Imaging blood-brain barrier function in aging

Summary

Neurovascular health is one of the factors that influences whether someone ages successfully and depends, among others, on the integrity of the blood-brain barrier (BBB). BBB disruption can disturb homeostasis in the brain tissue, which is detrimental to neuronal functioning. It may also impair the clearance of the neurotoxic biomolecules, for instance the amyloid-β protein (Aβ), which accumulates in Alzheimer's disease. BBB disruption might be a common trigger for age-related brain pathology and an underlying mechanism of the decline that accompanies aging, even before overt age-related brain pathology emerges. Interest in BBB disruption has increased due to the development of more sensitive in vivo imaging techniques such as dynamic contrast-enhanced magnetic resonance imaging (DCE MRI), which has for instance detected subtle BBB leakage in dementia. In DCE MRI, a contrast agent is intravenously injected during scanning and its biological distribution is imaged over time. In a healthy brain, the contrast agent remains in the blood stream. In brains with an impaired BBB, however, contrast material transfers from blood to brain tissue and the transfer constant then represents the amount of BBB leakage. However, DCE MRI studies looking into BBB disruption and its relation to normal aging and age-related cognitive decline have not been conducted. Therefore, this thesis aimed to investigate whether BBB leakage was significantly associated with older age and decline in cognitive performance in a healthy sample. Participants without major cognitive or neurological impairment were selected from the longitudinal Maastricht Aging Study (MAAS). We conducted neuropsychological assessment and used the MAAS data to calculate decline in cognitive performance over a 12-year period, and we performed dual-time resolution DCE MRI, which was sensitive enough to detect even the subtle leakage values found in normal aging individuals.

In **Chapter 1**, we provide an introduction and first discuss the importance of investigating what factors determine successful aging. We then discuss how neurovascular dysfunction and BBB disruption may contribute to age-related pathology and cognitive decline, by disrupting homeostasis in the brain tissue and triggering pathological processes, and impairing Aβ clearance. Also, we discuss the DCE MRI technique and how this technique has enabled us to measure in vivo even subtle BBB leakage.

Chapter 2 contains our DCE MRI study to investigate whether older age was associated with more BBB disruption, even in cognitively and neurologically healthy

individuals, and whether this association was stronger for brain regions sensitive to age-related impairment. We found a higher BBB leakage rate in the total cerebral white and grey matter for older individuals. Moreover, BBB disruption increases with age especially in those regions known to be most vulnerable to age-related deterioration, namely the brain regions involved in higher-order cognitive functions. Our results provide evidence that BBB breakdown may underlie normal age-related deterioration.

Chapter 3 contains our DCE MRI study to investigate whether larger BBB disruption was paired with stronger normal age-related cognitive decline. We found a significant association between BBB leakage in the white matter and 12-year decline in delayed recall score, which can be considered a measure of memory retrieval. Our results support the notion that white matter BBB disruption may be a contributing mechanism to cognitive aging, seemingly affecting memory retrieval first.

In **Chapter 4**, we discuss our feasibility study aiming to validate the DCE MRI technique by measuring contrast transfer in the circumventricular organs (CVOs). These structures regulate communication between the blood, cerebrospinal fluid (CSF) and brain and do not have a BBB. We indeed found significantly positive transfer constants in the CVOs, higher than in the normal-appearing brain matter and highest for the secretory CVOs. Our results introduce DCE MRI as a possible method to assess CVO permeability characteristics and how pathogens can potentially enter the brain via these structures.

In **Chapter 5**, a review study was conducted attempting to resolve how waste clearance from the brain through BBB transport relates to the recently discovered glymphatic system. The glymphatic system is a clearance mechanism using the microcirculation of the CSF, in which the CSF is exchanged with interstitial fluid to clear solutes from the interstitial space. BBB transport and glymphatic clearance likely serve complementary roles with partially overlapping mechanisms to provide a well-balanced neuronal environment. Properly functioning waste clearance systems protect against the accumulation of toxic waste products such as Aβ, and may delay or even prevent the onset of neurodegenerative disorders such as AD.

In **Chapter 6**, a review study was conducted on the use of contrast-enhancement on MRI to assess blood-CSF barrier (BCSFB) permeability. The BCSFB is involved in the composition of the CSF and thus the maintenance of homeostasis in the central nervous system. While the relation between BBB leakage, aging and neurodegeneration is being extensively studied using contrast-enhanced MRI, the use of this technique to investigate

BCSFB leakage in relation to age-related neurodegeneration has received little attention. Post-contrast gadolinium enhancement in the CSF has been used to indicate BCSFB disruption and new techniques are being developed, for instance imaging sequences highly sensitive to the CSF or the use of other contrast agents than gadolinium compounds.

Finally, in **Chapter 7**, we provide a general discussion on the meaning and implications of our results. We believe they provide evidence that BBB disruption may be an underlying mechanism of normal age-related decline and contributes to cognitive aging. We suggest that BBB disruption may in the future become a target for efforts to promote successful aging, especially those aiming to promote vascular health. However, further research is necessary, for instance to establish causal relations. The current studies demonstrate the suitability of the DCE MRI technique to measure in vivo subtle BBB leakage. We also suggest new study directions and imaging developments, such as methods to measure glymphatic function or BCSFB integrity.