Working Memory and Ageing

Edited by Robert H. Logie and
Robin G. Morris

Psychology Press
Taylor & Francis Group
LONDON AND NEW YORK

First published 2015
by Psychology Press
27 Church Road, Hove, East Sussex BN3 2FA

and by Psychology Press
711 Third Avenue, New York, NY 10017

Psychology Press is an imprint of the Taylor & Francis Group, an informa business

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
Working memory and ageing / edited by Robert H. Logie and Robin G. Morris.
pages cm
Includes bibliographical references and index.
ISBN 978-1-84872-117-3 (hardback) -- ISBN 978-1-84872-126-5 (softcover) -- ISBN 978-1-315-87984-0 (ebk) 1. Memory--Age factors. 2. Short-term memory. 3. Cognition--Age factors. 4. Aging--Psychological aspects. I. Logie, Robert H. II. Morris, Robin, 1958-
BF378.A33W67 2014
155.67'1312--dc23

ISBN: 978-1-84872-117-3 (hbk)
ISBN: 978-1-84872-126-5 (pbk)
ISBN: 978-1-31587-984-0 (ebk)

Typeset in Times
by Saxon Graphics Ltd, Derby

Printed and bound in Great Britain by
TJ International Ltd, Padstow, Cornwall

Contents

6 Adult age differences in working memory

Evidence from functional neuroimaging

Irene E. Nagel and Ulman Lindenberger

Introduction

The brain's neurochemistry, anatomy, and functional dynamics undergo marked age-related changes (Bäckman et al., 2006; Madden, Bennett & Song, 2009; Morgan & May, 1990; Morrison & Hof, 1997; Raz, 2004; Raz et al., 2008; Raz et al., 2005; Salat et al., 2004; Suhara et al., 1991; Tisserand & Jolles, 2003; Westleye et al., 2010). These anatomical changes are paralleled by cognitive declines, particularly with respect to fluid cognitive functions. One such function is working memory, the ability to hold information online over short periods of time (Baddeley, 2003; Jonides et al., 2008). Working memory is involved in almost any cognitive task, and is of vital importance for everyday competence. Relative to other cognitive functions, working memory is particularly compromised in old age (Babcock & Salthouse, 1990). Its decline typically starts in young or middle adulthood, and accelerates in old age, from about age 60 onwards (Bäckman et al., 1999; Craik & Salthouse, 2000; de Frias et al., 2007; Li et al., 2004; Park et al., 2002). The marked age-related decline of working memory and other higher cognitive functions like selection and monitoring is paralleled by a particularly early and strong age-related decline of a part of the brain that plays a key role within the working memory network, the prefrontal cortex (e.g. Lindenberger, Burzynska & Nagel, 2013; Raz et al., 2005; Tisserand et al., 2002; Tisserand & Jolles, 2003; West, 1996).

Brain declines are modulated by genetic differences, and, to some extent, malleable by experience. Individual differences in working memory increase rather than decrease with advancing adult age, presumably because individual differences that already exist in early adulthood are further augmented by normal aging (de Frias et al., 2007; Lindenberger et al., 2013; Lindenberger & Ghisletta, 2009; Schmiedek, Lövdén & Lindenberger, 2009; Wilson et al., 2002), and by an age-associated increase in the incidence and prevalence of cognition-related pathologies (Bäckman et al., 1999). Understanding the mechanisms underlying this heterogeneity may inform attempts at preserving working memory into advanced old age.

This chapter approaches working memory functioning in old age from the more general perspective of individual differences in brain aging. We start by

summarizing general adult age trends in functional brain activation in relation to working memory. In view of the substantial heterogeneity of aging trajectories, which often amplifies the between-person differences that are present in early adulthood, we note that individual differences in brain activation patterns and performance are particularly large in old age. Based on these considerations, we advance the claim that higher levels of performance on working memory tasks in old age are associated with greater neurochemical and structural preservation and more "youth-like" task-related brain activation patterns (see also Nyberg et al., 2012). We will report the results of two recent studies that support this claim (Nagel et al., 2009, 2011), adding a few cautionary notes on the interpretation of fMRI results in the context of aging studies. We discuss four different ways to address working memory aging and end with a plea for multimodal longitudinal studies of individual brain aging trajectories that are capable of shedding light on the ways in which preserved brain structure and function may help to preserve cognitive competence in old age.

General age trends from early to late adulthood in functional brain activation during working memory performance

Over the last decade, an increasing number of cross-sectional fMRI studies on cognitive aging in general and working memory aging in particular have been conducted. Typically, age differences in functional brain activation are observed (Spreng, Wojtowicz & Grady, 2010). The pattern of findings, though, is not easily interpretable, as some studies report underactivation of task-relevant brain areas in older adults, whereas others find overactivation relative to young adults (Rajah & D'Esposito, 2005; Reuter-Lorenz et al., 2000; Reuter-Lorenz & Lustig, 2005; Rypma & D'Esposito, 2000; Rypma et al., 2001). Accordingly, age differences in the amount and patterning of functional brain activation have been explained in different ways.

Underactivation typically is interpreted as a sign of age-related structural and neuromodulatory brain changes. As we will explain later in detail, age-related changes in the hemodynamic response and other changes in neurovascular coupling are likely to contribute as well (D'Esposito et al., 1999; Gazzaley & D'Esposito, 2003; Hock et al., 1997; Reuter-Lorenz, 2002). Overactivation has been reported in the form of larger activation in older compared to younger adults either in the same regions that are active among younger adults, or in additional regions. Particularly the latter has been suggested to serve a compensatory function. According to that interpretation, old-age-specific overactivation points to successful compensation if performance is high and to attempted compensation if performance is low (Cabeza, 2002; Cabeza et al., 2002; Cabeza et al., 1997; Grady et al., 1994; Rajah & D'Esposito, 2005; Reuter-Lorenz et al., 2000). Overactivation, however, may also be dysfunctional (Logan et al., 2002). It may reflect inefficient neuromodulation and inhibition resulting in noisier and less distinct patterns of brain activation (Li, Lindenberger & Sikström, 2001; Li & Sikström, 2002; Park et al., 2002; Reuter-Lorenz et al., 2000). More specifically,

declines in dopaminergic neuromodulation lower the signal-to-noise ratio of neural information processing, which, in turn, increases processing noise, resulting in less distinctive brain activation patterns (Braver & Barch, 2002; Li, Lindenberger & Sikström, 2001; Li & Sikström, 2002) and impaired cognitive performance (Bäckman et al., 2000; Bäckman et al., 2006; Erixon-Lindroth et al., 2005; Li, Naveh-Benjamin & Lindenberger, 2005; Volkow et al., 1998).

The concepts of compensation and dysfunction are not necessarily mutually exclusive. Instead, reductions in processing efficiency might lead to compensatory reactions (Buckner, 2004; Park & Reuter-Lorenz, 2009; cf. Bäckman & Dixon, 1992). Presumably compensatory overactivation occurs in response to deficient processing that is particularly pronounced in frontal regions (Reuter-Lorenz & Mikels, 2006; Reuter-Lorenz & Sylvester, 2005). Thus, activation of additional regions may function as an aid or scaffold to preserve working memory and other cognitive functions (Park & Reuter-Lorenz, 2009) in the presence of age-related losses in structure and function. Given their pivotal function for the organization of behavior (e.g. Miller & Cohen, 2001; Stuss, 2006), prefrontal regions carry the promise to attenuate the adverse effects of brain aging (Cappell, Gmeidl & Reuter-Lorenz, 2010; Grady, McIntosh & Craik, 2005). Hence, older adults are exposed to the quandary that prefrontal cortex is increasingly needed but at the same time decreasingly capable of counteracting the adverse consequences of senescence (Lindenberger, Marsiske & Baltes, 2000; Nagel et al., 2007; for review, see Seidler et al., 2010). Furthermore, it should be noted that the dynamic re-allocation of resources to compensate for brain declines might have its drawbacks. Over-recruitment of prefrontal or other working memory regions may be beneficial in simple tasks, but when task difficulty increases, activation may already be at its maximum and thus cannot be further increased (Reuter-Lorenz & Mikels, 2006).

Relative to young adults, functional imaging studies often report overactivation at low task difficulty (e.g. low working memory load) among older adults (e.g. Reuter-Lorenz & Lustig, 2005). As task difficulty increases, however, older adults tend to show a more constrained BOLD response than younger adults, particularly at high load (Nyberg et al., 2008; Mattay et al., 2006). Mattay and colleagues (2006), for example, found that activation patterns in left DLPFC increased with higher load in younger adults. In contrast, activation patterns in left DLPFC peaked at the lowest load in older adults, showing no further increase with higher loads. It has been suggested that the point of maximum activation may be a neural indicator of a working memory capacity limit (Todd & Marois, 2005; Callicott et al., 1999). Accordingly, Mattay and colleagues interpret their results to suggest that older adults reached their capacity limit already at the lowest load condition (see also Nyberg et al., 2008). These findings are in accordance with the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH), according to which older adults show overactivation at low load, presumably as a compensatory response to neurobiological decline. At higher load, activation cannot be further increased, leading to a compromised BOLD response (Cappell et al., 2010; Reuter-Lorenz & Cappell, 2008). Thus, older adults' possible range of brain activation seems to be diminished (Spreng, Wojtowicz & Grady, 2010).

Available evidence suggests that, generally, older adults tend to show overactivation in frontal regions rather than posterior regions compared to younger adults (Cabeza et al., 2004; Cappell et al., 2010; Grady, Yu & Alain, 2008; Rajah & D'Esposito, 2005; Reuter-Lorenz et al., 2000). The evidence also allows for various interpretations of the findings, including no age differences, dedifferentiation, or compensation. Furthermore, hemispheric differences seem to exist with left-lateralized overactivation in older adults being related to higher performance in older adults and right-lateralized overactivation being related to lower performance in older adults (Rajah & D'Esposito, 2005; Spreng, Wojtowicz & Grady, 2010).

As can be seen from the above description of interpretations of overactivation, the term compensation is often used in the context of fMRI studies on cognitive aging to describe situations in which overactivation in older adults is beneficial for task performance. It is, however, important to note that such a "compensatory response" is not necessarily a sign of successful aging, as is sometimes implied. Instead, it rather seems to be the case that such compensatory overactivation is the neural equivalent of increased effort, caused by age-related neurobiological declines, whereas even more successful aging would be marked by an absence or decreased need to show such overactivation in the first place. We will come back to this point when describing our fMRI studies on individual differences in working memory aging.

Normal aging not only affects functional brain activation locally, but also alters the coupling between different brain regions (Bennett et al., 2001; Cabeza et al., 1997; Cook et al., 2007; Grady, McIntosh & Craik, 2003). Given that working memory is based on a large-scale network spanning across a variety of brain regions (D'Esposito, 2007), it is conceivable that the coordination of processing across regions is of pivotal importance for efficient working memory performance. According to the Disconnection Hypothesis, age differences in cognitive ability are in part due to a disconnection of task-relevant brain regions caused by white matter changes. An increasing amount of studies confirm that white matter integrity declines with increasing adult age (Burzynska et al., 2010; Sullivan, Rohlfing & Pfefferbaum, 2010; Pfefferbaum et al., 2000; see also Charlton & Morris, Chapter 5 in this volume). Such declines in white matter integrity have been related to age differences in functional and effective connectivity of brain activation and to cognitive performance (Bennet et al., 2001). However, most of the work on this topic investigates resting state connectivity, episodic memory or age-changes in relation to mild cognitive impairment (e.g. Damaoiseaux, 2012; Schwindt et al., 2013; Hafkemeijer et al., 2012; Yi et al., 2012; Shu et al., 2012; Jones et al., 2011) rather than working memory in healthy older adults. Bennett and colleagues (2001) showed that the connections among brain regions activated during episodic memory differed between younger and older adults. Given that older and younger adults did not differ in performance levels, it is conceivable that the connections unique to older adults developed as a compensatory response to age-associated neurobiological declines. Andrews-Hanna and colleagues (2007) showed that the functional couplings between regions differed between age groups

such that older adults had decreased coupling between frontal and posterior regions, a finding that is in accordance with the disconnection hypothesis (see also Arnsten et al., 2010; Cook et al., 2007; Grady, McIntosh & Craik, 2003; Li et al., 2009). Although in some cases, particularly in low load conditions (Bennett et al., 2001), new connections might be established in older adults' brains, the more typical finding is one of decreased connectivity in older adults. Such a decline in task-related connectivity of functional activation is in accordance with findings of compromised white matter integrity in older adults (Gunning-Dixon & Raz, 2000; Sullivan, Rohlfing & Pfefferbaum, 2010; Pfefferbaum et al., 2000).

In summary, findings of over- and underactivation of the working memory network among older relative to younger adults are common. We discussed how findings of underactivation are typically explained by neurobiological brain declines, whereas findings of overactivation are either interpreted as dedifferentiation due to impaired neurotransmitter function or as compensatory activation. Three points are of note here. First, as summarized in the CRUNCH hypothesis, recruitment of additional compensatory regions may aid task performance at low load but may come with the cost that further recruitment at higher levels of task difficulty is no longer possible. Second, we pointed to the quandary that the very same – prefrontal – regions that are thought to aid older adults' processing are also the regions that are particularly vulnerable to age-related neurobiological declines. Third, we noted that compensatory activation, even if beneficial for task performance, is not a sign of entirely successful aging but instead points to neurobiological brain changes that need to be compensated for. Instead, we propose that older individuals who do not show a need for altered brain activation patterns to achieve high levels of working memory performance should be considered as more convincing instantiations of successful cognitive aging.

Generally, due to age differences in neurovascular coupling, a point we will come back to in a later section, it is advisable to compare younger and older adults in their relative differences in activation between, for example, different task load levels rather than comparing activation patterns contrasted with a fixation baseline. Furthermore, with regard to the interpretation of the age differences in functional brain activation related to working memory, it should be noted that meaningful interpretations can only be made if brain activation patterns are related to task performance (i.e. overactivation can only be interpreted as compensatory if performance is higher in individuals showing the additional activation). Some of the apparent inconsistencies in the fMRI literature on adult age differences in working memory aging reflect methodological problems of this sort (cf. Spreng, Wojtowicz & Grady, 2010). In particular, Schneider-Garces and colleagues (2010) convincingly demonstrated that load-related changes in BOLD activation are linked to load-dependent changes in memory span. Thus, it is important to consider task difficulty in fMRI studies on working memory aging.

Experimental investigations of age differences in functional brain activation during working memory such as the ones reported above generally examine group effects, with the aim of finding patterns that can be generalized to the population.

Hence, performance is commonly averaged across individuals and between-person variation is neglected (Conway, Jarrold, Kane, Miyake & Towse, 2008; Hertzog, 1996). Studies taking this approach have yielded important results about the pronounced working memory decline on the population level. However, findings from differential and developmental psychology show that individual differences in working memory are reliable and substantial at all age periods (Miyake, 2001). As pointed out above, these differences increase with advancing adult age because aging individuals differ in the onset and the severity of age-related cognitive declines (Bäckman et al., 1999; Craik & Salthouse, 2000; de Frias et al., 2007; Lindenberger, Burzynska & Nagel, 2013; Lindenberger & Baltes, 1997; Nesselroade & Salthouse, 2004). It therefore seems warranted to consider individual differences in cognitive aging research (cf. Baltes, Reese & Nesselroade, 1977; Hertzog, 1985, 1996). Thus, considering individual differences in task performance and corresponding brain activation patterns is likely to yield valuable new insights into the heterogeneity of working memory in old age. To illustrate this point, we now turn to two studies from our own lab that investigate individual differences in working memory aging.

Empirical illustrations of an individual differences approach to the investigation of working memory aging and related brain activation

Performance level modulates adult age differences in brain activation during spatial working memory

Nagel et al. (2009) examined individual differences in brain activation during spatial working memory performance in younger and older adults with the aim to address the increased heterogeneity in older adults' performance and processing. Spatial working memory, which refers to the online retention of spatial memory contents, appears to be more affected in aging than verbal working memory (Jenkins et al., 2000; Park et al., 2002). The neural network typically activated during spatial working memory tasks involves lateral PFC, premotor cortex (PMC), posterior parietal cortex (PPC), and temporal brain regions (D'Esposito et al., 1998). FMRI studies averaging across age groups reveal that decreased working memory performance in older adults is accompanied by age-related changes in functional brain activation patterns (Jonides et al., 2000; Gazzaley & Esposito, 2007; Rypma & Esposito, 2000; Reuter-Lorenz et al., 2000).

As described before, memory load is known to affect the degree and pattern of activation of the working memory network in younger adults (Braver et al., 1997; Callicott et al., 1999; Jansma et al., 2000). The load-dependent increase of the BOLD signal can be characterized as a dose-response function (Schneider-Garces et al., 2010). Some researchers have reported monotonically increasing functions that are either linear (Braver et al., 1997) or nonlinear (Smith & Jonides, 1998; Cohen et al., 1997). Others have found inverted U-shaped functions (Callicott et al., 1999), where activation in dorsolateral PFC increases with load up to a certain difficulty level, and then decreases (Schneider-Garces et al., 2010).

Only a few studies have investigated the shape of dose-response functions in older adults (Cappell et al., 2010; Mattay et al., 2006; Nyberg et al., 2008; Petrella et al., 2005; Schneider-Garces et al., 2010). Mattay et al. (2006) reported brain activations peaking at load three in younger and at load one in older adults during a spatial n-back task, and concluded that older adults reach their capacity limits at lower levels of difficulty than younger adults. By contrast, Petrella et al. (2005) reported that activation in task-relevant regions increased with load in a delayed recognition task among older adults as well. Conceivably, these discrepancies across studies reflect the dependency of the BOLD response on performance level, which may have differed across studies, both within and across age groups. Given that individual differences in working memory performance are substantial and increase with age, and that functional activation is associated with performance in both younger and older adults, it is surprising that the modulation of age differences in memory-related brain activation patterns by performance levels has only rarely been investigated thus far. Notably, most of these studies used episodic memory tasks rather than working memory tasks (e.g. Persson et al., 2006; Duverne, Motamedinia & Rugg, 2009). As a result, performance heterogeneity, which can be expected to be particularly high in samples of older adults, is often left unanalyzed, thereby confounding differences in BOLD responses across age groups with differences in performance level within age groups (Schneider-Garces et al., 2010).

To examine age whether performance level modulates the BOLD response to a working memory challenge in younger and older adults, we tested 30 younger adults and 30 older adults with a spatial working memory delayed matching task during fMRI scanning. We expected that performance modulation may differ between age groups, such that signal change increases linearly in young high performers and follows a quadratic pattern in old low performers, with young low and old high performers showing intermediate patterns (cf. Nyberg et al., 2008). We used a spatial delayed-matching task, in which subjects saw points appearing on a screen. After a mask and a fixation delay, a probe point appeared. Participants had to indicate by a button press whether the location of the probe matched the location of one of the stimulus points they had seen in a given trial. Working memory load was manipulated by showing 1, 3, or 7 points during a trial.

As expected, older adults were less accurate and responded more slowly. Also, accuracy decreased and response times increased with task load. Interactions with age group indicated that effects of task load on accuracy and response times were stronger in older adults than in younger adults. To examine the association between performance level and brain activation patterns within the two age groups, we formed extreme groups by selecting the ten highest and ten lowest performers of each age group, based on their mean accuracy levels at loads 3 and 7.

Next, we conducted a ROI analysis, with ROIs in bilateral DLPFC, rostrodorsal PMC, and PPC, based on functional activation during spatial working memory performance. To examine the influence of age and performance group on BOLD signal changes in the spatial working memory network under varying load conditions, we extracted percent signal change from ROIs in the left and right

DLPFC, rostrodorsal PMC, and PPC for both age groups and for high and low performers in each age group. Initial analyses of the two age groups as a whole (i.e. irrespective of performance level) seemingly confirmed earlier claims that the BOLD signal is less responsive to increasing spatial working memory demands in old age. However, these average age group effects were qualified by differences between high and low performers within each of the two age groups (see Figure 6.1). In the young group, the BOLD signal of high performers increased up to load 7 in left DLPFC and bilateral RDPMC and less so in right DLPFC and bilateral PPC. However, in the sample of old low performers, there was no increase in activation from load 3 to load 7 for any of the ROI. In fact, in old low performers, activation declined reliably in most ROI after load 3. In contrast, the dose-response functions of old high performers resembled those of the young, suggesting that similarities in functional activation patterns were related not only to chronological age, but also – and even more so – to performance level. Follow-up analyses also revealed that the compromised BOLD response observed in the total sample of older adults was due to the group of low performers. At the same time, increases in activation with load among old high performers that resembled activation patterns observed in younger adults would have gone unnoticed in the whole-group analysis.

In sum, the results of this study suggest that some of the discrepant results of earlier fMRI studies on working memory in old age may reflect differences in performance level (e.g. sampling variability). Given the marked heterogeneity in neuronal and behavioral aging, it seems necessary to qualify statements about adult age differences in brain activation patterns in light of individual differences in performance within age groups. Hidden heterogeneity in activation patterns may lead to inadequate generalizations.

BOLD responsivity to load predicts verbal working memory performance in younger and older adults

In a related study, Nagel et al. (2011) investigated whether individual differences in performance also contribute to adult age differences in BOLD responsivity during verbal, rather than spatial working memory performance. Based on earlier findings (e.g. Cappell et al., 2010), we expected that load-dependent changes in BOLD responses would differ between age groups. Informed by the previous study, we also hypothesized that individual differences in responsivity of local BOLD response would be related to individual differences in working memory performance, such that greater responsivity is related to better performance in both age groups. Finally, we expected that individual differences in task-dependent functional (e.g. effective) connectivity within the working memory network would be related to individual differences in working memory performance.

We administered a verbal version of the n-back task to 30 younger and 30 older adults. Participants were instructed to watch a sequence of letters on the screen and indicate for each letter by a button press whether the letter they currently saw was the same as the one they had seen before. Working memory load was varied

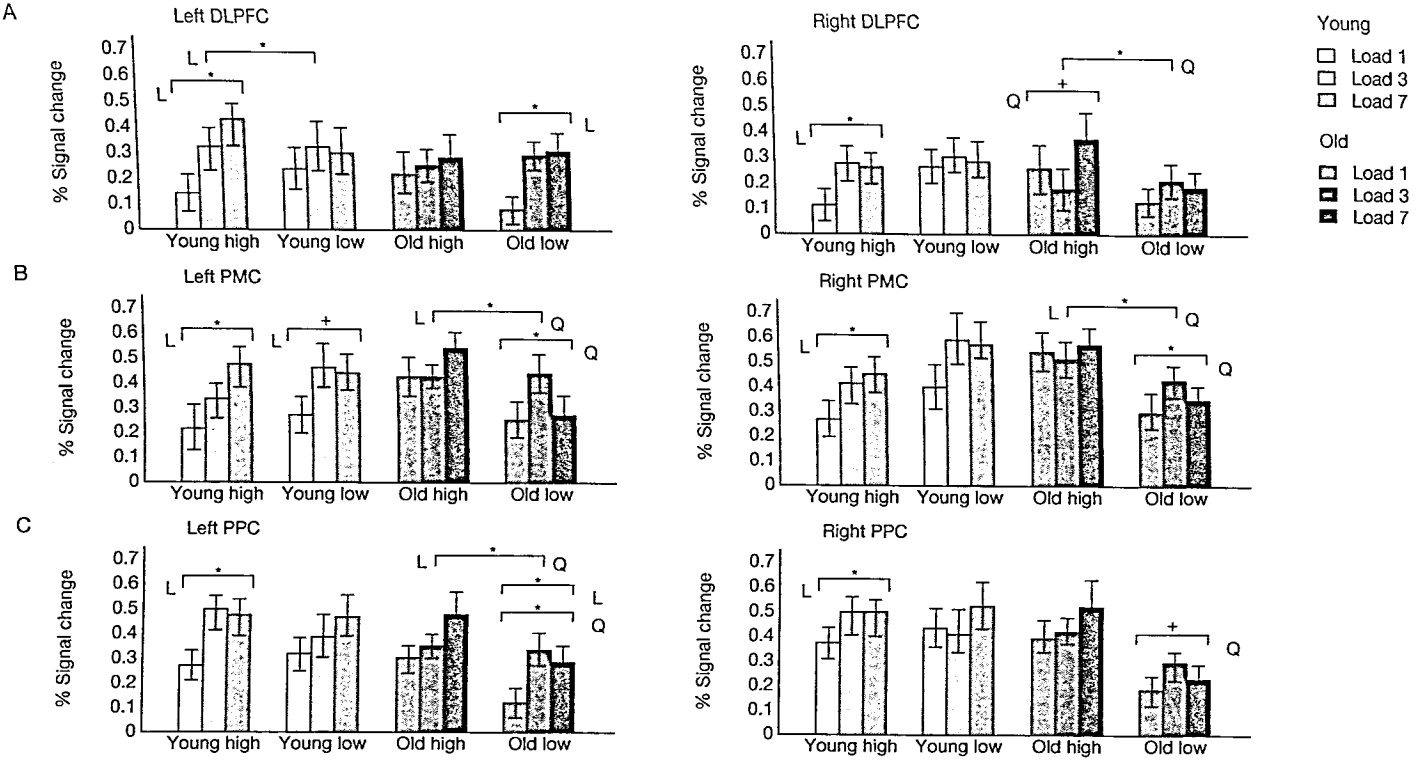

Figure 6.1 Region-of-interest analysis for extreme groups. BOLD signal changes in high- and low-performing younger and older adults across load (lower task demand is represented by lighter colors). There are marked differences in BOLD response between high and low performers within and across age groups. Source: Adapted from Nagel et al., 2009, with permission. Key: * $p < .05$; + = $.05 < p < .10$; L = linear contrast; Q = quadratic contrast.

by instructing participants to compare the current letter to the letter 1, 2, or 3 positions back in the sequence. As expected, older adults were less accurate and responded more slowly. Accuracy decreased and response times increased with task load. An interaction of load with age group indicated that effects of task load on response times were stronger in older adults than in younger adults; for accuracy, a trend in the same direction was observed.

To inspect group differences in load-dependent changes in BOLD signal in task-relevant regions, we conducted ROI analyses. Testing the age-by-load interaction revealed significant linear interaction contrasts in several ROIs, reflecting the linear increase of BOLD signal with load in younger but not older adults. In detail, interaction contrasts were reliable in left FPC, bilateral DLPFC, SMA, bilateral PPC, and at trend level in left PMC. Follow-up on analyses separately for each age group showed that activation increased linearly up to the highest load level (3-back) in all ROIs except right VLPFC in younger adults, but not in older adults.

In addition to forming subgroups based on performance level, we also created an index of responsivity, delta, by subtracting signal change in the 1-back condition from signal change in the 3-back condition. Hierarchical regression analyses using age group, delta, and their interaction term as factors were conducted to test whether delta accounted for individual differences in 3-back performance beyond age group. The corresponding R^2-change statistics were significant in left PMC, right PMC, and right PPC, and at trend level in left DLPFC and right DLPFC, showing that delta beyond age reliably predicted n-back performance. The interaction term of age group and delta was not significant for any of the ROIs, apart from a trend level significance in right PPC ($p = .09$). Figure 6.2 displays the scatterplots illustrating the associations between delta and accuracy.

Furthermore, a psycho-physiological interaction (PPI) analysis revealed that the load-dependent changes in connectivity between the left DLPFC and other brain regions differed between age groups. PPI provides a measure of effective connectivity by quantifying how the coupling of a seed region and any other voxel in the brain changes with task condition (Rogers et al., 2007; Friston et al., 1997). Younger adults showed changes in effective connectivity across load in key working memory regions including bilateral PFC, SMA, left PMC, and right PPC, whereas older adults showed load-dependent changes in coupling only in left anterior frontal cortex and temporal regions. To test whether changes in coupling predict working memory performance, we computed a hierarchical regression using age group and PPI scores as predictors and accuracy at 3-back as the dependent variable. As a trend ($p = .064$, uncorrected), load-dependent functional connectivity changes between the left DLPFC and the left PMC predicted 3-back performance beyond age group (see Figure 6.3), and the simple correlation (i.e. not controlling for age group) between connectivity changes and performance was reliable ($r = .31$, $p < .05$). Again, the interaction term did not account for significant additional amounts of variance in 3-back performance.

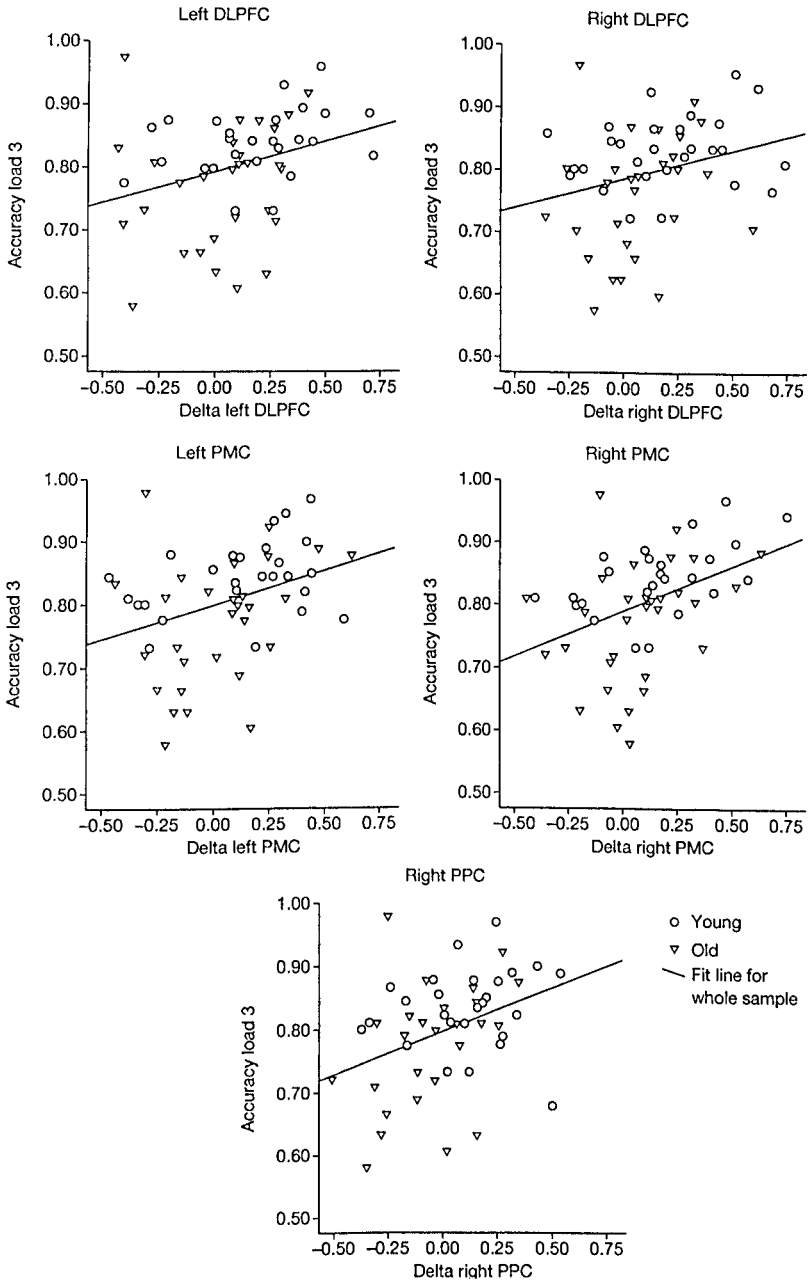

Figure 6.2 BOLD responsivity is related to verbal working memory performance. Delta (BOLD signal change 3-back minus 1-back condition, z-standardized) predicts accuracy at load 3 in bilateral PMC, right PPC and at trend level in bilateral DLPFC. The predictive relation does not differ reliably between groups of younger and older adults

Source: Adapted from Nagel et al., 2011, with permission.

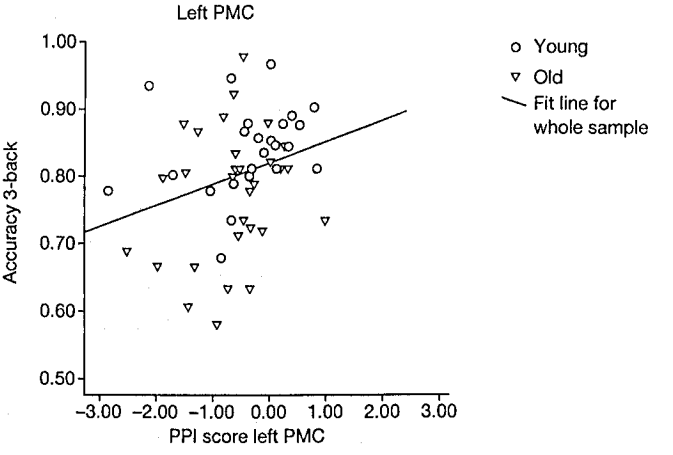

Figure 6.3 Psychophysical interaction analysis of verbal working memory performance. Task-dependent changes in coupling between left DLPFC and left PMC predict accuracy at load 3. This suggests that the coupling between left DLPFC and left PMC contributes to proficient verbal working memory in both younger and older adults

Source: Adapted from Nagel et al., 2011, with permission.

This study confirms and extends the results of the earlier study reported by Nagel et al. (2009) as well as related earlier work (e.g. Cappell et al., 2010; Mattay et al., 2006; Nyberg et al., 2008; Schneider-Garces et al., 2010). As a group, younger adults showed an increased BOLD response to a working memory challenge, whereas the corresponding response in older adults, as a group, was compromised. However, when examining individual differences in dose-response functions with the delta score, we found that local BOLD responsivity predicts working memory performance in both age groups, indicating that task-related modulation of activity in the prefrontal and parietal cortices contributes to proficient task performance.

Thus, the results of this study suggest that a substantial portion of the local and global network characteristics that permit individuals in the adult age range to adequately respond to working memory challenges is actually age-invariant (cf. Cappell et al., 2010; Nagel et al., 2009; Schneider-Garces et al., 2010). From this perspective, normal aging reduces the likelihood of an adequately responsive working memory network, due to factors that may be more or less similar to the reasons that bring about individual differences in working memory performance in age-homogeneous samples.

Summary: Functional neuroimaging investigations of age-related working memory decline

The two studies reported in detail above underscore the importance and magnitude of individual differences in working memory aging. They also serve as a demonstration that fMRI studies on cognitive aging need to take individual

differences into account. In both studies, older adults with relatively high levels of working memory performance were more likely to increase brain activity in task-relevant brain regions with increasing working memory load than low-performing older adults, who tended to show flat or inverted-U shape activation profiles. This heterogeneity would have gone unnoticed if older adults had been conceived and analyzed as a homogenous group (see also Craik, Byrd & Swanson, 1987). The patterns of local and coordinated brain activity that were associated with high working memory performance looked strikingly similar across age groups.

Cautionary note: Use of fMRI in aging research

FMRI is well suited to the investigation of cognitive aging because it provides the possibility to test non-invasively how age-related regional changes in functional activation are related to age-related changes in cognitive performance (D'Esposito, Deouell & Gazzaley, 2003). However, age-comparative fMRI studies rest on the assumption that both age groups have similar cerebral blood flow and hemodynamic responses. FMRI outcomes depend on neurovascular coupling, the process by which neural activity leads to a local change in the ratio of oxygenated and deoxygenated blood by influencing the cerebral blood volume and local oxygen consumption. During performance on a cognitive task, a hemodynamic response is generated that results in increased blood flow and volume. The increased blood flow leads to locally excessive amounts of oxygenated blood, which are reflected in the BOLD response that is measured in fMRI. In quasi-experimental imaging studies investigating group differences in functional brain activation, it is commonly assumed that vascular properties do not differ reliably across groups. In the course of the transition from early to late adulthood and old age, however, vascular structures become less elastic, reactivity to chemical modulators such as oxygen is reduced, and cerebral blood flow (CBF) decreases. Furthermore, various medical conditions like minor infarctions, stroke, and diabetes also alter the BOLD signal. These changes lead to a decrease in the signal-to-noise ratio, and a decrease in the amplitude and spatial extent of the BOLD signal (D'Esposito, Deouell & Gazzaley, 2003; Rajah & D'Esposito, 2005). Therefore, aging studies can be confounded by age-related differences in the hemodynamic response and resting CBF (D'Esposito, Deouell & Gazzaley, 2003; Gazzaley & D'Esposito, 2005).

It has been suggested that one way to tackle this problem is to establish baselines that are specific for each group or subject. By having each participant perform a simple visual or sensorimotor task in the scanner, one can determine the specific signal and noise characteristics and model the BOLD response accordingly. Modeling the response in one region based on the activation in another might, however, be problematic if the hemodynamic response differs between regions to a greater degree in older adults (Buckner et al., 2000). Another way to circumvent possible confounds is to use parametric designs. In parametric designs, between-group comparisons are made only with regard to the difference in activation from

one load level to the other (Rajah & D'Esposito, 2005). Finally, BOLD responses that correlate with behavior in a meaningful way are less likely to be entirely due to age differences in neurovascular coupling (Gazzaley & D'Esposito, 2005).

In the imaging studies reported above, parametric designs were used, and load-dependent differences in BOLD responses were correlated with load-dependent corresponding differences in behavior. Moreover, individuals with a self-reported history of strokes were excluded from the study. For all of these reasons, it is unlikely that age differences in the hemodynamic response account for the reported results.

Open issues and future directions

How to address cognitive aging: Compensation, preservation, restoration, and selection

When discussing common approaches to the interpretation of age differences in functional brain activation during performance of working memory tasks, we mentioned that both under- and overactivation in older adults are reported, which are both likely to reflect age-related neurobiological changes in prefrontal cortex and other regions of the working memory network. We pointed out that the prefrontal cortex is at the heart of a quandary: increasingly needed but decreasingly capable of counteracting the adverse consequences of senescence on behavior.

What are ways to confront these age-related declines and to reach high levels of performance in old age? In the following we describe four routes to face age-related declines on brain and cognition. In particular, we propose that compensatory activation might in some cases be beneficial for task performance, but, unlike "youth-like activation," may not necessarily be seen as a sign of successful aging.

Compensation

As pointed out above, high levels of cognitive functioning in old age may reflect instances of successful compensation (Cabeza, 2002; Cabeza et al., 2002; Grady, 2008; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008; Stern, 2009). Compensation is hard to define conceptually and difficult to pinpoint empirically because alternative explanations (some of which we will describe in the following) are not easily ruled out. Conceptually, a general and a developmental definition can be set apart. In general terms, compensation refers to any process or mechanism in response to a change in task demands. A typical example would be an increase in brain activation with increasing task demands, where the additional recruitment of cerebral resources compensates for the increase in difficulty. Note that this increase in difficulty is defined in relation to an individual's resources. Hence, a task may become more difficult either because the task itself has increased in difficulty or because brain resources have decreased (see also Cappell, Gmeindl & Reuter-Lorenz, 2010; Schneider-Garces et al., 2010).

According to a narrower definition, compensation in the context of normal aging refers to a structural or functional reorganization of the brain that evolves *in response to aging-induced losses in brain functioning* (Bäckman & Dixon, 1992; Baltes & Baltes, 1990; Park & Reuter-Lorenz, 2009; Riediger, Li & Lindenberger, 2006). This kind of compensation was described earlier in the chapter. It does not consist of the re-establishing of the substrate or function that was lost, but in creating something new in response to a loss (see Logie, Horne & Petit, Chapter 2 in this volume). This definition of compensation is analogous to compensation in response to discrete events such as stroke or other acute insults to the brain (Buckner et al., 1996; Kopp et al., 1999). However, it is likely that positive effects of compensation on performance, if present at all, do not extend to more advanced stages of brain aging (Persson et al., 2006).

Preservation

Even though compensation might be an important aspect of older adults' cognitive functioning, the studies reported in this chapter highlight another potential scenario. In the two studies by Nagel et al. (2009, 2011), older adults with more "youth-like" brain responsivity to increasing task demands showed higher levels of working memory performance than older adults whose brain responsivity differed from younger adults.[1] A straightforward interpretation of this finding is that individuals differ in the rate and extent of senescent alterations of brain metabolism and brain structure. According to this view, the brains of individuals whose cerebral anatomy and neurochemistry is relatively well preserved are more likely to show functional brain activation patterns that resemble those of younger adults, and that are germane to proficient performance. An important implication of this view is that cognitive interventions should aim at preserving or restoring "youth-like" brain structure and functions. Thus, only when preservation of working memory and related processing is no longer possible may compensatory processes need to come into play.

Restoration

Given that postponing and reducing brain aging is arguably the best way to avoid its negative effects on cognition, *preservation* is probably a generally accepted intervention goal. Similarly, restoration makes use of the remaining potential for plastic change (Lövdén et al., 2010a), and refers to attempts to re-install properties of the brain that were lost in the course of aging, with the hope that recovery of function and behavior will ensue. A recent study by Lövdén et al. (2010b) suggests that restoration through behavioral intervention may be a viable strategy. Lövdén et al. (2010b) used cognitive training (see Neely & Nyberg, Chapter 4 in this volume), DTI, and structural MRI to investigate the plasticity of white matter tracts that connect the left and right hemisphere of the frontal lobes. Over a period of about 180 days, 20 younger adults and 12 older adults trained for a total of 101 1-hour sessions on a set of three working memory, three episodic memory, and six

perceptual speed tasks. Control groups were assessed at pre- and post-test. Training affected several DTI metrics and increased the area of the anterior part of the corpus callosum. These results show that experience-dependent plasticity of white matter microstructure extends into old age. Moreover, they suggest that age-related disruptions of structural interhemispheric connectivity of the frontal lobes, which are common and pronounced in normal aging, can be restored through experience, at least to some extent. It should be noted that restoration differs from compensation in that it refers to re-installing properties that were lost rather than relying on the aid of additional regions that might then not be available when needed for their initial function.

Selection

Brain-behavior relations are often many-to-one in the sense that younger adults' brains can execute a given task in more than one way (cf. Edelman, 1987). Evidence supporting this proposition comes from studies using transcranial magnetic stimulation to implement temporary functional lesions in specific areas of the brain (Pascual-Leone et al., 2005). These studies have shown that younger adults can adapt to some of these functional lesions instantaneously by recruiting different brain areas (e.g. Lee et al., 2003). It is likely that different brain implementations of a given behavior are differentially vulnerable to aging. Some brain areas or activation patterns may be more resilient to normal aging than others. Thus, inclusion of these regions in certain functions was present as an option in younger adults' repertoire, and came to the fore under the selection pressures of normal aging. The increasing role of some regions with advancing age may thus in some cases signal selective survival rather than the compensatory development of new functional activation patterns.

The three cross-sectional, age-comparative studies reported above are generally consistent with the hypothesis that older adults who maintain higher white matter integrity or more "youth-like" brain activation patterns also show higher levels of working memory performance. The described four possible routes to confront working memory aging are not mutually exclusive, and their importance, feasibility, and reciprocal relations remain to be determined. Clearly, methodological advances are of importance here and are needed to better discriminate among preservation, restoration, selection, and compensation.

A Plea for an individual-differences-focused, multimodal and longitudinal investigation of working-memory aging

What differentiates older adults with shallower decline and higher levels of performance from those with steeper decline and lower levels of performance? Do high- and low-functioning individuals differ primarily in the burden of primary neurobiological aging changes, or rather in the way their brains adapt to these changes? And what are the factors contributing to either of these differences? The substantial heterogeneity in working memory aging and related functional brain

activation was the dominant theme of this chapter. Aging of the prefrontal cortex and other core regions of the working memory network is embedded in a web of grey matter changes, white matter changes, and neurochemical changes, but the timing and interrelations of these changes have not been examined in full. Therefore, currently, little is known about the mechanisms contributing to interindividual differences in aging trajectories (Hertzog et al., 2009; Nyberg et al., 2010). Accordingly, methodological advances in terms of a focus on individual differences, and multimodal and longitudinal designs are needed.

Individual differences

The studies reported in detail in this chapter provide important examples as to how an individual difference approach in research on working memory aging can help deepen the understanding of working memory aging. The prevailing focus on comparing group averages comes at a double cost. This focus hides the heterogeneity of working memory response patterns within the samples that are being contrasted, such as groups of younger and older adults. At the same time, the focus on average group differences also hides the notable degree of invariance in the brain characteristics that promote proficient working memory performance across age groups. To the degree that variations around the mean are governed by similar mechanisms as the mechanisms causing mean decline, the focus on individual differences bears the promise to help identify mechanisms that contribute to both the invariant and the malleable aspects of normal cognitive aging.

Multimodal approach

In this context, it is noteworthy that adult changes in neuroanatomy, neurochemistry, neural activation, and behavior have rarely been investigated in concert. Hence, little is known about the ways in which age-related changes at one level (e.g. brain structure) map onto changes at other levels (e.g. brain function), and how mechanisms observed at each of these levels generate both the invariant and the variable properties of normal cognitive aging (cf. Li & Lindenberger, 2002; Lindenberger, Li & Bäckman, 2006). Future studies need to further strengthen the links between structural, neurochemical, and functional properties of the brain, and their interacting and recursive links to behavior (Lindenberger, Li & Bäckman, 2006). To address structure-function-behavior relations in aging populations, the corresponding measures need to be assessed in samples that are sufficiently large to permit multivariate modeling of individual differences.

Longitudinal study design

Longitudinal studies comprising PET, SPECT, MRI, fMRI, and behavioral data (e.g. Beason-Held, Kraut & Resnick, 2008a, 2008b; Nyberg et al., 2010) along with assessment of vascular risk factors are needed to trace the evolution of

neurochemical, grey matter, white matter, functional, and working memory performance changes in greater detail. It will be of particular importance for the understanding of working memory aging to examine how far the rates of decline in frontal and striatal dopamine differ across individuals, relate to other aspects of brain aging, and are influenced by genetic factors. The early onset of dopamine decline may trigger or accentuate the effects of other physiological changes in the aging brain, such as grey matter loss, in part by compromising the functional integrity of subcortical-cortical connections. Longitudinal data on individual differences in age-related brain changes continue to be sparse. With respect to volume, reliable individual differences in shrinkage have been found, but similar data about individual differences in neurochemical changes and changes in white matter integrity are lacking (see Charlton & Morris, Chapter 5 in this volume). Given the volumetric and behavioral findings, it is likely that age trends in other dimensions of brain aging also show considerable variation across individuals. Longitudinal studies combining MR-based measures of regional volumes and structural connectivity with PET-based measures of transmitter availability would help researchers to study the temporal relation between changes in transmitter systems and anatomical alterations of the aging brain.

Such studies are needed to identify the antecedents and correlates of successfully preserved working memory functioning in old age. They will help to delineate the neural mechanisms underlying maintenance, restoration, selection, and compensation. To the extent that the relevant mechanisms can be manipulated, the resulting findings may inform interventions that foster successful working memory aging.

In this chapter we described and discussed common findings on age-related differences in functional brain activation during working memory. We reported two studies that used a quasi-experimental design to take a closer look at individual differences in working memory. A high degree of heterogeneity was noted among older individuals, with older adults performing at high levels showing youth-like activation patterns. Working memory functioning may be both more heterogeneous (e.g. within groups) and more invariant (e.g. across groups) than commonly assumed. Documenting this heterogeneity in neural processing in relation to performance opens a window to delineating mechanisms that promote positive cognitive outcomes.

Acknowledgments

The authors thank Lars Bäckman, Aga Burzynska, Hauke Heekeren, Shu-Chen Li, Lars Nyberg, and Claudia Preuschhof for their contributions to the empirical studies that are reported in detail in this chapter (Nagel et al., 2009, 2011).

Note

1 In the domain of episodic memory, studies by Rugg and colleagues have yielded a similar pattern of results (e.g. Duverne, Motamedinia & Rugg, 2009).

References

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E. et al. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron, 56*, 924–935.

Arnsten, A. F. T., Paspalas, C. D., Gamo, N. J., Yang, Y. & Wang, M. (2010). Dynamic network connectivity: A new form of neuroplasticity. *Trends, 14*, 365–375.

Babcock, R. L. & Salthouse, T. A. (1990). Effects of increased processing demands on age differences in working memory. *Psychology and Aging, 5*, 421–428.

Bäckman, L. & Dixon, R. A. (1992). Psychological compensation: A theoretical framework. *Psychological Bulletin, 112*, 259–283.

Bäckman, L., Ginovart, N., Dixon, R. A., Wahlin, T. B., Wahlin, A., Halldin, C. et al. (2000). Age-related cognitive deficits mediated by changes in the striatal dopamine system. *American Journal of Psychiatry, 157*, 635–637.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.-C. & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: Current status and future prospects. *Neuroscience and Biobehavioral Reviews, 30*, 791–807.

Bäckman, L., Small, B. J., Wahlin, A. & Larsson, A. (1999). Cognitive functioning in very old age. In F. I. Craik & T. Salthouse (Eds.), *Handbook of aging and cognition* (Vol. 2, pp. 499–558). Mahwah, NY: Erlbaum.

Baddeley, A. (2003). Working memory: Looking back and looking forward. *Nature Reviews Neuroscience, 4*, 829–839.

Baltes, P. B. & Baltes, M. M. (1990). Psychological perspectives on successful aging: The model of selective optimization with compensation. In P. B. Baltes & M. M. Baltes (Eds.), *Succcessful aging: Perspectives from the behavioral sciences* (pp. 1–34). New York: Cambridge University Press.

Baltes, P. B., Reese, H. W. & Nesselroade, J. R. (1977). *Life-span developmental psychology: Introduction to research methods.* Monterey, CA: Brooks-Cole Publishing.

Beason-Held, L.- L., Kraut, M. A. & Resnick, S. M. (2008a). I. Longitudinal changes in aging brain function. *Neurobiology of Aging, 29*, 483–496.

Beason-Held, L.- L., Kraut, M. A. & Resnick, S. M. (2008b). II. Temporal patterns of longitudinal change in aging brain function. *Neurobiology of Aging, 29*, 497–513.

Bennett, P. J., Sekuler, A. B., McIntosh, A. R. & Della-Maggiore, V. (2001). The effects of aging on visual memory: Evidence for functional reorganization of cortical networks. *Acta Psychologia, 107*, 249–273.

Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E. & Noll, D. C. (1997). A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage, 5*, 49–62.

Braver, T. S. & Barch, D. M. (2002). A theory of cognitive control, aging cognition, and neuromodulation. *Neuroscience & Biobehavioral Reviews, 26*, 809–817.

Buckner, R. L. (1996). Beyond HERA: contributions of specific prefrontal brain areas to long-term memory retrieval. *Psychonomic Bulletin & Reviews, 3*, 149–158.

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

Buckner, R. L., Snyder, A. Z., Sanders, A. L., Raichle, M. E. & Morris, J. C. (2000). Functional brain imaging of young, nondemented, and demented older adults. *Journal of Cognitive Neuroscience, 12*, 24–34.

Burzynska, A. Z., Preuschhof, C., Bäckman, L., Nyberg, L., Li, S.-C., Lindenberger, U. et al. (2010). Age-related differences in white matter microstructure: Region-specific patterns of diffusivity. *Neuroimage, 49*, 2104–2112.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging, 17*, 85–100.

Cabeza, R., Anderson, N. D., Locantore, J. K. & McIntosh, A. R. (2002). Aging gracefully: Compensatory brain activity in high-performing older adults. *Neuroimage, 17*, 1394–1402.

Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M. & Nyberg, L. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cerebral Cortex, 14*(4), 364–375.

Cabeza, R., McIntosh, A. R., Tulving, E., Nyberg, L. & Grady, C. L. (1997). Age-related differences in effective neural connectivity during encoding and recall. *NeuroReport, 8*, 3479–3483.

Callicott, J. H., Mattay, V. S., Bertolino, A., Finn, K., Coppola, R., Frank, J. A. et al. (1999). Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cerebral Cortex, 9*, 20–26.

Cappell, K. A., Gmeindl, L. & Reuter-Lorenz, P. A. (2010). Age differences in prefontal recruitment during verbal working memory maintenance depend on memory load. *Cortex, 46*, 462–473.

Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J. et al. (1997). Temporal dynamics of brain activation during a working memory task. *Nature, 386*, 604–608.

Conway, A. R. A., Jarrold, C., Kane, M. J., Miyake, A. & Towse, J. N. (2008). *Variation in working memory*. New York: Oxford University Press.

Cook, I. A., Bookheimer, S. Y., Mickes, L., Leuchter, A. F. & Kumar, A. (2007). Aging and brain activation with working memory tasks: An fMRI study of connectivity. *International Journal of Geriatric Psychiatry, 22*, 332–342.

Craik, F. I. M. & Salthouse, T. A. (Eds.) (2000). *The handbook of aging and cognition* (2nd ed.). Mahwah, NY: Erlbaum.

Craik, F. I. M., Byrd, M. & Swanson, J. M. (1987). Patterns of memory loss in three elderly samples. *Psychology and Aging, 2*, 79–86.

Damoiseaux, J. S. (2012). Resting-state fMRI as a biomarker for Alzheimer's disease? *Alzheimer's Res. Ther., 4*(2), 8.

D'Esposito, M. (2007). From cognitive to neural models of working memory. *Philosophical Transactions of the Royal Society of London, 362*, 761–772.

D'Esposito, M., Deouell, L. Y. & Gazzaley, A. (2003). Alterations in the BOLD fMRI signal with ageing and disease: A challenge for neuroimaging. *Nature Reviews Neuroscience, 4*, 863–872.

D'Esposito, M., Aguirre, G. K., Zarahn, E., Ballard, D., Shin, R. K. & Lease, J. (1998). Functional MRI studies of spatial and nonspatial working memory. *Cognitive Brain Research, 7*(1), 1–13.

D'Esposito, M., Zarahn, E., Aguirre, G. K. & Rypma, B. (1999). The effect of normal aging on the coupling of neural activity to the bold hemodynamic response. *Neuroimage, 10*, 6–14.

de Frias, C. M., Lövdén, M., Lindenberger, U. & Nilsson, L.-G. (2007). Revisiting the dedifferentiation hypothesis with longitudinal multi-cohort data. *Intelligence, 35*, 381–392.

Duverne, S., Motamedinia, S. & Rugg, M. D. (2009). The relationship between aging, performance, and the neural correlates of successful memory encoding. *Cerebral Cortex, 19*, 733–744.

Edelman, G. M. (1987). *Neural Darwinism. The theory of neuronal group selection.* New York: Basic Books.

Erixon-Lindroth, N., Farde, L., Robins Wahlin, T. B., Sovago, J., Halldin, C. & Bäckman, L. (2005). The role of the striatal dopamine transporter in cognitive aging. *Psychiatry Research: Neuroimaging, 138*, 1–12.

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E. & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage, 6*, 218–229.

Gazzaley, A. & D'Esposito, M. (2003). The contribution of functional brain imaging to our understanding of cognitive aging. *Science of Aging Knowledge Environment*, 2003(4), PE2.

Gazzaley, A., & D'Esposito, M. (2005). BOLD functional MRI and cognitive aging. In R. Cabeza, L. Nyberg & D. Park (Eds.), *Cognitive neuroscience of aging: Linking cognitive and cerebral aging* (pp. 107–131). New York: Oxford University Press.

Gazzaley, A. & D'Esposito, M. (2007). Top-down modulation and normal aging. *Annals of the New York Academy of Science, 1097*, 67–83.

Grady, C. L. (2008). Cognitive neuroscience of aging. *Annals of the New York Academy of Science, 1124*, 127–144

Grady, C. L., Yu, H. & Alain, C. (2008). Age-related differences in brain activity underlying working memory for spatial and nonspatial auditory information. *Cerebral Cortex, 18*(1), 189–199.

Grady, C. L., McIntosh, A. R. & Craik, F. I. (2003). Age-related differences in the functional connectivity of the hippocampus during memory encoding. *Hippocampus, 13*, 572–586.

Grady, C. L., McIntosh, A. R. & Craik, F. I. M. (2005). Task-related activity in prefrontal cortex and its relation to recognition memory performance in young and old adults. *Neuropsychologia, 43*, 1466–1481.

Grady, C. L., Maisog, J. M., Horwitz, B., Ungerleider, L. G., Mentis, M. J., Salerno, J. A. et al. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. *The Journal of Neuroscience, 14*, 1450–1462.

Gunning-Dixon, F. M. & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. *Neuropsychology, 14*, 224–232.

Hafkemeijer, A., van der Grond, J. & Rombouts, S. A. (2012). Imaging the default mode network in aging and dementia. *Biochimica et Biophysica Acta, 1822(3)*, 431–441.

Hertzog, C. (1985). An individual differences perspective: implications for cognitive research in gerontology. *Research on Aging, 7*, 7–45.

Hertzog, C. (1996). Research design in studies of aging and cognition. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging* (pp. 24–37), San Diego, CA: Academic Press.

Hertzog, C., Kramer, A. F., Wilson, R. S. & Lindenberger, U. (2009). Enrichment effects on adult cognitive development: Can the functional capacity of older adults be preserved and enhanced? *Psychology in the Public Interest, 9*(1), 1–65.

Hock, C., Villringer, K., Muller-Spahn, F., Wenzel, R., Heekeren, H., Schuh-Hofer, S. et al. (1997). Decrease in parietal cerebral hemoglobin oxygenation during performance of a verbal fluency task in patients with Alzheimer's disease monitored by means of

near-infrared spectroscopy (NIRS): Correlation with simultaneous rCBF-PET measurements. *Brain Research, 755*, 293–303.

Jansma, J. M., Ramsey, N. F., Coppola, R. & Kahn, R. S. (2000). Specific versus nonspecific brain activity in a parametric N-back task. *Neuroimage, 12*, 688–697.

Jenkins, L., Myerson, J., Joerding, J. A. & Hale, S. (2000). Converging evidence that visuospatial cognition is more age-sensitive than verbal cognition. *Psychology and Aging, 15*, 157–175.

Jones, D. T., Machulda, M. M., Vemuri, P., McDade, E. M., Zeng, G., Senjem, M. L. et al. (2011). Age-related changes in the default mode network are more advanced in Alzheimer disease. *Neurology, 77(16)*, 1524–1531.

Jonides, J., Lewis, R. L., Nee, D. E., Lustig, C. A., Berman, M. G. & Moore, K. S. (2008). The mind and brain of short-term memory. *Annual Review of Psychology, 59*, 193–224.

Jonides, J., Marshuetz, C., Smith, E. E., Reuter-Lorenz, P. A., Koeppe, R. A. & Hartley, A. (2000). Age differences in behavior and PET activation reveal differences in interference resolution in verbal working memory. *Journal of Cognitive Neuroscience, 12*, 188–196.

Jonides, J., Schumacher, E. H., Smith, E. E., Lauber, E. J., Awh, E., Minoshima, S. et al. (1997). Verbal working memory load affects regional brain activation as measured by PET. *Journal of Cognitive Neuroscience, 9*, 462–475.

Kopp, B., Kunkel, A., Mühlnickel, W., Villringer, K., Taub, E. & Flor, H. (1999). Plasticity in the motor system related to therapy-induced improvement of movement after stroke. *NeuroReport, 10*, 807–810.

Lee, L., Siebner, H. R., Rowe, J. B., Rizzo, V., Rothwell, J. C. et al. (2003). Acute remapping within the motor system induced by low frequency repetitive transcranial magnetic stimulation. *Journal of Neuroscience, 23*, 5308–5318.

Li, S.-C. & Sikström, S. (2002). Integrative neurocomputational perspectives on cognitive aging, neuromodulation, and representation. *Neuroscience & Biobehavioral Reviews, 26*, 795–808.

Li, S.-C., Lindenberger, U. & Sikström, S. (2001). Aging cognition: From neuromodulation to representation to cognition. *Trends in Cognitive Sciences, 5*, 479–486.

Li, S.-C., Naveh-Benjamin, M. & Lindenberger, U. (2005). Aging neuromodulation impairs associative binding: A neurocomputational account. *Psychological Science, 16*, 445–450.

Li, S.-C., Lindenberger, U., Hommel, B., Aschersleben, G., Prinz, W. & Baltes, P. B. (2004). Transformations in the couplings among intellectual abilities and constituent cognitive processes across the life span. *Psychological Science, 15*, 155–163.

Li, S.-C., Lindenberger, U., Nyberg, L., Heekeren, H. R. & Bäckman, L. (2009). Dopaminergic modulation of cognition in human aging. In W. Jagust & M. D'Esposito (Eds.), *Imaging the aging brain* (pp. 71–91). Oxford: Oxford University Press.

Li, K. Z. & Lindenberger, U. (2002). Relations between aging sensory/sensorimotor and cognitive functions. *Neuroscience and Biobehavioral Reviews, 26*(7), 777–783.

Lindenberger, U. & Baltes, P. B. (1997). Intellectual functioning in old and very old age: Cross-sectional results from the Berlin Aging Study. *Psychology and Aging, 12*, 410–432.

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 function* (2nd. ed., pp. 609–627). New York: Oxford University Press.

Lindenberger, U. & Ghisletta, P. (2009). Cognitive and sensory declines in old age: Gauging the evidence for a common cause. *Psychology and Aging, 24*(1), 1–16.

Lindenberger, U., Li, S.-C. & Bäckman, L. (2006). Delineating brain-behavior mappings across the lifespan: Substantive and methodological advances in developmental neuroscience. *Neuroscience & Biobehavioral Reviews, 30*, 713–717.

Lindenberger, U., Marsiske, M. & Baltes, P. B. (2000). Memorizing while walking: Increase in dual-task costs from young adulthood to old age. *Psychology and Aging, 15*, 417–436.

Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C. & Buckner, R. L. (2002). Under-recruitment and nonselective recruitment: Dissociable neural mechanisms associated with aging. *Neuron, 33*, 827–840.

Lövdén, M., Bäckman, L., Lindenberger, U., Schaefer, S. & Schmiedek, F. (2010a). A theoretical framework for the study of adult cognitive plasticity. *Psychological Bulletin, 136*, 659–676.

Lövdén, M., Bodammer, N. C., Kühn, S., Kaufmann, J., Schütze, H., Tempelmann, C. et al. (2010b). Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia, 48*, 3878–3883.

Madden, D. J., Bennett, I. L. & Song, A. W. (2009). Cerebral white matter integrity and cognitive aging: Contributions from diffusion tensor imaging. *Neuropsychology Review, 19*, 415–435.

Mattay, V. S., Fera, F., Tessitore, A., Hariri, A. R., Berman, K. F., Das, S. et al. (2006). Neurophysiological correlates of age-related changes in working memory capacity. *Neuroscience Letters, 392*, 32–37.

Miller, E. K. & Cohen, J. D. (2001). An integrative theory of prefontal cortex function. *Annual Review of Neuroscience, 24*, 167–202.

Miyake, A. (2001). Individual differences in working memory: Introduction to the special section. *Journal of Experimental Psychology: General, 130*, 163–168.

Morgan, D. G. & May, P. C. (1990). Age-related changes in synaptic neurochemistry. In Schneider and Row (Eds.), *Handbook of the biology of aging* (pp. 219–250). New York: Academic Press.

Morrison, J. H. & Hof, P. R. (1997). Life and death of neurons in the aging brain. *Science, 278*, 412–419.

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*, 22552–22557.

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 predict working memory performance in younger and older adults. *Journal of Cognitive Neuroscience, 23*, 2030–2045.

Nagel, I. E., Werkle-Bergner, M., Li, S.-C. & Lindenberger, U. (2007). Perception. In J. E. Birren (Ed.), *Encyclopedia of gerontology* (2nd ed., pp. 334–342). Oxford: Elsevier.

Nesselroade, J. R. & Salthouse, T. A. (2004). Methodological and theoretical implications of intraindividual variability in perceptual-motor performance. *The Journals of Gerontology. Psychological Sciences and Social Sciences, 59*, P49–P55.

Nyberg, L., Dahlin, E., Stigsdotter, N. A. & Bäckman, L. (2008). Neural correlates of variable working memory load across adult age and skill: Dissociative patterns within the fronto-parietal network. *Scandinavian Journal of Psychology, 50*, 41–46.

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U. & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences, 16*, 292–305.

Nyberg, L., Salami, A., Andersson, M., Eriksson, J., Kalpouzos, G., Kauppi, K. et al. (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.

Park, D. C. & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *The Annual Review of Psychology, 60*, 173–196.

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N.S., Smith, A. D. & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychology and Aging, 17*, 299–320.

Pascual-Leone, A., Amedi, A., Fregni, F. & Merabet, L. B. (2005). The plastic human brain cortex. *Annual Review of Neuroscience, 28*, 377–401.

Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L. G., Ingvar, M. et al. (2006). Structure-function correlates of cognitive decline in aging. *Cerebral Cortex, 16*, 907–915.

Petrella, J. R., Townsend, B. A., Jha, A. P., Ziajko, L. A., Slavin, M. J., Lustig, C. (2005). Increasing memory load modulates regional brain activity in older adults as measured by fMRI. *Journal of Neuropsychiatry and Clinical Neuroscience, 17*, 75–83.

Pfefferbaum, A., Sullivan, E. V., Hedehus, M., Lim, K. O., Adalsteinsson, E. & Moseley, M. (2000). Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magnetic Resonance Medicine, 44*, 259–268.

Rajah, M. N. & D'Esposito, M. (2005). Region-specific changes in prefrontal function with age: A review of PET and fMRI studies on working and episodic memory. *Brain, 128*, 1964–1983.

Raz, N. (2004). The aging brain observed in vivo: Differential changes and their modifiers. In R. Cabeza, L. Nyberg & D. C. Park (Eds.), *Cognitive neuroscience of aging: Linking cognitive and cerebral aging* (pp. 17–55). New York: Oxford University Press.

Raz, N., Lindenberger, U., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M. & Acker, J. D. (2008). Neuroanatomical correlates of fluid intelligence in healthy adults and persons with vascular risk factors. *Cerebral Cortex, 18*, 718–726.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A. et al. (2005). Regional brain changes in aging healthy adults: General trends, individual differences, and modifiers. *Cerebral Cortex, 15*, 1676–1689.

Reuter-Lorenz, P. A. (2002). New visions of the aging mind and brain. *Trends in Cognitive Sciences, 6*, 394–400.

Reuter-Lorenz, P. A. & Cappell, K. (2008). Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science, 18*, 177–182.

Reuter-Lorenz, P. A. & Lustig, C. (2005). Brain aging: Reorganizing discoveries about the aging mind. *Current Opinion in Neurobiology, 15*, 245–251.

Reuter-Lorenz, P. A. & Mikels, J. A. (2006). The aging mind and brain: Implications of enduring plasticity for behavioral and cultural change. In P. B. Baltes, P. A. Reuter-Lorenz & F. Rösler (Eds.), *Lifespan development and the brain* (pp. 255–276). New York: Cambridge University Press.

Reuter-Lorenz, P. A. & Sylvester, C.-Y. C. (2005). The cogntive neuroscience of working memory and aging. In R. Cabeza, L. Nyberg & D. C. Park (Eds.), *Cognitive neuroscience of aging: Linking cognitive and cerebral aging* (pp. 186–217). New York: Oxford University Press.

Reuter-Lorenz, P. A. et al. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *Journal of Cognitive Neuroscience, 12*, 174–187.

Riediger, M., Li, S.-C. & Lindenberger, U. (2006). Selection, optimization, and compensation as developmental mechanisms of adaptive resource allocation: Review and preview. In J. E. Birren & K. W. Schaie (Eds.), *The handbooks of aging: Vol. 2. Handbook of the psychology of aging* (6th ed., pp. 289–313). Amsterdam: Elsevier.

Rogers, B. P., Morgan, V. L., Newton, A. T. & Gore, J. C. (2007). Assessing functional connectivity in the human brain by fMRI. *Magnetic Resonance Imaging, 23*, 1347–1357.

Rypma, B. & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. *Nature Neuroscience, 3*, 509–515.

Rypma, B., Prabhakaran, V., Desmond, J. E. & Gabrieli, J. D. (2001). Age differences in prefrontal cortical activity in working memory. *Psychology and Aging, 16*, 371–384.

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E. et al. (2004). Thinning of the cerebral cortex in aging. *Cerebral Cortex, 14*, 721–730.

Schmiedek, F., Lövdén, M. & Lindenberger, U. (2009). On the relation of mean reaction time and intraindividual reaction time variability. *Psychology and Aging, 24*, 841–857.

Schmiedek, F., Lövdén, M. & Lindenberger, U. (2010). Hundred days of cognitive training enhance broad cognitive abilities in adulthood: Findings from the COGITO study. *Frontiers in Aging Neuroscience, 2, 27.*

Schneider-Garces, N. J., Gordon, B. A., Brumback-Peltz, C. R., Shin, E., Lee, Y., Sutton, B. P. et al. (2010). Span, CRUNCH, and beyond: Working memory capacity and the aging brain. *Journal of Cognitive Neuroscience, 22*, 655–669.

Schwindt, G. C., Chaudhary, S., Crane, D., Ganda, A., Masellis, M., Grady, C. L. et al. (2013). Modulation of the default-mode network between rest and task in Alzheimer's Disease. *Cerebral Cortex, 23(7)*, 1685–1694.

Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T. et al. (2010). Motor control and aging: Links to age-related brain structural, functional, and biochemical effects. *Neuroscience and Biobehavioral Reviews, 34*, 721–733.

Shu, N., Liang, Y., Li, H., Zhang, J., Li, X., Wang, L. et al. (2012). Disrupted topological organization in white matter structural networks in amnestic mild cognitive impairment: relationship to subtype. *Radiology, 265(2)*, 518–527.

Smith, E. E. & Jonides, J. (1998). Neuroimaging analyses of human working memory. *Proceedings of the National Academy of Sciences of the United States of America, 95*, 12061–12068.

Spreng, R. N., Wojtowicz, M. & Grady, C. L. (2010). Reliable differences in brain activity between young and old adults: A quantitative meta-analysis across multiple cognitive domains. *Neuroscience and Biobehavioral Reviews, 34*(8), 1178–1194.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*, 2015–2028.

Stuss, D. E. (2006). Frontal lobes and attention: Processes and networks, fractionation and integration. *Journal of the International Neuropsychological Society, 12*, 261–271.

Suhara, T., Fukudopamine, H., Inoue, O., Itoh, T., Suzuki, K., Yamasaki, T. et al. (1991). Age-related changes in human D1 dopamine receptors measured by positron emission tomography. *Psychopharmacology, 103*, 41–45.

Sullivan, E. V., Rohlfing, T. & Pfefferbaum, A. (2010). Longitudinal study of callosal microstructure in the normal adult aging brain using quantitative DTI fiber tracking. *Developmental Neuropsychology, 35*, 233–256.

Tisserand, D. J. & Jolles, J. (2003). On the involvement of prefrontal networks in cognitive ageing. *Cortex, 39*(4–5), 1107–1128.

Tisserand, D. J., Pruessner, J. C., Sanz Arigita, E. J., van Boxtel, M. P., Evans, A. C., Jolles, J. et al. (2002). Regional frontal cortical volumes decrease differentially in aging: An MRI study to compare volumetric approaches and voxel-based morphometry. *Neuroimage, 17*(2), 657–669.

Todd, J. J. & Marois, R. (2005). Posterior parietal cortex activity predicts individual differences in visual short-term memory capacity. *Cognitive, Affective, and Behavioral Neuroscience, 5*, 144–155.

Volkow, N. D., Gur, R. C., Wang, G. J., Fowler, J. S., Moberg, P. J., Ding, Y. S. et al. (1998). Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. *American Journal of Psychiatry, 157*, 344–349.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin, 120*, 272–292.

Westlye, L. T., Walhovd, K. B., Dale, A. M., Bjørnerud, A., Due-Tønnessen, P., Engvig, A., Grydeland, H., Tamnes, C. K., Østby, Y. & Fjell, A. M. (2010). Life-span changes of the human brain white matter: Diffusion tensor imaging (DTI) and volumetry. *Cerebral Cortex, 20*, 2055–2068.

Wilson, R. S., Beckett, L. A., Barnes, L. L., Schneider, J. A., Bach, J., Evans, D. A. et al. (2002). Individual differences in rates of change in cognitive abilities in older persons. *Psychology and Aging, 17*, 179–193.

Yi, L., Wang, J., Jia, L., Zhao, Z., Lu, J., Li, K. et al. (2012). Structural and functional changes in subcortical vascular mild cognitive impairment: a combined voxel-based morphometry and resting-state fMRI study. *PLoS One, 7(9)*, e44758.