Affective symptomatology in the prodromal and early stages of dementia

CHAPTER 8

Impact paragraph

Scientific Impact

As mentioned throughout this thesis, dementia is a syndrome characterized by loss of memory, language, problem-solving, and social abilities severe enough to interfere with daily life. It is a heterogeneous syndrome, with individuals being affected differently based on the type of dementia and e.g., those region(s) of the brain affected by pathology. The underlying cause of dementia is still unclear, but certain risk groups, such as patients with mild cognitive impairment (MCI) and subjective cognitive decline (SCD), and associated biological factors, such as age or genetics, are associated with an increased risk of developing dementia. Besides cognitive issues, those suffering from SCD, MCI, and dementia often experience affective symptoms including depressive- and anxiety-like symptomatology.

For decades, the amyloid and tau hypotheses have been investigated and, at this moment, the best method to diagnose Alzheimer's disease (AD) is by measuring the protein concentrations of amyloid beta 1-42 ($A\beta_{1\text{-}42}$), total tau, and phosphorylated tau biomarkers in the cerebrospinal fluid (CSF). Despite lumbar puncture being extremely useful in measuring biomarkers for dementia, its use is accompanied with complications. Thus, an alternative and less invasive diagnostic method is necessary. Currently, blood-based early diagnostic tools for AD have been developed and commercialized by companies such as C_2N Diagnostics and QuantaMatrix. However, these kits mainly measure Aβ and/or Apolipoprotein E, which only represents the tip of the (pathological) iceberg. As shown in this thesis, other mechanisms such as inflammation and metabolic dysregulation are likely to be involved as well and more insight into these mechanisms and the identification of associated signatures may contribute to better diagnostic (and prognostic) tools for disorders like AD.

In recent years, the tryptophan (TRP) metabolic pathway has gained attention because of its involvement in dementia, emotional dysregulation, and systemic inflammation. TRP is an essential amino acid and serves as precursor to e.g., the kynurenine pathway (KP), the serotonin pathway, and the tryptamine pathway. Multiple (pre)clinical studies have shown neuroactive properties of KP-associated metabolites. Additionally, activity of the KP is upregulated in the brain during systemic inflammation, a phenomenon often occurring in dementia and affective disorders. Although many cross-sectional studies have compared

KP metabolite levels in e.g., AD dementia patients and healthy controls, the findings are often different for every study. Therefore, **CHAPTER 2**, for the first time, systematically collected, summarized and re-analyzed all articles published on the relationship between levels of kynurenines in patients with evident cognitive decline and in normal aging, as well as the associations of kynurenines with age or cognition, up to April 21 2021. As such, we presented via meta-analysis, which kynurenine concentrations were lower, higher or showed no difference between patients with AD dementia and neurologically healthy controls in various biomaterials such as CSF, blood, plasma, serum, and CSF and blood combined. Additionally, we have identified various kynurenines to show an association with age or cognition. Lastly, through meta-regression, we have identified factors that influence the concentrations, thus demonstrated the importance of controlling covariates in clinical studies. The findings from this systematic review and meta-analysis could potentially serve as biomarkers for AD and hints at treatment targets to halt neurotoxic or to stimulate neuroprotective contributors.

While protein and metabolite levels may provide valuable insights into e.g., disease phenotypes and associated causal factors, additionally studying associated transcriptional and epigenetic profiles yields an even better understanding of the pathophysiology of disorders like AD. Therefore, **CHAPTER 3** described both a transcriptomic- and DNA (hydroxy)methylomic-profiling, as well as associated gene regulatory network (GRN) and network perturbation analyses on the TRP catabolic pathway making use of middle temporal gyrus (MTG) of AD and control brain tissue. Additionally, these findings were validated in two independent blood-based cohorts. From the approach taken in this chapter, we have demonstrated the scientific importance of applying various -omics approaches as well as using *in silico* models such as GRN and network perturbation analyses to select candidate gene(s) in AD pathology. Preclinical studies have investigated different KP enzyme inhibitors as neurotherapeutics, such as targeting indoleamine 2,3-dioxygenase (IDO), tryptophan 2,3-dioxygeanse (TDO2) kynurenine aminotransferase (KAT), and kynurenine-3-monooxygenase (KMO) enzymes. **CHAPTER 3** has shown dysregulation of several KP genes, including IDO and TDO2, and these findings, in combination with **CHAPTER 2**, could serve as a pillar to validate our current knowledge in KP involvements in cognitive disorders and open to new discoveries into biomarker application and, potentially, drug targets.

The KP associated metabolites and inflammatory dysfunctions are well documented in cognitive and affective disorders. Although dementia represents a syndrome primarily associated with cognitive decline, it is not uncommon for patients to exhibit depressive- and anxiety-like symptoms. However, the relationship between KP and inflammation with cognitive or affective disorder have been addressed independently from each other. As such it remains unclear whether these associations are shared between or specific for one disorder. Therefore, making use of a large cross-section study, **CHAPTERS 4** and **5** respectively investigated the association between affective symptoms and kynurenines or systemic inflammation in patients with or at risk for dementia. Both chapters used various models to adjust for different covariates. In **CHAPTER 4**, we have shown several kynurenines and their ratios to be associated with self-reported depressive symptoms, informant reported anxiety-like symptoms. In a similar manner, **CHAPTER 5** also showed several inflammatory and endothelial markers to be associated with self-reported depressive- and informant-reported anxiety-like symptoms. Moreover, the majority of these markers lost its association once adjusted for lifestyle-related covariates, demonstrating that lifestyle is an important factor to consider when investigating systemic inflammation. The findings in both chapters showed that several identical KP metabolites and inflammation markers showed difference in concentration between patients with dementia or its prodromal stages and were associated with affective symptoms while other markers were involved in one disorder. These findings could be implemented for biomarker purposes for individual cognitive and affective symptoms, but also used as a transdiagnostic tool and, potentially, develop a transdiagnostic treatment.

Societal Impact

Worldwide, 55 million people currently suffer from dementia, with 10 million new cases every year. Moreover, the global societal costs for dementia were estimated to represent a total of 1.3 trillion US dollars in 2019 illustrating the profound socio-economic impact dementia has. In addition, there is currently no treatment for e.g., AD, while the exact cause of this neurodegenerative disorder is still unclear. On top of this, AD remains underdiagnosed, underreported, and the diagnosis is delayed by an average of 2-3 years after onset of the symptoms [1, 2]. Since the pathophysiological changes due to AD may occur many years before symptoms appear, early detection of AD through measuring biomarkers

and monitoring lifestyle interventions such as education, diet, cognitive stimulation, and comorbidities in the prodromal stages of AD would facilitate improved diagnosis, decrease the risk of developing AD, and introduce early treatment options. Furthermore, preventing or treating affective symptoms in the early stage is an important intervention to prevent further deterioration since it is common for patients with dementia or its prodromal stages to have depressive- and anxiety-like symptoms. While this thesis provides valuable insights into new potential biomarkers in this respect, it is important to note that the findings in this thesis requires further validation before being able to have a direct impact on society. Nevertheless, the work described in this thesis adds to the foundation that will improve early diagnostics and treatment for dementia in the near future.

Reference

1. 2022 Alzheimer's disease facts and figures. Alzheimer's & Dementia. 2022;18(4):700-89.
2. Sabbagh MN, Lue LF, Fayard D, Shi J. Increasing Precision of Clinical Diagnosis of Alzheimer's Disease Using a Combined Algorithm Incorporating Clinical and Novel Biomarker Data. Neurol Ther. 2017;6(Suppl 1):83-95.