Imaging early brain characteristics of alzheimer's disease

IMPACT PARAGRAPH

Trials attempting to slow down or reverse Alzheimer's disease (AD) in the clinical phase have so far not been successful, which is potentially due to the interventions being applied too late in the disease process. Our main goal in this dissertation was to identify brain changes that can signal the earliest accumulation of amyloid-beta (Aβ) or tau in vivo and to identify individuals at-risk for AD earlier in the pathophysiological process. With this goal in mind, we examined early brain changes associated with Aβ and tau pathology and related them to functional and structural brain characteristics as well as early clinical symptoms. We also aimed assess the validity and reliability of methods used to measure these early brain changes.

Main findings

In this thesis, we show that brain characteristics of early AD pathophysiology can be studied in vivo, even before clinical amyloidosis. We achieved this by utilizing magnetic resonance imaging (MRI) as a non-invasive method for studying these processes in populations across the adult age span as well as in populations in different disease stages. We show functional, as well as structural MRI markers that may be used as indicators of early brain changes associated with Aβ and tau.

We show that Aβ burden is associated with patterns of functional connectivity patterns between large scale networks, and that the direction of inter-network connectivity adds information about the dose-response relationship between Aβ and longitudinal cognitive decline, already at the preclinical stage. The combined information from the direction of inter-network functionality and Aβ burden can reduce the required sample size in clinical trials by 88% to slow down memory decline by 30%.

Shifting our attention to tau, we investigated one of the earliest accumulation sites of tau pathology, namely the locus coeruleus (LC). The locus coeruleus is the main source of cerebral noradrenaline (NA) and we show that in the context of elevated AD pathology, the NA metabolite MHPG is associated with lower cortical thickness in the cortex and hippocampus, even at subthreshold amyloid levels. These findings imply an important role for the LC-NA system in the early AD pathophysiological process and highlight the downstream neurodegenerative

processes occurring at target sites of the long LC projections. This ties into our findings where we report that reduced MRI-based LC integrity is associated with reduced integrity of LC projections towards the thalamus and cerebellum in a cognitively healthy population. This possibly suggests that the deterioration of LC projections is involved in neurodegenerative processes at LC target sites, though this remains to be confirmed.

We also showed that integrity of the LC is associated with nocturnal awakenings in cognitively healthy individuals, especially in the context of tau pathology. The LC is important for sleep-wake regulation and sleep disturbances are associated with an increased risk of developing AD. Furthermore, previous research has suggested that up to 15% of AD-cases may be prevented by the treatment of sleep-related problems. This means that measures of LC integrity, tau burden and sleep disturbances may facilitate the selection of at-risk participants for AD in clinical trials targeting treatable aspects of sleep at the preclinical stage.

Finally, we investigated different methods for the anatomical delineation of the LC in a population covering the adult lifespan. We compared template-based methods to manual delineation and found that overall, a study-specific template approach produces the most reliable results. We argue that manual delineation of the LC is vulnerable to rater bias and the use of a study-specific template has potential to become a standard approach to LC delineation. Such a standard could reduce discrepancies in findings related to LC integrity due to methodological differences between studies. However, future studies should investigate more alternatives to LC delineation, such as a machine-learning based approach and compare measures of reliability and validity to our findings.

Relevance

Worldwide, people are reaching increasingly older ages as a result of our advancing knowledge and technology in the medical field. As a disease typically associated with older age, the prevalence of AD is also increasing and its impact resonates in the lives of patients, caregivers, and society at large. Meanwhile, to date, there is no effective form of treatment to halt, or reverse the AD process, potentially because most clinical trials target the disease in a late, symptomatic stage. With this dissertation, we hope to provide a small piece of the puzzle that may allow us to detect the earliest processes of AD, with the long-term aim to intervene before the disease process reaches a point of no return.

We provide evidence that functional and structural characteristics of the brain combined with established biomarkers of AD, can be used to obtain accurate selection criteria for clinical trials to intervene at preclinical stages of the disease. Ultimately, this knowledge may facilitate the fine-tuned development of primary prevention interventions. Existing treatments for the reduction of Aβ plaques may be utilized in a sample consisting of cognitively healthy participants with negative inter-network correlations, as per **chapter 2**, to investigate its effects on cognitive decline. Similarly, our findings in **chapters 3**, **4** and **6** may support the development of interventions targeting sleep consolidation and the LC-NA system, while **chapter 5** provides a starting point to homogenize future work aimed at studying the LC-NA system.

Target group

The findings presented in this thesis are initially relevant for researchers studying pathophysiological processes in AD. Researchers examining the temporal cascade of AD may investigate the early brain changes we describe in this thesis to further elucidate the temporal ordering of pathological events in AD. Furthermore, researchers trying to understand the neural correlates of sleep may find that LC integrity is potentially an informative measure for in vivo investigations. There are also companies investigating products such as special pillows and wearables to improve sleep quality. These companies may benefit from the findings in this thesis to refine their products and to better identify individuals who may benefit from these treatments. In addition, our findings have value for researchers investigating intervention strategies in AD. Recent work from the university of Cambridge has suggested that localized changes in LC integrity may be used as a biomarker for the selection of participants for clinical trials in Parkinson's disease and progressive supranuclear palsy, which are diseases that also involve significant deterioration of the LC. We encourage similar investigations towards the value of LC integrity as a biomarker for AD, given our findings relating LC integrity to underlying neurobiological characteristics and early sleep disturbances that may have predictive value for AD.

Additionally, our longitudinal work may be relevant to clinicians who may use the findings from **chapter 2** to improve the prognosis of cognitive decline for patients who present with normal cognition on cognitive tests, but report

subjective memory complaints. The AHEAD and A4 trials are focusing on cognitively normal individuals with high Aβ burden. These trials may benefit from information about inter-network connectivity for the selection of participants. Furthermore, we also report that patients with MCI show Aβ-related cognitive decline in the context of positive inter-network correlations, potentially giving clinicians tools to improve the prognosis in MCI patients. This information may help clinicians, patients and their caregivers make better informed decisions about the difficult choices that need to be made in a situation where the future for the patient is uncertain. However, it is important to note that resting-state functional MRI is a difficult tool that requires complex processing, for which the necessary expertise and equipment may not be readily available. Furthermore, the test-retest reliability of functional connectivity is relatively low and its specificity and sensitivity as a marker for cognitive decline needs to be further investigated. This means that careful interpretation is warranted regarding the use of functional connectivity for individualized prognosis, and the clinician should consider multiple other risk factors for cognitive decline in their prognosis.

Dissemination activities

The findings reported in this thesis have been presented to the scientific community through various forms of dissemination. Local disseminations were performed through poster presentations (annual MheNS research days) as well as oral presentations (MheNS external review committee visitation 2021; local working groups). Furthermore, these findings were presented at international conferences and scientific gatherings in the form of poster presentations (MINC 2018, AAIC 2020) and oral presentations (EURON PhD days 2018). In addition, some results from our work have been presented in layman terms through newsletters and other informal communication to the participants of the STRAIN study, who have provided us with a large portion of the data that made this thesis possible. Finally, **chapter 2** and **6** have been published in *Alzheimer's Research & Therapy* (2018 & 2021, respectively) (2021 2-year impact factor = 8.823) and **chapter 3** has been published in *Neurobiology of Aging* (2021) (2021 2-year impact factor = 5.133).