Neurobiological Aging and Memory

Average patterns and individual differences

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Abstract

Neurobiological aging is expressed at many different neuroscientific levels. In this chapter we adopt a systems-levels perspective and focus on findings from human brain-imaging studies of age-related changes in episodic memory. Drawing on data from multiple imaging modalities, we first outline typical (average) structural and functional neurobiological changes. These include gray-matter changes in the medial-temporal lobes and the prefrontal cortex, and also alterations in structural, and less consistently functional, connectivity. Next, heterogeneity in episodic-memory aging is considered. This discussion revolves around central concepts like brain maintenance as well as reserve and compensation. In a final section we consider possibilities to influence neurobiological aging by means of direct interventions. It is concluded that future progress in the field will depend upon relating central concepts in the neurobiology of memory and aging to timing and targets of interventions.

Keywords: Cortex, hippocampus, atrophy, brain imaging, episodic memory, maintenance, compensation, reserve, plasticity, intervention

Introduction

The title of this subsection of the present volume, *individual differences and development*, captures a major trend in the cognitive neuroscience of memory. While much past work was concerned with general trends and central tendencies in developmental cognitive and brain changes (see Cabeza, Nyberg, & Park, 2005), there is now broad agreement that the aging brain-mind is characterized by just as much, or even greater, inter-individual variation than what is seen in young adulthood (e.g., Lindenberger, 2014). Thus, while clearly many older adults suffer from detrimental neurocognitive alterations, there is also a growing literature on well preserved functioning in older age (see e.g., Nyberg & Pudas, 2019). This is good news in view of global population aging, but many unresolved issues and challenges remain. These challenges include furthering our understanding of the factors that predict declining or preserved abilities in older age, and whether trajectories can be influenced in a positive direction.

In this chapter we will consider some of these outstanding challenges. We focus on a highly age-sensitive form of memory; episodic long-term memory. Relevant cognitive processes and models of episodic memory are discussed in detail in several other chapters. The same is true for discussions of mnemonic changes in infancy, adolescence, middle-age, and aging. Therefore, to set the stage for the more in-depth consideration of relevant neurobiological changes, we only provide a cursory review of episodic-memory and its changes in aging. Thereafter, building on several previous in-depth reviews, we summarize typical patterns of aging-related neurobiological changes that have been linked to episodic memory decline. In the next section of the chapter, we discuss observations and theoretical models of heterogeneity in neurobiological aging and memory. Finally, we discuss the possibility of influencing neurobiological aging by means of various interventions.

Narrowing the scope: Human brain imaging and longitudinal designs

Admittedly, the term "neurobiological aging" is quite broad, and can encompass changes at many different levels of neuroscientific investigation. Here, we will adopt a systems-levels perspective and focus on findings from human brain-imaging studies. Of the many existing imaging modalities, we will particularly consider structural and functional magnetic resonance imaging studies (sMRI; fMRI). Most structural and functional MRI studies have whole-brain coverage but in relation to brain alterations of relevance for age-related decline in episodic memory, regions such as the hippocampus / medial temporal lobe (MTL) (see chapter 4.4) and frontoparietal regions (see chapter 5.9) will be of particular importance. Age-related changes in various kinds of neurotransmitter systems as measured by positron emission tomography (PET) have also been linked to episodic-memory decline, notably changes in dopaminergic neurotransmission (e.g., Bäckman et al., 2006; see also chapter 4.5). Correspondingly, we will present some PET findings on dopamine, and also for tau and beta-amyloid deposition.

For episodic memory (e.g., Rönnlund et al., 2005) as well as structural and functional MRI (e.g., Nyberg et al., 2010; Raz et al., 2005) it has been empirically demonstrated that inferences on age-related changes from cross-sectional designs may markedly deviate from data from longitudinal studies. While both designs come with challenges and threats to the validity of conclusions, only longitudinal observations capture true change (for an in-depth discussion of this topic, see Raz & Lindenberger, 2011). Therefore, we will put special emphasis on observations from longitudinal imaging studies. Here it should be noted that still to this date, the number of longitudinal brain-imaging studies is quite low and there is limited consensus on critical methodological aspects, such as how to handle missing data (see Nyberg, Pudas & Lundquist, 2016). We expect this state of affairs to be changed in the

near future, as the number of longitudinal imaging studies is increasing, and large-scale consortium studies are ongoing (e.g., *Lifebrain*; see Walhovd et al., 2018).

The average profile of episodic memory change

Episodic-memory changes in development and aging are reviewed in other chapters of this volume and elsewhere (see e.g. (Nyberg & Pudas, 2019) for a recent discussion), and here we will only highlight the most important conclusions. Generally, declarative episodic memory tasks show more decline with age than procedural and semantic memory tasks (Brickman & Stern, 2009; Ronnlund, Nyberg, Backman, & Nilsson, 2005). While cross-sectional studies have tended to report decline, sometimes even linear, across the adult lifespan (D. C. Park et al., 2002; Salthouse, 2009), longitudinal studies tell a different story. Results from the Swedish Betula study and the Seattle longitudinal study of aging converge on memory decline being detectable from around age 60 (Ronnlund et al., 2005; Schaie, 1994), with stability in function characterizing the preceding adult time period. Findings from the Whitehall II study indicated longitudinal memory decline also in the ten years before 60, which was the youngest age included (Singh-Manoux et al., 2012). Still, indices of accelerating decline with higher age were seen. Thus, accelerated decline in the last part of life seems to be a common feature in longitudinal studies. In the Whitehall II study, the authors suggested that the cross-sectional analyses over-estimated the age-effects in women, mainly due to higher levels of education in the younger compared to the older women (Singh-Manoux et al., 2012). Such generational differences may substantially affect cross-sectional age-estimates across many cognitive functions, verbal recall being among those showing the strongest cohort effect (Schaie, 1994). Longitudinal studies face their own challenges, such as improvements in scores due to repeated test-exposure and selective

attrition, but these can be addressed statistically in different ways depending on available data (Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012; Ronnlund et al., 2005). In conclusion, there is consensus that decline in episodic memory happens on a group level after approximately 60 years of age, while the amount of decline before that age is smaller or non-existing. There are individual differences in memory change, however, with many individuals deviating substantially from this general pattern. This will be reviewed and discussed in the next main section of the chapter.

As briefly hinted at above, the typical age-trajectory of memory function will depend on the specific type of memory being tested. A variety of tasks and stimuli have been used, and this factor impacts the derived age-functions. One particular line of research has focused on pattern separation vs. pattern completion, and possible specific effects of age on each of these processes – in particular pattern separation (Yassa & Stark, 2011). Pattern separation is the ability to discriminate among similar experiences, which is a critical feature of episodic memory encoding (Yassa & Stark, 2011). Pattern completion is achieved when recall of a complete representation is accomplished in the presence of partial or degraded input (Yassa et al., 2011a). Both pattern separation and pattern completion deficits are likely frequent in aging, contributing to the observed reductions in episodic memory function reviewed above. For instance, evidence from rodent studies has been interpreted to suggest that an inability to represent an identical environment as the same place is caused by excessive pattern separation in the CA1 region in older animals (Yassa & Stark, 2011). In CA3, the opposite change has been observed, where old rats exposed to distinct environments tend to retrieve the same map, indicative of excessive pattern completion mechanisms. These findings are interpreted as evidence for increased CA3 and dent ate gyrus activity linked to pattern separation/ completion deficits in aged humans (Yassa et al., 2011a).

Recent behavioral studies in humans have found evidence to support a hypothesis that age-related changes in hippocampal integrity shift the balance of these memory processes in favor of pattern completion - the retrieval of already stored information - to the detriment of pattern separation - encoding of new stimuli (Vieweg, Stangl, Howard, & Wolbers, 2015; Wilson, Gallagher, Eichenbaum, & Tanila, 2006). These investigations into the sub-processes of episodic memory are very interesting, but they have not yet been implemented in any larger longitudinal studies of episodic memory changes. Thus, the importance of pattern separation and pattern completion deficits in aging for the general age-trajectories of episodic memory remains to be characterized in more detail.

The changes in episodic memory with aging have their parallels in structural and functional brain changes. The next sections of this chapter review main age-changes in the brain relevant for episodic memory, and how these may explain both general trends in function across adult life as well as individual differences in level and change in episodic memory.

Brain aging – canonical patterns of change in relation to episodic memory

Brain structure and episodic memory-related brain activity change with age (L. Nyberg, 2017), with large variations in the magnitude of change across brain regions and in the shape of the age-trajectories. For instance, cortical thickness typically shows monotonous and relatively linear decline with age (Fjell, Westlye, et al., 2014; Salat et al., 2004; Storsve et al., 2014), while U-shaped trajectories are seen for white matter (WM) mean diffusivity (MD) and intracortical myelination (Grydeland et al., 2019; Grydeland, Walhovd, Tamnes, Westlye, & Fjell, 2013) and inverse U-shaped functions for WM fractional anisotropy (FA) (Fjell et al., 2010; Sexton et al., 2014). Structural brain changes tend to be larger in magnitude than

functional changes, but small to moderate age-effects are also seen for brain activity studied by positron emission tomography (PET) and functional MRI (fMRI) (Beason-Held, Kraut, & Resnick, 2009; Persson, Pudas, Nilsson, & Nyberg, 2014). Although the causes and the molecular underpinnings of structural brain changes remain to be fully understood, regional differences in cortical change seem to be governed by principles laid down in early development (Fjell et al., 2018), even at the embryonic stage (Rakic, 1988; Rakic, Ayoub, Breunig, & Dominguez, 2009). Cortical maturation to a certain degree proceeds along functional and structural networks known from research on adults (Alexander-Bloch, Raznahan, Bullmore, & Giedd, 2013; Krongold, Cooper, & Bray, 2017; Raznahan et al., 2011; Sotiras et al., 2017; K. B. Walhovd et al., 2015; Zielinski, Gennatas, Zhou, & Seeley, 2010), and it has been shown that the fundamental organizational principles for regional brain development in children can be traceable also in higher age (Fjell et al., 2018). This means that anatomical regions that develop together also show distinct lifespan trajectories of adult cortical change and decline in aging. Thus, when searching for neuroanatomical correlates of age-changes in memory function, it may often be beneficial to look at wider age-ranges, including middle-aged and even younger adults.

Cortical thickness changes more steeply with age and is more affected by later-life events than cortical surface area (Engvig et al., 2010; Storsve et al., 2014; Wenger et al., 2012). It seems as if cortical surface area is more strongly related to early life factors, and cortical thickness is relatively more sensitive to later life factors. Empirical support for this view comes from studies showing larger effects of birth weight and other obstetric factors on surface area than cortical thickness (Jha et al., 2018; Martinussen et al., 2005; Raznahan, Greenstein, Lee, Clasen, & Giedd, 2012; K. B. Walhovd et al., 2012), and environmental interventions affecting cortical thickness (Engvig et al., 2010; Wenger et al., 2012). As likely

more amendable to environmental influences through life, cortical thickness changes may also relate more strongly to more specific cognitive functions, indicated by lower loadings on the *g*-factor. Episodic memory is one such putatively more specific function (Deary, Penke, & Johnson, 2010), which shows different change trajectories across people (Josefsson et al., 2012; Salthouse, 2016). This is evidenced by weaker relationships between episodic memory change and global cognitive change compared to the relationships between global cognitive change and abstract reasoning and spatial visualization (Tucker-Drob, 2011). In line with this view, recent results suggest that lifespan changes in episodic memory are more closely related to cortical thickness changes while general cognitive function is more strongly associated with cortical surface area (Fjell et al., 2018). One implication of this differential pattern may be that the cortical measures most strongly related to episodic-memory change may be more influenced by the life-long accumulation of environmental factors than for instance cortical measures underlying general cognitive function. However, this speculation should be supported by more research. In a recent meta-analysis, episodic, prospective and working memory change were numerically more weakly related to global cognitive change than speed, spatial abilities and reasoning (Tucker-Drob, Brandmaier, & Lindenberger, 2019). Still, the authors noted that in general, shared variation in changes did not differ substantially across cognitive ability domain. More generally, the relationship between cognitive change and structural brain change is moderate at best, which means that correlated change at the level of cognition does not need to be accompanied by highly correlated changes on the brain level.

Studies of memory-related brain activity have identified core regions that seem to be highly involved in memory processing, many of which involve communication and interaction with the hippocampus and other medial temporal lobe structures (Moscovitch,

Cabeza, Winocur, & Nadel, 2016). This includes regions in for instance the prefrontal (Eichenbaum, 2017) and parietal (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008) cortex. Thus, successful episodic memory depends on the integrated contributions from multiple different brain regions.

As described above, most brain regions show considerable structural changes with age. Since episodic memory involves multiple brain regions that show substantial structural age-changes, it follows that it may not be realistic to find a simple one-to-one-relationship between episodic memory decline in aging and structural degradation of a smaller number of specific brain structures. Still, medial temporal and prefrontal decline – consistent with abundant evidence of core regions supporting episodic memory - arguably constitute the regions undergoing the most excessive atrophy in normal aging (Fjell et al., 2013). It is interesting to note that the accelerated decline in episodic memory function with increasing age shows similarities to the age-trajectories of hippocampal volume and partly entorhinal cortex thickness. Actually, the age-trajectories of episodic memory tend to be much more similar to the trajectories of medial-temporal volume compared to the trajectories of regions in the prefrontal cortex, which typically show more linear decline from an earlier point in life (see Figure 1).

Several studies have also shown that longitudinal brain changes in the medial temporal lobes are correlated with changes in cognitive capacity, and episodic memory function in particular (Fjell et al., 2013; Fjell, McEvoy, et al., 2014; Fjell et al., 2012; Gorbach et al., 2017; Murphy et al., 2010; Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012b; Persson et al., 2011; Rodrigue & Raz, 2004). However, it should be stressed that in normal aging, structural changes in the medial temporal lobe explain only a modest part of age-changes on the typically used episodic memory tests. This is in accordance with the tendency

in the literature that the relationship between cognitive function and any measurable property of the brain is of limited strength. This can be due to a number of reasons. Theoretical accounts such as reserve factors (Stern et al., 2018; Stern et al., 2019) and compensation theories (Cabeza et al., 2018) can partly explain why cognitive function and brain structural changes do not always go hand in hand (see further discussion below). The modest relationships can also be explained by non-perfect structural brain measures regarding precision and reliability. It also seems that models including multiple types of brain measures, such as multi-modal neuroimaging, tend to be superior in explaining cognitive changes (K. B. Walhovd & Fjell, 2016) compared to simpler, unimodal models.

The age-vulnerability of the medial-temporal lobe system fits well with the recent focus on age-decline in spatial processing and navigation (Lester, Moffat, Wiener, Barnes, & Wolbers, 2017). These functions are heavily dependent on a number of functionally specialized cell types in the medial temporal lobes such as place (O'Keefe & Dostrovsky, 1971) and grid cells (Fyhn, Hafting, Witter, Moser, & Moser, 2008; Hafting, Fyhn, Bonnevie, Moser, & Moser, 2008). Although spatial processing and navigation cannot be equated with episodic memory, they are functionally and anatomically highly interdependent systems. Episodic memories typically have a visual code, and inefficient retrieval from long-term memory is a likely contributor to decline in navigational abilities with higher age (Head & Isom, 2010; Iaria, Palermo, Committeri, & Barton, 2009). One mechanism by which spatial representations may be reinstated in the hippocampus is pattern completion (Lester et al., 2017), dependent on cells in the hippocampal subfield CA3 (Neunuebel & Knierim, 2014). As described above, increased CA3 and dentate gyrus activity has been linked to pattern separation/ completion deficits in aging, suggesting that the aging hippocampus is less efficient in distinguishing between similar stimuli (Yassa, Lacy, et al., 2011; Yassa, Mattfeld,

Stark, & Stark, 2011). Thus, age-related structural decline of the medial-temporal lobe system may account for reduced efficiency of multiple cognitive processes related to episodic memory function. At the same time, most agree that episodic memory in humans have unique features not shared by other species, including concepts such as self, subjective time, and autonoetic consciousness (Tulving, 2002). Such aspects of episodic memory are supported by structures outside the hippocampus and medial temporal lobe, and these cannot easily be studied by use of rodent models.

In addition to the morphometric age-changes, structural and functional connections between the widely distributed regions involved in episodic memory are also affected by age, although fewer longitudinal studies targeting structural and functional connectivity in aging exist. Based on partly cross-sectional and partly longitudinal studies, the conclusion so far is that indices of white matter microstructure as measured with diffusion tensor imaging (Fjell et al., 2010; Sexton et al., 2014) or other MR modalities (Grydeland et al., 2019; Grydeland et al., 2013) typically show protracted development curves, with apparent improvement often seen throughout young adulthood. It is tempting to speculate that these age-related differences in white matter microstructure can explain some of the canonical changes in memory function in aging. This question has been addressed in only a few longitudinal studies. Two studies did not find any relationship between changes in white matter indices and changes in episodic memory function (Lovden et al., 2014; S. J. Ritchie et al., 2015) while a third reported significant change-change relationships between microstructure and episodic memory (Fjell et al., 2016). One adult lifespan study found the expected positive relationships between white matter quality as measured by DTI and memory performance in the cross-sectional analyses, while the opposite relationships was observed in the longitudinal analyses (Bender, Prindle, Brandmaier, & Raz, 2016). How such

a discrepancy between cross-sectional and longitudinal results can be explained is not yet clear and serves as a reminder that more longitudinal studies are needed, both observational and interventional (see later sections for discussions of the latter). Further, more research is needed to illuminate whether longitudinal relationships between white matter microstructure and episodic memory can account for any substantial portion of the canonical age-related decline in memory function.

A related interesting question regards to what degree anatomical specificity exist in the cognition – white matter microstructure relationships. One longitudinal study found that changes in functional and structural connectivity were both related to episodic memory outcome over 3 years and that each class of measure explained unique variance (Fjell et al., 2016). Both hippocampal-cortical and fronto-striatal functional connectivity changes were predictive of memory change, underscoring the view that multiple regions and systems are important for memory maintenance in aging. Interestingly, the structural and functional connectivity changes that predicted memory change were anatomically closely aligned, suggesting at least some anatomical structure-function specificity. Other cross-sectional studies have shown that common variance across large parts of the human white matter account for most of the age-related variance in cognitive function (Hedden et al., 2016; Penke et al., 2010). A cross-sectional study directly testing whether a general factor could account for the age-effects on microstructure of white matter tracts found a substantial amount of tract-specific individual differences in white matter microstructure, and concluded that between-person differences in white matter microstructure partly generalized across the brain and partly played out differently for distinct tracts (Lovden et al., 2013).

Also, memory-related brain activity is often found to differ between younger and older persons. Successful memory encoding is associated with increased activity in widespread cortical regions, including left-lateralized fronto-parietal cortical networks and the hippocampus, and reduced activity in parts of the default-mode network (Kim 2011; Sneve et al. 2015). In older adults, memory encoding is often associated with smaller posteromedial deactivation, lower fronto-parietal activity and recruitment of additional prefrontal regions – typically contralateral to the dominant frontal activity patterns in young adults (Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2011; Düzel et al. 2011; Park et al. 2013; Maillet and Rajah 2014)(Cabeza et al. 2002). Such increased brain activity in higher age is sometimes regarded as compensatory, especially if it correlates with better memory performance (Grady 2012). However, if such age-specific activity increases do not correlate with better memory performance, it is less clear whether this reflects compensatory activity, neural inefficiency, or dedifferentiation (Grady 2012; Nyberg et al. 2012; Rugg 2016). Higher prefrontal activity in aging has been found to be both positively (Dennis et al. 2007; de Chastelaine et al. 2016) and negatively (Duverne et al. 2009; de Chastelaine et al. 2011) related to memory performance. Moreover, encoding activity in older age in the regions associated with successful memory encoding in younger adults – i.e. left inferior frontal gyrus and posteromedial cortex - often adheres more to a brain maintenance model as associations between activity and memory function emerge in higher ages (Miller et al. 2008; Duverne et al. 2009; Mattson et al. 2013; de Chastelaine et al. 2016;)Vidal-Pineiro et al., 2018). These issues will be further discussed in the next section.

Defining canonical patterns of age-trajectories for memory-related brain activity has been difficult, because the age-curves will depend on the specific task, the contrast used to isolate effects, and also vary greatly among brain regions. On top of this, there is a paucity of

longitudinal studies, most sample a limited age-range, and since task-fMRI requires considerable effort and investment, most studies have limited sample sizes (< 100). Thus, in contrast to structural studies of brain aging, the typical or average age-profile of memory-related brain activity is more difficult to describe. As reviewed above, hippocampal regions undergo substantial structural changes in aging. Hippocampus and nearby medial temporal lobe regions have also been scrutinized in aging studies of memory-related activity with fMRI. Some studies report lower hippocampal activity associated with successful episodic memory in older persons (Cabeza et al., 2004; Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006; Dennis, Hayes, et al., 2008; Dennis, Kim, & Cabeza, 2008; Murty et al., 2009), but many also find similar levels of activity between older and younger (Cansino et al., 2015; de Chastelaine, Mattson, Wang, Donley, & Rugg, 2016b; Duverne, Habibi, & Rugg, 2008; H. Park, Kennedy, Rodrigue, Hebrank, & Park, 2013)(for reviews, see (Leal & Yassa, 2013; Lars Nyberg, 2017). When age effects are seen, they are sometimes affected by differences in task performance between the groups (de Chastelaine, Mattson, Wang, Donley, & Rugg, 2016a), which seems reasonable given that longitudinal studies have found differences in activity change over time as a function of memory function (Persson et al., 2012; Pudas et al., 2013). Studies targeting different hippocampal regions have also found selective age-correlations in some but not others (Carr et al., 2017), such as anterior hippocampus during encoding (Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003; Salami, Eriksson, & Nyberg, 2012). A meta-analysis found that older persons activated right anterior hippocampus more than younger during retrieval of episodes and while envisioning the future (Viard, Desgranges, Eustache, & Piolino, 2012). Such findings suggest that increasing age may be selectively related to lower anterior hippocampus activation during encoding and higher anterior hippocampus activation during retrieval. Yet another study found that a

part of posterior hippocampus was sensitive to relational memory retrieval in older adults but not in younger (Wang & Giovanello, 2016). Thus, differential age effects on anterior vs. posterior hippocampus are often found, depending on the memory process examined , especially encoding vs. retrieval. A large cross-sectional study of encoding and retrieval in the anterior and posterior hippocampus found larger effects of age on retrieval activity than encoding activity (Langnes et al., 2018). Increased retrieval activity was seen throughout the adult lifespan, peaking at around 70 years, before negative age-relationships were seen towards the end of life. In contrast, encoding activity was very weakly related to age. In other brain regions, such as the posterior-parietal cortex, more expected age-curves have been reported, with reduced retrieval activity and smaller encoding-related task negativity (Amlien, Sneve, Vidal-Pineiro, Walhovd, & Fjell, 2018). Finally, a recent longitudinal study from the Betula project found process-specific (encoding, not retrieval) in anterior but not posterior hippocampus during a face-name task (Nyberg et al., 2019). Taken together, we are not at a stage where we can conclusively define canonical age-trajectories for memory-activity as measured with fMRI. Further data are needed to shed light on this issue., and high-resolution fMRI holds promise in this regard (Carr et al., 2017).

In sum, age-effects on brain structure and function are found for most measures and regions, but with substantial heterogeneity with regard to region and shape of trajectories. Regions heavily involved in episodic memory processing seem to be among those showing most age-changes (Fjell, McEvoy, et al., 2014). For medial temporal lobe cortex, as well as most white matter tracts, age-trajectories show accelerated decline in the last part of the life-span. This pattern shows similarities to what is typically observed for episodic memory test scores. In contrast, prefrontal regions, also showing involvement in episodic memory tasks, typically show a different trajectory, with close to linear declines.

Heterogeneity in brain aging

After having considered the canonical pattern of age-related changes in episodic memory and associated brain alterations, we now turn to heterogeneity in change. As noted in the Introduction, there are marked Individual differences in onset and rate of change for brain and cognitive variables. For episodic memory, longitudinal findings from the Swedish Betula project can serve as an illustration. In Betula, about 4500 participants have been extensively examined one or several times over a 30-years period (e.g., Nilsson et al., 2004). Three core samples of about 1000 individuals each were first examined in 1988 or 2003, and many individuals in these samples have then been re-tested every five years thereafter on a broad battery of cognitive, biological, and lifestyle measures. An important aspect of the Betula study is that it involves population-based sampling through random selection of names from the population registry, and comparative analyses with data from the entire population indicate that the included participants are quite representative. Thus, in contrast to studies that rely on various forms of convenience sampling, Betula is well suited for addressing questions related to normal variation in the general population.

Analyses of longitudinal data for episodic memory have revealed massive heterogeneity in trajectories (Figure 2a). To reveal distinct trajectories in episodic memory over time, data from about 1500 Betula participants with two or more test sessions were analyzed with a random-effects pattern-mixture model that considered the effect of non-random attrition (Josefsson et al., 2012). The findings showed that about two-thirds of the sample adhered to the canonical pattern described above, with significant decline after age 60. The remaining part consisted of individuals who either showed earlier-than-average

onset and more rapid memory decline ("decliners), or individuals who showed stable levels of memory performance over the examined time period ("maintainers").

Analyses of data from an independent north-American sample had revealed a similar pattern of distinct trajectories in episodic-memory decline (Yaffe et al., 2009). Together with findings from other longitudinal studies (Fjell et al., 2016) these observations (Josefsson et al., 2012; Yaffe et al., 2009) demonstrate substantial variability in the older population with regard to the magnitude of episodic-memory change. A key question is how such heterogeneity can be explained. A complete account will likely require examination at many levels, including the role of genetic, epigenetic, early life developmental, and lifestyle factors (e.g., Nyberg & Bäckman, 2011; Nyberg & Pudas, 2019). Here we concentrate on the neurobiological level and consider patterns of preservation and decline in brain structure and function in relation to variability in episodic-memory performance in aging. A foundation for pursuing this brain-cognition account of heterogeneity in memory aging is the existence of marked inter-individual variability in the degree of age-related brain changes (Figure 2b). We organize the presentation and discussion of relevant observations according to three dominant theoretical concepts in the cognitive neuroscience of aging: maintenance, reserve, and compensation (see Cabeza et al., 2018).

Brain maintenance

Brain maintenance has been defined as; "individual differences in the manifestation of age-related brain changes and pathology allow some people to show little or no age-related decline" (Nyberg et al., 2012). Thus, the maintenance concept is founded on variability in cognition as well as brain changes within the older population, and a key prediction of the brain-maintenance account is that older adults with relatively well-preserved episodic memory or other forms of cognition should display relatively minor brain changes. Several

studies using different neuroimaging methods provide support for this prediction, including (i) MRI studies of hippocampal volume in relation to episodic memory, (ii) MRI studies of cortical thickness in relation to executive functions, (iii) MRI studies of white-matter connectivity in relation to working memory, (iv) fMRI studies of episodic and working memory, (v) PET studies of dopamine D1 and D2 systems in relation to interference resolution, and (vi) PET studies of amyloid burden in relation to episodic and working memory (empirical evidence reviewed in Nyberg et al., 2012).

More recent evidence also supports the brain-maintenance account of preserved episodic memory in aging, in particular the link between maintained hippocampus structure and function and preserved memory (cf., Nyberg & Lindenberger, 2019). Starting with hippocampus structure, in a comprehensive structural MRI study, 15-year changes in episodic memory, word fluency, fluid IQ, and processing speed were related to 4-year changes in cortical and subcortical gray matter volume and white-matter connectivity and lesions (Gorbach et al., 2016). Of the many examined brain and cognitive parameters, only age-related hippocampal atrophy was significantly related to memory change.

Turning to functional responses of the hippocampus, longitudinal changes in functional connectivity at resting state have been related to 15-year changes in episodic memory (Salami et al., 2016). It was found that over time an elevation of functional connectivity in the posterior medial temporal cortex was associated with decreasing episodic memory. It should be stressed that no such relation was seen in the anterior medial-temporal lobe, which is in line with the notion of functional heterogeneity along the hippocampus longitudinal axis and among different hippocampus subfields, as reviewed elsewhere (e.g., Strange et al., 2014). Another longitudinal study found that while hippocampal-cortical functional connectivity predicted memory change in young, changes in

cortico-striatal functional connectivity were related to change in recall in older adults (Fjell et al., 2016). This was interpreted as suggesting that episodic memory deficits in normal aging are partly related to disturbance of a striatal-prefrontal network. However, there is a complex picture, as the functional connectivity–memory relationships were in opposite directions across age groups, while the relationships between structural connectivity and memory were in the same and expected directions regardless of age—less increase in mean diffusion was associated with more favorable memory outcome. Furthermore, in a targeted memory intervention study, lower resting-state activity of the hippocampus was predictive of more memory improvement in older adults (Brathen et al., 2018). Thus, cross-sectional and longitudinal studies have reported differences in functional connectivity with age, and that some of these differences may be related to memory performance or change in memory performance (but see Salami et al., 2016). Challenges remain with regard to interpretations, especially as the direction of effects vary across regions and studies. These issues seem to be less problematic in task-based fMRI studies.

A task-based fMRI study used episodic-memory longitudinal data from Betula, acquired prior to the imaging session, to classify participants into those with average memory decline versus older adults will well-preserved episodic-memory functioning (*maintainers*; Pudas et al., 2013). The two groups were compared on brain-activity patterns during an episodic-memory encoding task, and it was found that the *maintainers* showed higher hippocampus BOLD signal than the average group. Thus, maintained functionality of the hippocampus was related to preserved memory.

PET studies have provided additional relevant information on the link between maintenance of hippocampus integrity and episodic memory in aging. For example, a PET study of tau deposition found that increased tau tracer retention in the medial temporal

lobe predicted worse episodic memory performance (Schöll et al., 2016). Also, a PET study of dopamine D2 binding in a large (N=181) age homogeneous (64-68 years) sample found that high ("youth-like") hippocampal D2-binding was related to higher episodic-memory performance (Nyberg et al., 2016). In addition, in the same study caudate D2 was related to episodic memory, and caudate and hippocampus D2 binding were interrelated.

More generally, while the hippocampus has a prominent role in episodic memory, its network interactions with other regions have since long been recognized (e.g., Eichenbaum, 2017). Similarly, brain maintenance of relevance for episodic memory may extend beyond the hippocampal circuit (cf., Nyberg & Lindenberger, 2019), and for example involve cortico-striatal connections (Fjell et al., 2016). This more global perspective on brain maintenance also raises issues on "functional specificity or generality"; will individuals with well-preserved episodic memory also tend to show preserved functionality in other cognitive domains? For instance, a recent meta-analysis found that 60% of the variation in cognitive change was shared across cognitive abilities, and that this shared variance in change increased to approximately 70% at sage 85 (Tucker-Drob et al., 2019). Those declining more in memory function than their peers were also more likely to decline more steeply in reasoning and processing speed relative to others.

Another, largely unresolved, question concerns the underlying mechanisms of brain maintenance in general, and hippocampal maintenance in particular. Several, possibly interacting mechanisms have been proposed (Nyberg & Lindenberger, 2019). One such mechanism concerns maintaining neurons, and it includes avoiding pathological cell loss and preserving neurogenesis. It remains debated whether neurogenesis continues in older age, but this remains a possibility (Boldrini et al., 2018; Sorrells et al., 2018). Also, a higher degree of neurogenesis in younger age might contribute to brain maintenance in older age (Seib &

Martin-Villabe, 2015). A second class is maintaining neuronal morphology. There is evidence that cell death is quite modest in normal aging (Haug, Kuhl, Mecke, Sass, & Wasner, 1984; von Bartheld, 2017), but there is abundant evidence for alterations in synaptic efficacy (Lister & Barnes, 2009). For example, dendritic spine changes or preservation have been linked to cognitive aging (Dickstein et al., 2013). The third broad class of mechanisms, non-neural factors, include presentation of glia cells and vascular health. In particular, there is accumulating evidence for an early role of vascular and arterial alterations in cognitive aging, and for hippocampus and episodic memory in particular (Wåhlin & Nyberg, 2019). Possibly, then, promoting vascular health could contribute to brain maintenance, and we will return to the topic of prevention and intervention later in the chapter.

Reserve and compensation

Brain maintenance constitutes the primary path towards well-preserved episodic memory in aging, but most likely there exist multiple paths (Nyberg & Pudas, 2019). In particular, there is strong evidence that some individuals who have suffered age-related pathological brain alterations can still show relatively intact cognitive functioning. One way of explaining such a paradoxical pattern is by considering *reserve* and *compensation* factors.

The use of reserve and compensation concepts in this context has a rather long history. Rotschild (1937) examined 24 cases of 'senile psychosis' and observed no correlation between histologic changes and degree of intellectual impairment. It was concluded that the observed inconsistency reflected individual differences in the *capacity to compensate* for the cerebral damage. Blessed, Tomlinson, and Roth (1968) related a 'dementia score' and performance on tests such as 'remote and recent memory' to post-mortem cerebral plaque counts. They observed significant correlations for both the dementia (correlation of +0.77) and cognitive (correlation of -0.59) scores, supporting a strong relation between intensity of

plaque formation and intellectual deterioration. Still, there was marked inter-individual differences which prompted the conclusion that; “it would appear that a certain amount of the change estimated by plaque counts may be accommodated within the *reserve capacity* of the cerebrum without causing manifest intellectual impairment” (p. 807, italics added here).

Thus, in these early investigations as well as in many subsequent studies, the concepts of reserve and compensation have been used to account for a discrepancy between the degree of brain damage (e.g., following a head injury) or pathology (e.g., in neurodegenerative diseases such as Alzheimer’s dementia) and its clinical manifestation (e.g., performance on neuropsychological tests). Recent studies have shown neuropathology suggestive of Alzheimer’s Disease or related dementias in half of non-demented older adults, highlighting the far from perfect relationship between cognitive function and brain pathology (Hachinski, 2019). Some authors distinguish between passive and active forms of reserve, where the passive form has been denoted ‘brain reserve’. In an early study by Katzman and colleagues, they found that a subgroup (N=10) of a larger sample (N=137) displayed pathological features suggestive of Alzheimer’s disease, but had a high level of neuropsychological functioning (Katzman et al., 1988). In the spirit of passive brain reserve, the authors concluded that one explanation for this discrepancy could have been that they started with larger brains and more large neurons. Subsequent definition of brain reserve align with the Katzman version by stressing larger brains and more neurons or synapses, but also mention that life experiences can influence brain anatomy via factors like neurogenesis and resistance to apoptosis (Stern, 2009). By this more recent definition, there are apparent similarities between brain reserve and brain maintenance (Nyberg & Lindenberger, 2019).

Active forms of reserve are close in spirit to compensation, as in the definition of 'cognitive reserve' by Stern (2009); "individual differences in how people process tasks allow some to cope better than others with brain pathology" (p. 2016). In the domain of the cognitive neuroscience of aging, increased functional brain activity, notably in regions of the prefrontal cortex, has been frequently observed (see Cabeza, 2002). When related to task performance, there is evidence that elevated functional brain responses can reflect better as well as worse performance (see Grady, 2012; see also Cabeza et al., 2018). Still, there is some consensus that increased frontal activation with age is a reflection of compensatory 'scaffolding' in response to alterations in brain structure (Park & Reuter-Lorenz, 2009).

Longitudinal empirical findings consistent with this view were observed in the Betula study (Pudas et al., 2018). Episodic-memory performance was monitored over 25 years for 130 individuals. All individuals had stable performance over the first 2 decades, but thereafter a subgroup (N=41) displayed a marked drop in performance whereas the remaining 89 participants continued to display stable performance. Two MRI sessions, 4 years apart, were included at the end of the study period. Significant hippocampus atrophy was seen in both groups from the first to the second wave, but with a significantly smaller right hippocampus in the decline group. Functional MRI data revealed upregulated prefrontal functional responses in the decline group during memory encoding and retrieval.

Taken together, these longitudinal observations are in line with the notion that "increased frontal activation with age is a marker of brain that engages in compensatory scaffolding in response to the challenges posed by declining structures and function" (Park & Reuter-Lorenz, 2009, p. 173). It should be stressed that this conclusion presupposes longitudinal data; high cross-sectional frontal activity in older adults can still be consistent with declining frontal activity over time (see Nyberg et al., 2010). Moreover, a recent study

found that higher frontal encoding-related activity distinguished between high and low-performers among older adults, but not among middle-aged or younger (Vidal-Pineiro et al., 2018). The older high performers showed the same level of activity in the frontal cortex as the young participants, and also maintained stable memory function over the previous eight years. In contrast, the low-performers showed lower frontal activity, declining memory function, smaller hippocampi and steeper rates of entorhinal cortical atrophy over the same eight years. Although brain activity was examined cross-sectionally, these results are in line with the view that maintenance of prefrontal brain activity is a key to high memory function in aging. It has been proposed that it may be useful to distinguish between different forms of compensation; (i) by upregulation, (ii) by selection, and (iii) by reorganization (Cabeza et al., 2018). In the Pudas et al. (2018) study, the prefrontal regions in which increased functional recruitment was observed were located outside or on the borders of the regions that defined the core encoding and retrieval networks. As such, the findings could have reflected upregulation (expanding the borders of activated regions could signal greater effort) or reorganization (engaging new regions that do not typically support the examined mnemonic processes), but they are less compatible with selection (using qualitatively different processes and brain networks). As this example illustrates, it is hard to specify the exact form of compensation in a given study, and multiple forms of compensation may be expressed in the same individual. Still, the delineation of different forms of compensation and the activation patterns that define them take an important step away from the ad-hoc nature that has characterized interpretations of observed age-related brain changes.

Predictors of maintenance, reserve, and compensation

We have discussed heterogeneity in memory aging from the theoretical perspectives of maintenance, reserve, and compensation. In brief, the maintenance concept contributes

towards explaining heterogeneity in aging by highlighting the dimension of no/little age-related changes versus more typical age-related alterations. The reserve and compensation accounts contribute further by explaining variability in the magnitude of performance reduction for a given degree of age-related brain alteration. It has been proposed that individual differences in cognitive reserve explain variability in how well different individuals make use of compensatory strategies (Park & Reuter-Lorenz, 2009). Similarly, Cabeza and colleagues (2018) noted that differences in accumulated reserve may underlie individual differences in the repertoire of alternative neural strategies. Thus, an outstanding question is whether it is possible to promote brain maintenance as well as cognitive reserve (and by extension capabilities of compensation).

In the above described Betula study of distinct trajectories in episodic memory over time (Josefsson et al., 2012), the two-thirds of the sample with average memory decline after age 60 made up the reference group. The decliners and maintainers were compared with the reference group on a select number of genetic and lifestyle-related factors. Memory decline was characterized by a higher number of men, lower education, not active in the labor force, and more frequently carriers of the ApoE □4-allele. Maintainers were characterized by higher education, a higher number of women, carriers of the met allele of COMT, and higher levels of physical activity. In a subsequent examination, the maintainer group was also found to have a younger epigenetic age than the other groups (Degerman et al., 2016).

Thus, maintenance was related to genetic, epigenetic, and experience-related factors (cf., Nyberg & Pudas, 2019). Here we like to highlight education, being engaged in the labor force, and physical activity, as these factors also have been extensively discussed in relation to cognitive reserve (e.g., Richards & Deary, 2005; Scarmeas & Stern, 2003; Valenzuela &

Sachdev, 2006). Specifically, across the lifetime, aspects of educational and occupational attainment may help to increase the cognitive reserve. Moreover, it has been shown that lifestyle activities in mid-life can influence cognitive reserve and thereby cognitive performance – independent of education, occupation, and late-life activities (Chan et al., 2018; see also Boraxbekk et al., 2016). The similarity in observed associations for maintenance and reserve is indicative of a 'nested relationship', such that individuals who show fewer age-related brain changes (maintenance) are also less affected by pathology when it eventually manifests (reserve; cf., Nyberg et al., 2012).

Taken together, while genetic factors no doubt exert a marked influence, the observed associations of education, occupation, and activities with both brain maintenance and cognitive reserve suggest that they at least to some degree are modifiable. However, as has been noted (Barulli & Stern, 2013), the transition from observation to intervention is not straightforward. In the next and final section of the chapter we will focus on findings from direct intervention studies of relevance to heterogeneity in the neurobiology of memory.

Given heterogeneity in neurobiological aging, can memory be improved?

The abundant individual differences in memory performance and its neural substrates in aging (Nyberg & Pudas, 2019) beg the question whether we can influence our neurocognitive trajectories. There is ample evidence that both memory and brain characteristics in aging are associated with variation in the factors that can, at least theoretically, be modified. Indeed, it was recently estimated that about one third of dementia cases might be preventable (Livingston et al., 2017). Target factors include socioeconomic characteristics such as education and income (Elbejjani et al., 2017; Gianaros et al., 2017; Staff, Hogan, & Whalley, 2018) that may be less malleable in aging, but also,

among others, cardiovascular health, diet, overweight and obesity, and physical activity (Engvig et al., 2014) as well as intellectual and social engagement (Landau et al., 2012; Seeman et al., 2011).

Neuroprotection or neuroselection?

Relations based on observational or epidemiological data in part form the basis for policy makers to form lifestyle guidelines for the reduction of risk of cognitive decline and dementia (WHO, 2019). These recommendations may make it tempting to older individuals to change their hedonistic habits for prudency, inferring a belief of being in charge on one´s own memory function. However, while some recommendations can be strong, for instance for physical activity and tobacco cessation interventions, the quality of the evidence is known and acknowledged to be moderate to low in many instances (WHO, 2019). Thus, this kind of advice may be shaky on several grounds. First, we do not know based on the observed relations whether modifying such factors in aging has any effect– the relations in older age may potentially be due to these factors being present also early in life, i.e. there may be an age-specificity of the mechanism. For instance, it is likely that persons who are physically active in older age have also been physically active when young. Hence, when physically active older adults show less cortical atrophy (K. B. Walhovd, Storsve, Westlye, Drevon, & Fjell, 2014), one cannot readily conclude that older adults should be more physically active. It may well be that it is factors in development that are important. For instance, in principle, physical activity in childhood could help build cardiovascular health differently, or more efficiently, than physical activity in aging. Second, the influence of such factors on brain and cognition, even if in principle modifiable at any age, may be due to a lifetime of impact. Hence, it may still be that changing one´s favorite pastimes in the last couple of decades of life can result in little but a depressive state of mind (which is in itself

associated with both increased mortality and memory problems (Gilman et al., 2017; Sachs-Ericsson, Joiner, & Blazer, 2008)). Third, the relations may be of a non-causal nature, to be discussed below.

Indeed, the observed relationships between "lifestyle-related" factors and brain and cognitive characteristics have been interpreted differently. For instance, education has often been seen as boosting development and being neuroprotective (Livingston et al., 2017; Stuart J. Ritchie & Tucker-Drob, 2018; Staff et al., 2018), but ample evidence also exists for it being neuroselective (Ericsson et al., 2017; Selzam et al., 2017). The same reasoning can be applied to other factors as well – it is unknown whether people are physically and intellectually active because they have healthy brains and bodies or whether this activity serves to create healthier bodies and brains, with better memory function. The neuroprotection account implies a casual effect of factors such as socioeconomic status, whereas in a strict neuroselective view, such variables would be little more than markers or proxies of some other favorable, putatively genetic, trait (Ericsson et al., 2017; Selzam et al., 2017). As the individual's constitution normally considerably influences the environmental context he or she chooses or is exposed to, one needs to study the effects of "modifiable factors" in a controlled experimental intervention setting. That is, the only way to answer whether we can influence the fate of our memory function in aging is to experimentally test under which conditions, if any, one can influence memory and its neural substrates.

Effects of interventions

Recently, multidomain intervention initiatives encompassing attempts to broadly modify lifestyle factors have been undertaken. Three large randomized controlled trials (RCTs) aimed at reducing cognitive impairment and dementia have so far been completed: Prevention of dementia by intensive vascular care (preDIVA) (Moll van Charante et al.,

2016); The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (Ngandu et al., 2015), and Effect of long-term omega-3 PUFA supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT) (Andrieu et al., 2017). Whereas the preDIVA trial targeted older adults in their 70s through general health practices, and involved no cognitive training, The FINGER and MAPT trials specifically targeted at-risk older adults and involved cognitive training components. An intervention effect was found only in the FINGER trial (Ngandu et al., 2015). This trial included 1260 at-risk individuals above 60 years of age, randomized to either a control condition or an intervention encompassing diet, exercise, cognitive training, and vascular risk monitoring. While significant, albeit modest, effects were observed on some cognitive parameters, including processing speed and executive functioning, the broad 2-year intervention was not associated with significant change in memory (Ngandu et al., 2015). Notably, while this was a multidomain intervention, it was not specifically targeted at episodic memory change. There is ample evidence that episodic memory performance can be specifically improved by targeted memory training, to be discussed below. It should be noted that transfer effects of cognitive training across domains are controversial, and often have been found to be limited or non-existent (Melby-Lervag, Redick, & Hulme, 2016; Sala & Gobet, 2017). This suggests that training needs to be highly specific and targeted to the types of performance desired to be improved.

A central question which we focus on next, then, is to what extent such targeted training is suited to positively influence memory and its neurobiological substrates in aging, and also, if there are individual differences relevant to who should be targeted. Surprisingly, WHO recently indicated that “targeting individuals at increased risk could be the most effective strategy” (p.51) (WHO, 2019) to reduce cognitive decline and dementia. This

conclusion was based on the positive result in the at-risk population targeted in FINGER, and the other RCTs, albeit showing no effect in primary analyses, showing significant intervention effects in participants with an elevated dementia risk score in MAPT, and in individuals with untreated hypertension at baseline in preDIVA. However, what would be an effective strategy to reduce cognitive decline depends on the exact aim. If the goal is to keep as many as possible above a functional threshold, then it seems plausible that at risk-individuals should be targeted. However, this is actually at odds with what is known about plastic potential. Here it seems the Matthew effect of accumulated advantage applies, and there may be little that can be done to change plastic potential in aging, to be discussed below.

Is plasticity in aging predetermined?

Plasticity can be defined as the ability of the brain to undergo structural (i.e., anatomical) changes that are driven by a mismatch between environmental requirements (demand) and the organism's current capacity (supply). Altered environmental demands, but also changes in the organism's capacity (e.g., age-related atrophy), can induce such mismatches (Lovden, Backman, Lindenberger, Schaefer, & Schmiedek, 2010). The brain is made early in life, and given this obvious ontogenetic restriction (K.B. Walhovd & Lövdén, 2019), our ability to change may, for better or worse, not be subject to much change in aging. The central nervous system is formed well before we reach young adulthood, and gross structural characteristics cannot be highly influenced in aging. While brain development can permanently be halted by certain prenatal influences (Barnes & Ozanne, 2011), and is particularly vulnerable to deviations from species-mandatory experiences and expected environment early in life (Greenough, Black, & Wallace, 1987; Wiesel & Hubel, 1963), there is little to suggest that advancing age in adulthood poses any new shift in plastic potential.

The combined impact of genetic programming (Rakic, 1988) and early environment (Barnes & Ozanne, 2011) implies that *much of plastic potential through the lifespan is already determined at birth*. However, while your range of reaction may be restricted by the course charted out above, this should not be taken to imply that function cannot be impacted in aging. Shared genes have been found to influence both practice and general cognitive ability (Mosing, Madison, Pedersen, & Ullen, 2016). Therefore, it is likely that how we respond to environmental influences is to some extent predetermined, but those environmental influences, and hence the brain and cognitive outcomes, are not necessarily so. While there is no theoretical or empirical evidence for abolished plasticity in aging, there might likely be age differences in terms of the magnitude of plastic changes (K.B. Walhovd & Lövdén, 2019), to be discussed further below. However, the motivation to train may also be increasing with falling memory function. Collectively, this gives the hope that targeted interventions in older age can still impact memory outcomes.

Individual differences in memory-related plasticity in aging

While training studies show that performance can be more than doubled with strategy training, including in older age (de Lange et al., 2016; de Lange et al., 2017), there is huge individual variability in plastic cognitive responses (de Lange et al., 2016). While much of plastic potential seems predetermined, there is relatively scarce knowledge of the factors at work.

Age is a major predictor of behavioural gains from memory training. While episodic memory training effects on the types of tasks trained are seen throughout the lifespan (Baltes & Kliegl, 1992; Brehmer, Kalpouzos, Wenger, & Lovden, 2014; Brehmer, Shing, Heekeren, Lindenberger, & Backman, 2016; Carretti, Borella, & De Beni, 2007; de Lange et al., 2017; Lovden, Bodammer, et al., 2010; Nyberg et al., 2003; Schmiedek, Lovden, &

Lindenberger, 2010), cognitive training does not serve to even out inter-individual differences. Either, proportional differences stay the same, or more often, the Matthew effect applies, such that those who have more to begin with gain more from interventions. This also applies to the typical age differences in memory (Kliegl, Smith, & Baltes, 1990). At best, older adults may improve proportionately as much as younger (Brehmer et al., 2016; Carretti et al., 2007; Lovden et al., 2012), but more often training appears to widen individual differences in episodic memory (Baltes & Kliegl, 1992; de Lange et al., 2017; Kliegl et al., 1990), with lesser gains in older age (Baltes & Kliegl, 1992; Burki, Ludwig, Chicherio, & de Ribaupierre, 2014; Dahlin, Nyberg, Backman, & Neely, 2008; de Lange et al., 2017; Nyberg et al., 2003).

There is not a solid empirical basis from which to draw conclusions with regard to whether brain changes in response to memory intervention differ with age. Process-based training of the neural substrates and processes underlying memory, such as navigation, has been shown to affect grey matter in both young and older adults in terms of inducing relative hippocampal preservation (Lovden et al., 2012) compared to controls. However, for the navigation training, regional cortical thickening has been shown in younger, but not older adults (Wenger et al., 2012). With strategy-based mnemonic training, both hippocampal and cortical grey matter increases have been observed in older adults (Engvig et al., 2010; Engvig et al., 2014), but the extent of these relative to younger adults are unknown.

Possible age differences in structural brain responses to memory training may have to do with differential engagement of brain regions and networks with increasing age, as reviewed above. Investigations of brain activity changes in young and old following mnemonic training have found partly similar patterns across age (Brehmer et al., 2016;

Nyberg et al., 2003). However, in one study utilizing PET during encoding, older adults who failed to improve from training, did not show the increase in occipito-parietal and frontal activity seen in young adults who all benefited from training. This was interpreted as a processing and production deficiency in utilizing the visuospatial technique (Nyberg et al., 2003). Moreover, even those older adults who benefited showed only occipito-parietal and not frontal activity increase, indicative of a broader frontal processing deficiency in aging.

As for white matter, there is ample evidence to suggest effects of memory training in both young and older age. Increases in corpus callosum microstructural markers of integrity (in terms of decreased mean diffusivity (MD) and increased fractional anisotropy (FA)), as well as anterior callosal area, have been observed in both younger and older adults training on a set of different cognitive tasks, including memory (Lovden, Bodammer, et al., 2010). With mnemonic strategy training, regional changes in white matter microstructure, with decreases in MD and increased FA, encompassing in part the anterior corpus callosum, have been observed in older but not younger adults (de Lange, Brathen, Rohani, Fjell, & Walhovd, 2018; de Lange et al., 2017). However, there are difficulties in making the training equally subjectively challenging to young and older adults, which may impact neural changes.

While the above-reviewed evidence suggests that there is capacity for neural and behavioural gains from memory training also in older age, one still needs to acknowledge that the above discussed neurobiological declines in aging are likely to diminish memory-related plasticity. Indeed, the known age differences in grey and white matter characteristics (Sexton et al., 2014; Storsve et al., 2014) seem to restrict the capacity for change: Baseline hippocampal volumes are predictive of both learning and retention across minutes and days in development (Ostby, Tamnes, Fjell, & Walhovd, 2012; Tamnes et al., 2014), as well as

recall over weeks and months (K. B. Walhovd et al., 2004) in adulthood, and of cognitive training gains across weeks in aging (Engvig et al., 2012). Furthermore, white matter microstructure in areas of established vulnerability to age, has also been found to be predictive of cognitive training gains (de Lange et al., 2016).

Future prospects - an intervention perspective on brain reserve, cognitive reserve, compensation, and brain maintenance: *when, where and who*

Ultimately, the central concepts in the neurobiology of aging and memory have implications for timing and targets of intervention. A schematic model outlining roughly *what* can be targeted *when* is outlined in Figure 3. First, passive brain reserve, in terms of larger brains, more neurons and synapses, logically cannot be built in aging, but can be when the brain is developing. This points to the importance of securing optimal prenatal and early childhood conditions (Bjornebekk et al., 2015; Noble et al., 2015; K. B. Walhovd et al., 2012; K. B. Walhovd et al., 2016; K. B. Walhovd et al., 2009; K. B. Walhovd, Tamnes, & Fjell, 2014). However, while brain reserve is grounded early in life, the tail of the red brain-reserve function in Figure 3 illustrates the possibility, discussed above, that lifestyle factors may contribute to neurogenesis and resistance to apoptosis.

The development of cognitive reserve is also associated with relatively early life phases. For instance, in a recent study, after accounting for general cognitive ability at age 20 years, additional education, occupational complexity, or engagement in cognitive-intellectual activities accounted for little variance in late midlife cognitive functioning (Kremen et al., 2019). Hence, even if it may be possible to impact cognitive reserve to some extent also later in life (as indicated by the protracted shape of the blue cognitive-reserve

function in Figure 3) , it seems that the period before adulthood would be the prime target interventions aiming at boosting cognitive reserve.

Brain maintenance is clearly at play later in life, and is likely partly dependent on reserve (Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012a; Nyberg & Pudas, 2019). Thus, when maintenance fails and brain pathology becomes more apparent, it is likely that individuals who for quite some time showed little or no age-related brain changes (maintenance) can better cope with pathology when it manifests (reserve). By this view, when maintenance fails compensatory responses will follow, the success of which will depend on individual brain and cognitive reserve (intersection of green and yellow arrows in Figure 3).

It follows from this model that possibilities for intervention targeted at different concepts may be larger in some parts of the world than others. The current potential to improve brain and cognitive reserve with regard to early life conditions such as prenatal, neonatal and educational factors may be especially high in low and middle-income countries, where the demographic changes will also be more marked in terms of the aging population (WHO, 2019). About 200 million children in developing countries are not meeting their growth potential, and improving the prenatal environment is likely important to help children reach their full potential (McGovern, 2019) – and ultimately also to help them stay above a functional threshold into older age. On the other hand, medical services in high income countries entail the survival and future aging of a higher proportion of children born with biomedical risk, including more prematurely born and low birth weight children. This population is indicated to be at increased risk for neurocognitive impairment in aging (Heinonen et al., 2015), and should be of focus in preventive efforts. As for interventions

directed toward later life factors to support brain maintenance, for instance by reducing cardiovascular risk, the potential may be vast across most parts of the world.

Critical unresolved issues include the extent to which the same factors underlie the build-up of brain and cognitive reserve and maintenance. These factors will necessarily include genetic and perhaps epigenetic regulation. Based on findings of genetic effects on e.g. medial temporal lobe volumes even in infancy and childhood (Knickmeyer et al., 2014; Piers, 2018), our prediction would be that shared genetic factors are at play along the entire lifespan. By implication, shared genetic factors must also be at play in the build-up of brain reserve and maintenance. Still, these processes are necessarily influenced by different environmental factors. We argue that the simple model outlined in Figure 3, pointing to the importance of understanding the timing of effects, is key to further preventive efforts aimed at positively influencing the neurobiology of memory aging.

Figure captions

1. **Canonical adult lifespan trajectories** Canonical lifespan trajectories for hippocampal volume (upper left), entorhinal cortex thickness (upper middle), verbal recall as exemplified with scores on the California Verbal Learning Test 30 min recall (lower left), and pars triangularis thickness (lower middle). Curves were estimated by use of generalized additive mixed models on combined cross-sectional and longitudinal data from Center for Lifespan Changes in brain and Cognition (approximately 2400 observations). The shaded area around the curves denote 95% confidence interval. For details, see https://www.biorxiv.org/content/10.1101/564732v1. Right panel shows encoding activity in an associative memory task from 290 participants from 18 to 83 years, for a contrast between source memory and item ("familiarity") memory. Red-yellow indicates significantly higher activity during source encoding, blue-cyan indicates higher activity during item encoding. As illustrated by the arrows, entorhinal cortex and pars triangularis are examples of cortical regions showing high activity during source memory encoding. For details, please see (Vidal-Pineiro et al., 2018).
2. **Heterogeneity in memory and brain aging** (a) Plot of data from a subset of 300 participants (35-90 years) from Betula, where the red curve denotes mean change on a composite score of episodic-memory tasks, and the black lines illustrate inter-individual differences in intercept and slope (figure courtesy of Sara Pudas). (b) Plot of lifespan trajectory in whole hippocampus volume change, with average volume increase up to age 20, stability or slight decline until age 55-60, and thereafter accelerated decline along with marked inter-individual differences in level and slope.

3. **Schematic model of interactions among brain reserve, cognitive reserve, brain maintenance, and compensation across the life span** The red and blue curves illustrate that brain and cognitive reserve are to a large extent established very early in life and during development. The build-up of reserves will likely contribute to brain maintenance and also to the efficient use of compensation in aging when maintenance fails. Therefore, early efforts at supporting reserve are likely to be the most effective when it comes to primary prevention and intervention to reduce age-related neurobiological changes (figure courtesy of Inge Amlien; Fetus by Hea Poh Lin from the Noun Project and Aging Process by Gan Khoon Lay from the Noun Project).

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