Classification and early detection of dementia and cognitive decline with magnetic resonance imaging

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Chapter 1

General introduction

1.1 Introduction

1.1.1 Background

Dementia is a devastating disease that millions of people suffer from. In 2018, 50 million people were suffering from dementia, and this is estimated to increase to 82 million in 2030, and 152 million in 2050 (World Alzheimer Report, 2018). About two-thirds of people with dementia have Alzheimer's Disease (AD), the remainder suffers from vascular dementia, Lewy body dementia, fronto-temporal dementia (FTD) or other less common types of dementia. All variants suffer from irreversible brain cell losses (World Alzheimer report, 2018). Despite many attempts, currently, there is no effective treatment for AD. Two types of drugs are being prescribed, but they only aim to reduce some of the symptoms, and they only work for some of the people. Between 2002 and 2012, only one new treatment for AD was approved for clinical use, which corresponds to a success rate of only 0.4% (Cummings et al., 2014). Possibly, the AD patients that participate in treatment trails are already too far in the disease development for possible treatments to be effective. Reliable early diagnosis of dementia is therefore of paramount importance for finding a cure to prevent or slow down the disease.

It is not yet fully understood what causes AD exactly, but there is substantial evidence that the proteins amyloid β (A_β) and tau are causally related to neurodegeneration in AD patients (Scheltens et al., 2016). A_β is the main component of amyloid plaques, that are found in the brains of AD patients (Hardy and Allsop, 1991; Karran et al., 2011). The other most pronounced hallmark of

AD are neurofibrillary tangles, which are formations of tau inside neurons that are thought to cause neural death (Mudher and Lovestone, 2002). The original amyloid hypothesis postulates a linear causal relation between extracellular amyloid β (A_β) deposits and neural death (Hardy and Allsop, 1991). However, while a strong relationship with the proposed neurodegenerative pathologies exists, much of the variance in cognitive decline remains unexplained, which suggests a multitude of unidentified mechanisms that contribute to dementia (Boyle et al., 2013). Also, many therapeutics that reduce A_β aggregation or production failed as an effective treatment for AD (Karran et al., 2011).

1.1.2 Biomarkers based on group differences

Several biomarkers are being used for diagnosis of AD, mainly focusing on the detection of A_β or by measuring neuronal damage, which is closely associated with tau (Jack et al., 2010). Levels of A_β and tau can be detected in the cerebral spinal fluid (CSF). A_β is a sensitive biomarker for AD, while an AD-like profile of tau and A_β was detected in mild cognitive impairment subjects who later converted to AD (Shaw et al., 2009). Furthermore, neuronal damage can be inferred from measuring metabolism with fluorodeoxyglucose PET (FDG-PET). AD is characterized by a specific pattern of reduced metabolism in the parietotemporal areas, posterior cingulate cortex, and medial temporal lobe (Mosconi et al., 2010). More recently, PET tracers have been developed for A_β, such as the most widely used Pittsburgh Compound-B (PIB), which can be used to determine the location of A_β depositions in the brain. This technique is especially useful for distinguishing AD from other types of dementia (Rowe et al., 2007; Mosconi et al., 2010).

A non-invasive alternative for PET is magnetic resonance imaging (MRI). Arterial spin labeling can provide similar information to FDG-PET, but is less expensive and is easily obtained in the same session as other MRI measures (Wolk and Detre, 2012). Structural MRI (sMRI) can be used to reliably obtain volumetric measurements, which correlate to neuronal numbers (Bobinski et al., 2000). The rate of brain atrophy measured longitudinally with sMRI correlates well to cognitive decline in patients (Fox et al., 1999). It has been hypothesized that resting-state functional MRI (rs-fMRI) might be suitable to detect subtle changes in functional connectivity between brain regions in an earlier, preclinical, phase (Sheline and Raichle, 2013; Jack et al., 2013). Diffusion MRI (dMRI) provides a way to study alterations in the white matter

and has been used to detect alterations in AD and mild cognitive impairment (Douaud et al., 2011). Additionally, dMRI can be used to study structural connectivity between brain regions (Behrens et al., 2007).

1.1.3 Machine Learning Classification

The drawback of studies that focus on group differences is that they are often not suited for individual predictions. If an average group difference for some measure exists, but there is considerable overlap between groups, then the measure will not perform well for individual classification. However, if the sample size is sufficiently large, there may be a highly significant group difference (Arbabshirani et al., 2017). Contrarily, even when groups do not differ on average for some measure, a multivariate combination of measures may still reliably separate groups and make individual predictions. Furthermore, when applied to a new dataset, predictions about the unseen data can be made, which opens up major opportunities for accurate, automated, differential diagnosis.

While MRI research on AD and dementia has traditionally focused on group differences, more recently attention has shifted towards individual classification (Rathore et al., 2017; Arbabshirani et al., 2017). Specifically, machine learning techniques have been applied to MRI data that are aimed to detect multivariate patterns that are specific to a disease.

A large number of studies evaluate classification of Alzheimer's disease using public databases such as Alzheimer's Disease Neuroimaging Initiative (ADNI). In an extensive study, Samper-González et al. (2018) evaluated different classification methods based on T1 MRI and PET on a number of open databases including ADNI. They found that PET outperformed MRI, and that out of commonly used classification methods, linear support vector machines and regularized logistic regression performed similarly, and both outperformed random forest. Furthermore, various choices in preprocessing, such as the use of atlasses versus voxel-wise, or the size of smoothing kernels, had minimal effect on classification performance.

In addition to using only structural MRI or PET for AD classification, multiple modalities can be combined. By using a combination of structural MRI, PET, levels of A_β in the cerebral spinal fluid, and genotype, classification can be improved over using a single modality (Young et al., 2013). Additionally, by identifying subtypes within the heterogeneous group of AD patients, disease progression can be predicted more accurately (Lorenzi et al., 2019).

In order to study how well computer aided classification generalizes to unseen data the CADDementia challenge was organized. The goal of the challenge was for independent teams to provide AD and mild cognitive impairment classification algorithms based on structural MRI, which were subsequently evaluated with data that the organizers held back. The best performing algorithms used voxel-based morphometry, or a combinations of multiple measures derived from structural MRI (Bron et al., 2015).

1.2 Aims and outline of this thesis

From previous research we know that combining data sources, and multiple representations of the data can improve classification performance. In this thesis we aim to extend upon this knowledge by using various types of MRI data and combining MRI modalities and representations of these modalities.

In Part I of this thesis we explore different approaches to classify patients with AD and controls on an individual basis using machine learning with MRI scans. In chapter 2 we combine measures from multiple MRI modalities. In chapter 3 we dive deeper into multiple approaches to analyze diffusion MRI data to explore which diffusion MRI measures are most suitable for AD classification.

Early detection of dementia is an important goal that could help develop treatments. Therefore we explore how our methods perform in cases of early pre-symptomatic dementia in Part II. In chapter 4 we explore a sample of symptomatic and pre-symptomatic hereditary cerebral amyloid angiopathy mutation carriers. These mutation carriers are almost certain to develop a form of dementia similar to cerebral amyloid angiopathy. We compare these mutation carriers to normal controls in a presymptomatic and symptomatic phase. In chapter 5 we perform the prediction of cognitive test scores on a dataset of elderly who are at risk for future cognitive decline. We use baseline multimodal MRI to predict cognitive decline after a follow-up period of four years.