Full text provided by www.sciencedirect.com

Brain aging: reorganizing discoveries about the aging mind

Patricia A Reuter-Lorenz and Cindy Lustig

New discoveries challenge the long-held view that aging is characterized by progressive loss and decline. Evidence for functional reorganization, compensation and effective interventions holds promise for a more optimistic view of neurocognitive status in later life. Complexities associated with assigning function to age-specific activation patterns must be considered relative to performance and in light of pathological aging. New biological and genetic markers, coupled with advances in imaging technologies, are enabling more precise characterization of healthy aging. This interdisciplinary, cognitive neuroscience approach reveals dynamic and optimizing processes in aging that might be harnessed to foster the successful aging of the mind.

Addresses
Department of Psychology, University of Michigan, 525 East University, Ann Arbor, MI 48109-1109, USA

Corresponding author: Reuter-Lorenz, Patricia A (parl@umich.edu)

Current Opinion in Neurobiology 2005, **15**:245–251

This review comes from a themed issue on
Cognitive neuroscience
Edited by Angela D Friderici and Leslie G Ungerleider

Available online 17th March 2005

0959-4388/$ – see front matter

DOI 10.1016/j.conb.2005.03.016

Introduction

The big story in the cognitive neuroscience of aging is the recent discovery of what appears to be functional reorganization and compensation in the aging brain. Here, we review several key chapters to this developing story: neurocognitive aging revealed by functional imaging, protective factors that mitigate age decline and the emerging socio-affective neuroscience of aging. The backdrop for these recent discoveries is decades of documentation of pervasive neurobiological, cognitive and performance declines with advancing age [1••,2]. The shrinkage of human brain gray matter volume measured *in vivo* is widespread and is especially evident in the lateral prefrontal cortex, hippocampus, cerebellum and caudate nucleus [3,4]. Pervasive white matter loss is especially prevalent in the prefrontal cortex [3,5,6,7•]. Cholinergic and dopaminergic declines are particularly pronounced, and compromise attentional and memory processes [8••,9]. Thus, until relatively recently [10], the dominant view of aging has been one of pervasive, irreversible decline.

Neurocognitive aging viewed from the brain scanner

Accordingly, a longstanding model for neurocognitive aging was the lesioned brain [10]. Based on this model, the initial assumption was that performance deficits arose from diminished contributions of specialized brain regions and that older adults (typically aged 60 years and older), being atrophic and less able to engage the relevant neural circuitry, would show less brain activation than younger adults (typically aged 18–30 years) performing the same task. Initially, studies focused on these patterns of underactivation [11], and it remains a frequent result in memory, cognitive control and executive processing tasks [12–14]. Interestingly, these patterns might reverse if a strategy is provided, such as instructions that focus attention on the meaning of words, which can facilitate later memory [15]. This result offers support for behaviorally derived theories suggesting that age differences in performance sometimes reflect a failure of older adults to self-initiate the use of controlled, effortful processing strategies to support their performance.

Underactivations fit well with a brain-damage model of aging; the largely unanticipated result from functional neuroimaging is overactivation, or greater brain activity in older than in younger adults. Age-related, region-specific overactivation is now well documented for a wide range of processes, including executive functions [16–19]; motor control [20,21]; and episodic [22••,23,24,25••,26], autobiographical [27] and working memory [24,28] (see [1] for reviews of age-specific activations reported before 2003).

Do these overactivations reflect compensation? Several lines of evidence support this possibility. First, older adults show more regions of activity, including cross-hemispheric homologous loci, on tasks that show minimal adverse performance effects due to age — such as autobiographical memory and verb generation [18,27] — and when performance levels, effort exerted or both are matched [21]. In addition, a recent study using repetitive transcranial magnetic stimulation (TMS) interference reported that retrieval was impaired in young adults when unilateral TMS was applied, whereas for older adults left or right TMS impaired performance, suggesting that both hemispheres contributed to performance in the older but not in the younger group [29••]. Second, activation levels have been shown to correlate positively with overall performance levels [20,26,30–32] in older adults. In some cases, when subgroups of elderly individuals are examined, region-specific overactivations characterize the groups that perform best [33,34]. Third, overactivations have been linked to trial outcome using event-related functional magnetic resonance imaging (fMRI); greater activity in prefrontal regions, especially lateral and inferior prefrontal sites, has been found in older adults than in young adults in an encoding task when items are successfully remembered [22••,25••], and in successful trials in tasks requiring response inhibition [16,17]. Fourth, in some studies this prefrontal overactivation is accompanied by medial temporal lobe underactivation [25••,35], which has been taken to support the view that strategic processes mediated by the prefrontal cortex compensate for declining medial temporal lobe function with age.

Although a compensation interpretation of overactivation in older adults is an exciting and optimistic one, it is clearly not the whole story. For example, even if overactivation is compensatory, it might have a hidden cost. To the extent that older brains engage more neural circuitry at lower levels of task demand than do younger adults, seniors rely more on 'cognitive reserve' [32] and are thus more likely to reach a limit on the resources that can be brought to bear on task performance [36]. Reuter-Lorenz and Mikels [37] have referred to this as CRUNCH, compensation-related utilization of neural circuits hypothesis.

Furthermore, the functional significance of overactivation in seniors might vary depending on the locus of activation and the task context. For example, there are indications that some inhibitory interactions between brain areas might break down with age [38], in which case overactivation could reflect the nonselective recruitment of disinhibited regions [15]. Dedifferentiation is another possible account of overactivation, as suggested by a recent investigation of specificity in the ventral visual cortex. Unlike younger adults, who show discrete, anatomically and functionally separable peaks of activation for faces, places and words, older adults showed less differentiation of such material-specific subregions, activating all regions of interest, regardless of material type [39••]. These human results parallel the breakdown of selective tuning profiles for individual neurons recorded in the monkey visual cortex [40] and in the rat somatosensory cortex [41]. A breakdown in the integrity of perceptual representations could increase neural noise [42] and stimulate a cascade of compensatory adjustments at subsequent stages of processing downstream.

Overactivations might also indicate inefficient processing, as suggested by the results from the Stroop task, in which older adults show greater activity in perceptual areas and in the anterior cingulate in conditions that elicit conflict [43]. Likewise, one study found that, compared with young adults and older adults with good memories, older adults with poorer memories showed more widespread activations during retrieval attempts. This outcome suggests that inefficient or compensatory search strategies might attempt to overcome poorer encoding [23]. Areas of overactivation have also been reported in patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) compared with nondemented adults. Again, the particular locus of overactivation varies according to the task that is performed, and the significance of this additional recruitment is not entirely clear. On the one hand, prefrontal overactivation has been associated with better memory performance by AD patients [26], yet on the other hand, an analysis focusing on medial temporal lobe structures in MCI patients found that, despite similar performance, subjects with the most structural atrophy showed the largest extent of overactivation, and that overactivation was predictive of longitudinal decline [44•]. A tempting interpretation is that overactivation might support good performance in the short term but could also be a sign that an individual is compensating for a progressive pathology and therefore predicts future decline. However, it is important to note that the regions of interest for these two studies [26,44•] were quite different, and that a great deal more work is needed to establish the relationships among performance, activation and structural differences, and longitudinal change.

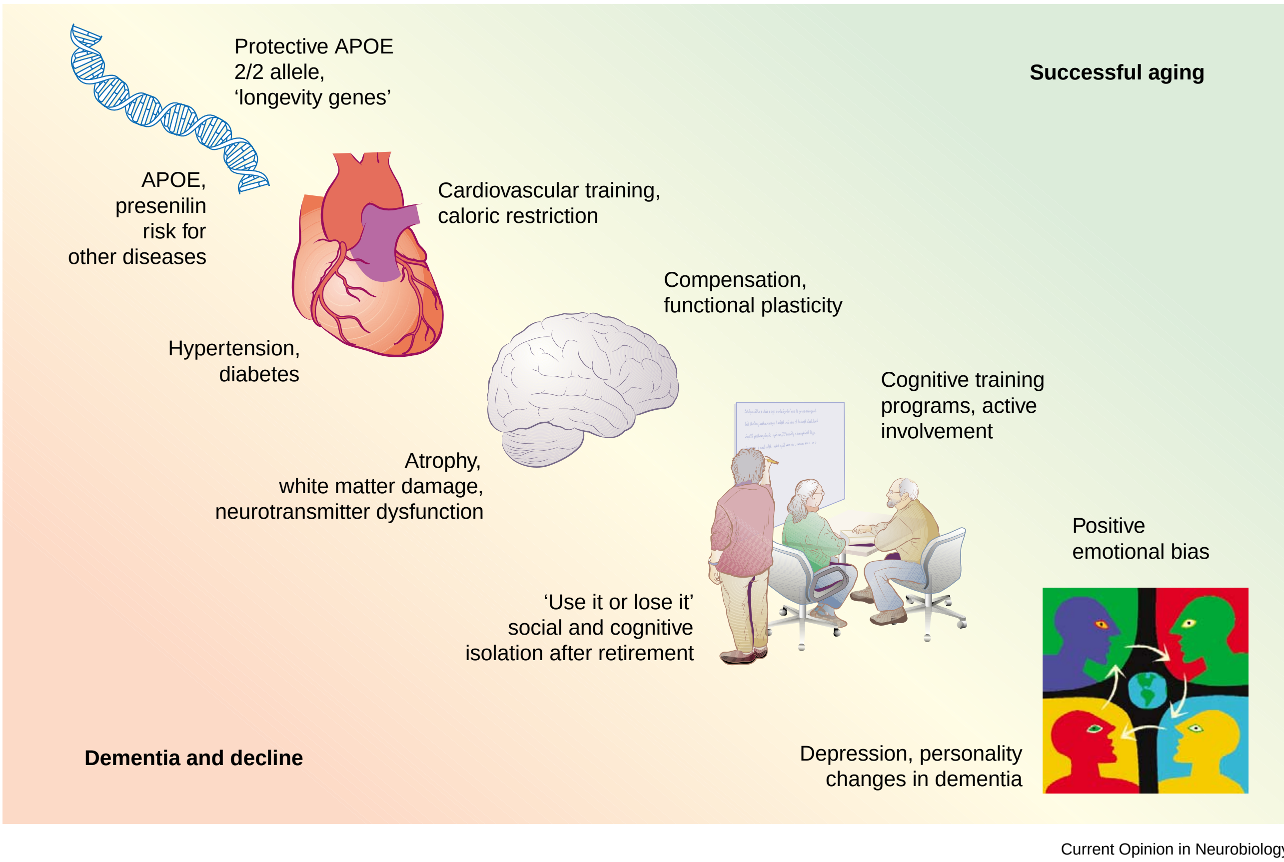
Some of the most important — and complicated — questions for the cognitive neuroscience of aging lay in linking age differences in activation patterns to age differences in cognition (Figure 1 and Table 1). When do overactivations reflect beneficial compensatory processing, and what are they compensating for? Are there brain and cognitive processing changes for which compensation is not possible? Does bilateral homologous overactivation differ in origin and function from other forms of overactivation in seniors? To what extent are age differences in brain activation and performance modifiable by providing older adults with the 'correct' strategy or by other means?

Preservation and reversal

Evidence is mounting for the importance of good cardiovascular health and a low-calorie diet as means of maintaining — and even returning to — youthful states of brain and behavior [45]. The largest benefits are on higher level, controlled, executive functions, which show the largest changes in normal aging. Critically, these are not only correlational findings; a randomized intervention study found a return to young adult-like patterns of behavior and brain activation for those assigned to cardiovascular training, benefits that were not found for those assigned to other forms of exercise [46•,47].

Do cognitive training programs produce similar benefits? Practice, whether through a lifetime of experience or in some instances short term intervention regimens, can

Figure 1



Factors influencing neurocognitive aging. The figure illustrates several factors influencing whether aging will be successful or lead to impairment. This list is not intended to be comprehensive but instead summarizes factors of recent interest that are highlighted in the text. Abbreviations: APOE, apoliprotein E.

lead to improved performance in older age. For example, bilingual older adults, having developed the skill of flexibly negotiating two language systems across their lifetime, show smaller age-related performance declines compared with those in monolinguals [48•]. Again, these benefits occurred for a task with high demands on executive control. Programs founded on basic techniques from cognitive psychology — in particular, temporally spaced practice — show substantial and long-lasting benefits to memory performance in older adults, even those with AD [49,50•].

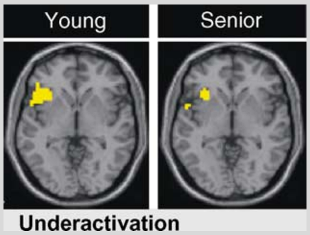
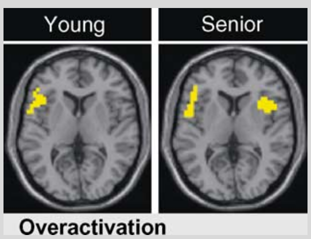
Neuroimaging data might inform our understanding of how these behavioral training programs exert their effect. Do they result in older adults returning to a younger adult-like state, as in cardiovascular training, or do they lead to compensation and the adoption of different strategies and activation patterns? One study found that even successfully trained older adults activated posterior but not frontal regions to the same degree as young adults, suggesting alternative strategies and deficient engagement of higher-level processing, even after training. By contrast, another investigation found equivalent practice effects and neural activity reductions for young adults, older adults and even AD patients [12,51]. However, besides the general need for more studies to explore this question, there is an important temporal gap; neuroimaging studies thus far have focused on short-term, within-session training benefits, whereas behavioral studies often examine training benefits over weeks and months. The neural correlates of these long-term changes remain a largely open but important question.

A positive side to aging?

Despite the losses that accompany normal aging, it is increasingly evident that older adults have a more positive emotional bias than their younger counterparts. Several studies show that older adults give preferential processing to emotional information, particularly positive information, in attention and memory tasks [52]. Although these differences might reflect age-related changes in social and emotional goals, there are some

Table 1

Age differences in activation: impairment or compensation?

Age-specific pattern	Interpretation	Hypothesized mechanisms	Candidate 'diagnostic' criteria	Examples
	Impairment	Circuitry dysfunction Region-specific atrophy Poor strategy use	Linked to poor performance Correlates with structure Might be reversed with instructions	[13–15]
	Compensation	Strategic or neural adjustments to local processing inefficiency Strategic or neural adjustments to processing inefficiency elsewhere in the brain	Linked to good performance Overactivation correlates with regions of underactivation activation elsewhere in the brain Deactivating TMS impairs performance	[18,25••,29••,35]
	Impairment	Disinhibited or nonselective recruitment Strategic or neural processing inefficiency Selectivity breakdown or dedifferentiation Nonfunctional activity	Linked to poor performance Deactivating TMS improves or has no effect on performance	[23,39••,43,44•]

This table summarizes the current state of knowledge pertaining to the two major patterns that characterize the results from functional neuroimaging studies comparing younger with older adults and lists several reports that exemplify these results. Underactivation refers to less activation in regions of interest in older relative to younger adults, and overactivation refers to the opposite pattern.

indications that neural mechanisms mediating affective information processing might also change with age [53]. One fMRI study indicated decreased processing of negative emotional scenes by older adults; relative to younger adults, older adults gave lower arousal ratings and showed less amygdala activation to negative emotional pictures, whereas there were no age differences in subjective or activation responses to positive images [54•]. However, the role of neural decline in these effects is unclear in light of other data suggesting that decreased processing of negative information might be specific to AD [55].

Conclusions and future directions

The question of how to divide aging phenomena into categories of healthy, normal or disease-related remains a difficult but important goal in neuroscience (e.g. the upcoming AD Neuroimaging Initiative sponsored by NIH [5,6,56]). Many recent advances point to a medial parietal-frontal cortex network associated with reduced metabolism in AD and genetic risk [57]. A newly developed compound identifying amyloid plaques, the hallmark of AD, heavily tags these regions [58••], and new methods of analyzing resting-state fMRI data suggest strong functional connectivity with medial temporal regions, including the hippocampus [59]. This network, which is implicated in memory processing, also shows age disruptions in activity during memory-related tasks that are exacerbated by AD [60••].

What lies ahead for aging research? The interdisciplinary approach taken with AD might be a model for improving our understanding of normal and healthy aging. We have highlighted emerging patterns in the neuroimaging of aging — under- and over- activations by older adults, the potential reversal of age declines via training and health improvements, and the influence of emotion — and enduring questions. What is the short- and long- term significance of age differences in activation patterns? How do training programs and emotional influences have their effects? These will be joined by new questions, with genetic and personality factors and circadian influences probably next on the horizon.

New technologies have developed with these new questions, including a better understanding of age differences in the hemodynamic response, and methods to enable increasingly detailed structural images [61–63,64••]. We expect that neuroimaging methods will become increasingly integrated with behavioral, genetic and pharmacological approaches to investigate not only disease processes but also the normal individual differences that underlie successful aging.

These future directions share an important feature with the current focus of the field: a shift from the dismal characterization of aging as an inevitable process of brain damage and decline. Instead, the emerging story from cognitive neuroscience is that aging can be successful, associated with gains and losses. It is not necessarily a unidirectional process but rather a complex phenomenon characterized by reorganization, optimization and enduring functional plasticity that can enable the maintenance of a productive — and happy — life.

Acknowledgements

This work was supported by National Institute of Health grant AG18286 to the first author. We thank J Persson for the Figures in Table 1 and J Cummings for assistance with the references.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Cabeza R, Nyberg L, Park DC (Eds): *Cognitive neuroscience of aging: Linking cognitive and cerebral aging*. Oxford University Press; 2004.
••

This edited volume consists of chapters covering the major topics in the field of cognitive aging and offering a comprehensive, up-to-date review of the cognitive neuroscience approaches to aging.

2. Raz N: **The aging brain observed *in vivo*: Differential changes and their modifiers**. In *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging.* Edited by Cabeza R, Nyberg L, Park DC. New York, NY: Oxford University Press; 2004:19-57.

3. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C: **Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain**. *J Neurosci* 2003, **23**:3295-3301.

4. Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RSR, Busa E, Morris JC, Dale AM, Fischl B: **Thinning of the cerebral cortex in aging**. *Cereb Cortex* 2004, **14**:721-730.

5. Bartzokis G, Sultzer D, Lu PH, Neuchterlein KH, Mintz J, Cummings JL: **Heterogeneous age-related breakdown of white matter structural integrity: implications for cortical 'disconnection' in aging and Alzheimer's disease**. *Neurobiol Aging* 2004, **25**:843-851.

6. Head D, Buckner RL, Shimony JS, Williams LE, Akbudak E, Conturo TE, McAvoy M, Morris JC, Snyder AZ: **Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging**. *Cereb Cortex* 2004, **14**:410-423.

7. Madden DJ, Whiting WL, Huettel SA, White LE, MacFall JR, Provenzale JM: **Diffusion tensor imaging of adult age differences in cerebral white matter: relation to response time**. *Neuroimage* 2004, **21**:1174-1181.
•

The authors found that fractional anisotropy measures of white matter integrity decreased with age and were predictive of response time. Regions of predictive value differed for young and old adults but were consistent with fMRI measures of cortical activation taken from the same participants.

8. Castner SA, Goldman-Rakic PS: **Enhancement of working memory in aged monkeys by a sensitizing regimen of dopamine D-1 receptor stimulation**. *J Neurosci* 2004, **24**:1446-1450.
••

Intermittent stimulation of dopamine D1 receptor systems improved delayed response performance for older monkeys but had a small detrimental effect for young monkeys. Beneficial effects remained >1 year following stimulation; young monkeys returned to baseline. Dopamine stimulation might thus have a specific benefit for populations (such as older adults) with deficiencies and could provide the basis for treating even normal age-related declines. Importantly, the results suggest that even a relatively short treatment regimen can have long-lasting benefits.

9. Sarter M, Bruno JP: **Developmental origins of the age-related decline in cortical cholinergic function and associated cognitive abilities**. *Neurobiol Aging* 2004, **25**:1127-1139.

10. Reuter-Lorenz PA: **New visions of the aging mind and brain**. *Trends Cogn Sci* 2002, **6**:394-400.

11. Grady CL, McIntosh AR, Horwitz B, Maisog JM, Ungerleider LG, Mentis MJ, Pietrini P, Schapiro MB, Haxby JV: **Age-related reductions in human recognition memory due to impaired encoding**. *Science* 1995, **269**:218-221.

12. Nyberg L, Sandblom J, Jones S, Neely AS, Petersson KM, Ingvar M, Backman L: **Neural correlates of training-related memory improvement in adulthood and aging**. *Proc Natl Acad Sci USA* 2003, **100**:13728-13733.

13. Johnson MK, Mitchell KJ, Raye CL, Greene EJ: **An age-related deficit in prefrontal cortical function associated with refreshing information**. *Psychol Sci* 2004, **15**:127-132.

14. Thomsen T, Specht K, Hammar A, Nyttingnes J, Ersland L, Hugdahl K: **Brain localization of attentional control in different age groups by combining functional and structural MRI**. *Neuroimage* 2004, **22**:912-919.

15. Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL: **Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging**. *Neuron* 2002, **33**:827-840.

16. Langenecker SA, Nielson KA: **Frontal recruitment during response inhibition in older adults replicated with fMRI**. *Neuroimage* 2003, **20**:1384-1392.

17. Langenecker SA, Nielson KA, Rao SM: **fMRI of healthy older adults during Stroop interference**. *Neuroimage* 2004, **21**:192-200.

18. Persson J, Sylvester CY, Nelson JK, Welsh KM, Jonides J, Reuter-Lorenz PA: **Selection requirements during verb generation: differential recruitment in older and younger adults**. *Neuroimage* 2004, **23**:1382-1390.

19. Hester R, Fassbender C, Garavan H: **Individual differences in error processing: a review and reanalysis of three event-related fMRI studies using the GO/NOGO task**. *Cereb Cortex* 2004, **14**:986-994.

20. Mattay VS, Fera F, Tessitore A, Hariri AR, Das S, Callicott JH, Weinberger DR: **Neurophysiological correlates of age-related changes in human motor function**. *Neurology* 2002, **58**:630-635.

21. Ward NS, Frackowiak RSJ: **Age-related changes in the neural correlates of motor performance**. *Brain* 2003, **126**:873-888.

22. Morcom AM, Good CD, Frackowiak RSJ, Rugg MD: **Age effects on the neural correlates of successful memory encoding**. *Brain* 2003, **126**:213-229.
••

The results from this experiment provide important evidence favoring a compensatory account of age-related overactivation using a trial-by-trial analysis of the subsequent memory effect. The study demonstrated that when the encoding of verbal stimuli leads to subsequent successful memory, younger adults show left lateralized activation in the inferior prefrontal cortex, whereas older adults show activity in the homologous left and right inferior prefrontal region.

23. Daselaar SM, Veltman DJ, Rombouts S, Raaijmakers JGW, Jonker C: **Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects**. *Brain* 2003, **126**:43-56.

24. Cabeza R, Daselaar SM, Dolcos F, Prince SE, Budde M, Nyberg L: **Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval**. *Cereb Cortex* 2004, **14**:364-375.

25. Gutchess AH, Welsh RC, Hedden T, Bangert A, Minear M, Liu LL, Park DC: **Aging and the neural correlates of successful picture encoding: frontal activations for decreased medial temporal activity**. *J Cogn Neurosci* 2005, **17**:84-96.
••

This subsequent memory study serves as an excellent example of evidence meeting criteria for compensation (Table 1). Increased prefrontal activations were observed for older adults during good performance (equivalent to young adults). Furthermore, these increased activations were observed for successful trials, specifically the contrast between remembered and forgotten items. Finally, prefrontal activations for older adults were negatively correlated with medial temporal lobe activations, whereas for young adults correlations were positive, suggesting that the increase in prefrontal activation for older adults reflects compensation for medial temporal atrophy or dysfunction.

26. Grady CL, McIntosh AR, Beig S, Keightley ML, Burian H, Black SE: **Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease**. *J Neurosci* 2003, **23**:986-993.

27. Maguire EA, Frith CD: **Aging affects the engagement of the hippocampus during autobiographical memory retrieval**. *Brain* 2003, **126**:1511-1523.

28. Park DC, Welsh RC, Marshuetz C, Gutchess AH, Mikels J, Polk TA, Noll DC, Taylor SF: **Working memory for complex scenes: age differences in frontal and hippocampal activations**. *J Cogn Neurosci* 2003, **15**:1122-1134.

29. •• Rossi S, Miniussi C, Pasqualetti P, Babiloni C, Rossini PM, Cappa SF: **Age-related functional changes of prefrontal cortex in long-term memory: a repetitive transcranial magnetic stimulation study**. *J Neurosci* 2004, **24**:7939-7944.

This is one of the few studies to date to have used TMS to investigate hemispheric organization as a function of age. The results demonstrated that repetitive TMS, which has transient interfering effects on the underlying circuitry, disrupts retrieval only when applied unilaterally to the right hemisphere in young adults, whereas disruptions occur in older adults following either left or right TMS. This outcome suggests greater bilateral involvement in retrieval operations with advancing age. An important next step will be to combine neuroimaging and TMS methods to demonstrate increased bilateral activation and the effects of TMS disruption of that activation in the same participants.

30. Reuter-Lorenz PA, Marshuetz C, Jonides J, Smith EE, Hartley A, Koeppe R: **Neurocognitive ageing of storage and executive processes**. *Eur J Cogn Psychol* 2001, **13**:257-278.

31. Madden DJ, Whiting WL, Provenzale JM, Huettel SA: **Age-related changes in neural activity during visual target detection measured by fMRI**. *Cereb Cortex* 2004, **14**:143-155.

32. Scarmeas N, Zarahn E, Anderson KE, Hilton J, Flynn J, Van Heertum RL, Sackeim HA, Stern Y: **Cognitive reserve modulates functional brain responses during memory tasks: a PET study in healthy young and elderly subjects**. *Neuroimage* 2003, **19**:1215-1227.

33. Cabeza R, Anderson ND, Locantore JK, McIntosh AR: **Aging gracefully: compensatory brain activity in high-performing older adults**. *Neuroimage* 2002, **17**:1394-1402.

34. Rosen AC, Prull MW, O'Hara R, Race EA, Desmond JE, Glover GH, Yesavage JA, Gabrieli JDE: **Variable effects of aging on frontal lobe contributions to memory**. *Neuroreport* 2002, **13**:2425-2428.

35. Grady CL, McIntosh AR, Craik FIM: **Age-related differences in the functional connectivity of the hippocampus during memory encoding**. *Hippocampus* 2003, **13**:572-586.

36. DiGirolamo GJ, Kramer AF, Barad V, Cepeda NJ, Weissman DH, Milham MP, Wszalek TM, Cohen NJ, Banich MT, Webb A *et al.*: **General and task-specific frontal lobe recruitment in older adults during executive processes: a fMRI investigation of task-switching**. *Neuroreport* 2001, **12**:2065-2071.

37. Reuter-Lorenz PA, Mikels J: **The aging brain: implications of enduring plasticity for behavioral and cultural change**. In *Lifespan Development and the brain: The perspective of biocultural co-constructivism*. Edited by Baltes P, Reuter-Lorenz P, Roesler F. Cambridge, UK: Cambridge University Press (in press).

38. Peinemann A, Lehner C, Conrad B, Siebner HR: **Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex**. *Neurosci Lett* 2001, **313**:33-36.

39. •• Park DC, Polk TA, Park R, Minear M, Savage A, Smith MR: **Aging reduces neural specialization in ventral visual cortex**. *Proc Natl Acad Sci USA* 2004, **101**:13091-13095.

This study is noteworthy for its use of localizer scans to identify material-specific regions of interest for each individual subject. This method enabled the researchers subsequently to assess the material specificity of each region of interest for each age group, which revealed less specificity (referred to by this group as dedifferentiation) for the older than for the younger adults.

40. Schmolesky MT, Wang YC, Pu ML, Leventhal AG: **Degradation of stimulus selectivity of visual cortical cells in senescent rhesus monkeys**. *Nat Neurosci* 2000, **3**:384-390.

41. Godde B, Berkefeld T, David-Jurgens M, Dinse HR: **Age-related changes in primary somatosensory cortex of rats: evidence for parallel degenerative and plastic-adaptive processes**. *Neurosci Biobehav Rev* 2002, **26**:743-752.

42. Li SC, Lindenberger U, Hommel B, Aschersleben G, Prinz W, Baltes PB: **Transformations in the couplings among intellectual abilities and constituent cognitive processes across the life span**. *Psychol Sci* 2004, **15**:155-163.

43. Milham MP, Erickson KI, Banich MT, Kramer AF, Webb A, Wszalek T, Cohen NJ: **Attentional control in the aging brain: insights from an fMRI study of the Stroop task**. *Brain Cogn* 2002, **49**:277-296.

44. • Dickerson BC, Salat DH, Bates JF, Atiya M, Killiany RJ, Greve DN, Dale AM, Stern CE, Blacker D, Albert MS *et al.*: **Medial temporal lobe function and structure in mild cognitive impairment**. *Ann Neurol* 2004, **56**:27-35.

In this fMRI study of older individuals with mild cognitive impairment, greater medial temporal lobe activation was associated with better performance on a memory test that immediately followed the scan. However, it was also associated with greater clinical impairment at baseline and a greater probability of longitudinal decline.

45. Bruce-Keller AJ, Umberger G, McFall R, Mattson MP: **Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults**. *Annals of Neurology* 1999, **45**:8-15.

46. • Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S: **Cardiovascular fitness, cortical plasticity, and aging**. *Proc Natl Acad Sci USA* 2004, **101**:3316-3321.

Two separate experiments demonstrate the positive cognitive effects of fitness, and the neural correlates associated with these performance benefits in seniors. One study is cross-sectional, comparing high and low fit older adults, and the other is longitudinal, comparing a 6-month aerobic versus stretching and toning intervention program. In both studies higher cardiovascular fitness is associated with better performance on measures of cognitive control, and greater activity in task-relevant brain regions.

47. McDowell K, Kerick SE, Santa Maria DL, Hatfield BD: **Aging, physical activity, and cognitive processing: an examination of P300**. *Neurobiol Aging* 2003, **24**:597-606.

48. • Bialystok E, Craik FIM, Klein R, Viswanathan M: **Bilingualism, aging, and cognitive control: evidence from the Simon task**. *Psychol Aging* 2004, **19**:290-303.

Compared with monolinguals, bilingual adults demonstrate less conflict from irrelevant information (e.g. more cognitive control). These effects were evident in younger, middle-age and older adults, with the older groups showing the largest bilingual advantage. These results suggest that negotiating two languages on a daily basis increases cognitive control, and that a lifetime of practice can mitigate age-related declines.

49. Jennings JM, Jacoby LL: **Improving memory in older adults: training recollection**. *Neuropsychol Rehabil* 2003, **13**:417-440.

50. • Loewenstein DA, Acevedo A, Czaja SJ, Duara R: **Cognitive rehabilitation of mildly impaired Alzheimer disease patients on cholinesterase inhibitors**. *Am J Geriatr Psychiatry* 2004, **12**:395-402.

This study used training principles based on the cognitive psychology literature (e.g. temporally spaced retrieval practice) with mild AD patients. Patients showed substantial memory improvements when tested immediately following the training program that were largely maintained at a 3-month follow up.

51. Lustig C, Buckner RL: **Preserved neural correlates of priming in old age and dementia**. *Neuron* 2004, **42**:865-875.

52. Lockenhoff CE, Carstensen LL: **Socioemotional selectivity theory, aging, and health: the increasingly delicate balance between regulating emotions and making tough choices**. *J Pers* 2004, **72**:1395-1424.

53. Gunning-Dixon FM, Gur RC, Perkins AC, Schroeder L, Turner T, Turetsky BI, Chan RM, Loughead JW, Alsop DC, Maldjian J *et al.*: **Age-related differences in brain activation during emotional face processing**. *Neurobiol Aging* 2003, **24**:285-295.

54. • Mather M, Canli T, English T, Whitfield S, Wais P, Ochsner K, Gabrieli JDE, Carstensen LL: **Amygdala responses to emotionally valenced stimuli in older and younger adults**. *Psychol Sci* 2004, **15**:259-263.

This study is one of the first to examine the neural bases of age-related changes in emotional information processing. Greater amygdala activation to positive than to negative pictures in older but not younger adults is a potential a neural correlate of a putative positive emotional bias in later life.

55. Kensinger EA, Anderson A, Growdon JH, Corkin S: **Effects of Alzheimer disease on memory for verbal emotional information**. *Neuropsychologia* 2004, **42**:791-800.

56. Rusinek H, De Santi S, Frid D, Tsui WH, Tarshish CY, Convit A, de Leon MJ: **Regional brain atrophy rate predicts future cognitive decline: 6-year longitudinal MR imaging study of normal aging**. *Radiology* 2003, **229**:691-696.

57. Reiman EM, Chen KW, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J: **Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia**. *Proc Natl Acad Sci USA* 2004, **101**:284-289.

58. •• Klunk WE, Engler H, Nordberg A, Wang YM, Blomqvist G, Holt DP, Bergstrom M, Savitcheva I, Huang GF, Estrada S *et al.*: **Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B**. *Ann Neurol* 2004, **55**:306-319.

This was a landmark study, demonstrating the feasibility of human *in vivo* imaging of amyloid plaques, the hallmark of AD. Although still under development, this technique holds significant promise for early detection, discriminant diagnosis and treatment monitoring.

59. Greicius MD, Srivastava G, Reiss AL, Menon V: **Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI**. *Proc Natl Acad Sci USA* 2004, **101**:4637-4642.

60. •• Lustig C, Snyder AZ, Bhakta M, O'Brien KC, McAvoy M, Raichle ME, Morris JC, Buckner RL: **Functional deactivations: change with age and dementia of the Alzheimer type**. *Proc Natl Acad Sci USA* 2003, **100**:14504-14509.

Older adults and AD patients showed a reduction or even reversal of task-related deactivations (task $<$ fixation baseline) typically shown by young adults. This represents an age difference in activation somewhat different from the under- and over- activation patterns discussed in the text. The functional significance is unclear but it is important to note that these regions overlap heavily with those showing reduced metabolism in aging and AD, and might be related to memory or emotional processing.

61. Aizenstein HJ, Clark KA, Butters MA, Cochran J, Stenger VA, Meltzer CC, Reynolds CF, Carter CS: **The BOLD hemodynamic response in healthy aging**. *J Cogn Neurosci* 2004, **16**:786-793.

62. D'Esposito M, Deouell LY, Gazzaley A: **Alterations in the bold FMRI signal with ageing and disease: a challenge for neuroimaging**. *Nat Rev Neurosci* 2003, **4**:863-872.

63. Small SA: **Measuring correlates of brain metabolism with high-resolution MRI: a promising approach for diagnosing Alzheimer disease and mapping its course**. *Alzheimer Dis Assoc Disord* 2003, **17**:154-161.

64. •• Small SA, Chawla MK, Buonocore M, Rapp PR, Barnes CA: **Imaging correlates of brain function in monkeys and rats isolates a hippocampal subregion differentially vulnerable to aging**. *Proc Natl Acad Sci USA* 2004, **101**:7181-7186.

The authors performed high-resolution functional imaging of hippocampal subregions combined with a molecular analysis of gene expression related to memory function. The study is important both for its findings (the dentate gyrus is vulnerable to normal aging, in contrast to pyramidal cells targeted by AD) and as a demonstration of integrating positron emission tomography or MRI imaging techniques with other measures of brain structure and function.