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REVIEW

Cognitive reserve, cortical plasticity and resistance to Alzheimer's disease

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Abstract

There are aspects of the ageing brain and cognition that remain poorly understood despite intensive efforts to understand how they are related. Cognitive reserve is the concept that has been developed to explain how it is that some elderly people with extensive neuropathology associated with dementia show little in the way of cognitive decline. Cognitive reserve is intimately related to cortical plasticity but this also, as it relates to ageing, remains poorly understood at the present time. Despite the shortcomings in understanding, we do have some knowledge on which to base efforts to minimise the likelihood of an elderly person developing dementia. For some risks the evidence is far from secure, but resistance to Alzheimer's disease (AD) appears from epidemiological studies to be contributed to by avoiding hypertension in middle life, obesity, depression, smoking and diabetes and head injury and by undertaking extended years of education, physical exercise, and social and intellectual pursuits in middle and late life. Nutritional factors may also promote healthy brain ageing. Resistance to AD is also contributed to by genetic factors, particularly apolipoprotein E2, but some combinations of other genetic polymorphisms as well. Although multiple factors and possible interventions may influence cognitive reserve and susceptibility to dementia, much more work is required on the mechanisms of action in order to determine which, if any, may improve the clinical and epidemiological picture. Understanding of how such factors operate may lead to new initiatives to keep the elderly population in the 21st century able to lead active and fulfilling lives.

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Introduction

The early 21st century confronts us with a dual dilemma concerning old age: first, there is going to be an enormous increase in the number of elderly people, and second, there is at present very little that can be offered to help those many people who become demented. The best way to confront these twin difficulties must be to maximise the chances of elderly people avoiding cognitive decline and dementia. But how is this to be done?

We know that advancing age is by far the largest risk factor for developing sporadic dementia but we also know that there is a wide range of cognitive performance in old age. What attributes determine the cognitive fate of individual elderly people? Here we review what is known about this important subject.

The concept of cognitive reserve

The brain undergoes changes in structure, metabolism and function as it ages [1,2]. While some of these changes are apparent on examining the brain of an elderly person, whether by imaging when they are alive or by post-mortem examination, others are not. Some of the changes are well established as relating to cognitive decline and dementia, most notably the pathological features of Alzheimer's disease (AD), but also cerebrovascular disease and alpha synuclein pathology. Yet it has become clear from unselected epidemiological studies linked to neuropathology that there is not infrequently a mis-match between pathological changes found post-mortem and the recorded cognitive performance of a person before they died [3]. In some cases cognitive performance is below the level expected for the amount of pathology found but more frequently someone with a substantial load of pathology had nonetheless performed cognitively within the normal range before death. A recent large study found that careful quantification of neuropathology and brain weight accounted for only between a third and a half of the variance in cognitive performance in a relatively unselected group of elderly people, leaving the rest unaccounted for [4]. Cognitive reserve is the concept that has been developed to deal with this discrepancy [5].

Potential issues of measurement error arise when considering the concept of cerebral reserve relating to

ceiling and floor effects in testing instruments but, in general terms, most investigators attribute at least some cognitive reserve to having a well developed and nourished brain with an abundance of synapses and healthy neurons in those parts of the brain that are concerned with cognition - mainly association cortex, hippocampus and the parts of the brain that these are connected to. This hypothesised basis for cognitive reserve fits quite well with the fact that longer years of education protect against dementia and, conversely, with the enhanced risk of dementia experienced by those who have had a serious head injury. This concept particularly links cognitive reserve to grey matter regions of the brain and to the cortical plasticity inherent in these. However, there are also changes in the white matter of the brain that are increasingly recognised with ageing, and some of these are not readily explained as secondary to the grey matter changes. Thus, we need to consider the evidence for both grey and white matter contributions to cognitive reserve.

Grey matter, cortical plasticity and cognitive reserve

Not all forms of reserve are the same, and they depend on the forms of brain insult and neuroplasticity that may be involved. Stern [6] has compared neural compensation, neural reserve, and cognitive reserve. Neural compensation and neural reserve are characterised as 'task-dependent' in contrast to more generalised cognitive reserve. Compensation is a response to pathologically altered processing, whereas reserve refers to differences in task-related processing without pathology. Stern considers all three to be 'neural mechanisms' in the sense that they are attributed to interactions within neural networks. However, the relationship between cognitive reserve and its architectural neural basis is not clear. Part of the explanation for the large proportion of variance that remains unexplained in the study by Dowling and colleagues [4] is that neuropathological measures are unlikely to account fully for cognitive ability. Reed and colleagues [7] have used the mis-match between pathology and cognitive performance as an index of neural reserve. This measure merges the neuropsychological domain and the neuropathological domain. However, such a measure depends on the presence of pathology and therefore does not offer insight into the potential reserve that exists prior to the onset of pathology. As an alternative, an appropriate measurement of intact architecture should provide a neuroanatomical index that precedes pathology, changes with normal ageing, and correlates with cognitive ability [8].

In previous work [9] we have drawn attention to a distinction in the neuroanatomical domain - between the markers of neuropathological processes, such as plaques and tangles, and measurement of the remaining, intact cerebral architecture that is presumably the basis for ongoing cognitive function. It is notable that most assessments of cognitive deficit are in fact measures of remaining function (that is, reduced measures of positive ability). Therefore, assessing the degeneration of intact structure is as important as the accumulation of pathology. Synapse loss [10] and minicolumn change [9] have shown some of the clearest structural relationships with functional deficits in ageing and dementia. In the context of identifying a neural basis for cognitive reserve, pathological markers may be identified with deficit, whereas measures of intact architecture should correspond to reserve.

Structural changes

At the large scale, total brain size contributes significantly to the variance in cognitive ability between individuals [4]. Total brain shrinkage typically occurs with ageing in humans, which a recent report suggests may be unusual compared to other primates who do not show this reduction [11]. In a longitudinal MRI study of twins in adulthood, progressive thinning of the frontal cortex and thickening of the medial temporal cortex is heritable and related to cognitive ability (IQ) [12]. (IQ measures are taken to be a good indicator of premorbid cognitive reserve [13].) Genes influencing variability in both intelligence and brain plasticity partly drive these regional associations. In particular, training in alternative problem solving strategies likely to be associated with prefrontal cortex (PFC) function has been linked to enhancement of cognitive reserve. Our own data have found a closer relationship between cognitive function and micro-anatomical measures in association cortex than with total brain size [9] (see below).

Older adults are capable of counteracting age-related neural decline through plastic reorganization of neurocognitive networks. At the small scale, on the structural level, several aspects of neuroplasticity occur in adult brains, including alterations of dendritic arborisation, synaptic remodelling, axonal sprouting, neurite extension, synaptogenesis, and neurogenesis [14]. The hippocampus is a region of high neuroplasticity, with ongoing myelination and neurogenesis during adulthood [15,16]. The PFC is also a dynamic structure, capable of a neuroplastic response to changes or damage with an extended period of development during childhood and adolescence, and a decline in adulthood in humans [17].

The neuroplasticity hypothesis therefore offers a mechanism to help explain differential regional vulnerability in AD [18,19]. It suggests that differences in disease progression are due to different intrinsic rates of neuropathological change, related to regional differences in neuroplasticity. Ageing makes neurons work harder to meet neuroplastic demands. A model incorporating

intrinsic vulnerability (for example, [14]) therefore offers a link to normal aging. Grafman and Litvan [20] have identified four major forms of neuroplasticity: map expansion (mainly due to skill learning), cross-modal reassignment (by rewiring following injury), homologous area adaptation (the shift of function, often to the opposite hemisphere, due to injury in early life), and compensatory masquerade (an alternative processing strategy for a task). These forms of neuroplasticity tend to be responses to specific events or tasks. However, there is also evidence of an over-arching trajectory of change in structure across the lifespan [21], to which the contribution of these event-driven forms of plasticity is uncertain. Rosenzweig [22] has reviewed the range of mechanisms of neuroplasticity across the lifespan, and Gopnik [23] describes a contrast in learning strategies and plasticity in childhood compared to adulthood. It is the latter stage of persistent adult neuroplasticity that is likely to be most relevant for determining the effects of age and dementia on cognitive reserve (although see 'Stem cells and neurogenesis' section below).

Age-related dendritic growth reflects hierarchical organisation between cortical regions [24], with greater growth in limbic and association cortex where there is greater arborisation contrasted with stability or regression in less complex primary cortex [25]. Regional differences in the width of minicolumns (the radial columns of cells that constitute the cerebral cortex) also reflect this hierarchy [19]. The minicolumns become thinner with age [24] and we have shown that the relationship between minicolumns and cognitive function in association cortex is independent of general brain atrophy [8]. Furthermore, in AD, a higher density of tangles occurs in the more plastic regions and is correlated with the degree of minicolumn disruption [26].

Not all regions associated with extended plasticity in adulthood are early casualties in AD; for example, dorsolateral PFC is affected later. The expression of plasticity as a risk factor may be compensated by the availability of neural reserve. A study of the dorsolateral PFC found that the microstructure changed with normal ageing and that minicolumn thinning and accumulating plaque load mirrored the decline in IQ [8]. The role of the PFC in cognitive reserve indicates that the thinning of minicolumns in the PFC may reflect the loss of the initial neural reserve (for example, loss of neuropil and neuronal connections) in early aging. We also found that AD patients with a high IQ were older at time of death compared to patients with a low IQ score and the density of tangles was less in the patients with high IQ. The implication is that individuals with greater reserve tend to develop dementia later in life. Moreover, the low density of tangles with high IQ raises the possibility that, in addition to neural reserve and neural compensation, cognitive reserve may be associated with 'neural resistance' to the spread of pathology.

One possibility is that different regional connectivity contributes to different plastic demands and different aspects of cognitive reserve. For example, the serial connections of the entorhinal-hippocampal pathway are more constrained than the diverse connections of the polymodal prefrontal cortex, reducing the options for neural compensation. One consequence may be the requirement for sustained adult neurogenesis in the hippocampal region while the preservation of white matter connectivity may be relatively more important in the PFC.

White matter and cognitive reserve

White matter atrophy was highlighted in 1989 when, in a quantitative neuropathological study of elderly brains, it was found that people without cognitive decline but with some AD pathology had atrophy of white matter but not of grey matter, whereas those with dementia and more extensive AD pathology had both grey and white matter atrophy. It was suggested that white matter atrophy may precede whole brain atrophy in ageing brains [27].

Neuroimaging has taken this concept further. O'Sullivan and colleagues [28] described reduced diffusional anisotropy, a measure of white matter integrity, and higher mean diffusivity in elderly people with normal cognitive performance for age compared with young control subjects. Another early diffusion tensor imaging study identified reduced white matter integrity in the splenium of the corpus callosum, superior longitudinal fasciculus, and cingulum whereas the pyramidal tracts were spared [29]. Bartzokis and colleagues [30] found, using the transverse relaxation rate, that people who were ApoE4-positive, and therefore at increased risk to develop AD (though they performed cognitively normally when examined), had a reduced cognitive processing speed, which was significantly correlated with myelin breakdown in late myelinating white matter regions. Presymptomatic carriers of familial AD mutations have altered diffusion tensor imaging signal in white matter throughout the brain and particularly in the perforant pathways, the fornix, and orbito-frontal white matter [31]. It was suggested that the changes in the fornix in particular may provide a biomarker for early disease in sporadic AD.

Andrews-Hanna and colleagues [32] used functional MRI signal correlations between regions within large-scale brain systems in young and old cognitively normal subjects (mean Mini-Mental State Examination in the elderly score of 28.8) and showed marked reductions with age in normally present functional correlations within two higher order brain systems. The worst affected system was the anterior to posterior components within

the default network. Reduced correlations were associated with loss of white matter integrity.

Abnormalities in the default mode network were also detected using resting state paradigms in mild cognitively impaired subjects [33]. The level of deactivation differed in the anterior frontal, precuneus and posterior cingulate in AD when compared to controls, and the level of deactivation was intermediate in mild cognitive impairment. Both studies suggest activity in the default mode network may provide a marker for early changes and indicate continuity between normal ageing and so-called pathological ageing.

The pathological basis of this purported white matter deterioration with ageing, which occurs in the absence of overt white matter changes such as hyperintensity on T2 imaging, is not well delineated, but Bartzokis [34] has suggested that dysfunction of oligodendrocytes and the myelin sheaths they maintain may be to blame.

Resistance to Alzheimer's disease

This review has so far considered mainly changes that occur in the brain with normal ageing. Although there are some investigators who prefer to consider AD as distinct from ageing, we believe that there may be more advantages in regarding it as part of the spectrum of change that occurs in the brain with age. This approach is borne out by the enhanced associations that have been found of pathology with AD genetic susceptibility alleles if analyses involve not only neuropathological cases of definite AD but also other elderly cases with less marked AD pathology, referred to in the study by Bennett and colleagues [35] as 'intermediate phenotypes'. This was also the approach to linking neuropathological variables and a range of cognitive scores in elderly subjects that was taken by Dowling and colleagues [4]. There are so many changes that are seen to a severe degree in definite AD and to a milder degree in normal ageing that this 'intermediate phenotype' model seems to make eminent sense. These include evidence in the brain of oxidative and other free radical damage, reduced anti-oxidative capacity, loss of synapses, expression of cell division cycle markers and neurons displaying hyperploidy, to name but a few. It is acknowledged that there may be step-wise blips within a spectrum of age-related changes encompassing AD that may influence cognitive performance and be marked by particular pathological changes, as suggested by Herrup [36]. Nevertheless, in the rest of this review, in which we consider what may constitute 'resistance' to AD, we shall follow this 'intermediate phenotype' approach and include 'resistance to brain ageing'.

Factors that may protect an individual from progressing to the AD end of the spectrum of possible change as they age are legion. A recent review considered seven modifiable risk factors for AD and calculated that up to half of cases of AD might be attributable to such factors: diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity or low educational attainment and physical activity [37]. These factors are derived mainly from epidemiological studies and not from interventional studies, which at present remain inadequate [38]. These can be classified according to whether they are thought to act by strengthening brain reserve before it is assaulted by the effects of age on the one hand and those that constitute a reaction to such assaults on the other. It is beyond the scope of this review to examine these factors in detail but we shall give them brief consideration here.

Psychosocial factors

The important factors here are avoidance of depression, itself seemingly partly dependent on healthy maternal influences on the fetus, or, more realistically, prompt recognition and treatment of depression; extended years and quality of education, captured by tests of reading ability; and abundant leisure, exercise and cognitive activities in middle and early old age [7,37,39]. A broad category of cognitive enrichment includes physical, mental, and social activities that may improve adult cognitive function [40]. Clare and colleagues [41] have identified three categories of intervention: 'cognitive stimulation' involves non-targeted procedures to enhance general mental function, 'cognitive training' involves theory-driven intervention, and 'cognitive rehabilitation' tackles impairments resulting from neuropsychiatric disorders. In normal ageing, engagement in daily arithmetic puzzles has been shown to improve function in a randomized controlled trial [42]. How behavioural and psychosocial enrichment strategies might interact with psychopharmacological enhancement in healthy subjects is unclear, but it seems reasonable to hypothesise that it strengthens cognitive reserve. Rozzini and colleagues [43] found enduring improvement in mild cognitive impairment patients receiving combined pharmacological therapy and cognitive training in a one-year randomized study (although subjects receiving only pharmacological intervention also improved). However, it has been suggested that cognitive training is of limited benefit in demented subjects [41].

Vascular risk factors

Vascular risk factors seem, from epidemiological studies, to operate particularly at the middle stages of life. Hypertension, in particular, needs to be avoided and other risk factors for AD that probably act through an effect on vascular risk also need to be avoided: smoking, obesity and diabetes. Diet, which also feeds into the risks of obesity and vascular disease, may also be protective if it avoids much saturated fat and is rich in sources of

vitamins, omega-3 fatty acids and anti-oxidants (for example, curcumin). There is some evidence that vitamins B12, folate and B6 are protective (by reducing blood homocysteine levels) [44], as is resveratrol in red wine. While epidemiological evidence for these protective factors is quite strong, evidence that adopting them is effective in preventing AD is less sound or even negative, probably because they have been applied in trials too late in the course of the disease and for too short a period of time. These factors likely operate by preventing brain pathology.

There are several putative mechanisms through which such dietary factors may act. Taking omega-3 fatty acids as an example, docosahexaenoic acid (DHA) is the main omega-3 fatty acid in the brain and an essential component of synaptic membrane phospholipids, and consequently may play a role in synaptic remodelling [45]. DHA attenuates amyloid-β secretion, an effect accompanied by neuroprotectin D1 formation, which promotes brain cell survival [46]; DHA also protects from dendritic pathology in an AD mouse model [47]. Furthermore, another omega-3 fatty acid, eicosahexaenoic acid, is an anti-inflammatory precursor. Consequently, omega-3 fatty acids are involved in gene expression differences, synaptic plasticity and dendritic structural changes that plausibly contribute to cognitive reserve.

Evidence for an effect of hormones on AD risk is controversial but increasing. Thus, testosterone acts as a protective factor in men [48] and oestrogen replacement therapy may be protective if administered initially at or shortly after the menopause (but not later) in women [49]. Raised cortisol levels are thought to represent a risk factor for AD and therefore need to be avoided by limiting stress. Raised cortisol levels may explain, at least in part, the manner in which depression promotes AD.

There is good evidence that physical activity both in old age and earlier in life protects against AD. It may do this in part by protecting against vascular risk factors such as hypertension, obesity and diabetes, but it also appears to protect the brain more directly by promoting growth factor production and neurogenesis (see below).

Much has been written about the importance of systemic and brain inflammation in influencing AD risk. The pathology of AD includes enhanced activation of microglial cells, and the remarkable ability of macrophages to eliminate beta amyloid from the brain in experimental AD drew attention to the power of these cells to influence pathological events in this disease [50]. There is some epidemiological evidence that chronic inflammatory diseases such as rheumatoid arthritis and leprosy, requiring long-term treatment with anti-inflammatory agents, are protective against AD [51] but attempts to treat AD or mild cognitive impairment with anti-inflammatory therapy have had disappointing results. Avoidance of head injury may be protective against AD at least in part because head injury is a cause of brain inflammation, although there may be a more direct link between head injury and amyloid plaque formation [52]. Inflammation may be influenced by systemic and local infections. For example, latent herpes simplex infection of the brain is one of several infections that have been suggested to influence risk of AD [53].

Cellular mechanisms in the brain

Cortical and hippocampal neurons are critical elements that need protection in old age and as a part of the resistance to AD. Neurons' dependency on oxidative metabolism is a source of danger as mitochondria become less efficient with age as a consequence of their generation of free radicals, which then damage the mitochondria themselves as well as other cellular constituents. The enormous cell surface area that requires constant maintenance is also an Achilles' heel for many neurons as it increases the need for energy, which, in turn, is dependent on mitochrondrial function. A third source of difficulty in maintaining healthy neurons in old age is their vulnerability to excitotoxic damage mediated through excess stimulation of glutamate receptors. To defend themselves against free radical damage, cells require effective anti-oxidant mechanisms, with which neurons are not overly endowed. Some of the dietary and lifestyle habits that protect against AD probably operate through boosting anti-oxidant mechanisms either directly or indirectly.

Glial cells also play important protective roles. Astrocytes are known for their neuroprotective properties, such as release of growth factors, control of potentially neurotoxic transmitters and promotion of neuroprotective effects of oestrogens [54,55], although they have recently been shown in co-cultures of neurons and astrocytes to be critically involved in the toxicity that beta-amyloid has for neurons [56]. Microglia may have altered properties in the ageing brain that enhance their ability to exert neurotoxic effects [57,58].

As reviewed by Iadecola [59], brain endothelial cells have critical roles to play in the fine tuning of oxygen and metabolite supply from the blood to the brain in response to neural activity and in enabling waste products of such activity to be removed. They also exert a protective effect on nerve cells by producing growth factors such as brain-derived neurotrophic factor. These endothelial cells are subjected to oxidative damage and toxic effects of beta-amyloid produced in the brain, which can compromise these functions during ageing and promote endothelial cell autophagy. In transgenic AD in mice there are changes in cerebral blood flow regulation long before there is evidence of beta-amyloid deposition in the brain, suggesting that vascular changes occur at a very early stage in the pathogenesis of genetically determined AD.

Table 1. Some protective genetic effects against Alzheimer's disease

Gene(s)	SNP(s)	Control allelic frequency	Control combination frequency	Odds ratio of AD (95% CI)
Effects attributable to single genetic loci				
CLU	rs1113600AvsG	A:40%		0.88 (0.86-0.90)[a]
PICALM	rs3851179AvsG	A:36%		0.88 (0.86-0.90)[a]
CD33	rs3865444VvsC	A:32%		0.89 (0.86-0.92)[a]
Effects attributable to two-locus combinations				
APOE	rs429358/rs7412		9.1%	0.44 (0.39-0.50)[b]
	ε2 vs others			
PPARA, *IL1A*	rs4253766/rs378550		11.4%	0.71 (0.57-0.90)[b,c]
	(TC+TT)/(CA+CC) vs others			
PPARA, *IL1B*	rs1800206/rs16944		11.6%	0.74(0.60-0.92)[b,c]
	(GC+GG)/(GA+GG) vs others			

[a]Data from the AlzGene (Caucasians) [72]. [b]Data from Farrer and colleagues (APOE) [73], the Epistasis Project (*PPARA*, *IL1A*, *IL1B*; all Caucasians). [c]Controlling for age, sex and *APOE4*. AD, Alzheimer's disease; *APOE*, apolipoprotein E; *CD33*, CD33 antigen; CI, confidence interval; *CLU*, clusterin; *IL1A*, interleukin-1α; *IL1B*, interleukin-1β; *PICALM*, phosphatidyl inositol-binding clathrin assembly protein; *PPARA*, peroxisome proliferator-activated receptor-α. Data in Table 1 are courtesy of DJ Lehmann.

Stem cells and neurogenesis

In animal experiments, both voluntary exercise and environmental enrichment stimulate adult hippocampal neurogenesis. Running can in part reverse the decrease in neurogenesis observed in aged animals and improves learning in aged animals [60]. Sequentially combining the effects of physical activity with environmental enrichment has been shown to have an additive effect on the number of new neurons in the dentate gyrus [61]. Kempermann and colleagues [62] have proposed that continued physical and mental activity maintains a 'neurogenic reserve' of potential neurons that may be integrated into the hippocampal network. However, the number of precursor cells that may be recruited is limited by the proliferative cells, whose survival may depend on activity in early life. This links later life reserve to activity in early life and indicates that early life behaviour can only be partly compensated later. The interaction is reminiscent of Hebb's original finding that early experience influences problem-solving ability in maturity [63].

New cells in the hippocampus initially express increased synaptic plasticity and it has been claimed that all long-term potentiation in the dentate gyrus originates from new cells; meanwhile, long-term potentiation has been shown to induce adult hippocampal neurogenesis *in vivo* [62]. Of additional interest, considering that therapeutic neuropharmacology for AD has predominantly targeted the cholinergic neurotransmitter system, cholinergic input from the medial septal area promotes precursor cell proliferation in the dentate gyrus [64]. Environmental enrichment also leads to increased cortical acetylcholinesterase activity [65], although the clinical manipulation of acetylcholine levels in dementia has met with limited success.

The potential role of neurogenesis in cognitive reserve and its manipulation in old age has received considerable attention [66], although much is yet unknown regarding possible intervention in humans. The indication of neurogenesis in association cortex but not in a primary sensory area (striate cortex) in monkeys [67] hints at more widespread neurogenesis reflecting some of the brain region hierarchical differences already mentioned. However, the generality of ongoing neurogenesis in 'higher' neocortical regions is uncertain (for example, [68]), especially in humans.

Genes

Genes are thought to have a major impact on AD risk and probably many of the psychosocial and lifestyle factors mentioned above exert their effects by altering the epigenetic control of gene expression [69]. Although the gene encoding apolipoprotein E is most well established as influencing risk of late onset AD, several other gene polymorphisms have also emerged from recent studies as having a modest effect on AD risk (Table 1). Combinations of gene polymorphisms appear to have a stronger influence than single gene effects.

SIRT1 is a gene that profoundly influences life span in rodents and is activated by calorie restriction, an intervention that has long been recognised as extending the lifespan of rodents by 50% or more. *SIRT1* codes for an acetylase that counteracts the effects of stress on cells. Overexpression of *SIRT1* in AD transgenic mice reduced beta-amyloid production, inflammation, tau phosphorylation and improved learning [70]. A substance in red wine, resveratrol, has SIRT1-activating effects. Another signalling pathway that influences life span and experimental expression of AD transgenes is the target of

rapamycin (mTOR) pathway. Long-term inhibition of this pathway by the drug rapamycin delayed the expression of cognitive decline and pathology in AD transgenic mice [71]. The *SIRT1* and mTOR pathways are promising with regard to the development of interventions to prevent or slow the development of AD in humans.

Conclusion

We already have some knowledge on which to base preventive strategies to keep AD at bay. These strategies are already recognised to promote healthy ageing of the vascular system, and they are likely to be joined within a few years by additional novel measures based on rapidly developing understanding of the effects of ageing on the brain. But there are formidable challenges to be overcome, as witnessed by the widespread surge in obesity that could threaten to undermine attempts to improve the chances of many people enjoying a prolonged and fulfilled old age.

Abbreviations

AD, Alzheimer's disease; DHA, docosahexaenoic acid; MRI, magnetic resonance imaging; PFC, prefrontal cortex.

Competing interests

The authors declare that they have no competing interests.

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