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Title: Cardiovascular and hemodynamic contribution to brain aging
Issue Date: 2014-04-02
General Introduction
Brain aging: demographic and biological perspectives

With a rapid rise in the number of old and very old individuals, the need for a comprehensive understanding of brain aging is growing\(^1\). Current data indicate that age-related disorders such as dementia and stroke impose a great burden on patients, families and health care systems\(^2\,3\). The term “Brain Aging” denotes a constellation of morphological and neurophysiological alterations in the brain that ultimately leads to impairments in motor, cognitive and social skills\(^4\). A progressive accumulation of damaged molecules and impaired energy metabolism, in the absence or failure of healing mechanisms, has been implicated in the pathogenesis of brain aging\(^4\,5\). Neuronal loss and diminished neuronal activity and connectivity are among the key features in an aging brain\(^6\). While these changes appear in many older individuals, recognition of factors that accelerate the process is crucial. Unique features of the brain like its metabolic demand and circulation might provide us with some clues for better understanding of the mechanisms leading to the accelerated brain aging. Strategies to slow down the process of brain aging might have implications in the treatment of age related disorders of the brain and contribute in better regulation of homeostasis which is a main function of the brain.

The brain: a vascular organ

Although the brain accounts for about 2% of body weight, it consumes about 20% of total body oxygen and 25% of total body glucose. High metabolic demand of the brain necessitates a remarkable fraction of cardiac output as well as a relatively constant level of blood flow\(^7\). Cerebral blood flow is tightly regulated by a harmonized function of the systemic and cerebrovascular circulations\(^8\). The heart provides a driving force for cerebral perfusion, extra-cranial vessels serve as a conduit for blood flow and send regulatory signals to the brain stem and intra-cranial vessels act in concert to maintain adequate cerebral blood flow despite fluctuations in systemic blood pressure\(^9\). In addition, there is a tight coordination between neuronal activity and blood flow within the brain parenchyma, known as functional hyperemia\(^10\). After a long-lasting exposure to cardiovascular risk factors, these regulatory mechanisms may fail to function properly which ultimately results in cerebral hypoperfusion\(^11\). Ultimately, chronic hypoperfusion might lead to neuronal energy crisis and impairs structural and functional integrity of the brain\(^12\).
Cardiovascular and hemodynamic contribution to brain aging: missing links

Different lines of evidence from epidemiological, pathological and neuroimaging studies show that midlife cardiovascular risk factors are associated with impaired brain structure and function in old age\textsuperscript{13,14}. Whether similar risk factors in late life have similar influence on the brain is a matter of debate. For instance, midlife hypertension has a well-established link with cerebrovascular events, cerebral small vessel disease and cognitive impairment\textsuperscript{15}. Nevertheless, it is controversial whether all old and very old subjects benefit from lowering blood pressure for preservation of their brain function\textsuperscript{16}. On one hand systemic hypertension might be seen as a risk factor that promotes brain vascular pathologies and on the other hand in older people who carry a great load of brain vascular pathologies higher blood pressure might be needed to overcome critical threshold for brain perfusion\textsuperscript{17}. Cerebral perfusion is dependent on the normal function of the heart-brain axis\textsuperscript{9}. During last couple of years several reports have shown that heart failure is closely linked with structural and functional features of brain aging\textsuperscript{18}. Patients in advance stages of heart failure suffer from brain hypoperfusion and it has been shown that restoration of cardiac function, for example with cardiac transplantation, improves level of cerebral blood flow and cognition\textsuperscript{19}. Whether older people free of heart failure but with sub-optimal cardiac function are also at a high risk for structural brain changes and cognitive impairment is yet to be determined\textsuperscript{20}. Decline in cognitive performance is one of the key aspects of brain aging\textsuperscript{21}. Cognitive impairment is common in old age and is strongly associated with covert brain vascular pathologies such as white matter hyperintensities, lacunar infarcts and cerebral microbleeds\textsuperscript{22}. In line with this evidence, previous studies reported that about 10% of patients with first-time stroke suffer from pre-existing dementia\textsuperscript{23}. Furthermore, it is frequently reported that subjects with dementia and cognitive impairment have lower cerebral blood flow which may predispose them to develop cerebral infarcts\textsuperscript{24}. Further studies are needed to confirm whether assessment of cognitive performance in old age can be a tool to identify subjects at high risk for developing stroke. The brain acts as a central regulator of homeostasis by coordinating the physiology of extraneural tissues\textsuperscript{4}. Therefore, it is possible that accelerated brain aging has detrimental effects not only on the brain function but also on the whole body and might affect survival of older people. Accordingly, it has been shown that structural and functional brain changes such as white matter hyperintensities, brain atrophy and cognitive impairment associate with shorter survival in old age\textsuperscript{25-27}. However, role of cerebral perfusion, which is closely related to brain aging, in the maintenance of health and survival remained unknown.
Outline of this thesis

In the second chapter of this thesis, association between blood pressure and cognitive decline in a general population of the oldest old people is tested. The aim of chapter three is to answer the question whether the association between higher blood pressure and cerebrovascular events in very old people is dependent on the level of disability. Chapter four presents independent relationship of visit-to-visit blood pressure variability with cognitive impairment and manifestations of cerebral small vessel disease. Chapters five, six and seven are dedicated to the link between cardiac functioning and features of brain aging in two general populations of older people as well as in older subjects at high risk for cardiovascular disease. In a systematic review and meta-analysis (chapter eight), alterations of cerebral hemodynamics in patients with Alzheimers disease and vascular dementia were evaluated. Chapter nine compares the predictive value of cognitive impairment with Framingham stroke risk score in relation to future risk of stroke in the oldest old. Chapter ten expands current knowledge on the role of endothelial cells in regulation of cerebral blood flow. Chapter eleven presents new evidence on the relationship between level of cerebral blood flow and survival in old age. Chapter twelve summarizes key findings of this thesis and discusses them in the context of current knowledge about cardiovascular aspects of brain aging.
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