in neural cell size, or an increase in interstitial fluid or blood flow within the organ.

Cognitive and leisure activities that stimulate different areas of the cortex and hippocampus seem to have the potential to modulate and improve the function of the areas affected by the activity. Further studies are needed to confirm these emerging findings, and to establish a therapeutic regimen involving activities that might be protective against cognitive impairment with ageing.

### Physical fitness

Exercise in midlife is associated with a reduced risk of MCI or dementia in late life. In a population-based
study of 1,324 individuals without dementia at baseline, moderate exercise in midlife was associated with a 32% reduction in the odds ratio for developing MCI. In other research, a linear correlation was evident between improved fitness and large hippocampi in elderly individuals (Table 2). An observational study found that walking more than 1 mile daily was associated with increased hippocampal size and a reduced risk of developing AD.

A randomized controlled trial confirmed that moderate-intensity aerobic exercise (brisk walking) could significantly increase the size of the hippocampus, improve memory, and reduce cognitive impairment, compared with gentle activity (stretching or mild yoga). A significant increase in mean hippocampal size, of 2.12% and 1.97% in the left and right hippocampus, respectively, was seen in participants in the intervention group. These individuals also had higher serum levels of BDNF and increased with antidepressant use, and these proteins promote survival and proliferation of both neural and synaptic levels of serotonin and noradrenaline, which activate pathways involving the second messengers cAMP and CREB-1. This action of antidepressant agents suggests that these treatments might increase neuronal plasticity, proliferation and survival. Levels of BDNF and vascular endothelial growth factor are also increased with antidepressant use, and these proteins promote survival and proliferation of both neural and.
Table 4 | Effects of treating medical conditions that cause hippocampal atrophy

<table>
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<th>Study design and inclusion criteria</th>
<th>Outcome measures and results</th>
<th>Further comments</th>
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<tr>
<td>**Yucel et al. (2007)**¹⁵⁶</td>
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<td>4-year longitudinal study of lithium therapy: 12 patients with bipolar affective disorder with no prior pharmacological therapy, mean age 28.8 years; 40 age-matched controls with no history of psychiatric illness</td>
<td>Hippocampal volumetry using manual segmentation of MRI scans After 4 years of treatment, hippocampal volume increased by 4–5% (P&lt;0.001), with most growth occurring in first 9–12 months</td>
<td>Improved performance in verbal memory with treatment Association between improvement in memory (number of items recalled in a memory task) and increase in size of left and right hippocampi (P&lt;0.01)</td>
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<td>**Yucel et al. (2008)**¹⁵⁷</td>
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<td>8-week prospective, controlled study of lithium therapy; 21 patients with bipolar affective disorder who had no prior pharmacological therapy and no history of substance abuse (12 patients treated with lithium, mean age 25.7 years; 9 patients not receiving treatment, mean age 24.4 years); 30 controls without bipolar affective disorder, mean age 25.3 years</td>
<td>Hippocampal volumetry using manual segmentation of MRI scans Bilateral increases in hippocampal volume after 1–8 weeks of treatment compared with patients not receiving medication (left hippocampus, P=0.03; right hippocampus, P=0.02)</td>
<td>Head of hippocampus was most affected; structural changes apparent even after a short course of lithium treatment</td>
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<td>**Gazdzinski et al. (2008)**¹⁵⁸</td>
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<td>1-month prospective study; 24 men with alcohol dependency* who underwent a period of abstinence from alcohol (intervention group: 13 smokers, mean age 50.7 years, and 11 nonsmokers, mean age 50.2 years; 14 age-matched, nonsmoking controls who were light drinkers (mean age 47.3 years)</td>
<td>Hippocampal volumetry using three-dimensional atlas-based segmentation of MRI scans No significant differences observed at baseline between hippocampal volumes of nonsmoking participants intervention group and those of control group, but smokers with alcohol dependency had 6.9% smaller hippocampal volumes than controls (P=0.08) 1 month after alcohol cessation, intervention group (smokers and nonsmokers) demonstrated increased hippocampal size (P&lt;0.01)</td>
<td>Spectroscopic analysis of NAA levels supports the idea that alcohol-related hippocampal volume deficits are mostly glial losses, as demonstrated by histological analysis: 10.4% lower concentration of NAA in alcohol-dependent smokers than controls, P=0.02; 12.8% lower concentration of NAA in alcohol-dependent nonsmokers compared with controls, P=0.008</td>
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<td>**Canessa et al. (2011)**¹⁵⁹</td>
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<td>3-month prospective study of treatment for obstructive sleep apnoea; 17 patients who had received no prior treatment for the condition, mean age 44.00 years; 15 controls without obstructive sleep apnoea, mean age 42.15 years</td>
<td>MRI and voxel-based morphometry Treated group had increased left and right hippocampal volume after 3 months (P&lt;0.05 for left and right hippocampi)</td>
<td>Improvements in memory, attention, and executive functioning also noted in treatment group</td>
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<td>**Nordansko et al. (2010)**¹⁶¹</td>
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<td>2-week prospective study of ECT in 12 patients with clinical depression refractory to pharmacological treatment; mean age 40 years, range 19–67 years</td>
<td>Hippocampal volumetry using manual segmentation of MRI scans 1 week after ECT, patients had bilateral 4–5% increase in hippocampal volume (left hippocampus, P&lt;0.001; right hippocampus, P&lt;0.01)</td>
<td>None</td>
</tr>
<tr>
<td>**Tendolkar et al. (2012)**¹⁶²</td>
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<td>1-year, randomized controlled trial of cholesterol-lowering therapy (including statins); 34 elderly patients with atrial fibrillation but no history of stroke and normal cognition, mean age 74.5 years, randomly assigned to treatment (atorvastatin and ezetimibe) or placebo</td>
<td>Hippocampal volumetry using manual segmentation of MRI scans Bilateral hippocampal volume declined in both groups; however, patients on treatment had less atrophy of right hippocampus than did controls (P=0.068).</td>
<td>Improvement in cognitive speed (assessed usingdigit symbol substitution test, P&lt;0.010) and short-term and long-term memory (P&lt;0.030) with treatment</td>
</tr>
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</table>

*Alcohol dependence defined as more than 150 drinks per month for at least 8 years. Abbreviations: ECT, electroconvulsive therapy; NAA, N-acetylaspartate.

Endothelial cells. Lithium treatment in patients with bipolar affective disorder can also produce a significant increase in hippocampal volume bilaterally and a significant improvement in memory after 9–12 months of therapy.¹⁵⁶,¹⁵⁷ In a follow-up study, significant bilateral hippocampal growth was already present after only 1–8 weeks of lithium therapy.¹⁵⁷

Treatment of alcoholism is effective in reversing, to some extent, the hippocampal atrophy seen in patients with clinical depression. Enlargement of the hippocampus was found in individuals with a history of chronic alcohol abuse, after abstaining from alcohol for 1 month.¹⁵⁸ Furthermore, individuals in this study who smoked cigarettes (in addition to alcohol abuse) demonstrated a slower recovery of metabolic activity in the medial temporal lobe than did nonsmokers. These findings suggest that providing advice and/or treatment for smoking cessation is just as important as treating alcoholism.

To our knowledge, no studies have investigated the prevention of hippocampal atrophy after TBI in humans. However, animal studies have shown that both resveratrol¹⁵⁹ and docosahexaenoic acid (an omega-3 fatty acid that is abundant in fish)¹²⁶ confer neuroprotection after TBI. Sir2α—a mediator of cellular stability—is present in fish oil, although it seems to have no beneficial effect on hippocampal size in the absence of TBI. Other
Evidence suggests that vitamin E, a potent antioxidant, confers neuroprotection after TBI.60

Integrating positive and negative factors

Various conditions and processes, individually or in combination, contribute to a reduction in the size of the hippocampus. These include hypertension, diabetes mellitus, obesity, obstructive sleep apnoea, PTSD, head trauma, and neurodegenerative processes that cause excessive aggregation of toxic proteins in the brain (Box 1). Conversely, several interventions, including improved fitness, cognitive stimulation, and meditation, can, individually or in combination, increase the size of the hippocampus (Box 3). The net balance of these negative and positive factors ultimately seems to determine the size and health of the hippocampus and, in turn, the extent to which cognitive acuity is preserved with ageing or dementia.

An attempt to integrate the positive and negative factors (and their associated biochemical processes) that have an effect on the hippocampus has led to the formulation of a new model that encompasses the effects of these factors in late-life dementia. In this model, which is called the dynamic polygon hypothesis, the specific constellation of genetic and environmental risk factors (including apolipoprotein E genotype, obesity, diabetes mellitus, hypertension, head trauma, systemic illnesses, and obstructive sleep apnoea) that is present in a given individual is considered to contribute to the development of late-life brain atrophy and dementia.61 Essentially, this model considers the interaction of genes with environmental exposures that are known to modulate the size and integrity of the neocortex and hippocampus. The model also emphasizes the dynamic nature of the mechanisms involved in determining the baseline size of the hippocampus and, ultimately, the individual's baseline cognitive function.50 Understanding the details of processes that have an effect on the hippocampus is important when designing interventions that could reduce memory loss and cognitive impairment in ageing individuals, but long-term clinical trials are needed to determine whether such interventions might prevent or delay the onset of dementia.

Conclusions

Late-life dementia is a process that involves atrophy in both the hippocampus and the cortex. However, the hippocampus is unique in that it has not only heightened vulnerability to a variety of mechanisms of injury to the brain (such as hypoxia, obesity and concussion), but also an enhanced capacity for neuroplasticity, which provides neuroprotection. With the ageing process, the hippocampus has a greater propensity to atrophy than other regions of the brain. The rate of hippocampal atrophy accelerates with a number of conditions, including diabetes mellitus, white matter disease, cardiac arrest, clinical depression, head trauma, and obstructive sleep apnoea. Reversal of this process can be achieved by improving physical fitness and by engaging in cognitively stimulating endeavours. Consistent observations by researchers that elderly individuals with large hippocampi can withstand high brain concentrations of amyloid-β plaques and neurofibrillary tangles without exhibiting signs of dementia, combined with results from studies that demonstrate the slowing of hippocampal atrophy in individuals with AD who join fitness programmes, emphasizes that the hippocampus is a dynamic structure with the potential to change in size throughout life. Given the large number of medical conditions that have a role in hippocampal atrophy the development of a single drug to prevent late-life dementia is highly unlikely. A more realistic approach would be to combine the strategies that improve brain health, such as improved cardiovascular fitness and diet, and to minimize stress-inducing factors.

Review criteria

MEDLINE was searched for articles in English published from January 1980 to December 2011. The search terms used were “hippocampus size”, “MRI”, “brain size”, “brain volume”, “atrophy”, “memory”, “cognition”, “dementia”, “aging”, “neuroplasticity”, “neurogenesis”, “voxel-based morphometry”, “vascular risk factors”, “concentration”, “inflammation” and “measurements”. The reference sections of relevant articles were checked for additional important publications.


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Author contributions

All authors contributed to discussions of the article content, writing the article and to review and/or editing of the manuscript before submission. In addition, M. Fotuhi and D. Do researched the data for the article.
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.


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 7th century BC.1 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 18th 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.2 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.3

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
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.

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, including this case report in his leading textbook of psychiatry and used the term ‘Alzheimer’s disease’. 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.”

For much of the early 20th 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 Rothchild, 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. David Wilson wrote, “lonesomeness, 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.” 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.

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. The discovery of mutations in the genes encoding γ-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. This hypothesis proposes that aggregation of amyloid-β (Aβ) 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. 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. 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. 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. 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. 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.

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. 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. 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. The possibility that cerebral amyloid angiopathy could contribute to dementia through mechanisms other than parenchymal AD pathology was also recognized. 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. 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.

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. 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. 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. 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. 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. 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.

![Figure 1](image) | 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.

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 ε4 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 B12 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). 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. 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)\textsuperscript{38}
- 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)\textsuperscript{40}
- 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)\textsuperscript{41}
- 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)\textsuperscript{45}
- 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)\textsuperscript{46}
- 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

Savva et al. (2009)\textsuperscript{42}
- 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 octogenarians or nonagenarians

White (2009)\textsuperscript{43}
- 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)\textsuperscript{44}
- Odds ratios of clinically probable AD increase significantly when different neuropathological lesions are combined
- Most elderly people with clinically diagnosed AD exhibit mixed pathologies

Erteng-Lyons et al. (2009)\textsuperscript{47}
- Large hippocampal and total brain volume allows elderly people to remain cognitively healthy despite a high AD pathology burden

no consensus could be reached for a widely accepted diagnosis of vascular dementia.\textsuperscript{20}

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.\textsuperscript{34} In a retrospective analysis, when ‘pure AD’ was defined as dementia in the 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%.\textsuperscript{34} 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.\textsuperscript{35,40} 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.\textsuperscript{35–40}

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.\textsuperscript{42} 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).\textsuperscript{36,38,42–47} 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.\textsuperscript{44} 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).\textsuperscript{46} In the Honolulu–Asia Aging Study, only 18.6% of elderly patients with a clinical diagnosis of dementia had pure AD pathology.\textsuperscript{41} 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.\textsuperscript{48}

Two studies reported in 2009 have highlighted the size of the cortex and hippocampus as the main determinants of late-life dementia. Erteng-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.\textsuperscript{47} 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.\textsuperscript{42} The degree of atrophy in the cortex and hippocampus remained the most consistent correlate of dementia in the last decades of life.
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. Some midlife risk factors are associated with marked late-life dementia and with a smaller cortex and hippocampus. 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.

**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). 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, nonmodifiable 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. In turn, high blood and AD pathology are both linked to loss of neurons in the hippocampal gyri, parietal cortex, and cingulate cortex—many of the same cortical areas that are known to be affected by AD pathology.

![Figure 2](https://example.com/figure2.png)

**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. 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. Other potential mediators include insulin resistance, insulin-like growth factor, inflammation, ghrelin, leptin, or other as yet unidentified hormones. High insulin levels could suppress the insulin-degrading enzyme and lead to higher levels of Aβ oligomers, as well as reduce Aβ clearance and increase tau hyperphosphorylation. In the setting of metabolic syndrome or diabetes, obesity can heighten levels...
the presence of genetic susceptibility factor for AD, increases the risk of both genes and environment. Dynamic and complex network of factors encompassing obesity–dementia link, therefore, illustrates how various components among a larger set of factors that modulate synaptic density and the size of the cortex and hippocampus, 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: Aβ, amyloid-β; APP, amyloid precursor protein; APOE ε4, apolipoprotein E ε4; PS2, presenilin.

The amyloid cascade hypothesis

- Missense mutations in APP, PS1 or PS2 genes
- Increased Aβ42 production and accumulation
- Aβ42 oligomerization and deposition as diffuse plaques
- Subtle effects of Aβ42 oligomers on synapses
- Microglial and astrocytic activation (for example, by complement factors, cytokines)
- Progressive synaptic and neuritic injury
- Altered neuronal ionic homeostasis; oxidative injury
- Altered kinase and phosphatase activities → Tangles
- Widespread neuronal and neuritic dysfunction and cell death with transmitter deficits
- Alzheimer disease

The dynamic polygon hypothesis

- Neurofibrillary tangles
- Apolipoprotein E
- Amyloid plaques
- Apolipoprotein E4
- Stroke
- Inflammation
- Hypertension
- Diabetes

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: Aβ, amyloid-β; APP, amyloid precursor protein; APOE ε4, apolipoprotein E ε4.

Thus, presence of the APOE ε4 or APOE ε2 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). 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). In animals, exercise selectively increases BDNF gene expression in the hippocampus and reduces the load of amyloid plaques throughout the brain.

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.81,82 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.83 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.84,85

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.86 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).84,85 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.80,87–89 In animal studies, consumption of apple juice or curcumin seemed to lower amyloid levels.80,81 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.85 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 11C-labeled Pittsburgh compound B (PiB) have unveiled the distribution of amyloid in the brain in patients with or without dementia.93 Studies are now in progress that correlate PIB imaging data with cerebrospinal fluid findings.94 Standard MRI techniques have enabled us to establish that hippocampal volume is an excellent predictor of further deterioration in patients with MCI and dementia.95,96 New MRI techniques, such as diffusion tensor imaging, are beginning to reveal the degree and relevance of white matter changes with aging.97

More than 100 clinical trials of approaches to prevent and treat patients with varying degrees of cognitive impairment are currently underway.98,99 Drugs being tested include immune-related medications (for example, immunoglobulin or vaccines), inhibitors of amyloid and tau, and nerve growth factor-like agents.99,100 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.101,102 Research is also underway to detect ‘cognitively normal’ individuals at risk of late-life dementia at the presymptomatic stage, and to determine the ideal disease-modifying medications for these individuals.100 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.102 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.103,104 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?105 Alternatively, should the focus shift toward the dissolution of amyloid plaques, given that the density of neurofibrillary tangles correlates more closely with the degree of cognitive impairment than does amyloid pathology?99

Strong evidence in support of the amyloid cascade hypothesis links toxic soluble amyloid dimers and oligomers to AD.106 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.102 These findings have called the amyloid cascade into question, and investigators must now consider how, and indeed whether, this hypothesis should be tested further.102,107–111
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.\textsuperscript{112} 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?\textsuperscript{40,46} 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.\textsuperscript{47} 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.\textsuperscript{48} 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.\textsuperscript{113} 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 20th 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-define 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.\textsuperscript{28,33,92,114,115}

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.


