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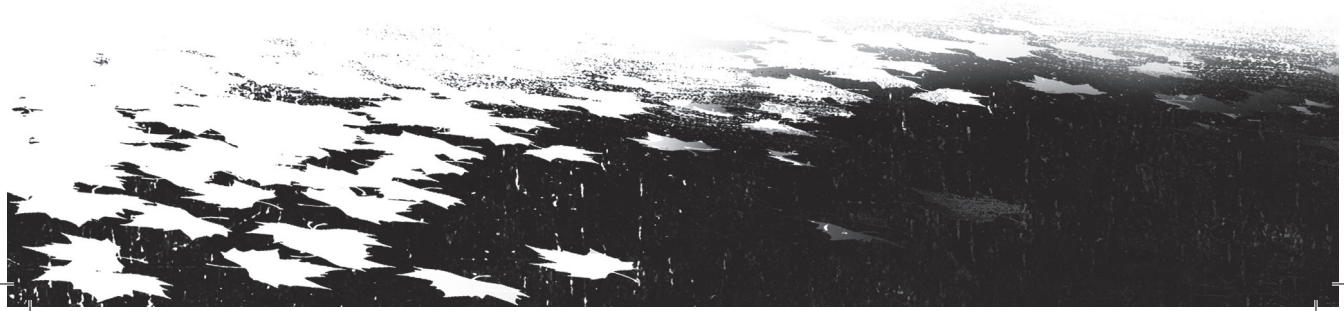
General introduction



INTRODUCTION

Biomarkers in Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease that causes dementia, followed by dementia with Lewy Bodies (DLB) and frontotemporal dementia (FTD).[1-5] Mild cognitive impairment (MCI) is a syndrome diagnosis, defined by the presence of an objective memory deficit in the absence of dementia.[6] Patients with MCI have an increased risk of developing dementia, particularly AD.[7] On structural MRI, AD is characterized by medial temporal and parietal cortical atrophy.[8] Recently proposed dynamic biomarker models for AD illustrate that the manifestation of cortical atrophy on structural MRI occurs in a late stage of AD, when signs of clinical dementia are already present (Figure 1).[9-11]

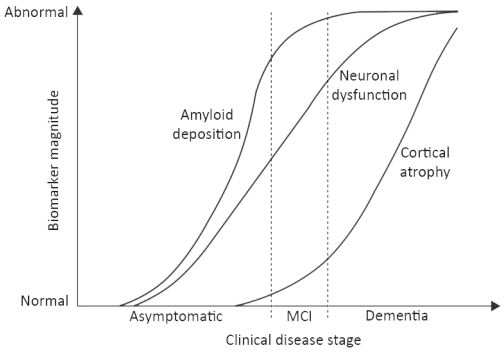


Figure 1. Hypothetical model of imaging biomarkers in Alzheimer's disease.[9-11]

Earliest pathological signs of AD, in the form of amyloid-$\beta_{1\text{-}42}$ (Aβ) plaque deposition, can be detected up to decades before clinical symptoms occur.[12] Molecular markers, such as abnormally reduced cerebrospinal fluid (CSF) Aβ and Aβ-binding positron emission tomography (PET) tracer uptake, can be used to detect these earliest AD changes. Disadvantage of Aβ as a marker for AD is that the amount of plaque deposition does not correspond with the clinical course of the disease, and that it reaches a plateau-like stage in an early phase of the disease.[13] This makes Aβ less suitable as a measure for disease severity.

Functional markers can be used to detect neuronal dysfunction prior to the stage of cortical atrophy.[14] Functional changes are also present in an early stage of the disease, but differ from Aβ plaque deposition in that they continue to gradually change as the

disease progresses.[10, 15] Functional markers, such as glucose metabolism and cerebral blood flow (CBF), are therefore more suitable to monitor disease progression. Currently, ^{18}F-fluorodeoxyglucose (FDG) PET and ^{99m}Tc-hexamethylpropylene amine oxime (HMPAO) single-photon emission computed tomography (SPECT) are the standard clinical imaging tools to assess functional changes in terms of hypometabolism and hypoperfusion in (prodromal) AD. As such, they form part of the diagnostic algorithm in the workup of memory clinic patients. Disadvantages of these techniques are their high costs and relatively high patient burden because of a long acquisition time and/or intravenous radioactive tracer injection. These disadvantages have stimulated the search for noninvasive MRI-based alternatives.

Functional and perfusion MRI

Blood oxygen level-dependent (BOLD) functional MRI (fMRI) and arterial spin-labeling (ASL) MRI are two examples of noninvasive MRI-based techniques that provide functional measures to study neuronal dysfunction in early stage AD. The suggestion that these measures may serve as early disease markers made them methods-of-choice to study AD-related functional changes in this thesis. A further explanation of both techniques is given below.

Blood oxygen level-dependent functional MRI

Spontaneous neuronal activity causes local changes in the blood oxyhemoglobin to deoxyhemoglobin ratio, resulting in what is referred to as the BOLD signal.[16, 17] Spatially distinct brain regions with co-varying resting state fMRI signals are considered to be functionally connected (Figure 2). Where task-based BOLD fMRI answers questions about local functional changes in response to specific external stimuli, resting state BOLD fMRI is a useful tool to study the brain's global functional organization, and to examine alterations in functional organization caused by neurological and psychiatric diseases.[18, 19] The growing use of resting state fMRI in brain function studies has stimulated the development of different analysis techniques. Seed-based analysis[20-22] and independent component analysis[23-25] are examples of nowadays commonly applied methods to study functional connectivity - between specific pre-defined brain regions and within independently functioning brain sub-networks, respectively - and improvements of these techniques are ongoing. Graph analytic methods, known from the field of clinical neurophysiology, have more recently been introduced in fMRI studies,[26, 27] and contribute by investigating global organization of the whole-brain network (i.e., the functional connectome), as opposed to focusing on specific brain regions.

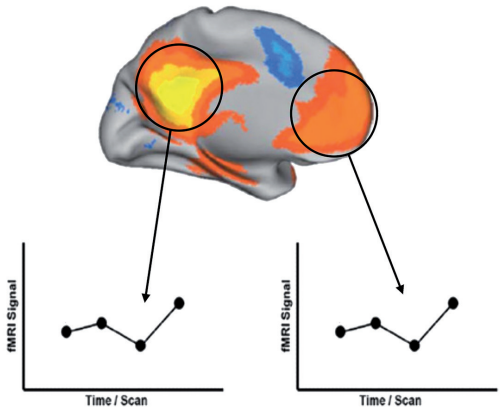


Figure 2. Spatially distinct brain regions with co-varying resting state BOLD fMRI signal timecourses are considered to be functionally connected.

Arterial spin-labeling perfusion MRI

ASL perfusion MRI is an alternative functional imaging technique. It uses magnetically labeled arterial blood that flows through the carotid and vertebral arteries as an endogenous contrast medium, in order to measure CBF (Figure 3). Several different ASL schemes have been developed over the past decades, aiming to improve scan quality (signal-to-noise ratio; SNR) and shorten acquisition time. The pseudo-continuous variant of ASL uses a multitude of millisecond-long pulses in order to achieve a high labeling efficiency and effective compensation of magnetization transfer effects.[28] The

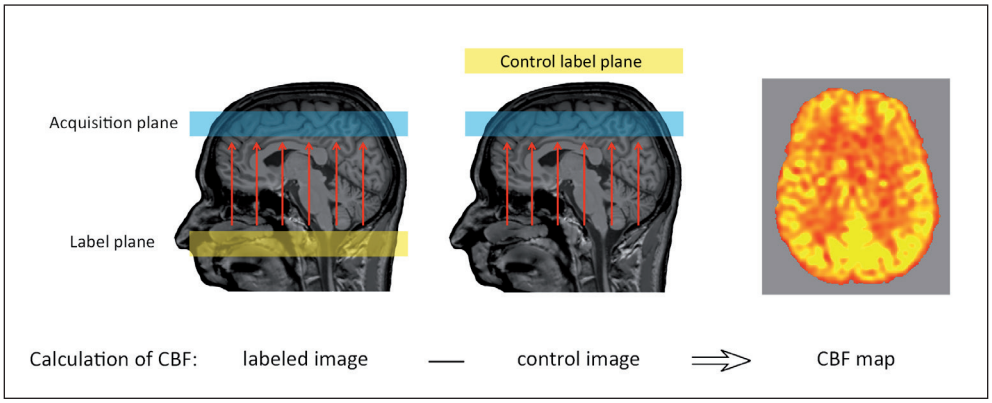


Figure 3. Schematic overview of the realisation of ASL perfusion images.
Arterial blood flowing through the carotid and vertebral arteries is magnetically labeled in order to serve as an endogenous contrast medium. Images are acquired after labeling and in control conditions (i.e., no labeling of carotid and vertebral arterial blood). Subsequently, CBF is calculated by subtraction of the signal in the labeled and control images.

quantification of ASL-measured CBF in units of mL/100g/min makes it possible to compare CBF across sites and scanning sessions.

ASL is considered a potential alternative for the visualization of cerebral (and neuronal) function in the workup of dementia patients.[29-31] The fact that ASL may not only contribute to a better understanding of AD, but also play a future part in the diagnostic workup of dementia makes this tool particularly interesting in relation to the investigation of AD.

AIMS OF THE THESIS

The general objective of this thesis was to further explore functional connectivity and cerebral perfusion in patients with (early) AD and other neurodegenerative diseases, by making use of newly developed imaging techniques and analysis methods. With this objective, we aimed to obtain a better understanding of the diseases under study, and to attribute to the possible future role of functional and perfusion MRI in the workup of dementia patients.

THESIS OUTLINE

Chapter 2 describes the studies we performed on resting state BOLD fMRI data, making use of newly developed analysis methods. In **chapter 2.1** we studied functional connectivity within ICA-based resting state networks (RSNs) in patients with AD and MCI, by using the "dual-regression" analysis technique.[32] Moreover, we compared baseline functional connectivity of converting and non-converting MCI patients. In **chapter 2.2** we used the "dual-regression" method to examine functional connectivity within RSNs of early-onset and late-onset AD patients. In **chapter 2.3** we used a graph analytic method called Eigenvector Centrality Mapping (ECM) to examine whole-brain functional connectivity in AD, and its relation to cognition and AD biomarkers in cerebrospinal fluid (CSF).

Chapter 3 consists of studies exploring cerebral perfusion with pseudo-continuous ASL. First, we examined total and regional CBF of patients with AD, MCI and subjective complaints in **chapter 3.1**. Then, in **chapter 3.2**, we compared the perfusion patterns of patients with AD, FTD and DLB. **Chapter 3.3** follows chapter 3.1 with a further exploration of CBF in the predementia stages of AD. In **chapter 3.4** we investigated the relationship of CBF with measures for neurodegeneration and small vessel disease.

Chapter 4 summarizes the main findings, followed by a discussion of the results and recommendations for future research.

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