Quantitative imaging biomarkers and imaging genetics in neurodegenerative disease

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Quantib

Rotterdam Study
Population Study initiated in 1990
Population-based cohort studies

- subjects free of disease at baseline
- assess potential determinants
- follow prospectively for occurrence of disease
- assess association between determinants and risk of disease

Determinants
- genetic
- environmental
- life-style
- ....

Outcomes
- dementia
- cardiovascular
- osteoarthritis
- ....

etiology

prediction

healthy
diseased

screening
diagnosis

population-based studies
clinical studies

subclinical changes

population imaging
Rotterdam Scan Study (> 11000 MRI data acquired)

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

‘Textbook’ examples

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

Hippocampus shape analysis
Combining tractography and atlas-based masking

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

Automated white matter tract definition
Library of quantitative imaging biomarkers

Brain structures

Subcortical WML
Periventricular WML

Structural connectivity
Hippocampal shape and volume

Prognostic value of hippocampal volume and shape: case control study

Cases developed dementia
Controls remain non-demented
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

- 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?

Study aim

- 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
Tissue segmentation

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

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

Continuous FLAIR signal intensity

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

Maillard et al., Stroke 2011
Design

Population-based longitudinal MRI-study

<table>
<thead>
<tr>
<th>Age</th>
<th>66.9 (5.0)</th>
</tr>
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<tbody>
<tr>
<td>Female</td>
<td>52% (355)</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>3.5 (0.2)</td>
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</table>

Analysis

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
Conclusions

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

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.

Population Imaging Genetics
Integrating imaging and genetics for improved understanding of disease processes, and improved detection, diagnosis and therapy planning.
POPLATION IMAGING GENETICS: NEUROLOGIC DISEASE

Risk factors:
- Genetic
- Blood pressure
- Smoking

Brain changes:
- Atrophy, infarcts
- White matter lesions

Outcome:
- Stroke
- Dementia

FIRST RESULTS:

Risk factors:
- Genetic
- Blood pressure
- Smoking

Brain changes:
- Hippocampal volume
HOWEVER:

Full potential population imaging genetics databases not nearly utilized

Techniques for integrated imaging genetics analyses lacking

Rotterdam Study:
15000 GWA; 8000 MRI

CHARGE Consortium:
> 30,000 GWA/MRI

Nelson Study/Maastricht Study

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

Model-based imaging genetics analyses

Data

Non-imaging data

Imaging data

Structural measurements
Structural/Functional Connectivity

ALLEN Brain Atlas

Prioritize Genes: Increase Power
Identify other candidate Genes
Spatial Co-expression of Genes

Brain Structures (~1,000)
IT infrastructure essential!

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Alzheimer</th>
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<tbody>
<tr>
<td>p000</td>
<td>67</td>
<td>no</td>
</tr>
<tr>
<td>p001</td>
<td>70</td>
<td>yes</td>
</tr>
<tr>
<td>p002</td>
<td>83</td>
<td>no</td>
</tr>
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<td>...</td>
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</tbody>
</table>

- MR image
- Segmentation

Volume GM = 790 ml
Volume WM = 497 ml

Data-archive infrastructure

**XNAT**
- anonymised DICOM images, processed images, and annotations

**OpenClinica**
- other study data

Image Processing Unit
- Workflow based approach; standardization; data provenance
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.

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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
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Questions?