INSIGHTS INTO THE AGEING MIND: A VIEW FROM COGNITIVE NEUROSCIENCE

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As we grow older, we may grow wiser, but we can also experience memory loss and cognitive slowing that can interfere with our daily routines. The cognitive neuroscience of human ageing, which relies largely on neuroimaging techniques, relates these cognitive changes to their neural substrates, including structural and functional changes in the prefrontal cortex, medial temporal lobe regions and white matter tracts. Much remains unknown about how normal ageing affects the neural basis of cognition, but recent research on individual differences in the trajectory of ageing effects is helping to distinguish normal from pathological origins of age-related cognitive changes.

EXECUTIVE PROCESSES
General purpose cognitive mechanisms for goal-oriented organization and manipulation of information stored in working memory, and for switching among several tasks and sources of information.

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Behavioural research on ageing has mapped contrasting patterns of decline and stability in cognition across the adult lifespan. Both cross-sectional and longitudinal studies find robust declines in abilities such as encoding new memories of episodes or facts, working memory (the simultaneous short-term maintenance and manipulation of information involving EXECUTIVE PROCESSES) and processing speed (the speed with which information can be processed). By contrast, short-term memory (a component process of working memory), autobiographical memory, semantic knowledge and emotional processing remain relatively stable. This variable vulnerability of human abilities across the adult lifespan indicates that ageing has distinctive effects on the neural systems that subserve various abilities.

Understanding age-associated changes in cognition is challenging for several reasons. First, it is often difficult to separate the effects of normal ageing from those of pathological processes that compromise cognition. Most older adults experience some form of age-related neural pathology, because ageing is associated strongly with risk for Alzheimer's disease, Parkinson's disease, diabetes, hypertension and arteriosclerosis. However, research involving highly select and healthy older adults indicates that even in the best case, normal ageing is associated with changes in the neural basis of cognition. Second, because age cannot be experimentally manipulated, conclusions regarding the effects of ageing are necessarily correlational. Third, studies of ageing are often based on cross-sectional comparisons between age groups, to avoid the time and expense of longitudinal research. Few studies have followed individuals from young adulthood into old age, although an increasing number of studies have examined longitudinal changes above the age of 60. Fourth, many brain and mental changes occur in parallel during ageing, and correlational approaches make it challenging to relate particular changes in the brain with particular mental changes. In an effort to infer causal relationships with ageing, researchers attempt to show that age is related to some, but not other, neurocognitive functions. Even with these challenges, advances in brain imaging methods have allowed unprecedented insights into the neural correlates of healthy ageing. This review summarizes recent work in the cognitive neuroscience of ageing, with an emphasis on human neuropsychological and neuroimaging research, that demonstrates the varied nature of age-related neural and psychological changes. We discuss several of the most pressing issues in the cognitive neuroscience of ageing in an attempt to sketch a research agenda for the future.

Box 1 | **Measurement issues in the study of ageing**

Inferences about age-related changes in cognition depend on how changes are measured and on the individuals being sampled. The literature is dominated by cross-sectional comparisons of young adults in their 20s and older (60–80) adults, because these are the most efficient comparisons. Cross-sectional studies, however, are potentially confounded by cohort differences and might therefore overestimate age-related differences[119,120]. Cohort differences are group differences that result from historical influences, such as educational opportunity, cultural factors and socioeconomic status. By contrast, longitudinal studies might underestimate age-related changes because of practice effects and selective attrition. At younger ages and at shorter retest intervals, practice effects are particularly likely to diminish the measurement of age-related changes[7,118]. When patterns of age-related decline and stability are both observed within a cross-sectional sample, alternative explanations involving cohort effects must account for both patterns of results. Differences in recruitment methods might also affect estimates of age-related change. Studies that test participants in their homes, in senior centres or in care-giver facilities are likely to recruit fewer cognitively intact individuals and might overestimate the effects of normal ageing through the inclusion of individuals with various pathologies. Conversely, recruitment methods that place high demands on older people, such as volunteering to come to a university for testing, might over-represent the highest performing older adults.

Behavioural research

A large body of behavioural research on the effects of ageing on human cognition has found at least three descriptive patterns of age-related change in cognitive behaviour — life-long declines, declines that occur late in life, and relative stability across life. The contrasts among these patterns indicate that, although ageing might have global effects, it influences certain cognitive functions disproportionately[1].

Life-long declines. Functions that are thought to be basic mechanisms of the cognitive information processing architecture, such as processing speed, working memory and encoding of information into episodic memory, tend to decline across the adult lifespan[2], although cross-sectional and longitudinal data sets have produced different results (BOX 1). In two cross-sectional studies that sampled individuals from each age decade from 20 to 80 and matched younger and older adults for education, health and demographic variables, processing speed, working memory and episodic memory showed linear life-long declines with little or no evidence for accelerated decline in the later decades[3,4]. In the cross-sectional data from the Seattle Longitudinal Study, linear age-related declines were observed for speed, episodic memory, spatial ability and reasoning[5] (FIG. 1). In longitudinal comparisons, age-related changes from age 20 to 60 tend to be small or non-existent, with speed of processing showing the largest change, whereas changes after the age of 60 have a slope that is roughly equivalent to that found in cross-sectional data[5–7]. In some cases, the age-related slope is curvilinear, with a more rapid decline at older ages[5,6]. When performance is plotted as a function of time to mortality, there is an acceleration of cognitive decline that begins 3–6 years before death[8,9]. This acceleration indicates that pathology influences estimates of age-related cognitive changes in advanced age, whereas normal ageing processes might be manifest in linear slopes.

Late-life declines. Well-practiced tasks or tasks that involve knowledge show little or no decline in performance until very late in life. In the case of short-term memory, which involves phonological storage and is most often measured by the digit span task, in which an ordered series of digits is heard and then repeated, most of the adult lifespan is characterized by slight declines, with sharper declines observed after the age of 70 (REF. 10). Measures of vocabulary and semantic knowledge are also stable until late in life, in both cross-sectional and longitudinal studies[4,5]. Longitudinal studies tend to show greater declines in vocabulary after the age of 60 than do cross-sectional studies[5]. As before, these accelerated declines are probably due to the influence of disease processes.

The relative stability of semantic memory and knowledge until late in life indicates that life experience might breed knowledge, and that the combination of these might lead to the wisdom that is often exhibited by older adults[11]. One possibility is that older adults use preserved knowledge and experience to form more efficient or effective strategies when performing tasks in which younger adults rely on processing ability[12–14].

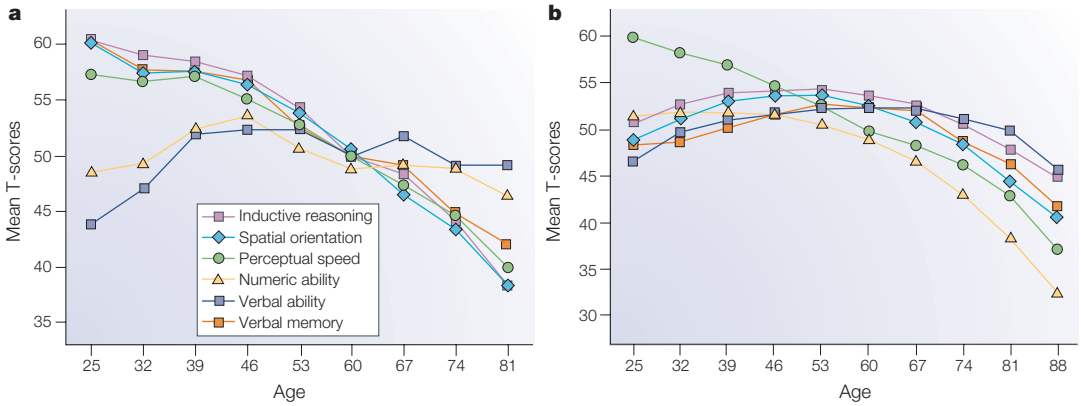

Figure 1 | **Cross-sectional and longitudinal estimates of age-related change in cognition. a** | Cross-sectional data from the Seattle Longitudinal Study. Declines are evident in all domains, with the exception of preserved verbal and numeric ability. **b** | Seven-year longitudinal data from the same study. Declines are evident in all domains after age 55, with only processing speed displaying declines before 55. Reproduced, with permission, from REF. 5 © (1996) Cambridge University Press.

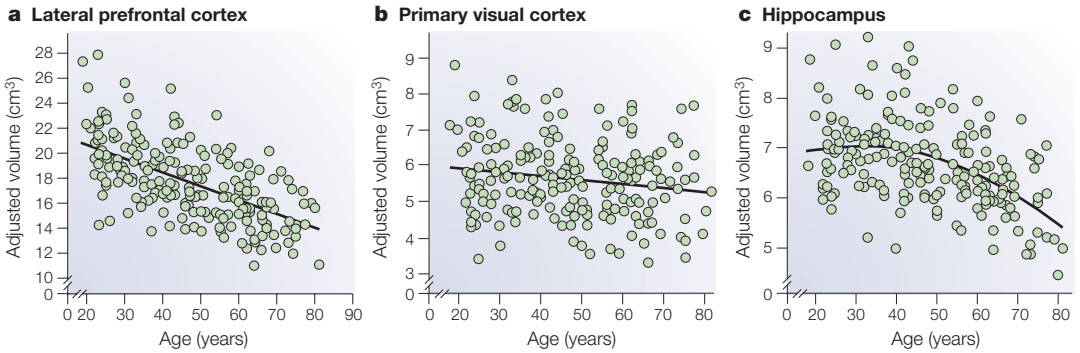

Figure 2 | **Cross-sectional estimates of age-related volumetric change in lateral prefrontal cortex, visual cortex and hippocampus measured with magnetic resonance imaging.** Points on each scatterplot indicate volumetric estimates from individuals, and the line of best fit is shown. Lateral prefrontal cortex volume declines steadily across the adult lifespan, while hippocampal volume has a curvilinear slope, with its largest declines occurring after age 60. Other areas, such as primary visual cortex, have only slight age-related volume declines. Data from REF. 25; figure courtesy of N. Raz.

Life-long stability. Not all cognitive abilities decline during adult development. Autobiographical memory, emotional processing and automatic memory processes seem to be unchanged throughout life. Autobiographical memory for one's life events seems to be preserved throughout much of adulthood and the same general pattern of recall is seen even in centenarians[15]. Performance on 'theory of mind' tasks, which involve the attribution of mental states to other individuals, also remains intact in old age[16]. Older adults seem to pay as much or more attention to their emotional lives as do younger adults, selectively attending to the emotional content of memories and particularly to positive emotional memories[17]. Implicit memory, defined as the unconscious influence of previously encountered information on subsequent performance, is often stable with age or shows only slight age-related changes[18]. Using a procedure to separate the effects of effortful and automatic processes on memory, Jacoby and colleagues have found that automatic feelings of familiarity continue to be relied on even when effortful recollection fails with age[19]. These studies involve only comparisons between college-aged and very old adults, but indicate that overlearned or automatic processes are unchanged throughout life, congruent with the finding that age-related changes in recognition performance, which relies heavily on automatic processes, show relatively small effects[18,20].

Age-related neural changes

The emerging cognitive neuroscience of ageing has been concerned with the question of how changes in neural structure and function map onto age-related behavioural changes. In attempting to understand the neurobiological aspects of ageing, researchers hope to distinguish normal from pathological ageing and to develop behavioural, pharmacological and technological therapies for each.

In post-mortem and *in vivo* studies, the brains of older adults tend to have lower volumes of grey matter than do the brains of younger adults[21,22]. These volume declines seem to result not from cell death, but rather from lower synaptic densities in older adults[23]. Neocortical synapse density declines steadily between the ages of 20 and 100, and, by extension, synaptic density in non-demented older humans would reach the reduced density that is seen in Alzheimer's disease by the age of 130 (REF. 24). However, regional changes in volume are not uniform, with some regions, such as the prefrontal cortex (PFC) and medial temporal structures, being particularly affected by either normal or pathological ageing, and other regions, such as the occipital cortex, remaining relatively unaffected[22,25–27] (FIG. 2).

Normal and pathological ageing. The differential effects of ageing on specific brain regions support a two-component view of ageing[28]. The first component involves changes in the FRONTOSTRIATAL SYSTEM, with decreases in dopamine, noradrenaline and serotonin, and declines in the volume and function of the PFC[25,29]. Frontal white matter tracts also undergo an age-related loss of integrity that might affect memory circuits involving the frontostriatal cortices[30]. These changes are observed even in individuals without dementia symptoms or hypertension, develop gradually throughout adulthood and are correlated with age-related declines in behavioural memory measures. All of these patterns indicate that such frontostriatal changes are a consequence of normal neurocognitive processes that are related to ageing. The dopaminergic deficits that accompany Parkinson's disease might provide a model for normal age-related cognitive changes in the frontostriatal system, as dopamine depletion in this system reduces the speed of processing, thereby affecting working memory, and this results in deficits in strategic memory[28]. In keeping with this possibility, recent computational models have found that age-related cognitive deficits can be accounted for by changes in a gain parameter modelled after declines in dopamine levels in PFC[31,32]. However, patients with Parkinson's disease do have lesions in the entorhinal cortex, the CA2 hippocampal region and the amygdala, although these lesions are not associated with overt intellectual dysfunction[33]; so, the severe dopaminergic dysfunction of Parkinson's disease might have more widespread effects than are observed in normal ageing.

FRONTOSTRIATAL SYSTEM
The frontal lobes and the basal ganglia (striatum and other related structures) are powerfully interconnected by several anatomically segregated loops from the frontal cortex to the striatum through the thalamus and back to the frontal cortex. So, many motor, cognitive and emotional actions are mediated by interactions among the components of this frontostriatal system.

Box 2 | **Mild cognitive impairment**

Mild cognitive impairment (MCI) is a transitional stage between normal ageing and dementia in which a patient presents memory complaints and poor performance on memory tasks, but does not meet the diagnostic criteria for Alzheimer's disease[123]. In a sample of normal older adults, approximately 3–5% of individuals will develop MCI each year[124]. There is increasing evidence that individuals with MCI have a greatly increased likelihood of progression to Alzheimer's disease, with an annual rate of progression of 10–15% (REF. 123)**. In contrast to the normal age-related volumetric declines in subiculum and dentate gyrus, the entorhinal cortex shows declines in patients with Alzheimer's disease and in individuals with MCI relative to healthy older adults[85,125]. Individuals with MCI exhibit an increase in neurofibrillary tangles in the temporal lobes relative to normal elderly subjects that is correlated with their poorer memory performance[126], indicating that MCI is characteristic of the prodromal stage of Alzheimer's disease[127]. By following participants after initial imaging and observing their progression from normal status to MCI and from MCI to Alzheimer's disease, researchers have found that entorhinal cortex volume and metabolism are reduced in those participants who subsequently develop MCI or Alzheimer's disease[34,35,124].**

The second component involves changes that occur primarily with pathology associated with Alzheimer's disease, beginning with a loss of volume in the entorhinal cortex, an important relay between the hippocampus and association cortices, and progressively affecting the hippocampus proper. The progression from healthy ageing to frank Alzheimer's dementia occurs in a subtle and graded fashion for perhaps a decade or longer, while pathological changes in the entorhinal cortex begin before clinical diagnosis of Alzheimer's disease[34,35]. So, individuals in the prodromal stage of pathology could often be inadvertently included in samples of apparently normal elderly subjects[36]. However, behavioural measures of cognitive impairment can be used to predict progression from healthy ageing to mild cognitive impairment (MCI) to Alzheimer's disease, so that individuals with MCI can be selectively excluded on the basis of such performance (BOX 2).

PFC and striatal circuits. On the basis of similarities between the behavioural deficits that are exhibited by older adults and those shown by patients with frontal lesions, such as a failure to suppress interfering information, making perseverative errors and decreases in working memory capacity, neuropsychologists speculated that prefrontal deficits were the underlying cause of cognitive ageing[27,37]. Subsequent research has shown that structures of the PFC undergo the largest age-related volumetric changes in adulthood[21,22,38], with an estimated average linear decline of about 5% per decade after the age of 20 (REF. 25). In healthy older adults, the largest declines in volume are in lateral regions of the PFC[39]. By contrast, patients with Alzheimer's disease show the greatest degeneration in the inferior PFC[40], although deterioration of the PFC is not observed early in the disease[41]. These volume declines are probably due, in part, to decreased synaptic density in the PFC with ageing, which is observed in both monkeys[42] and humans[43]. Smaller, but reliable, age-related declines have been found in the human striatum, an area that has extensive connections to the PFC and is responsible for a large proportion of dopamine production, and might therefore affect cognitive processes that are subserved by dopamine-dependent circuits. Cross-sectional studies find that striatal volume declines by about 3% per decade[44], and longitudinal studies produce even larger estimates of change[26].

In keeping with these volumetric changes, various neurotransmitters in the PFC and striatum undergo age-associated changes. Dopamine concentration[45], transporter availability[46] and dopamine D2 receptor density[29,46] all decline with age. Age-related declines of about 8% per decade in D2 receptors begin by age 40 and are associated with lower glucose metabolism in the frontal cortex, as well as with hypometabolism in the anterior cingulate cortex, temporal cortex and caudate nucleus[29,47]. Serotonin receptor ($5\text{-}HT_2$) availability in the frontal cortex also declines with age and is correlated with striatal declines of dopamine receptors[48], although serotonergic declines seem to be largest in mid-life, with smaller declines in later life[49].

Volumetric and neurotransmitter changes in the PFC and the striatum have been associated with age-related declines in cognitive performance. PFC volume was negatively correlated with perseverative errors on the WISCONSIN CARD SORTING TASK (WCST)[38] and positively correlated with a composite measure of FLUID INTELLIGENCE[50]. In rhesus monkeys, the use of noradrenaline agonists in the PFC can mitigate age-related cognitive deficits[51]. Treatment of aged rhesus monkeys with a D2 receptor agonist reduced the decline in performance on a delayed memory task[52]. Positron emission tomography (PET) imaging of D2 receptors in humans has found a correlation between receptor availability and performance on attention and response inhibition tasks and on the WCST, and have also shown that striatal D2 receptor binding accounts for a greater amount of variation in performance on processing speed and episodic memory tasks than does chronological age[53,54].

Functional magnetic resonance imaging (fMRI) and PET studies have shown that subregions of the PFC subserve executive processes invoked by increases in working memory demand[55,56], attempts to control interference from recently presented but currently irrelevant information[55,57], selecting among competing response alternatives[58], switching among multiple task goals[59,60], and strategic episodic encoding and retrieval[61,62]. In keeping with the hypothesis that differences in prefrontal function underly age-related differences in memory performance, PET and fMRI studies show that older adults tend to exhibit less PFC activity during executive processing tasks than do younger adults[63–65], although the PFC subregions that are affected differ across tasks, and older adults sometimes show increased activity in PFC regions not activated in younger adults[66,67]. These increases in PFC activity often occur in areas contralateral to those activated in the young, a pattern — referred to as reduced hemispheric asymmetry — which indicates that such additional activations aid processing by older adults[66]. While performing a working memory task, older and younger adults had similar activations in ventrolateral PFC, but older adults had reduced activation in dorsal PFC and greater activation in left rostral PFC at

WISCONSIN CARD SORTING TASK
A test that is used to measure behavioural flexibility in which subjects receive cards with different symbols and are asked to sort them by a certain feature (such as their colour). After the rule is learned, the subjects, without warning, are required to 'shift set' and sort them by a different feature (such as the shape of the symbols). People with prefrontal cortex lesions show impaired performance on this task and 'perseverate' — they carry on sorting the cards by a particular feature despite being told that it is incorrect.

FLUID INTELLIGENCE
The ability to reason rapidly about new problems, as contrasted with crystallized intelligence, which involves the use of previously acquired semantic or procedural knowledge.

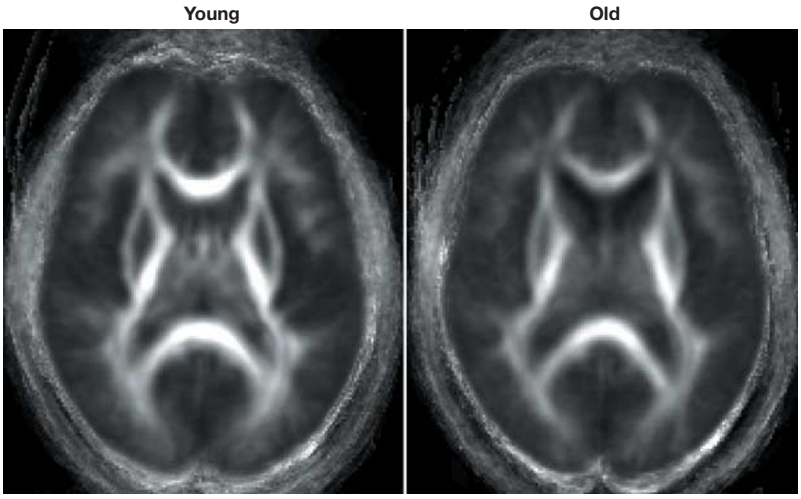

Figure 3 | **Diffusion tensor images of anisotropy of white matter in young and normal elderly subjects.** Group-averaged diffusion tensor images of anisotropy of white matter in young and normal elderly. Parallel movement of water molecules through white matter results in anisotropic diffusion, with greater anisotropy (and so greater white matter density) indicated by brighter areas. Older adults tend to show decreased white matter integrity compared with younger adults, with the greatest age-related declines occurring in anterior cortex. Data from REF. 30; figure courtesy of R. Buckner.

high memory loads[68]. In a condition in which recently presented items were likely to interfere with working memory, older adults showed more behavioural interference and lower activation in left inferior PFC than did younger adults, indicating that older adults were unable to control such interference[69]. In a task-switching experiment, older adults performing a single task activated the dorsolateral and medial PFC regions that were recruited by younger adults switching among several tasks[70]. In general, the pattern of results indicates that older adults experience greater difficulty than younger adults in performing executive processes, and that this difficulty sometimes manifests as a failure to activate PFC regions and sometimes as increased recruitment of PFC regions under relatively easy conditions.

White matter. Ageing affects not only grey matter density, but also white matter density and the number of white matter lesions[71,72]. Diffusion tensor imaging (DTI) (BOX 3) studies have found that the greatest age-related alterations in white matter are in the PFC and the anterior corpus callosum (REFS 30,73 and Stebbins, G. T. *et al.*, personal communication), although all regions show some age-related decline in white matter integrity[30,74] (FIG. 3). These white matter changes seem to be related to normal ageing, as a comparison of patients with Alzheimer's disease and normal elderly subjects showed no selective effects of Alzheimer's disease on frontal-lobe white matter[30]. White matter abnormalities are associated with poor performance on tasks of processing speed, executive function and immediate and delayed memory, but not with declines in general intelligence measures[75]. Age-related decreases in frontal white matter coherence measured with DTI are correlated with decreases in processing speed and reasoning ability (Stebbins, G. T. *et al.*, personal communication). These findings support an interpretation in which age-related changes in the grey and white matter of the frontal cortex mediate behavioural patterns of cognitive ageing in non-demented older populations. The loss of white matter integrity with age probably influences the interaction of the PFC with structures such as the hippocampus and striatum.

Box 3 | **Imaging white matter**

Diffusion tensor imaging (DTI) is a technique that uses magnetic resonance technology to detect the direction and magnitude of water diffusion through cellular tissues *in vivo*[121]. The direction of diffusion is constrained by the organization of the tissues. Cerebrospinal fluid allows near-random diffusion, grey matter cell membranes and organelles impede diffusion to a medium degree, and highly-organized white matter tracts greatly constrain the direction of diffusion. So, directional diffusion within and across three-dimensional volumes in the brain can be used to measure integrity and coherence of white matter tracts and their relation to cognition[122].

Hippocampus and medial temporal lobes. The importance of the hippocampus and related medial temporal lobe (MTL) structures to declarative memory makes them of particular interest for understanding age-related memory changes[76]. In contrast to the relatively large age-related changes that occur in the PFC and frontal white matter tracts, studies of the human hippocampus and adjacent MTL structures have observed relatively slight age-related changes in the absence of Alzheimer's disease[25]. Anatomical studies in humans, monkeys and rodents have found that there is no loss of neurons in hippocampal CA subregions and the parahippocampus with age[77–79], that dendritic growth continues until after the age of 90 in humans[80] and that functional neurons continue to be generated in aged rodents[81]. Nonetheless, the results of structural MRI research show a 2–3% per decade decline in the volume of the hippocampus and the parahippocampal gyrus[25,82], which might increase to a 1% per annum decline after the age of 70 (REF. 83). These small volume declines are unrelated to cognitive function over most of the adult lifespan; however, after the age of 60, hippocampal volume tends to predict explicit memory performance[38,84]. Recent MRI studies have been able to measure the volumes of individual hippocampal subregions in non-demented elderly subjects and in patients with Alzheimer's disease. These studies show that although the entorhinal cortex and CA1 region are preserved, the subiculum and dentate gyrus show age-related declines in non-demented individuals[85]. This result is substantiated by post-mortem observation of selective age-related neuronal loss in these two subregions[79]. Advances in analytic MRI techniques allow researchers to 'unfold' the human hippocampus, opening the way for more specific characterization of age-related changes in separate hippocampal regions[86].

Functional imaging studies of memory have found that even in healthy older adults, activity in the left hippocampus is decreased relative to younger controls during tasks that require maintenance of pictures, encoding of subsequently remembered words, and representation of conjunctions of stimulus features[87–90] (FIG. 4); hippocampal activation is further decreased in patients with Alzheimer's disease relative to healthy

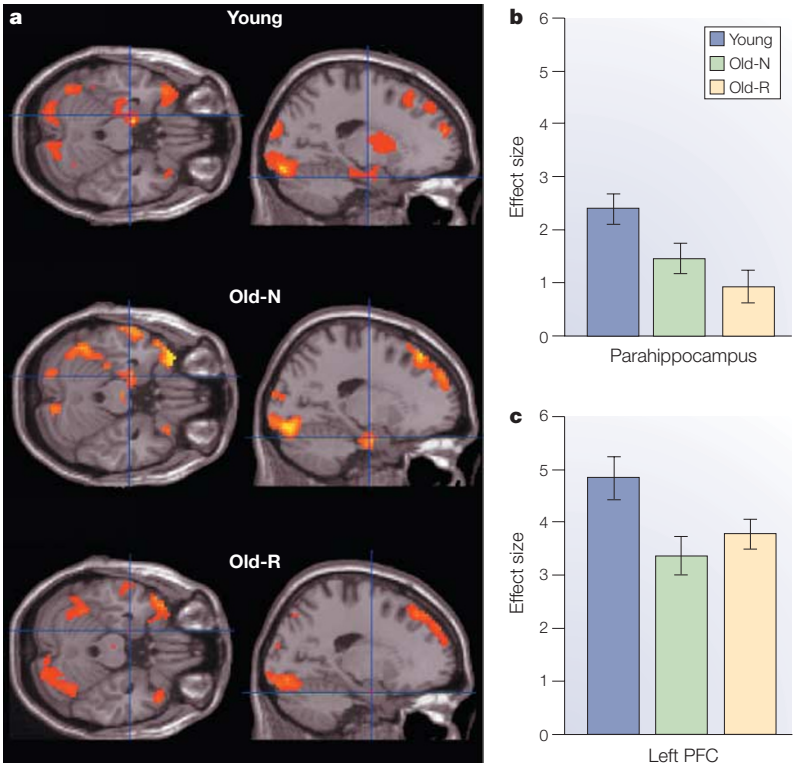

Figure 4 | **Functional magnetic resonance imaging activations for subsequently remembered words. a** | Young adults and older adults with normal memory performance (old-N) exhibit similar activation in the parahippocampus, while older adults with reduced memory (old-R) exhibit less parahippocampal activation. **b**, **c** | Group comparison of effect sizes (percent signal change) in parahippocampus (**b**) and left prefrontal cortex (PFC) (**c**). Bars indicate standard errors. Modified, with permission, from REF. 87 © (2003) Oxford University Press.

elderly subjects[91]. In all of these fMRI studies, healthy older adults also showed changes in prefrontal activation relative to young adults, indicating that hippocampal activity in normal ageing is part of a circuit that involves the PFC. Reductions in hippocampal function could be reflected in modulations of PFC activation as older adults attempt to process task information by alternative routes[92,93]. Another memory-related structure in the MTL, the amygdala, is less active in older adults than in younger adults in response to emotionally negative stimuli, but exhibits similar activity among age groups to emotionally positive stimuli[94,95], and shows little volume loss with age[96,97]. These results support the behavioural findings that there is diminished emphasis on negative emotions with age[17] and indicate that amygdala function remains largely intact with age, although there is evidence that it might be differentially modulated by frontal regions in old age[98].

These results indicate that normal ageing has minimal structural effects on the hippocampus and adjacent MTL, although age-related functional changes might affect circuits that involve interactions between the PFC and the hippocampus, thereby causing age-related decrements in memory function that is mediated by hippocampal neurons. Pathological processes, by contrast, begin by affecting the entorhinal cortex, thereby crippling hippocampal involvement in memory.

Individual variability

A common finding in cognitive ageing that is observed behaviourally and with *in vivo* imaging is that decreases in function tend to be accompanied by increases in variability[99]. It has been argued that increased variability with age is an indication of pathological processes, whereas similar variance in younger and older samples indicates normal ageing[85,100]. However, there are several potential scenarios in which increased variability could accompany normal ageing. These include increases in strategic options through life-long learning, plasticity in response to varied life experience, or greater variation in physical or mental activity levels (for example, before and after retirement). Similarly, pathological processes could lead to variance in older groups that is equivalent to, or even smaller than, that in younger groups. For example, if Alzheimer's disease severely limits retrieval speed, and therefore constrains the implementation of various strategies, patients' performances might be less variable. The effective ceiling for performance could be lower for older age groups and a restricted range of scores could lead to decreased variance. Rather than comparing variability between age cohorts, searching for regularities in individual differences within older populations is likely to inform a distinction between normal and pathological ageing processes.

In studying variability within ageing populations, several types of variability might be of interest[101,102]. First, variability across individuals, often referred to as individual differences, might include different life experiences, genetic influences, preferred strategies and susceptibility to neuropathology. Such individual differences can be quite large, with some older adults performing as well as their younger counterparts, sometimes creating bimodal distributions in performance for older populations[103,104]. Second, variability within individuals across tasks might change with age. The dedifferentiation hypothesis, which postulates that ageing affects many behaviours simultaneously through a 'common cause' (such as a decline in processing speed or a sensory deficit), is supported by reduced variability of this type, accompanied by increased correlations among cognitive measures[1,4,105]. Third, longitudinal studies allow researchers to measure variability within individuals across time, referred to as stability or reliability. Such studies often find remarkable stability before the age of 60, with increased variability occurring only in later life[5,7,106]. Even after the age of 60, however, there are substantial individual differences in rates of change, with some individuals improving, some being stable and others declining[106].

Variability within individuals across tasks and time has been examined in humans primarily through behavioural studies. Owing to the expense and difficulty of performing longitudinal or large sample research with imaging techniques, cognitive neuroscientists have largely examined individual differences in older adults. Using neuropsychological measures of frontal function and MTL function, Glisky and colleagues characterized older adults with low frontal function but high MTL function, and vice versa[107].

Box 4 | **Looking after the ageing brain**

Recent research has identified several potential predictors of accelerated cognitive decline in older adults. Many of these involve lifestyle choices that can be controlled by individuals who are concerned about the risk of developing cognitive difficulties.

Stay intellectually engaged

At best, mental activity seems to protect against age-related declines and progression to Alzheimer's disease. At worst, it increases an individual's baseline level so that age-related declines begin to affect everyday functioning later in life[12,128–130]. Enriched environments stimulate neurogenesis in aged rats, indicating a possible mechanism for the benefits of cognitive stimulation[131].

Maintain cardiovascular physical activity

Exercise aids executive function[132], reduces declines in tissue density in frontal, parietal and temporal cortex[133], and might have global effects on the brain[134].

Minimize chronic stressors

Proneness to distress, measured by the personality trait of neuroticism, is associated with increased risk of Alzheimer's disease and a faster rate of cognitive decline[135]. Increased glucocorticoid levels, which accompany stress, might damage hippocampal neurons over the lifespan[136]. Cortisol administration reduces glucose metabolism in the hippocampus in normal older adults[137].

Maintain a brain-healthy diet

A diet that is high in poly- and mono-unsaturated fatty acids (as found in fish and olive oil)[138,139], vitamin E (REF. 140) and polyphenols and antioxidants (found in citrus and dark-skinned fruits and vegetables)[141] might slow cognitive decline and prevent progression to Alzheimer's disease.

HAEMODYNAMIC RESPONSE FUNCTION
The time course of changes in blood flow, volume and oxygenation level that occur in the brain in response to neural activity.

Those with low frontal function performed more poorly on measures of explicit recollection[108] and on source memory judgements[107], indicating that individual differences in frontal-lobe integrity account for much of the variance in older adults' performance.

These neuropsychological differences are also observed using imaging techniques. The HAEMODYNAMIC RESPONSE FUNCTION, on which fMRI signal is based, might vary with age and could therefore account for some age-related individual differences in inferred neural activity, although the age differences seem to be minimal in motor cortex and limited to reductions in amplitude in visual cortex in non-demented elderly subjects[109]. Nonetheless, when behavioural performance is similar, functional activations associated with that behaviour often differ among individuals, and such variability is often larger in older than in younger samples[100]. In some cases, younger and older adults exhibit qualitatively different relationships between functional activity and behaviour; for instance, in a working memory task, increases in frontal-lobe activation were associated with decreases in reaction time in younger adults, but with increases in reaction time in older adults[63]. This indicates that age-related declines might affect the neural correlates of processing efficiency and that higher activation levels might be necessary for older adults to maintain the same level of performance as their younger counterparts[63].

A topic of great interest in the study of age-related individual differences is the characterization of those older adults who tend to perform as well as younger adults[92,104,107]. What is unique about these 'successful seniors' and how might we improve the likelihood of mimicking their success (BOX 4)? Neuropsychological studies indicate that MTL function does not distinguish high-performing from low-performing elderly subjects in source memory or strategic memory tasks, but frontal function does[107,108]. Neuroimaging studies have found that elderly individuals often show greater functional activation of brain regions (usually in the PFC) that are less active in younger adults, and that such additional activations are often seen only in high-performing older adults[66,92,110,111]. For instance, in a strategic encoding task, high-performing older adults exhibited bilateral PFC activation, whereas younger adults and low-performing seniors showed only left-sided PFC activation[93] (FIG. 5). Such additional activations in complementary PFC regions might reflect compensatory activity, possibly due to the engagement of general-purpose mechanisms to assist in resolving difficult task demands[66,112], to changes in neural plasticity with ageing[111] or to strategic differences in the subgroup of resilient older adults[113].

Additional activations in older adults are not always exhibited only by those with better performance, and can be modified, in part, by providing older adults with a specified strategy, indicating that additional areas of activation might sometimes represent non-selective recruitment of irrelevant or competing brain regions[65]. Such non-selective recruitment could occur if a breakdown in inhibitory connections accompanies ageing[30,114]. One possibility is that high-functioning older individuals might show neural compensation, whereas their low-functioning counterparts, who experience failures of inhibition, show decreased activations or non-selective recruitment. It might be expected that non-selective recruitment in low-functioning older adults would co-occur with deterioration of white matter integrity, resulting in disinhibition of competing areas. In general, the evidence indicates that individual differences in older populations are due to variability in the severity of deficits in the two components identified

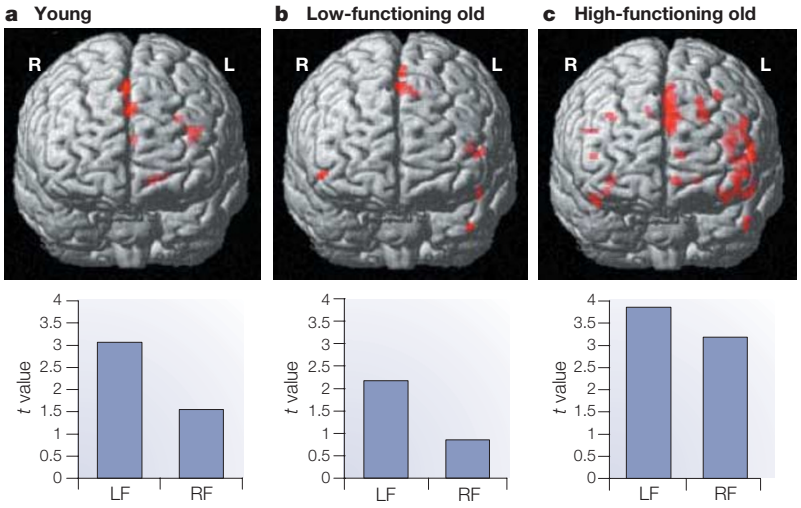

Figure 5 | **Neural activations in prefrontal cortex during a memory encoding task.** Activations are shown for young adults, low-performing older adults and high-performing older adults. Low-performing older adults exhibit a similar pattern as do young adults, with lower overall levels of activation. High-performing older adults exhibit greater bilateral activation. RF, right frontal; LF, left frontal. Data from REF. 93.

earlier. Individual differences in normal ageing are probably due to variability in PFC integrity, and individuals might also differ in their susceptibility to the pathology of Alzheimer's disease. Variability in pathology might have a genetic component, as recent studies have found that polymorphisms in the gene for brain-derived neurotrophic factor are associated with Alzheimer's disease, poor memory performance and poor hippocampal function[115,116].

Conclusion

As this review indicates, much progress has been made in characterizing the behavioural and neural changes, particularly in memory systems, that are associated with advancing age. Nonetheless, much remains unknown and researchers are grappling with several controversial questions. Are age-related declines due to normal or pathological processes? It is difficult to separate the effects of normal ageing from the effects of age-associated diseases with long, progressive preclinical histories. Alzheimer's disease and Parkinson's disease have specific aetiologies, but healthy older adults with intact behaviour also seem to show age-related neural changes. Structural imaging techniques show that grey and white matter in the PFC and in subregions of the hippocampus lose volume in ageing non-demented humans[30,38,85]. Work with a popular animal model of ageing, the nematode *Caenorhabditis elegans*, has found gradual age-related degeneration of muscle tissue, but preservation in the nervous system, thereby providing hope that the cognitive effects of ageing are not inevitable[117].

Do normal age-related differences occur throughout adulthood, or only after some critical age? Although longitudinal studies of behaviour find little evidence for age-related decline before the age of 60 (REFS 5,106), cross-sectional studies in healthy samples find linear declines across the lifespan[4], and studies that combine cross-sectional and longitudinal methods find evidence of age-related memory decline[118]. Early results from longitudinal MRI research show volume loss in the striatum throughout adulthood, indicating a gradual age-related change in dopaminergic pathways[26]. There is, however, little information about age-related changes that occur between the ages of 30 and 60, and this limits our ability to distinguish changes that occur across the adult lifespan from changes that occur late in life. Even normal age-related changes might prove to be reversible and might be mitigated through lifestyle changes or with therapeutic techniques.

To what extent does individual variability in behavioural, genetic and neurobiological markers of cognitive ageing reflect normal and pathological ageing? More attention should be paid to variability in older populations rather than merely to differences between age groups. Emphasis on determining the bases of individual differences in older populations should continue, but investigators should also seek to understand variability within individuals across tasks and across time.

What neural mechanisms do age-related differences in anatomy and functional activations represent? Anatomical volume losses could have several causes at the cellular level, including loss of synaptic density. The changes in blood flow observed with PET and fMRI are indirect measures of neural activity and could have several underlying causes. Decreased activation with ageing could be due to activity in smaller neuronal populations, greater variance or less synchrony in population firing, decreased neurotransmitter binding, decreased neuronal metabolic activity or failures in afferent excitatory connections, among other possibilities. Increased activations with ageing could be caused by failures of inhibitory connections, for example. These connections between *in vivo* imaging findings and their underlying neural substrates are most likely to be understood in animal models, where both kinds of observation can be made in the same animal, and, to a limited but interesting extent, longitudinal post-mortem studies in which imaging is performed near to death.

To what extent are strategy changes in older adults responsible for, or a response to, neural changes? A number of researchers now suggest that age-related activation changes can be modulated by strategy choice[65,113]. Ageing individuals might adopt strategies in response to declines in cognitive ability or neural deficits. To resolve these possibilities, there is a need to relate neural structure and function more closely to behaviour and to characterize the strategies that are used to perform behavioural tasks. Researchers should emphasize not only age-related neural differences, but also their association with performance. Only when the answers to these questions are resolved will we be able to determine what constitutes normal ageing, and whether normalcy implies the inevitability of cognitive ageing effects. As we seek to understand individual differences in the trajectories of cognitive ageing, we will hope to discover why some individuals show resilience in ageing, and the extent to which such resilience is due to genetic predispositions and to neuroprotective lifestyles.

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Competing interests statement
The authors declare that they have no competing financial interests.

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At-a-glance

- A number of physical and mental changes accompany the developmental process of ageing; some of the most prominent of these involve changes in memory function. This article reviews the main behavioural findings in cognitive ageing research, and the structural and functional brain basis of the memory changes that occur with age.
- Cross-sectional behavioural research has found robust declines across the adult lifespan in the ability to form new episodic memories, to process information quickly and to invoke executive processes, although longitudinal studies indicate that these declines might occur primarily after the age of 60. Semantic memory and short-term memory show remarkable preservation across most of the adult lifespan, with declines occurring only very late in life. By contrast, autobiographical memory, emotional memory and implicit memory are relatively unaffected by ageing.
- Structural changes in both grey and white matter map onto these behavioural changes in memory. The largest volumetric declines occur in the prefrontal cortex, which subserves strategic episodic encoding and executive processes. The loss of anterior white matter integrity and of dopamine receptors in the striatum and prefrontal cortex accompany these volumetric declines, further providing mechanisms for the disruption of circuits that underlie memory function.
- Hippocampal volume declines are less apparent during normal ageing, although declines in functional activations of the hippocampus and surrounding cortex have been observed in healthy older adults. By contrast, pathological processes, such as those that accompany Alzheimer's disease, severely affect hippocampal regions. In particular, entorhinal cortex, which serves as an important relay between the prefrontal cortex and the hippocampus, is disproportionately affected by pathology.
- The differential pattern of age-related changes in the prefrontal cortex and the hippocampus indicates a two-component model of cognitive ageing, with normal ageing primarily affecting prefrontal areas, and pathological ageing affecting medial temporal regions.
- There is, however, wide variability among individuals in the extent, rate and pattern of age-related changes that are exhibited at both neural and behavioural levels. Some older adults have relatively intact memory function and also show patterns of functional activity in the prefrontal cortex that are often interpreted as being compensatory. Through investigation of differences among those older adults that are most resistant to and affected by ageing, researchers hope to determine how normal ageing affects cognition and how these effects might be mitigated.

Biographies

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