Imaging Amyloid: Now That We Can See It, What Does It All Mean?

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Rapid growth research area

- Human
- Preclinical

"Pibliography" >150
(I will not get to them all)

PUBLISHED PAPERS PUBLISHED REVIEWS

2001 2002 2003 2004 2005 2006 2007 2008 2009

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Overview

- Can we REALLY see amyloid?
  - Pathological correlation
- What does it all mean?
  - Confirming what post-mortem studies have already told us
  - Going beyond the limitations of post-mortem studies

The story of PiB begins with Thioflavin-T...

Uncharged Thioflavin-T derivatives:

BenzoThiazole-Aniline

6-OH-BTA-1 (PiB)

<table>
<thead>
<tr>
<th>Ki</th>
<th>%DI</th>
<th>t-1/2</th>
</tr>
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<tbody>
<tr>
<td>&lt;10 nM</td>
<td>&gt;100</td>
<td>&lt;10 min</td>
</tr>
<tr>
<td>557</td>
<td></td>
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 Doesn't get into brain due to positive charge
Can we REALLY see amyloid (fibrillar $A\beta$) in vivo?

PiB in a living 22 month Tg2576 mouse – 2-Photon imaging (Bacskai/Hyman)

First human PiB study: Uppsala/Karolinska
February 14, 2002 (presented at ICAD 2002)

PiB retention in vivo correlates well with $A\beta$ levels determined post-mortem

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PiB retention in vivo correlates well with Aβ levels determined post-mortem

Frozen tissue (right hemisphere)

\[ \text{Total Aβ (pmol/mg tissue)} \]

\[ r=0.73; p<0.003 \]

...and with Aβ levels determined by biopsy

Leinonen Arch Neurol 2008; 65: 1304

PiB retention in vivo correlates well with post-mortem PiB and Aβ measures...but not NFT measures

Ikonomovic Brain 2008; 131: 1020

PiB retention in vivo correlates well
with Aβ levels determined post-mortem

Frozen tissue (right hemisphere)

\[ (r=0.73; p<0.003) \]

...and with Aβ levels determined by biopsy

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Amyloid imaging in dementia

Confirming post-mortem studies: In vivo pathology

Going beyond: Amyloid imaging allows a 3-D quantitative rendering across the entire brain
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Going beyond: PET data are quantitative; The pictures come from the numbers

Going beyond: Voxel-wise comparisons across complementary modalities become possible

Going beyond: Aβ deposition and hypometabolism show different regional distributions

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Going beyond: In some areas PiB and FDG PET correlate and in some they do not

- In the temporal and parietal regions there is a significant correlation between PiB retention and metabolic rate for glucose
- In contrast, in the frontal region there is no significant correlation

Edison et al., Neurology 2006; 68: 501

Going beyond: Regional & Voxel-wise comparisons across modalities become possible

PIB (precuneus seed) and metabolism (by FDG PET) show predominantly negative correlations in AD

Cohen J. Neurosci, 2009; 29: 14770

Going beyond: Amyloid imaging in familial, autosomal-dominant early-onset AD

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PET amyloid ligand (1°C)PIB uptake shows predominantly striatal increase in variant Alzheimer’s disease

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A New Amyloid β Variant Favoring Oligomerization in Alzheimer’s-Type Dementia

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Going beyond: CSF Aβ levels are a good predictor of PIB retention > clinical diagnosis

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Going beyond: CSF Aβ levels and PiB retention show significant correlation

Going beyond: some groups report lesser degrees of CSF vs. PiB correlation

Going beyond: CSF Aβ levels may primarily reflect periventricular brain Aβ load

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Going beyond: Defining pathology in vivo
does PiB(+) = Alzheimer’s disease or mixed?

11C-PiB
FTLD-9
FTLD-10
FTLD-6

Retiressi et al., Neurology 2007; 68: 1205

Going beyond: Defining pathology in vivo
does PiB(+) = Alzheimer’s disease or mixed?

Neocortical DVR

Rowe et al., Neurology 2007; 68: 1718
Gomperts et al., Neurology 2008; 71: 503

Going beyond: Defining pathology in vivo
Does PiB(+) = Alzheimer’s disease or mixed?

• SPM showing a significantly increased PiB uptake in DLB
  compared to control subjects

• Very AD-like pattern

Edison, JNP 2008; 79: 1331
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Going beyond: Defining pathology in vivo does PiB(+) = Alzheimer's disease or mixed?

- Johansson et al., Park Rel Disc 2008; 14: 345
- 5/5 PD patients PiB(-)

PD and PDD patients “low” PiB(+)

- Gomperts et al., Neurology 2008; 71: 303

Does PiB(+) = Alzheimer's disease or mixed?

- 5/5 PD patients PiB(-)

Does PiB(-) = NOT Alzheimer's disease?

- Ikonomovic Alzheimer's & Dementia 2009; 5: 202

 Imaging of Amyloid Burden and Distribution in Cerebral Amyloid Angiopathy

- Johnson et al., Ann Neurol 2007 62 (3): 229-34

How well can we go beyond: In vivo pathology does PiB(-) = NOT Alzheimer's disease?

- Johnson et al., Ann Neurol 2007 62 (3): 229-34
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Amyloid imaging in MCI

Confirming post-mortem studies:
MCI subjects can be PiB(+) or PiB(-)

Going beyond: Most MCI patients are clearly PiB(+) or PiB(-); Few are between AD & Cont.
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Going beyond: 50-60% of MCI are PiB(+) and amyloid-positivity predicts clinical conversion

Going beyond: 50-60% of MCI are PiB(+) and amyloid-positivity predicts clinical conversion

Amyloid imaging in cognitively normal elderly
Confirming post-mortem studies:
20-40% of cognitively normal elderly show some amyloid deposition

- One AD
- One MCI
- One Control
  (no specific order)

Haroutunian Arch Neurol 1998; 55, 1185
Price and Morris Ann Neurol 1999; 45, 158
Wolf ADAD 1999; 13, 226

In some cases it is visually obvious,
in some cases it is very subtle

Younger Controls  Older Controls Subjects with DAT
(AD) (mild depends on CDR 0.5 and 1)
Mintun et al., Neurology 2000; 57, 446
Rowe et al., Neurology 2007; 68, 1710

Confirming post-mortem studies:
20-50% of cognitively normal elderly show some amyloid deposition

- One AD
- One MCI
- One Control
  (no specific order)

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**Confirming post-mortem studies:**
Fibrillar Aβ burden in normal elderly is associated with APOE 4 gene dose

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**Confirming post-mortem studies:**
Significantly higher PiB retention (but not atrophy) was found in ε4-positive AD

- Significantly higher PiB retention in ε4-positive AD patients, but no significantly higher atrophy, suggests that the effects of ε4 are mediated through Aβ, but don’t necessarily drive atrophy

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**Going beyond:** PiB(+) controls are distinguished from AD by the amount of amyloid; MCI are not

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Going Beyond:
PiB(+) controls are distinguished from AD by the amount of amyloid; MCI are similar to AD

The consequences of being amyloid-positive

Going beyond: PiB(+) controls and MCI are the ones who show reductions in metabolism over 12-24 months

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Going beyond: PiB(+) normal elderly show a greater degree of brain atrophy

Fotenos et al., Arch Neurol 2008; 65: 113

Going beyond: PiB(+) elderly show more cortical thinning

Dickerson Cereb Cortex 2009; 19: 497

Going beyond: Memory impairment is correlated with PiB retention in controls and MCI

Pike Brain 2007; 130: 2837

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Clinical severity of Alzheimer’s disease is associated with PIB uptake in PET


Going beyond: Aβ drives down cognition through downstream effects such as HC atrophy

Mormino et al., Brain 2009; 132: 1310

Going beyond: The effects of Aβ can be mitigated by brain/cognitive reserve

Kemppainen Ann Neurol 2006; 63: 112

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Going beyond the limitations of post-mortem studies:
Longitudinal studies of amyloid deposition

- Does PiB retention increase over time?
  - How else would you get from control to AD levels?
  - But does PiB retention continue to increase in AD?

No group change in PiB retention in AD

Engler et al., Brain 2006; 129: 2856
Jack et al., Brain 2009; 132: 1205

Baltimore longitudinal study of aging:
PiB(+) subjects increase slowly; PiB(-) do not

NIA-IRP/JHU Courtesy of Susan Resnick
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AIBL: PiB(+) subjects increase 3% per year

"Reliable change index": Compares change in individual subjects to test-retest variability

PiB(+) subjects are 3 times more likely to increase
Two cognitively stable controls

The emerging model: Aβ usually requires mediators to effect cognitive dysfunction (e.g., CVD)

Conceptual model: Aβ-centric view

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Aβ-centric view

The Aβ-centric model does not explain how people with similar levels of Aβ deposition can have very different cognitive status.

Vascular compensation model:
Lower vulnerability to Aβ

1. Normal neuronal function
2. Aβ deposition
3. Disrupted metabolism
4. Inc. rCBF; Normal metab.
5. Further Aβ deposition
6. Disrupted metabolism
7. Neocortical tangles
8. Synapse loss – Atrophy
9. Cell loss
10. Less need for perfusion

Normal MCI Dementia Cognition

No compensation due to vascular disease:
Higher vulnerability to Aβ

1. Normal neuronal function
3. Less Aβ deposition required for:
4. Disrupted metabolism
5. Neocortical tangles
6. Synapse loss – Atrophy
7. Cell loss
8. Decreased need for perfusion

Normal MCI Dementia Cognition
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What does it all mean?
- Pathological AD:
  - Propensity toward Aβ deposition
- Clinical AD:
  - Vulnerability to Aβ deposition
- Cognitively healthy aging:
  - Avoidance of Aβ deposition (e.g. APOE ε2/3) OR
  - Resisting the effects of Aβ (e.g. brain/cognitive reserve)

Pittsburgh amyloid imaging project collaborators/supporters
- Molecular Neuropharm. Lab
  - Manik Debnath, Li Shao
  - Ann Cohen
- Psychiatry/WPIC
  - Bob Nebes, Howard Aizenstein
- Radiology/UPMC PET Facility
  - Chet Mathis - Director
  - Jude Price
  - Scott Mason, Brian Logresti
  - G-F Huang, Wenhu Bi
- Uppsala University PET Centre
  - Bengt Långström, Henry Engler
  - Agneta Nordberg (N, Huddinge)

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