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Review

Differential aging of the brain: Patterns, cognitive correlates and modifiers

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Abstract

Deciphering the secret of successful aging depends on understanding the patterns and biological underpinnings of cognitive and behavioral changes throughout adulthood. That task is inseparable from comprehending the workings of the brain, the physical substrate of behavior. In this review, we summarize the extant literature on age-related differences and changes in brain structure, including postmortem and noninvasive magnetic resonance imaging (MRI) studies. Among the latter, we survey the evidence from volumetry, diffusion-tensor imaging, and evaluations of white matter hyperintensities (WMH). Further, we review the attempts to elucidate the mechanisms of age-related structural changes by measuring metabolic markers of aging through magnetic resonance spectroscopy (MRS). We discuss the putative links between the pattern of brain aging and the pattern of cognitive decline and stability. We then present examples of activities and conditions (hypertension, hormone deficiency, aerobic fitness) that may influence the course of normal aging in a positive or negative fashion. Lastly, we speculate on several proposed mechanisms of differential brain aging, including neurotransmitter systems, stress and corticosteroids, microvascular changes, calcium homeostasis, and demyelination.

Keywords: MRI; Brain; Cognitive aging; Longitudinal; Volumetric; White matter; Vascular risk; Hypertension

Contents

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1. Inroduction

> For the gods alone there comes no old age, nay nor even death;
> but all other things are confounded by all-mastering time ... (Sophocles, Oedipus at Colonus, 607).

Aging—a biological companion of time—spares no organ or system, and in due course affects everything, from cell to thought. However, the pace of aging varies among individual organisms, organs and systems, and the very existence of such variability merits some measure of hope. If the positive extreme of healthy aging can be made more prevalent and if its worst and most negative expressions can be delayed if not completely eliminated, the viable and enjoyable segment of the lifespan can be prolonged into the later decades of lifespan. In other words, successful aging (Rowe and Kahn, 1987) enjoyed by relatively few may become the norm. To succeed in promoting such a shift, we ought to understand how successful aging is expressed in the structure, physiology and behavior of the organisms and their systems, among which arguably the brain is one of the (if not *the*) most important. In this review, we summarize the extant literature on age-related differences and changes in the brain as well as on their potential cellular underpinnings. We also discuss the putative links between the pattern of brain aging and the pattern of cognitive decline and stability. Finally, we discuss examples of activities and conditions that may influence the normal aging trajectory in a positive or negative fashion.

2. Postmortem studies

Postmortem (PM) studies of individuals within the adult age span reveal panoply of age-related differences in brain structure. The gross differences include reduced brain weight and volume, ventriculomegaly and sulcal expansion (Kemper, 1994; Skullerud, 1985). Microscopic studies documented myelin pallor (Kemper, 1994), loss of neuronal bodies in the neocortex (Pakkenberg and Gundersen, 1997), the hippocampus (Simić et al., 1997) and the cerebellum (Ellis, 1920; Nairn et al., 1989), loss of myelinated fibers across the subcortical cerebrum (Pakkenberg and Gundersen, 1997; Marner et al., 2003; Meier-Ruge et al., 1992), shrinkage and dysmorphology of neurons (Haug, 1985), accumulation of lipofuscin (Terman and Brunk, 1998), rarefication of cerebral vasculature (Riddle et al., 2003), reduction in synaptic density (Morrison and Hof, 1997), deafferentation (Bertoni-Freddari et al., 2002), loss of dendritic spines (Jacobs et al., 1997), cumulative mitochondrial damage (Brunk and Terman, 2002), reduction in DNA repair ability, and failure to remove neurons with damaged nuclear DNA (Rutten et al., 2003). In nonhuman primates, no significant loss of neuronal bodies was found (Peters et al., 1998) but substantial loss and deformation of the myelin sheath was observed (Peters and Sethares, 2002). Some of the effects of aging on the brain are global and affect the central nervous system as a whole, but in many cases, age-related differences are highly circumscribed and confined to specific regions and laminae (Uylings and de Brabander, 2002). The latter study is illustrative of the main strength of PM investigations: anatomic precision that permits interrogation of the brain at its most detailed level. By default, PM literature is limited to cross-sectional inquiries into the remains of persons whose medical and behavioral history is skimpy and whose concurrent assessment cannot be accomplished. Thus, considerably more global in vivo examinations of the living brain have added significant new information about structural and functional neuroanatomy of living people.

3. Cross-sectional volumetric studies in vivo

3.1. Regional brain volume, density and cortical thickness

In vivo volumetry of the healthy aging brain has been conducted since the advent of magnetic resonance imaging (MRI) almost 20 years ago. Summarizing the results of these two decades or research is a challenging task, for variability among the studies is significant and not easily interpretable. Nonetheless, a general trend that emerges from this literature (for detailed reviews and tabulation of relevant studies see Raz (2000, 2004)) suggests that the prefrontal cortices are more significantly affected than the rest of the neocortical regions (median correlation of volume with age $r = -0.56$), whereas the correlations of temporal volumes with age suggest more moderate declines (median $r = -0.37$), with even smaller differences in parietal ($r = -0.20$), and occipital ($r = -0.19$) cortices (Raz, 2004). In addition, the hippocampal volume shows moderately negative association with age, as do the amygdala, the cerebellum and the neostriatum (median correlations ranging between -0.30 and -0.43). Little age-related differences have been observed in the globus pallidus ($r = -0.20$) and the thalamus ($r = -0.28$), although the reports on the latter are highly discrepant (from Raz (2004) with addition of Walhovd et al. (2005)). The ventral pons consistently appears insensitive to aging (median $r = 0.07$, Raz, 2004).