Published in final edited form as:
Neuropsychol Rev. 2009 December ; 19(4): 411–414. doi:10.1007/s11065-009-9122-1.

Decline and Compensation in Aging Brain and Cognition: Promises and Constraints

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Abstract

Age-related cognitive declines are common and inevitable, but life trajectories of brain and cognitive functions are variable and plastic. To identify the mechanisms of decline, the prospects for improvement, and the constraints on the remedial approaches, the contributors of this special issuer examine several diverse areas of cognitive and brain aging: from structural and metabolic brain aging to genetics, and from age-sensitive cognitive domains to those that resist aging. In spite of such thematic diversity, several common threads are clear. To achieve better compensation for age-related changes in cognition, we need to understand their brain substrates, telling cognitively relevant from epiphenomenal. We also need to understand the sources of profound individual variability in aging trajectories, and to learn to tailor interventions to specific individual profiles of decline.

Keywords

Aging; Longitudinal; Training; MRI; Strategies; Health; Cognition

Aging, even under the optimal circumstances, brings decline and deterioration of multiple organs and systems (Biondo-Simões et al. 2006; Epstein 1996; Weinert and Timiras 2003; Wolf-Maier et al. 2003; Ito and Barnes 2009), and the brain is just one instantiation of that general rule (Raz and Kennedy 2009). Nonetheless, like other organs, the brain is not a passive and static subject of the aging process, but a flexible and responsive system that might literally "fight back" albeit with diminishing success (Gould et al. 1999). Studies of fine structure, gross anatomy, and multiple vascular and metabolic indicators demonstrate brain's propensity to alter its structure and functional organization in response to behavioral, nutritional, and exercise interventions (Pereira et al. 2007; Head et al. 2009; Joseph et al. 2009). Whereas brain's capacity for change in the late years of the adult lifespan is not in doubt, the questions of the direction, extent and implications of those changes remain largely unanswered. The collection of review articles assembled in this special issue aims at addressing at least some of those questions. The reviews cover a wide range of topics pertaining to age-sensitive and age-resistant aspects of brain and cognition, and elucidate the constraints on alleviating the former and strengthening the latter.

In the first article of this series, a comprehensive review of the diffusion-tensor imaging (DTI) literature, Madden and colleagues demonstrate that the brains of older adults differ from those of their younger counterparts in their microstructural integrity. The challenges of identifying just what is successful or optimal aging and what is the expression of age-related disease are coming to a fore with introduction of neuroimaging methods that allow *in vivo* examination of amyloid load in the brains of asymptomatic older adults. As Rodrigue and her colleagues show in their review, ostensibly pathological processes leading to accumulation of amyloid occur in the brains of a sizeable proportion of clinically intact older persons. What drives those changes

and how they affect adult cognitive development is still unknown. That review reminds us that the road between identifying the potential deficit and tracing it to specific behavioral consequences is long.

Age differences in fluid intelligence, speed of processing, executive functions, and episodic memory are well known (Horn 1986) and observed deterioration in those skills is viewed as a harbinger of impending cognitive declines. However, other less complex and less analytically loaded skills may present an important window into the decline and stability of the aging brain. As Moffat concludes in his review of the extant literature on that age differences in spatial navigation, performance on virtual reality (VR) tasks such as water maze evidences substantial age-related differences. According to Moffat, spatial navigation tasks deserve greater attention in cognitive aging research as they allow relatively easy transition between animal models and human experiments, and tap into a vital cognitive function that is lost at relatively early stages of cognitive decline.

Yet not all cognitive skills decline with age, and on some tasks, age differences are minor (priming, Lustig et al) or absent (serial learning, Riekmann and Bäckman). What makes implicit tasks so age-invariant is unclear. One thing we know, when explicit and effortful contaminating factors are controlled, performance improves with practice at all ages. Hence, the appeal of training-based interventions in cognitive aging. Indeed, multiple studies show success in alleviation at least some age-related deficits in cognitive performance. It is unclear what cognitive skills are best candidates for training that can yield the broadest benefits. Following a comprehensive critical review of cognitive training literature in the context of aging (Hertzog et al. 2009), Lustig and her colleagues offer a much needed discussion of the role cognitive neuroscience may play in evaluating and guiding that field of research. Their approach offers a plan for improving the precision of targeting in training studies. The plan boils down to identifying what is wrong with the aging brain first and designing cognitive interventions based on those findings. Not surprisingly, the studies in that area are still quite scarce. The authors of the review, however, identify several core trends. One, described as “reversal of negative plasticity” seems to coalesce with the view that aging exerts its negative influence on the brain mainly in the neural circuits that are marked by high degree of plasticity. According to such “dark side of plasticity” view (Raz 2000), intervention should target cognitive processes that rely on malleable (vulnerable) brain regions. By doing so, the intervention would reverse or slow down the decline at the crux of its dynamic. Paradoxically, such approach calls for targeting brain regions that show the greatest age-related decline. A recent study by Dahlin et al. (2008), analyzed in detail by Lustig and her colleagues, is probably the most promising example of that approach.

Age-related changes in brain and behavior exhibit significant individual variability that is considered a *sine qua non* of later life development (Lindenberger and von Oertzen 2006). However, the sources of variability in the trajectories of aging are unclear. Many genetic variants and interactions among them modify age-sensitive abilities and affect the magnitude of age differences in cognitive performance (Lindenberger et al. 2008). Moreover, genetically dependent risk may be amplified by pathological factors such as elevated blood glucose and blood pressure (Raz et al. 2008, 2009). However, genetic variability is vast, and the unique role of each individual variant is relatively meager. In his expansive review, Payton surveys the promising and disappointing findings of the past decade and offers a sober analysis capped by specific recommendations for future research.

In all their diversity of topics and approaches, the reviews of this collection, exhibit several common threads. First, there is a clear need for longitudinal studies. It is a commonplace that cross-sectional design is a suboptimal way of studying change. However, regression-based estimates of age differences provide at least an idea of age-related change. What they cannot

supply is the estimate of variance in change. Because increase in variability is a hallmark of cognitive aging (Lindenberger and von Oertzen 2006), such an omission is a significant barrier to understanding of cognitive deficits and designing intervention for their alleviation. For example, in reading Moffat's review, one can only wonder why in such an important field of inquiry as spatial navigation there are no longitudinal studies. At the time of this writing, there are no longitudinal studies of white matter integrity (see the review by Madden et al in this issue) and very few investigations of genetic differences in the longitudinal course of cognitive aging (Payton). Longitudinal studies of the aging brain reveal a pattern of changes that differs from the one predicted by cross-sectional studies, and significant variability of change across multiple brain regions is quite clear (e.g., Raz et al. 2005). With the advent of genomic technology, the number of studies that examine the effect of specific genetic variants on age-related differences has grown exponentially. Unfortunately, these studies, frequently lacking sufficient statistical power to discover subtle but important effects, rarely examine interactions among several genes and between genes and environment (Payton, this issue). Moreover, the effects of a polymorphism may vary across the life span and can be modified by life experiences. Thus, the reviewed studies support the need for longitudinal studies of at least middle-aged and older adults with multiple measurement occasions are imperative. As we do not have a clear idea when important cognitive changes occur, inclusion younger adults and expanding the sampled age range over entire life span is desirable.

Second, the extant studies routinely ignore the confounding and modifying effects of age-related health characteristics, such as vascular risk, on age differences in brain and cognition. When those factors are taken into account, as in some spatial navigation studies reviewed by Moffat, they explain a significant proportion of variance that would be otherwise ascribed to "age." As Payton demonstrates in his survey of the literature, evaluation of conjoint effects of age, genetic variation, and vascular risk on cognitive performance only recently entered the rapidly growing stream of genetic association studies. In an effort to design training strategies for typical older adults, genetic and health-related variables are largely ignored in the training literature. This is remarkable because training programs geared specifically to improvement of cardiovascular fitness lead to significant benefits on laboratory-based measures of cognition (Lustig et al, this issue). Notably, the effects on complex cognitive performance exceed the improvements in sensory-motor functions and a high percentage of participants in those training programs persist in maintaining their healthy lifestyle after discontinuation of training (Lustig et al, this issue).

Third, whenever cognitive aging is concerned, all reviews in this special issue, are unanimous in their recognition that older adults do not use the same efficient strategies as their younger counterparts do and as they presumably did themselves before entering the golden years. The strategic deficiency is readily acknowledged in the literature on cognitive performance (Moffat) and training (Lustig et al) but the central questions are rarely asked and to date remain unanswered. Why do perfectly sensible human beings abandon optimal strategies and when does that fateful event occur? Does such a shift stem from inability to support high costs of strategic overhead by dwindling resources? If so, do the declines in specific brain substrates of strategic management have anything to do with those strategy deficits and what would be the most sensitive locus of intervention in alleviating the deficiency? A hint if not an answer is found in spatial navigation literature reviewed by Moffat: older adults seem to eschew the optimal allocentric strategy and do not activate the acknowledged substrate of that strategy, the hippocampus. Moreover, individual variations in hippocampal volume seem to matter only in younger adults. Thus, it is possible that because of declining hippocampal infrastructure, older navigators switch to different, more affordable strategies that rely on extrahippocampal circuitry. As it happens, and there may be a message for training studies in that happening, acquisition of more "affordable" strategies necessitates use of brain regions that are exceptionally vulnerable to aging—the prefrontal cortex and white matter as well as the caudate

nucleus. Moreover, significant age differences in white matter integrity (as reviewed by Madden and his colleagues) might make acquisition and automatization of new strategies particularly difficult. Another disconcerting finding that tempers optimistic expectations from training studies is that although older adults can acquire novel skills, a long-term retention record is not particularly encouraging (Lustig et al., this issue). Thus, what is needed is an intervention approach that will act as a gift that keeps on giving, a training program whose gains can be maintained after its termination without or with only minimal formal booster activity. A high maintenance rate of the fitness programs alumni is an important advantage of that intervention approach.

Recently, two of the contributing authors (Park and Reuter-Lorenz 2009) hypothesized that the aging brain undergoes compensatory changes that either create new supportive structure (scaffolding) or boost the existing one. This is an appealing idea, and one can only hope that it is true. Then, understanding of neurobiology behind the scaffolding may lead to design of better, more targeted intervention that would prolong the active health span. One can hope that examination of genetic, neural, and cognitive constraints on the aging brain and behavior will result in a better understanding of the processes involved in scaffolding and other hypothesized forms of support and self-maintenance exercised by the aging brain. Understanding such mechanisms is a foundation of a greater hope of alleviating and slowing down age-related cognitive declines.

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