



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).

***In vivo* Magnetic Resonance Imaging and
Spectroscopy of Alzheimer's Disease in
Transgenic mice**

Niels Braakman

Niels Braakman

In vivo Magnetic Resonance Imaging and Spectroscopy of Alzheimer's Disease in Transgenic mice
PhD Thesis, Leiden University, 10 December 2008

ISBN: 978-90-9023693-3

© Niels Braakman, except the following chapters:

- Chapter 3 JMRI 2006, 24(3):530-536; 2006 © John Wiley & Sons, Inc. Reprinted with permission of Wiley-Liss, Inc. a subsidiary of John Wiley & Sons, Inc.
- Chapter 4 MRM 2008, 60(2):449-456; 2008 © John Wiley & Sons, Inc. Reprinted with permission of Wiley-Liss, Inc. a subsidiary of John Wiley & Sons, Inc.

Cover photograph courtesy of Wim van Oordt

No part of this thesis may be reproduced in any form without the express written consent of the copyright holders.

In vivo Magnetic Resonance Imaging and Spectroscopy of
Alzheimer's Disease in Transgenic mice

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. P.F. van der Heijden,
volgens besluit van het College voor Promoties
te verdedigen op 10 december 2008
klokke 10.00 uur

door

Niels Braakman

geboren te Curaçao, Nederlandse Antillen
in 1976

Promotiecommissie**Promotor:**

Prof. dr. H.J.M. de Groot

Copromotor:

Dr. A. Alia

Referent:

Prof. dr. K. Nicolay, Technische Universiteit Eindhoven

Overige leden:

Prof. dr. R. Schliebs, Paul Flechsig Institute for Brain Research, Leipzig, Germany

Prof. dr. J. Brouwer

The most exciting phrase to hear in science, the one that heralds new
discoveries, is not 'Eureka!' but 'That's funny...'
- *Isaac Asimov*

Voor Charlotte
Voor mijn ouders

Contents

List of abbreviations	11
1 General introduction	15
1.1 Alzheimer's disease	15
1.2 Alzheimer mouse models	17
1.3 Magnetic resonance techniques in studies of Alzheimer's disease	19
1.4 Thesis scope	27
References	29
2 Theoretical background: MRI and MRS	37
2.1 Magnetic Resonance Imaging	39
2.2 Magnetic Resonance Spectroscopy	43
2.3 Two-dimensional Magnetic Resonance Spectroscopy	46
References	50
3 Longitudinal assessment of Alzheimer's β-amyloid plaque development in transgenic mice monitored by <i>in vivo</i> magnetic resonance microimaging	53
3.1 Abstract	53
3.2 Introduction	53
3.3 Methods	55
3.4 Results	57
3.5 Discussion	62
Acknowledgements	65
References	66

4	High resolution localized two dimensional magnetic resonance spectroscopy in mouse brain <i>in vivo</i>	69
4.1	Abstract	69
4.2	Introduction	69
4.3	Materials & Methods	70
4.4	Results and discussion	73
	Acknowledgements	80
	References	80
5	Correlation between the severity of amyloid-β deposition and altered neurochemical profile in a transgenic mouse model of Alzheimer's disease, observed by μMRI and high resolution two-dimensional MRS	83
5.1	Abstract	83
5.2	Introduction	83
5.3	Materials & methods	85
5.4	Results & Discussion	88
	Acknowledgements	95
	References	96
6	General discussion and future outlook	101
6.1	Visualization of AD hallmarks: amyloid plaques and beyond	101
6.2	2D MRS applications in AD	103
6.3	Potential challenges for the translation to humans	105
	References	106
	Appendix: L-COSY pulse program	109

Summary	113
Samenvatting	115
Curriculum Vitae	119
List of publications	121
Nawoord	123

List of abbreviations

μ MRI	Magnetic Resonance micro-Imaging
1D	One-dimensional
2D	Two-dimensional
3D	Three-dimensional
ACQ	Acquisition
AD	Alzheimer's Disease
Ala	Alanine
APP	Amyloid Precursor Protein
ASL	Arterial Spin Labeling
Asp	Aspartate
A β	Amyloid β
CAA	Congophilic Amyloid Angiopathy
CFC	Contextual Fear Conditioning
Cho	Choline
COSY	Correlation Spectroscopy
cPLA ₂	Calcium-dependent Phospholipase A ₂
CNR	Contrast-to-Noise Ratio
Cr	Creatine
CRAZED	COSY revamped with asymmetric z-GE detection
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DW	Diffusion Weighted
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
FSB	(<i>E,E</i>)-1-fluoro-2,5-bis(3-hydroxycarbonyl-4-hydroxy)styryl-benzene
FSE	Fast Spin Echo
FWHH	Full Width at Half Height
GABA	γ -Aminobutyric acid
GE	Gradient Echo

Glc	Glucose
Gln	Glutamine
Glu	Glutamate
Glx	Glutamine + Glutamate
GPC	Glycerophosphocholine
GPE	Glycerophosphoethanolamine
Gro	Glycerol
GSH	Glutathione
HCar	Homocarnosine
HPLC	High Performance Liquid Chromatography
IR-RARE	Inversion Recovery RARE
Lac	Lactate
L-COSY	Localized Correlation Spectroscopy
MAPT	Microtubule Associated Protein Tau
MCI	Mild Cognitive Impairment
mI	<i>myo</i> -Inositol
MION	Monocrystalline Iron Oxide Nanoparticles
MM	Macromolecule
MMSE	Mini Mental State Examination
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MRM	Magnetic Resonance Microscopy
MRS	Magnetic Resonance Spectroscopy
MSME	Multi-Slice Multi-Echo
MTX	Matrix
NA	Number of Averages
NAA	N-Acetylaspartate
NAAG	N-acetylaspartylglutamate
NEX	Number of Excitations
NFT	Neurofibrillary Tangle
NMDA	N-methyl-D-aspartate
NMR	Nuclear Magnetic Resonance
OR	Object Recognition
OVS	Outer Volume Suppression
PCh	Phosphocholine
PCr	Phospho-creatine

PEA	Phosphoethanolamine
PET	Positron Emission Tomography
PIB	Pittsburgh-B compound
PLA ₂	Phospholipase A ₂
PPI	Pre-Pulse Inhibition
PRESS	Point Resolved Spectroscopy
PS1, PS2	Presenilin 1, Presenilin 2
PUT	Putrescine
PtdCho	Phosphatidyl Choline
QSINE	Squared Sine function
RARE	Rapid Acquisition with Relaxation Enhancement
ROI	Region Of Interest
SE	Spin Echo
sI	<i>scyllo</i> -Inositol
SNR	Signal-to-Noise Ratio
SPECT	Single Photon Emission CT
T	Tesla
T_1	Longitudinal or spin-lattice relaxation time
T_2	Transverse or spin-spin relaxation time
Tau	Taurine
tCr	Total Creatine (Creatine + Phosphocreatine)
TE	Echo Time
Tg	Transgenic
Thr	Threonine
TR	Repetition Time
Tyr	Tyrosine
VAPOR	Variable Pulse power and Optimized Relaxation delays
VOI	Volume Of Interest
WT	Wild-type

