Imaging early brain characteristics of alzheimer's disease

SUMMARY

Disease-modifying treatments acting in the symptomatic phase of the disease may occur too late in the Alzheimer's disease (AD) pathophysiological process, after the occurrence of irreversible brain damage. Guided by recent animal and autopsy studies, we identified specific brain changes that are related to and predict either amyloid-beta (Ab) or tau pathology in the asymptomatic stages of the disease. We aimed to evaluate the corresponding magnetic resonance imaging (MRI) measures of these early brain changes, functional connectivity and locus coeruleus (LC) integrity, by relating them to established AD-related brain changes and cognitive and behavioral symptoms of AD. Early identification of these processes in vivo may enable earlier intervention in the disease process and potentially improve clinical outcomes of clinical trials. Therefore, the aim of this dissertation was to examine imaging measures of these early processes in vivo using MRI and to investigate their potential as markers of AD-related processes.

In **chapter 2**, we investigated whether functional connectivity patterns between large-scale brain networks and Aβ burden are synergistically related to cognition in a longitudinal cohort spanning the disease spectrum from healthy to clinical AD. We found that patterns of inter-network functional connectivity differed depending on the level of Aβ burden and that the directionality of inter-network connectivity predicted memory decline in an Aβ dose-dependent manner. Specifically, in the cognitively healthy group, we found that when inter-network correlations were negative, higher Aβ burden was associated with greater memory decline. However, when inter-network correlations were positive, there was no association between Aβ burden and memory decline. For the mild cognitive impairment group, we found that the dose-dependent association between Aβ and cognitive decline was only present in the group with positive inter-network connectivity. These findings suggest that the direction of functional organization between large-scale networks adds additional information about the rate of Aβ-related cognitive decline in preclinical groups, and may be used to optimize patient selection and reduce the required sample sizes in clinical trials during the presymptomatic phase.

In **chapter 3**, we discovered that the noradrenaline (NA) metabolite 3-Methoxy-4-Hydroxyphenylglycol (MHPG), together with information about Aβ and tau burden, is associated with volume of the hippocampus and cortical thickness in multiple cortical regions. This association was present at preclinical levels of Aβ in the cerebrospinal fluid and involved target sites of LC projections. These

findings imply involvement of the LC-NA system in early AD pathophysiological processes, possibly before clinical amyloidosis, making this system a potential target for pharmaceutical modulation.

In **chapter 4**, we take a closer look at the microstructural correlates of in vivo measures of LC integrity. We show that LC integrity is associated with quantitative anisotropy in tracts originating from the LC, but not with measures of neurite density and arborization within the LC. Specifically, our findings suggest that axonal integrity of projections to the thalamus and cerebellum, rather than changes to the neuropil of LC cells, is associated with in vivo measurements of LC integrity. In accordance with animal research previously suggesting similar patterns in early AD model rats, we conclude that in vivo measures of LC integrity likely reflect early stages of the AD pathophysiological process.

In **chapter 5**, we aimed to make a side-by-side comparison of several approaches to tackle the methodological difficulties that are associated with accurate and consistent delineation of the LC in vivo. We found study-specific template-based approaches for LC delineation to be the most consistent tool for reliable LC delineation. When compared to a manual delineation approach, the template-based approaches showed considerably higher reliability scores across the bilateral LC. However, we recommend caution, as template-based approaches remain vulnerable to registration issues, and further refinement of template creation pipelines and careful manual quality checks on all registrations are to be advised.

In **chapter 6**, we take a closer look at LC integrity and sleep disturbances in the context of AD pathology. The sleep-wake cycle involves the LC-NA system and sleep disturbances are recognized as a risk factor for AD. We find that in vivo MRI markers of LC integrity are associated with the number of self-reported nocturnal awakenings in cognitively healthy older individuals, and that this association is particularly strong in the presence of tau pathology. These findings show an important role for LC integrity in sleep-wake regulation in preclinical AD and suggest that the combined knowledge about nocturnal awakenings and LC integrity may aid in the selection of at-risk individuals for clinical trials targeting AD at an early stage.

Finally, in **chapter 7**, we explore the implications and limitations of our findings, as well as propose directions for future research. Overall, we outline brain changes and clinical symptoms that are associated with the earliest accumulations of Aβ and tau pathology with the aim to facilitate earlier detection of at-risk individuals for clinical trials targeting AD in the preclinical phase.