Review

Feature Review

Memory aging and brain maintenance

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Episodic memory and working memory decline with advancing age. Nevertheless, large-scale population-based studies document well-preserved memory functioning in some older individuals. The influential 'reserve' notion holds that individual differences in brain characteristics or in the manner people process tasks allow some individuals to cope better than others with brain pathology and hence show preserved memory performance. Here, we discuss a complementary concept, that of brain maintenance (or relative lack of brain pathology), and argue that it constitutes the primary determinant of successful memory aging. We discuss evidence for brain maintenance at different levels: cellular, neurochemical, gray- and white-matter integrity, and systems-level activation patterns. Various genetic and lifestyle factors support brain maintenance in aging and interventions may be designed to promote maintenance of brain structure and function in late life.

Adult age changes in human memory

Many older adults feel that their memory does not serve them as well as when they were younger [1,2]. Yet, objective assessments of memory have yielded a more differentiated picture. For one thing, subjective memory complaints may correlate more strongly with mood states than with objective memory performance [3]. Moreover, not all forms of human memory are equally affected by advancing age. Positive age gradients have been found for semantic memory [4]. Other types of memory (i.e., primary memory, procedural memory, priming) may also change relatively little from early to late adulthood [5]. Episodic memory is considered to be the form of long-term memory that displays the largest degree of age-related decline [4–7]. Working-memory performance is also reduced in old age [8,9]. Studies in the cognitive neuroscience of aging [10] have begun to link declining episodic and working memory to neurochemical, structural and functional brain changes. There has been much progress in this interdisciplinary area, partly due to increased availability of brain-imaging technology, a trend toward refined experimental designs with larger sample sizes and greater attention to longitudinal evidence.

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Glossary

BOLD-signal responsivity: the load-dependent modulation of the BOLD signal. The function relating the BOLD signal to load can be monotonically increasing (e.g., linear) or follow a non-monotonic course (e.g., inverted U).
Cross-sectional study: measurement of individuals of different ages at the same point in time. This design allows for the assessment of age-related differences.
Diffusion tensor imaging (DTI): MRI technique for measuring random translational motion of molecules, called Brownian motion. Usually, the movement of intra- and extra-cellular water is measured in several dimensions in real 3D. Anisotropy can result from a physical arrangement of the tissue or be a result of disturbed molecular movements in, for instance, brain ischemia.
Episodic memory: Long-term memory of personally experienced events that can be located in time and space.
Functional MRI (fMRI): a method dependent on venous blood oxygen level in the brain. Changes in deoxyhaemoglobin level, which are related to neuronal activity, acts as an endogenous paramagnetic contrast agent.
Longitudinal study: repeated measurement of the same individuals over time, allowing for the estimation of age-related changes.
Magnetic resonance imaging (MRI): technique based on nuclear spin resonance. A radio signal is applied to the examined object that is placed in a strong magnetic field. At the resonance frequency, Larmour frequency, the positrons absorb energy and receive higher energy. When the radio signal is switched off, the positrons return to their normal lower energy level and the absorbed energy emits a signal, which is recorded and used for reconstructing an image.
Neurotransmission imaging with PET or SPECT: based on the use of a biological compound or an analogue for imaging of neurotransmission, reuptake, receptor status or displacement.
Positron emission tomography (PET): technique based on 3D detection of coincidence photons from a radioactive tracer for molecular imaging of different physiological processes with high sensitivity.
rCBF imaging: imaging of the regional cerebral blood flow, using MRI, PET or SPECT techniques.
Regions of interest (ROIs) evaluation: based on defining a priori regions to be evaluated in the image data. ROIs can be delineated manually or automatically from the imaging data.
Single photon emission computed tomography (SPECT): a technique based on the use of rotating scintillation cameras to create 3D images of the distribution of different radiopharmaceuticals.
Statistical parametric mapping (SPM): technique for detailed analysis of structural or functional image data. Based on voxel-based analysis (VBA) to evaluate statistical differences between imaging data without the need to define a priori ROIs.
Structural MRI: measures gray matter volume, which can be quantified by automated or manual techniques.
Tracer: a substance used for PET imaging which takes part in physiological or molecular processes, labelled with a positron emitting radionuclide. The choice of tracer determines which molecular or physiological function is imaged with the PET scanner.
Voxel based analysis (VBA): technique for image processing and analysis of structural and functional image data voxel by voxel.
Working Memory: temporary maintenance, storage and updating of representations.

We begin this review by considering studies on average cross-sectional age differences and longitudinal changes in episodic and working memory, and by discussing interindividual differences in level and change of cognitive functioning in old age. We then place particular focus on describing the structure and function of the brain, as measured by neuroimaging techniques (see Glossary), in individuals who maintain high episodic memory and working memory performance in old age. We introduce the concept of brain maintenance to characterize high-performing older adults, contrasting it to the concept of cognitive/brain reserve, and discuss conditions supporting brain maintenance in later adulthood.

Onset of average age-related decline in episodic and working memory: early or late?

Although episodic and working-memory performance decline in adulthood and old age, evidence on the age of onset of decline is mixed. Most cross-sectional studies suggest linear deterioration in episodic memory performance across the adult life span, beginning as early as in the 20s [11–13]. Longitudinal studies that apply appropriate control for practice effects (i.e., test-retest effects) have yielded a very different pattern, indicating that episodic memory performance remains relatively stable until about 60–65 years of age, after which accelerating decline is typically observed [6,7]. One source of this discrepancy is that cross-sectional estimates of age-related change are biased by cohort effects, including generational differences in educational attainment. When age differences in educational level are statistically controlled for in cross-sectional analyses, age differences in episodic memory appear at a much later age [6]. This pattern is illustrated in Figure 1. This figure also shows how appropriate control of practice effects, through the introduction of new samples at subsequent test waves [6,7], influences longitudinal estimates of average age-related change in episodic memory performance.

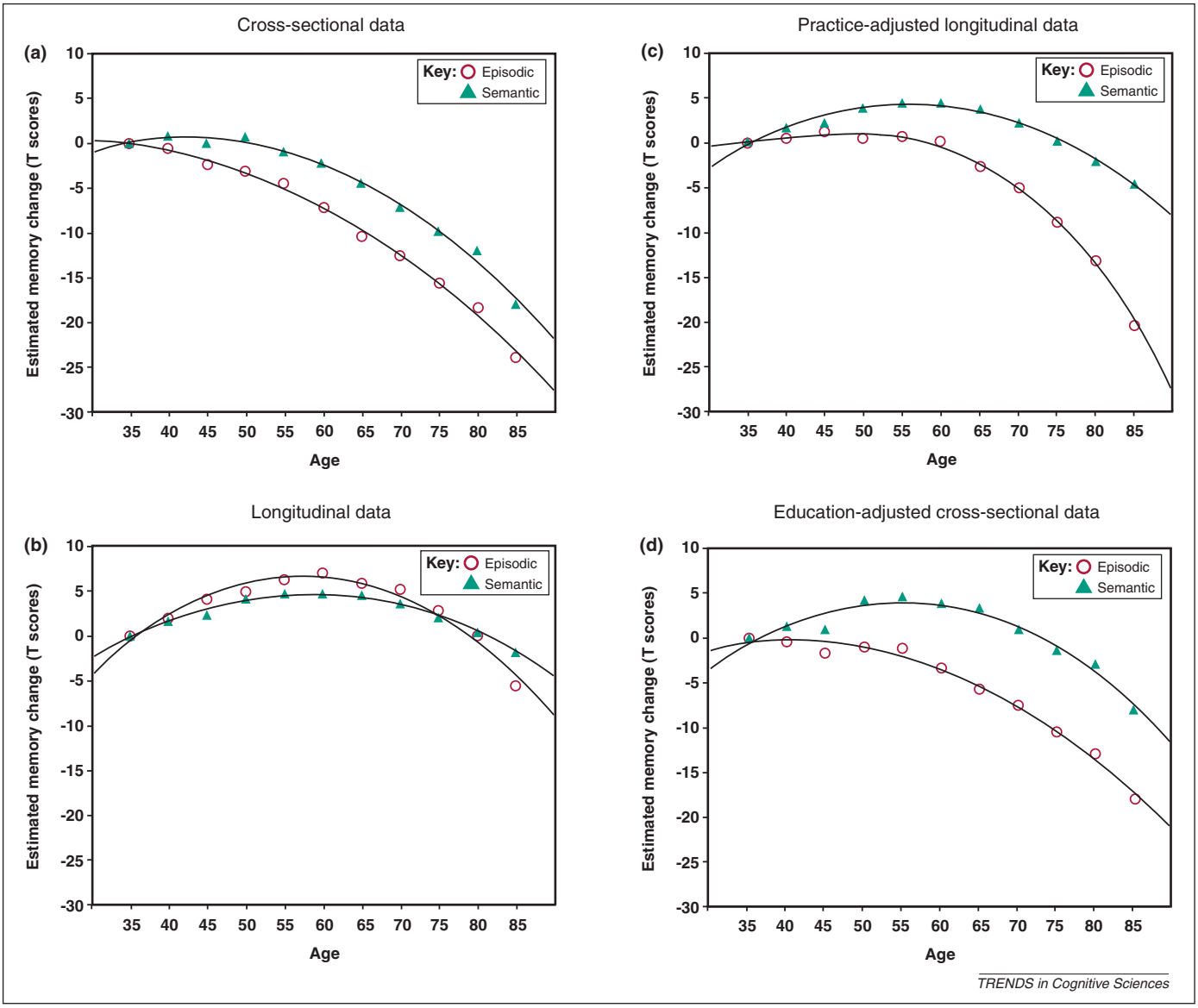

Figure 1. Illustration of assessment of age-related episodic-memory change with cross-sectional and longitudinal methods. **(a)** Cross-sectional data reveal early onset of decline. **(b)** Longitudinal data indicate a positive gradient into high age. **(c)** When effects of previous testing are statistically controlled (assessed relative to new samples at subsequent waves), longitudinal data indicate episodic-memory decline after age 60. **(d)** Education-adjusted cross-sectional data portray a similar picture with significant episodic-memory decline at approximately age 60. Reproduced, with permission, from [6].

Less is known about the average onset of decline in working memory performance. The reason for this lacuna is the absence of lifespan longitudinal studies on working memory that apply appropriate control for practice effects. However, longitudinal evidence exists for some cognitive abilities, such as reasoning [7,14,15], that are highly related to working memory performance [16,17]. Similar to episodic memory, this evidence suggests a relatively late onset of average age-related decline [7,14,15]. For example, longitudinal data on visuo-spatial reasoning indicate that decline starts after age 55 [14].

Taken together, the available longitudinal evidence does not support a view of an early onset of decline in episodic and working memory. Rather, significant episodic-memory decline is not evident until after age 60 and the limited evidence lends no support for a much earlier onset of working-memory decline.

The variable nature of memory decline

Findings from several large-scale population-based studies demonstrate substantial inter-individual differences in how episodic and working memory change in old age [12,18–20]. These interindividual differences in change of memory performance increase as a function of advancing adult age [21]. A more rapid than average decline for a certain age group has attracted much interest, as it might be indicative of forthcoming diseases such as dementia [22]. Relatively less attention has been paid to individuals who display little or no memory decline. A main reason for this is methodological difficulties – identifying individuals with preserved memory functioning is a challenge and often involves measuring large samples.

In one study [23], cognitive and non-cognitive data from approximately 1500 adults in the Betula longitudinal study [12] were analyzed with a factor analytic technique in order to classify individuals in terms of 'usual' versus 'successful' aging [24]. Results revealed substantial heterogeneity in levels of cognitive performance (Figure 2). Almost 10% of the participants older than 70 years were categorized as meeting the criterion of successful cognitive aging. Longitudinal studies provide additional evidence for heterogeneity in aging trajectories of cognitive performance, including identifying sub-groups of elderly individuals who maintain superior levels of cognitive performance over time [25,26]. In sum, extant evidence points to substantial individual differences in both level and change of memory performance in old age and to the existence of high-performing older individuals who display little or no performance decline.

Concepts for capturing brain mechanisms of successful memory aging

The large heterogeneity in memory aging and the existence of older adults who show little evidence of decline have led researchers to propose general mechanisms that may protect against imminent age-related decline in cognitive performance [27,28]. One of these concepts is 'reserve', which, according to a general definition [29], denotes the 'supply of a commodity not needed for immediate use but available if required'. The reserve concept has been used to capture properties of brain ('brain reserve'; [30,31]) and cognition ('cognitive reserve'; [32]). In either case, the amount of reserve is assumed to determine the relation between senescent and age-graded pathological alterations of the brain and behavioral manifestations:

- Brain reserve: 'Individual differences in the brain itself allow some people to cope better than others with brain pathology' ([33], p. 2016).
- Cognitive reserve: 'Individual differences in how people process tasks allow some to cope better than others with brain pathology' ([33], p. 2016).

The brain reserve concept invokes a passive threshold model [30]. That is, this model presupposes that the amount of intact brain (e.g., size, neuronal counts, synaptic density), rather than the amount of a given brain pathology (e.g., beta amyloid), is the best predictor of between-person differences in cognitive functioning. Only when brain resources fall below a given threshold will the pathology begin to dominate behavior. According to this view, successful memory performance in old age is primarily determined by having reached high levels of performance prior to the onset of senescent decline than about minimizing decline itself. That is, an individual with a larger brain reserve will have better memory performance and therefore reach the threshold for functional impairment (e.g., a dementia

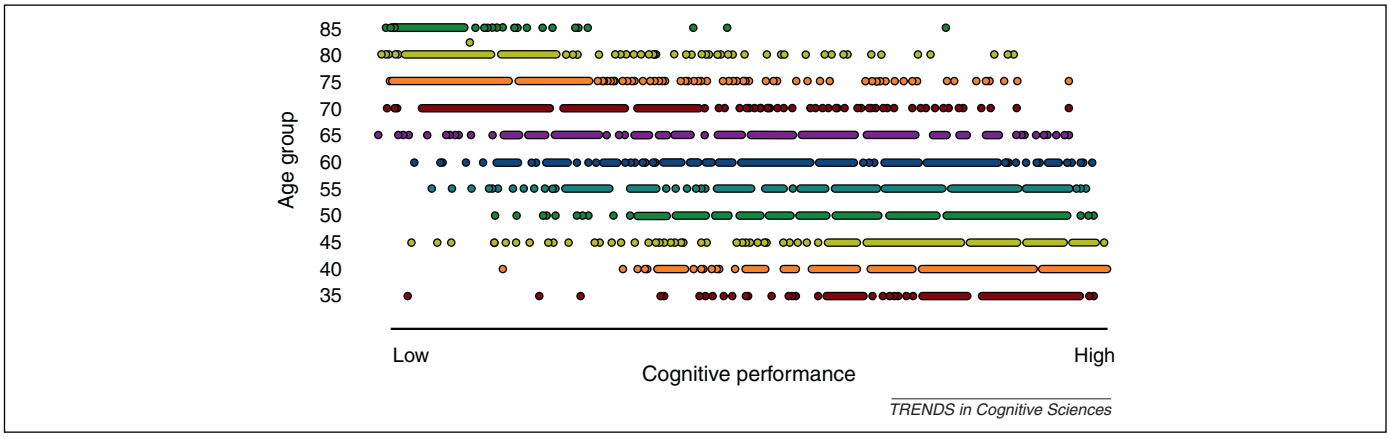

Figure 2. Illustration of variability in memory aging. The graph shows the results of a Q-mode factor analysis that sorted individuals into high versus low cognitive performers (each circle denotes the average score of an individual). Although a negative age trend is clearly visible, several older individuals performed at high levels. Reproduced, with permission, from [23].

diagnosis) at a later age. In contrast, the cognitive reserve concept is more 'active' [32,33] in the sense that some individuals will cope better with age-related pathology because they react to and compensate for their evolving brain changes. The reserve concepts are undoubtedly of great heuristic value; they have informed the search for conditions that promote successful cognitive aging and continue to be refined and specified in neural terms.

'Brain maintenance' is introduced here as a complementary concept (see also [34]). Maintenance denotes 'the process of preserving a condition' [29]. That is, whereas the reserve concept seeks to explain why some individuals have intact functioning in the presence of brain pathology, the concept of maintenance focuses on the conditions that promote the preservation of neurochemical, structural and functional brain integrity in old age. Thus, the focus is on the relative lack or postponement of senescent brain changes including pathology, rather than on ways of coping with its presence. We define brain maintenance as follows:

- Brain maintenance: 'Individual differences in the manifestation of age-related brain changes and pathology allow some people to show little or no age-related cognitive decline'.

Maintenance underscores the evident, but currently undervalued, notion that the primary characteristic of the brains behind successful memory aging is preserved chemistry, structure and function. According to the maintenance hypothesis, minimization of senescent brain changes and absence of pathology are the best predictors of successful memory development in old age. Two patterns of evidence would support the utility of this hypothesis for explaining individual differences in memory aging. First, aging individuals are expected to differ widely in the amount of neurochemical, structural and functional brain changes that they display. Second, the concept assumes a positive association between age-graded losses in brain and cognition: individuals displaying fewer losses in task-related brain properties will display lesser decline in memory performance.

Evidence that brain maintenance characterizes successful memory aging

As with cognitive functioning, there are marked inter-individual differences in the extent to which the brains of older adults deviate from those of younger adults. Findings from MRI studies show that some older adults have larger hippocampal volumes ([35]; Figure 3a) and show less annual hippocampal volume change than younger adults ([36]; Figure 3b). Similar cross-sectional and longitudinal patterns have been reported for other cortical and subcortical structures, including the caudate nucleus ([37–39]; Figure 3c), as well as for the brain's white matter ([38,39]; Figure 3d). On average, then, aging is associated with changes in brain integrity, often non-linearly, such that volume shrinkage and white-matter pathologies accelerate as a function of age [35,38–40]. At the same time, aging individuals differ reliably in rate of structural brain changes and brain integrity is relatively well preserved in some older adults.

Executive functions comprise several cognitive abilities including working memory [16,17,41,42]. Up to the present, attempts to link aging-related structural alterations of the brain to executive functioning have yielded mixed results [43–46]. Burzynska *et al.* (47) assessed cortical thickness and executive functioning in samples of younger and older healthy adults. The Wisconsin Card Sorting Test (WCST) was administered as an indicator of executive functioning. On average, older adults showed lower performance on the WCST than younger adults and also had a thinner cortex than their young counterparts. Age-related cortical thinning was most pronounced in bilateral frontal cortex, parietal cortex, posterior cingulate gyrus and temporal cortex, as well as the medial part of the precuneus. As shown in Figure 4a, a thicker cortical mantle in the fronto-parietal network, presumed to be engaged during WCST performance, was related to better WCST performance. Cortical thickness was a reliable predictor of WCST performance beyond chronological age (see Figure 4b). Importantly, the authors also observed reliable age-group × cortical-thickness interactions in several task-relevant areas, reflecting stronger positive associations between cortical thickness and WCST performance in older than in younger adults. Although the cross-sectional design of this study does not permit direct conclusions about individual differences in rate of decline, the finding that the associations between cortical thickness and executive performance increased reliably from early to late adulthood renders it likely that individual differences in rates of performance-related cortical thinning do in fact exist. Individual differences in the thinning of the cortical mantle may be due to a combination of several processes, such as rarefaction of dendritic arbors, spines and synapses, cell shrinkage, and cortical myelin loss [48,49]. The interaction between cortical thickness and age further suggests that between-person variations in thickness are more likely to result in functional impairments if cortical thickness has fallen below a certain level. Conversely, executive functions are more likely to be maintained into old age if cortical thinning progresses at a slow pace.

Longitudinal studies on the link between changes in cognition and brain volume are relatively sparse. In a recent review, Salthouse [50] reported eight studies, half of which showed a significant association between fewer senescent changes in grey or white matter volume and higher cognitive performance, whereas the other half showed no significant association. To our knowledge, there is only one longitudinal study investigating the association between changes in white matter integrity, measured with diffusion-tensor imaging, and cognition [51]. In this study, fewer alterations in whole-brain white matter microstructure were weakly linked to less negative changes in working-memory performance. In sum, although limited, the available evidence supports the notion that less structural brain change is associated with better memory performance in old age.

Additional evidence for brain maintenance in aging is provided by fMRI studies, but the findings form a rather complex pattern. First, functional neuroanatomical correlates of age-related cognitive deficits have been documented in numerous studies in the form of reduced regional

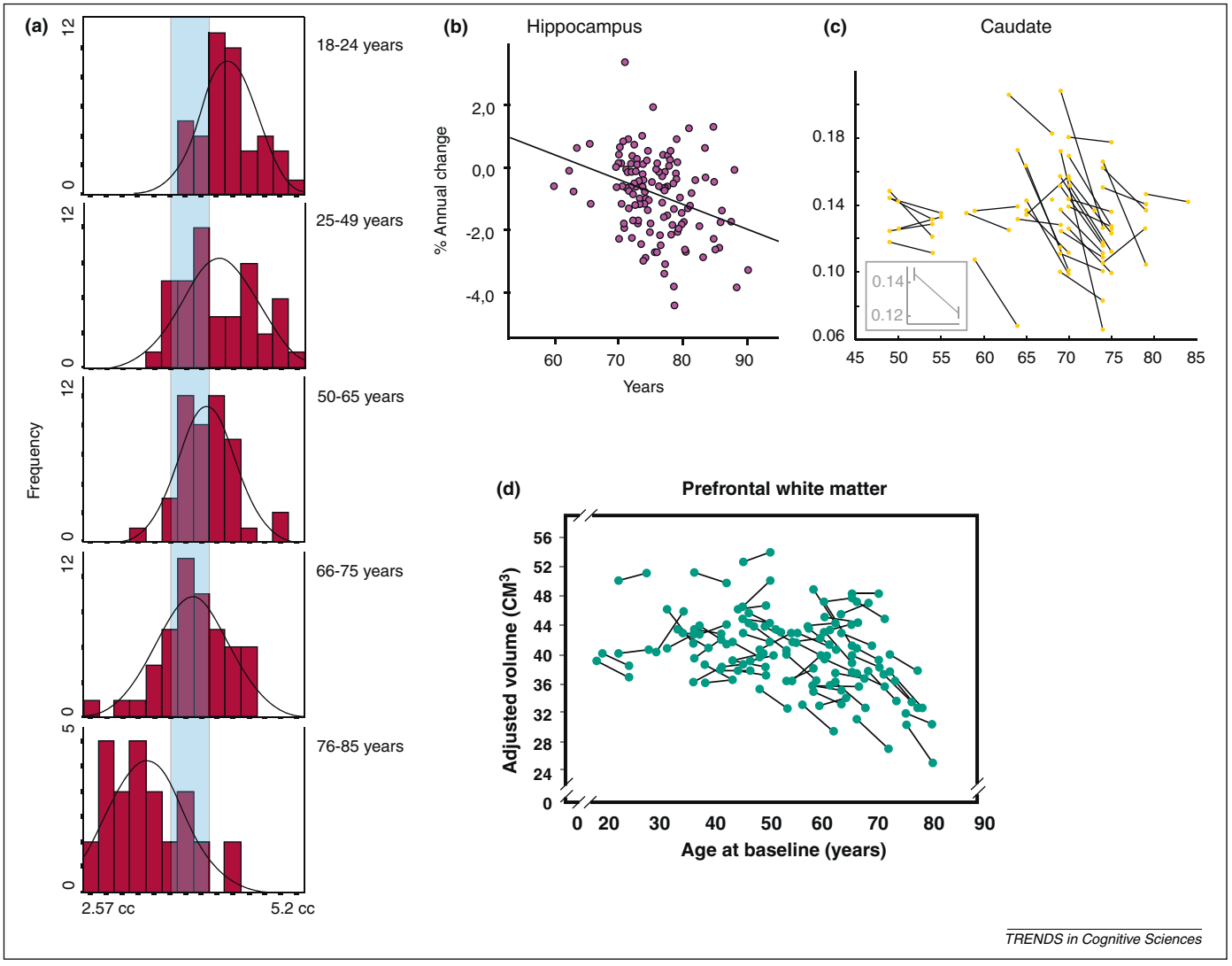

Figure 3. Illustration of inter-individual variability in age-related structural brain changes. **(a)** This panel illustrates that several individuals in their 70s have similar hippocampal volumes as 20-30 year old individuals. Reproduced, with permission, from [35]. **(b)** This panel shows interindividual variability in annual change in hippocampal volume, with some 80+-year-old individuals showing less shrinkage than 60-70-year olds. Reproduced, with permission, from [36]. **(c)** This panel portrays five-year change in caudate volume and highlights marked variability across the age span. Reproduced, with permission, from [37]. **(d)** This panel illustrates variability in age-related change in prefrontal white matter, such that some individuals in their 70s have larger volume and exhibit less change than 40-50-year-old individuals. Reproduced, with permission, from [38].

BOLD signal change in older compared to younger adults. Such reductions in BOLD signal change have been linked to age-related changes in grey matter [37,52], white-matter tracts [25,53], and dopamine functioning [54,55].

Second, fMRI studies have also revealed patterns of age-related regional over-recruitment [56–58]. Such findings of greater recruitment of certain brain regions by older than younger adults have attracted much interest, presumably because they suggest that the aging brain may functionally re-organize itself to combat age-related changes. As such, over-recruitment in aging might relate to the cognitive reserve concept [32,33]. However, note that the studies that support the notion of age-related over-recruitment have used a cross-sectional design, which does not permit any conclusions on decline-induced re-organization. Indeed, findings from a recent longitudinal fMRI study provided evidence that cross-sectional findings of over-recruitment can be driven by the inclusion of high-performing elderly who, when followed over time, showed age-related reductions in the fMRI signal [37]. The latter findings challenge the notion of age-related re-organization of functional brain networks, showing that cross-sectional findings of over-recruitment do not necessarily imply up-regulation of functional networks within individuals over time.

A third pattern of results from fMRI studies, most closely related to the concept of brain maintenance, is that of comparable recruitment of functional networks in younger and older adults. Such observations have been made when high-performing older adults have been compared with younger adults. For example, Nagel *et al.* [59] examined individual differences in BOLD signal responsivity during spatial working memory performance in younger and older adults. Initial analyses confirmed earlier claims that the BOLD signal is less responsive to increasing spatial working memory demands in old age. However, these overall age group differences were qualified by differences between high and low performers within each of the two age groups (Figure 5). The dose-response functions

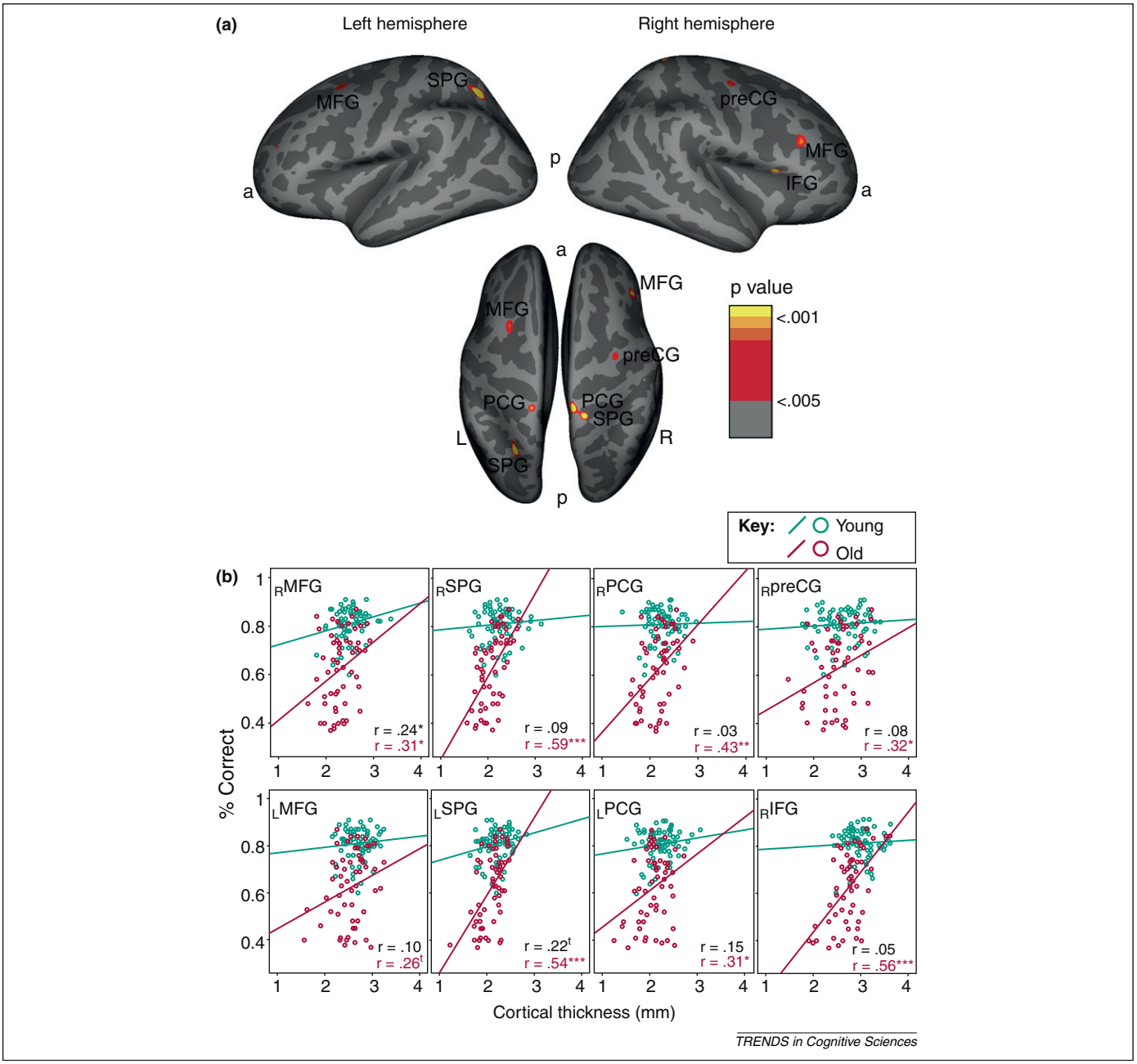

Figure 4. The relation between cortical thickness and executive control increases from early to late adulthood, suggesting that individuals who experience less cortical thinning are more likely to maintain high levels of executive control in old age. **(a)** Areas where a thicker cortical mantle is associated with better performance on the Wisconsin Card Sorting Test (WCST), a measure of executive control in the total sample, statistically controlling for age. **(b)** Mean cortical thickness regressed on WCST performance. x-axis: cortical thickness in mm; y-axis: WCST accuracy (% correct); *r*: Pearson's correlation coefficient, $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$, ^{t} = trend ($.07 > p > .05$). MFG, middle frontal gyrus; IFG, inferior frontal gyrus; SPG, superior parietal gyrus; preCG, precentral gyrus; PCG, post-central gyrus; a, anterior; p, posterior; L, left; R, right. Adapted, with permission, from [47].

of old high performers resembled those of the young, suggesting that similarities in functional activation patterns were related not only to chronological age but also – and even more so – to performance level.

Similarly, Nagel *et al.* [60] investigated whether individual differences in performance also contribute to adult age-differences in BOLD signal responsivity during verbal, rather than spatial, working memory performance. As in the previous study, older adults as a group showed compromised BOLD signal responsivity to increasing working memory load. At the same time, BOLD signal responsivity as well as load-dependent functional connectivity changes between left dorsolateral prefrontal cortex (DLPFC) and left premotor cortex (PMC) predicted working memory performance at high load across younger and older adults, indicating that task-related modulation of activity in the prefrontal and parietal cortices contributes to proficient task performance regardless of adult age.

In summary, these two working-memory fMRI studies indicate that older adults with relatively high levels of performance increase brain activity in task-relevant brain regions as a function of load, whereas low-performing older adults show flat or inverted-U shape activation profiles. Hence, the patterns of local and coordinated brain activity

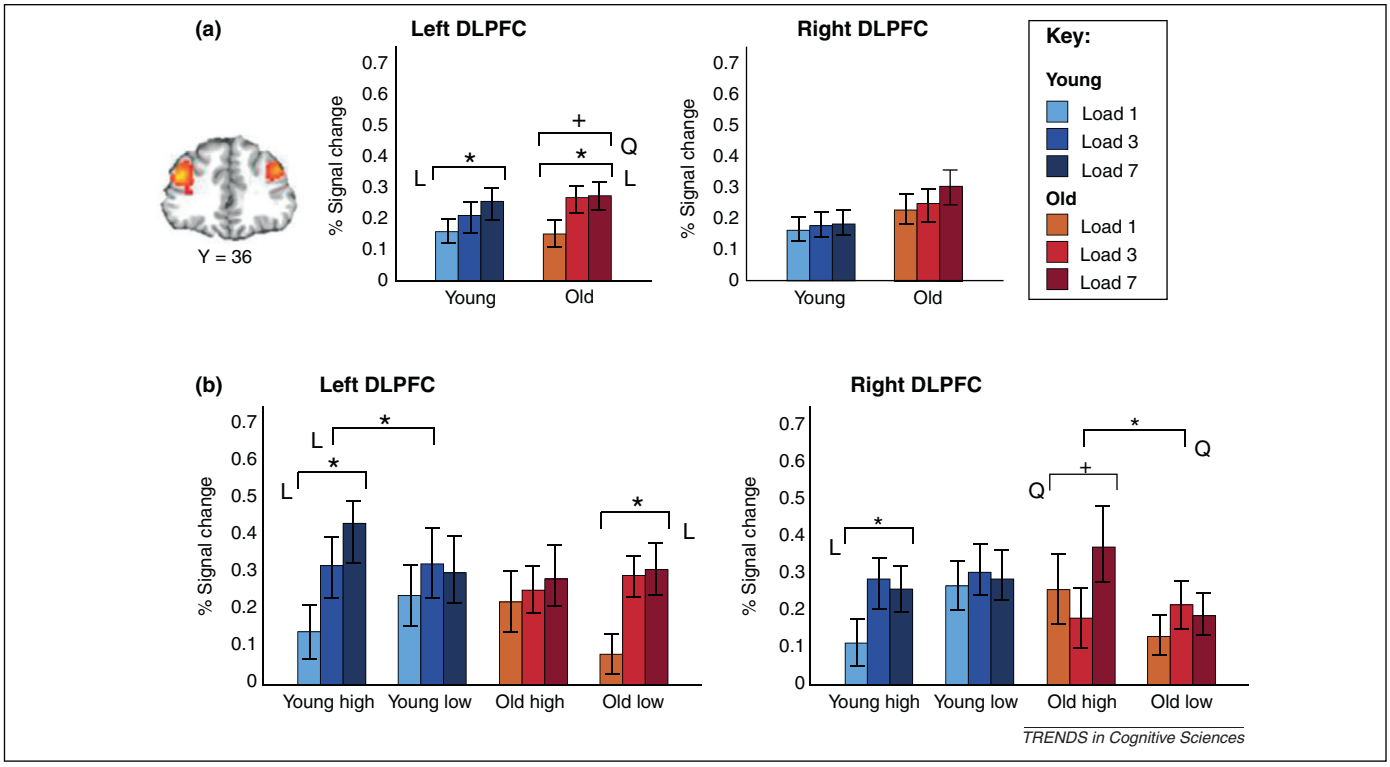

Figure 5. Age-related reduction in load-dependent modulation of working-memory related BOLD responses. **(a)** This panel shows that younger adults have a linear up-regulation of frontal BOLD responses as a function of load, whereas older adults show no up-regulation from load 3 to load 7. **(b)** This panel shows that high-performing elderly persons exhibit a load-dependent BOLD response that mimics that of younger adults. DLPFC, dorsolateral prefrontal cortex. Reproduced, with permission, from [59].

associated with high working memory performance look strikingly similar across age groups. Put differently, older adults with more 'youthful' brain responsivity to increasing task demands show higher levels of working memory performance than older adults whose brain responsivity differs from younger adults.

An fMRI study of episodic long-term memory addressed brain changes in relation to different cognitive aging trajectories [27]. Twenty-six 55-79-year-old individuals were followed behaviorally over 20 years and assessed with fMRI at two occasions spaced six years. All participants had a stable level of episodic memory performance up until the first fMRI session. However, there was pronounced variability thereafter, such that some remained stable or even increased slightly, whereas others declined (Figure 6a). Critically, the longitudinal fMRI analysis revealed that the BOLD signal in the left hippocampus (Figure 6b) showed a time-related decrease for individuals with a declining, but not for those with stable, memory performance (Figure 6c). Also, individuals with declining memory performance had declining hippocampus volume. Thus, in keeping with the critical role of the hippocampus for episodic memory, individual differences in structural and functional changes of the hippocampus were related to individual differences in memory change.

Additional evidence for brain maintenance in the context of episodic memory was provided by an fMRI study of brain activity patterns associated with encoding processes [61]. Older adults were classified with regard to their magnitude of 'Functional Activity Deviation during Encoding (FADE)'. Elderly individuals with high FADE scores showed impaired recollection, whereas those with low FADE scores had well preserved recollection. Consistent with the notion of brain maintenance, the authors concluded that 'successful aging in long-term memory reflects the preservation of a functionally specific memory network, and can occur in the absence of compensatory brain activity' ([61], p. 803).

PET and SPECT findings of how aging influences neurotransmitter systems, notably the dopamine (DA) D1 and D2 systems, provide additional evidence for brain maintenance underlying successful cognitive aging. Numerous molecular imaging studies have linked DA losses to age-related deficits in multiple cognitive domains, including episodic and working memory [62,63]. Although the cross-sectional nature of this research calls for longitudinal work on the interplay among aging, DA and cognition to substantiate causative links, it is evident that individual differences in DA binding are pronounced [64,65]. Of particular relevance here are findings that such differences persist in old age. Rieckmann *et al.* [66] examined the links between different DA D1 pathways in young and old adults. They found that the associations of nigrostriatal to mesolimbic and mesocortical DA pathways were reduced in aging along with slower responding in an interference resolution task. This pattern suggests that aging is associated with reduced connectivity among DA pathways. Of key significance, however, some older adults showed preserved relationships of D1 binding in sensorimotor and frontal regions (Figure 7a) and these individuals were as fast as their young counterparts on the cognitive task (Figure 7b). Thus, corroborating the MRI work, preserved DA functioning in aging was associated with preserved cognitive performance.

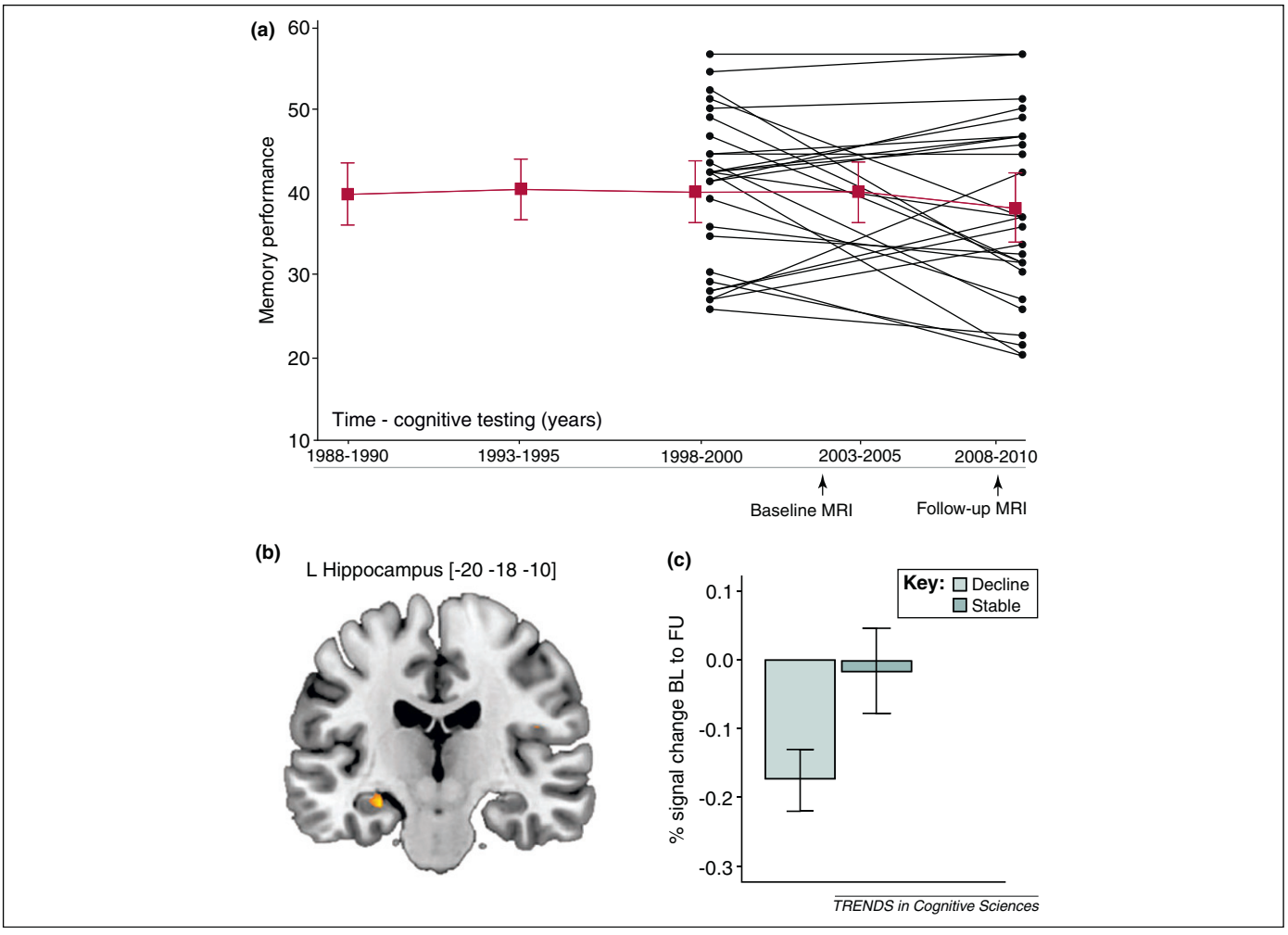

Figure 6. Functional brain changes in relation to different cognitive aging trajectories. All participants had a stable level of episodic memory performance until the first fMRI session, but there was pronounced variability thereafter, such that some individuals remained stable or even increased slightly whereas others declined **(a)** Longitudinal fMRI analysis revealed that the BOLD signal in left hippocampus **(b)** showed a time-related decrease for individuals with a declining memory performance but not for those with stable performance (c). BL, baseline; FU, follow-up. Reproduced, with permission, from [26].

Brain maintenance may manifest itself in other ways than the specific MR- and molecular-imaging applications discussed above, including vascular influences [67]. On a more microscopic level, brain autopsy can reveal dementia-related neuropathological lesions and it has been shown that neurofibrillary tangles, cerebral infarction and neocortical Lewy bodies contribute to age-related cognitive decline [21]. Critically, consistent with the concept of brain maintenance, little age-related cognitive decline has been observed in the absence of such lesions [21]. Independent studies provide converging evidence for marked individual differences in neuropathological burden in aging [68]. PET can be used to provide *in vivo* information on pathological processes that underlie Alzheimer's dementia (AD), including amyloid burden [69–72]. Analyses of the relation between PET measures of amyloid burden and memory performance in non-demented older individuals have yielded mixed findings [73,74]. Nevertheless, in keeping with the brain maintenance view, several studies have found that high memory performance is related to low amyloid burden in frontal and parietal areas [75,76]. In a large sample of 137 adults, Rodrigue and colleagues [77] observed that many adults even in their 80s had modest levels of amyloid (Figure 8) and high amyloid burden was systematically related to working-memory performance but not episodic memory performance. The authors noted that cross-sectional age estimates might not be sensitive enough to detect amyloid effects on episodic memory [77]. In fact, a longitudinal study showed that high amyloid deposition predicted a transition from normal to impaired cognition, whereas low amyloid deposition predicted cognitive stability [78].

Taken together, a wide range of findings provides converging evidence for marked heterogeneity in brain aging. Critically, some older adults show little or no brain changes relative to younger adults, along with intact cognitive performance, which supports the notion of brain maintenance. In other words, maintaining a youthful brain, rather than responding to and compensating for changes, may be the key to successful memory aging.

The conditions and factors supporting brain maintenance in aging

Individual differences in complex phenotypes, such as memory, result from gene-gene and gene-context interactions [79–81]. Twin studies indicate that individual

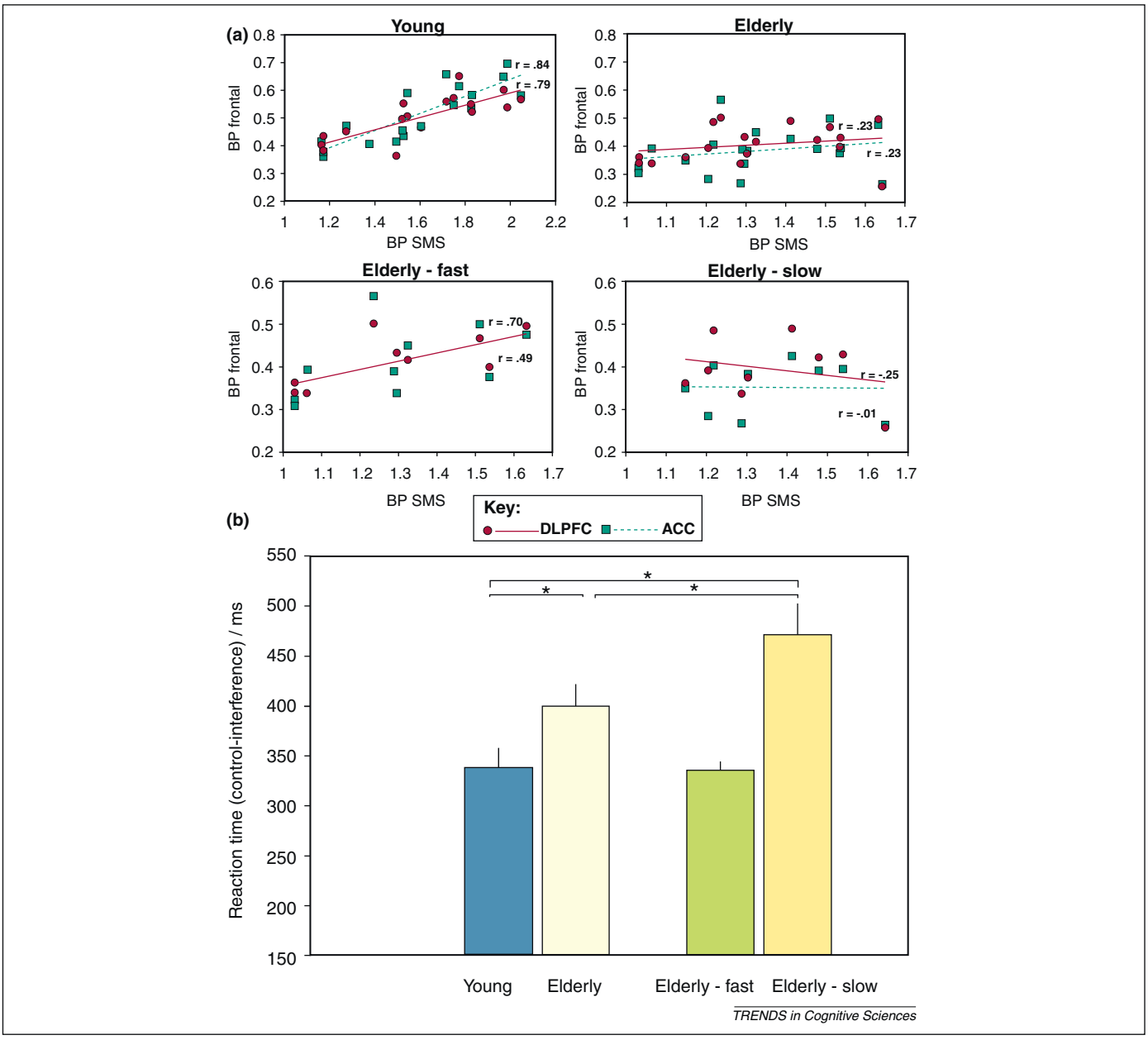

Figure 7. Inter-individual differences in connectivity among dopaminergic pathways. **(a)** Correlations of D1 binding potential (BP) in sensorimotor striatum (BP SMS) to D1 BP in frontal areas [dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC)] during performance of the Multi-Source Interference Task by age group and performance level (fast vs. slow) for elderly adults **(b)** Bars denote mean RTs (with standard errors) for interference control items. *Significant at $p < 0.05$. Reproduced, with permission, from [66].

differences in human cognition are closely linked to genetic variability [82,83]. In normal populations, more than half of individual differences in cognitive abilities are heritable, including episodic memory [84,85] and working memory [86]. Furthermore, individual differences in cognition are remarkably stable across the adult lifespan [87,88], suggesting a powerful synergy between genetic and environmental conditions [89].

Some genetic variants may be more conducive to maintaining high levels of brain functioning than others, thereby contributing to the large heterogeneity of memory functioning in old age. It has been hypothesized that losses in neurochemical and structural brain resources associated with aging magnify the influence of common genetic variations on cognitive functioning ([90]; cf. [27]). This hypothesis rests on the assumption that the function relating brain resources to cognitive performance is nonlinear, such that genetic variability is more likely to result in performance differences when resources move away from close-to-optimal levels, as in aging.

Based on this hypothesis, one would expect that individuals with more favorable genetic variants are more likely to maintain high levels of brain integrity and less likely to show memory loss. In line with this argument, twin studies suggest that individual differences in the acceleration of cognitive decline from adulthood to old age are strongly influenced by genetic factors [91]. Furthermore, age-comparative studies linking allelic variations in single nucleotide polymorphisms (SNPs) to memory performance support the hypothesis that common genetic differences contribute to heterogeneity of memory functioning in old age. One example concerns the brain-derived neurotrophic

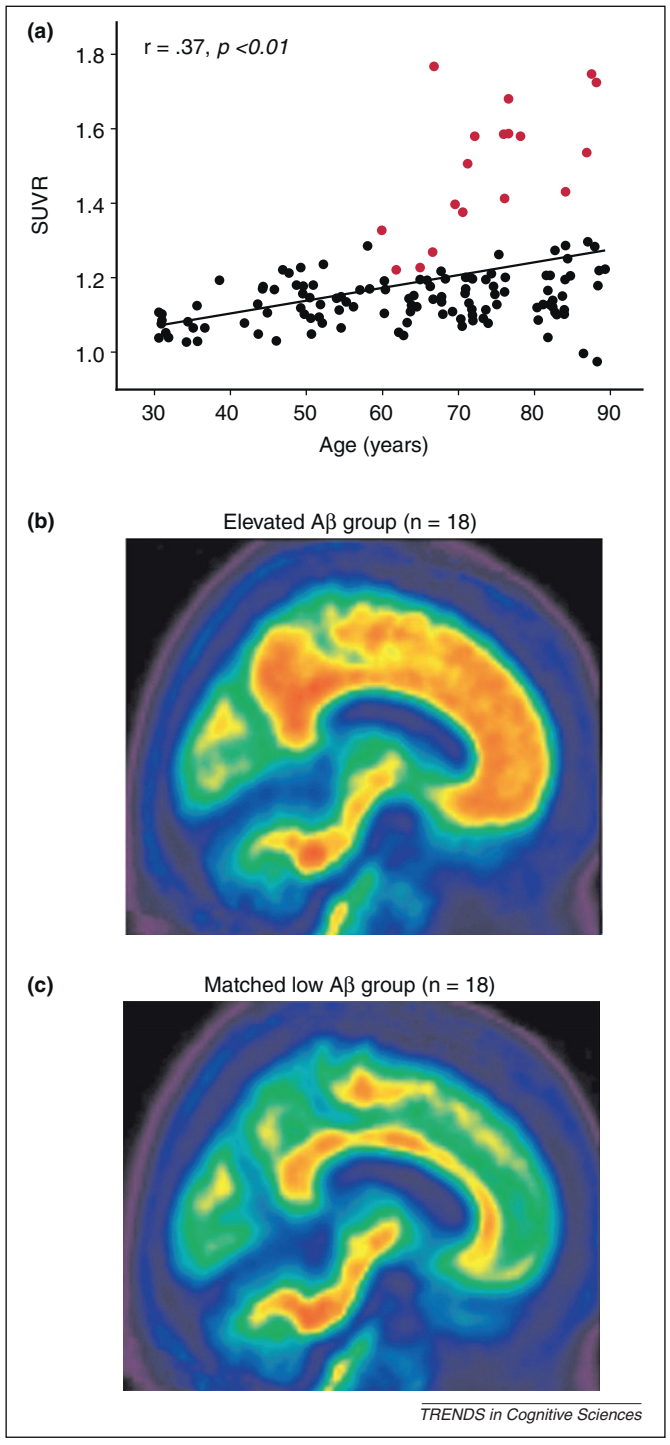

Figure 8. Mean cortical amyloid uptake across the adult lifespan. **(a)** Amyloid burden increases with age but older adults also show marked interindividual variability in amyloid levels. Individuals in red displayed elevated amyloid uptake. **(b)** Average cortical amyloid levels in the subgroup of individuals who displayed elevated amyloid uptake. **(c)** A comparison image for individuals with low amyloid burden (N = 18 per group). SUVR = standardized uptake value ratio. Reproduced, with permission, from [77].

factor (BDNF), which plays an important role in learning and memory by regulating activity-dependent synaptic plasticity. In a sample of 948 younger and older adults, Li *et al.* [92] investigated whether a common Val66Met missense polymorphism (rs6265) in the BDNF gene affects the serial position curve in backward and forward free recall. The authors observed a BDNF polymorphism effect for backward recall in older adults only, with Met-allele carriers (i.e., individuals with reduced BDNF signaling) recalling fewer items than Val homozygotes. This effect was specific to the primacy and middle portions of the serial position curve, where intralist interference and associative demands are especially high. These results suggest that the effects of the BDNF polymorphism on episodic memory are most likely to be observed when the associative and executive demands are high, and is in line with the hypothesis that maintenance of memory functioning in old age depends, in part, on genetic factors.

In addition to genetic determinants, environmental factors and lifestyle choices may play a role in maintaining brain integrity and cognitive performance in old age [93,94]. In the literature on cognitive and brain reserve, education has been a much discussed such factor. Accumulating evidence consistently showS that education is reliably associated with level of memory performance in old age but not with interindividual differences in change [95–97]. Thus, the association between education and cognitive functioning in old age likely reflects individual differences in cognitive functioning that have survived since early adulthood. Although the causal mechanism is unclear, education may therefore provide brain reserve, but it does not provide cognitive reserve nor does it play a crucial role in maintaining cognitive performance in old age.

In contrast, the available epidemiological evidence indicates that engagement in socially, mentally and physically stimulating leisure activities in old age reliably predict change in cognitive performance in old age [98–100]. Findings in the reserve literature point to an association between a more enriched lifestyle and larger amount of pathology in some patient groups, when cognitive performance is controlled for (e.g., in AD; [101]), suggesting that lifestyle-induced changes may allow patients to cope better with disease. At the same time, greater engagement in socially and mentally stimulating activities predicts less subsequent decline in cognitive performance [99,102,103]. Moreover, higher complexity of main lifetime occupation is associated with higher cognitive performance [104] but these effects are reduced after retirement [105], supporting the 'use-it-or-lose-it' adage. Collectively, these findings suggest that preserving level of late-life cognitive functioning (i.e., avoiding negative change) is more a matter of what you do in old age than reflecting what you did in earlier periods of the lifespan [94].

Even though the empirical evidence of an association between an enriched lifestyle and cognitive performance in aging is convincing, we hasten to add that the brain mechanisms mediating this association are unknown. Nonetheless, a large body of evidence suggests that brain integrity is modifiable by experience and learning [105]. For example, motor learning [106] and the acquisition of abstract knowledge [107] are associated with alterations in gray matter morphology in early adulthood. Such experience-dependent plasticity of brain volume extends into old age [108,109]. For example, Lövdén and colleagues [108] reported that spatial navigation training protected hippocampal volume against age-related decline in both young and older adults. Similarly, white matter integrity of the

brain is modifiable by experience in younger [110] and older [111] persons. Thus, lifestyle factors such as engagement in stimulating leisure activities may affect cognitive performance by preserving the brain's grey and white matter integrity.

In sum, evidence indicates that both genetic and lifestyle factors support brain maintenance in aging. In addition, preserving the brain may not only be a matter of avoiding negative influences on brain integrity, such as cerebrovascular conditions [38,112], but also reflect direct positive influences on brain plasticity [111].

Concluding remarks

Performance on episodic and working memory tasks declines with advancing age. Although cross-sectional studies have most likely overestimated both the onset and rate of memory decline [113], education-adjusted cross-sectional and practice-corrected longitudinal data converge to show that several individuals will experience memory decline in their 60s. However, there is marked interindividual variability in memory performance and such differences may be magnified with advancing age [114]. Some individuals may show reliable decline as early as in their 50s. Conversely, and of main concern here, others may show relatively preserved memory functioning well into their 70s.

Preserved memory functioning in old age may be accounted for in terms of brain reserve [30], cognitive reserve [32] or both, such that some individuals can tolerate more senescent changes and greater brain pathology before various forms of behavior are compromised. Here we have focused on brain maintenance in order to highlight the fact that the brains of some older adults seem to age less rapidly and show little or no pathology. According to the maintenance view, the brains of individuals whose cerebral anatomy and neurochemistry is relatively well preserved are more likely to show functional brain activation patterns that resemble those of younger adults and that are germane to proficient performance. Thus, whereas the reserve concept, in its different manifestations, stresses ways of coping with brain pathology, the maintenance concept focuses on relative lack or postponement of senescent brain changes as the key to preserved cognition in older age.

The association of intact memory functioning in old age with maintenance and preservation of a functionally young and healthy brain may seem obvious. However, up to the present the focus has largely been on possible forms of compensatory brain responses [32,57,58,115,116]. This is so, even though it remains unclear whether memory performance in old age can benefit from altered patterns of brain activation, with almost as many studies showing positive as negative relationships [116]. Furthermore, as almost all past functional imaging studies have relied on a cross-sectional design, it cannot be concluded with certainty that findings of age-related over-recruitment reflect reorganization [37].

Specific life-style and genetic factors are related to brain maintenance. A related issue concerns the influence of various forms of training and intervention. A potentially important implication of the maintenance view is that cognitive interventions should aim at maintaining, and possibly restoring, youthful brain structure and functions [34]. That is, rather than expecting that training will evoke novel brain responses in older adults, interventions may improve performance by reducing or remediating age changes in various aspects of brain physiology. Support for this position comes from functional imaging studies, where both cognitive [117] and physical [118] interventions served to make the activation patterns of older adults more similar to those of younger adults. Similarly, structural brain imaging has provided evidence for restoration after both cognitive [111] and physical [119] intervention programs.

In conclusion, we argue that maintaining the integrity of the brain is a crucial determinant of preserved memory as well as other forms of cognition [120] in old age. It is important to stress, though, that maintenance should not be viewed in absolute terms. Rather, even successful aging is associated with some brain changes [121,122]. It remains a fundamental challenge to link age-related brain changes to alterations in memory and cognition ([50]; Box 1). Longitudinal, multimodal imaging studies hold great promise in this regard [114,115,123].

Box 1. Questions for future research

- Cognitive assessment: how can measurements of memory and cognition be optimized to index brain maintenance? Can latent factor models be used to compensate for poor reliability and validity of individual tasks, and hence better capture subtle age-related decline?
- Brain maintenance: will a multimodal imaging approach provide a more comprehensive account of inter-individual variability in brain maintenance? Will future longitudinal PET data confirm cross-sectional estimates of marked average age-related decline in dopamine system integrity? Can brain maintenance, similar to liability to diseases, be quantified? Are some aspects of brain integrity more critical than others in relation to brain maintenance?
- Predictors of brain maintenance: are there genetic and lifestyle determinants of brain maintenance still to be discovered? What is the potential for restoring a youthful brain signature after age-related change has commenced and how durable are potential reversals?
- Conceptual development: what is the relation among brain reserve, cognitive reserve and brain maintenance? Are reserve and maintenance related, such that some individuals show fewer age-related brain changes (maintenance) as well as less vulnerability to brain pathology when it eventually manifests (reserve)?

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