
This copy is for your personal, non-commercial use only.

If you wish to distribute this article to others, you can order high-quality copies for your colleagues, clients, or customers by [clicking here](#).

Permission to republish or repurpose articles or portions of articles can be obtained by following the guidelines [here](#).

The following resources related to this article are available online at www.sciencemag.org (this information is current as of November 2, 2014):

Updated information and services, including high-resolution figures, can be found in the online version of this article at:

<http://www.sciencemag.org/content/346/6209/572.full.html>

A list of selected additional articles on the Science Web sites **related to this article** can be found at:

<http://www.sciencemag.org/content/346/6209/572.full.html#related>

This article **cites 107 articles**, 19 of which can be accessed free:

<http://www.sciencemag.org/content/346/6209/572.full.html#ref-list-1>

This article appears in the following **subject collections**:

Neuroscience

<http://www.sciencemag.org/cgi/collection/neuroscience>

REVIEW

Human cognitive aging: *Corriger la fortune?*

Ulman Lindenberger^{1,2}

Human cognitive aging differs between and is malleable within individuals. In the absence of a strong genetic program, it is open to a host of hazards, such as vascular conditions, metabolic syndrome, and chronic stress, but also open to protective and enhancing factors, such as experience-dependent cognitive plasticity. Longitudinal studies suggest that leading an intellectually challenging, physically active, and socially engaged life may mitigate losses and consolidate gains. Interventions help to identify contexts and mechanisms of successful cognitive aging and give science and society a hint about what would be possible if conditions were different.

Around the world, the older segment of the adult population is increasing in size, proportion, or both. Advances in medicine and public health measures, rising standards of living, and improvements in education and nutrition have lengthened the human life span. Demographic evidence suggests that the debilitating effects of senescence are not being stretched out in time but delayed to later ages (1). Cognitive development in adulthood and old age follows a similar pattern. Longitudinal studies show that the onset of average decline in cognitive abilities occurs at considerably later ages than suggested by cross-sectional studies, which confound effects of age and birth cohort (2, 3).

Comparisons across countries and of birth cohorts within countries (1), coupled with findings from cognitive neuroscience (4, 5) and developmental psychology (6), indicate that adult cognitive development is variable across and malleable within persons (7). Evolutionary theories propose that human senescence reflects evolved limitations in somatic maintenance, resulting in a buildup of damage (8). In the absence of programmed aging, modifiers and modulators come to the fore, and individual differences abound. Hence, the shape and course of adult cognitive development is best conceived as a range of potential developmental trajectories that reflect person-specific endowments and environmental opportunities and constraints (7, 9) (Fig. 1). Actual paths through life are sampled from this range and depend, in part, on the choices that people make. Readers hoping to reach a ripe old age with grace inevitably ask the question, what will become of their own cognitive abilities and what can be done to maintain them. Leading an intellectually challenging, physically active, and socially engaged life bodes well for enhanced cognitive stability and growth and may serve as a hedge against cognitive decline (7). However, invoking the impression that cognitive aging is

under personal control would be just as wrong as claiming that its course cannot be altered, to some extent, through experience and goal-directed action. Life-span development is inherently probabilistic (10, 11), and the range of potentially available developmental trajectories is likely to differ from person to person (12).

Neuroscience and, in particular, neuroepigenetics offer mechanistic explanations for the influence of common genetic variation, environmental conditions, and lifestyles on adult cognitive development. Multiple factors associated with vascular and metabolic risk, inflammation,

stress, and deposition of iron and beta-amyloid accelerate brain aging (7, 13). At the same time, the continued potential for neuroplasticity helps to maintain the viability of neural structures and postpone the onset of cognitive decline (7, 9, 14, 15). Epigenetics has begun to identify mechanisms through which earlier experiences influence genome expression, which affects later development (16). Animal models have been proposed to capture the path dependency of cognitive development (10).

In the following, key features of human cognitive aging will be summarized from the combined perspectives of life-span psychology and the cognitive neuroscience of aging.

Fluid and crystallized cognitive abilities

Mechanisms related to maturation and senescence shape the course of cognitive development from conception to old age (6). In adulthood and old age, human brains show increasing marks of aging. At the same time, they accumulate knowledge about the world and continue to express potential for new learning. The life-span trajectories of cognitive abilities reflect dynamic equilibria of these interacting forces and form the empirical basis of two-component theories of intellectual development (17). Such theories distinguish between experience-based “crystallized” abilities, such as vocabulary, and “fluid” abilities that are less supported by acquired knowledge, such as reasoning and working memory, but are helpful in acquiring that knowledge in the first place.

As a summary observation, the ages at which cognitive skills reach their peak are likely to reflect a balance among competing processes of knowledge accumulation and deterioration of the supporting neural infrastructure. For instance, in correspondence chess tournaments, where players have 3 days to make each move, players achieve the title of world correspondence champion at a mean age of 46, which is about 10 years later than the mean age for becoming the world chess champion at tournaments, where players have an average of 3 min or less to make a move (18).

The senescent brain

A plethora of correlated processes contribute to human brain senescence, resulting in decreasing differentiation and integration of brain function and behavior (19, 20). Senescence cumulatively affects the neurochemistry and anatomy of the human brain (13). Many neurotransmitters show marked age-related differences in concentration and receptor density. Dopaminergic

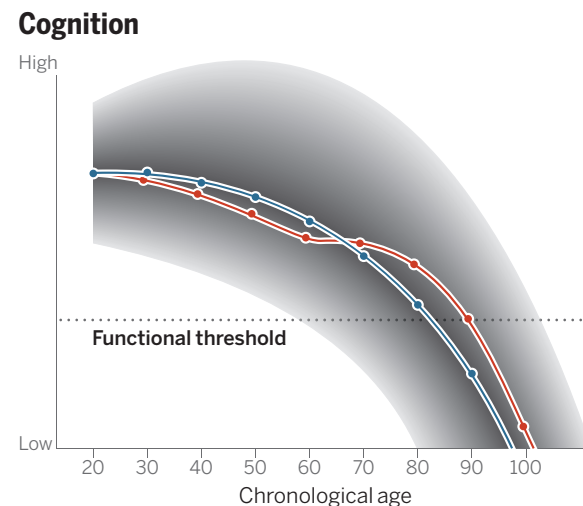


Fig. 1. An individual's range of possible cognitive developmental trajectories from early to late adulthood. The blue curve shows the most likely developmental path under normal circumstances. The fading of the background color indicates that more extreme paths are less likely. The functional threshold represents a level of functioning below which goal-directed action in the individual's ecology will be severely compromised. The red curve represents the hope that changes in organism-environment interactions during adulthood move the individual onto a more positive trajectory. Beneficial changes may consist in the mitigation of risk factors, such as vascular conditions, metabolic syndrome, or chronic stress; the strengthening of enhancing factors, such as neuroplasticity; or both. [Modified from (7)]

¹Center for Lifespan Psychology, Max Planck Institute for Human Development, Lentzeallee 94, 14195 Berlin, Germany.

²Max Planck University College London Centre for Computational Psychiatry and Ageing Research, London WC1B 5EH, UK. E-mail: seklindenberger@mpib-berlin.mpg.de

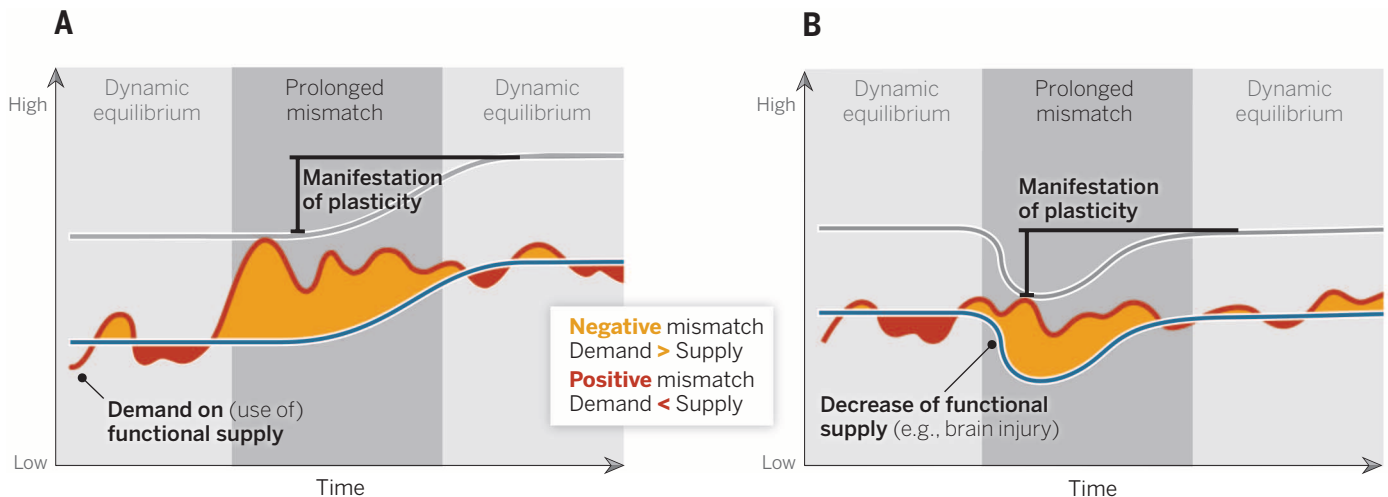


Fig. 2. The supply-demand mismatch model of adult cognitive plasticity. The mismatch between functional supply and experienced environmental demands can be caused by primary changes in demand (**A**) or functional supply (**B**). Functional supply denotes structural constraints imposed by the brain on function and performance, and permits a given range of performance and functioning. Flexibility denotes the capacity to

optimize the brain's performance within this range. Deviations in functional demand that are within the available range of functional supply constitute the impetus for plasticity. Mismatches between supply and demand need to be prolonged to overcome the inertia and sluggishness of plasticity and to push the system away from its current dynamic equilibrium. [Adapted from (9)]

neuromodulation has received particular attention (21–23). Originating in the midbrain, dopamine neurons reach various subcortical and cortical regions. Positron emission tomography and single-photon emission computed tomography show a pronounced age-related decrease in dopaminergic neuromodulation in healthy older adults. Converging evidence from patient studies, animal research, pharmacological intervention, and molecular genetics indicates that dopamine plays a critical role in cognitive functioning (21, 22). Longitudinal work (24) is needed to better understand the correlative triad among adult age, dopamine, and cognition (22).

Postmortem studies document age-related differences in various morphological aspects of the brain, such as reduced size and weight, expansion of cerebral ventricles and sulci, deformation and loss of myelin sheathing, region-specific loss of dendritic arborization and neuronal bodies, rarefaction of cerebral vasculature, and reduced synaptic density (13). Magnetic resonance imaging (MRI) permits the study of age differences and age changes in vivo, yielding indicators of gray and white matter volume and integrity, neural activity, and metabolites. Increasing adult age is associated with markedly smaller volumes of gray and white matter. Polymodal cortical regions display greater volume reductions than other neocortical areas, whereas primary visual cortices show relatively little volume loss (25, 26). Cross-sectional age trends are less clear for hippocampal volume, with some but not all studies suggesting accelerating shrinkage with advancing age. This inconsistency in results is likely to reflect sample differences in the admixture of preclinical pathology and the extent to which positive selection correlates with age. Longitudinal studies, which permit the efficient and unbiased assessment of change and of individual differences in change, report that hippocampal

shrinkage accelerates with age and is exacerbated by vascular factors (25).

Diffusion tensor imaging (DTI) and T2-weighted (spin-spin relaxation) MRI imaging are increasingly used to study age changes and differences in the integrity of white matter. White matter hyperintensities, which reflect ischemic lesions, microbleeds, demyelination, and expansion of perivascular spaces, increase from middle to late adulthood and show associations with vascular risk and genetic variants related to inflammation (27). DTI indices point to decreasing white matter integrity with advancing adult age (28, 29). The same holds true for life-span differences and changes in white matter volumes, which may reflect either the pruning of cortical connections in the course of maturational or experience-dependent plasticity, or alterations due to senescence and pathology.

Animal models help to identify mechanisms of age-related cognitive decline at the cellular level. In nonhuman primates, the degeneration of thin synaptic spines in dorsolateral prefrontal cortex, as well as synaptic alterations in the dentate gyrus of the hippocampus, contribute to age-related losses in memory (30). Rodent models indicate that normal aging alters excitatory synaptic transmission in hippocampal granule cells and in CA3 and CA1 pyramidal cells (31).

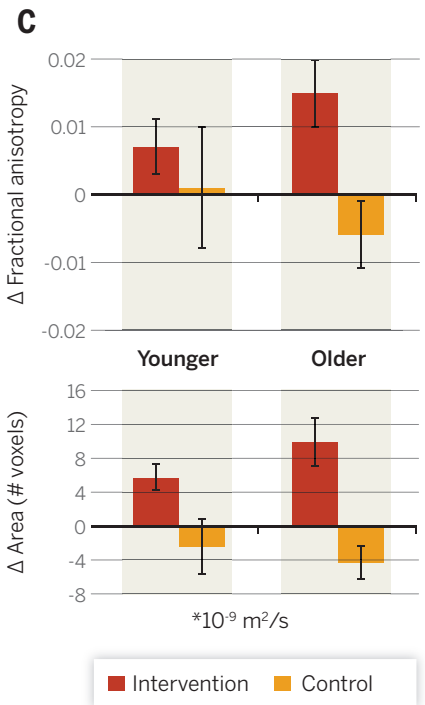
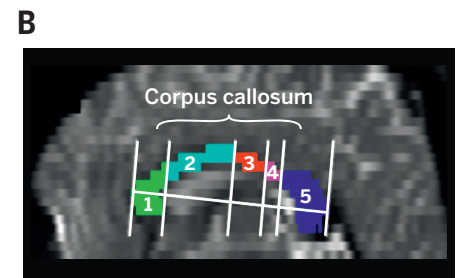
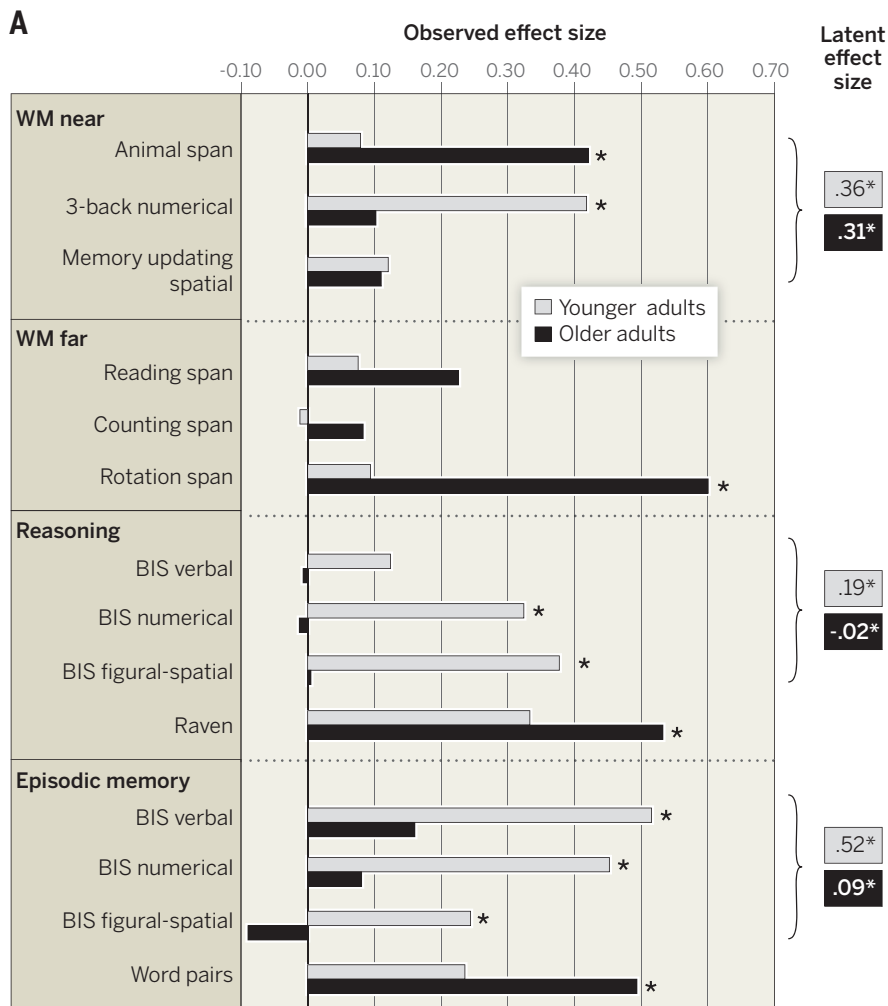
Individual differences in change

The extent of age-related differences and changes in brain and behavior varies markedly across individuals. The brains of adults differ reliably in the onset and degree of age-related volume losses. Lateral prefrontal cortex, prefrontal white matter, and the hippocampus are among the regions that show particularly large individual differences in age-related shrinkage (25). Rates of shrinkage are increased by risk factors such as treated hypertension and metabolic syndrome (25, 32). The adverse effects of vascular and meta-

bolic factors on brain health are not confined to individuals with a diagnosis of cardiovascular disease or diabetes. Instead, these risks operate well within the healthy range of functioning (33).

Adults who maintain high levels of general cognitive ability into very old age stand in sharp contrast to age peers whose cognitive resources are waning or depleted by later adulthood. Longitudinal studies reveal that individual differences in cognitive performance increase from early to late adulthood and old age (34, 35). Both genetic and environmental factors contribute to individual differences in change (36, 37). To some extent, the age-related increase in heterogeneity is absorbed by age-related increments in the prevalence of pathological conditions such as dementia (38). The remaining, ever more positively selected individuals who qualify as “generally healthy” or “normal” represent a continuously decreasing proportion of the aging population (39). But even within this positively selected segment, individual differences in various aspects of brain and behavior increase with advancing age.

Attempts to establish the dimensionality of cognitive aging help identify environmental, epigenetic, and genetic factors that impair or promote cognition in old age. If age-related changes are indeed correlated across different cognitive abilities, searching for factors with generalized effects on cognitive functioning seems worthwhile. Cross-sectional studies are inadequate for uncovering the covariance dynamics of change (40, 41). Multivariate longitudinal panel studies are more informative because they allow researchers to examine whether between-person differences in age-related change are correlated across different aspects of brain and behavior. At the anatomical level, studies reporting such covariance information are rare. One study found that shrinkage of prefrontal white matter correlated with shrinkage of lateral prefrontal cortex ($r = 0.71$)



and with shrinkage of hippocampal volumes ($r = 0.70$), indicating that volume losses in the frontal lobes and in medial-temporal cortex are interdependent (25). Such structural interdependencies are in good agreement with studies showing that deficits in both prefrontal and hippocampal activation patterns contribute interactively to adult age differences in associative episodic memory (42).

Behaviorally, several longitudinal studies show that human cognitive aging has a strong general component. One study analyzed 20-year longitudinal data of 6203 middle-aged to very old adults (43). Participants were assessed up to eight times on 20 tasks of fluid intelligence, perceptual speed, memory, and vocabulary. Notably, 66% of the variance in cognitive change was shared across tasks. In another study, 39% of individual differences in change were shared across all tasks, and 33% were shared at the level of general cognitive abilities (44).

These findings support an early plea by Salt-house (45) to overcome “issue isolationism” and search for age-related mechanisms with general effects on adult cognition. Promising candidate mechanisms with some degree of empirical support are decrements in dopamine availability in striatal and cortical brain regions (21–23); anatomical

changes in medial-temporal (46) and prefrontal (47) areas; structural and functional connectivity decrements due to white matter alteration (27, 48, 49); a compromised dynamic range of neural activation (50); and deficient synchronization of oscillatory activity within and across fast and slow frequencies (51). The lead-lag relations and reciprocal interdependencies among these and additional putative drivers of age-related declines in adult cognition are largely unknown. This lack of knowledge about the cascade of events associated with maintained or impaired cognition in late life points to the dire need for launching and sustaining multivariate longitudinal studies with a comprehensive range of ages, imaging techniques, and behavioral assessments (52, 53).

There are reliable associations of individual differences in cognition at 11 years of age with late-life individual differences in cognition (54), brain status (55), and somatic health (56). Individuals with lower cognitive abilities are more likely to engage in behaviors that carry risks for late-life cognition, such as smoking (57). Also, the genetic contributions to individual differences in cognition overlap with those observed for socioeconomic status and education (58, 59), underscoring the inadequacy of making unidirectional

causal attributions on the basis of cross-sectional or short-term longitudinal data.

Although specific genetic variants play only a modest role in determining how long individuals live (60), they may influence age-related differences in cognition. The effects of common genetic polymorphisms on cognition are expected to increase with advancing adult age if the function that relates brain resources to behavior is assumed to be sigmoid rather than linear (61). Larger effects on episodic memory performance in samples of older adults than in samples of younger adults have been observed for variants in the brain-derived neurotrophic factor (BDNF) gene (62), the dopamine D2 receptor and transporter genes (63), and the dopamine and glutamate receptor genes (64). Similar effects on forgetting rates have been observed for D2 and D3 receptor genes and the DA transporter gene (65) and on response inhibition for dopamine D2 receptor genes (66). These results are consistent with the long-standing observation that broad heritability increases from early to late adulthood (67). However, the observed associations between variations at specific gene loci and individual differences in cognition are small, and causal accounts of the heritability of complex behavioral traits are “still

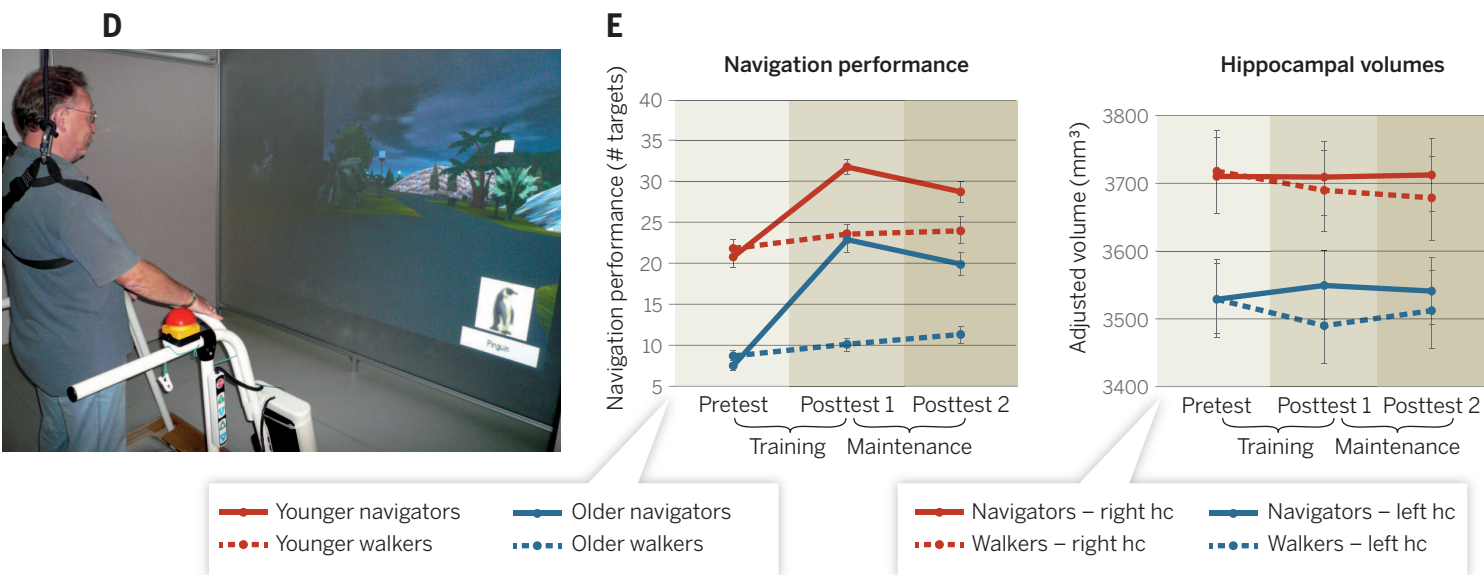


Fig. 3. Experience-dependent cognitive plasticity subsists into later adulthood. (A to C) In the COGITO study (76), 101 younger and 103 older adults practiced six tests of perceptual speed, three tests of working memory, and three tests of episodic memory over a period of 6 months for 101 daily 1-hour sessions. Transfer effects were assessed with unpracticed cognitive tests administered before and after training. (A) Effect sizes (ES) (standardized changes in the experimental group minus standardized changes in the control group), separately for younger adults (gray bars) and older adults (black bars). Statistically significant ES correspond to reliable interactions ($*p < 0.05$) between group (experimental versus control) and occasion (pretest versus posttest). Observed ES refer to individual tests, latent ES to cognitive abilities estimated with structural equation modeling. At the level of cognitive abilities, younger and older adults show transfer of training to working memory (WM); in addition, younger adults also show transfer to reasoning and episodic memory. (B) A midsagittal

slice of a mean diffusivity data set, with the corpus callosum segmented into five different regions. The first region refers to the genu, which connects the prefrontal cortices. (C) Changes in fractional anisotropy and area of the genu assessed in subsamples of younger and older COGITO participants. Changes differ reliably between intervention and control groups but not by adult age (78). (D and E) In the SPACE study (80), healthy younger and older men performed a cognitively demanding spatial navigation task every other day over 4 months. The training group navigated in a virtual environment while walking on an exercise treadmill (D); a walk-time-yoked control group walked on a treadmill without the virtual environment. (E) Navigators show navigation-related gains in performance (middle panel) and stable hippocampal (hc) volumes that are maintained 4 months after termination of training (right panel). Error bars, mean \pm SEM. Control groups show volume decrements in line with longitudinal estimates of age-related decline.

missing" (68). Cognitive abilities and their associated endophenotypes are highly polygenic; given the multitude of interactions among genes and environments, and the path-dependent nature of epigenetic effects, this renders it unlikely that individual allelic variations will account for a sizeable portion of phenotypic variance.

Experience-dependent plasticity in adulthood

Experience-dependent plasticity of brain and behavior subsists into late adulthood (15). Adults respond to a variety of challenges with structural changes in task-relevant brain areas. Similarly, physical exercise programs induce plasticity at neural and behavioral levels of analysis, effects that tend to be more pronounced among older sedentary adults, and presumably reflect the attenuation of vascular and metabolic risk factors (69).

According to one model (9), plastic changes are elicited by a mismatch between environmental demand and organismic supply, provided that the organism possesses the potential for a plastic response. The central tenet of this model is the distinction between plasticity and flexibility. Whereas flexibility refers to the capacity for variations in behavioral repertoire that do not require

reorganization of brain structures and connections, plasticity refers to changes in behavior that do. Mismatches between supply and demand need to be prolonged to overcome the inertia and sluggishness of plasticity and to push the system away from its current dynamic equilibrium (Fig. 2).

Older brains accumulate an increasingly large behavioral repertoire, and plastic reorganization of the brain is metabolically costly (30, 70). Presumably for both of these reasons, the brains of healthy older adults are less likely, and may have less need, to react to environmental challenges with a plastic response than the brains of children and adolescents. In other words, older adults have a richer model of the world that enables deployment of established behavioral repertoires. Down-regulating plasticity during adulthood may favor the emergence of stable social structures, which in turn may facilitate the deployment of plastic potential in the next generation [for a related but distinct line of reasoning, see (71)].

Are adult plastic changes elicited by intervention studies sufficiently large and persistent to improve cognitive competence in everyday life? One indicator of practical relevance is transfer of training: Does improvement on the trained tasks generalize to untrained tasks that tap into the

same cognitive ability or to tasks measuring affiliated cognitive abilities? The experimental design and statistical analysis procedures of most intervention studies to date are not well suited to answer this question (72). The most common threat to validity concerns the distinction between task-specific effects and improvements at the ability level. Positive transfer to multiple indicators of a given cognitive ability is a necessary condition for claiming that the intervention has led to improvements at that level. Latent factor models (73) are an effective method for estimating intervention-induced changes at the ability level and for comparing observed transfer gradients with theoretical predictions (74–76).

In one exceptionally extensive intervention study (Fig. 3), transfer of training to cognitive abilities was observed, but transfer effects were reduced in scope (76) and maintenance (77) in older relative to younger adults. In both younger and older adults, the intervention was associated with improved white matter integrity in the anterior part of the corpus callosum (78) and reduced age-related shrinkage in the cerebellum (79). In another study (Fig. 3), 4 months of spatial navigation training protected the hippocampus against age-related shrinkage (80), both in younger

and older adults. However, training-related cortical thickening in the left precuneus and paracentral lobule was observed in younger adults alone (81). These results provide some reason to hope that cognitive interventions may ameliorate the course of cognitive aging but also suggest that plasticity decreases from early to late adulthood.

The increasing importance of environmental support

Thirty years ago, Craik *et al.* (82) placed findings on adult age differences in memory on a continuum ranging from self-initiated processing to environmental support. Memory performance is particularly impaired when retrieval depends on self-generated cues and active control processes. By contrast, when retrieval cues (e.g., hints, reminders, and contextual reinstatement) are provided by the environment, age-related deficits decrease or disappear altogether. Accordingly, the effect sizes of the performance advantage of younger over older adults are large for free recall, moderate for recognition memory, and small for associative and item priming (83).

Self-initiated processing and constructive cue generation require maintenance of task representations through recurrent connections between prefrontal and more posterior brain regions (84). The ability to hold task representations in mind declines with age (85), as reflected by impairments in a variety of cognitive functions such as attention, working memory, and executive control (86, 87). We recently proposed that the resulting greater reliance on environmental control is not confined to memory but forms a general developmental trend (88). In perception, learning and remembering, and action management, older adults tend to rely more on external information than younger adults do, probably both as a direct reflection and indirect adaptation to difficulties in internally triggering and maintaining cognitive representations.

If greater reliance on the environment were always a direct reflection of weakened internal representations, the performance of older adults would suffer as soon as environmental support is eliminated. This is not always the case—removal of environmental sources of information may sometimes even benefit the performance of older adults (89, 90). Such findings are inconsistent with the notion that increasing environmental control is a direct mirror image of waning internal control. Rather, the greater reliance of older adults on the environment may reflect a long-term adaptation to a cognitive system that is generally—but not necessarily in every specific instance—less capable of directing behavior in a top-down, internally regulated manner (5, 91). There is thus a certain amount of slack between deficits in self-initiated processing and reliance on environmental support, such that aging individuals remain capable, in some situations at least, of reducing their degree of reliance on the environment when they need to do so. Therefore, direct and indirect pathways from the waning of top-down control to a greater reliance on environmental support likely coexist, but little is known

about their relative importance and developmental interdependence.

When they have reached old age, individuals have acquired a relatively stable behavioral repertoire that is likely to match the regularities and affordances of the environments in which they live. The tendency of older adults, both automatic and deliberate, to outsource control to the environment may be inefficient at times but cost-effective in the long run if the cuing structure of the environment corresponds to their goals and needs.

Mechanisms of successful cognitive aging

Cognitive aging is highly individualized, and information based on between-person differences or averages may misrepresent the individual aging process to some degree (92, 93). Hence, attempts at promoting successful cognitive aging (94) should also be directed toward the physical and social environment of the aging individual. In particular, assistive adaptive technology (95) provides individuals with cuing structures that connect properties of the environment to their personal action goals. However, both risks and opportunities need to be kept in mind. Chronic reliance on technological aids may deplete brain resources through disuse of skills and abilities, undermine motivation, and engender loss of autonomy. Conversely, assistive adaptive technology may foster cognitive maintenance and plasticity by combining support with challenges, thereby enhancing motivation (96), social participation, and a sense of autonomy, with positive repercussions on cognitive development in old age (7).

Turning toward aging individuals' brain and behavior, a number of general mechanisms have been linked to more favorable aging trajectories (4, 5, 14, 52, 97–99). These mechanisms are not mutually exclusive, and their viability and reciprocal relations remain to be determined. Animal models of individual differences in adult development play an important role in this effort (10, 30, 100).

Maintenance

As a general observation, older adults with more “youth-like” brain structure and functional brain responses show higher levels of cognitive performance than older adults whose brain structure and function deviates markedly from that of younger adults (52, 101) (Fig. 4). This observation holds true cross-sectionally (101–104) and longitudinally (105). Brains with relatively well preserved anatomy and neurochemistry are more likely to generate functional activation patterns that resemble those of younger adults and that are germane to proficient performance. An important implication is that cognitive interventions should aim at preserving or, at least partially, restoring youth-like brain physiology.

Compensation

High levels of cognitive functioning in old age may reflect instances of successful compensation (5, 106). According to one definition (107, 108), compensation in the context of normal aging refers to structural or functional reorganization of the brain that evolves in response to aging-

induced losses in brain functioning. Other than maintenance and restoration, compensation does not consist in preserving or reestablishing the substrate or function that was lost but in creating something alternative in response to a loss. Compared with discrete damaging events, such as a stroke, cerebral senescence is a process without clear boundaries in space and with no clear onset in time. Rather, the gradual loss in functional capacity in normal aging is distributed over many different brain areas, networks, and neurotransmitter systems. Compensatory reactions to normal aging may evolve differently and arguably less often than compensatory reactions to discrete damaging events. Brain circuitry potentially capable of compensating for a loss may itself be particularly vulnerable to normal aging. Compensatory recruitment of the prefrontal cortex may attenuate the adverse effects of aging on other areas of the brain (4), given its pivotal role for the organization of behavior (109). However, far from being spared by senescence, prefrontal areas and associated corticoatrial circuits show early and precipitous age-related decline (22, 25). Hence, although the frontal lobes are increasingly needed, they are decreasingly able to counteract the adverse consequences of senescence on sensory, perceptual, and motor aspects of behavior (98).

Selection

A potentially powerful but rarely considered mechanism in the context of successful brain aging is selection. Younger adults' brains can execute a given task in more than one way (110, 111). Different brain implementations of a given behavior may be differentially vulnerable to aging because some brain areas, circuits, and activation patterns are more resilient than others. More robust brain processing routes and areas with advancing adult age may signal selective survival due to differential robustness rather than compensatory development of alternate functional activation patterns. Individuals with a larger pool of available processing routes in early adulthood may draw on a greater cognitive reserve (14) or functional cerebral space (112) that provides a modicum of protection against the adverse effects of normal and pathological age-related changes on behavior because it offers a greater choice set for selection.

Multimodal longitudinal and experimental evidence is needed to probe the relative importance of maintenance, compensation, and selection as mechanisms of successful cognitive aging.

Outlook

Cognitive development in adulthood and old age differs substantially from person to person and is malleable within individuals. Maintaining cognitive abilities into old age and postponing or preventing pathologies leading to a diagnosis of dementia late in life are key aims for science and society. Exploring and exploiting the continued potential for cognitive maintenance and plasticity are major means to these ends. In the absence of strong genetic control, the course of human cognitive aging is open to a host of risk and protective or enhancing factors.

Beneficial lifestyle choices may attenuate partially modifiable risks, such as vascular and metabolic conditions, and promote changes that are likely to enhance cognition, such as angiogenesis, synaptogenesis, and neurogenesis. The developmental dependencies between risk and protective factors, and their modulation by behavior, are not well understood. Regions of the brain that are particularly plastic and provide the substrate for new learning and plasticity, such as the hippocampus, are also particularly vulnerable to risk factors such as stress and vascular conditions, suggesting that modifiability comes at a price (12, 113, 114). Nevertheless, interventions that attenuate the adverse effects of risk factors, such as physical exercise, extensive cognitive interventions (Fig. 3), and intellectually stimulating lifestyles, inspire cautious optimism about mitigating age-related declines (7).

Although maturation and senescence operate continuously throughout life, their relative importance and interactions change from childhood to old age. Direct experimental comparisons between

children, younger adults, and older adults are particularly informative in this regard, as they point to the ways in which brain-behavior mappings reorganize during ontogeny. For instance, medial-temporal and prefrontal regions of the brain contribute differently to working memory and episodic memory in childhood and old age, presumably because medial-temporal lobe maturation progresses more rapidly than that of the frontal lobes, whereas both regions of the brain show signs of decline with advancing adult age (115, 116).

Research on neuroepigenetics (16) is likely to lead to a better understanding of the effects of early life events and choices on adult cognitive development. Animal models of emerging individuality will play a pivotal role in this endeavor (10). Combining pharmacological (117) and behavioral interventions may reopen “windows of plasticity” in adulthood and old age (118). If the relevant molecular mechanisms are function-specific and can be brought under control, they

may provide a basis for regulating plasticity in adulthood and old age (119).

Advances in understanding how behavior influences brain aging, and how brain aging influences behavior, are facilitated by taking a life-span perspective that conceptually integrates evidence across time scales, age periods, functional domains, and levels of analysis. Neurocomputational models are a powerful tool for theory development, because they bridge the gaps that hinder integration (23, 120) and elucidate the constraints on what the brain can and cannot do. In this context, the connections between short-term variability and long-term change (121) deserve special attention, because they point to mechanisms and allow prediction. For instance, lack of processing robustness at an earlier point in time predicts longitudinal cognitive decline in old age (122).

To effectively foster cognitive health in old age, we need to better understand the malleable causes of individual differences in human cognitive aging. This requires long-term, multivariate, longitudinal

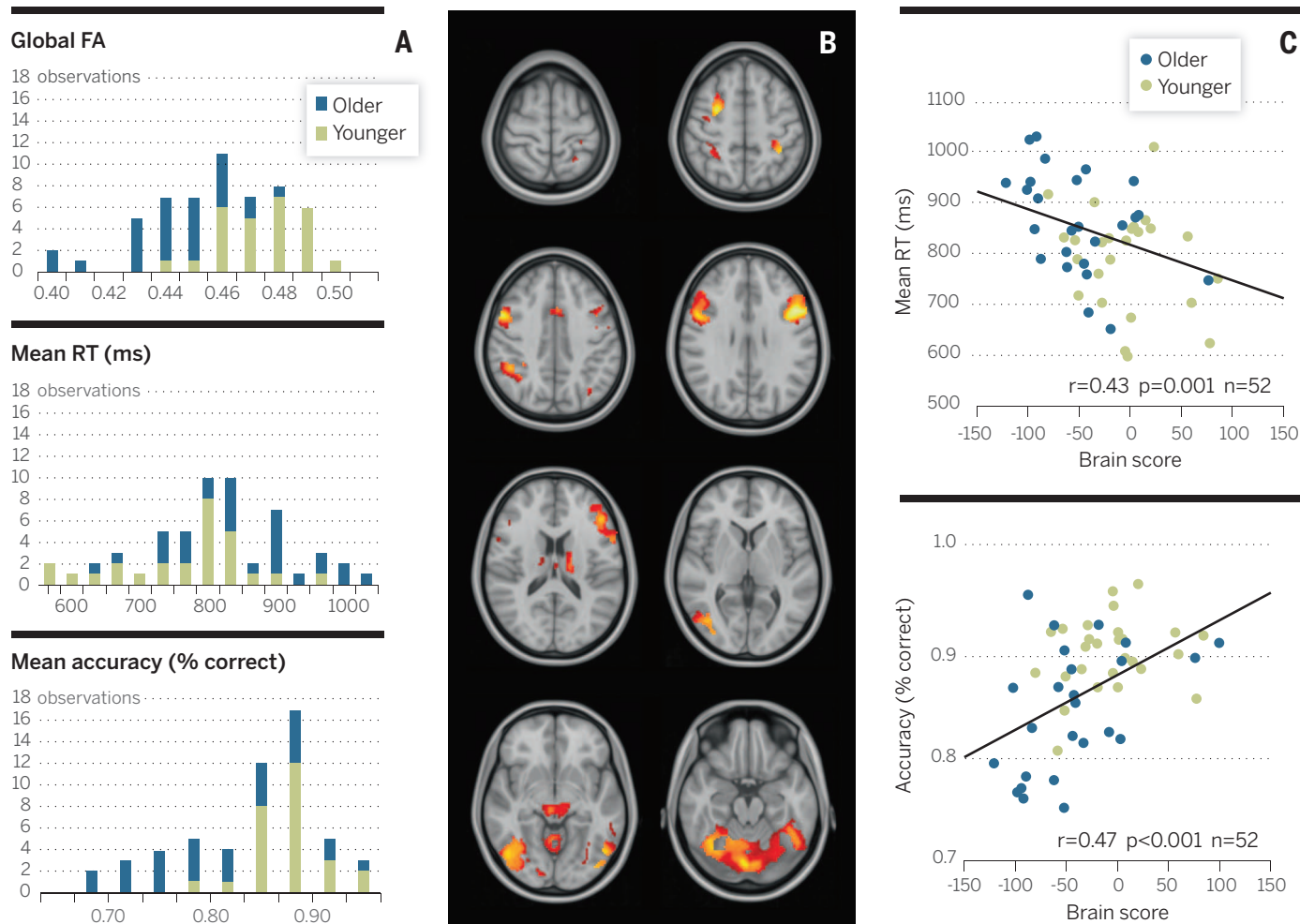


Fig. 4. A scaffold for efficiency in the human brain: Associations among white matter microstructure, task-related gray matter activation, and working memory performance in younger and older adults. (A) Overlap between age groups in white matter microstructural integrity, indexed by global fractional anisotropy (FA) of the diffusion tensor, task reaction time (RT), and task accuracy. (B) Higher FA values in most major white matter

tracts are negatively related to the blood oxygenation level–dependent (BOLD) signal on task in task-positive gray matter regions. (C) Associations between working memory performance and a structure-function brain score representing higher FA values and a lower task-related BOLD signal. Higher brain scores are associated with faster RT and higher accuracy, regardless of age. [Modified from (102)]

studies of brain and behavior. When planning such studies, design factors such as the number and the spacing of measurement occasions, the number of participants, the number of indicators per construct, and measurement reliability need to be chosen with care (123). These choices influence the likelihood of correct identification of individual differences and mean trends in the age of onset, the functional form, and the rate of age-graded changes in adult cognition. In addition, longitudinal observations should be augmented by interventions to induce positive deviations from the modal path that help to identify contexts and mechanisms of successful aging and give science and society a hint about what would be possible if conditions were different. A more thorough understanding of mitigating, protective, and enhancing factors may provide the foundation for individualized interventions that promote successful cognitive development in adulthood and old age (9).

REFERENCES AND NOTES

- J. W. Vaupel, *Nature* **464**, 536–542 (2010).
- M. Rönnlund, L. Nyberg, L. Bäckman, L.-G. Nilsson, *Psychol. Aging* **20**, 3–18 (2005).
- K. W. Schaie, *Intellectual Development in Adulthood: The Seattle Longitudinal Study* (Cambridge Univ. Press, New York, 1996).
- C. Grady, *Nat. Rev. Neurosci.* **13**, 491–505 (2012).
- D. C. Park, P. Reuter-Lorenz, *Annu. Rev. Psychol.* **60**, 173–196 (2009).
- P. B. Baltes, U. Lindenberger, U. M. Staudinger, in *Handbook of Child Psychology: Vol. 1. Theoretical Models of Human Development*, W. Damon, R. M. Lerner, Eds. (Wiley, New York, 2006), chap. 11, pp. 569–664.
- C. Hertzog, A. F. Kramer, R. S. Wilson, U. Lindenberger, *Psychol. Sci. Public Interest* **9**, 1–65 (2009).
- T. B. L. Kirkwood, *Cell* **120**, 437–447 (2005).
- M. Lövdén, L. Bäckman, U. Lindenberger, S. Schaefer, F. Schmiedek, *Psychol. Bull.* **136**, 659–676 (2010).
- J. Freund et al., *Science* **340**, 756–759 (2013).
- P. C. M. Molenaar, D. I. Boomsma, C. V. Dolan, *Behav. Genet.* **23**, 519–524 (1993).
- J. Belsky et al., *Mol. Psychiatry* **14**, 746–754 (2009).
- N. Raz, K. M. Rodrigue, *Neurosci. Biobehav. Rev.* **30**, 730–748 (2006).
- D. Barulli, Y. Stern, *Trends Cogn. Sci.* **17**, 502–509 (2013).
- M. Lövdén, E. Wenger, J. Mårtensson, U. Lindenberger, L. Bäckman, *Neurosci. Biobehav. Rev.* **37** (9 Pt B), 2296–2310 (2013).
- J. D. Sweatt, *Neuron* **80**, 624–632 (2013).
- U. Lindenberger, in *International Encyclopedia of the Social and Behavioral Sciences*, N. J. Smelser, P. B. Baltes, Eds. (Elsevier Science, Oxford, 2001), vol. 13, pp. 8848–8854.
- E. A. Bosman, N. Charness, in *Perspectives on Cognitive Change in Adulthood and Aging*, F. Blanchard-Fields, T. H. Hess, Eds. (McGraw-Hill, New York, 1996), pp. 428–453.
- J. Park, J. Carp, A. Hebrank, D. C. Park, T. A. Polk, *J. Neurosci.* **30**, 9253–9259 (2010).
- P. B. Baltes, U. Lindenberger, *Psychol. Aging* **12**, 12–21 (1997).
- A. F. Arnsten, M. J. Wang, C. D. Paspalas, *Neuron* **76**, 223–239 (2012).
- L. Bäckman, L. Nyberg, U. Lindenberger, S.-C. Li, L. Farde, *Neurosci. Biobehav. Rev.* **30**, 791–807 (2006).
- S.-C. Li, U. Lindenberger, S. Sikström, *Trends Cogn. Sci.* **5**, 479–486 (2001).
- N. Nevalainen et al., *Brain Res.* **2014**, 10.1016/j.brainres.2014.09.010 (2014).
- N. Raz et al., *Cereb. Cortex* **15**, 1676–1689 (2005).
- A. Pfefferbaum et al., *Neuroimage* **65**, 176–193 (2013).
- N. Raz, Y. Yang, C. L. Dahle, S. Land, *Biochim. Biophys. Acta* **1822**, 361–369 (2012).
- A. Z. Burzynska et al., *Neuroimage* **49**, 2104–2112 (2010).
- L. T. Westlye et al., *Cereb. Cortex* **20**, 2055–2068 (2010).
- J. H. Morrison, M. G. Baxter, *JAMA* **71**, 835–837 (2014).
- S. N. Burke, C. A. Barnes, *Trends Neurosci.* **33**, 153–161 (2010).
- Z. S. T. Tan et al., *Diabetes Care* **34**, 1766–1770 (2011).
- K. B. Walhovd, A. B. Storsve, L. T. Westlye, C. A. Drevon, A. M. Fjell, *Neurobiol. Aging* **35**, 1055–1064 (2014).
- C. M. de Frias, M. Lövdén, U. Lindenberger, L.-G. Nilsson, *Intelligence* **35**, 381–392 (2007).
- B. J. Small, R. A. Dixon, J. J. McArdle, *J. Gerontol.* **66B** (suppl. 1), i153–i161 (2011).
- I. J. Deary et al., *Nature* **482**, 212–215 (2012).
- D. Finkel, N. Pedersen, M. McGue, *Psychol. Aging* **10**, 437–446 (1995).
- R. S. Wilson, S. E. Leurgans, P. A. Boyle, D. A. Bennett, *Arch. Neurol.* **68**, 351–356 (2011).
- U. Lindenberger, T. Singer, P. B. Baltes, *J. Gerontol. B* **57**, P474–P482 (2002).
- S. M. Hofer, B. P. Flaherty, L. Hoffman, *Multivar. Behav. Res.* **41**, 165–187 (2006).
- U. Lindenberger, T. von Oertzen, P. Ghisletta, C. Hertzog, *Psychol. Aging* **26**, 34–47 (2011).
- Y. Fandakova, U. Lindenberger, Y. L. Shing, *Cereb. Cortex* **24**, 1832–1844 (2014).
- P. Ghisletta, P. M. A. Rabbitt, M. Lunn, U. Lindenberger, *Intelligence* **40**, 260–268 (2012).
- E. M. Tucker-Drob, *Dev. Psychol.* **47**, 331–343 (2011).
- T. A. Salthouse, *A Theory of Cognitive Aging* (North Holland, Amsterdam, 1985).
- Y. L. Shing et al., *Front. Aging Neurosci.* **3**, 2 (2011).
- N. Raz et al., *Cereb. Cortex* **18**, 718–726 (2008).
- J. R. Andrews-Hanna et al., *Neuron* **56**, 924–935 (2007).
- G. Bartzokis, *Neurobiol. Aging* **32**, 1341–1371 (2011).
- D. D. Garrett et al., *Neurosci. Biobehav. Rev.* **37**, 610–624 (2013).
- M. Werkle-Bergner, R. Freunberger, M. C. Sander, U. Lindenberger, W. Klimesch, *Neuroimage* **60**, 71–82 (2012).
- L. Nyberg, M. Lövdén, K. Riklund, U. Lindenberger, L. Bäckman, *Trends Cogn. Sci.* **16**, 292–305 (2012).
- N. Raz, U. Lindenberger, *Psychol. Bull.* **137**, 790–795 (2011).
- I. J. Deary, M. C. Whiteman, J. M. Starr, L. J. Whalley, H. C. Fox, *J. Pers. Soc. Psychol.* **86**, 130–147 (2004).
- M. C. Valdés Hernández et al., *Neurobiol. Aging* **34**, 2740–2747 (2013).
- R. Möttus, M. Luciano, J. M. Starr, I. J. Deary, *J. Psychosom. Res.* **75**, 275–278 (2013).
- J. Corley, A. J. Gow, J. M. Starr, I. J. Deary, *J. Psychosom. Res.* **73**, 132–138 (2012).
- D. Falkstedt, K. Sorjonen, T. Hemmingsson, I. J. Deary, B. Melin, *PLOS ONE* **8**, e82031 (2013).
- R. E. Marioni et al., *Intelligence* **44**, 26–32 (2014).
- K. Christensen, T. E. Johnson, J. W. Vaupel, *Nat. Rev. Genet.* **7**, 436–448 (2006).
- U. Lindenberger et al., *Front. Neurosci.* **2**, 234–244 (2008).
- S.-C. Li et al., *J. Cogn. Neurosci.* **22**, 2164–2173 (2010).
- S.-C. Li, C. Grattan, M. Fabiani, R. T. Knight, *Neurobiol. Aging* **34**, 477–488 (2013).
- G. Papenberg et al., *Neurobiol. Aging* **35**, 1213.e3–1213.e8 (2014).
- G. Papenberg et al., *Science* **341**, 571–579 (2013).
- L. S. Colzato, W. P. van den Wildenberg, B. Hommel, *Neuropsychologia* **51**, 1377–1381 (2013).
- G. E. McClearn et al., *Science* **276**, 1560–1563 (1997).
- E. Turkheimer, *Res. Hum. Dev.* **8**, 227–241 (2011).
- L. Bherer, K. I. Erickson, T. Liu-Ambrose, *J. Aging Res.* **2013**, 657508 (2013).
- C. W. Kuzawa et al., *Proc. Natl. Acad. Sci. U.S.A.* **111**, 13010–13015 (2014).
- R. J. Moran, M. Symmonds, R. J. Dolan, K. J. Friston, *PLOS Comput. Biol.* **10**, e1003422 (2014).
- H. Noack, M. Lövdén, F. Schmiedek, *Psychol. Res.* **2014**, 10.1007/s00426-014-0564-6 (2014).
- J. J. McArdle, *Annu. Rev. Psychol.* **60**, 577–605 (2009).
- J. J. McArdle, J. J. Prindle, *Psychol. Aging* **23**, 702–719 (2008).
- T. S. Redick et al., *J. Exp. Psychol. Gen.* **142**, 359–379 (2013).
- F. Schmiedek, M. Lövdén, U. Lindenberger, *Front. Aging Neurosci.* **2**, 27 (2010).
- F. Schmiedek, M. Lövdén, U. Lindenberger, *Dev. Psychol.* **50**, 2304–2310 (2014).
- M. Lövdén et al., *Neuropsychologia* **48**, 3878–3883 (2010).
- N. Raz et al., *Brain Cogn.* **82**, 171–180 (2013).
- M. Lövdén et al., *Neurobiol. Aging* **33**, 620.e9–620.e22 (2012).
- E. Wenger et al., *Neuroimage* **59**, 3389–3397 (2012).
- F. I. M. Craik, D. A. Routh, D. E. Broadbent, *Philos. Trans. R. Soc. London Ser. B* **302**, 341–359 (1983).
- D. La Voie, L. L. Light, *Psychol. Aging* **9**, 539–553 (1994).
- S. Ardid, X.-J. Wang, A. Compte, *J. Neurosci.* **27**, 8486–8495 (2007).
- M. Wang et al., *Nature* **476**, 210–213 (2011).
- A. Gazzaley, in *Principles of Frontal Lobe Function*, D. T. Stuss, R. T. Knight, Eds. (Oxford Univ. Press, New York, 2013), pp. 593–608.
- L. Hasher, R. T. Zacks, *Psychol. Learn. Motiv.* **22**, 193–225 (1988).
- U. Lindenberger, U. Mayr, *Trends Cogn. Sci.* **18**, 7–15 (2014).
- D. H. Spieler, U. Mayr, S. LaGrone, *Psychon. Bull. Rev.* **13**, 787–793 (2006).
- D. R. Tournon, E. T. Swaim, C. Hertzog, *J. Gerontol. B* **62**, P149–P155 (2007).
- A. M. Freund, P. B. Baltes, in *Control of Human Behavior, Mental Processes, and Consciousness*, W. J. Perrig, A. Grob, Eds. (Lawrence Erlbaum Associates, Mahwah, NJ, 2000), pp. 35–58.
- A. Brose, F. Schmiedek, M. Lövdén, U. Lindenberger, *Emotion* **12**, 605–617 (2012).
- M. C. Voelkle, A. Brose, F. Schmiedek, U. Lindenberger, *Multivariate Behav. Res.* **49**, 193–213 (2014).
- J. W. Rowe, R. L. Kahn, *Science* **237**, 143–149 (1987).
- U. Lindenberger, M. Lövdén, M. Schellenbach, S.-C. Li, A. Krüger, *Gerontology* **54**, 59–68 (2008).
- L. L. Carstensen, J. A. Mikels, M. Mather, in *Handbook of the Psychology of Aging*, J. Birren, K. W. Schaie, Eds. (Academic Press, San Diego, CA, 2006), pp. 343–362.
- G. Kempermann, *Nat. Rev. Neurosci.* **13**, 727–736 (2012).
- U. Lindenberger, A. Z. Burzynska, I. E. Nagel, in *Principles of Frontal Lobe Function*, D. T. Stuss, R. T. Knight, Eds. (Oxford Univ. Press, New York, 2013), pp. 609–627.
- A. Gutches, *Science* **346**, 579–582 (2014).
- R. P. Haberman, C. Colantuoni, M. T. Koh, M. Gallagher, *PLOS ONE* **8**, e83674 (2013).
- E. Düzel, H. Schütze, A. P. Yonelinas, H.-J. Heinze, *Hippocampus* **21**, 803–814 (2011).
- A. Z. Burzynska et al., *J. Neurosci.* **33**, 17150–17159 (2013).
- S. Duvernois, S. Motamedinia, M. D. Rugg, *Cereb. Cortex* **19**, 733–744 (2009).
- I. E. Nagel et al., *J. Cogn. Neurosci.* **23**, 2030–2045 (2011).
- J. Persson et al., *Cereb. Cortex* **22**, 2297–2304 (2012).
- R. Cabeza, N. A. Dennis, in *Principles of Frontal Lobe Function*, D. T. Stuss, R. T. Knight, Eds. (Oxford Univ. Press, New York, 2013), pp. 628–652.
- L. Bäckman, R. A. Dixon, *Psychol. Bull.* **112**, 259–283 (1992).
- P. B. Baltes, M. M. Baltes, in *Successful Aging: Perspectives from the Behavioral Sciences*, P. B. Baltes, M. M. Baltes, Eds. (Cambridge Univ. Press, New York, 1990), pp. 1–34.
- J. Duncan, E. K. Miller, in *Principles of Frontal Lobe Function*, D. T. Stuss, R. T. Knight, Eds. (Oxford Univ. Press, New York, 2013), pp. 292–301.
- G. M. Edelman, *Neural Darwinism. The Theory of Neuronal Group Selection* (Basic Books, New York, 1987).
- J. Laury, in *Models of Intelligence: International Perspectives*, R. J. Sternberg, J. Laury, T. I. Lubart, Eds. (American Psychological Association, Washington, DC, 2003), pp. 117–131.
- M. Kinsbourne, R. E. Hicks, in *Attention and Performance VII*, J. Requin, Ed. (Lawrence Erlbaum Associates, Hillsdale, New Jersey, 1978), pp. 345–362.
- N. Raz, *Neuropsychology* **21**, 676–677, discussion 680–683 (2007).
- P. Rakic, *Science* **227**, 1054–1056 (1985).
- M. C. Sander, U. Lindenberger, M. Werkle-Bergner, *Neurosci. Biobehav. Rev.* **36**, 2007–2033 (2012).
- Y. L. Shing et al., *Neurosci. Biobehav. Rev.* **34**, 1080–1091 (2010).
- R. Chowdhury et al., *Nat. Neurosci.* **16**, 648–653 (2013).
- J. Gervain et al., *Front. Syst. Neurosci.* **7**, 102 (2013).
- A. E. Takestan, T. K. Hensch, *Prog. Brain Res.* **207**, 3–34 (2013).
- K. E. Stephan, C. Mathys, *Curr. Opin. Neurobiol.* **25**, 85–92 (2014).
- J. R. Nesselrode, in *Visions of Aesthetics, the Environment and Development: The Legacy of Joachim F. Wohlwill*, R. M. Downs, L. S. Liben, D. S. Palermo, Eds. (Lawrence Erlbaum, Hillsdale, NJ, 1991), pp. 213–240.
- M. Lövdén, S.-C. Li, Y. L. Shing, U. Lindenberger, *Neuropsychologia* **45**, 2827–2838 (2007).
- T. von Oertzen, *Br. J. Math. Stat. Psychol.* **63**, 257–272 (2010).

ACKNOWLEDGMENTS

U.L. thanks R. Dolan, M. Lövdén, N. Raz, and F. Schmiedek for providing valuable comments on an earlier version of this article, and the Max Planck Society for continued research support. Parts of the research described in this article were financed by a Gottfried Wilhelm Leibniz Award 2010 of the German Research Foundation (DFG) to U.L. and a grant from the Federal Ministry of Education and Research (“The Berlin Aging Study II”).

10.1126/science.1254403