ADNI PET CORE
Washington DC
4/20
2015

Susan Landau, Allie Fero, Suzanne Baker, Bob Koeppe, Eric Reiman, Kewei Chen, Norman Foster, Chet Mathis, Julie Price

2015 Recipient: Society of Nuclear Medicine and Molecular Imaging Hal Anger Lectureship and Award
### FDG scan counts (as of 04/14/15)

<table>
<thead>
<tr>
<th>Number of FDG scans</th>
<th>N</th>
<th>SMC</th>
<th>EMCI</th>
<th>LMCI</th>
<th>AD</th>
<th>Total</th>
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<td>343</td>
<td>106</td>
<td>307</td>
<td>410</td>
<td>241</td>
<td>1407</td>
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<td>0</td>
<td>5</td>
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<td>106</td>
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<td>1371</td>
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## Florbetapir scan counts (as of 04/14/15)

<table>
<thead>
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<th>Number of Florbetapir scans</th>
<th>N</th>
<th>SMC</th>
<th>EMCI</th>
<th>LMCI</th>
<th>AD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
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<td>1089</td>
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<td>493</td>
<td>111</td>
<td>549</td>
<td>440</td>
<td>175</td>
<td>1768</td>
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</tbody>
</table>
Distributions of 3 biomarkers across ~1000 ADNI participants
ADNI florbetapir stratified by ApoE4 status

Frequency

ApoE4-
- 26% of ApoE4- are florbetapir+
- 24% of ApoE4- are florbetapir+
- 33% of ApoE4- are florbetapir+
- 40% of ApoE4- are florbetapir+
- 60% of ApoE4- are florbetapir+

ApoE4+
- 50% of ApoE4+ are florbetapir+
- 62% of ApoE4+ are florbetapir+
- 69% of ApoE4+ are florbetapir+
- 88% of ApoE4+ are florbetapir+
- 99% of ApoE4+ are florbetapir+

Normal
N=265

SMC
N=79

Early MCI
N=299

Late MCI
N=219

AD
N=188

Total N=1050
The Centiloid Project: Standardizing quantitative amyloid plaque estimation by PET

William E. Klunk, Robert A. Koepp, Julie C. Price, Tammie L. Benzinger, Michael D. Devous, Sr., William J. Jagust, Keith A. Johnson, Chester A. Mathis, Davneet Minhas, Michael J. Pontecorvo, Christopher C. Rowe, Daniel M. Skovronsky, Mark A. Mintun

Abstract

Although amyloid imaging with PiB-PET ([C-11]Pittsburgh Compound-B positron emission tomography), and now with F-18-labeled tracers, has produced remarkably consistent qualitative findings across a large number of centers, there has been considerable variability in the exact numbers reported as quantitative outcome measures of tracer retention. In some cases this is as trivial as the choice of units, in some cases it is scanner dependent, and of course, different tracers yield different numbers. Our working group was formed to standardize quantitative amyloid imaging measures by scaling the outcome of each particular analysis method or tracer to a 0 to 100 scale, anchored by young controls (C20-45 years) and typical Alzheimer's disease patients. The units of this scale have been named “Centiloids.” Basically, we describe a “standard” method of analyzing PiB PET data and then a method for scaling any “nonstandard” method of PiB PET analysis (or any other tracer) to the Centiloid scale.

Keywords: Amyloid imaging; Positron emission tomography; Pittsburgh compound B; Centiloid scale; Standardize

Standardize reporting of amyloid PET results by performing studies with F18 ligands and PIB in the same subjects and translating SUVr measures to a scale from 0-100
Approximate Centiloid Scaling

- **[A]** ADNI reference data: Linear correlation between PiB and Florbetapir SUVR (scans acquired within 24 months)
  
  \[ y = 0.585x + 0.408 \]
  \[ R^2 = 0.930 \]

- **[B]** Comparison of the distribution of PiB SUVR values (or SUVRs):
  - **Left**: ADNI reference data
  - **Right**: Centiloid Level-1 anchor data (available via GAAIN website)

- **[C]** Scaling Steps:
  - **Left**: 510 measured ADNI Florbetapir SUVRs
  - **Middle**: Calculated “PiB-calibrated” Florbetapir SUVRs
  - **Right**: The converted approximate Centiloid units, or aCU

- **CTX ROI (Reference ROI: Whole cerebellum)**
- **median and mean depicted by red bar and cross, respectively**
Improved longitudinal $[^{18}F]$-AV45 amyloid PET by white matter reference and VOI-based partial volume effect correction

Matthias Brendel$^1$, Marcus Högenuer$^2$, Andreas Delker$^4$, Julia Sauerbeck$^4$, Peter Bartenstein$^4$, John Seibyl$^5$, Axel Rominger$^6$, for the Alzheimer’s Disease Neuroimaging Initiative$^1$

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$^2$BNH, New Haven, USA

Measurement of Longitudinal β-Amyloid Change with $[^{18}F]$-Florbetapir PET and Standardized Uptake Value Ratios

Susan M. Landau$^1$, Allison Fero$^2$, Suzanne L. Baker$^2$, Robert Koeppel$^3$, Mark Mintun$^4$, Kewei Chen$^5$, Eric M. Reiman$^6$, and William J. Jagust$^1$

$^1$Helen Wills Neuroscience Institute, University of California, Berkeley, California; $^2$Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California; $^3$Radiology Department, University of Michigan, Ann Arbor, Michigan; $^4$Avid Radiopharmaceuticals, Inc., Philadelphia, Pennsylvania; and $^5$Banner Alzheimer’s Institute, Phoenix, Arizona

Key Words: amyloid; Alzheimer’s disease; PET imaging

J Nucl Med 2015; 56:567–574
DOI: 10.2967/jnumed.114.149732
Mean Cortical and Cerebellar, Pontine and White Matter ROIs

Chen, et al., JNM, 2015
Greater Power to Track 24-mo SUVR Increases Using a Cerebral White Matter ROI

Chen, et al., JNM, 2015
Subjects with positive CSF Aβ at baseline, normal or EMCI, should be increasing florbetapir SUVR from visit 1 to visit 2.

Fewer decliners with white matter in reference region.

Landau et al, J Nucl Med 2015
**Tau Ligands: Molecular Families**

THK Series - Tohoku Compounds

![Chemical structures](image)

- **[11C]PBB-3**
- **[18F]T807 ➔ [18F]AV-1451**
Tau Imaging with $[^{18}F]AV-1451$

- **Control: Male 22**
  - Hippocampus: 0.8
  - Entorhinal Ctx: 0.9
  - Temporal Ctx: 0.9

- **Control: Male 74**
  - Hippocampus: 1.3
  - Entorhinal Ctx: 1.2
  - Temporal Ctx: 1.1

- **Control: Male 90**
  - Hippocampus: 1.4
  - Entorhinal Ctx: 1.2
  - Temporal Ctx: 1.2

- **Control: Female 75**
  - Hippocampus: 1.3
  - Entorhinal Ctx: 1.4
  - Temporal Ctx: 1.6

- **AD: Female 75**
  - MMSE 17
  - Hippocampus: 1.7
  - Entorhinal Ctx: 1.7
  - Temporal Ctx: 2.3

- **AV-1451**

- **PIB**
  - **DVR=1.05**

- **DVR=1.03**

- **DVR=1.76**
Case D (75 year old control, DVR = 1.76)

Case E (AD, 75 year old, MMSE=17)
[\textsuperscript{18}F]AV-1451 Pharmacokinetics

**Time Activity Curves**

- **C_{REF} = cerebellar gray**
- **ROI\textsubscript{1} = temporal cortex**
- **ROI\textsubscript{2} = hippocampus**
- **ROI\textsubscript{3} = putamen**

**SUVRs over time**

- **temporal cortex**
- **hippocampus**
- **putamen**
Tau Deposition by Age and Aβ

18 Cognitively Normal People Mean Age 79

Significant associations with age and PIB

Age ~ Tau

x = 32  
y = 65  
z = 22

x = 48  
y = 74  
z = 27

PiB⁺ ~ Tau

x = 37  
y = 59  
z = 31
Time activity curves of [$^{18}$F]THK-5351
Healthy controls vs AD patients
ADNI3 Specific Aims

Continue Amyloid Imaging every 2 years
   All continuing subjects and new

Multiple amyloid imaging agents

Tau Imaging every year
   All continuing subjects and new

Eliminate FDG?
Major Hypotheses

Tau accumulation will conform to Braak staging

Tau accumulation will occur in MTL in Aβ negative controls

The presence of Aβ in controls and MCI patients will be associated with neocortical tau

Longitudinal accumulation of tau in neocortex will be more rapid in those with Aβ

Tau Imaging will be related to cognition cross-sectionally and longitudinally
Amyloid Imaging in ADNI3

Multiple amyloid imaging agents are planned
- Florbetapir (amyavid)
- Florbetaben (neuraceq)
- Flutemetamol (vizamyl)

Companies to perform centiloid standardization
- Compound vs PIB
- Publicly available data

Delivery to a reasonable number of sites
Tau Imaging: Tracer Characteristics

Multisite Study
Tracer delivery to multiple sites
Management of regulatory issues is clear
PET data acquisition protocol is simple, well tolerated, reliable

Tracer “validation”
Preclinical data showing specificity, affinity, brain uptake
Pharmacokinetics are favorable
Clinical data in a reasonable number of subjects with diverse diagnoses
Data analysis methods yield results with face validity, parallel the biology

Full kinetic models in comparison to SUVr
Plans for tau Imaging in ADNI3

To the extent possible, application will review the state of the field as of mid-2015

Application will propose $[^{18}\text{F}]$AV-1451 for multisite tau imaging in ADNI3

Application will outline the features of acceptable tracers and note that we will use the best tracer at the time ADNI3 starts
FDG?

**Pros**
- Parallels phenotype/correlates with behavior
- Relationship to tau?
- May be predictive of outcomes

**Cons**
- Another scan – subject burden
- Is FDG being included in clinical trials?
- ADNI already has considerable longitudinal FDG data