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Linking Cognitive and Cerebral Aging

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Edited by
Roberto Cabeza
Lars Nyberg
Denise C. Park

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The Link of Intellectual Engagement to Cognitive and Brain Aging

Martin Lövdén

Lars Bäckman

Ulman Lindenberger

Is human cognitive ability static and is the brain fixed? Certainly not. An individual's cognitive performance varies systematically from day-to-day, minute-to-minute, and second-to-second (Rabbitt et al., 2001; Schmiedek et al., 2013). Flux at the level of the brain is not in any way an exception, but rather the normal *modus operandi* of brain structure and function (Faisal et al., 2008). Cognitive performance also changes over longer time periods: it improves considerably during child development (Jones and Conrad, 1933) and declines in aging (Schaie, 1994). The volume and integrity of the brain change in a similar way over the lifespan (Giedd et al., 1999; Raz et al., 2005).

Can humans improve their cognitive performance? Certainly. Eating breakfast is a good idea (Hoyland et al., 2009). Drinking a cup of coffee may sometimes enhance performance (Nehlig, 2010). Though long-term side effects prevail, the right dosage of nicotine improves attention and working memory (Heishman et al., 2010). Acquiring knowledge and strategies in a domain affects memory for domain-relevant information (Bartlett, 1932; Chase and Simon, 1973). Education in childhood and early adulthood improves performance on tests of intelligence (Cliffordson and Gustafsson, 2008; Brinch and Galloway, 2012). During the 20th century, each new generation performed better than their parents on tests measuring a variety of cognitive functions (Flynn, 1984). No doubt, then, human behavior can modify cognitive performance, but of course, not every aspect of human behavior does the trick. In this chapter, we evaluate the evidence for and against the hypothesis that engagement

in cognitively demanding activities positively influences cognitive performance in healthy aging, and we review which brain mechanisms can be linked to such effects. We focus this review on whether cognitive activity influences processing efficiency (Lövdén et al., 2010a); that cognitively healthy older adults can acquire new skills and enhance their task-relevant cognitive strategies is undisputed.

Between-Person Differences in Intellectual Engagement and Cognitive Performance

One approach to investigate whether engagement in cognitively demanding activities improves performance in old age is to sample, typically with questionnaires, individuals' involvement in various types of cognitively stimulating activities (e.g., leisure activities of various kinds, such as reading books, solving cross-words, and playing board games). Between-person differences in engagement (e.g., frequency, duration) in these activities are then related to differences in cognitive performance in various ways. Obviously, longitudinal within-person data provide the most powerful foundation for estimating these various associations (e.g., Hertzog et al., 2009).

Results from the Victoria Longitudinal Study (VLS) reveal that decline in cognitive leisure activities over a 6-year period in old age was associated with decline in cognitive performance, including fact recall (Hultsch et al., 1999) and aspects of processing speed (Bielak et al., 2007; see also Bielak et al., 2014). The magnitude of these associations was, however, relatively small, with the median correlation between change in cognitive activity and change in the various measures of cognitive performance in the VLS studies being only 0.10. However, a comprehensive analysis of four different longitudinal studies with up to 21 years of follow-up data support these initial findings, with changes in participation in cognitively stimulating leisure activities being consistently associated with changes in reasoning, verbal fluency, memory, and knowledge ($r_s = .23-.50$; Mitchell et al., 2012).

Note that correlations between cognitive performance and lifestyle are generally not informative of the causal direction of influence (Hultsch et al., 1999; Lövdén et al., 2005; Gow et al., 2012b). That is, the cognitive engagement hypothesis would predict such associations, but reverse causation, with decline in cognitive performance leading to a less active life, is equally tenable, given that people are not randomly assigned to lifestyles that differ in the degree of cognitive challenge. In addition, changes in some third variable (e.g., health) may drive both activity and cognitive changes. Investigating the association between level of engagement in cognitive stimulating activities at one point in time and subsequent change in cognitive performance has been one way to try to approach these issues of causality. Several findings of a positive association between engagement levels and change in performance have been reported from longitudinal studies (e.g., Hultsch et al., 1999; Schooler and Mulatu, 2001; Bosma et al., 2002; Wilson et al., 2003; Wang et al., 2013). However, other studies have failed to find such associations (e.g., Aartsen et al., 2002; Gow et al., 2012b; Gow et al., 2012a; Mitchell et al., 2012). Some have found that cognitive performance predicts subsequent change in activity engagement (e.g., Schooler and Mulatu, 2001; Aartsen et al., 2002; Bosma et al., 2002). A comprehensive way to

approach these level-change associations is to apply a statistical model for longitudinal data termed the *dual-change score model* (McArdle and Hamagami, 2001). In this model, both hypothetical level-change influences can be simultaneously estimated, while accounting for the effect of previous level of a variable on subsequent change in that variable, as well as for the overall linear change. With respect to intellectual activities, Ghisletta et al. (2006) found that media consumption (e.g., radio, TV, newspapers) and intellectual leisure activities (games and cross-words) were related to subsequent changes in perceptual speed, but not vice versa (see also Lövdén et al., 2005). Supporting this pattern, Small et al. (2012) observed that cognitive activities were associated with change in episodic and semantic memory, without the reverse influence. However, Small et al. (2012) also reported reciprocal associations between cognitive activities and speed of lexical access.

The mixed nature of the findings likely reflects the presence of several sources of influence (Hertzog et al., 2009; Bielak, 2010). For example, the sampled activities and the variables that they form vary substantially across studies, and different activities may mean different effects for different individuals (Salthouse et al., 2002). A related problem is that individuals' engagement in select leisure activities is only a very small portion of the cognitive demands in their lives, and the importance of this portion may vary among older adults and certainly across the lifespan. For example, during extensive periods of life we spend more time in work than in leisure activities. This balance shifts across the lifespan, with retirement perhaps being the most dramatic change. Indeed, support for positive associations between intellectually challenging occupations and level and change trajectories of cognitive performance in old age is available (Jorm et al., 1998; Schooler et al., 1999; Bosma et al., 2003; Andel et al., 2007; Finkel et al., 2009; Marquie et al., 2010; Van der Elst et al., 2012). Also here reverse causation might, however, operate. Individuals higher in cognitive ability are more likely to make their way into more demanding jobs, and the cognitive ability differences, rather than intellectual engagement, may drive old-age differences in level and change of cognitive performance (Salthouse, 2006). A few attempts to account for early differences in cognitive ability have been reported. In one study, Gow et al. (2014) observed a seemingly counterintuitive negative association between occupational demands and cognitive performance after statistically controlling for early cognitive ability. This finding implies that, of two persons with the same cognitive ability at age 50, the individual with the more intellectually demanding job had lower cognitive ability in old age (60–80 years) than the one with the less demanding job. Even if we take these findings at face value and disregard potential methodological problems with controlling for earlier performance at the observed level (Glymour et al., 2005), we note that such findings are not incompatible with the hypothesis that cognitive engagement is beneficial for performance. This becomes clear when, for example, factoring in evidence indicating that retirement can have a detrimental effect on cognitive performance (Schaie, 2005; Finkel et al., 2009; Rohwedder and Willis, 2010; Roberts et al., 2011; Bonsang et al., 2012; Mazzonna and Peracchi, 2012). For example, Finkel et al. (2009) reported that individuals in occupations characterized by high complexity of work with people (e.g., jobs with mentoring and negotiations demands) displayed steeper decline after retirement than individuals with jobs scoring low on this dimension (but see Fisher

et al., 2014). For individuals in occupations with higher complexity, retirement may constitute a greater change in life conditions, and cognitive performance may thus be differentially affected. With such a background, the findings reported by Gow et al. (2014) could also make sense from the point of view of the engagement hypothesis: Of two persons with the same cognitive ability at age 50, the individual with the more intellectually demanding job may have the same cognitive ability as the person in the job with lower demands just because job conditions positively affect cognitive ability. When this influence is not there anymore, the individual in the more intellectually demanding job may have lower cognitive performance. In this sense, failure to find that level of engagement positively affects subsequent change (i.e., differential preservation of cognitive abilities; Salthouse, 2006) is not inconsistent with the engagement hypothesis. Such findings could just be reflecting that individuals' current engagement in cognitively demanding activities is what matters for performance, which would play out in observations of level–level and change–change associations. Level-change associations, such as whether initial differences are preserved or whether they are differentially preserved, are not necessarily informative, and may differ depending on the time frame they capture. In line with this view, studies with shorter longitudinal time spans are also the ones that more often find significant level-change associations (Lövdén et al., 2005; Ghisletta et al., 2006; Small et al., 2012). Such a pattern fits theoretical models of adult plasticity that pinpoint ongoing adaptations to a mismatch between experiential demands and functional capacity as partially determining performance (Lövdén et al., 2010a). That is, what you do, rather than what you did, could be the key player. However, we also note that retirement may affect cognitive performance via mechanisms other than reductions of cognitive stimulation, so that effects of retirement on performance do not provide strong evidence for the engagement hypothesis.

Overall, this line of inquiry may thus benefit from a more systematic approach to sampling intellectual activities, including the entire life space of intellectual demands (leisure activities, work, family life, and so forth) and from more attention to individual differences in the balance of these aspects of life and how they change in importance over time. As things stand, it seems safe to conclude that there is an association between engagement in cognitively demanding activities and cognitive performance in aging. Studies of the association between level of engagement and subsequent change that focus on a shorter longitudinal time span (around 2–3 years) support the notion that cognitive activity influences subsequent change in performance. The causal nature of the association is, however, likely to be complex and scientific consensus on this issue is unlikely to be reached based on studies of naturally occurring between-person differences alone. Progress in this field is likely to come from abandoning simplistic attempts to pit the hypothesis that activity affects cognitive ability against the prediction that ability affects selection of activities. The path dependency of the life course needs more careful conceptual consideration and longitudinal study: People with higher cognitive abilities may be more likely to select or be selected into more challenging environments, and these environments, in turn, may further improve their abilities, whereas the reverse may be true for individual with lower cognitive abilities (Schooler et al., 1999; Schooler and Mulatu, 2001). Individuals with higher abilities may experience the

same environment differently from individuals with lower abilities. The resulting scenario would be one in which the two directions of influence—abilities affecting lifestyles, and lifestyles affecting abilities—are positively correlated over time. This would be consistent with theoretical and empirical claims pointing to the importance of gene–environment correlations in understanding individual differences in development (e.g., Beam and Turkheimer, 2013).

Effects of Cognitive Training on Performance in Old Age

Intervention studies could provide less ambiguous support for the hypothesis that intellectual engagement affects performance. A few such studies have used multi modal engagement interventions (e.g., group-based diverse problem solving tasks, computer and photo-editing courses), with encouraging results for memory (Park et al., 2014) and reasoning (Stine-Morrow et al., 2008; Tranter and Koutstaal, 2008). Studies focusing on cognitive training promise to more specifically localize such effects to the impact of cognitive activity. The first generation of such studies generally included teaching individuals to use efficient cognitive strategies (e.g., method-of-loci for memorizing words). Results were disappointing in the sense that improvements on the trained tasks did not transfer to related but nontrained tasks (Verhaeghen et al., 1992; Ball et al., 2002; Hertzog et al., 2009). Probing transfer of improvements is important because this provides a tool for examining whether processing efficiency has been improved (Lövdén et al., 2010a). That is, if improvements can be observed on tasks where training-related acquisition of knowledge (e.g., better strategies and improved response mapping) can be reasonably well excluded as a factor behind any improvements, then it can be assumed that training has affected processing efficiency. A more recent generation of studies has examined the effects of practice on various types of cognitively challenging tasks, such as off-the-shelf video games (Basak et al., 2008), working memory tasks (Dahlin et al., 2008b), and a mix of cognitive tasks (Schmiedek et al., 2010). Karbach and Verhaeghen (2014) recently summarized this literature in a meta-analysis that focused on training of working memory and executive tasks. This analysis yielded net training effects (gains for training group minus gains for controls) of 0.5 *SD* for near transfer (measuring the trained ability using untrained tasks) and 0.2 *SD* for far transfer (measuring any nontrained ability, such as reasoning, episodic memory, and speed). Younger and older adults displayed similar effects sizes.

With near-transfer effects, it is, without a detailed model or task analysis, difficult to exclude that acquisition of knowledge (e.g., strategies) is responsible for the observed gains. One may therefore argue that this type of outcome measure is problematic in a meta-analysis. A skeptical reader may also argue that far-transfer effects suffer from the same problem, especially when selected far-transfer tasks are heterogeneous, so that the tasks in each individual study need to be carefully analyzed. We therefore conducted our own meta-analysis, focusing exclusively on reasoning as an outcome measure. To gain power and generality we included all types of processing-based cognitive training (e.g., working memory, inhibition, episodic memory, and computer game training, but no combinations with other activities, such a physical

training, and no strategy training, general enrichment interventions, and meditation studies). Further, we only included studies if the method sections were sufficiently detailed to make sure that training procedures did not directly include reasoning or strategy training. Further inclusion criteria were (1) a pretest–posttest design including a control group; (2) a healthy older sample (mean age > 60); and (3) publication of the study between January 2000 and July 2014.

Our initial screening of search results from Pubmed, Web of Science, and available meta-analyses and reviews (Kueider et al., 2012; Reijnders et al., 2013; Karr et al., 2014; Kelly et al., 2014; Noack et al., 2014; Brehmer et al., 2014; Karbach and Verhaeghen, 2014) resulted in 73 candidate studies, of which 20 were eligible according to the above criteria. These studies reported results for samples with a mean age of 69 years (range 61–79 years) and a mean total sample size of 51 (29–139) individuals. The training groups trained on average 993 minutes (range = 180–6000 minutes). Eleven studies had an active control group. Thirteen studies focused on working-memory training, one on task switching, one on computer game training, one on inhibition, and four on several cognitive domains. Ten studies had Raven’s matrices as a single reasoning outcome, four had Cattell’s culture fair test, one had reasoning tasks from WAIS III, one had a letter series task only, and four had several reasoning tasks. As main measures for the meta-analyses we computed one Standardized Mean Difference (SMD; Hedges’ g) for each study of the difference between the training and control groups at pretest and one at posttest. An average SMD was computed across tasks for the studies reporting multiple reasoning tasks.

Results of a random effects analysis (maximum likelihood in Open Meta Analyst; Wallace et al., 2012) of the post-test difference in reasoning performance between training and control groups showed a significant weighted mean group differences favoring the training group ($g = 0.192$, $SE = .097$, $p = .049$). There was no such difference at pretest ($g = -0.012$, $SE = .081$, $p = .878$). The standardized mean increase for the training groups was 0.342 ($SE = .076$, $p < .001$). The increase for the control groups was .160 ($SE = .067$, $p = .018$). The difference between these effects (i.e., the net training effect) is 0.182, which corresponds well with the observed post-test difference between the groups.

Publication bias was addressed by first computing standardized net effect sizes for each study, which arguably is the effect that may drive a publication bias. We are not aware of a way to compute the standard errors for these effects, so we related this effect size to total sample size (rather than SE, which is otherwise the preferred measure; Sterne and Egger, 2001). The scatterplot (Figure 18.1) of this association showed no indication of publication bias, and sample size was not significantly related to effect size ($p = .61$). However, the plot shows that two of the small-sized (and thus likely low-powered) studies (Borella et al., 2010; Carretti et al., 2013) report somewhat deviant net effect sizes. We therefore excluded these two studies in a sensitivity analysis, which showed a lower and nonsignificant posttest difference between the groups ($g = 0.136$, $SE = .094$, $p = .148$). The pretest difference was essentially zero ($g = -0.007$, $SE = .091$, $p = .939$). The increase for the training groups included in this analysis was 0.255 ($SE = .062$, $p < .001$). The increase for the control groups was .158 ($SE = .071$, $p = .025$). The difference between these effects (i.e., the net training effect) is 0.097. Figure 18.2 shows a forest plot of the

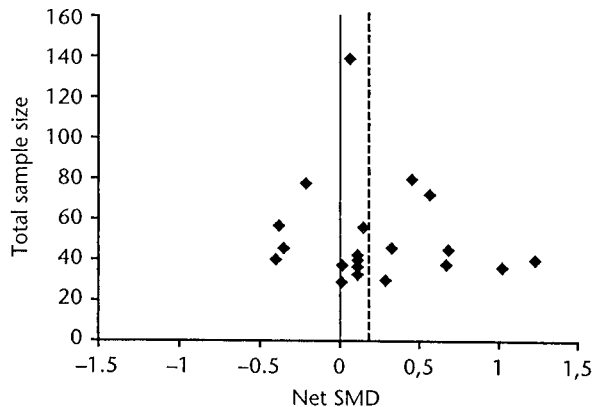


Figure 18.1 Funnel plot relating total sample size to net SMD (Standardized Mean Difference) of cognitive training on reasoning ($SMD_{\text{post-pre}}$ for the training group— $SMD_{\text{post-pre}}$ for the control group). The dashed line indicates the mean net SMD.

individual effect sizes and the weighted mean effect sizes across all studies and when excluding the two deviant studies. Figure 18.3 shows the corresponding information at pretest.

The effect sizes were significantly heterogeneous at posttest ($I^2 = 52.59$, $p = 0.002$), but not at pretest ($I^2 = 32.84$, $p = 0.058$). Increases were significantly heterogeneous for the training groups ($I^2 = 38.33$, $p = 0.029$), but not for the control groups ($I^2 = 0.00$, $p = 0.959$). These results suggest that the training regimens used in the various studies may differ in efficiency (e.g., due to differences in sample composition, outcome variables, and training paradigms). We therefore explored associations with a few potentially moderating factors.

Mean age of the sample was unrelated to posttest differences ($p = .911$) and to gains in the training groups ($p = .37$). Training length was also unrelated to posttest differences ($p = .174$) and not related to gains in the training groups ($p = .419$). When mutually adjusted, neither training length nor age had a significant effect (both $ps > .217$). Excluding the two studies with outlying positive effects and two studies with outlying length of training did not change these findings. Studies with Raven's matrices as an outcome did not demonstrate larger posttest differences than other studies ($p = .361$), and gains were not larger in these studies either ($p = .146$). Studies with working memory training tended to report larger posttest differences than other studies ($p = .079$), but gains were not larger in these studies ($p = .827$). Excluding the two studies with outlying positive effects did not substantially alter these results. Studies with an active control group did not report smaller posttest differences than other studies ($p = .844$), and neither gains in the training group ($p = .387$) nor gains in the control group differed between active and passive control groups ($p = .897$). Thus, we conclude that the observed heterogeneity remains unexplained.

In summary, studies of the effects of practicing cognitive tasks on reasoning performance in old age report a significant but small average effect size (roughly $0.2 SD$). This estimate is virtually identical to the far-transfer effect reported by Karbach

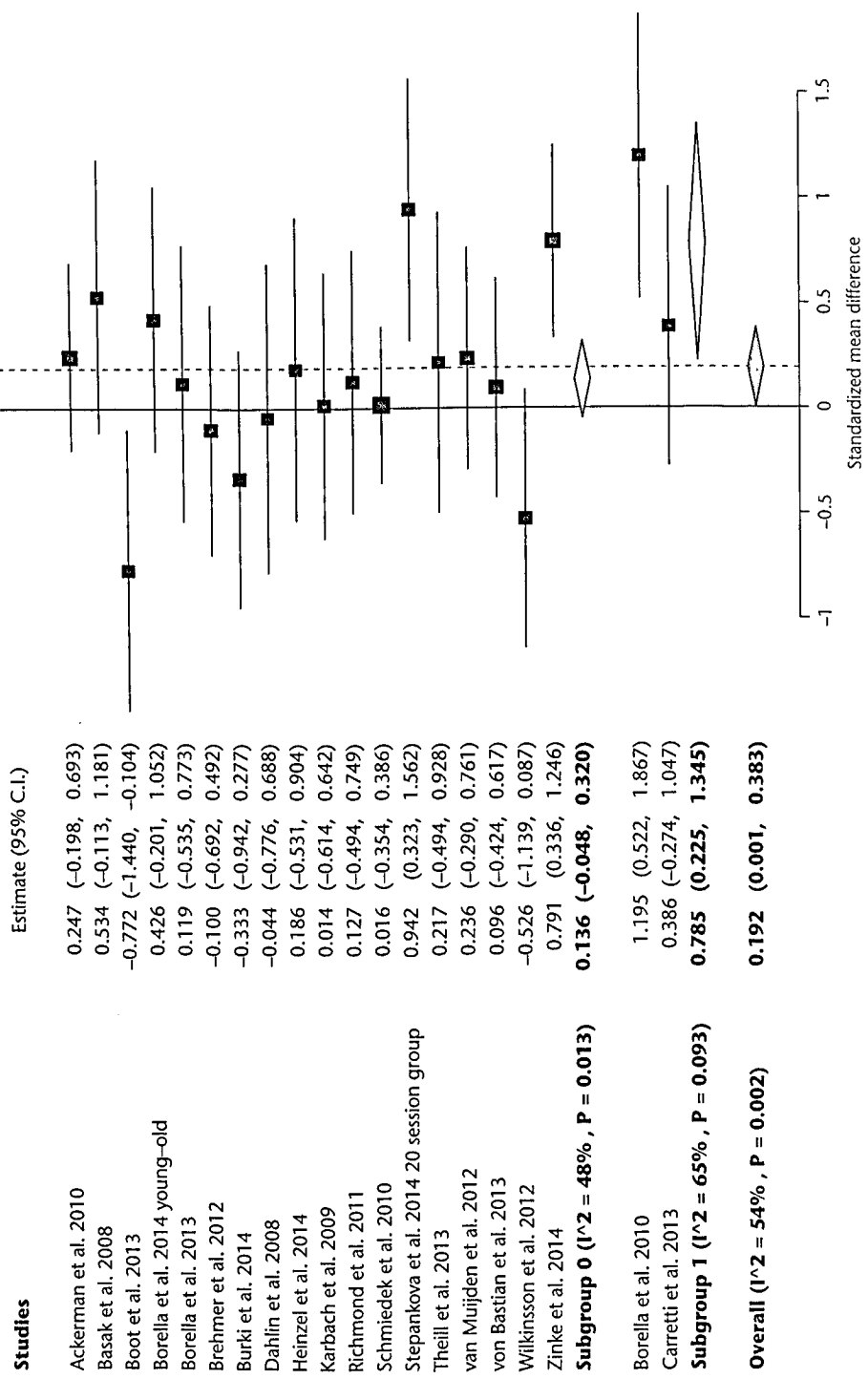


Figure 18.2 Forest plot of the effect sizes (and 95% confidence intervals) for the difference between training and control groups (SMD; Hedges g) at *posttest* in studies investigating effects of cognitive training on reasoning in older adults. Overall weighted effect size is displayed at the bottom of the figure. The overall weighted effects for subgroup 0 (upper triangle) does not include the two studies in subgroup 1 that report outlying net effect sizes (see Figure 18.1).

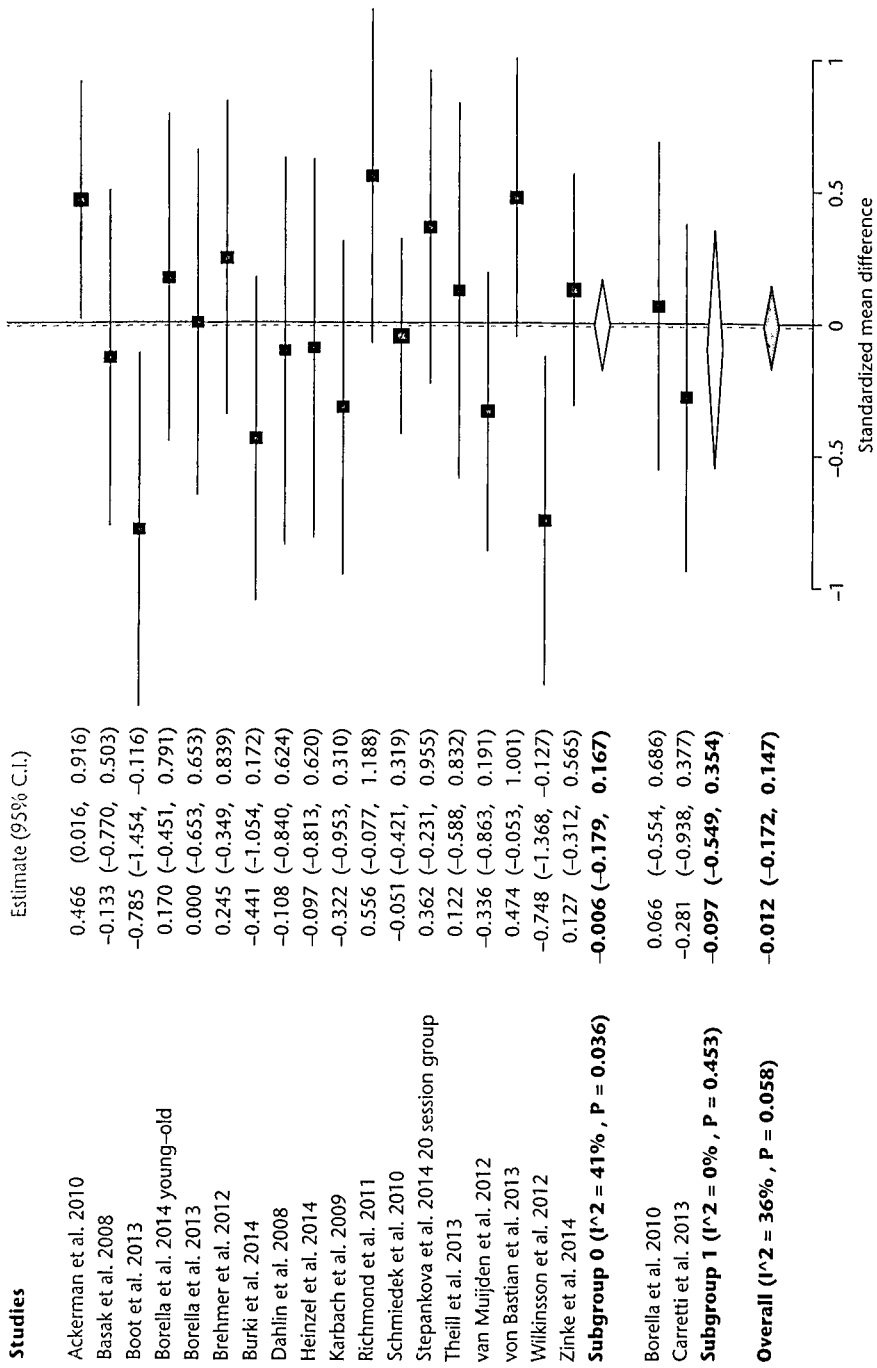


Figure 18.3 Forest plot of the effect sizes (and 95% confidence intervals) for the difference between training and control groups (SMD; Hedges g) at *pretest* in studies investigating effects of cognitive training on reasoning in older adults. Overall weighted effect size is displayed at the bottom of the figure. The overall weighted effects for subgroup 0 (upper triangle) does not include the two studies in subgroup 1 that report outlying net effect sizes (see Figure 18.1).

and Verhaeghen (2014). The effect is not very robust. In particular, the exclusion of two extreme effect sizes reduced the overall effect to a nonsignificant point estimate of around 0.13 *SD*. Similar positive outliers were also included in the analysis by Karbach and Verhaeghen (2014). The effect size tends to be lower than a report of a significant average effect of working memory training on reasoning performance in younger adults of 0.24 *SD* (Au et al., 2015). Note however that the effect size in these studies of younger adults that had an active control group was only 0.06. In our analysis of studies on older adults, the difference between an active and passive control group was, however, minimal. Though power is low with only 20 studies and with, at best, a small overall effect, it is worrisome that theoretically-predicted moderators of the effects, such as for example length of training (Lövdén et al., 2010a), are not associated with effect sizes (see also Au et al., 2015; Karbach and Verhaeghen, 2014). We thus conclude that cognitive training, as currently implemented, at best has a very small effect on cognitive processing efficiency, as indexed by transfer to reasoning tasks, in old age. A firm conclusion of the trustworthiness of this effect must await accumulation of more studies. We also note that almost all of the published studies are seriously underpowered (a total sample of around 200 subjects is needed to detect a net effect of 0.2 *SD* with a power of 0.8; the power for the typical study with a total sample size of 40 subjects is only around 0.20 (Faul et al., 2009)). This fact substantially limits the value of reviewing results from individual studies in this field. At the same time, we note that meta-analyses are no methodological remedy for flawed studies. Several factors, such as publication bias, which we tested for, but also other confounds that are harder to detect, such as selective reporting of only significant findings, may positively bias the average effect size. Finally, we note that, with only observed indicators of reasoning ability, it is difficult to entirely exclude that ability-extraneous changes, such as strategy improvements, influence the measures of reasoning. To reduce this problem, future studies should obtain several measures of the target ability and form a factor of the common variance of these measures (Noack et al., 2009; Lövdén et al., 2010a; Schmiedek et al., 2010; Noack et al., 2014).

Effects of Intellectual Engagement on the Brain in Old Age

Understanding how the brain responds structurally to cognitive activity and how such changes relate to cognitive performance may provide much credibility to the engagement hypothesis by providing feasible mechanistic pathways. Reports from cross-sectional studies have shown that individual differences in participation in leisure activities, including cognitively demanding activities, in old age are related to individual differences in a variety of brain measures, including total brain volume, grey matter volume, white matter volume, white matter lesions (Hafsteinsdottir et al., 2012), and beta-amyloid deposition (Landau et al., 2012). Interestingly, the associations between activity levels (both physical and cognitive) and cognition, as well as with beta-amyloid deposition, have been reported to be stronger for individuals who have greater genetic risk regarding cognitive impairment and dementia (most notably APOE $\epsilon 4$ carriers; (Kivipelto et al., 2008; Head et al., 2012; Ferencz et al., 2014; Wirth et al., 2014). Under the assumption that a sedentary lifestyle is a phylogenetically recent

phenomenon, these results suggest that this variation in genetic risk has remained in the population because it is relatively inconsequential under non-sedentary living conditions and now becomes effective for some individuals (Raichlen and Alexander, 2014). It may even have been advantageous for offspring not to carry the burden of an older individual that for some reason (e.g., injury) cannot remain active and contribute to bringing food on the table. This line of reasoning is consistent with the notion that so-called “vulnerability alleles” may also serve as plasticity alleles (Belsky et al., 2009).

The association between educational attainment, as a proxy for early exposure to cognitively demanding activities, and brain variables has also been studied quite intensively. For cognitive performance in healthy aging, educational exposure is related to levels of cognitive performance, but not to trajectories of change, in old age (Lövdén et al., 2004; Zahodne et al., 2011). Causal pathways are likely to be complex here, but there is evidence from natural quasi-experiments that education may partly serve to improve cognitive performance (Ceci, 1991; Cliffordson and Gustafsson, 2008; Brinch and Galloway, 2012). When triangulating individual differences in education and cognition with measures of brain integrity, interesting patterns have emerged. For example, Bennett et al. (2003) reported a study of older Catholic priests, nuns, and monks who underwent annual clinical evaluations and brain autopsy at death. A composite index of amyloid plaques and neurofibrillary tangles (i.e., classic Alzheimer’s disease pathology) was associated with lower level of cognitive function in close proximity to death. This association was, however, smaller in participants with higher levels of education. This finding suggests that cognitive activities may result in long-term advantages (e.g., availability of alternative cognitive strategies, better integrity of other aspects of the brain that matter for cognitive performance) that may offset the effect of this type of pathology on cognitive performance. In general, this notion has been supported in studies of both education (Wilson et al., 2004) and other types of cognitive activity (Scarmeas et al., 2003; Helzner et al., 2007; Hall et al., 2009). The relative absence of long-term longitudinal brain data in this domain of research is, however, a major shortcoming. To our knowledge, the few published longitudinal studies with extensive brain measurements and activity measures have only longitudinal data of activities and not of brain structure (e.g., Gow et al., 2012c; Vaughan et al., 2014), which limit the conclusions that can be drawn.

Again, effects of training studies offer a more direct test of whether and how cognitive engagement affects the brain. In humans, a large body of literature has reported that regional grey-matter volume and cortical thickness, probed with T1-weighted magnetic resonance (MR) imaging, changes in response to motor (Draganski et al., 2004), cognitive (Draganski et al., 2006), and physical (Erickson et al., 2011) activity in younger adults. The biological nature, behavioral correlates, and time-course of these changes are, however, largely unknown (for reviews, see May, 2011; Zatorre et al., 2012; Lövdén et al., 2013). Evidence on effects of cognitive activity on brain volume in older adults is also scarce. In one of the few available studies, Engvig et al. (2010) studied middle-aged and older adults taking part in an 8-week training regimen in a mnemonic (the Method of Loci) aimed at improving episodic memory. Compared to controls, the trained persons showed a regional increase of cortical thickness in right insula, left lateral orbitofrontal cortex, and fusiform cortex. Increases in right fusiform and lateral orbitofrontal cortex were related to larger

improvement in memory performance. Lövdén et al. (2012) investigated the effects of spatial navigation training on hippocampal volume and integrity in younger and older men. The training group navigated in a virtual world while walking on a treadmill for 45 minutes every other day over a period of four months. A walking-only control group was also included. Results showed navigation-related performance gains and stable hippocampal volume that were also maintained four months after termination of training. In contrast, control groups showed the typical age-related hippocampal decrease in volume. Follow-up analyses revealed training-related cortical thickening in precuneus and paracentral lobule in younger, but not in older, participants (Wenger et al., 2012). In the COGITO study (Schmiedek et al., 2010), younger and older adults trained for a total of 101 1-hour sessions on a set of working memory, episodic memory, and perceptual speed tasks. Using data from this study, Raz et al. (2013) showed that cognitive training was associated with less decrease of cerebellar volumes, but that training did not modify cortical volume changes. Thus, also older adults may display experience-dependent changes in grey matter structure, but the magnitude of these changes may sometimes be reduced. This pattern is consistent with corresponding animal work (for a review, see Lövdén et al., 2013).

Animal research shows that also the brain's white matter can be shaped by experience (Fields, 2008). In humans, amount of piano practicing in childhood and early adulthood relates to white-matter microstructure, as assessed with diffusion-tensor imaging (DTI; Bengtsson et al., 2005). Practicing juggling (Scholz et al., 2009), meditation (Tang et al., 2010), and reasoning (Mackey et al., 2012) in younger adulthood also results in microstructural changes in regional white matter of the brain. Lövdén et al. (2010b) reported that such experience-dependent plasticity extends into old age. In this study, younger and older adults trained for a total of 101 1-hour sessions on a set of working memory, episodic memory, and perceptual speed tasks. As compared with a control group, training affected several DTI metrics and increased the area of the anterior, but not the posterior, part of corpus callosum. These brain changes were of similar magnitude in both age groups. Effects on white-matter microstructure in old age have also been observed after other types of cognitive interventions (Strenziok et al., 2014), including training that has been mainly strategy based (Engvig et al., 2012; Chapman et al., 2015). For example, Engvig et al. (2012) reported training-related changes in DTI metrics from their study of method-of-loci training. Participants in the training group showed a relative increase in fractional anisotropy (FA), a measure of density and coherence of the white matter tissue, in a frontal region compared with a decrease in controls. Increases in memory performance correlated with changes in FA. Though biological interpretations of changes in DTI metrics are difficult, the pattern of changes (i.e., primarily decreases of radial diffusivity) in some of these studies suggests a role for myelin-related processes in plasticity of white matter (Lövdén et al., 2010b; Engvig et al., 2012).

Considering the theoretical importance of efficient large-scale connectivity for higher-order cognition in general (Fields, 2008) and for cognitive performance in aging (O'Sullivan et al., 2001; Andrews-Hanna et al., 2007; Bartzokis, 2011; but see Lövdén et al., 2014), as well as effects of cognitive activity on white-matter structure, attention to effects of training on functional connectivity is warranted. In line with this notion, Anguera et al. (2013) reported that older adults training in dual tasking

increased their task-related long-range phase (theta) coherence, as assessed with EEG, between frontal and parietal areas. In another study, Chapman et al. (2015) found increases in cerebral blood flow, particularly in the default mode network and the central executive network, as well as greater connectivity at rest in these networks, as observed with functional MR imaging, after strategy-based reasoning training (see also Li et al., 2014). Other studies have, however, also observed decrease in connectivity in a ventral attention network at rest (Strenziok et al., 2014). Studies of training-related changes in classic measures of functional activity in old age are delivering even worse scattering of results. Just as in studies of younger adults (Kelly and Garavan, 2005), practice on cognitive tasks has been associated with both cortical activity decreases (e.g., Dahlin et al., 2008a; Brehmer et al., 2011) and increases (e.g., Erickson et al., 2007; for reviews, see Lustig et al., 2009; Brehmer et al., 2014). In a study by Erickson et al. (2007), performance increases after dual-task training were related to activity increases during the dual-task condition in left ventro-lateral frontal cortex and in right dorsolateral prefrontal cortex among trained older adults. Dahlin et al. (2008b) reported training-related cortical activation decreases (in right anterior prefrontal cortex, right somatosensory association cortex, and right supramarginal gyrus) in younger and older adults after five weeks of updating training. In addition to these cortical decreases, younger adults who, in contrast to older adults, also improved in a near-transfer task, showed striatal increases in both the trained and the transfer task, but these changes were not observed in older adults. Increases in striatal activity after updating training in younger adults have later been replicated, but are also shown to decrease again after an initial increase (Kuhn et al., 2013). These findings suggest that the time course of training-related brain changes needs to be studied with better resolution to develop, test, and refine cerebral models of learning and transfer (see also Lövdén et al., 2013).

Mechanisms behind the Influence of Intellectual Engagement in Aging

Which are the brain mechanisms that mediate potential effects of cognitive activity on cognitive processing efficiency in aging? From a general perspective, these mechanisms may come in three major and complementary forms (Barulli and Stern, 2013): (a) through improving brain functioning and performance in younger age without altering brain aging per se (Satz, 1993; Lövdén et al., 2010a); (b) by aiding compensatory reactions to primary brain aging (Baltes et al., 1999; Stern, 2002; Park and Reuter-Lorenz, 2009; Stern, 2009); and (c) by fostering maintenance of a young-adult like brain in old age (Nyberg et al., 2012).

According to the first form, cognitive activities during the life course (e.g., education, occupation) may improve brain integrity in the life period during which they operate (Satz, 1993; Stern, 2002, 2009). To the extent that these improvements are maintained, it will take more time before a critical threshold for functional impairments (e.g., compromised independence, dementia diagnosis) will be reached. This simple but important point is sometimes called “brain reserve” (Satz, 1993; Stern, 2002, 2009).

Lifetime cognitive activities may also aid compensatory reactions to primary aging, so that effects of brain aging on performance may be reduced in old age, which implies different trajectories of performance change in old age for individuals with the same change in brain integrity but who differ in life time cognitive activity. This notion, often referred to as cognitive reserve (Stern, 2002, 2009) or simply flexibility (Lövdén et al., 2010a), holds that lifetime cognitive activities (e.g., education) may give individuals better opportunities to handle the negative effects of brain aging on cognitive performance, perhaps by giving the individual a larger and more flexible set of neurophysiological routes and cognitive skills (e.g., knowledge and strategies) to handle different situations (see also Lövdén et al., 2010a). This notion has received tentative support by studies reporting a negative association between a cognitively engaged lifestyle and brain integrity in some groups (e.g., in dementia; Scarmeas et al., 2003) when cognitive performance is controlled for.

In the likely absence of an active gene program that causes human aging (Kirkwood, 2005), the major goals in the cognitive neuroscience of aging must be to identify the mechanisms causing damage to accumulate in the brain and the variety of mechanisms that operate to protect us from this damage. Related to this view, individuals that decline less in cognitive performance in aging do not have to be those individuals who can compensate for decline in brain integrity, but rather those who can maintain brain integrity in the first place (Nyberg et al., 2012). According to this “brain maintenance” view, mechanisms protecting the brain against age-graded risks differ in number and strength across and within individuals. Certain types of behavior may lead to neurophysiological effects that modify brain aging directly, but others may also indirectly protect the brain by offsetting negative conditions. For example, an engaged lifestyle in old age may confer advantages for brain aging because negative pathways, such as loneliness, depression, stress, and malnutrition, become less likely. Cognitive activity may also have direct effects on brain integrity through a multitude of mechanisms. For example, basic neuroscience work indicates that neural activity can induce myelination (Fields, 2008; Wake et al., 2011). Cognitive training may improve white matter integrity (Lövdén et al., 2010b). Myelin undergoes many negative changes in aging (Bartzokis, 2011), and white matter integrity in general also shows negative adult age differences (Madden et al., 2012), of which some thus could be postponed by positive effects of cognitive activities. To the extent that aging of white-matter integrity contributes to cognitive aging (Salthouse, 2011; Lövdén et al., 2014), one may thus speculate that cognitive activity could serve to maintain cognitive functioning through relatively preserved white-matter integrity. Many other similar direct mechanisms are also available, such as activity-dependent release of growth factors (Lövdén et al., 2011), alterations of release of neurotransmitters (Bäckman et al., 2011), and activity-dependent structural changes of the neuron (Zatorre et al., 2012; Lövdén et al., 2013; Lindenberger, 2014).

At first glance, the brain-maintenance concept seems unable to deal with the finding that commonly measured aging-related brain changes (Salthouse, 2011) and putative markers of pathology (Boyle, 2013) leave a major portion of age-related cognitive decline unexplained. However, such findings do not require that a cognitive reserve account must be evoked to explain the remaining individual differences in cognition. Rather, the presence of such residual variability may simply mean that our current

knowledge of the mappings between brain changes and changes in behavior is incomplete. These mappings may also differ across individuals if there is more than one physiological pathway into cognitive decline. In addition, such mappings may change within individuals, possibly reflecting selection mechanisms (Lindenberger, 2014; see also Edelman, 1987; Lautrey, 2003).

In particular, aging-related cognitive decline and dementia are likely to have related and multifactorial etiologies (Drachman, 2007). Seventy percent of all individuals suffering from dementia are older than 75 years (Fratiglioni and Qiu, 2011). A majority of these persons show not only the pathology typically associated with Alzheimer's disease (e.g., plaques) but also vascular injuries (Viswanathan et al., 2009). To this we must add a wide range of known (e.g., changes in neurotransmitter functioning; Bäckman et al., 2010) and as yet unknown aging-related brain changes, all of which may contribute to individual differences in late-life cognitive functioning. Of course, determinants of individual differences in cognitive abilities before aging-related changes have emerged must also be factored into the equation.

In summary, researchers are confronted with many-to-many mappings between brain integrity and cognitive abilities in aging and dementia. For example, assume that the amyloid burden of two individuals is identical. Assume also that one of these individuals is diagnosed with dementia or has low cognitive performance, whereas the other individual has no dementia diagnosis or shows high performance. Further assume that the low-functioning individual has fewer years of education than the high-functioning individual. Reserve concepts offer viable explanations of such a scenario. The cognitive reserve notion describes well the possibility that the high-performing individual may have been able to better cope with the accumulation of amyloid, perhaps due to the higher flexibility that comes with added years of education (Lövdén et al., 2010a). However, an alternative explanation in terms of brain maintenance seems just as viable: The high-functioning individual may have accumulated fewer vascular injuries—or any number of other unknown, imperfectly measured, or unmeasured alterations—perhaps reflecting advantageous lifestyle habits associated with education. Thus, the presence of residual variability in functioning after accounting for select aspects of age-related brain pathology does not discriminate between the reserve and maintenance views, because several aspects of brain integrity determine functioning and dementia diagnosis in old age, including those that have not been observed in the particular study in question, or that have not yet been discovered.

Thus, although these general models never have been proposed as mechanistic theories of aging, but rather as general frameworks, further progress in the field is likely to come from operationally defining the concepts and from the generation of predictions that can tease the models apart. Future work needs to develop models that can estimate the contribution of brain reserve, cognitive reserve, and maintenance to successful cognitive aging. Conceivably, these general models in the cognitive neuroscience of aging are complementary, related across individuals, and differing in importance across the adult life span. To delineate the multiple sources of individual differences in aging and the potential effects of cognitive activity on cognitive aging, we need to intensify our efforts at discovering and measuring what matters. In our view, what matters are the between-person differences in change that we can

predict and explain, rather than speculations about why there is variance that we cannot account for.

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