THE COGNITIVE NEUROSCIENCES

Sixth Edition

David Poeppel, George R. Mangun,
and Michael S. Gazzaniga, *Editors-in-Chief*

Section Editors:

Danielle Bassett
Marina Bedny
Sarah-Jayne Blakemore
Alfonso Caramazza
Maria Chait
Anjan Chatterjee
Stanislas Dehaene
Mauricio Delgado
Karen Emmorey
Kalanit Grill-Spector
Richard B. Ivry
Sabine Kastner
John W. Krakauer
Nikolas Kriegeskorte
Steven J. Luck
Ulman Lindenberger
Josh McDermott
Elizabeth Phelps
Liina Pylkkänen
Charan Ranganath
Adina Roskies
Tomás J. Ryan
Wolfram Schultz
Daphna Shohamy

THE MIT PRESS
CAMBRIDGE, MASSACHUSETTS
LONDON, ENGLAND

7 Brain Maintenance and Cognition in Old Age

LARS NYBERG AND ULMAN LINDENBERGER

ABSTRACT The aging brain is notorious for detrimental changes. However, some older adults display *brain maintenance*, defined as a lack of senescent brain changes and age-related brain pathology. While general brain maintenance seems possible, the selective maintenance of some brain systems in the presence of age-related decline in others appears more likely. Here we focus on the structural and functional maintenance of the hippocampus. We propose that hippocampal maintenance is the primary determinant of preserved episodic-memory functioning in old age. We discuss several potential neural and nonneural mechanisms promoting hippocampal maintenance, including neuronal survival and generation, intact neuronal morphology, and vascular integrity. We provide evidence suggesting that correlated genetic and environmental factors cumulatively influence the operation of these mechanisms, in part through lifestyle choices. Future work should study the contributions of specific connections, transmitter systems, and subregions to hippocampal maintenance; further explore its etiology, prevalence, and behavioral relevance; and examine the generalizability of the maintenance concept for understanding individual differences in human cognitive aging to other regions and circuits.

More than 30 years ago, Rowe and Kahn (1987) introduced the notion of *successful aging* as a complement to the distinction between pathological and normal aging. While defining the criteria for success has stirred some debate, the preservation of broad cognitive abilities, such as episodic memory, is generally considered a hallmark of successful aging. Hence, the sizeable heterogeneity and malleability of human cognitive aging, including the potential for brain maintenance, have attracted increasing attention in recent years (Lindenberger, 2014; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012).

Cognitive abilities such as episodic memory, perceptual speed, reasoning, and semantic memory are characterized by large individual differences in age-related longitudinal change (e.g., Ghisletta, Rabbitt, Lunn, & Lindenberger, 2012; Lindenberger, 2014; Tucker-Drob, Brandmaier, & Lindenberger, 2019). Some individuals show a precipitous decline with advancing adult age, whereas others display high and stable levels of performance well into old age. In the following, we focus on the preservation of episodic memory as a particularly important aspect of successful cognitive aging (i.e., successful memory aging; see also Nyberg & Pudas, 2019.

Complex interactions among genetic and environmental factors underlie successful memory aging by influencing brain integrity. Major brain changes are linked to pathological memory aging—for example, in Alzheimer's dementia, as reviewed in detail elsewhere (e.g., Jack, Barrio, & Kepe, 2013). Also, while not of a pathological nature, brain changes at multiple levels (e.g., cellular, regional, and large-scale networks) are normative in aging (Fjell, McEvoy, Holland, Dale, & Walhovd, 2013) and underlie normal memory decline. Even in the presence of normative age-related brain changes, memory aging might be ameliorated through compensatory processes, as, for example, proposed by Reuter-Lorenz and Park (2014). Hence, successful memory aging is likely to proceed along multiple paths (Cabeza et al., 2018; Nyberg & Pudas, 2019; figure 7.1).

We have previously argued that the primary determinant of preserved cognition in older age is *brain maintenance*, or a relative lack of senescent and pathological brain changes in aging (Lindenberger, Burzynska, & Nagel, 2013; Nyberg et al., 2012). Despite its face validity and conceptual appeal, the relative maintenance of structural and functional brain integrity in aging remains an underexplored path toward successful memory aging. In this chapter we summarize relevant findings from studies of brain maintenance and cognition in old age and offer some thoughts on conceptual and theoretical refinements of the maintenance concept.

Brain Maintenance—General or Specific?

Will a group of older individuals who are characterized by, say, minimal cortical and subcortical atrophy, also display other kinds of brain maintenance (e.g., intact neurotransmitter systems, preserved structural connectivity, or low amyloid retention)? Alternatively, in the spirit of a multiple-factor framework (Buckner, 2004; Gabrieli, 1996), will different groups of individuals show

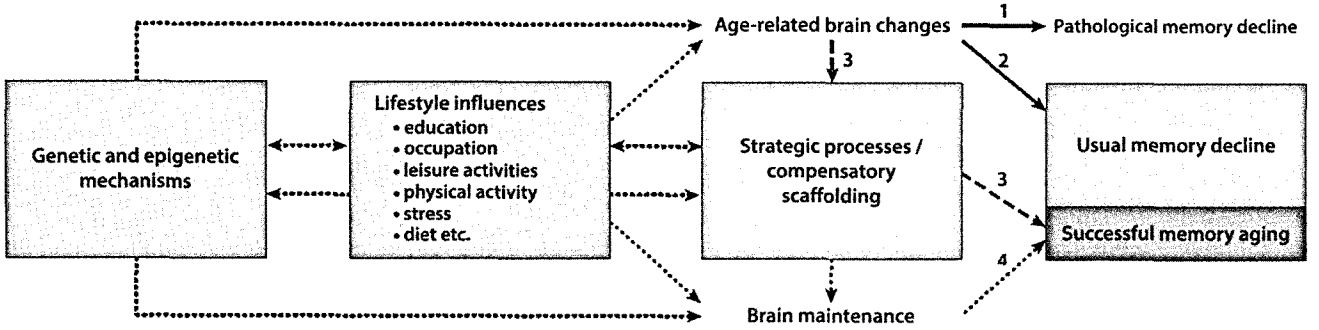

FIGURE 7.1 Model of life course paths to pathological, usual, and successful memory aging. Path 1 (not the focus of this chapter) represents trajectories characterized by pathological memory decline (e.g., dementia). Paths 2, 3, and 4 lead to normal memory aging (usual and successful). Path 2 represents usual memory decline in response to age-related brain changes (e.g., hippocampus atrophy). Path 3 (*dashed line*) is an indirect path to successful memory aging via compensation for age-related brain changes. Path 4 leads directly to successful memory aging via brain maintenance. The dotted lines reflect the influences of genetics, epigenetics, and lifestyle ("what" factors) as well as strategies ("how" factors) on brain integrity (maintenance versus decline) and memory outcomes. From Nyberg & Pudas (2019). (See color plate 6.)

distinct cascades of age-related degenerative changes that target different brain systems and vary in the rate of progression? In the latter view, it is conceivable that some individuals would display brain maintenance of certain major systems (such as the hippocampal/medial temporal lobe (MTL) system) while showing normal age-related changes in other systems (e.g., the frontostriatal system). These competing accounts make distinct predictions for patterns of age-related cognitive changes (cf., Rabbitt, 1993).

Some findings from studies comparing the magnitude of age-related changes among different cognitive abilities, which should tax distinct brain circuits, at least in part, are in line with the generality of brain maintenance. For example, Ghisletta and colleagues (2012) found that about two-thirds of the age-based changes in memory are shared with those of other cognitive abilities, including reasoning, vocabulary, and perceptual speed (see also Dekhtyar et al., 2017; Tucker-Drob, Reynolds, Finkel, & Pedersen, 2014). These results were recently confirmed in a meta-analysis comprising 89 effect sizes representing shared variance in cognitive change from 22 unique data sets composed of over 30,000 individuals (Tucker-Drob, Brandmaier, & Lindenberger, 2019).

Broad cognitive abilities require multiple brain circuits and regions for their operation. Hence, individual differences in aging-induced cognitive change may covary across different abilities in the presence of distinct patterns of cerebral deterioration and maintenance. Longitudinal studies of brain aging do not portray a coherent picture as to the generality or specificity of brain maintenance in aging. For instance, analyses of individual five-year changes in the volumes of specific regions revealed correlations for some of the examined brain volumes, but not others (Raz et al., 2005). The highest change-change correlations were observed for the prefrontal white matter and the hippocampus ($r = .71$) and for the prefrontal white matter and the lateral prefrontal cortex ($r = .70$).

Some cross-sectional studies point to a certain degree of specificity of maintenance (Hedden et al., 2016; Lövdén et al., 2018; Salami, Pudas, & Nyberg, 2014). In a recent report from the COBRA Study, Salami and colleagues used a latent-profile analysis of data from 181 older adults aged 64 to 68 years who performed an n-back working-memory task during functional magnetic resonance imaging (fMRI) scanning. They identified one subgroup with higher performance ($n = 113$; 63%) and a second subgroup ($n = 55$; 31%) with lower performance. Analyses of data from an extensive off-line cognitive test battery confirmed that the lower-performing group had lower working-memory performance but nevertheless relatively intact episodic-memory performance. Moreover, analyses of different markers of brain integrity (cortical and subcortical volumes; functional connectivity; dopamine D2 system integrity) revealed specific alterations in the second group in frontoparietal regions, along with no group differences for other markers, such as hippocampal/default-mode regions.

Taken together, the degree of generality in brain maintenance remains a significant unresolved issue. Future large-scale longitudinal studies with multiple indicators of brain integrity, along with reliable measures of different cognitive functions, are needed to more conclusively address this topic. Awaiting such evidence, we focus on brain maintenance of the

hippocampal system in relation to episodic memory, which is known to be hippocampus-dependent. We will draw on findings from longitudinal studies when available, as they provide more direct evidence on maintenance than cross-sectional comparisons. Select examples of nonhippocampal forms of brain maintenance will be provided in a separate section.

Hippocampus and Successful Episodic Memory

There is evidence that the amount of age-related atrophy, and by inference likely also maintenance, is not uniform across subregions of the hippocampal formation (Leal & Yassa, 2015; Pini et al., 2016; Shing et al., 2011). However, with only a few exceptions that will be noted, the available evidence relevant to brain maintenance refers to the whole hippocampus.

Mounting evidence indicates that hippocampal atrophy in aging underlies normal episodic-memory decline—notably, from change-change analyses (e.g., Gorbach et al., 2016). Hippocampal atrophy has been observed even in normal individuals who, according to genetic, biomarker, and cognitive criteria, are at minimal risk for showing early signs of pathological brain aging (Fjell et al., 2013; Raz et al., 2005). Importantly, there is evidence that some older individuals suffer minimal hippocampal atrophy with advancing adult age (Fjell et al., 2009; Raz et al., 2005), along with intact episodic memory (see Nyberg & Pudas, 2019). For example, Sun and colleagues (2016) reported that a group of "memory super-agers" had hippocampal volumes comparable to those of younger adults, in contrast to typically performing older adults, who had smaller volumes than younger individuals (see also Dekhtyar et al., 2017).

In addition to structure, functional integrity of the hippocampal formation matters as well. An fMRI study from the Betula project (Pudas et al., 2013) compared the brain activity of a group of individuals with maintained memory, as defined by baseline level and change over two to four test waves covering up to 15 years (Josefsson, De Luna, Pudas, Nilsson, & Nyberg, 2012), with individuals with normal memory development (i.e., moderate decline). The successful older adults were found to have a higher activity in the left hippocampus and prefrontal cortex during encoding of face-name pairs compared to the normal participants, and this activity was as high as the average activity observed in a young reference group (see also Düzel, Schütze, Yonelinas, & Heinze, 2011). Hippocampal activity correlated positively with memory performance, and this association continued to be present after statistically controlling for group differences in hippocampal volume. Further evidence for the importance of hippocampal functional integrity was obtained in a study showing that Betula participants who maintained their memory over up to 20 years had better-preserved hippocampal resting-state connectivity than older individuals with typical memory decline (Salami, Pudas, & Nyberg, 2014).

Additional aspects of hippocampal maintenance include dopaminergic neurotransmission (e.g., Nyberg et al., 2016) and neurovascular functions (Düzel, van Praag, & Sendtner, 2016), as well as minimal tau protein deposition (Schöll et al., 2016). Schöll and colleagues noted that tau is abundant in normal aging, in particular in the medial temporal lobes, and they observed that the amount of tau deposition across individuals was negatively related to episodic memory.

Not all of the above-mentioned studies used a longitudinal design. It has been acknowledged that cross-sectional data cannot serve as proxies for estimating associations between age changes in brain maintenance and age changes and cognitive performance (Lindenberger, von Oertzen, Ghisletta, & Hertzog, 2011; Nyberg et al., 2010; Raz & Lindenberger, 2011). Nevertheless, a cross-sectional data pattern in which older adults with more "youth-like" brain structures and functions show higher levels of cognitive performance is at least consistent with the brain maintenance notion. Hence, the longitudinal and cross-sectional findings taken together give some credence to the maintenance hypothesis as far as the hippocampal formation and episodic memory are concerned.

Brain Maintenance beyond the Hippocampus

Going beyond the focus on the hippocampal formation, other brain characteristics have also been related to well-preserved episodic memory in aging. One prominent example is greater thickness of the cingulate cortex, particularly its anterior segments (Gefen et al., 2015; Sun et al., 2016). Another example is stronger and more youth-like functional connectivity between the hippocampus and anterior brain regions, which have been found to correlate with better memory performance in old age (Fandakova, Lindenberger, & Shing, 2015; Lin, Ren, et al., 2017).

Minimal β-amyloid deposition might also be a salient, more general characteristic of brain maintenance, and it has been found to relate to high episodic-memory functioning in aging (Dekhtyar et al., 2017; Farrell et al., 2017). Also, recent findings suggest that integrity of the locus coeruleus and associated noradrenergic pathways may play an important role in maintaining memory performance in old age (Dahl et al., 2019; Hämmerer et al., 2018; Mather, this volume).

Possibly, minimal cortical pathology could also have contributed to observations of a youth-like pattern of functional brain activity in high-performing older adults while performing tasks assessing processing speed (Waiter et al., 2008), executive functioning (Burzynska et al., 2012), and working memory (Burzynska et al., 2013; Nagel et al., 2009, 2011). For instance, Burzynska et al. (2013) found that a more intact white matter microstructure was associated with less signal increase from rest to task in task-relevant brain regions and better performance on a working-memory task (n-back), regardless of adult age.

Moderators of Brain Maintenance

In view of global population aging, a pressing question for individuals as well as society is whether it is possible to influence successful aging in general and successful memory aging in particular (cf. Lindenberger, 2014; Nyberg & Pudas, 2019). In this chapter we have argued that the primary path to well-preserved episodic-memory functions in older age is via brain maintenance—notably, hippocampal integrity (Nyberg et al., 2012). Both genetic and environmental factors influence brain integrity (maintenance and change) in aging. The age-related increase in heritability for most cognitive abilities from childhood to adulthood suggests that genetic and environmental factors are correlated across ontogeny (Beam & Turkheimer, 2013). In particular, differences in lifestyle choices are likely to reflect, in part, genetic differences (Pedersen et al., 2013). Hence, genetic and environmental factors contribute synergistically and cumulatively to individual differences in brain maintenance.

Among the genetic factors, *APOE* stands out in relation to an accelerated cognitive decline in aging (e.g., Davies et al., 2014; Josefsson et al., 2012). APOE has also been identified as a characteristic of older adults displaying successful memory aging (Lin, Wang, et al., 2017). In addition, APOE has repeatedly been linked to hippocampal volume and atrophy (e.g., Davies et al., 2014; Li et al., 2016), though large-scale genome-wide association studies (GWAS) also point to other genetic loci in determining individual differences in hippocampal volume (Hibar et al., 2017) and atrophy (e.g., Mather et al., 2015).

Some lifestyle features may also promote brain maintenance, in part through epigenetic mechanisms (e.g., Mather, Kwok, Armstrong, & Sachdev, 2014; Spiegel, Sewal, & Rapp, 2014). In line with observational longitudinal data (Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008), intervention studies have linked cognitively stimulating activities, such as spatial navigation, to less hippocampal atrophy (e.g., Lövdén et al., 2012). Physical activity is also a crucial lifestyle factor, and there is evidence from epidemiological and intervention studies in older age for positive associations among physical exercise, hippocampal integrity, and memory (e.g., Düzel, van Praag, & Sendtner, 2016; Maass et al., 2015).

Specifically, physical activity may contribute to hippocampal maintenance by reducing the risk for hypertension. There is evidence that midlife hypertension increases the risk for hippocampal atrophy (e.g., Korf, White, Scheltens, & Launer, 2004), and it has been shown that accelerated hippocampal atrophy in older age is selective for individuals with hypertension (Raz et al., 2005). Also, hypertension has been linked to impaired hippocampus-related neurogenesis (Shih et al., 2016) and to smaller hippocampal subfield volumes and a greater propensity for false memories among older adults (Shing et al., 2011). Thus, the prevention and treatment of hypertension may be crucial for promoting hippocampal maintenance in aging, and physical exercise may be relevant in this regard.

In sum, genetic and environmental factors interactively and cumulatively contribute to brain maintenance, in part through individual differences in lifestyle. Next, we turn to the more mechanistic issue of what is maintained, and how.

Etiology and Expressions of Brain Maintenance

Evolutionary theories propose that human senescence reflects evolved limitations in somatic maintenance, resulting in a buildup of damage (Kirkwood, 2005). In light of the brain's disproportionately high energy needs, general theories of human brain aging stress the importance of bioenergetic mechanisms (Lindenberger, 2014; Raz, this volume; Raz & Daugherty, 2018). By this account, the "core cause of cognitive aging is a generalized and chronic decline in the availability of energy resources" (Raz & Daugherty, 2018, p. 55). As a corollary of this view, maintenance processes that are particularly expensive metabolically, such as myelin repair and regeneration (Hill, Li, & Grutzendler, 2018), are especially likely to suffer from normal aging. Brain maintenance, from this point of view, can be seen as the postponement and attenuation of a looming energy crisis.

In relation to the hippocampus, several possible etiologies of atrophy and functional impairment have been put forward (e.g., Dawe, Bennett, Schneider, & Arfanakis, 2011). These include (1) neuronal loss, (2) the loss of axons and dendrites, and (3) the loss of non-neural elements (e.g., glia, vessels). Each of these can be considered in relation to brain maintenance.

Starting with neuronal loss, postmortem MRI quantification of hippocampal volume was found to correlate with histology-based measurements in a sample of 11 patients with Alzheimer's disease and 4 healthy older controls (Bobinski et al., 2000). Specifically, in the study by Babinski and colleagues, a strong correlation between neuronal counts and MRI volumes was found (cf. Zarow et al., 2005). Hence, by inference, in vivo MRI observations of hippocampal atrophy in aging might reflect neuronal loss. Cell loss is a characteristic feature of pathological aging in Alzheimer's disease, but it has been argued that a marked loss of neurons in the hippocampus is not typical for normal aging (e.g., Dickstein, Weaver, Luebke, & Hof, 2013; Lister & Barnes, 2009; Wilson, Gallagher, Eichenbaum, & Tanila, 2006). Still, although the rate is higher in pathological aging, aging neurons seem to become more vulnerable to cell death (e.g., Mattson & Magnus, 2006), in particular in the CA1 region (Šimić, Kostović, Winblad, & Bogdanović, 1997). Moreover, it remains an open possibility that neuronal loss is more abundant in usual than in successful aging, resulting in a nonlinear loss gradient (successful < usual << pathological aging).

A related mechanism is age-related alteration in neurogenesis. New hippocampal neurons are generated throughout development, and perhaps throughout life (Spalding et al., 2013). Spalding and colleagues reported only a modest reduction in neurogenesis in aging, with marked interindividual differences from about age 20 to 80. Other studies have observed age-related reductions in neurogenesis and related such reductions to memory impairment in normal aging (see Seib & Martin-Villalba, 2015). Collectively, these past studies suggest that maintained neurogenesis could contribute to hippocampal integrity and preserved memory in certain older individuals, and some recent results further underscore this interpretation (Boldrini et al., 2018). It should be noted, though, that findings from another recent study suggested that neurogenesis in the dentate gyrus is rare or nonexistent in adult humans (Sorrells et al., 2018). Thus, at present, the evidence that effective neurogenesis in older age is a vital mechanism underlying brain maintenance is inconclusive (Snyder, 2019). Still, a role for neurogenesis in brain maintenance, even in view of the recent findings by Sorrells and colleagues, is bolstered by the suggestion that high degrees of neurogenesis at younger ages might protect against memory decline in old age (Seib & Martin-Villalba, 2015).

We turn now to the second class of possible etiologies of hippocampal atrophy, the loss of axons or dendrites (Dawe et al., 2011). Dendritic spine changes in aging

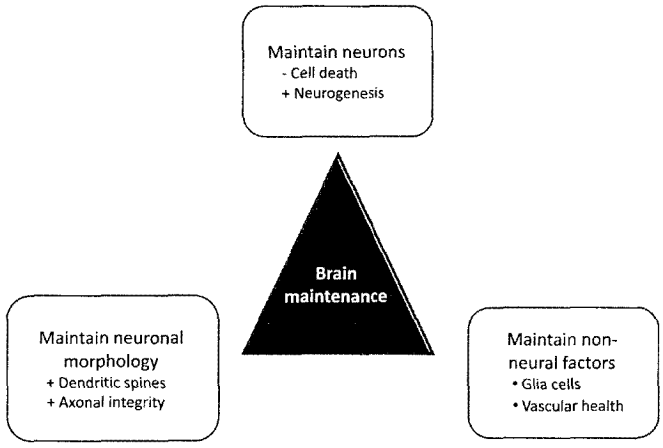

FIGURE 7.2 Putative underlying mechanisms of (hippocampal) brain maintenance.

have been suggested to potentially distinguish unsuccessful from successful cognitive aging (Dickstein et al., 2013). Alterations of myelin and nerve fibers in normal aging have been linked to cognitive decline (Peters, 2002). Morphological neuronal changes may also relate to decreased brain connectivity and disrupted neuronal synchrony in aging (Pannese, 2011). Relatedly, subtle synaptic alterations, including in the hippocampus, have been linked to cognitive impairment in normal aging (Morrison & Baxter, 2012).

In the third class, nonneural contributions to hippocampal atrophy, a recent study indicated that genes specific for astrocytes and oligodendrocytes, but not neurons, shift their expression patterns in aging—notably, in the hippocampus (Soreq et al., 2017)—thus pointing to a key role of glia cells in aging. Another example of a relevant nonneural contribution was revealed in a study of the neuropathological basis of age-associated brain atrophy (Erten-Lyons et al., 2013). Multiple antemortem MRI measurements of brain volumes were related to several neuropathological markers. Accelerated hippocampal volume decline trajectories were found to be significantly associated with the presence of amyloid angiopathy, and it was suggested that subtle chronic ischemia may contribute to elevated atrophy. More generally, there is much evidence that vascular pathology in normal and pathological aging negatively affects the brain and cognition in old age (see Farkas & Luiten, 2001).

In summary, we have reviewed some potential neural and nonneural mechanisms underlying brain maintenance (figure 7.2)—in particular, the maintenance of hippocampal integrity. Each of these mechanisms is likely influenced by the individual differences in lifestyles summarized above. Perhaps the most prominent example is physical exercise, which has been linked to

each of the three domains in figure 7.1, such as increased neurogenesis (van Praag, Shubert, Zhao, & Gage, 2005), vascular health (see Düzel et al., 2016), and dendritic branching (Redila & Christie, 2006).

Future Directions

We have argued that brain maintenance is the primary path to preserved cognition in later adulthood, and more specifically that hippocampal maintenance is a key determinant of intact episodic-memory functioning in old age. Such specification of the general concept of brain maintenance has been called for (Cabeza et al., 2018; Nilsson & Lövdén, 2018). In future work, the underlying mechanisms of hippocampal maintenance should be explored in greater detail. This work will benefit from considering specific connections and subregions of the hippocampal formation, which in human MRI studies may require MR research at high field strengths (e.g., Maass et al., 2014).

At a more general level, the etiology, dimensionality, and promotion of brain maintenance needs to be addressed in large-scale studies that combine long-term longitudinal observations with interventions targeting behaviorally relevant brain regions and neural circuitry. At the same time, more detailed insights into the metabolic preconditions and molecular mechanisms of brain maintenance are needed to gauge their contributions to successful cognitive aging.

REFERENCES

Beam, C. R., & Turkheimer, E. (2013). Phenotype-environment correlations in longitudinal twin models. *Development and Psychopathology, 25*(1), 7–16. doi:10.1017/S0954579412000867

Bobinski, M., De Leon, M. J., Weigiel, J., Desanti, S., Convit, A., Saint Louis, L. A., ... Wisniewski, H. M. (2000). The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer's disease. *Neuroscience, 95*(3), 721–725. doi:10.1016/s0306-4522(99)00476-5

Boldrini, M., Fulmore, C. A., Tartt, A. N., Simeon, L. R., Pavlova, I., Poposka, V., ... Mann, J. J. (2018). Human hippocampal neurogenesis persists throughout aging. *Cell Stem Cell, 22*(4), 589–599.e585. doi:10.1016/j.stem.2018.03.015

Buckner, R. L. (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*(1), 195–208. doi:10.1016/j.neuron.2004.09.006

Burzynska, A., Garrett, D. D., Preuschhof, C., Nagel, I. E., Li, S.-C., Bäckman, L., ... Lindenberger, U. (2013). A scaffold for efficiency in the human brain. *Journal of Neuroscience, 33*(43), 17150–17159. doi:10.1523/jneurosci.1426-13.2013

Burzynska, A. Z., Nagel, I. E., Preuschhof, C., Gluth, S., Bäckman, L., Li, S.-C., ... Heekeren, H. R. (2012). Cortical thickness is linked to executive functioning in adulthood and aging. *Human Brain Mapping, 33*(7), 1607–1620. doi:10.1002/hbm.21311

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., ... Rajah, M. N. (2018). Maintenance, reserve, and compensation: the cognitive neuroscience of healthy aging. *Nature Reviews Neuroscience, 19*(11), 701–710. doi:10.1038/s41583-018-0068-2

Dahl, M. J., Mather, M., Düzel, S., Bodammer, N. C., Lindenberger, U., Kühn, S., & Werkle-Bergner, M. (2019). Locus coeruleus integrity preserves memory performance across the adult life span.

Davies, G., Harris, S. E., Reynolds, C. A., Payton, A., Knight, H. M., Liewald, D. C., ... Deary, I. J. (2014). A genome-wide association study implicates the APOE locus in nonpathological cognitive ageing. *Molecular Psychiatry, 19*(1), 76–87. doi:10.1038/mp.2012.159

Dawe, R. J., Bennett, D. A., Schneider, J. A., & Arfanakis, K. (2011). Neuropathologic correlates of hippocampal atrophy in the elderly: A clinical, pathologic, postmortem MRI Study. *PLoS One, 6*(10), e26286. doi:10.1371/journal.pone.0026286

Dekhtyar, M., Papp, K. V., Buckley, R., Jacobs, H. I. L., Schultz, A. P., Johnson, K. A., ... Rentz, D. M. (2017). Neuroimaging markers associated with maintenance of optimal memory performance in late-life. *Neuropsychologia, 100*, 164–170. doi:10.1016/j.neuropsychologia.2017.04.037

Dickstein, D. L., Weaver, C. M., Luebke, J. I., & Hof, P. R. (2013). Dendritic spine changes associated with normal aging. *Neuroscience, 251*, 21–32. doi:10.1016/j.neuroscience.2012.09.077

Düzel, E., Schütze, H., Yonelinas, A. P., & Heinze, H.-J. (2011). Functional phenotyping of successful aging in long-term memory: Preserved performance in the absence of neural compensation. *Hippocampus, 21*(8), 803–814. doi:10.1002/hipo.20834

Düzel, E., van Praag, H., & Sendtner, M. (2016). Can physical exercise in old age improve memory and hippocampal function? *Brain, 139*(3), 662–673. doi:10.1093/brain/awv407

Erten-Lyons, D., Dodge, H. H., Woltjer, R., Silbert, L. C., Howieson, D. B., Kramer, P., & Kaye, J. A. (2013). Neuropathologic basis of age-associated brain atrophy. *JAMA Neurology, 70*(5), 616–622. doi:10.1001/jamaneurol.2013.1957

Fandakova, Y., Lindenberger, U., & Shing, Y. L. (2015). Episodic memory across the lifespan: General trajectories and modifiers. In A. Duarte, D. R. Addis, & M. D. Barense (Eds.), *The cognitive neuroscience of human memory* (pp. 309–325). Hoboken, NJ: Wiley-Blackwell.

Farkas, E., & Luiten, P. G. M. (2001). Cerebral microvascular pathology in aging and Alzheimer's disease. *Progress in Neurobiology, 64*(6), 575–611. doi:10.1016/S0301-0082(00)00068-X

Farrell, M. E., Kennedy, K. M., Rodrigue, K. M., Wig, G., Bischof, G. N., Rieck, J. R., ... Park, D. C. (2017). Association of longitudinal cognitive decline with amyloid burden in middle-aged and older adults: Evidence for a dose-response relationship. *JAMA Neurology, 74*(7), 830–838. doi:10.1001/jamaneurol.2017.0892

Fjell, A. M., McEvoy, L., Holland, D., Dale, A. M., & Walhovd, K. B. (2013). Brain changes in older adults at very low risk for Alzheimer's disease. *Journal of Neuroscience, 33*(19), 8237–8242. doi:10.1523/JNEUROSCI.5506-12.2013

Fjell, A. M., Walhovd, K. B., Fenneman-Notestine, C., McEvoy, L. K., Hagler, D. J., Holland, D., ... Dale, A. M. (2009). One-year brain atrophy evident in healthy aging. *Journal of*

Neuroscience, 29(48), 15223–15231. doi:10.1523/JNEUROSCI.3252-09.2009

Gabrieli, J. D. E. (1996). Memory systems analyses of mnemonic disorders in aging and age-related diseases. *Proceedings of the National Academy of Sciences of the United States of America, 93*(24), 13534–13540.

Gefen, T., Peterson, M., Papastefan, S. T., Martersteck, A., Whitney, K., Rademaker, A., … Geula, C. (2015). Morphometric and histologic substrates of cingulate integrity in elders with exceptional memory capacity. *Journal of Neuroscience, 35*(4), 1781–1791. doi:10.1523/JNEUROSCI.2998-14.2015

Ghisletta, P., Rabbitt, P., Lunn, M., & Lindenberger, U. (2012). Two thirds of the age-based changes in fluid and crystallized intelligence, perceptual speed, and memory in adulthood are shared. *Intelligence, 40*(3), 260–268. doi:10.1016/j.intell.2012.02.008

Gorbach, T., Pudas, S., Lundquist, A., Orädd, G., Josefsson, M., Salami, A., … Nyberg, L. (2016). Longitudinal association between hippocampus atrophy and episodic-memory decline. *Neurobiology of Aging, 51*, 167–176. doi:10.1016/j.neurobiolaging.2016.12.002

Hämmerer, D., Callaghan, M. F., Hopkins, A., Kosciessa, J., Betts, M., Cardenas-Blanco, A., … Düzel, E. (2018). Locus coeruleus integrity in old age is selectively related to memories linked with salient negative events. *Proceedings of the National Academy of Sciences of the United States of America, 115*(9), 2228–2233. doi:10.1073/pnas.1712268115

Hedden, T., Schultz, A. P., Rieckmann, A., Mormino, E. C., Johnson, K. A., Sperling, R. A., & Buckner, R. L. (2016). Multiple brain markers are linked to age-related variation in cognition. *Cerebral Cortex, 26*(4), 1388–1400. doi:10.1093/cercor/bhu238

Hibar, D. P., Adams, H. H. H., Jahanshad, N., Chauhan, G., Stein, J. L., Hofer, E., … Ikram, M. A. (2017). Novel genetic loci associated with hippocampal volume. *Nature Communications, 8*, 13624. doi:10.1038/ncomms13624

Hill, R. A., Li, A. M., & Grutzendler, J. (2018). Lifelong cortical myelin plasticity and age-related degeneration in the live mammalian brain. *Nature Neuroscience, 21*, 683–695. doi:10.1038/s41593-018-0120-6

Jack, C. R., Barrio, J. R., & Kepe, V. (2013). Cerebral amyloid PET imaging in Alzheimer's disease. *Acta Neuropathologica, 126*(5), 643–657. doi:10.1007/s00401-013-1185-7

Josefsson, M., De Luna, X., Pudas, S., Nilsson, L.-G., & Nyberg, L. (2012). Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. *Journal of the American Geriatrics Society, 60*(12), 2308–2312. doi:10.1111/jgs.12000

Kirkwood, T. B. L. (2005). Understanding the odd science of aging. *Cell, 120*(4), 437–447. doi:10.1016/j.cell.2005.01.027

Korf, E. S. C., White, L. R., Scheltens, P., & Launer, L. J. (2004). Midlife blood pressure and the risk of hippocampal atrophy. *Hypertension, 44*(1), 29–34. doi:10.1161/01.HYP.0000132475.32317.bb

Leal, S. L., & Yassa, M. A. (2015). Neurocognitive aging and the hippocampus across species. *Trends in Neurosciences, 38*(12), 800–812. doi:10.1016/j.tins.2015.10.003

Li, B., Shi, J., Gutman, B. A., Baxter, L. C., Thompson, P. M., Caselli, R. J., … Alzheimer's Disease Neuroimaging Initiative. (2016). Influence of APOE genotype on hippocampal atrophy over time: An N=1925 surface-based ADNI study. *PLoS One, 11*(4), e0152901. doi:10.1371/journal.pone.0152901

Lin, F. V., Ren, P., Mapstone, M., Meyers, S. P., Porsteinsson, A., & Baran, T. M. (2017). The cingulate cortex of older adults with excellent memory capacity. *Cortex, 86*, 83–92. doi:10.1016/j.cortex.2016.11.009

Lin, F. V., Wang, X., Wu, R., Rebok, G. W., Chapman, B. P., & Alzheimer's Disease Neuroimaging Initiative. (2017). Identification of successful cognitive aging in the Alzheimer's Disease Neuroimaging Initiative study. *Journal of Alzheimer's Disease, 59*(1), 101–111. doi:10.3233/JAD-161278

Lindenberger, U. (2014). Human cognitive aging: Corriger la fortune? *Science, 346*(6209), 572–578. doi:10.1126/science.1254403

Lindenberger, U., Burzynska, A. Z., & Nagel, I. E. (2013). Heterogeneity in frontal-lobe aging. In D. T. Stuss & R. T. Knight (Eds.), *Principles of frontal lobe functions* (2nd ed., pp. 609–627). New York: Oxford University Press.

Lindenberger, U., von Oertzen, T., Ghisletta, P., & Hertzog, C. (2011). Cross-sectional age variance extraction: What's change got to do with it? *Psychology and Aging, 26*(1), 34–47. doi:10.1037/a0020525

Lister, J. P., & Barnes, C. A. (2009). Neurobiological changes in the hippocampus during normative aging. *Archives of Neurology, 66*(7), 829–833. doi:10.1001/archneurol.2009.125

Lövdén, M., Karalija, N., Andersson, M., Wåhlin, A., Jan, A., Köhncke, Y., … Lindenberger, U. (2018). Latent-profile analysis reveals behavioral and brain correlates of dopamine-cognition associations. *Cerebral Cortex, 28*(11), 3894–3907. doi:10.1093/cercor/bhx253

Lövdén, M., Schaefer, S., Noack, H., Bodammer, N. C., Kühn, S., Heinze, H.-J., … Lindenberger, U. (2012). Spatial navigation training protects the hippocampus against age-related changes during early and late adulthood. *Neurobiology of Aging, 33*(3), 620.e629–620.e622. doi:10.1016/j.neurobiolaging.2011.02.013

Maass, A., Düzel, S., Goerke, M., Becke, A., Sobieray, U., Neumann, K., … Düzel, E. (2015). Vascular hippocampal plasticity after aerobic exercise in older adults. *Molecular Psychiatry, 20*, 585–593. doi:10.1038/mp.2014.114

Maass, A., Schütze, H., Speck, O., Yonelinas, A., Tempelmann, C., Heinze, H.-J., … Düzel, E. (2014). Laminar activity in the hippocampus and entorhinal cortex related to novelty and episodic encoding. *Nature Communications, 5*, 5547. doi:10.1038/ncomms6547

Mather, K. A., Armstrong, N. J., Wen, W., Kwok, J. B., Assareh, A. A., Thalamuthu, A., … Sachdev, P. S. (2015). Investigating the genetics of hippocampal volume in older adults without dementia. *PLoS One, 10*(1), e0116920. doi:10.1371/journal.pone.0116920

Mather, K. A., Kwok, J. B., Armstrong, N., & Sachdev, P. S. (2014). The role of epigenetics in cognitive ageing. *International Journal of Geriatric Psychiatry, 29*(11), 1162–1171. doi:10.1002/gps.4183

Mattson, M. P., & Magnus, T. (2006). Ageing and neuronal vulnerability. *Nature Reviews Neuroscience, 7*(4), 278–294. doi:10.1038/nrn1886

Morrison, J. H., & Baxter, M. G. (2012). The ageing cortical synapse: Hallmarks and implications for cognitive decline. *Nature Reviews Neuroscience, 13*, 240–250. doi:10.1038/nrn3200

Nagel, I. E., Preuschhof, C., Li, S.-C., Nyberg, L., Bäckman, L., Lindenberger, U., & Heekeren, H. R. (2009). Performance level modulates adult age differences in brain activation during spatial working memory. *Proceedings of the National Academy of Sciences of the United States of America, 106*(52), 22552–22557. doi:10.1073/pnas.0908238106

Nagel, I. E., Preuschhof, C., Li, S.-C., Nyberg, L., Bäckman, L., Lindenberger, U., & Heekeren, H. R. (2011). Load modulation of BOLD response and connectivity predicts working memory performance in younger and older adults. *Journal of Cognitive Neuroscience, 23*(8), 2030–2045. doi:10.1162/jocn.2010.21560

Nilsson, J., & Lövdén, M. (2018). Naming is not explaining: Future directions for the "cognitive reserve" and "brain maintenance" theories. *Alzheimer's Research & Therapy, 10*(1), 34. doi:10.1186/s13195-018-0365-z

Nyberg, L., Karalija, N., Salami, A., Andersson, M., Wahlin, A., Kaboovand, N., ... Bäckman, L. (2016). Dopamine D2 receptor availability is linked to hippocampal-caudate functional connectivity and episodic memory. *Proceedings of the National Academy of Sciences of the United States of America, 113*(28), 7918–7923. doi:10.1073/pnas.1606309113

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences, 16*(5), 292–305. doi:10.1016/j.tics.2012.04.005

Nyberg, L., & Pudas, S. (2019). Successful memory aging. *Annual Review of Psychology, 70,* 2019–243. doi:10.1146/annurev-psych-010418-103052

Nyberg, L., Salami, A., Andersson, M., Eriksson, J., Kalpouzos, G., Kauppi, K., ... Nilsson, L.-G. (2010). Longitudinal evidence for diminished frontal cortex function in aging. *Proceedings of the National Academy of Sciences of the United States of America, 107*(52), 22682–22686. doi:10.1073/pnas.1012651108

Pannese, E. (2011). Morphological changes in nerve cells during normal aging. *Brain Structure and Function, 216*(2), 85–89. doi:10.1007/s00429-011-0308-y

Pedersen, N. L., Christensen, K., Dahl, A. K., Finkel, D., Franz, C. E., Gatz, M., ... Reynolds, C. A. (2013). IGEMS: The Consortium on Interplay of Genes and Environment across Multiple Studies. *Twin Research and Human Genetics, 16*(1), 481–489. doi:10.1017/thg.2012.110

Peters, A. (2002). The effects of normal aging on myelin and nerve fibers: A review. *Journal of Neurocytology, 31*(8–9), 581–593. doi:10.1023/A:1025731309829

Pini, L., Pievani, M., Bocchetta, M., Altomare, D., Bosco, P., Cavedo, E., ... Frisoni, G. B. (2016). Brain atrophy in Alzheimer's disease and aging. *Ageing Research Reviews, 30,* 25–48. doi:10.1016/j.arr.2016.01.002

Pudas, S., Persson, J., Josefsson, M., de Luna, X., Nilsson, L.-G., & Nyberg, L. (2013). Brain characteristics of individuals resisting age-related cognitive decline over two decades. *Journal of Neuroscience, 33*(20), 8668–8677. doi:10.1523/JNEUROSCI.2900-12.2013

Rabbitt, P. (1993). Does it all go together when it goes? The Nineteenth Bartlett Memorial Lecture. *Quarterly Journal of Experimental Psychology A, 46*(3), 385–434. doi:10.1080/14640749308401055

Raz, N., & Daugherty, A. M. (2018). Pathways to brain aging and their modifiers: Free-radical-induced energetic and neural decline in senescence (FRIENDS) model—a mini-review. *Gerontology, 64*(1), 49–57. doi:10.1159/000479508

Raz, N., & Lindenberger, U. (2011). Only time will tell: Cross-sectional studies offer no solution to the age-brain-cognition triangle: Comment on Salthouse (2011). *Psychological Bulletin, 137*(5), 790–795. doi:10.1037/a0024503

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., ... Acker, J. D. (2005). Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex, 15*(11), 1676–1689. doi:10.1093/cercor/bhi044

Redila, V. A., & Christie, B. R. (2006). Exercise-induced changes in dendritic structure and complexity in the adult hippocampal dentate gyrus. *Neuroscience, 137*(4), 1299–1307. doi:10.1016/j.neuroscience.2005.10.050

Reuter-Lorenz, P. A., & Park, D. C. (2014). How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychology Review, 24*(3), 355–370. doi:10.1007/s11065-014-9270-9

Rowe, J. W., & Kahn, R. L. (1987). Human aging: Usual and successful. *Science, 237*(4811), 143–149. doi:10.1126/science.3299702

Salami, A., Pudas, S., & Nyberg, L. (2014). Elevated hippocampal resting-state connectivity underlies deficient neurocognitive function in aging. *Proceedings of the National Academy of Sciences of the United States of America, 111*(49), 17654–17659. doi:10.1073/pnas.1410233111

Schöll, M., Lockhart, S. N., Schonhaut, D. R., O'Neil, J. P., Janabi, M., Ossenkoppele, R., ... Jagust, W. J. (2016). PET imaging of tau deposition in the aging human brain. *Neuron, 89*(5), 971–982. doi:10.1016/j.neuron.2016.01.028

Seib, D. R. M., & Martin-Villalba, A. (2015). Neurogenesis in the normal ageing hippocampus: A mini-review. *Gerontology, 61*(4), 327–335. doi:10.1159/000368575

Shih, Y. H., Tsai, S. F., Huang, S. H., Chiang, Y. T., Hughes, M. W., Wu, S. Y., ... Kuo, Y. M. (2016). Hypertension impairs hippocampus-related adult neurogenesis, CA1 neuron dendritic arborization and long-term memory. *Neuroscience, 322,* 346–357. doi:10.1016/j.neuroscience.2016.02.045

Shing, Y. L., Rodrigue, K. M., Kennedy, K. M., Fandakova, Y., Bodammer, N., Werkle-Bergner, M., ... Raz, N. (2011). Hippocampal subfield volumes: Age, vascular risk, and correlation with associative memory. *Frontiers in Aging Neuroscience, 3,* 2. doi:10.3389/fnagi.2011.00002

Šimić, G., Kostović, I., Winblad, B., & Bogdanović, N. (1997). Volume and number of neurons of the human hippocampal formation in normal aging and Alzheimer's disease. *Journal of Comparative Neurology, 379*(4), 482–494.

Snyder, J. S. (2019). Recalibrating the relevance of adult neurogenesis. *Trends in Neurosciences, 42*(3), 164–178. doi:10.1016/j.tins.2018.12.001

Soreq, L., Rose, J., Soreq, E., Hardy, J., Trabzuni, D., Cookson, M. R., ... Ule, J. (2017). Major shifts in glial regional identity are a transcriptional hallmark of human brain aging. *Cell Reports, 18*(2), 557–570. doi:10.1016/j.celrep.2016.12.011

Sorrells, S. F., Paredes, M. F., Cebrian-Silla, A., Sandoval, K., Qi, D., Kelley, K. W., ... Alvarez-Buylla, A. (2018). Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature, 555,* 377–381. doi:10.1038/nature25975

Spalding, K. L., Bergmann, O., Alkass, K., Bernard, S., Salehpour, M., Huttner, Hagen B., ... Frisén, J. (2013). Dynamics of hippocampal neurogenesis in adult humans. *Cell, 153*(6), 1219–1227. doi:10.1016/j.cell.2013.05.002

Spiegel, A. M., Sewal, A. S., & Rapp, P. R. (2014). Epigenetic contributions to cognitive aging: Disentangling mindspan and lifespan. *Learning & Memory, 21*(10), 569–574. doi:10.1101/lm.033506.113

Sun, F. W., Stepanovic, M. R., Andreano, J., Barrett, L. F., Touroutoglou, A., & Dickerson, B. C. (2016). Youthful brains in older adults: Preserved neuroanatomy in the

default mode and salience networks contributes to youthful memory in superaging. *Journal of Neuroscience, 36*(37), 9659–9668. doi:10.1523/JNEUROSCI.1492-16.2016

Tucker-Drob, E. M., Brandmaier, A. M., & Lindenberger, U. (2019). Coupled cognitive change in adulthood: A meta-analysis. *Psychological Bulletin, 145*(3), 273–301. doi: 10.1037/bul0000179

Tucker-Drob, E. M., Reynolds, C. A., Finkel, D., & Pedersen, N. L. (2014). Shared and unique genetic and environmental influences on aging-related changes in multiple cognitive abilities. *Developmental Psychology, 50*(1), 152–166. doi:10.1037/a0032468

Valenzuela, M. J., Sachdev, P., Wen, W., Chen, X., & Brodaty, H. (2008). Lifespan mental activity predicts diminished rate of hippocampal atrophy. *PLoS One, 3*(7), e2598. doi:10.1371/journal.pone.0002598

van Praag, H., Shubert, T., Zhao, C., & Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *Journal of Neuroscience, 25*(38), 8680–8685. doi:10.1523/JNEUROSCI.1731-05.2005

Waiter, G. D., Fox, H. C., Murray, A. D., Starr, J. M., Staff, R. T., Bourne, V. J., ... Deary, I. J. (2008). Is retaining the youthful functional anatomy underlying speed of information processing a signature of successful cognitive ageing? An event-related fMRI study of inspection time performance. *NeuroImage, 41*(2), 581–595. doi:10.1016/j.neuroimage.2008.02.045

Wilson, I. A., Gallagher, M., Eichenbaum, H., & Tanila, H. (2006). Neurocognitive aging: Prior memories hinder new hippocampal encoding. *Trends in Neurosciences, 29*(12), 662–670. doi:10.1016/j.tins.2006.10.002

Zarow, C., Vinters, H. V., Ellis, W. G., Weiner, M. W., Mungas, D., White, L., & Chui, H. C. (2005). Correlates of hippocampal neuron number in Alzheimer's disease and ischemic vascular dementia. *Annals of Neurology, 57*(6), 896–903. doi:10.1002/ana.20503