Visualizing the Shrinking Brain: Longitudinal MR Studies in the Spectrum of Cognitive Decline

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Chapter 1

Introduction

Purpose and motivation

Alzheimer's disease (AD) is a growing socio-economic problem, due to an in increase in population and the longer average lifespan. The changes associated with this neurodegenerative disease start years before the clinical diagnosis can be made.[1] The pathological hallmark of AD is an accumulation of amyloid plaques and neurofibrillary tangles, which are associated with neuronal loss.[2] It is believed that neurons have very limited regenerative abilities. As a result it is imperative to prevent neuronal loss as early in the disease as possible, and future treatments should be given in the earliest possible stages.[3] So far no single diagnostic modality or biomarker is available with high enough sensitivity and specificity to establish an accurate diagnosis in the individual patient. Consequently there is a need for biomarkers to detect the disease at an earlier stage in the individual.

Magnetic Resonance Imaging (MRI) offers the possibility to visualize structural changes associated with neurodegenerative disease in *vivo*. The use of neuroimaging in clinical practice has shifted from excluding other causes of cognitive complaints (e.g. hemorrhage, tumors, hydrocephalus), to early detection (e.g. AD versus normal ageing) and nosological diagnosis (e.g. AD versus FTLD).[4] Nevertheless, the diagnostic accuracy leaves room for improvement, partly because cross-sectional analysis has the disadvantage of confounding influence of inter-individual variability in brain structure and ageing. Furthermore, there is need for prognostic factors that can accurately track disease progression. Longitudinal imaging might not have these restrictions, and can possibly be used to determine brain tissue loss (atrophy) in the individual in *vivo*.[5]

This thesis aspires to expand insights in the use of longitudinal whole-brain and regional MR imaging in the early detection, diagnosis and prognosis of AD. Furthermore, it explores the association of these atrophy markers with clinical, genetic and cerebrospinal fluid (CSF) biomarkers, aiming to develop a better understanding of the course of the disease, eventually improving the effectiveness of patient management.

General introduction

Alzheimer's disease and MCI

Alzheimer's disease is characterised by an insidious onset of progressive cognitive decline. The term mild cognitive impairment (MCI) has been introduced to describe patients who do not fulfil clinical criteria for dementia, but who do have objective evidence of memory deficits.[1] MCI patients are at an increased risk of developing AD, with about 10-15% progressing to AD per year. In these subjects MCI may be considered to be a transitional phase for AD.[3] However, not all patients diagnosed with MCI progress to AD: some develop another type of dementia, while others improve or remain clinically stable.[6] The course of AD itself is also variable: not all patients progress at the same rate and the factors that influence or predict progression are not well known.[7] Neuropathological studies suggest that Alzheimer's pathology spreads throughout the brain in a relatively predictable fashion, starting well before clinical onset of the disease. Accumulation has pathologically been observed to start at the medial temporal lobe and to gradually affect other parts of the cerebral cortex in later stages.[2] However, by definition, neuropathological studies are post hoc and cross-sectional in design, and clearly cannot track disease progression in the individual. Hence, clinical, biologic, and imaging markers are needed to detect the earliest stage of underlying pathology in *vivo*. Most commonly, diagnosis requires impaired cognition, and progression of the disease is measured by change in cognition over time.[8] Nonetheless, clinical and neuropsychological measures may lack sensitivity to change, are subject to day-to-day variability, and are influenced by behavioral fluctuations, intercurrent illness, and medication.

Magnetic Resonance Imaging

Structural MR imaging allows atrophy to be assessed in *vivo*. Neuroimaging markers provide an alternative and objective assessment of diagnosis and progression.[4] Many studies in AD focussed on the medial temporal lobe, known to be affected early in the disease, but tissue loss is not limited to this region. Neocortical loss and enlargement of the ventricles have also been reported at an early stage.[7,9,10]

Most of the previous MR imaging studies were cross-sectional by design, which has the disadvantage of confounding influence of inter-individual variability. It has been suggested that longitudinal atrophy rates are more sensitive to the earliest disease changes than brain volume measurement at a single time point.[7,11] Therefore, longitudinal MR imaging might provide more sensitive and specific diagnostic measures, and be able to track the brain changes over time.

Computational Neuroanatomy

A standard feature of modern MRI scanners is the acquisition of three-dimensional images (3D volume). Faster computers and parallel computer networks allow for the implementation of algorithms developed for powerful analysis and comprehensive comparison of these 3D volumes. Using the following unbiased neurocomputational analyses, we calculated whole-brain as well as regional atrophy measures:

VBM (voxel-based morphometry), is an unbiased method to analyze 3D volumes at the voxel level.[10] It consists of a registration step to spatially align the 3D images -often this is an affine linear registration (12 degrees of freedom)-, followed by a segmentation of the image to identify the grey matter, white matter and CSF. Then, a statistical analysis is performed, where a voxel-wise comparison between or within groups can be made. Outcome measures are statistical parametric maps, and when quantified within standard normalized brain regions, whole-brain and regional volumes.

SIENAX (Structural Image Evaluation, using Normalisation, of Atrophy; Cross-sectional)[12] is a cross-sectional measure of whole-brain volume, used to quantify global brain atrophy. It automatically segments brain from non-brain tissue; subsequently it estimates brain volume and applies a normalization factor to correct for head size. The normalization factor is acquired by registering the patients scan to the Montreal neurological institute 152 (MNI152) standard brain image using the skull to normalize spatially. The corrected brain volume is expressed as Normalized Brain Volume (NBV), from now on referred to as brain volume (ml).

SIENA (Structural Image Evaluation, using Normalisation, of Atrophy)[12] is a method to measure the loss of brain volume over time. SIENA aligns the baseline and follow-up scan using the skull as scale and skew constraint. Next,

the displacement of the brain edge for each point is estimated. Finally, all edge points are taken together to calculate the overall Percentage Brain Volume Change (PBVC) expressed as a single value, further referred to as whole-brain atrophy rate (%/year).

Fluid is a non-linear registration algorithm, which is based on the principles of fluid dynamics (Navier-Stokes equations), developed at the Dementia Research Centre (University College London).[13] Before non-linear registration can take place, a number of preprocessing steps have to be executed to spatially align the baseline and follow-up 3D volumes of a single individual, and normalize image intensity by eliminating scanner related bias-fields artifacts. Subsequently the fluid algorithm performs an intensive non-linear registration based on voxel intensity. The voxelwise volumetric contraction or expansion, derived from the transformations imposed by the Fluid registration, is used as the outcome measure. By quantifying the total change in a specific region, whole-brain and regional atrophy rates are obtained.

Biomarkers in cerebrospinal fluid

CSF biomarkers are increasingly used to detect and characterise brain changes associated with AD in *vivo*. In CSF, decreased beta-amyloid 1–42 ($Aß_{1-42}$) levels, and increased tau, and tau phosphorylated at threonine-181 ($P\text{-}tau_{181}$) levels are thought to reflect the presence of AD pathology.[14] These CSF biomarkers have been shown to differentiate patients with AD from control subjects with reasonable accuracy.[15] Moreover, these changes can be detected in patients with MCI who will progress to AD.[16] Although both MRI and CSF biomarkers have been shown to be valuable markers of disease in MCI and AD, the relation between these markers has been less extensively studied. In cross-sectional studies, CSF biomarkers have been reported not to be related to MRI measures of atrophy, suggesting that these markers reflect different aspects of Alzheimer type neuropathology.[17] However, longitudinal studies are needed, to clarify the relationship between these markers. The few studies that have reported CSF biomarkers and MRI measures in a longitudinal design, have used relatively small sample sizes, and have shown conflicting results in terms of whether or not these markers are associated.[17,18] The relation between CSF biomarkers and MRI derived atrophy measures remains unclear.

Cohort

The studies described in this thesis are based on a cohort of 147 patients who underwent repeated MRI. Between 2004 and 2006, patients visiting the memory outpatient clinic of the Alzheimercentre (VU University Medical Center) were approached to participate. At baseline patients underwent a standardized clinical assessment including medical history, physical and neurological examination, psychometric evaluation, and brain MR examination. Diagnoses were established during a multidisciplinary consensus meeting according to the Petersen criteria for MCI,[19] the NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) for probable AD,[8] and according to published consensus criteria for frontal-temporal lobar degeneration (FTLD),[20] vascular dementia (VaD),[21] and dementia with Lewy bodies (DLB).[22] When all clinical investigations were normal (i.e. MCI criteria were not fulfilled), patients were considered to have subjective complaints. Additionally, we included normal controls without cognitive complaints, recruited from caregivers, who were willing to undergo the same diagnostic procedure as patients attending our memory clinic. At follow-up patients were re-examined, and underwent a second MR examination. If they were willing, patients also underwent a second lumbar puncture. Non-demented subjects (patients with MCI and patients with subjective complaints) visited the memory clinic annually; diagnostic classification was re-evaluated at follow-up. Patients were included only if they had two MR examinations of adequate quality, performed on the same scanner using the same imaging protocol. MR examinations were reviewed by a radiologist to exclude non-neurodegenerative pathology that could explain the cognitive impairment. NINDS-AIREN criteria were used to exclude patients with vascular dementia.[21]

Aims of this thesis

The objective of this thesis was to examine in *vivo* atrophy patterns using serial MRI, calculated with advanced neurocomputational analyses. The application of longitudinal whole-brain and regional atrophy rates in research and clinical practice was investigated in a cohort that covers the spectrum of cognitive decline, from normal ageing to AD. Firstly this thesis focuses on accurate and early detection of AD, by prospectively determining atrophy rates in MCI and

AD, and its association with cognitive decline. Secondly, it tries to identify the prognostic value of atrophy rates within MCI and AD by exploring if whole-brain and regional atrophy rates are suitable as markers for disease progression, as well as investigate the risk of progression to dementia in initially non-demented patients. Finally, the association of the MRI derived atrophy rates with clinical parameters, genetic factors, and CSF biomarkers was studied.

Outline per chapter

In chapter 2 we used VBM to find out whether structural differences on MR imaging offer insight in the development of clinical AD in patients with amnestic MCI at 3-year follow-up.

In chapter 3, we prospectively determined baseline brain volume and whole-brain atrophy rate in the aforementioned cohort, using SIENAX and SIENA respectively. We assessed its association with cognitive decline, as well as investigated the risk of progression to dementia in initially non-demented patients, based on baseline brain volume and whole-brain atrophy rate.

In chapter 4, we used Fluid, a robust and accurate non-linear registration algorithm, to calculate regional atrophy rates. Our objective was to track the regional lobar atrophy pattern in the progression from normal aging to Alzheimer's disease.

In chapter 5, we looked into the added value of hippocampal atrophy rates over whole brain atrophy measurements. We examined the applicability of different types of measurements of regional hippocampal and whole-brain atrophy by comparing their ability to distinguish between controls, MCI and AD, and their ability to predict progression to AD within controls and MCI. Finally, we compared cross-sectional and longitudinal measurement of the hippocampus and whole brain.

In chapter 6, we evaluated which baseline clinical and MRI measures influence rate of progression within AD, using whole-brain atrophy rates measured from serial MR imaging, derived with SIENA as outcome measure.

In chapter 7 we investigated associations between cross-sectional and longitudinal CSF biomarker levels and MRI-based whole-brain atrophy rate in MCI and AD.

Finally, in chapter 8, results are summarized and discussed.

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