



Universiteit
Leiden
The Netherlands

In vivo magnetic resonance imaging and spectroscopy of Alzheimer_s disease in transgenic mice

Braakman, N.

Citation

Braakman, N. (2008, December 10). *In vivo magnetic resonance imaging and spectroscopy of Alzheimer_s disease in transgenic mice*. Retrieved from <https://hdl.handle.net/1887/13328>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/13328>

Note: To cite this publication please use the final published version (if applicable).

Summary

Alzheimer's disease is the most frequently occurring neurodegenerative disorder, with currently no effective treatment or definitive ante-mortem diagnostic test. AD is characterized clinically by progressive memory loss that eventually leads to dementia. The incidence of AD increases exponentially with age and may emerge as a major health problem due to the current rapid aging of societies. The neuropathology of AD is characterized by neuronal and synaptic loss, and by the development of two lesions: the extracellular senile plaque, which is composed mostly of the β -amyloid peptide, and the intraneuronal neurofibrillary tangle, which is composed of hyperphosphorylated forms of tau protein. Current standards for assessing the progression of Alzheimer's disease are clinical and neuropsychological measures, however, the post-mortem observation of amyloid plaques and neurofibrillary tangles is still necessary for a definitive diagnosis.

Since no definitive *in vivo* biomarker of Alzheimer's disease is available, this impedes both clinical diagnosis in humans and drug development in transgenic animal models of AD. Structural magnetic resonance imaging is capable of visualizing anatomical changes in the brain, such as amyloid plaque deposition or changes in volume due to atrophy of affected regions. Alternatively, magnetic resonance spectroscopy provides a non-invasive way to investigate *in vivo* neurochemical abnormalities, and hence a link between the biochemical alterations and the pathophysiology of disease. Either of these techniques, individually or in combination, may have the potential to provide an *in vivo* biomarker of AD.

This thesis contains the results of studies employing several different MR approaches to study age-dependent changes in the brain of a transgenic mouse model of Alzheimer's disease. The context and relevance of this work is summarized in **Chapter 1**. Provided in **Chapter 2** is a brief theoretical background of the different MR techniques used in the studies presented in this thesis.

In **Chapter 3** it was demonstrated that amyloid plaques can be detected in AD mouse brain using μ MRI in combination with a T_2 weighted RARE sequence. The age-dependent development of plaque deposition was followed over time by imaging live Tg2576 mice at regular intervals between the age of 12 and 18 months. There was a remarkable degree of correspondence between the $A\beta$ plaque distribution detected by μ MRI and immunohistochemistry. In addition to the visualization of plaques, changes in T_2 relaxation times were followed with age. Following the plaque development in the same animals with

age showed that the plaque-load and plaque size increased markedly, while T_2 relaxation times showed a decreasing trend with age. These results demonstrate that μ MRI may be used to follow the plaque developmental characteristics *in vivo* in the same animals and suggest that monitoring the effect of future therapeutic interventions over time in the same animals will be possible by μ MRI.

In addition to structural changes, AD causes alterations in the neurochemical profile. MR spectroscopy is an ideal method for obtaining neurochemical information non-invasively from a localized region in the brain. In **Chapter 4**, a 2D MRS method (L-COSY) is implemented and optimized on a 9.4T scanner to study the neurochemical profile in mouse brain with the added resolution afforded by the second spectral dimension. Optimization of the sequence was done using a phantom solution containing several known metabolites in physiological concentrations. Subsequently the L-COSY method was used to study the neurochemical composition of mouse brain. Using this method, highly resolved 2D spectra were obtained, for the first time, from localized regions in the mouse brain *in vivo*. The combination of the optimized 2D sequence and high field strength allowed detection of cross-peaks of up to 16 brain metabolites from localized regions of mouse brain *in vivo*.

In **Chapter 5** the 2D L-COSY sequence was used, in addition to conventional localized one-dimensional MRS, to study the neurochemical profile in the brains of AD transgenic mice and non-transgenic controls between the ages of 8 and 22 months. Results from the one-dimensional study revealed an increase in taurine and decreases in N-acetylaspartate and glutamate. A remarkable observation in the 2D MRS study was that, until approximately 20 months of age, glycerophosphocholine was found to increase in transgenic animals compared to controls. At ages above ~20 months GPC levels dropped to values in the same range as observed in controls, which may reflect gross membrane impairment at later stages of AD or down-regulation of the membrane phospholipid turnover. The observed increase in GPC levels correlates well with the increasing plaque-load in the transgenic mice visualized by μ MRI. This confirms that there may be a link between plaque deposition and membrane phospholipid breakdown, as suggested in *ex vivo* and *in vitro* studies by other groups. This study provides the first direct *in vivo* evidence for the increase in GPC in plaque affected areas and suggests that altered GPC may be a valuable marker for early diagnosis and for testing therapeutics in the AD mouse model.

Finally, **Chapter 6** provides a general discussion of this work and future outlook.