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General review

Vascular correlates of aging in the brain: Evidence from imaging data

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Abstract

With aging, the brain undergoes a variety of changes with behavioral impacts, including cognitive decline even in healthy aging. In particular, vascular changes in the brain have been shown to be linked to cognition and furthermore influence the widely used neuroimaging measurements that are based on hemodynamics. In this article, we review part of the previous literature on the effects of aging on brain and cognition, and present recent work which helps further our understanding of vascular brain aging.

1. Introduction

Several decades of research have demonstrated that aging affects a multitude of components in the brain. In particular, evidence is accumulating on the relation between brain function and vascular health, including cerebral blood flow (CBF) and cardiopulmonary fitness, in aging. Several brain imaging techniques commonly used in research, such as the magnetic resonance imaging blood oxygenation level dependent signal (BOLD-fMRI), are based on the vascular correlates of neural activity. The interpretation of the data is complicated as they result from combined changes in flow, volume and oxygenation [1]. This makes them very sensitive to the vascular effects of aging in the brain.

In parallel, studies in animals can make use of microscopic invasive direct imaging techniques which can complement and further our understanding of the results obtained in human studies. This article reviews some of the literature on the effects of aging on the brain based on a variety of imaging techniques, both in humans and animals, and presents recent contributions from the author. First, the changes in brain baseline physiology and response to stimuli, mostly from non-invasive human studies, are reviewed. Second, the cognitive aspects of aging are presented along with their relation to vascular physiology and cardiovascular fitness. Then, we focus on the microscopic effects of aging, mainly from animal studies, which might explain the results from humans. The accent is on vascular physiology, and the article concludes with our recent results on baseline vascular physiology in aging. The implications for current and future aging studies are briefly discussed.

2. Age-related changes in cerebrovascular physiology

Aging has been associated with decreased regional baseline Cerebral Metabolic Rate of glucose (CMRglc) or oxygen ($CMRO_2$) measured by PET [2], though this finding has been controversial [3,4]. Regional baseline CBF (CBF_0) was found to decrease with increasing age, though not always in a linear fashion, in studies using MRI [5–9], SPECT [10] and PET [3,11,12]. In [13,14] an age-related decrease in total CBF_0 measured by MR phase-contrast angiography was found. Cortical thinning and ventricular enlargement, resulting in brain atrophy, as well as decreases in cerebral blood volume [11,15] have also been reported. Some researchers [7,16,17] have suggested that at least a part of the age-related decrease in CBF_0 or CMRglc

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is attributable to brain atrophy, and that flow might decrease only in proportion to gray matter volume (in whole brain or in a voxel) with no change in brain tissue perfusion.

3. The hemodynamic response in aging

Upon stimulation of the brain, the activation of neurons and astrocytes creates an energy expenditure which requires the provision of oxygen and glucose in the blood. The consequent increase in the consumption of oxygen and glucose, and in blood flow, locally increases blood volume and blood oxygenation level; this cascade of events is termed "hemodynamic response". Various elements of the hemodynamic response are all targets for so-called functional imaging techniques, which measure neuronal activity via its hemodynamic correlates. The interpretation of such imaging measures is therefore based on fundamental assumptions about the nature of neurovascular coupling, yet still an active research topic to this day. In particular, several findings suggest that the neurovascular coupling may be affected by aging.

As a consequence of either modified vascular reactivity or changes in neural and metabolic response to stimuli or both, measurements from neuroimaging studies show age-related differences in the hemodynamic response to functional activation. It is generally observed that aged brains show less lateralized and less specific regions of activation (reviewed by [18]), with greater response variability and noise [19], and different effect sizes [20] which may or may not be attributed to partial volume effects, due to brain atrophy or biased ROI selection from increased inter-voxel variability [21]. Changes in the temporal dynamics of the response have also been observed, though not consistently [19], for example slowing of the response [22,23] and apparition of a CBF undershoot [5].

Mehagnoul-Schipper et al. [24] measured blood-oxygen level dependent functional magnetic resonance (BOLD-fMRI) and near-infrared spectroscopy (NIRS) simultaneously during a simple motor task in two age groups. They found smaller HbO responses in NIRS and smaller regions of activation in BOLD in elderly compared to young. Studies combining BOLD and arterial spin labeling (ASL) fMRI measurements in elderly have found conflicting results. Ances et al. [5], using calibrated MRI, found reduced BOLD amplitude but unchanged number of activated voxels, % change in CBF and in $CMRO_2$ in response to visual stimulation in the older group. In contrast, Restom et al. [6] found no significant age-related difference in BOLD amplitude despite an increased % CBF response to a memory task, which would be consistent with a larger $CMRO_2$ response in the older group. Recently Mohtasib et al. found a larger BOLD response with an equal CBF response to a Stroop task, interpreted as a decrease in metabolism and neural activity [25]. Whether these discrepancies are due to methodological differences or different tasks and brain regions remains to be elucidated.

4. Aging and cognition

Healthy aging is associated with cognitive losses measured as decreases in performance (typically increases in reaction time) in a variety of cognitive tasks. However, it is still debated whether age-related increases in reaction time are merely a result of general slowing of information processing [26] or if some specific deficits are disproportionately affected in the aging brain [27]. The latter hypothesis posits that the high-order cognitive construct responsible for goal-directed behavior and organization/modulation of basic cognitive functions, termed "executive function" [18,28], is particularly affected by aging. In studies of aging and cognition, executive function has been epitomized by specific processes rooted in the frontal cortex, including inhibition, task-switching, coordination, planning, and working memory [29].

The partisans of this so-called "frontal aging" theory link executive function loss to bio-physiological correlates in the frontal cortex, the control center of executive function. Indeed, some studies (reviewed by [18,27]) have concluded that age-related declines in cerebral blood volume [30], gray matter volume [31] and white matter integrity [32] are greatest in the frontal lobe, and have linked this to deficits in frontal (executive) tasks [33]. The frontal aging hypothesis has nonetheless been questioned and a review of literature concluded that there was only weak evidence that frontal regions are disproportionately affected by aging [34,35].

Amongst tasks used in studies of executive functions, the color-word Stroop task [36] requires successful inhibition of task-irrelevant ("interfering") information. A large body of literature has associated aging with an increase in the interference effect of the incongruent stimuli [37–42], including normative data from a sample of 1856 [43]. However several other studies [44–47] and meta-analyses [48–50] have challenged this view.

Recently neuroimaging studies have allowed a new insight into higher cognitive processing in the elderly [51,52]. The Stroop task has been studied in various neuroimaging experiments, using event-related potentials [37], NIRS [53,54], BOLD-fMRI (reviewed by [55,56]), and recently calibrated-BOLD [57]. In studies utilizing the Stroop task, age-related differences in response to interference were found in various cortical regions including the prefrontal cortex, with older adults recruiting additional regions related to attention [42,45,46] and showing more diffuse and bilateral patterns of activation [41] as well as larger effect sizes [41,42,46,47]. However, all these results must be interpreted with caution, because the age-related physiological differences are possible confounds in neuroimaging studies.

5. Vascular correlates of cognition in aging

Vascular correlates of cognitive impairments and dementias have long been noticed [58,59]. Even in healthy aging, recent studies have highlighted vascular correlates of cognition. In healthy 65–75 year-olds, a relationship was recently established [60] in a randomized intervention linking an increase in local CBF_0 in the prefrontal cortex, despite constant gray matter volume, to improved cognitive performance. Heo et al. [61] found a correlation between memory performance and hippocampal CBF_0 in older adults, also highlighting vascular correlates of cognition in aged adults. However, the results from some other