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Age-associated cognitive decline

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Introduction: Age-associated cognitive decline—or normal (non-pathological, normative, usual) cognitive ageing—is an important human experience which differs in extent between individuals. The determinants of the differences in age-related cognitive decline are not fully understood. Progress in the field is taking place across many areas of biomedical and psychosocial sciences.

Areas of agreement and controversy: The phenotype of normal cognitive ageing is well described. Some mental capabilities are well maintained into old age. From early adulthood, there are declines in mental domains such as processing speed, reasoning, memory and executive functions, some of which is underpinned by a decline in a general cognitive factor. There are contributions to understanding individual differences in normal cognitive ageing from genetics, general health and medical disorders such as atherosclerotic disease, biological processes such as inflammation, neurobiological changes, diet and lifestyle. Many of these effect sizes are small; some are poorly replicated; and in some cases, there is the possibility of reverse causation, with prior cognitive ability causing the supposed 'cause' of cognitive ability in old age.

Emerging areas for developing research: Genome-wide scans are a likely source to establish genetic contributions. The role of vascular factors in cognitive ageing is increasingly studied and understood. The same applies to diet, biomarkers such as inflammation and lifestyle factors such as exercise. There are marked advances in brain imaging, affording better *in vivo* studies of brain correlates of cognitive changes. There is growing appreciation that factors affecting general bodily ageing also influence cognitive functions in old age.

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Introduction

The impact of age itself on cognition—not dementia, and not mild cognitive impairment, nor the other specific cognitive decline syndromes—is such a large, immediate problem for current science, and so ignored by current scientists, that Brayne[1] called it, 'the elephant in the room'.

With an increasingly aged population, both in the UK and internationally, cognitive impairment is a major health and social issue. Cognitive decline is among the most feared aspects of growing old. It is also the most costly, in terms of the financial, personal and societal burdens. It is important, because cognitive decline heralds dementia, illness and death. In the UK, cognitive failure is the cause for 40% of admissions to institutional care. It is widely agreed that more research is needed to understand the mechanisms of cognitive ageing and the factors that contribute to its individual differences.[1] Committees have been formed, and book-length calls have gone out from national organizations, enumerating the problems of the ageing brain and the necessary research agenda: from the Scottish National Health Service,[2] from the UK's House of Lords,[3] from the USA's National Academies[4] and the USA's National Institutes of Health.[5] The latter stated that, 'identifying the demographic, biological, and psychosocial factors that can help people maintain or enhance their cognitive and emotional health as they grow older becomes a major public health goal for this country' (p. 13). The present summary of some aspects of non-pathological cognitive ageing focuses on studies that have examined older people. However, the state of the brain in old age is the summary of effects across the lifecourse, from conception. This long view is well represented in the UK Government Office for Science's Foresight Report, 'Mental Capital and Wellbeing',[6] and it is highly recommended.

The above-mentioned sources[1–6] on cognitive ageing and its causes make it clear—to a greater or lesser extent—that it is far from straightforward to separate non-pathological from pathological cognitive decline. Often, in the studies that are summarized below, this is done by brief tests such as the Mini-Mental State Examination and/or by the absence of a clinical diagnosis, and sometimes by exclusion using a standardized psychiatric interview. However, it is recognized and must be remembered that: people's differences in age-related cognitive decline form a continuum, not entirely discrete groups (of course, defining into groups is needed for treatment decisions); diagnostic criteria for Mild Cognitive Impairment (and its alternative terms) and dementia change, and so the points on the continuum that are deemed pathological or not can change; people's cognitive level in old age

depends to a large extent on their prior intelligence and that is not always taken into account in reckoning whether a given level of cognitive function in old age represents a decline—in absolute terms, or relative to their age cohort—for that person; the same measured level of cognitive ability in old age can occur in the presence of very different levels of brain pathology (e.g. Alzheimer-type); and even people with no apparent cognitive decline can have Alzheimer-type pathology in their brains. In summary, studies that purport to describe contributions to non-pathological cognitive ageing must be examined with these caveats, and bearing in mind the possibility that some people in such studies might be in the early, undiagnosed stages of pathological cognitive impairment.

If the first warning about studies in non-pathological cognitive ageing is that the subjects in such studies will not invariably be non-pathological, the second warning is that apparent causes of cognitive ageing will not always be causes at all. It is quite common to read a report in which a variable is associated significantly with a cognitive test score in old age. Typically, the study is cross-sectional. Typically, too, the suggestion is made that the variable is a possible cause of cognitive differences in old age, of cognitive decline perhaps. It might be. But there are other possibilities. The follow-up studies of the Scottish Mental Surveys,[7] for example, have shown that intelligence test scores from childhood are associated with health variables and health risk factors in middle and old age. Therefore, the cross-sectional 'variable X versus cognitive ability scores' finding in old age might—in part or whole—be the result of reverse causation: intelligence traits from early life affect later health. Another possibility is that the cross-sectional correlation is caused by some third—confounding—variable or set of variables and that the correlation is spurious, being the result of some more basic factor(s) that affect both the apparent cause and effect. Therefore, discovering associations between putative causes of cognitive ageing and cognitive ability test scores are only the beginning. Ideally, they should be studied longitudinally and be the subject of mechanistic investigations.

The landscape of cognition and how it ages

There is little age-associated decline in some mental functions—such as verbal ability, some numerical abilities and general knowledge—but other mental capabilities decline from middle age onwards, or even earlier.[8,9] The latter include aspects of memory, executive functions, processing speed and reasoning. All of these so-called 'fluid' mental abilities are important for carrying out everyday activities, living

independently and leading a fulfilling life. When one fluid mental domain declines others tend to do so also.[10] Second, slowed speed of information processing appears to account for a substantial proportion of age-associated decline in all affected cognitive domains, and the slowing has begun by the 30s,[11] as has the age-associated decline in some other aspects of cognitive function.[12] Within the range defined by 'normal cognitive ageing'—i.e. in people who would not meet the criteria for dementia or any of the varieties of 'mild cognitive impairment'—people differ greatly in the degree to which their brains decline with age. Identifying the risk factors for, and mechanisms of, individual differences in age-associated cognitive decline is among the greatest challenges to improve the wellbeing of older people.

Here, we address some contributions—general medical, genetic, vascular, physiological, dietary and lifestyle—to non-pathological cognitive ageing. This is an especially important problem because it involves such large numbers of people compared with the dementias. The USA's NIH emphasized the importance of studying the processes of 'normal' and 'successful' cognitive ageing.[5] We should state at the start that individual differences in cognitive ability in old age reflect two things: differences in prior cognitive ability and differences in the degree to which change (typically deterioration) has taken place. Of the many possible contributors to cognitive ability level in old age, none yet known approaches the effect size of mental ability measured in childhood. Even as late as age ~80, childhood intelligence contributes ~50% of the variance, or more, to cognitive ability in old age in people without dementia.[7]

Disease, health and normal cognitive ageing

Inasmuch as age is the major risk factor for dementing illnesses, such as Alzheimer's disease, there is a case for considering these as representing an extreme end of the spectrum of age-associated cognitive decline. However, the dementias are not only quantitatively different in the degree of cognitive decline, but also they are often qualitatively different in the pattern of decline across the various cognitive abilities. For example, Alzheimer's disease is characterized by marked impairment of episodic memory and frontotemporal dementia by impaired executive function. Moreover, people with dementia often exhibit changes in behaviour and other aspects of mental state as well as declines in performing activities of daily living. Having said this, in advanced old age, when dementia has a high prevalence, distinguishing between normative and non-normative ageing is not simple. Indeed, this difficulty has been recognized by introducing categories such as

mild/minimal cognitive impairment which have a position somewhere between normal cognitive ageing and dementia.

One problem in distinguishing between normative and non-normative cognitive ageing is that neuropathological changes of Alzheimer's disease are widespread in older peoples' brains. In the MRC Cognitive Function in Aging Study (CFAS), around one-third of participants without dementia had moderate or severe neuritic plaque scores at autopsy.[13] Another challenge is the observation that risk factors for dementia also increase risk of normative cognitive decline (age, hypertension, diabetes, physical fitness and education).[1,5–7] Mirroring the problems distinguishing normative and non-normative cognitive ageing is a similar set of challenges differentiating normal physical ageing from age-associated disease. Disease, as defined by diagnosis and excepting dementia, is a poor predictor of cognitive decline,[14] whereas physiological markers of health status are significantly correlated among themselves and with cognitive ageing.[15] This mirroring has suggested that physiological and cognitive functions decline together in old age and led to what is termed the 'common cause' theory of ageing. This theory hypothesizes that although there are individual measure-specific mechanisms leading to decline, a considerable proportion of decline is attributable to some core biological processes that deteriorate with ageing. Candidates for such core processes include oxidative stress, telomere attrition, hormonal dysregulation and immunosenescence. Research on the relationship between physical and cognitive ageing has thus sought to measure biomarkers of these processes to establish which pathways are implicated.

Another problem has been recognized that impacts upon our understanding of the relationship between physical health and age-associated cognitive decline: several disease states thought to affect cognition adversely are more common in people with lower early life IQ, including childhood IQ.[7] Since childhood IQ, itself, is a strong predictor of cognitive abilities in later life, the disease state may be acting as a marker of lower childhood IQ and this might explain in whole or in part any association with lower cognitive ability in old age. For example, lower childhood IQ is associated with elevated blood pressure in middle age even after adjustment for social class, smoking and other factors.[16] High blood pressure is thought to lead to cognitive decline, but few studies that examine this relationship adjust for the contribution made by childhood IQ to cognition in later adult life. Hence age-associated cognitive decline is best considered in terms of a life-course perspective. What appears to be the effect of an illness state on cognitive ability in old age might in part be the reverse: the effect of early life cognition on the risk of developing the disease state.

Genetic contributions to cognitive ageing

Heritability studies—using data from twins and families with adopted children—have estimated that the heritability of general cognitive ability is ~50%, increasing from childhood to adulthood and into old age. Some studies have shown that heritability decreases in very old age, though the contribution of genes to cognitive ability remains above 50%. It is likely that there are genetic influences on both the lifelong trait of intelligence and specifically on age-associated cognitive decline.[17,18]

Candidate genes studies have looked for associations between variations in specific genes and age-associated cognitive decline. Candidate genes include those previously associated with cognitive ability, dementia, cardiovascular disease, oxidative stress and longevity.[17] There have been a number of published associations between candidate genes and cognitive ageing, but the gene coding for apolipoprotein E (*APOE*), a risk factor for Alzheimer's disease, is one of the few to have been replicated in multiple studies.[19,20] In people within the normal range of cognitive ageing, possessors of the E4 allele of the *APOE* gene perform slightly worse on general cognitive ability and on the specific domains of perceptual speed, episodic memory and executive functioning. The influence of specific variants in 10 genes—e.g. *BDNF*, *COMT*, *DISC1* and *PRNP*—that had been previously associated with cognitive ageing, cognitive ability, Alzheimer's disease and autism were recently examined, and there was no evidence that they were associated with cognitive ageing in a cohort of ~1000 Scots with cognitive ability test scores available from ages 11 and 70 years.[21] There are several reasons why candidate gene studies have identified so few replicable associations with age-associated cognitive decline. First, the genetic variants so far identified each account for at most only a small percentage (1–2%) of the variance in cognitive ageing and, as most studies contain only hundreds of participants, they are often underpowered for detecting such effect sizes. Second, many of the studies have been performed on participants from different populations and it is possible that different genes are important in different populations. Third, not all studies have used participants of the same age range. It may be that different genes influence cognition at different ages, even within what is classified as old age. Finally, the major limitation of candidate genes studies is that they rely on our limited understanding of both the biology of cognitive ageing and the functions of the candidate genes. This is where genome-wide association studies will be more useful, allowing up to one million genetic variants (both single nucleotide polymorphisms and copy number variations) spread throughout the genome to be

Table 1 Types of genetic contributions to understanding non-pathological cognitive ageing.

Types of genetic studies	Targets	Example results	Future	References
Heritability studies	Genetic influences on cognitive ability studied using twin, adoption and family designs	Genetic contributions to intelligence variation are: 41% childhood; 55% adolescence; 66% in young adulthood; about 60% in old age	Determine source of heritability by searching for molecular genetic influences	14,48
Candidate gene studies	Genes for cognitive ageing sought among genetic influences on: cognitive ability; dementia and other neurodegenerative disorders; cardiovascular disease; oxidative stress; longevity etc.	Variants in the following genes reported as associated with differences in cognitive ageing: *APOE*, *BDNF*, *COMT*, *DISC1*, *PRNP*	*APOE* is well established; other genes have largely failed to replicate	15–17
Whole-genome association	Whole-genome analysis used to reveal common variants influencing cognitive ageing	*LRP1B* haplotypes associated with successful ageing without cognitive decline	Replication in larger samples; improved genome coverage; detailed cognitive testing	49

The gene names are as follows: *APOE*, apolipoprotein E; *BDNF*, brain-derived neurotrophic factor; *COMT*, catechol-*O*-methyltransferase; *DISC1*, disrupted in schizophrenia 1; *PRNP*, prion protein; *LRP1B*, low-density lipoprotein-related protein 1B.

genotyped. They are not biased towards a particular gene or genes.[22] Table 1 summarizes and exemplify genetic approaches to the study of non-pathological cognitive ageing.

Cardiovascular disease and cognitive ageing

A delicate relationship exists between the circulatory system and the brain which, if upset by vascular disease, may affect normal brain functioning.[23] Diverse neurological symptoms may follow either transient or permanent disruption of blood flow to the brain. Long-lasting sensorimotor and behavioural disabilities are frequently observed after acute ischaemic stroke caused by complications of large-artery atherosclerosis.[24] A single large or repeated brain infarcts increase the risk of cognitive impairment, hence the term multi-infarct dementia. Even without dementia, stroke patients tend to perform poorly on cognitive

tests compared with healthy, non-stroke controls. Depending on the criteria used, cognitive impairment may affect up to 70% of patients.[25] Deficits in multiple cognitive domains are frequently observed, including general mental status, abstract reasoning, attention and specific memory functions, but usually some improvement occurs with time following the stroke event. Different stroke characteristics, including lesion laterality, may also influence cognitive outcomes in these patients; for example, left-hemisphere stroke is consistently associated with general cognitive impairment.[24] Although focal neurobehavioural deficits are common after stroke, general mental functions which depend on the integrity of the entire brain may also be affected.

Symptomatic atherosclerotic disease in one arterial site may represent similar pathology in other arteries.[23] For example, stroke patients frequently have concomitant coronary heart disease (CHD). Even in the absence of stroke, CHD predisposes to cognitive impairment which, in addition to systemic atherosclerosis, may result from cerebral hypoperfusion due to impaired cardiac function or infarcts caused by cardiogenic emboli travelling to the brain.[23] Although few studies have examined cognitive deficits in patients with milder CHD syndromes—including angina—poorer mental status, memory and executive functions have been reported in survivors of acute myocardial infarction (AMI).[23] However, known CHD risk factors, which often cluster in individual patients, may independently influence cognition. When appropriately controlled for, AMI may no longer associate with cognitive performance.[26] In contrast, end-stage congestive heart failure is associated with deficits in executive function, memory, concentration and psychomotor speed.[23] Cardiac output, which may be severely reduced due to impaired ventricular function, predicts cognitive function in these patients, although as yet, it is unknown whether heart transplantation actually improves cognitive outcomes in patients with long-standing heart failure.

Similarly, patients with peripheral arterial disease (PAD) affecting the lower extremities commonly have atherosclerotic lesions in major arteries supplying the heart muscle and the brain. Deficits in psychomotor speed, problem solving and abstract reasoning are common in neurologically intact patients with very advanced PAD, such as leg amputees.[27] The extent of these deficits may differ only marginally from that seen following overt stroke. In these patients, disease severity may be an important predictor of cognitive function. In population-based studies, elderly people who experience leg pain while walking, the clinical hallmark of PAD, have been found to be at an increased risk of progressive cognitive decline, particularly in verbal memory, which is not explained by the influence of a previous stroke, depressed mood or concomitant vascular risk factors on cognition.[26]

Inflammation and cognitive ageing

There is strong evidence linking markers of inflammation with atherosclerosis and cardiovascular disease, but its relationship with cognition is less well defined. Current prospective and cross-sectional studies provide conflicting views with positive and null findings being reported between late-life biomarker levels and cognitive ability.[28,29] Of these studies, few have assessed a large cohort of subjects over a long-term follow-up using an extensive battery of cognitive tests.

In terms of the inflammatory biomarkers studied, there is a reasonably large body of work on the downstream acute-phase protein C-reactive protein (CRP), and the upstream cytokines tumour necrosis factor alpha and interleukin-6. The magnitude of the effect sizes between these markers and cognition is typically small, with the biomarkers explaining ~1% of the variance of the cognitive test scores. In addition to inflammatory biomarkers, some studies have also integrated rheological and thrombotic factors, such as plasma viscosity and fibrinogen into their analyses. Initial findings for these markers are again mixed, although a causal rheology-cognition association is certainly plausible via a 'sticky blood' hypothesis. Explicitly, some suggest that increased blood viscosity has an effect on cerebral blood flow at a microvascular level.[30]

One study showed associations between both CRP and fibrinogen with cognitive ability at age 70 years.[31] However, upon adjustment for a measure of IQ at age 11, the associations were markedly attenuated. Further, the age-11 IQ scores also predicted age-70 CRP levels. This again raises the possibility of a reverse causation argument, in which lower childhood IQ leads to more inflammation in later life. Longitudinal data such as these are clearly a desirable study feature, although investigators might also consider the inclusion of a vocabulary-based test to estimate peak prior cognitive function. Measures such as the National Adult Reading Test are fairly robust estimates with scores on vocabulary-based tests showing little evidence of change over time.[32]

Given the high variability and acute nature of some inflammatory biomarker levels in old age, especially CRP, it may be relevant to use genetic variants as predictors of lifetime exposure to inflammation. Such an approach treats the intermediate phenotype (the biomarker level, such as CRP) as a biased measure. Instead, it models directly a gene-cognition association using genetic information, such as single nucleotide polymorphisms. Because genetic variants are determined at conception, they are less likely to be affected by confounding. Therefore, the use of such variants as predictors may be an approach

that will help to elucidate causal mechanisms. A caveat with this approach is the very large sample size required to detect significant associations. It may be that collaborative work with replication across different populations is required to reduce the possibility of false-positive findings and to ensure adequate power to detect what are almost certain to be small associations.

Neurobiology and cognitive ageing

The brain undergoes pronounced age-associated structural changes in old age. The most obvious is a steady decrease in brain size, balanced by an increase in ventricular spaces and cerebrospinal fluid. Brain atrophy accelerates in old age and shows an anterior–posterior gradient, with the most severe effects occurring in prefrontal regions.[33] Compared with overall brain, age-associated shrinkage is much smaller in the cerebral parenchyma. In the latter, atrophy starts much earlier in life and is more steady in grey matter (the neuron cell bodies) and cortical thickness than in white matter (the nerve fibres connecting different brain areas). Brain white matter volume tends to be relatively stable in healthy adults until about age 70, when steep decline, with an even more pronounced anterior–posterior gradient, can set in.[8,33,34] Also, cerebral dopamine receptor density depletes with age, which plays a central role in regulating attention and in modulating response to contextual stimuli.[8] A variety of mechanisms are likely to be causal in the normative age-associated decline in brain structure, including hypertension, age-associated vascular and microvascular changes, oxidative stress, recurrent inflammation and stress-related corticosteroid levels.[33,35]

It has been proposed that the loss of white matter integrity is an especially critical factor in normal cognitive ageing, since it leads to impaired information transfer between different cortical areas, from a loss of transfer speed in the case of demyelination to complete disconnection when axonal disruptions occur. Interactions between distant cortical areas are considered as crucial for the emergence of higher cognitive functions.[34] Until recently, problems with white matter integrity could mainly be detected as lesions that appear as hyperintensive patches on structural magnetic resonance imaging (MRI) scans and were mostly quantified using visual rating scales. Even though this procedure is laden with various measurement issues, small but consistent relationships with higher cognitive functions have been detected this way.[36] The advent of various new neuroimaging techniques, most notably diffusion tensor MRI, now allow for a much more detailed look at microstructural changes in cerebral white matter, including

fibre tract-specific assessments of white matter integrity (quantitative tractography).[34] However, despite these technological advances, the studies to date report associations between structural brain differences and cognitive ability measures in old age that tend to be modest in size and sometimes elusive.[8,33,34]

Two major explanations have been brought forward for this rather surprising pattern of results. First of all, people are assumed to differ in their cognitive reserves, which can be defined as the brain's capacity to buffer the effects of insults. The main determinants of cognitive reserve are early life cognitive ability (the 'baseline'), education level and occupational complexity, with the former being a strong predictor of the latter two.[12,35] Second, it is assumed that the ageing brain compensates structural losses in functional areas by recruiting previously unrelated parts of the brain (preferably in the prefrontal cortex and in corresponding contra-hemispheric areas) to take over the role in cognitive functions.[8,34] Both accounts have received some empirical support,[8,34,35] so they might explain why normative age-associated structural brain changes do not inevitably lead to cognitive decline.

Diet, lifestyle and cognitive ageing

The role of diet and other lifestyle factors in successful brain ageing has been attracting increasing scientific and public interest. Recent findings suggest that improving the diet of older people might help to delay the onset, or slow the progression, of age-associated cognitive decline. Current research has focused on the role of specific dietary elements and dietary patterns.

Some research supports the importance of a diet rich in B-vitamins, antioxidants and omega-3s for mental fitness. B-vitamins are essential for maintaining normal brain function and memory. Epidemiologic data suggest a protective role for B vitamins, particularly vitamin B12, B6 and folate (B9) on cognitive function. Moreover, B-vitamins help to regulate homocysteine levels, which is a risk factor for cognitive decline.[37] Oxidative damage has been implicated in ageing and age-associated cognitive decline. Dietary antioxidants (such as vitamins C, E, beta-carotene and flavonoids) found in fruits and vegetables may help protect against oxidative damage by boosting antioxidant defences. Evidence from cross-sectional studies supports a link between antioxidant status and cognitive function in older people.[38] In addition to antioxidant vitamins, fruits (such as blueberries) and vegetables contain plant polyphenols—compounds thought to interact with ageing neurons, increasing their capacity to maintain proper functioning during ageing.[39] Omega-3 fatty acids (particularly DHA) are

highly concentrated in the brain and the habitual consumption in later life of oily fish, rich in omega-3s, is associated with a reduced risk for cognitive decline and dementia.[37,40] They have been found to have anti-inflammatory, antioxidant and neuro-protective properties. Experimental evidence supporting a cognitive benefit to micronutrient supplementation in old age has been inconclusive. However, nutritional intake is based on a complex interaction of both macro- (proteins, fats, carbohydrates) and micronutrients (vitamins, minerals). For that reason, some researchers have directed their attention to the effects of dietary patterns. Prevailing scientific opinion points to a pattern of intake reflected in a 'Mediterranean diet'—rich in vegetables, legumes, fruit, nuts, cereals, fish and moderate amounts of alcohol (particularly red wine) and low in meat, poultry and dairy products—to maximize one's cognitive abilities into old age. Conversely, a diet high in refined sugars, cholesterol and trans-fats might be associated with poorer cognitive outcomes in older adults.[37] The interaction between genes and nutrition in recent research highlights the interplay between internal and external environments. Cognitive benefits were found in older adults consuming omega-3 fatty acids but only in non-*APOE* e4 carriers.[41] This finding supports the concept of an individual response to dietary intake and heterogeneity in cognitive ageing.

In conjunction with diet, other lifestyle factors such as smoking, drinking, physical activity and sleep influence cognitive ageing.[6,12] Evidence is growing that moderate levels of alcohol intake in older people can be beneficial; they are associated with better cognitive performance than either abstinence or heavy drinking and may have a protective effect against dementia and cognitive decline.[42] This risk reduction is partly attributable to the protective effects of alcohol on cardiovascular and cerebrovascular health. Smoking, primarily via detrimental effects on vascular disease, is a significant risk factor for cognitive impairment. A dose–response effect is evident for the number of cigarettes smoked during the lifetime and the degree of cognitive decline.[43] Giving up smoking at any age may prevent further smoking induced cognitive harm.

Future research should consider the full impact of socio-demographic factors; education, for example, is known to shape food choices in adulthood and therefore plays an important confounding role in the relationship between diet and cognition. Although further investigation is needed to clarify whether specific nutrients help to protect the brain from damage and counteract the effects of ageing, human epidemiologic studies provide some supporting evidence that a diet rich in plant matter and fish could offer protection against cognitive decline.

Active lifestyle and cognitive ageing

When considering potential determinants of age-associated cognitive decline, engaged and active lifestyles are often reported as protective.[44] This may be of particular interest to clinicians and indeed the public more generally, as it presents opportunities for delivered interventions or purposeful changes to habits intended to reduce cognitive decline. A recent UK Government review incorporated research linking physical activity or exercise and cognitive function, the consensus being that age-associated cognitive decline is apparently delayed or reduced in more physically active individuals.[6] An important caveat to this is that the physical activity need not be strenuous; individuals who walk more may experience less decline in later life.[6,44] Further investigation is warranted, particularly to examine whether there are critical periods across the life-span when physical activity needs to be initiated and maintained and what type of physical activity (e.g. aerobic versus anaerobic) might confer the greatest benefits.[6] Not all studies report an exercise-cognitive decline association, perhaps due to variability in the physical activity measurements, the validity of the cognitive assessments and length of follow-up in old age, and the timing and duration of the physical activity itself.[44] That said, there are a number of mechanistic hypotheses which could account for an association between increased physical activity and reduced cognitive decline. Most notably, cardiovascular risk and disease profiles are known to play a role in the trajectory of cognitive decline in later life; physical activity lowers these risk factors.[5,6,44]

Participation in activities of a mental or intellectually stimulating nature has also been shown to predict reduced cognitive decline. In this domain, the notion of 'use it or lose it' is proposed: the continued deployment of cognitive abilities through activities requiring cognitive effort may have direct effects on the brain, in terms of structure and/or function.[44,45] This is closely linked to the 'cognitive reserve' hypothesis. Individuals who are more cognitively active or engaged may accrue greater 'reserve capacity' across the lifecourse, and subsequently delay the onset of age-associated cognitive decline or reduce the impact of this.[6,35] However, any association found between mentally stimulating activities and cognitive decline must be clearly shown to be independent of premorbid cognitive function.[46] That is, the association must not be driven by the fact the higher ability individuals are more likely to be cognitively active throughout life and into old age (not just in terms of leisure but occupationally also); another example of possible reverse causation. The presumed protective effect may be due to the high degree of stability in cognitive function across the lifespan and not from participation in the activities themselves. To examine if there is

Table 2 Some other potential contributors to non-pathological cognitive ageing.

Potential contributor	Details
Self-reported health status	Individuals reporting poorer health status experience greater cognitive decline. Likely mechanisms would implicate increased burden of cardiovascular disease and its risk factors, increased levels of inflammatory and oxidative stress markers etc. (see below)
Cardiovascular disease and its risk factors	Normal cognitive functioning affected by vascular disease, e.g. by disruption of blood supply to the brain after stroke, or atherosclerotic lesions in major arteries. Risk factors including high blood pressure also associated with poorer cognitive function, although caution needed as earlier cognitive ability itself may be predictive of the presence/severity of risk factors in later life, an example of possible reverse causation
Physiological markers of health status	Associations between physiological markers of health (including inflammation, oxidative stress etc.) and cognitive decline are often discussed in terms of the common cause hypothesis: this suggests there may be shared biological processes of decline across domains of physical and cognitive health. It is necessary to identify biomarkers of decline processes to elucidate potential pathways. Markers of inflammation (i.e. CRP, IL-6, TNF-α) are linked to cardiovascular disease and atherosclerosis, but associations with cognitive decline are in need of further study. There are indications that levels of some markers in old age may be predicted by earlier cognitive function; possible reverse causation
Diet and nutrition	Some research links diets higher in B-vitamins, antioxidants and omega-3s with higher cognitive function. Mechanisms for association could include regulation of homocysteine or oxidative stress pathways; however, experimental studies are inconclusive. 'Mediterranean diet' is thought to be protective—with the presence of vegetables, fish and moderate alcohol
Smoking and alcohol	Smoking increases the risk of vascular disease and thus has been linked to poorer cognitive health; moderate alcohol consumption appears to be, if anything, beneficial
Activity participation and physical fitness	Active and engaged lifestyles seen as beneficial for later cognitive function, with particular emphasis on physical activity, which may reduce likelihood of CVD or related conditions, and also association between measures of physical fitness and cognition, again thought to be part of 'common cause' hypothesis of ageing. Mental engagement is often promoted as one of the key ingredients for successful cognitive ageing; however, there are large potential confounds in terms of participation in these activities and earlier level of cognitive ability. Suggested mechanisms often cite direct effects of mental stimulation on brain structure and function
Education and social class	More years spent in formal education and higher social class are associated with less cognitive decline. Mechanisms could include increased 'cognitive reserve' through educational and occupational trajectories, safer working and living environments, access to better health care etc. Both factors are highly correlated, and likely to be partly predicted by earlier cognitive level

truly a protective effect, more studies are needed which are able to control for an early measure of premorbid cognitive function.

The reason such activities are of particular interest derives from the fact that they may suggest simple, cost-effective lifestyle interventions

to ameliorate or delay age-associated cognitive decline. To date, however, cognitive intervention trials have not produced robust, replicable benefits. A recent review including 10 randomized control trials reported a mean effect size of 0.16 across a range of interventions, although the authors noted that most studies failed to include matched, active controls or placebos and that the benefit of the intervention often failed to generalize across varied cognitive outcomes.[47] Few studies included a lengthy follow-up to determine whether any apparent short-term gains in cognitive test performance were reflected at a more distal time point. This area will benefit from increased scrutiny and well-designed trials. Furthermore, it should be remembered that any beneficial interventions suggested need the compliance of those at risk in real world settings, as with other forms of medical treatment or medication use. Such behaviours are confounded by the ability to seek out and comprehend the information provided.

Conclusion

The interest in cognitive ageing is as understandable as it is compelling, for personal, scientific and practical interest. Personally, as we become aware of cognitive processes deteriorating, we witness the diminishing of something at the core of our rational self. Scientifically, it is a fascinating problem, namely to construct the multivariate recipe for successful cognitive ageing (a summary of the current review is provided in Table 2). Practically, demographic changes mean that our care services and economies will be better placed to cope with the increasing burden of cognitive ageing if there are clues to amelioration and prevention. Some contributions to cognitive ageing are clearly more open to intervention than others: smoking, exercise, and diet can be changed following advice. Mechanistically, even the contributions from genetics and from childhood intelligence should not be looked on too pessimistically; even these factors have mechanisms which might afford interventions.

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