PET neuroimaging approaches to characterizing underlying molecular pathology in neurodegenerative disease

Susan M Landau, PhD

Helen Wills Neuroscience Institute
University of California, Berkeley

Lawrence Berkeley National Lab
Disclosures

Cortexyme
NeuroVision
Overview

Detection of $\beta$-amyloid (A$\beta$) and tau pathology in Alzheimer’s disease
   - Time course of changes
   - Regional specificity
   - NIA-AA Research Framework

Practical considerations for PET in clinical trials

Future imaging biomarkers in neurodegenerative diseases
   - $\alpha$-synuclein, inflammation, synaptic density, vascular disease, TDP-43
Age Related Neuropathology

- Amyloid plaques (Aβ)
- Neurofibrillary Tangles (tau)

**NFTs**
- 0
- I/II
- III/IV
- V/VI

**Aβ plaques**
- 0
- A
- B
- C

**Graph**
- Percentage vs. Age
- NFTs: Purple
- A-beta: Green

Age:
- 26-40
- 41-50
- 51-60
- 61-70
- 71-80
- 81-90
In vivo Measurement of Aβ and Tau with PET Imaging

**Aβ PET Imaging**
e.g. $[^{11}C]$ PIB, $[^{18}F]$ florbetapir, $[^{18}F]$ flutemetamol

**Fibrillar Aβ**

**Paired helical filament tau**

**Tau PET Imaging**
e.g. $[^{18}F]$ flortaucipir (AV1451), $[^{18}F]$ MK-6240, $[^{18}F]$ GTP1, $[^{18}F]$ PI-2620
Aβ PET imaging in aging and dementia

~30% of cognitively normal people in their 70s and above have substantial Aβ accumulation by PET
Amyloid Hypothesis: AD Biomarker progression

β-amyloid

Neurodegeneration:
- Tau pathology
- Synaptic dysfunction
- Metabolic decline
- Brain atrophy

Cognitive Decline and Dementia
Regional specificity

Amyloid PET

Florbetapir SUVR:
cortical summary region mean/
whole cerebellum mean
Cortical Aβ accumulation over the disease trajectory

- 32% florbetapir+
- 35% florbetapir+
- 48% florbetapir+
- 65% florbetapir+
- 86% florbetapir+

Total N=1064

Subjective Memory Complaint
Early MCI
Late MCI
AD
Aβ PET imaging – postmortem associations

Cortical Aβ PET retention is highly associated with Aβ plaques at autopsy in 179 diverse cases

La Joie et al. Alz & Dementia (in press)
Elevated Aβ predicts ADAS-cog decline in MCI and AD

In cognitively normal, Aβ—individuals, negative but increasing Aβ is associated with memory decline

Cortical Aβ accumulation predicts cognitive decline

Landau et al Neurology 2016

Donohue et al JAMA 2017

Landau et al Neurology 2018
Time course of changes

Rate of Aβ accumulation is not constant throughout the disease trajectory

Regional specificity

**Amyloid PET**

Florbetapir SUVR:
- cortical sumary region mean/whole cerebellum mean

**Tau PET**

Flortaucipir SUVRs:
- Braak stage-based region means/cerebellar grey matter mean

- Braak I/II Medial temporal
- Braak III/IV Inferolateral temporal/limbic
- Braak V/VI Neocortical (extra-temporal)
Tau increases with impairment and elevated Aβ
Co-occurrence of Aβ and tau are linked to cognitive decline

Higher tau is linked to poorer cognition for Aβ+ individuals

Higher tau is linked to retrospective cognitive decline in Aβ+ individuals
### 2018 NIA-AA Research Framework

#### Biomarker profiles and categories

<table>
<thead>
<tr>
<th>AT(N) profiles</th>
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<tbody>
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<td>A-T-(N)-</td>
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<tr>
<td>A+T-(N)-</td>
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Distributions differ across A, T, N biomarkers

Determining standardized cut-points for positivity is challenging
Tau increases with impairment and elevated Aβ

Medial temporal AV1451

Inferolateral temporal/limbic AV1451

Neocortical (extra-temporal) AV1451

90% upper threshold of 141 Aβ-normals

Unimpaired | Impaired

Unimpaired | Impaired

Unimpaired | Impaired

Atypical/EOAD

ADNI LOAD

Maass et al. NeuroImage 2017

Lowe et al. Brain 2018
Longitudinal tau PET

Still early!

Jack et al. Brain 2018
PET in Clinical Trials: Practical considerations

Cross-sectional PET (Subject selection)

- Participant burden and cost
  - Multiple PET scans (+ MRI?)
  - Radiation exposure
  - PET vs blood-based vs CSF markers
- Multisite studies
  - Different scanners
  - Different tracers
- Identification of intervention “sweet spot” (biomarker-specific)

Longitudinal PET (Target Engagement)

- Scan cost
- Scanner changes
- Scan-rescan variability;
  - Longitudinal changes are usually small
- Ligand-specific methodological challenges
- Determining a followup time period with adequate power (biomarker-specific)
## Amyloid clearance

### Gantenerumab

**Continued amyloid reduction with gantenerumab at 2 years**

*Examples from five patients in OLEs*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 52</th>
<th>Week 104</th>
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<tbody>
<tr>
<td>Centiloid reduction</td>
<td>-28</td>
<td>-61</td>
<td>-92</td>
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<tr>
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<td>-89</td>
<td>-79</td>
<td>-107</td>
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Klein et al. AAIC 2018

### LY3002813 (N3pG)

<table>
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<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
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<tr>
<td>Centiloid reduction</td>
<td>1.50 / 97</td>
<td>1.64 / 123</td>
<td>1.60 / 116</td>
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<tr>
<td>Centiloid reduction</td>
<td>1.12 / 28</td>
<td>1.45 / 88</td>
<td>1.24 / 50</td>
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<tr>
<td>Centiloid reduction</td>
<td>1.01 / 8</td>
<td>1.38 / 75</td>
<td>1.11 / 26</td>
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Baseline

3 months

6 months
2018 NIA-AA Research Framework

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Alzheimer’s continuum

Beyond amyloid and tau

- AD+VaD; 27.4%
- AD+LBD; 16.7%
- AD+LBD+VaD; 7.2%
- Other; 5.1%
- AD+tau; 1.7%
- AD+HS; 0.5%
- AD+VaD+tau; 0.7%
- AD+VaD+HS; 0.6%
- AD+LBD+tau; 0.6%
- AD+LBD+HS; 0.2%
- AD+LBD+VaD+HS; 0.5%
- AD+LBD+VaD+tau; 0.2%

Biomarker targets in development

- [A] Plasma or retinal amyloid
- [T] New tau PET ligands
- [N] Neurofilament light, Synaptic density ([C11] UCB-J)
- [V] Vascular disease
- [I] Inflammation
- [S] α-synuclein
- TDP-43

Jack et al. Alz & Dementia 2018
Upcoming imaging biomarkers

Synaptic density with $[^{11}\text{C}]$ UCB-J

PET markers of $\alpha$-synuclein and TDP-43 in development

Neuroinflammation with $[^{11}\text{C}]$–($R$)–PK11195

Chen et al. JAMA Neurol 2018

Parbo et al. Neurobiol Dis 2018
Cerebrovascular Disease

Genetics (ApoE)

Age

Other pathology (α-synuclein, TDP-43)

Lifestyle and environment

Cerebrovascular Disease

Neurodegeneration:
- Tau pathology
- Synaptic dysfunction
- Metabolic decline
- Brain atrophy

β-amyloid

Cognitive Decline and Dementia
Recent Aβ and tau PET work has emphasized detection of earliest pathological AD changes, and associations with cognitive decline.

Research framework relies on amyloid [A], tau [T], and neurodegenerative [N] biomarkers to identify and stage AD pathological changes.

PET has been used successfully in clinical trials for participant selection and tracking of target engagement despite methodological challenges.

In vivo characterization of other comorbid pathology is a key developing area.
Thank you

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Karen Crawford

ADNI sponsors
Example [18F] flortaucipir tau PET cases

MCI: 80yo male
- Aβ- (4 scans)
- ApoE4-
- CDR-sb=0.5
- ADAS-cog=12
- Braak III/IV = 1.72

MCI: 78yo male
- Aβ+ (4 scans)
- ApoE4-
- CDR-sb=1.0
- ADAS-cog=6
- Braak III/IV = 1.14

MCI: 83yo male
- Aβ+ (4 scans)
- ApoE4+
- CDR-sb=1.5
- ADAS-cog=9
- Braak III/IV = 1.35

Aβ- High FTP
Aβ+ Low FTP
Aβ+ Low FTP
High vs low FTP groups

Inferolateral temporal/limbic AV1451

Unimpaired vs Impaired

Aβ - (N=80)
- Non-AD dementia: 81%
- Primary Age Related Tauopathy (PART): 19%

Aβ + (N=71)
- Possible AD with comorbid pathology: 29%
- Typical MCI/AD: 71%
Flortaucipir is variable among impaired (MCI / AD) individuals

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- Fewer AD-specific biomarker characteristics
- Mostly male
- Cerebrovascular or TDP-43 pathology may account for cognitive symptoms (e.g. Schneider et al Brain 2016)

Greater hippocampal atrophy + hypometabolism supports a medial temporal predominant role that could be AD-independent

Understanding the characteristics of “atypical tau” individuals will be important for effective selection of participants for clinical trials of tau-modifying treatments
Tau PET variability

Whitwell et al Ann Neurol 2018

Ossenkoppele et al JAMA 2018
Distribution of suprathreshold (>1.4 SUVR) voxels

Unimpaired (N/SMC)

Impaired (Early/Late MCI, AD)

% subjects with suprathreshold voxels

10%  50%  80%
Figure 4. Hypothetical model of dual peaks of microglial activation in the Alzheimer's trajectory. Top: The hypothetical model of pathological changes in microglia in Alzheimer's disease trajectory, where ramified microglia transform to anti-inflammatory (protected) microglial phenotype and pro-inflammatory (toxic) microglial phenotypes. Bottom: The microglial activation in relation to other biomarkers detectable using positron emission tomography where two peaks of microglial activation are present in Alzheimer's trajectory. Modified from Jib et al. (2015).
Considerable overlap within the low tau range among individuals across the disease spectrum (in LOAD)

Conversely, high neocortical tau in unimpaired subjects has also been reported (e.g. Lowe et al. Brain 2018) ➔ PART
Medial temporal AV1451 resembles MAPT406W mutation pattern.
High vs low FTP group comparison

FDG comparison

**Impaired $\beta^+$**: High inferotemporal/limbic FTP < Low FTP
- $N=57$
- $N=23$
- $p<0.001$ uncorr

**Impaired $\beta^-$**: High inferotemporal/limbic FTP < Low FTP
- $N=13$
- $N=56$

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All Unimpaired (N/SMC)
- Entire AV1451 range  $p=0.04$
- “Normal” AV1451 range  ns

All Impaired (EMCI/LMCI/AD)
- Entire AV1451 range  $p<0.001$
- “Normal” AV1451 range  ns