Erasmus MC
University Medical Center Rotterdam

Quantitative imaging biomarkers and imaging genetics in neurodegenerative disease

Wiro Niessen

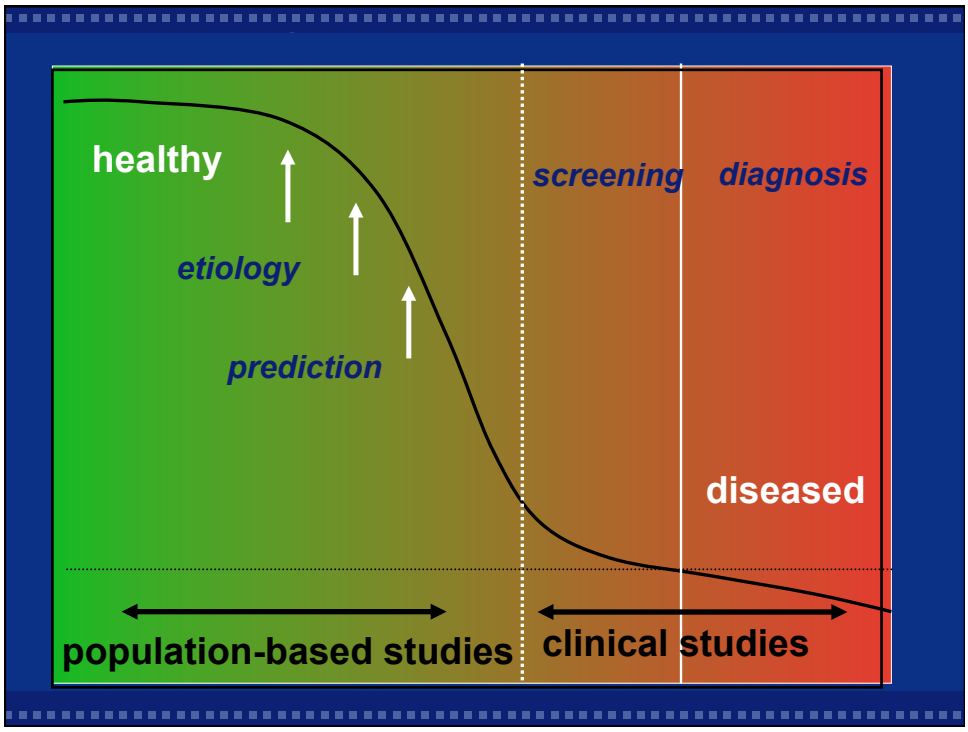
Biomedical Imaging Group Rotterdam
Departments of Radiology & Medical Informatics
Erasmus MC

Imaging Physics
Faculty of Applied Sciences, Delft University of Technology

Quantib

Rotterdam Study

Population Study initiated in 1990

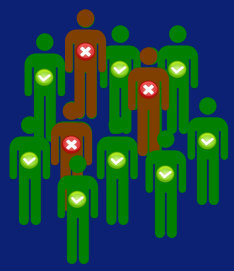


Population-based cohort studies

Erasmus MC

- subjects free of di
- assess potential
- follow prospective
  disease
- assess associatio
  and risk of diseas

ts



determinants

- genetic
- environmental
- life-style
- ….

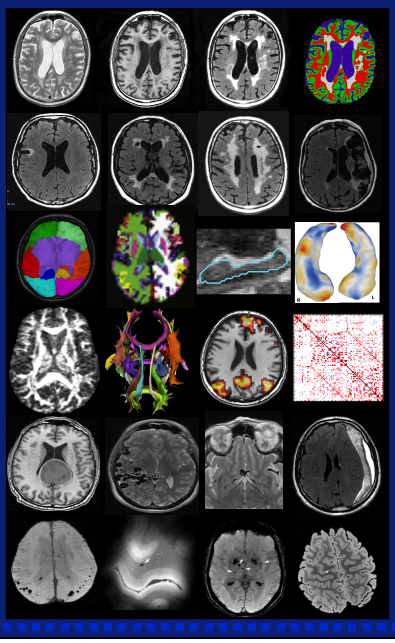
outcomes

- dementia
- cardiovascular
- osteoarthritis
- …..

Rotterdam Scan Study (> 11000 MRI data acquired)

Erasmus MC

- *Tissue quantification*
- *Lesion assessment*
- *Segmentation & shape*
- *Microstructure & function*
- *Incidental brain findings*
- *Cerebral microbleeds*

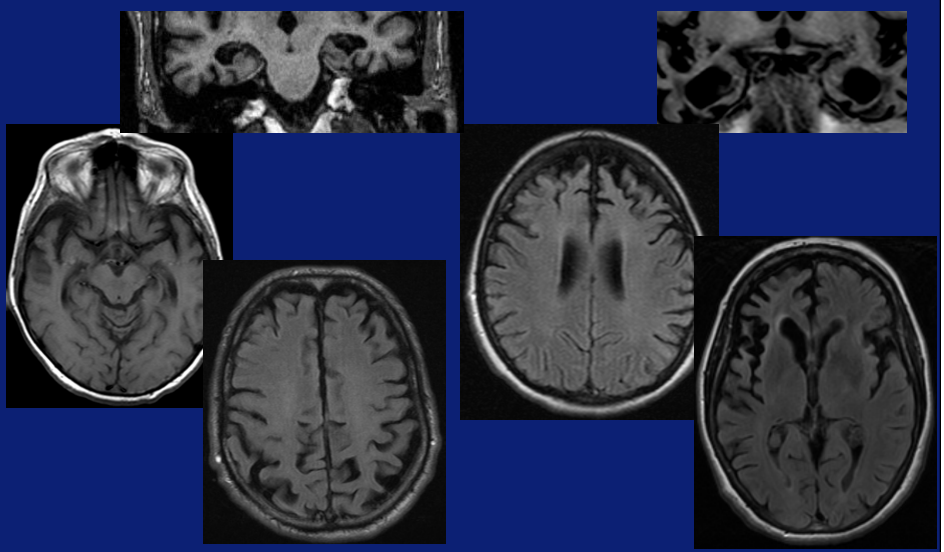


'Textbook' examples

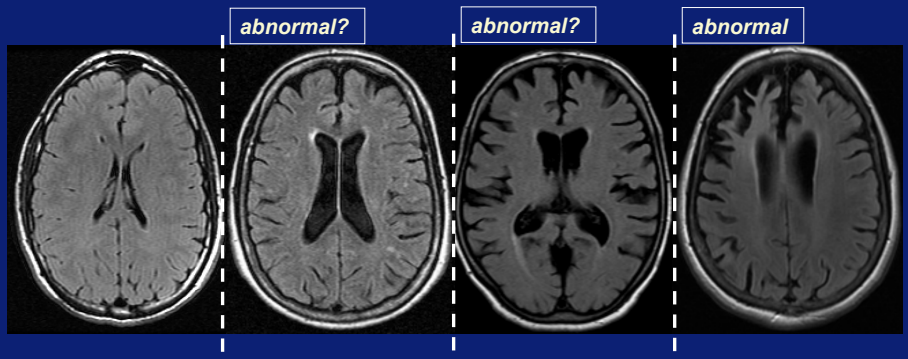
Erasmus MC

Alzheimer disease

Frontotemporal dementia



However… what is normal?



Evidence based medicine

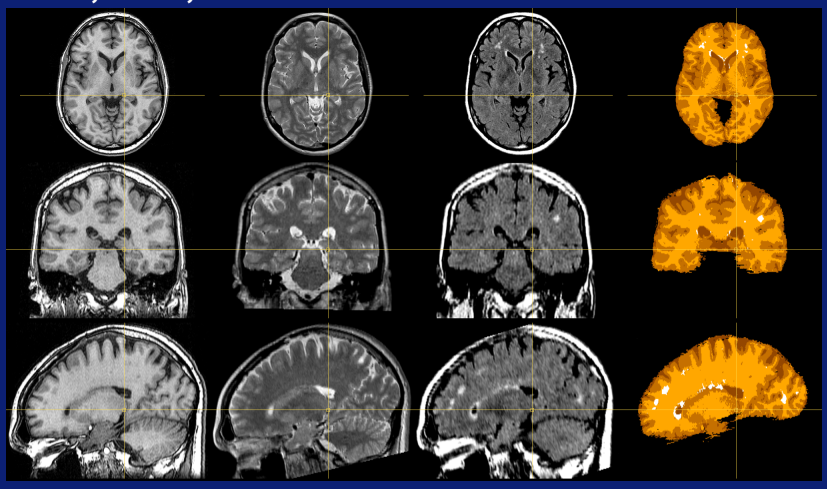
"The practice of medicine with treatment recommendations that have their origin in **objective tests** of efficacy published in the scientific literature rather than anecdotal observations"

Imaging biomarkers (white paper ESR)

"***Biomarkers are characteristics that are objectively measured as indicators of normal biological processes, pathological processes, or pharmaceutical responses to a therapeutic intervention*** "

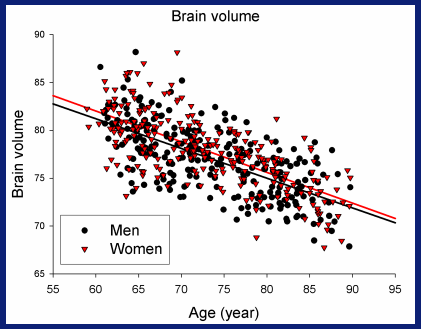
"Compared with biochemical and histological biomarkers, imaging biomarkers have the advantage of remaining non-invasive and being spatially and temporally resolved"

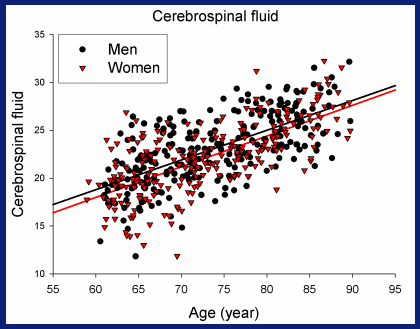
Automated segmentation grey/white matter, CSF, WML



kNN classification: Atlas registration for automatic training; WML segmentation on FLAIR image (Cocosco et al. Media, De Boer et al. / Vrooman et al. NeuroImage)

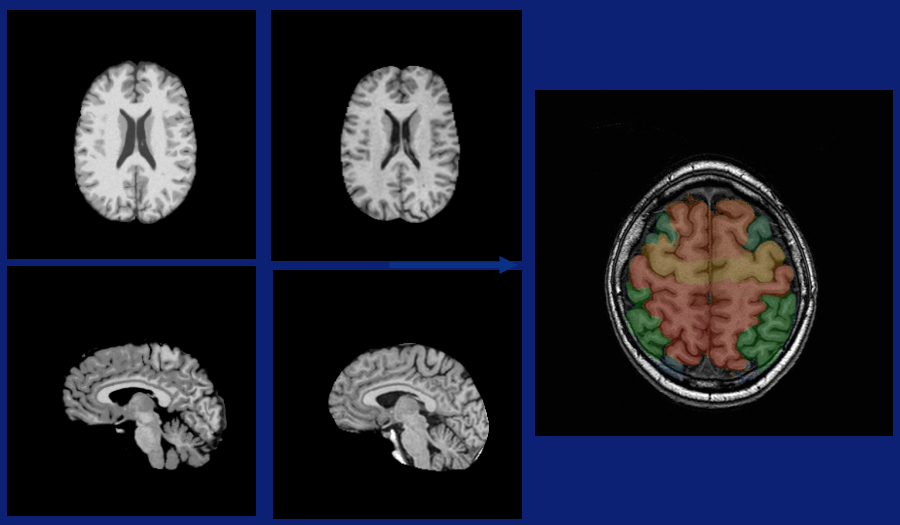
Brain changes during lifetime





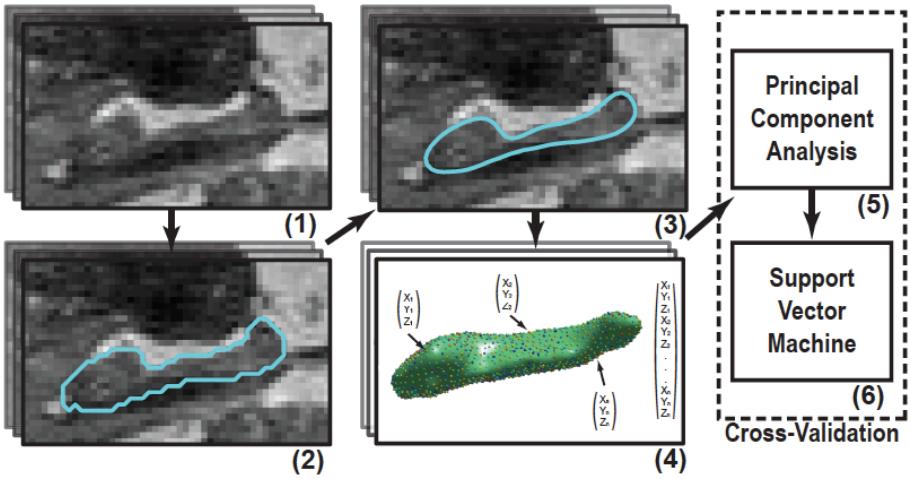
Ikram et al., Neurobiology of Aging, 2008

Automatic, atlas registration based segmentation



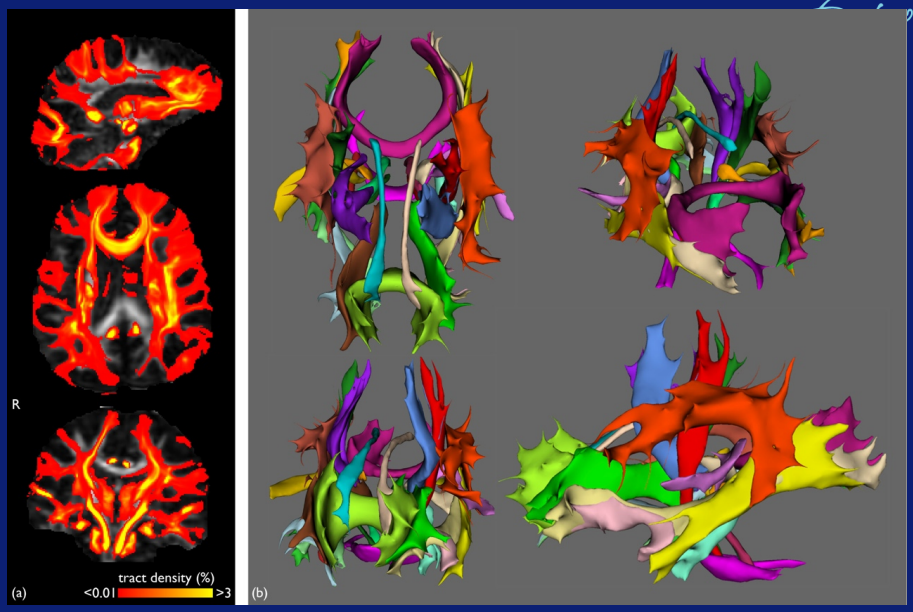
Courtesy movies: Rueckert, Hammers Imperial College

Hippocampus shape analysis



Combining tractography and atlas-based masking

Erasmus MC

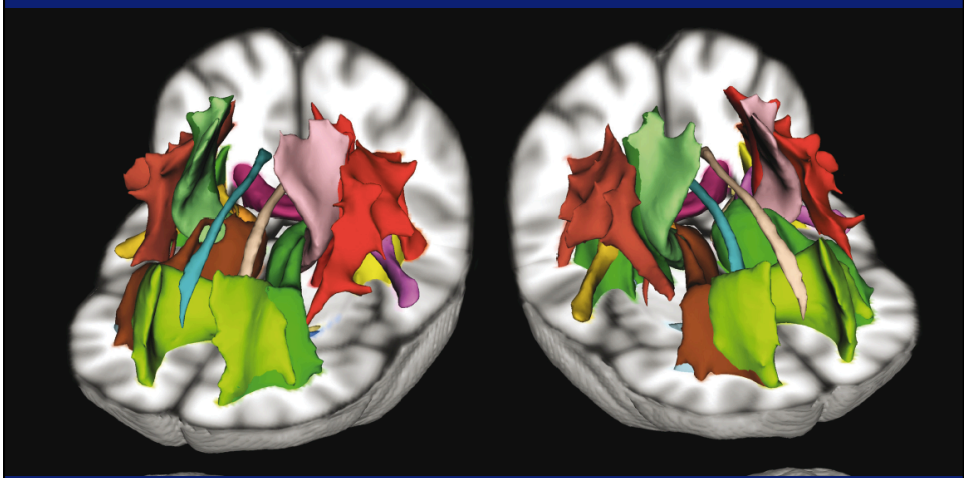


http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/AutoPtx

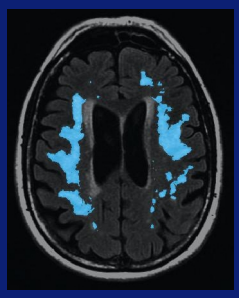
13

Automated white matter tract definition

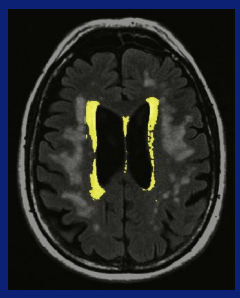
Erasmus MC



Library of quantitative imaging biomarkers

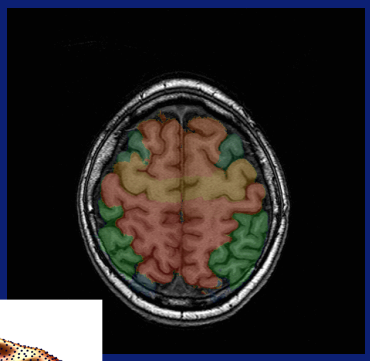


Subcortical WML

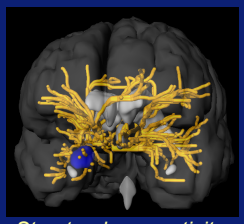


Periventricular WML

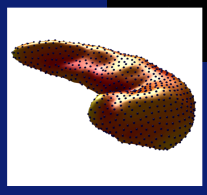
Brain structures



Courtesy Alexander Hammers, Imperial College

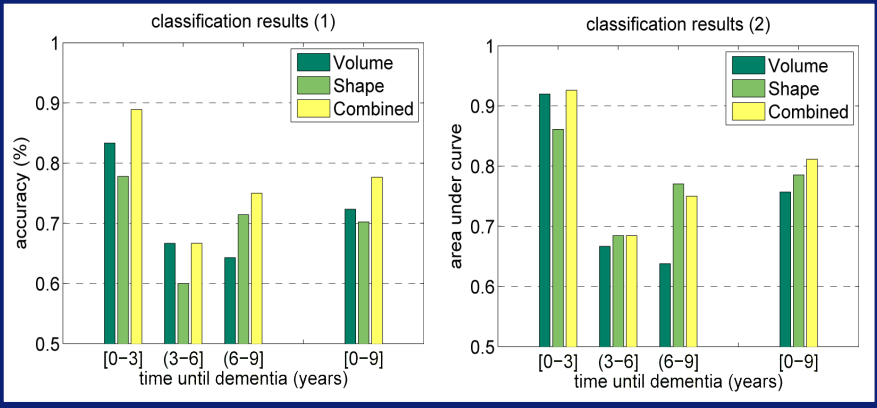


Structural connectivity



Hippocampal shape and volume

Prognostic value of hippocampal volume and shape: case control study



- *Cases developed dementia*
- *Controls remain non-demented*

Erasmus MC

Longitudinal analysis:

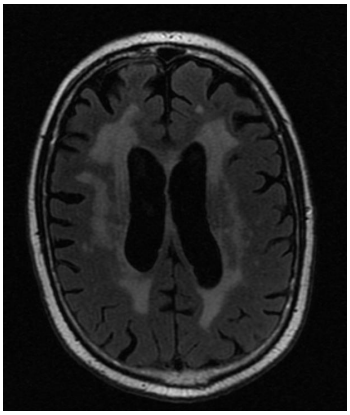
Is the tissue that converts to a WML different from tissue that persists as NAWM?

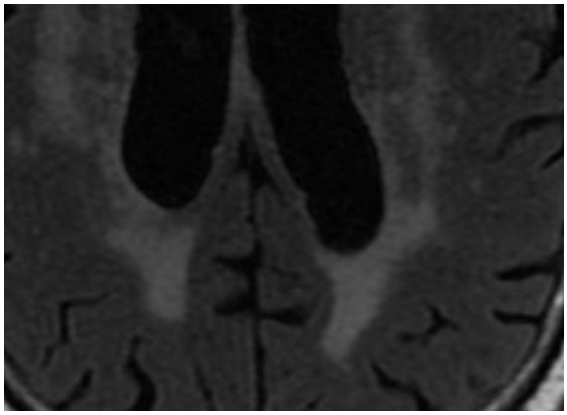
Courtesy: Marius de Groot et al., Stroke 2013

Cerebral white matter lesions

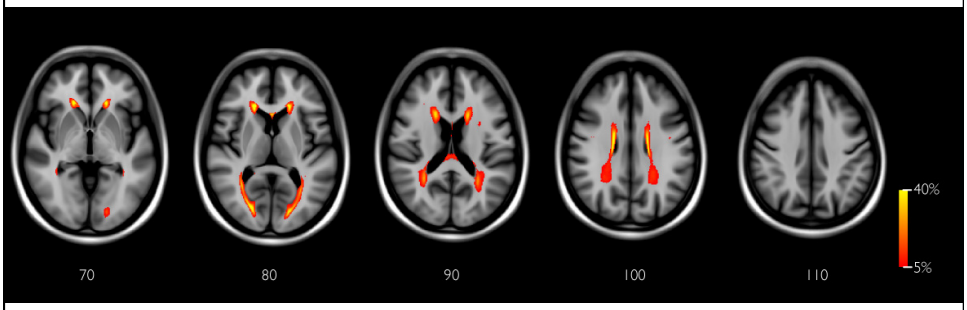
Erasmus MC

- Highly frequent in aging
- Increase the risk of dementia and stroke



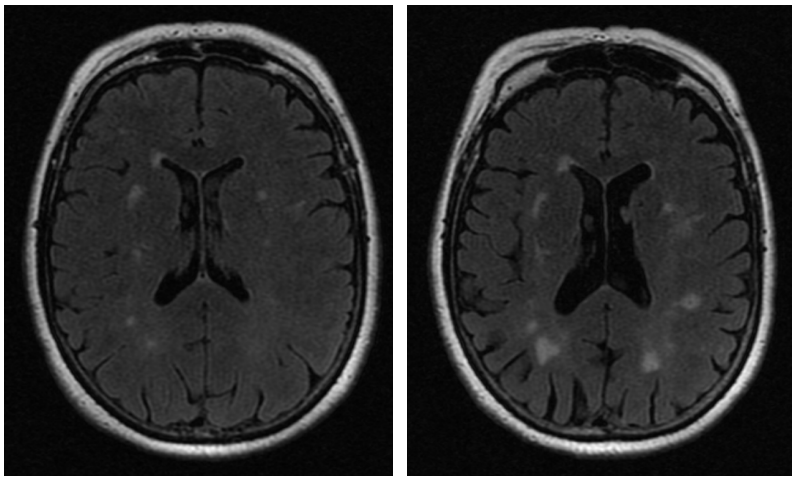


Spatial distribution of WML



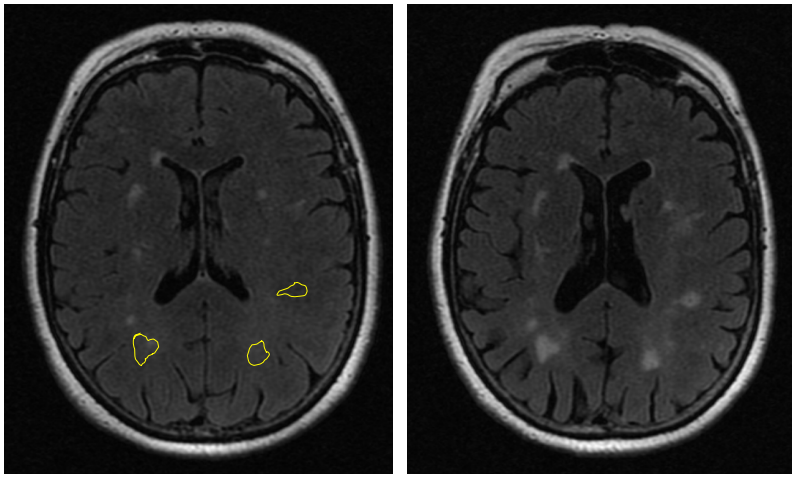
WML are especially prevalent in periventricular areas

Unknown how WML develop



Can we detect subtle differences here?

Erasmus MC



21

Study aim

Erasmus MC

- Is the tissue that converts to a WML different from tissue that persists as NAWM?

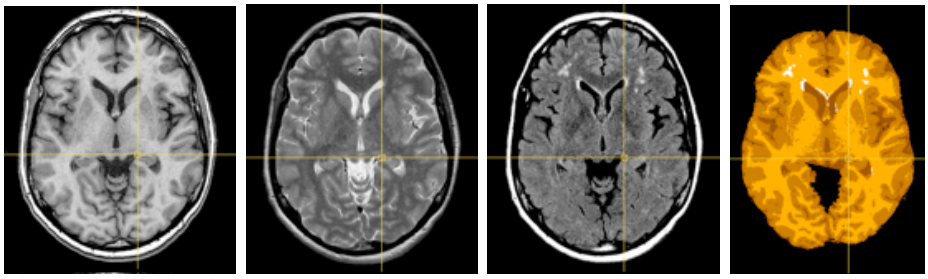
  Focussed on microstructure with DTI measures and continuous FLAIR intensity

  In a large longitudinal sample from the general population

22

Tissue segmentation

Erasmus MC



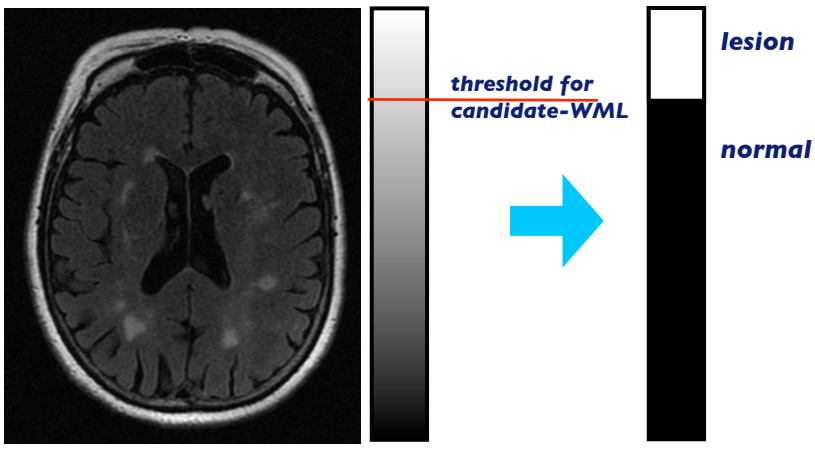
- ***multi-atlas registration for mask and sampling***
- ***KNN based segmentation on T1w and PDw scans***
- ***WML segmentation as post processing step on FLAIR***

Vrooman et al., NeuroImage 2007, De Boer et al., NeuroImage 2009

23

Continuous FLAIR signal intensity

Erasmus MC



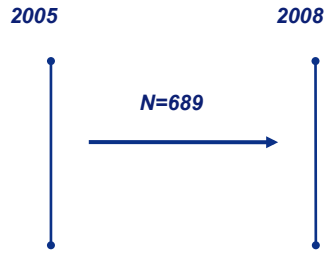
However, there appears to be more information in the FLAIR intensity!

Maillard et al., Stroke 2011

24

Design

Erasmus MC

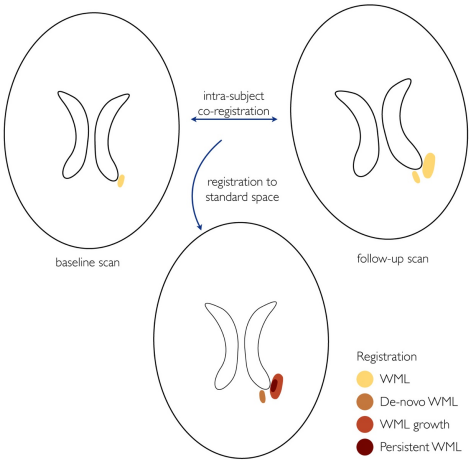


Population-based longitudinal MRI-study

Age	66.9 (5.0)
Female	52 % (355)
Follow-up time	3.5 (0.2)

Analysis

Erasmus MC



Find WML in both scans

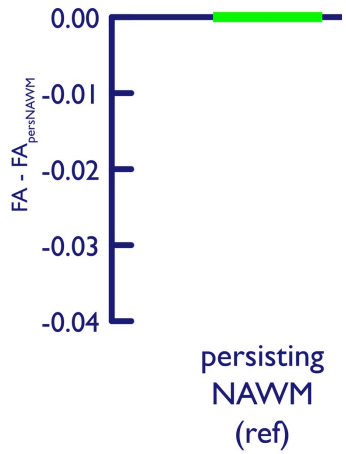
Symmetric analysis*

Standard space analysis

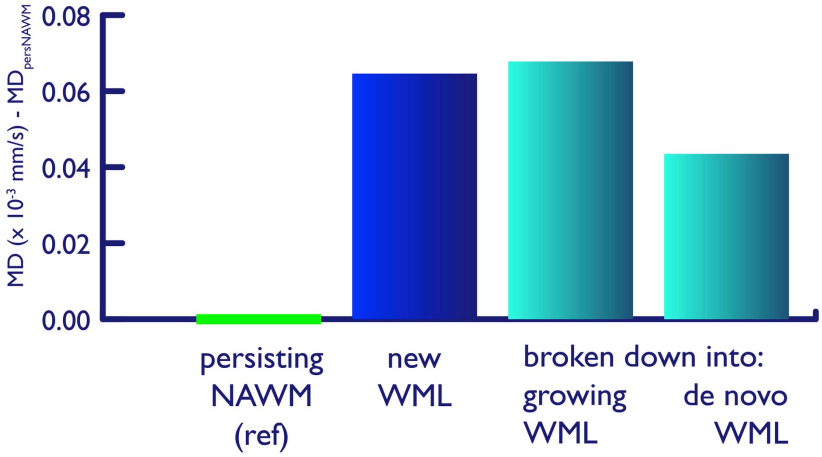
Matches new WML to persistent NAWM in other subjects

* *see Reuter and Fischl, NeuroImage 2011*

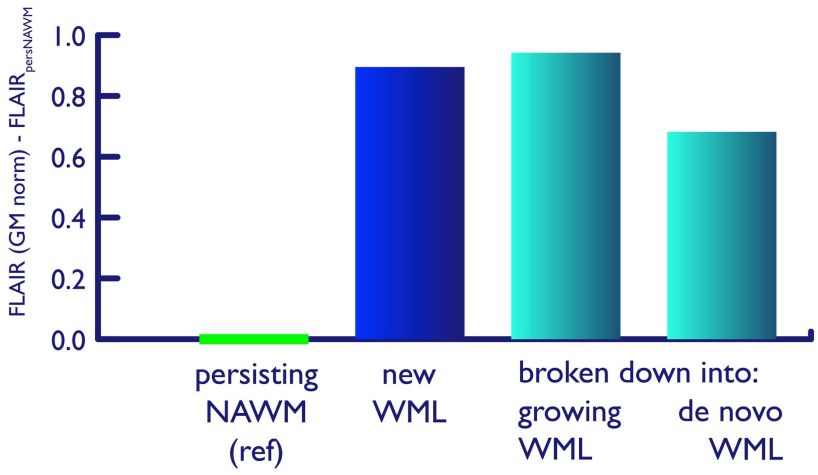
Results: FA difference



Results: MD difference



Results: Normalized FLAIR



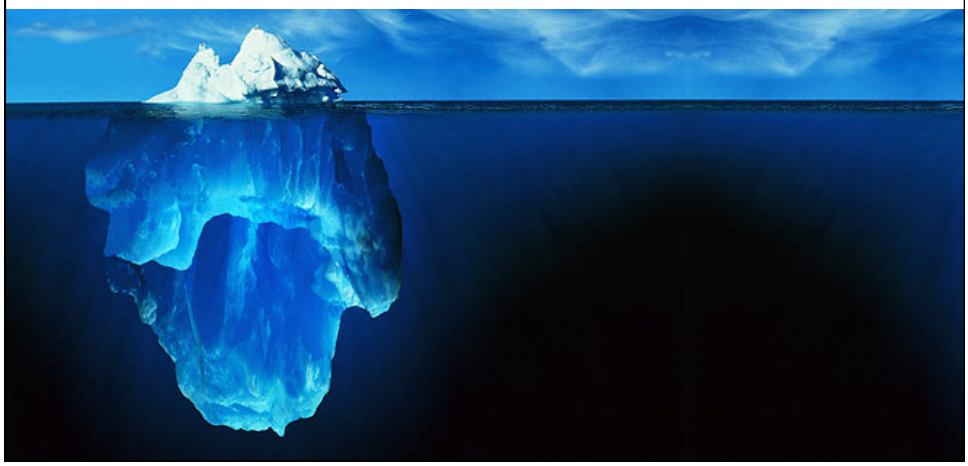
Conclusions

- The normal appearing white matter is altered before white matter lesions develop

Conclusions

Erasmus MC

- This suggests that white matter lesions develop gradually, and that visually appreciable white matter lesions are only the tip of the iceberg of white matter pathology



ImaGene

Population Imaging Genetics

Integrating imaging and genetics for improved understanding of disease processes, and improved detection, diagnosis and therapy planning

POPULATION IMAGING GENETICS: NEUROLOGIC DISEASE

Erasmus MC

Risk factors:

Genetic

Blood pressure
Smoking

?

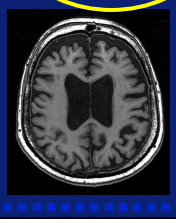
Brain changes:

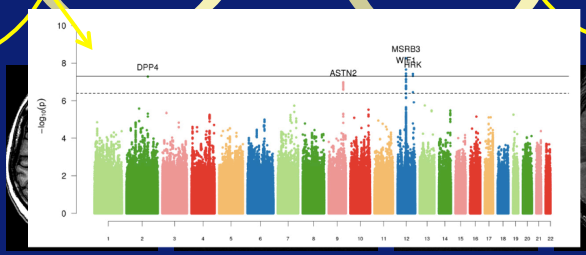
Atrophy, infarcts
White matter lesions
.....

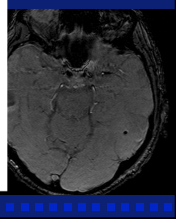
?

Outcome:

Stroke
Dementia







FIRST RESULTS:

Erasmus MC

Risk factors:

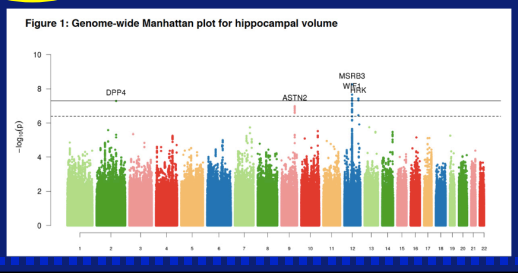
Genetic

Blood pressure
Smoking
.....

?

Brain changes:

Hippocampal
volume

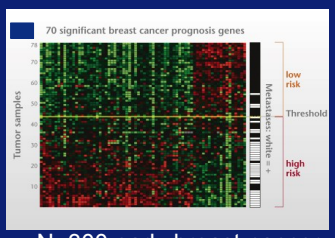


Erasmus MC

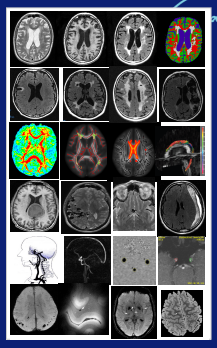
HOWEVER:

Full potential population imaging genetics databases not nearly utilized

Techniques for integrated imaging genetics analyses lacking



N=300 early breast-cancer gene-expression arrays + MRI data



Rotterdam Study:
15000 GWA; 8000 MRI

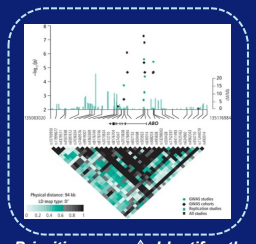
CHARGE Consortium:
> 30.000 GWA/MRI

Nelson Study/Maastricht Study

Model-based imaging genetics analyses

Erasmus MC

GWAS



Prioritize Genes: Increase Power

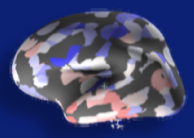
Identify other candidate Genes

Data

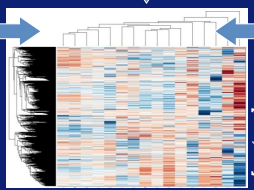
Non-imaging data

Imaging data

Structural measurements Structural/Functional Connectivity



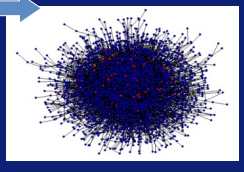
ALLEN Brain Atlas



Genes [~30,000]

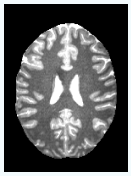
Brain Structures [~1,000]

Spatial Co-expression of Genes



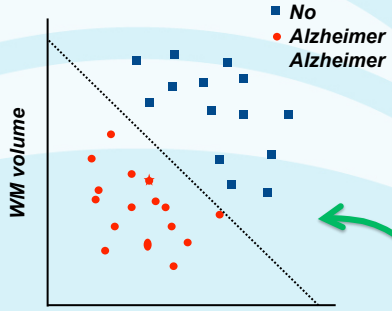
IT infrastructure essential!

- Infrastructure to facilitate centralised correlative analysis between image-derived data and clinical data in multi-centre studies



MR image

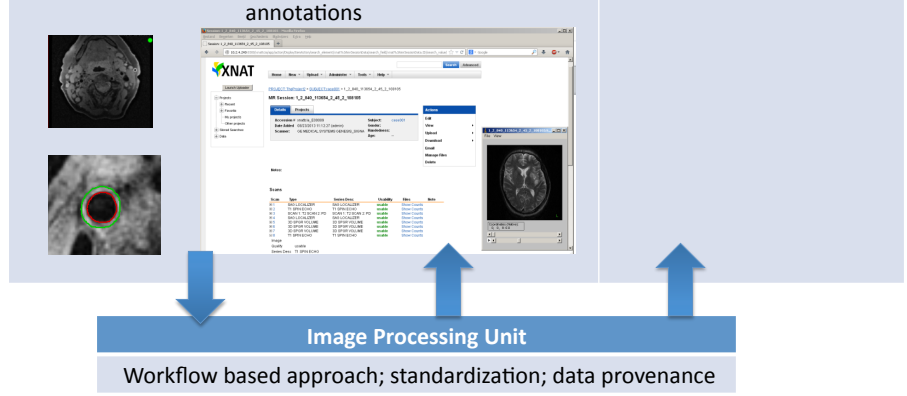
Patient	Age	Alzheimer
p000	67	no
p001	70	yes
p002	83	no
...	....	....

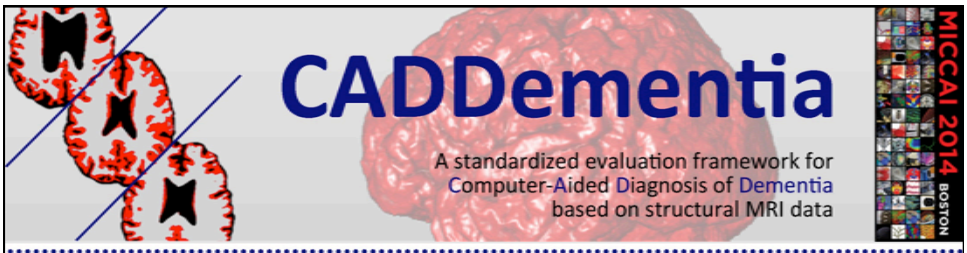


Segmentation

Volume GM = 790 ml
Volume WM = 497 ml

BioMedBridges





Algorithms are not used in clinical practice owing to lack of validation

1. ***The validation data set and evaluation methods vary, which makes it hard to compare performances between different methods.***
2. ***For clinical implementation, the generalizability of the methods should be evaluated on previously unseen multicenter data***
3. ***For clinical applicability is multi-class classification of AD, MCI and controls is required.***

Esther Bron, MSc, Stefan Klein, PhD, Marion Smits, MD PhD
John van Swieten, MD PhD, Wiro Niessen, PhD

Erasmus MC, Rotterdam, the Netherlands

Data

- Structural MRI (T1w) scans of AD patients, MCI, and controls
  - Erasmus MC, the Netherlands: 174 scans
  - VU Medical Center, the Netherlands: 180 scans
  - University of Porto / Hospital de São João, Portugal: 30 scans
  - Imperial College London, UK: TBA
- Training
  - Any suitable training data can be used, e.g. ADNI
  - Small training set from our database, 30 data sets

Acknowledgements

Erasmus MC

Department of Radiology:

Bas Jasperse, Marion Smits, Aad van der Lugt, Meike Vernooij

Department of Epidemiology:

Monique Breteler, Arfan Ikram, Marielle Poels, Ben Verhaaren

Department of Neurology:

Tom den Heijer

Biomedical Imaging Group Rotterdam:

Hakim Achterberg, Renske de Boer, Marleen de Bruijne, Marius de Groot, Stefan Klein, Marcel Koek, Fedde van der Lijn, Dirk Poot, Erwin Vast, Henri Vrooman

Imperial College London

Alexander Hammers, Daniel Rueckert

Erasmus MC
University Medical Center Rotterdam

Thanks!

Questions?