Brain Scans and Biomarkers

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Structural, functional, and molecular imaging are all crucial components of research evaluations of dementia patients today.
1984: Publication of widely accepted clinical diagnostic criteria for Alzheimer’s disease

2018: Publication of a novel research framework – Alzheimer’s disease as a biological disorder

34 years to move from a clinical diagnosis to a biological model of AD
Alzheimer’s Disease: Neuropathology

- β-amyloid (Aβ)
- Plaque pathology
- Tau
- Neurofibrillary Tangles

Brain atrophy is a sign of neurodegeneration
Positron Emission Tomography

Cyclotron for production of short-lived radionuclides (C11, F18)

Fast Radiochemical synthesis of PET tracers

Injection into participant

Image reconstruction and data analysis

Central Radiopharmacy for F18

PET Scan
Fluorodeoxyglucose (FDG) – PET
Reduced glucose metabolism in Alzheimer’s Disease likely reflects synaptic dysfunction

Normal

Alzheimer’s Disease
FDG-PET in Alzheimer’s and FTLD

F = frontal cortex, TP = Temporoparietal cortex, PC = posterior cingulate/precuneus
Glucose Metabolism Declines in AD

Characteristic brain regions affected in Alzheimer’s disease:

- Medial parietal lobe
- Lateral temporal/parietal cortex
- Medial temporal lobe

Similar regional vulnerability in structure and function

Wirth et al J Neuroscience 2013
In vivo Amyloid Imaging with Pittsburgh Compound B (PIB)

PET Imaging - \([^{11}C]6\text{-OH-BTA-1 (PIB)}\)

Histology - Thioflavin T

Fibrillar \(\text{A}\beta\)

Amyloid Plaques

Chet Mathis and Bill Klunk, University of Pittsburgh
FDG (glucose metabolism) vs PIB (β-amyloid)
Neurodegeneration vs Molecular Pathology

Normal

FDG

PIB

Alzheimer’s Disease

FDG

PIB
**Molecular Biomarkers vs Neurodegeneration Biomarkers**

**Neurodegeneration**
- Indicative of brain damage
- Non-specific (as to cause)
- May be complex to interpret
- Correlation with symptoms
- Questionable utility for therapeutic testing

**Molecular**
- Indicative of pathology
- Specific
- Relatively straightforward
- May or may not correlate with symptoms
- Should be useful for therapeutic testing
Multiple tau radiopharmaceuticals are now available for PET imaging

Villemagne et al, Nat Rev Neurol 2018
### Tau Imaging with Flortaucipir

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample Size</th>
<th>Description</th>
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<tbody>
<tr>
<td>Young Adults (N=5)</td>
<td></td>
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<tr>
<td>PIB- Older Adults (N=17)</td>
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<tr>
<td>PIB+ Older Adults (N=16)</td>
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<tr>
<td>Alzheimer's Disease (N=15)</td>
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#### Key regions of tau accumulation:
- Medial temporal lobe (MTL) and inferior/middle temporal regions
- Retrosplenial cortex/posterior cingulate
- Precuneus
- Inferior parietal

#### Braak staging (t-tests)

**Supra-threshold voxels**
- Alzheimer's disease (AD) vulnerable regions

Topography of tau deposition in the AD continuum reflects Braak Pathological staging

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Utility of Tau PET in Differential Diagnosis

719 participants from Lund, Seoul, SF

Tau PET 90% sensitivity & specificity discriminating AD from other disorders

Ossenkoppele et al JAMA 2018
Biomarker Patterns: Similarities and Differences

Aβ
$^{18}$F-NAV4698

Tau
$^{18}$F-PI2620

Neuronal/Synaptic dysfunction
$^{18}$F-FDG

Cortical atrophy
MRI

RT.LAT  LT.LAT  RT.MED  LT.MED
Biomarker Measurement in Autosomal Dominant AD Supports the Amyloid Hypothesis

The Dominantly Inherited Alzheimer’s Disease (DIAN) Study

Cross-sectional data on biomarkers from autosomal dominant, symptomatic and asymptomatic family members

Because age-at-onset is preserved across generations, biomarker values in relation to age-at-onset can be calculated

Results show that the earliest biomarker change is elevation of Aβ in brain, about 20 years before expected onset

The Amyloid Hypothesis: Amyloid deposition is the initiating event in AD, leading to NFTs-tau, brain degeneration, and dementia
NIA-AA Research Framework

Alzheimer’s disease defined by 3 pathological processes: β-amyloid deposition (A), tau deposition (T), and neurodegeneration (N)

<table>
<thead>
<tr>
<th>AT(N) profiles</th>
<th>Biomarker category</th>
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<tbody>
<tr>
<td>A-T-(N)-</td>
<td>Normal AD biomarkers</td>
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<tr>
<td>A+T-(N)-</td>
<td>Alzheimer’s pathologic change</td>
</tr>
<tr>
<td>A+T+(N)-</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>A+T+(N)+</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>A+T-(N)+</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change</td>
</tr>
<tr>
<td>A-T+(N)-</td>
<td>Non-AD pathologic change</td>
</tr>
<tr>
<td>A-T-(N)+</td>
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</table>

Alzheimer’s Continuum: Amyloid Positivity (A+)

Alzheimer’s Disease: Amyloid and tau positivity (A+T+)

This is currently a framework meant only for research, not clinical care
Amyloid Status Predicts Clinical Conversion

Normal $\rightarrow$ MCI conversion  MCI $\rightarrow$ AD conversion

Roberts et al. JAMA Neurol 2018
AD Neuropathology in Normal Cognitive Aging

- **β-amyloid plaques (Aβ)**
  - MRI: Neurodegeneration
  - PET: Amyloid

- **Neurofibrillary Tangles (NFTs)**
  - Tau Protein
  - MRI: Neurodegeneration
  - PET: Tau

- **Tau-NFTs in aging accumulate in the medial temporal lobe**
  - (atrophy on MRI, tau with PET)

- **Aβ plaques appear diffusely throughout the brain**
  - (visible with PET)

- **PET**: Tau
  - NFTs
  - A-beta
How Well Does Aβ Predict Cognition in Normal Aging?

Cross-sectional meta-analysis

No Aβ effect for: FCSRT, MMSE, Trails, Frontal Assessment Battery

N = 2908
Jansen et al JAMA Psychiatry, 2018

N = 313
Dubois et al Lancet Neurology 2018

N = 445
Donohue et al JAMA 2017
β-amyloid → Tau → Neurodegeneration → Weak!!
Amyloid (FBP/FBB) is Associated with Tau (FTP)

N = 646

Entorhinal cortex
Braak 1

Inferolateral temporal tau
Braak 34

Neocortical tau
Braak 56

Male
Female

Unimpaired | Impaired
---|---

N = 646
Aβ within the Negative Range Affects FTP Control Subjects

Predictors: Age, Sex, Edu, APOE4, FTP, Aβ (continuous)
Age, Aβ, and tau associations among healthy elderly

Schöll, Lockhart et al, Neuron 2016
Medial Temporal Lobe tau is Associated with Reduced Glucose Metabolism in Amyloid+ Aging

Increases of tau in MTL regions are associated with decreases of FDG in temporal, parietal, and orbitofrontal regions.

21 Cognitively normal amyloid positive older people (78 years)

The hypometabolic brain regions reflect downstream neural targets in medial temporal lobe pathways and are also the brain regions affected by Alzheimer’s disease.

Adams et al, Cerebral Cortex, 2018
Tau Accumulates Over Time and Parallels Brain Atrophy in Cognitively Normal Older People

42 Cognitively normal adults followed for ~2 years

Harrison et al, Ann Neurol 2019
Baseline Tau Predicts Longitudinal Atrophy in AD
(N = 26 PIB+ AD)

A. Global associations

![Graphs showing the correlation between baseline PIB and longitudinal atrophy, baseline FTP and longitudinal atrophy, and baseline cortical thickness and longitudinal atrophy.]

Renaud LaJoie
**Tau Correlates with AD Phenotypes**  
*(Aβ does not)*

Marginal mean maps | centered for age (~65yo), CDR-SB (~4), and global cortical SUVR

**Group comparison**  
cov: age, CDR-SB + cortical SUVR

- **AD**  
  - (N=60)

- **LvPPA**  
  - (N=19)

- **PCA**  
  - (N=18)

Renaud La Joie/Gil Rabinovici
Cognitively normal individuals with more tau in these brain regions (entorhinal cortex) show worse performance on memory tests.
Clinical Trials: Biomarkers for subject selection and target engagement

Aducanumab: Mild AD and MCI

**Amyloid PET Scans:**
Reductions in \( A\beta \)

Antibodies directed at \( \beta \)-amyloid lowered PET scan measurements after 26 and 54 weeks of treatment – dose effect

**Cognitive Testing:**
Dose-Related Improvement

Clinical benefit by 1-year: less cognitive decline with higher doses

The Future?

Therapeutic trials of amyloid lowering therapies
  Asymptomatic people with genetic risks
  Asymptomatic individuals with positive amyloid biomarkers

Other targets
  Tau lowering therapies
  Lifestyle interventions (POINTER study)

Biomarkers will play a major role in subject selection and treatment monitoring
Thanks

National Institutes of Health
Tau Consortium