MRI in the Evaluation of Dementia

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Available MRI methods in AD

Structural MRI findings in non-AD dementias

11C PIB and MRI provide complimentary information in AD

Will not cover prediction, natural history longitudinal studies, or treatment trials using MR
AD Pathology: Reductionist View

- Amyloid dysregulation
- Neurodegeneration, neuronal dystrophy
  - Loss, shrinkage of synapses, neurons and supporting glial cells
  - Clinical symptoms
  - Neurofibrillary tangles
Imaging = in vivo pathology

**Amyloid**
- PET - amyloid plaque imaging

**Neurodegeneration, neuro dystrophy**
- Structural MRI
- MR Spectroscopy
- Diffusion MRI
- Functional MRI
- Perfusion MRI
- FDG PET
Imaging Methods
Sensitive to AD Pathology

- Abbreviations:
  - AD = Alzheimer's Disease;
  - MCI = (amnestic) Mild Cognitive Impairment
  - CN = cognitively normal elderly control

- What does each method measure?
- How does this relate to the pathology of AD?
- Use clinical group categorization and autopsy correlation to illustrate validity of each imaging method
Mild Cognitive Impairment – Intermediate Stage

Pathologic Progression

Normal Elderly
Amnestic MCI
Alzheimer’s Disease

**Structural MRI**

- What property of tissue is measured?
  - volume, tissue density, atrophy

- How is this related to AD pathology?
  - Loss, shrinkage of neurons and supporting glial cells
Three ways to evaluate structural MRI

- Visual inspection – clinical
- ROI quantification – extract data from regions of interest – convert grey scale images into numbers, used in traditional biostatistical analysis
- Mapping – analysis is done using voxel-wise tools in “image space”
Visual inspection: Atrophy and AD Stage

Control, 70 F
MCI, 72 F
AD, 74, F
Hippocampus & ERC volume Measurement - tracing
Structural MRI ROI measures in control, aMCI, and AD

Usefulness of MRI Measures of Entorhinal Cortex vs Hippocampus, Neurology 2000; 54: 1760-1767

Entorhinal cortex vol. \( \times 10^3 \)

Total intracranial vol.

Control (n = 30)  MCI (n = 30)  AD (n = 30)
Correlation between hippocampal volume score and Braak stage in AD: -0.63 (<0.01)
Stages of Alzheimer’s disease

transentorhinal I - II

limbic III - IV

neocortical V - VI

Neurofibrillary changes
Voxel-wise methods capture time dependent progression from aMCI to AD (n = 33)

3D Maps from Multiple MRI Illustrate Changing Atrophy Patterns as Subjects Progress from MCI to AD
MR Spectroscopy

- What property of tissue is measured? – concentration of metabolites
- How is this related to AD pathology?
  1. N-acetyl aspartate – neuron/synapse density and "health"
  2. Myo-Inositol – glial activation
$^1$H MRS in control, aMCI, and AD

Control | Amnestic MCI | AD

NAA | NAA | NAA

ml Cho ml Cho ml Cho Cr

1H MRS in Normal, aMCI, and AD Posterior Cingulate Gyri Metabolite Measurements, Neurology 2000; 55 (2): 210-217
Neuropathological Correlates of Antemortem 1H MRS in Alzheimer’s Disease. Radiology 2008
Diffusion Weighted Imaging

- What property of tissue is measured? – microscopic random motion of water in tissue → tissue microstructure
- How is this related to AD pathology? – loss of microstructural complexity → increased diffusion (increased ADC and decreased FA)
Random brownian motion of water molecules:

ADC: measure of diffusivity - average area of displacement of a water molecule per unit time (mm²/s).

ADC in the brain depends on the integrity of microscopic structural barriers:
- membranes of neurons
- myelin sheets,
- intracellular organelles,
- macromolecules.

Loss of structural barriers → ↑ ADC
Diffusion weighted imaging in control, aMCI, and AD

ADC Measurements in MCI and AD, Radiology 2001; 219: 101-107
1.5T, volume coil, DWI

3T, 8 channel, 21 dir DTI

Hippocampal ADC 1998 to 2000

Hippocampal ADC 2007 to 2008

Source: Kantarci et al. (2001)

Source: Unpublished data

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Distribution of diagnoses in community-dwelling persons with (A) and without (B) dementia

Schneider, JA et al, **Mixed brain pathologies account for most dementia cases in community-dwelling older persons**
Neurology 2007 69: 2197-2204
Hippocampal Atrophy, Cortical Infarctions and Decreased NAA/Cr have Additive Effects on the Risk of Progression to Dementia in MCI

OUTLINE

- Available MRI methods in AD
- Structural MRI findings in non-AD dementias – clinically useful differential diagnostic findings
  - Vascular Disease
  - DLB
  - FTLD
  - Other dementias - CJD, NPH
- 11C PIB and MRI provide complimentary information in AD
Vascular Dementia

- 2nd most common (?) cause of dementia – although striking discrepancies in literature as to prevalence
- Often co-exists with other neurodegenerative dementias (esp AD) that are prevalent in elderly, and contributes to impairment
Fronto Temporal Lobar Degeneration

- Behavioral FTLD – frontal (& right temporal)
- Semantic – left temporal
- Non-fluent aphasia – left frontal
FTLD Immunocytochemistry

- **Tau positive - dysfunctional protein: microtubule-associated tau**
- Pick disease
- PSP – progressive supra nuclear palsy
- CBD – cortical basal degeneration
- FTDP-17 (MAPTau) (autosomal dominant)
- **Tau Negative - dysfunctional protein: TAR-DNA binding protein (TDP-43)**
- FTLD – U: (60% ), ubiquitin-positive inclusions in frontotemporal cortices and the dentate cell layer of the hippocampus
- FTD – 17 (PGRN) (autosomal dominant) (ubiquitin positive)
- FTLD – MND
- **Dementia Lacking Distinctive Histology**
FTLD behavioral, PGRN
Semantic dementia
Progressive non-fluent aphasia
CJD
DWI in CJD
NPH
OUTLINE

- Available MRI methods in AD
- Structural MRI findings in non-AD dementias
- 11C PIB and MRI provide complimentary information in AD
Objective: to compare structural MRI and PIB measures cross sectionally in prevalent normal aging (CN), amnestic Mild Cognitive Impairment (aMCI), and AD

- PIB – global cortical uptake normalized by cblm
- MRI – hippocampal volumes
  - Descriptive group-wise comparisons
  - Analysis of added value diagnostically
Group-wise scatter plots of PiB and hippocampus

Global cortical PiB
(P < 0.001)

Hippocampal W score
(P < 0.001)
Scatter plot showing relationship between global cortical PiB retention and hippocampal W score – CN, aMCI, AD only
MRI and PIB provide complementary info in predicting more impaired dx for four key “quartile transitions”
Summary

- Dementia is most often multifactorial
- Imaging = in vivo pathology (or consequence)
- Different imaging methods provide insight into different underlying mechanisms
- Multi-modality imaging should provide greatest insight into substrates of dementia – mild cognitive impairment
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