OPINION

Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing

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Abstract | Cognitive ageing research examines the cognitive abilities that are preserved and/or those that decline with advanced age. There is great individual variability in cognitive ageing trajectories. Some older adults show little decline in cognitive ability compared with young adults and are thus termed 'optimally ageing'. By contrast, others exhibit substantial cognitive decline and may develop dementia. Human neuroimaging research has led to a number of important advances in our understanding of the neural mechanisms underlying these two outcomes. However, interpreting the age-related changes and differences in brain structure, activation and functional connectivity that this research reveals is an ongoing challenge. Ambiguous terminology is a major source of difficulty in this venture. Three terms in particular — compensation, maintenance and reserve — have been used in a number of different ways, and researchers continue to disagree about the kinds of evidence or patterns of results that are required to interpret findings related to these concepts. As such inconsistencies can impede progress in both theoretical and empirical research, here, we aim to clarify and propose consensual definitions of these terms.

In all parts of the world, the proportion of older adults in our population is rapidly expanding[1]. Advances in medicine and public health measures, rising standards of living, and improvements in education and nutrition have lengthened the human lifespan. Cohort comparisons suggest that the debilitating effects of senescence are increasingly delayed to later ages[2]. Nevertheless, advancing adult age continues to be associated with cognitive decline in many individuals, and major challenges remain in our efforts to understand the mechanisms of cognitive loss versus those of optimal ageing (defined as the situation in which cognitive abilities are preserved throughout ageing).

Research in the cognitive neuroscience of ageing[3] seeks to understand the neural mechanisms of age-related cognitive decline, as well as those of optimal ageing. These mechanisms — that is, the putative causal explanations of age-related changes — presumably exist at multiple levels of analysis (including the genetic, cellular and systems levels). As the field has grown, several specific terms, including reserve[4–6], maintenance[7] and compensation[8–13], have been introduced. These terms have been used both to describe the qualitative and quantitative differences in brain structure and function that occur with age and to advance current theories of the mechanisms of brain ageing and cognitive decline. However, over the years, these terms have been used inconsistently, creating confusion and slowing progress. For example, age-related increases in brain activity have been interpreted as compensation for declines elsewhere in the brain, even when there is no direct association between activity levels and performance in older adults[14,15]. By contrast, other studies have used the term compensation more restrictively to describe situations in which age-related increases in brain activity are directly correlated with better performance in older adults[16]. Moreover, it has also been unclear in the literature how the concepts of reserve, compensation and maintenance relate to one another.

To address this terminological confusion, the authors of this Opinion article met in 2017 and worked to sharpen the definitions of these popular terms. Some differences in opinion about the definitions persist; however, in this article, we emphasize the points of agreement. The terms maintenance, reserve and compensation can of course be applied to aspects of ageing beyond the brain and cognition (such as bone changes). However, here, we focus on their use in structural and functional neuroimaging studies in healthy ageing humans (defined here as ageing in individuals who are apparently free of brain disease), although other related terms and methods are also discussed. Given this focus, the use of the terms maintenance, reserve and compensation in this article should be considered to refer specifically to neurocognitive maintenance, neurocognitive reserve and neurocognitive compensation, respectively. We do not discuss in detail how the mechanisms of reserve, maintenance and compensation interact with pathological processes (but see BOX 1), but it is worth noting that this is an important question and that these three mechanisms may also attenuate pathological processes[17].

Cognitive neuroscience of ageing

Ageing affects neurobiological functions at multiple levels[18]. It can alter genes and gene expression[19–22], interfere with the functions of cells and molecules[23–32] and lead to changes in the overall structure and function of the brain[33,34]. In recent decades, the advent and availability of MRI methods have significantly advanced our understanding of how the brain changes with age at the gross anatomical and functional levels[35–37]. For example, healthy ageing is known to be associated with grey matter volume reductions and functional

Box 1 | **Maintenance, reserve and compensation in Alzheimer disease and mild cognitive impairment**

The trajectory of Alzheimer disease (AD), which progresses from normal cognitive performance to mild cognitive impairment (MCI) and then to full-blown dementia[93] is, by definition, an example of poor brain maintenance. However, the trajectory from healthy ageing to AD is modulated by reserve and compensation[6,94,95]. Studies have reported that β-amyloid deposition — a putative biomarker of AD — is lower in older adults with higher scores on reserve proxies, such as education[5], and in those who participate in cognitively stimulating activities across the lifespan[96]. Even in individuals in whom biomarkers of AD are present, higher scores on reserve proxies are associated with a lower risk of progression from normal cognition to the onset of clinical symptoms[97]. The neural bases of these protective effects remain to be identified.

Functional MRI studies have shown that individuals with MCI[98–100] and carriers of the apolipoprotein E (*APOE*) ε4 allele, a known risk factor for late-onset AD[101], show increased task-related activity in the brain regions first affected by AD: the hippocampus, cingulate and precuneus[102,103]. Some studies have associated greater activity in these regions with better cognition in individuals with MCI[98,100], consistent with compensation. Furthermore, some cognitively normal older individuals with high β-amyloid levels have shown both greater activity in the superior and lateral parietal cortex and the occipital cortex and better memory than older adults with low β-amyloid levels[104].

In some cases, however, hyperactivation may reflect the underlying neuropathology[104] and excitotoxicity rather than compensation. It has been suggested that poor clearance of β-amyloid and tau proteins in the brain contributes to the accumulation of amyloid plaques and neurofibrillary tangles, respectively, and that this increases the production of glutamate and inhibits its recapture[105,106], leading to hyperexcitation. Consistent with this hypothesis, a study found that low doses of an antiepileptic drug reduced hippocampal hyperactivity and improved memory in individuals with MCI[89]. An intriguing possibility is that hyperactivation is, at first, compensatory but later reflects excitotoxicity[99]. Compensatory processes thus might characterize the early course of AD and contribute to its long prodrome. If this is the case, compensatory non-pharmacological interventions could be used to reduce cognitive symptoms. In turn, hyperactivation has the potential to contribute to an early signature of AD, and approaches might be developed to reduce hippocampal hyperactivity or to promote reliance on unimpaired brain networks[107].

alterations in several regions that are crucial for higher cognitive function: that is, the prefrontal, medial temporal and parietal cortices[3,38–40]. Similarly, diffusion MRI methods have shown age-related changes in white matter connectivity between prefrontal and posterior cortical regions and within posterior sensory cortices[41–43]. These age-related declines in brain structure and function are associated with cognitive decline in a variety of domains, including episodic memory, working memory and attention[44,45].

One of the most fundamental and urgent goals of research in the cognitive neuroscience of ageing is to understand why some individuals experience faster cognitive decline than others during healthy ageing[46]. Inter-individual variability in cognitive ageing is striking. Indeed, in cross-sectional studies, some 80-year-old individuals can perform as well as, or better than, some 40-year-old individuals on cognitive tasks that assess functions often impaired by ageing (such as episodic memory)[47]. However, when investigating individual differences among older adults, it is important to consider the limitations of such study designs when compared with longitudinal designs. For example, older participants are typically recruited only from the subset of well-educated people who have aged in relatively good health and are free of brain disease, whereas the young adult samples with which they are compared are more heterogeneous. Cross-sectional study designs can also be contaminated by birth cohort effects, including inter-generational IQ increases (known as the 'Flynn effect')[48,49]. Moreover, cross-sectional designs cannot distinguish between age-invariant and age-related differences in cognitive ability; this is important because it has been shown that a large proportion of the variance in cognitive performance observed among older adults already existed when they were children[50]. Although they have their own limitations[51], longitudinal study designs avoid these problems. It is therefore important to note that longitudinal studies have consistently demonstrated large individual differences in rates of age-related cognitive decline[52,53].

The individual differences in age-related cognitive decline described above undoubtedly reflect a complex interaction between genetic and environmental factors. The outcomes of these factors have been proposed to be partly mediated by three interacting mechanisms: reserve, maintenance and compensation (FIG. 1a). In the case of reserve[6] and maintenance[7] (FIG. 1b), it has been proposed that the processes of age-related neural decline (which include brain atrophy, synaptic loss and white matter degradation) are countered by processes of neural enhancement: that is, the creation, replenishment and repair of neural resources. Specifically, it has been hypothesized that reserve supports the creation of neural resources that help withstand the neural decline and that maintenance supports the replenishment and repair of these neural resources. Neural resources here refers to the brain anatomy and physiology that mediate cognitive processes. In its simplest form, a neural resource could be the grey matter volume of a brain region or the white matter quality of a fibre tract. However, neural resources could also refer to the function of a region, as measured by functional neuroimaging, or the operation of a brain network, as assessed by functional connectivity methods. In the case of compensation (FIG. 1c), the heightened cognitive demands that arise owing to the combined effects of task difficulty and age-related cognitive decline are counteracted by recruiting additional neural resources, including those established by neural enhancement. It is important to emphasize that the mechanisms of reserve, maintenance and compensation are not static but dynamic and modifiable and that it is likely that they are not only responsible for modifying behaviour but are, in turn, modified by changes in behaviour.

Below, we propose one way to define and link the terms reserve, maintenance and compensation to provide greater coherence in an evolving field. Nevertheless, we recognize that these concepts are the subject of continuing debate. Our goal is therefore to initiate an open dialogue about what these three concepts mean. For the sake of simplicity, we use examples involving single brain regions to illustrate our arguments; however, each of the concepts is equally applicable to measures that account for covariance between multiple brain regions, including functional connectivity and multivariate activation patterns[54].

Reserve

We believe that reserve should be defined as a cumulative improvement, due to genetic and/or environmental factors, of neural resources that mitigates the effects of neural decline caused by ageing or age-related diseases. Reserve is hypothesized to result in the accumulation of neural resources before the brain is affected by age-related processes and to take place over a period of years.

A good example of a factor that promotes reserve is education, which improves neural resources during childhood and young adulthood (possibly by enhancing synaptic density[55]) and attenuates age-related cognitive decline in later adulthood[56,57]. The beneficial effect of education on cognitive performance might also be mediated partly by its effects on a range of other outcomes that have also served as proxy measures of reserve, including health, stress, profession and lifestyle. In the ideal case, accumulated reserve is enough to completely offset age-related neural decline; however, in a more typical case, it only attenuates this decline. Presumably, most reserve accumulates during childhood and in young adulthood; however, it may also continue to build up in older age[9], which arguably underscores the importance of intellectual engagement throughout the lifespan.

Some authors have used the more specific terms 'brain reserve' to refer to aspects of reserve that are easily quantified in anatomical brain images and 'cognitive reserve' to refer to aspects that are difficult to detect in anatomical images and either require functional imaging measures or cannot be delineated at the neural level given current technology[6,58]. Given that cognition depends on the brain, we believe that this distinction is somewhat artificial and prefer to use only the term 'reserve'. However, we recognize that different aspects of reserve require different technologies for their measurement and that some cannot be assessed with the current technology (but could be measurable in the future).

Genetic[59] and environmental[6,60] factors, including longer education[5], greater physical activity[61], active participation in demanding leisure activities[62] and bilingualism[63,64] affect individual differences in reserve. Because it is not possible to measure reserve directly, most studies of reserve have focused on a particular proxy of reserve and investigated how individuals with high or low levels of this proxy measure differ in their brain structure or function. For example, functional neuroimaging studies have compared the brain activity of individuals who exhibit high or low scores in IQ, education level or occupational attainment, which are all considered proxy measures of reserve[65]. One such study found that greater cognitive reserve, as measured using IQ and education–occupation as proxies, was associated with lower brain activity in a variety of brain regions (including the superior temporal and superior parietal cortices) during cognitive processing, suggesting that reserve is linked to more

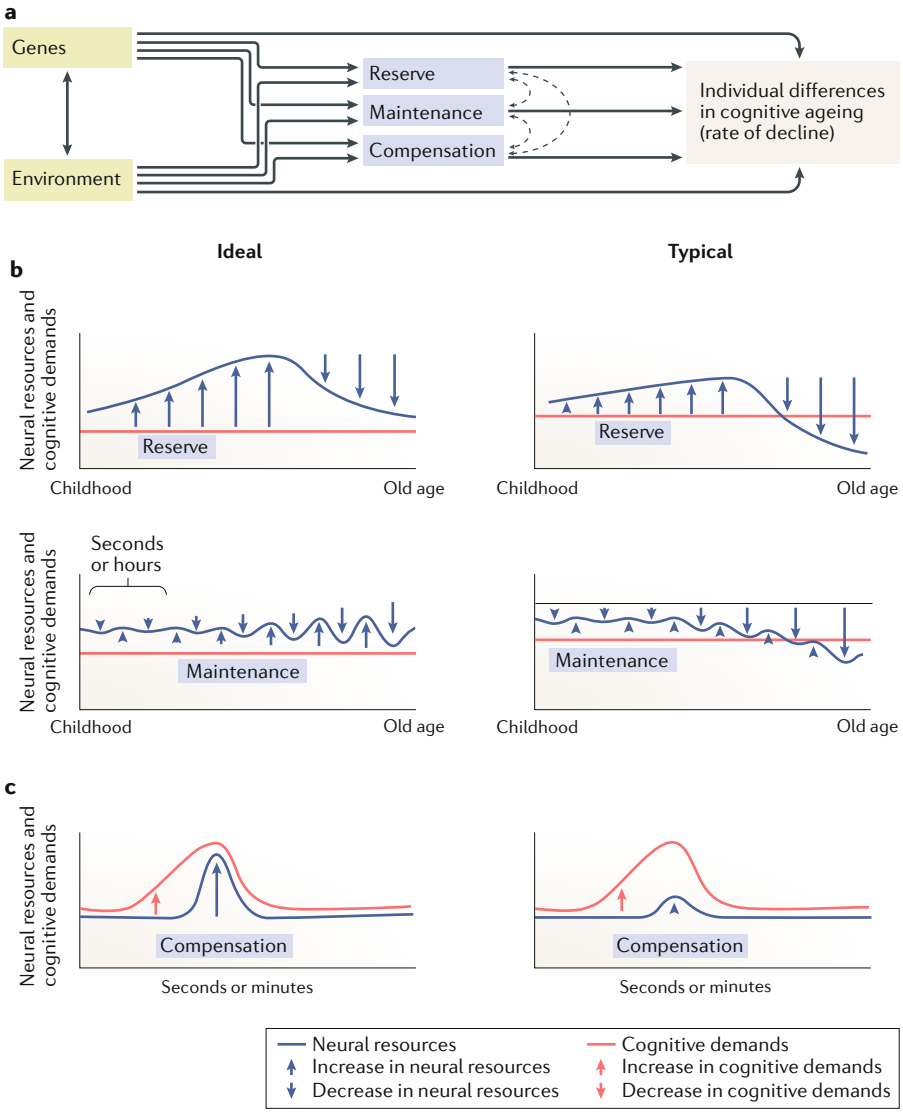


Fig. 1 | **Similarities and differences between reserve, maintenance and compensation.** **a** | Individual differences in cognitive ageing have been attributed to the effects of three interacting mechanisms: reserve, maintenance and compensation. As illustrated in the schematic, these mechanisms are assumed to mediate some (but not all) of the effects of interacting genetic and environmental factors on cognitive ageing. **b** | Schematic charts illustrate the hypothesized changes in neural resources and cognitive demand that occur across the lifespan as a result of reserve and maintenance mechanisms. In the ideal scenario shown on the left, these mechanisms completely counteract the effects of ageing, with resources meeting or exceeding demands throughout life. However, in the typical scenario, they only attenuate the effects of ageing. Reserve and maintenance are both hypothesized to involve an increase in neural resources; however, they differ in terms of whether this increase occurs before or after the effects of ageing on neural function and the timescale of the changes. In the case of reserve, neural resources accumulate beyond what is required to satisfy current cognitive demands, such that when these resources start to decline in old age, cognitive decline is attenuated. It is important to note that although the graph shows resources accumulating during childhood and young adulthood, cognitive reserve can continue to accumulate in old age. In the case of maintenance, processes of neural decline are continuously offset by processes of neural enhancement. Given that neural decline increases in old age, greater maintenance is also required to maintain the same level of performance. The figure shows neural decline and neural enhancement processes in alternation for illustration purposes only, as these processes can occur simultaneously. **c** | Schematic charts illustrate the hypothesized changes in neural resources and cognitive demand that occur during short-term increases in cognitive demands as a result of compensation mechanisms. In the ideal scenario, a task-related increase in cognitive demands is completely counteracted by the recruitment of additional neural resources whereas, in the typical scenario, the additional resource recruitment reduces but does not eliminate the gap between task demands and available resources.

effective use of cerebral networks[4]. It remains debatable what type of variable would serve as a good proxy measure of reserve. However, it is worth noting that it is critical to specify the proxy factors and mechanisms that are assumed to build and constitute reserve a priori when developing one's experiment. If reserve is defined merely as the factor that individuals with greater reserve have and then this factor is used to explain why some individuals have greater reserve, the argument is clearly circular.

When using functional neuroimaging to investigate reserve, it is important to distinguish between the across-individual activity differences that are related to reserve and those that are related to compensation (see below). Differences related to reserve might be expected to manifest as trait-like effects: that is, they would be evident across a range of different cognitive domains and would correlate with multiple independent proxies of reserve, such as IQ and educational level. Individual differences reflecting compensation, by contrast, would be expected to differ according to the nature of the cognitive challenge and to correlate with individual differences in task performance to a greater extent than with proxy measures of reserve. However, complicating the distinction, reserve and the capacity for compensation may interact. For example, highly educated individuals may show different activation patterns than individuals with lower educational attainment because their greater reserve allows them to deploy more effective compensatory processes.

One analytical approach to the measurement of the neural correlates of reserve (and to other concepts that cannot be directly measured owing to current technological limitations) is to regress out (control for) the effects of cognitive performance on neural variables known to affect cognitive decline (including volume and white matter hyperintensities) and then to examine the correlation of the residual neural measures with a hypothesized proxy of reserve (or other concept of interest)[66–68]. Using this approach, one study decomposed variance in episodic memory performance into a component predicted by demographics, a component predicted by pathology (as measured by structural MRI) and a residual reserve component, which was then shown to moderate cognitive decline[68].

In addition, it is likely that different proxy measures of reserve may engage different neural mechanisms and reflect different aspects of reserve, such as neural capacity (the total amount of neural resources available for cognition) and/or neural efficiency (the use of less neural resources — often operationalized as neural activity — to perform a cognitive task)[6,60]. One example of how increased capacity is associated with a proxy measure of reserve is the aforementioned effect of education on synaptic density[55]. An example of an increase in neural efficiency is the development of expertise in a particular domain through training, which in turn is often associated with reduced regional brain activity[69–72]. The development of expertise is associated with the presence of richer and more differentiated conceptual representations, which can attenuate age-related decline in the domain of expertise[6,73–75]. This idea may explain why older individuals can remain highly effective in their specific professional domain[76].

When adults with high levels of reserve, as indicated by one or more reserve proxies, do eventually display cognitive decline, they do so at a rapid rate[77]. It is possible that at some level, the burden of age-related neuronal decline becomes great enough to overcome the protective mechanisms of reserve, resulting in rapid cognitive decline[6,58].

Maintenance

We propose that the term maintenance be used to refer to the preservation of neural resources, which entails ongoing repair and replenishment of the brain in response to damage incurred at the cellular and molecular levels owing to 'wear and tear'[7]. Maintenance occurs throughout the lifespan but may become more critical in old age, as neural deterioration becomes more severe. The timescale of maintenance processes is likely to depend on the neural level at which they take place (molecules, cells or systems). In the optimal case, repair processes fully counteract decline. In the typical scenario, however, repair processes do not completely offset neural deterioration, leading to a gradual process of age-related neural deterioration. Some individuals may be relatively spared from detrimental brain changes in the first place, resulting in a likelihood of displaying high levels of maintenance regardless of the capacity for repair. Thus, the efficacy of maintenance depends both on the magnitude of decline and the efficacy of repair.

The concepts of reserve and maintenance are clearly related to each other but, here, we highlight what distinguishes them: although both involve enhancing current resources, reserve is about augmenting resources beyond their current level, whereas maintenance is about returning them to their former higher level. We acknowledge that reserve has an impact on later maintenance because the accumulation of reserve must be maintained. What may most differentiate reserve and maintenance are the mechanisms by which these factors influence healthy brain ageing and cognition. In the case of reserve, these factors cumulatively influence neural capacity and neural efficiency (and other mechanisms not yet identified owing to limits of technology). In the case of maintenance, these factors influence neural mechanisms of repair and plasticity (and others not yet identified). Therefore, although the concepts of reserve and maintenance are similar, we view them as complementary perspectives on how environmental and biological factors influence brain ageing and cognition.

In principle, it is possible to distinguish different forms of maintenance and for these to be operational to a different extent in different individuals. For example, maintenance can relate to different aspects of the brain, such as the grey matter or white matter, to different neurotransmitter systems or to different brain regions, such as the hippocampus or the prefrontal cortex (PFC). For example, given the link between exercise and white matter integrity[78], it is possible that individuals who exercise regularly maintain white matter integrity better than they maintain other aspects of the brain. However, because there is a close interaction between different brain structures and processes, it is also possible to talk about general brain maintenance. Maintenance is often defined as a relative lack of decline in one or more neural measures and not in absolute terms. Therefore, so-called 'brain maintainers' include individuals who start with above-average levels of a neural measure in early adulthood (such as a larger hippocampus) and maintain these high levels into older age, as well as individuals who start below average and maintain functioning at that lower level. It is also theoretically possible that maintenance mechanisms differ for those who start with high levels of a neural measure and those who start with low levels of the same measure.

The notion of maintenance is consistent with evidence that adults who display stable cognitive performance as they age tend to show minimal brain decline or pathology[7]. For example, a longitudinal structural MRI study[79] found that individuals aged 65 years or older who exhibited little or

no episodic memory decline over a 4-year period showed less hippocampal atrophy during the same period than individuals with substantial memory decline (FIG. 2a) (see also REF.[80]). Similarly, in a longitudinal fMRI study[81], hippocampal activity during an episodic memory task was significantly higher in older adults whose memory function was stable over the previous two decades ('maintainers') than in older adults whose memory abilities had declined over this period ('decliners') (FIG. 2b). Importantly, higher hippocampal activity in maintainers compared with decliners was observed after matching both groups on initial memory levels. However, because hippocampal activity was not measured at initial testing (20 years prior), it is unclear whether the maintainers exhibited higher hippocampal activity than decliners at the start of the experiment. Whereas hippocampal maintenance has been associated with episodic memory maintenance, the maintenance of other brain regions is likely to be associated with the preservation of other cognitive abilities[7]. For example, PFC maintenance could be associated with the maintenance of cognitive control[82]. To reduce the number of multiple comparisons when investigating the maintenance of different brain regions using neuroimaging, it is advisable to propose beforehand specific hypotheses about the relationship between specific brain measures (such as volume) from particular brain regions (such as the hippocampus) and specific cognitive measures (such as episodic free recall). At the same time, the high degree of covariance between changes in different cognitive abilities suggests that maintenance in one functional domain is likely to be related to maintenance in another domain[53].

As demonstrated by the examples described above, maintenance mechanisms are ideally investigated using longitudinal data, as only within-person assessments can truly quantify change (or, in the case of maintenance, lack thereof)[83]. However, this does not imply that cross-sectional brain data cannot be informative. For example, successful maintenance could explain cross-sectional findings that the brains of high-performing older adults look similar in anatomy and physiology to young brains, whereas the brains of low-performing older adults look different from young brains[7]. However, as reserve may also contribute to differences in neural resources available to distinct performance groups, to argue that this difference is indeed related to maintenance and not reserve, one would need to match performance groups by proxy measures of reserve or statistically control for proxy measures of reserve before testing for maintenance effects. Nevertheless, when considering cross-sectional studies, it is important to remember that some differences between young and older adults could be due to cohort effects, such as early life influences, and not ageing per se[84].

In summary, we consider maintenance to be a dynamic process that engages neural mechanisms of cellular repair and may overlap to a large degree with mechanisms of brain plasticity in adulthood[85]. Similar to the concept of reserve, the mechanisms contributing to maintenance are also likely to have both genetic[86] and environmental origins, with the latter including factors such as diet, exercise and cognitive and social engagement[7,61,87]. Behavioural genetic studies suggest that genetic and environmental contributions to maintenance become increasingly correlated with advancing age[86]. The specific mechanisms remain to be determined but are likely to include both neural components (such as neurogenesis) and non-neural components (such as vascular changes).

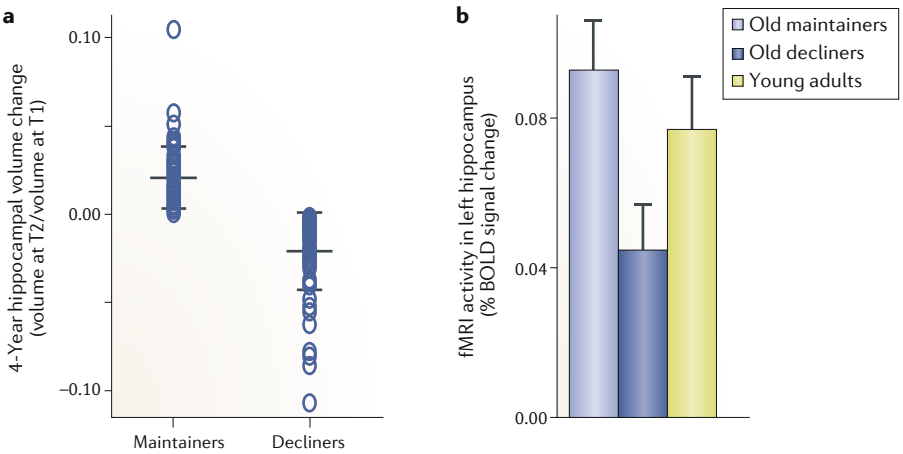


Fig. 2 | **Stable cognitive performance is associated with brain maintenance. a** | Graph showing that individuals aged 65–80 years old who showed minimal episodic memory decline on verbal immediate free recall and delayed cued recall tasks over a 4-year period (referred to as maintainers) also showed less hippocampal volume decline over the same period than decliners (graph created using data from REF.[79]). **b** | Also consistent with the concept of maintenance, a group of old maintainers (individuals with a mean age of 68.8 years who showed no significant episodic memory decline on verbal immediate free recall and delayed cued recall tasks over a period of two decades compared with young adults with a mean age of 35.3 years) displayed levels of hippocampal activity comparable to those of young adults during a fMRI study of face–name associative encoding[81]. By contrast, old decliners showed longitudinal episodic memory decline in the aforementioned verbal tasks and exhibited significantly lower hippocampal activity during associative encoding than young adults and old- maintainers. Consistent with the idea that there are individuals who exhibit high levels of maintenance and those who exhibit low levels of maintenance, maintainers and decliners were defined independently of their absolute levels of memory and hippocampal activity. However, it is impossible to know whether the maintenance observed involved repair or just an absence of a decline. BOLD, blood-oxygen-level-dependent. Part **b** is adapted with permission from REF.[81], Society for Neuroscience.

Compensation

We propose that the term compensation should be used to refer to the cognition-enhancing recruitment of neural resources in response to relatively high cognitive demand. Compensation is temporally linked to variations in cognitive demands and can occur rapidly, in a matter of seconds. As explained below, we reserve the term compensation for neural recruitment that enhances cognitive performance. In the ideal case, the cognition-enhancing recruitment is sufficient to meet the task demands, whereas in the typical scenario, it is insufficient to match the demands. Our definition of compensation is not limited to healthy and pathological ageing; it also applies to the cognition-enhancing recruitment of resources in response to task demands in other age groups and other forms of pathology. It is possible, however, that compensation mechanisms differ across these different populations.

In functional neuroimaging studies, the term compensation is often used to describe a situation in which brain activity or functional connectivity is greater or more widespread in older adults than it is in younger adults[88]. Greater brain activity or connectivity is sometimes interpreted as

being beneficial to older adults without any additional supporting evidence. However, we believe that two basic criteria must be fulfilled to attribute any greater activity or connectivity observed in older adults to compensation. First, it should be clear what is being compensated for: that is, evidence should be available that the increased activation in older adults is directly or indirectly related to some insufficiency or gap between available neural resources and task demands (the supply–demand gap)[85,88]. This gap may be due to an age-related reduction in neural resources (for example, resulting from brain atrophy, reduced blood flow, neurotransmitter deficits or reduced neural specificity), to an increase in task demands, or to both. This can be explained using a metaphor: using eyeglasses for reading compensates for an insufficiency in visual acuity, and the magnitude of the supply–demand gap depends both on the visual deficit of the individual and the size of the letters. In the context of ageing, the supply–demand gap is primarily due to the age-related decline in neural resources. That is, we assume that, owing to age-related neural decline, some older adults have difficulty implementing cognitive operations that would not have taxed their younger selves.

Second, evidence should be available that the enhanced activation in older adults is related to a beneficial effect on cognitive performance. To be compensatory, the use of eyeglasses should be associated with better reading performance than when eyeglasses are not used. This is a point on which our view departs from some uses of the term compensation in the literature, in which the term is often applied to any age-related increase in brain activity or to the recruitment of additional brain regions in older but not young adults, regardless of the relationship with performance[14,15]. In our view, without a link to performance, these findings should be simply described as age-related differences (increases or decreases) in activity and not as compensatory activity. Linking compensation to successful performance (BOX 2) helps to distinguish compensation from activation differences due to inefficiency, dedifferentiation or pathology[89] (BOX 1).

We believe that it is necessary to distinguish between three different mechanisms or forms of compensation (all incorporating the two criteria above): upregulation, selection and recruitment of additional processes (FIG. 3). We posit that these forms of compensation are not mutually exclusive such that one or more may co-occur within or across individuals.

Compensation by upregulation. One form of compensation relates to the enhancement of cognitive performance by boosting a neural process in response to task demands. In such cases, the processes recruited by older adults would be the same as those engaged by younger adults, and the primary difference between the ages would be quantitative: older adults would engage the process to a greater extent than younger adults. Compensatory upregulation could explain the frequent finding that at least some age-related activity increases are evident within the brain regions that younger adults recruit during the same task[90]. Although reports of greater activity in older adults could reflect inefficiency[13], this interpretation is less likely when the greater activity is shown to correlate positively with cognitive performance.

It is worth noting that young adults may also upregulate activity in response to increased task demands but that the demand threshold for such upregulation may be higher in young adults than it is for older adults[24,36]. As task difficulty increases, neural activity (particularly in frontal regions) tends to increase up to a certain level[33], beyond which activation asymptotes and ultimately declines[36,37] (FIG. 3a). It is assumed that the asymptote reflects the limit of available neural resources and that the final decline reflects the breakdown in cognitive performance when these resources are exceeded. Several studies[36,38–41] have found that, consistent with the reduced availability of neural resources in these individuals, older adults show a greater increase in activity, a lower asymptote and an earlier decline than younger adults (FIG. 3a,b). Because age-related differences in brain activity can depend on task difficulty, researchers should ideally investigate multiple levels of task demands.

Compensation by selection. Another mechanism of compensation is the recruitment, by older adults, of neural circuitry associated with cognitive processes that are available to but not engaged by young adults under the same objective task conditions. For example, older adults may engage a less effective but also less demanding process, whereas younger adults may prefer a more effective but more demanding one. To explain this idea with a metaphor, during a swimming competition, an older adult may prefer to swim breaststroke, which is slower but easier, whereas a younger adult may choose freestyle, which is faster but harder. It is important to note that selecting a neural implementation of a behavioural strategy need not be as deliberate as choosing a swimming stroke — the important point is that the process selected by older adults is also available to young adults but is less likely to be the one that supports their performance. An experimental example of compensation by selection is shown in FIG. 3c.

Unlike compensation by upregulation, compensation by selection involves a qualitative difference in the cognitive processes engaged by older and younger individuals and hence is likely to be associated with the recruitment of different brain regions rather than with the recruitment of the same region with differential levels of activity. However, to avoid mistakenly attributing overactivation in a particular brain region in older adults to selection rather than upregulation, it is important to examine the effects of manipulating task demands. Furthermore, in some cases, older adults may show activation in a different region than young adults, suggesting selection, but further investigation may show that this region is a different component of the functional network recruited by younger adults, suggesting compensation by upregulation. One possible method to distinguish compensation by upregulation from compensation by selection is to use repetitive transcranial magnetic stimulation to determine the effects of altering the function of a particular region in younger and older individuals (BOX 2).

It is also important to note that compensation by selection is related to individual differences in reserve: some older adults may have a larger repertoire of alternative neural strategies to implement a given behaviour than others, and this may reflect differences in accumulated reserve.

Compensation by reorganization. Compensation may also occur when older adults use a neural mechanism to respond to ageing-induced losses that is not available to younger individuals[85]. The closest analogy to this type of compensation would be the development of new neural mechanisms following brain damage. For example, there is evidence that recovery from aphasia following a left-hemisphere stroke is associated with the recruitment of right hemispheric regions that do not support language processes in the normal brain[91]. Although these alternative circuits

may be less effective than the original ones, their recruitment may still benefit performance. In the case of ageing, such reorganization could underlie the well-established finding that older adults often show more bilateral patterns of brain activity than younger adults[43–45] (FIG. 3d). If the new regions engaged by older adults are sometimes recruited by younger adults in other similar (or more difficult) conditions, this would support the notion of compensation by selection. It is, however, worth noting that reorganization due to ageing and due to brain damage differs in several ways, including the fact that the time course of ageing is slow, whereas the course of brain injury is fast. It is not clear which time course is better for reorganization: a slow change gives the brain more time to adapt, but a fast change provides a clear trigger for reorganization. Clarification of this issue awaits future research.

Distinguishing between a narrow and a broad notion of compensation has been suggested to be useful. According to this distinction, compensation by reorganization would meet the stringent criterion of compensation in the narrow sense because a new process is generated in response to a loss. By contrast, compensation by upregulation or by selection would only qualify as compensation in the broader sense because these forms of compensation rely on an already existing process (which is upregulated) or an already existing strategy (which is selected) and do not require the evolution of a new process or structure.

Conclusions

In this Opinion article, we have tried to elucidate three important concepts that are widely used in studies of brain and cognitive ageing: reserve, maintenance and compensation. We propose that reserve is used to refer to the accumulation of brain resources during the lifespan, maintenance to the preservation of these resources via constant recovery and repair, and compensation to the deployment of these resources in response to task demands. In other words, reserve is about how much you have, maintenance is about how well you keep it, and compensation is about when and how you use it.

Although we have discussed reserve, maintenance and compensation in separate sections, they can operate concurrently and affect each other. For example, if education augments reserve by increasing synaptic density, this can attenuate age-related cognitive decline if the new synapses are

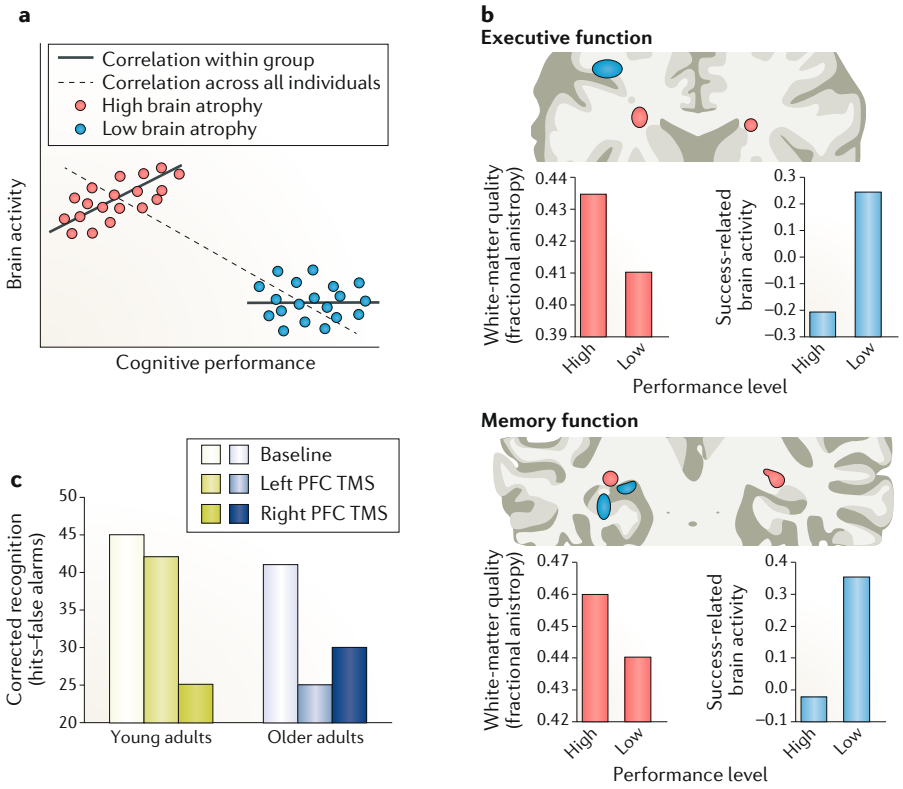
Box 2 | Linking compensatory activity to successful cognitive performance

There are three basic methods by which brain activations measured by functional imaging can be linked to successful cognitive performance.

Correlation across participants is the most common approach and the only one available when using blocked functional MRI (fMRI) designs. If the activity of a brain region that is recruited to a greater extent by older adults than by younger adults is positively correlated with performance in older adults, the finding is consistent with compensation. A potential problem associated with correlation across participants is known as Simpson's paradox: the direction of association at the population level may be different in the subgroups or the individuals composing the population[108]. For example, if one hypothesizes that increased activity compensates for brain atrophy, then a positive activity–cognition correlation should be expected in individuals with high brain atrophy; however, if one calculates the correlation using all individuals (including those with minimal brain atrophy), a negative correlation could be found (see the figure, part **a**, which shows a hypothetical data set that illustrates this point). Thus, correlations should be conducted within the group in which compensation is assumed to take place.

Correlation within participants requires an event-related design (using fMRI or electroencephalography (EEG)) and bypasses Simpson's paradox, but it requires the reasonable assumption that compensatory processes vary from trial to trial. The activity–performance association should be stronger in individuals with greater brain decline (that is, those in whom there is a larger supply–demand gap). Consistent with this idea, a study[16] found that older adults with worse white matter quality and worse cognitive performance showed greater success-related fMRI activity (defined as the difference between activity for hits and activity for misses), an effect that they described as "less wiring, more firing". This negative association between structure and function was found in the frontal lobes and in the medial temporal lobes, depending on whether individual differences were based on executive function or memory function scores (see figure **b**, based on data from REF. [16]).

Non-invasive brain stimulation is another approach. If a brain region is engaged during a task by older but not younger adults, then disrupting or enhancing the function of this region using brain stimulation should have a greater impact on task performance in older than younger adults. For example, a study found that repetitive transcranial magnetic stimulation (rTMS) of the right prefrontal cortex (PFC) disrupted episodic memory retrieval in all individuals, regardless of age, whereas rTMS of the left PFC disrupted retrieval in older adults but not in younger adults[109]. This suggested that the left PFC region contributed to retrieval only in older adults (see the figure, part **c**). Brain stimulation goes beyond correlations by establishing a causal link between localized brain activity and performance.



Part **c** is adapted with permission from REF. [88], from Ch.37 'Frontal Lobes and Aging: Deterioration and Compensation' by Roberto Cabeza and Nancy A. Dennis from "Principles of Frontal Lobe Function", 2E edited by Stuss, D. T. & Knight, R. T. (2013), by permission of Oxford University Press.

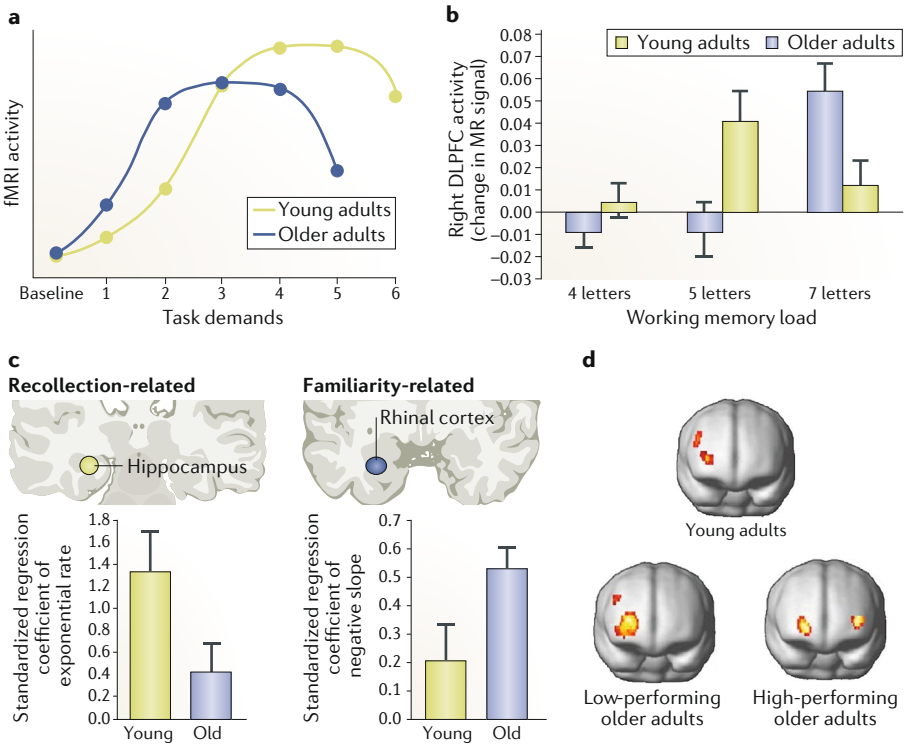


Fig. 3 | **Compensation mechanisms: upregulation, selection and reorganization. a** | Compensation by upregulation occurs when neural activity increases in response to greater task demands. The hypothetical relationship between cognitive demand and brain activity illustrated in the graph is that as task demands increase, activity first rises, then asymptotes and finally declines[13,88]. Because of reduced neural resources, this demand–activity function is hypothesized to be shifted to the left in older adults, and hence, they would tend to show greater activity in the same regions as younger adults at lower levels of task difficulty but lower activity at higher levels of task difficulty. **b** | An example of compensation by upregulation that is consistent with the hypothetical function in panel **a**: in a functional MRI (fMRI) study, older adults showed greater working memory-related activity in the right dorsolateral prefrontal cortex (DLPFC) than younger adults at lower levels of task demands but less activity at higher levels of task demands when there was a higher working memory load[110]. **c** | Compensation by selection occurs when older adults engage in a process not currently recruited by young adults but available to young adults, who may use it in other tasks or conditions. An example of compensation by selection is shown. This fMRI study compared the effects of ageing on the rich form of memory known as recollection and the less precise form of memory known as familiarity, measured in the same recognition memory task. Compared with younger adults, older adults showed reduced recollection-related activity in the hippocampus but increased familiarity-related activity in the rhinal cortex. Thus, older adults compensated for deficits in an optimal but demanding process (recollection) by recruiting a suboptimal but less demanding process (familiarity)[111]. **d** | The idea of compensation by reorganization is that older adults may use a neural mechanism to respond to ageing-induced losses that is not available to younger individuals. An example of compensation by reorganization is shown. During an episodic memory retrieval task, young adults and low-performing older adults showed unilateral frontal activity, whereas high-performing older adults showed bilateral frontal activity, suggesting a reorganization of the episodic retrieval network[12]. Part **a** is adapted with permission from REF.[88], from Ch.37 'Frontal Lobes and Aging: Deterioration and Compensation' by Roberto Cabeza and Nancy A. Dennis from "Principles of Frontal Lobe Function", 2E edited by Stuss, D. T. & Knight, R. T. (2013), by permission of Oxford University Press. Part **b** is adapted with permission from REF.[110], Elsevier. Part **c** is adapted with permission from REF.[111], Daselaar, S. M. et al. Effects of healthy aging on hippocampal and rhinal memory functions: an event-related fMRI study. *Cereb. Cortex* (2006) **16**(12), 1771–1782, by permission of Oxford University Press. Part **d** is adapted with permission from REF.[12], Elsevier.

preserved via maintenance. Thus, when considering the potential effects of, for example, cognitive training on reserve, one has to consider whether age-related deficits in maintenance will render any positive effects less effective. Likewise, it is not enough to accumulate reserve and maintain it; it is also necessary to deploy these resources during task performance in response to task demands, that is, to engage in compensation. Future neuroimaging research should aim to more directly link the predictions derived from studies of maintenance, reserve and compensation. Such studies will result in stronger models of successful cognitive ageing, which are essential for the interpretation of findings from studies of pathological ageing (BOX 1).

In addition, we note that, despite our focus on healthy ageing, the concepts we have discussed can also be applied in other domains, including child development, acute brain injury, neurodegeneration and psychiatric illness. We therefore hope that the present paper will help promote consensus in these domains as well. That is, individuals with a neurological disease or disorder may compensate for their disorder-related deficits in ways similar to those described here for healthy older adults. We also note with caution that most studies of cognitive ageing to date have been limited to testing samples of high-functioning, highly educated and mostly Caucasian healthy older adults. To develop more representative models of cognitive and brain ageing, we strongly recommend expanding inclusion criteria to encompass individuals from diverse backgrounds[92]. This will, of course, require funding sufficient to support the large, ideally longitudinal, studies that such research requires, with an emphasis on combining longitudinal observations with intervention studies to gauge the long-term effects of physical exercise, cognitive training and other variables. Such studies will allow researchers to better understand age-related changes in brain and cognition in terms of biological ageing (senescence), variations in environmental and genetic factors for a given birth cohort, and the secular trends in health, education and technology that will determine the ageing trajectories of future generations.

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Competing interests

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