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

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Chapter 8

General Discussion, Summary & Future perspectives

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The general objective of this thesis was 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 explored the association of these atrophy markers with clinical, genetic and cerebrospinal fluid biomarkers, aiming to develop a better understanding of the course of the disease. In this thesis, we showed that the clinical role of longitudinal neuroimaging extends beyond diagnosis, and can play an important part in prognosis as well. In the present chapter, the main findings of the thesis are summarized, followed by a discussion of the disease pathology, methodology, and implications of these findings for research and clinical practice. Finally, recommendations for future research are given.

Summary of findings

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. By studying the converting versus the non-converting MCI population, we found atrophy beyond the medial temporal lobe to be characteristic of patients with MCI prone to progress to dementia. Atrophy of several gray matter structures, including the left lateral temporal lobe and left parietal cortex independently predicted conversion.

In chapter 3, we prospectively determined baseline brain volume and whole-brain atrophy rate, using SIENAX and SIENA respectively. We assessed their association with cognitive decline, and also investigated the risk of progression to dementia in initially non-demented patients, based on whole-brain volume at baseline and whole-brain atrophy rate. We showed that whole-brain atrophy rate discriminates between controls, patients with subjective complaints, MCI and AD, better than cross-sectional brain volume does. Furthermore, whole-brain atrophy rate was strongly associated with the rate of cognitive decline. In non-demented participants, a high whole-brain atrophy rate (fast volume loss) was associated with an increased risk of progression to dementia. The

association with cognitive decline indicates that rate of atrophy could be valuable as a measure for tracking disease progression. Moreover, whole-brain atrophy rates might be used to predict conversion to dementia.

In chapter 4, we used Fluid, a robust and accurate non-linear registration algorithm, to estimate regional atrophy rates. Our objective was to track the regional lobar atrophy pattern in the progression from normal aging to AD. We observed that atrophy spreads through the brain with development of AD: MCI is marked by temporal lobe atrophy. In AD, the medial temporal lobe atrophy rate remains comparable to MCI, whilst the other parts of the temporal lobe demonstrate an even higher atrophy rate. Moreover, atrophy also accelerates in parietal, frontal, insular and occipital lobes when patients reach the AD stage. Finally, we showed that in non-demented elderly, the rate of medial temporal lobe atrophy was most predictive of progression to AD, demonstrating the importance of this region in the early detection of AD.

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 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. We demonstrated that hippocampal measures, especially hippocampal atrophy rate, best discriminate MCI from controls. Whole brain atrophy rate discriminates AD from MCI. Hippocampal atrophy is the strongest predictor of progression to AD. We conclude that hippocampal atrophy rates have added value of over whole brain volume measurements in the early diagnosis of AD.

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. Our results suggest it is possible to characterise a subgroup of AD patients that are at risk of faster loss of brain volume. Patients with more generalized atrophy, rather than focal hippocampal atrophy, with an onset of disease before the age of 65, and who are APOE $\varepsilon 4$ negative, seem to be at risk of faster whole-brain

atrophy rates than the more commonly seen AD patients, who are generally older, APOE ε4 positive and mainly have pronounced hippocampal atrophy. This implies there are different phenotypes within AD.

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. We found that across groups, baseline $A\beta_{1-42}$ and tau were modestly associated with whole-brain atrophy rate. Adjusted for age, sex and diagnosis, we found no association between $A\beta_{1-42}$ or tau, and whole-brain atrophy rate. By contrast, high CSF levels of P-tau_{181} showed a mild association with a lower whole-brain atrophy rate in AD but not in controls or MCI patients. Finally, whole-brain atrophy rate was associated with change in MMSE, but change in CSF biomarker levels was not. We concluded that whole-brain atrophy rate and CSF levels of $A\beta_{1-42}$, tau or P-tau_{181} provide complementary information in patients with MCI and AD.

General discussion & Conclusions

Disease pathology

Neuropathological studies report that AD pathology spreads through the brain in a predictable fashion.[1] For neurofibrillary tangles the accumulation can be described in six stages: Stages I-II show alterations in the transentorhinal regions, stages III-IV are known as the limbic stage, while stage V-VI are marked by isocortical destruction. The accumulation of amyloid deposits can be divided in three stages: Stage A shows initial deposits in the basal portions of the isocortex, stage B shows amyloid in virtually all isocortical association areas, but the hippocampal formation is only mildly involved, while in stage C end-stage deposits can be observed throughout the isocortex. However, by definition, autopsy studies are post hoc and cross-sectional in design. Even though they are essential in uncovering the biological basis of clinical AD, they clearly cannot provide clinical–histological correlations in the individual during life.

This thesis shows that atrophy rates accelerate throughout the brain with the progression of cognitive decline, as observed in *vivo* using serial MRI. In controls, only a mild acceleration of medial temporal lobe atrophy is seen, in

concurrence with previous studies,[2-4] which is thought to be associated with normal ageing.[5] In MCI, the temporal lobe shows the greatest atrophy rate, but atrophy already extends beyond the medial temporal lobe, as atrophy rates in the remaining part of the temporal lobe are equally high. Atrophy rates in the medial temporal lobe were no higher in the AD patients than in the MCI patients, implying that rate of neurodegeneration in this region may already be at a maximum prior to the clinical diagnosis of AD. The progression to AD is characterised by increasing atrophy rates in the rest of the temporal lobe, and atrophy also accelerating in parietal, frontal and occipital lobes. This entails that neocortical involvement is an important characteristic of progression from MCI to clinical AD.[6,7] We conclude that the pattern of regional atrophy rates changes with the development of neurodegenerative disease. In addition, we show that the regional atrophy pattern closely follows the pattern of accumulating neurofibrillary tangles as described by Braak.[1]

Methodology

Cohort

We strived to create a cohort that included the whole cognitive spectrum. We included a relatively large number of subjects from one center where all subjects have been carefully defined using a standardized diagnostic battery. As a consequence, subjects are characterized in a uniform manner and the diagnosis was determined by a multidisciplinary team. Besides patients with AD and MCI, we included both patients with subjective complaints and volunteers without complaints. At baseline, we found no differences between healthy volunteers and patients with subjective complaints, and we therefore pooled these subjects in one control group. However, patients presenting at a memory clinic with subjective complaints are known to have a higher risk of developing AD.[8-10] In fact, during follow-up three patients converted to AD and one to FTLD. One could argue that these patients should have been excluded, as they did not remain control-like throughout the study. However, we feel that, since they fulfilled initial inclusion criteria, excluding these patients would have biased the results. Nevertheless, their influence on the overall results is limited and exclusion of these patients had no major effects.

Computational analyses

In this thesis we analyzed 3D volumes acquired using MR imaging with three different neurocomputational analyses. Firstly, we used VBM,[11] which uses a moderate non-linear registration, and is driven by both voxel-intensity and anatomical probability maps. Statistical analysis entails a voxel-wise comparison between or within groups, and if desired, differences in volume can be quantified within defined standardized brain regions. An advantage of VBM is the unbiased way in which atrophy throughout the brain is assessed throughout the brain. The main disadvantage of VBM as applied in this thesis is the cross-sectional nature of the analysis, which suffers from inter-individual variety in brain structure and ageing. Nowadays, the application of longitudinal VBM has become available. Secondly, we acquired whole brain volumes and atrophy rates with SIENA(X),[12] a volumetric analysis that uses a linear registration, which can be performed cross-sectional as well as longitudinal. An advantage is the low calculation time. A disadvantage is the fact that only whole-brain atrophy measures were available. Nevertheless, it can be used to distinguish patients on a group level. Thirdly, we used Fluid,[13] a robust non-linear registration algorithm driven by voxel-intensity, developed at the Dementia Research Centre (University College London). A disadvantage of this technique is the long calculation time. We have overcome this problem by using a powerful network of parallel computers for analyses (Virtual Laboratory for e-Science; www.vl-e.nl). Clear advantages of this technique are the robust nature and the detailed information generated about regional atrophy in the individual, which makes it possible to accurately track the pattern of atrophy throughout the course of the disease.[9,10]

Implications for Clinical practice and Research

At present the diagnosis of AD is made according to clinical criteria, in these guidelines neuroimaging is mainly used to exclude non-neurodegenerative pathology.[14] Currently in clinical practice cross-sectional neuroimaging -amongst clinical, neuropsychological and other biomarkers- is used more often to establish a diagnosis, by gathering positive evidence to support the diagnosis.[10,15] Nevertheless, diagnostic accuracy leaves room for improvement, as there is substantial overlap between groups.[16] In this thesis we use two approaches to improve the diagnostic accuracy. Firstly, it is known that

cross-sectional imaging suffers the confounding influence of inter-individual variability in brain structure and ageing. Longitudinal imaging offers a means to overcome this problem. Secondly, more sensitive methods can be used to analyze the data. We demonstrate that longitudinal MRI measures are more sensitive than cross-sectional volumes, as atrophy rates were able to separate AD from MCI, and MCI from controls. The clinical relevance of longitudinal atrophy rates is further demonstrated by the association with cognition and cognitive decline. Moreover, since individuals with a higher whole-brain and regional atrophy rate had greater risks of progression to dementia, repeat MR imaging can be helpful in the diagnostic work-up of patients suspected of having dementia. Within subjects without dementia, regional hippocampal measures were the strongest predictors of progression to AD, but whole brain and regional atrophy rates had an additional independent predictive effect. In this thesis we confirm the early involvement of the medial temporal lobe, as observed in neuropathological and clinical studies,[17,18] and its clinical importance in the detection of incipient AD.[19] Furthermore, we show that neocortical involvement is an important characteristic of progression from MCI to clinical AD.[6,19]

Moreover, there is need for prognostic factors, and biomarkers that can accurately track disease progression. We show that longitudinal MRI might be used in clinical practice to give an accurate prognosis, and can track disease progression, as it is strongly associated with cognitive decline. In research, longitudinal neuroimaging can play an important role in more effective patient selection for trials. In addition, atrophy rates can provide valuable objective information about disease progression. The effect of newly developed therapies can be monitored, according to changes in the brain tissue loss. This is particularly important considering that disease-modifying therapies, early detection and monitoring of progression are main research goals in AD.

Fast progressors: a specific subgroup

Clinically, different phenotypes of AD have been described.[20] We show that a younger age, absence of APOE $\varepsilon 4$ and a low MMSE at baseline were associated with higher whole-brain atrophy rate, as measured using serial MR imaging. Furthermore, a relatively spared baseline hippocampus predicted faster decline for AD patients with a smaller baseline brain volume and a lower MMSE score.

Moreover, a smaller brain volume was associated with a higher rate of whole brain atrophy in patients with a relatively younger age. It has been suggested that AD patients with an onset before the age of 65, who are APOE ε 4 negative often have a distinct clinical profile, with prominent parietal dysfunction.21 It is tempting to think that these patients have early biparietal and more generalized atrophy, rather than focal medial temporal lobe atrophy. Our data suggest that these patients may be at risk of faster global disease progression than the more commonly seen sporadic AD patients, who are older, APOE ε 4 positive and have pronounced hippocampal atrophy.

Association of MRI en CSF biomarkers

Furthermore, in this thesis the association between MRI and CSF biomarkers was studied. Notwithstanding modest correlations of baseline CSF biomarker levels and whole-brain atrophy rate across groups, hardly any association within diagnostic groups was found. Whole-brain atrophy rate was associated with clinical progression, but longitudinal changes in the CSF biomarker levels were not. Thus, MRI and CSF biomarkers appear to reflect different aspects of AD: whole-brain atrophy rate appears to be linked to the clinical progression of the disease, whereas CSF biomarkers seem to reflect disease state rather than rate of progression.[9] We conclude that for tracking the rate of progression of AD, atrophy rates are more useful than CSF levels of $Aß_{1-42}$, tau, and $P\text{-}tau_{181}$; by contrast these CSF markers can be considered to be disease state markers, which may be more sensitive as diagnostic tools, possibly in earlier stages of AD.

Future recommendations

Important goals in future neurodegenerative research are to improve the methods to detect incipient AD, to monitor disease progression, and unravel underlying neuropathological changes. To achieve this, firstly larger cohorts are needed to increase power and sensitivity. This can be achieved by either large multicentre and / or population studies. Uniform data should be collected, including at least clinical and neuropsychological data, and serial MR imaging. Preferably, CSF biomarkers and PET imaging could be obtained as well. Secondly, patients could undergo multiple consecutive MR examinations to gain more insight in the development of brain tissue loss in the individual

in *vivo*. MR examinations ought to be collected with constant intervals, using identical protocols, throughout the disease. Protocols should at least contain 3D volumes. This protocol could be expanded with Diffusion Weighted Imaging, which gives information about the white matter tracts, functional MRI, which can be used to measure functional connectivity of brain networks, and ASL (arterial spin labeling), a non-invasive MRI technique for the quantification of cerebral perfusion. Thirdly, analysis methods could be optimized to detect pathology as accurately as possible. Non-linear registration seems to perform best; data should be analyzed regionally, as it is able to more accurately distinguish patients. Furthermore, this adds to the understanding of the pattern of atrophy throughout the disease. Depending on the goal research should focus on the medial temporal lobe and/or key neocortical regions. Fourthly, for the detection of early AD research should center on patients with subjective complaints, as patients and their relatives are still the most sensitive in detecting their cognitive decline, especially at the earliest stages. Finally, post-mortem verification should be obtained, as it still is the gold standard, even if it is by definition post-hoc. Perhaps by combining different techniques which can be applied in *vivo*, a new gold standard can be developed.

In conclusion, this thesis expands insights in the use of longitudinal imaging in the early detection of incipient AD, and nosological diagnosis. We showed that the clinical role of neuroimaging extends beyond diagnosis, and can play an important part in prognosis as well. The association of atrophy markers with clinical, genetic and cerebrospinal fluid biomarkers was studied, aiming to develop a better understanding of the course of the disease. In research, longitudinal imaging can help to select patients eligible for specific treatment, and monitor the effect for disease modifying therapy. The combination of neuroimaging markers with other biomarkers will play an important role in future research and clinical practice, in establishing an accurate early diagnosis and prognosis.

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