The Many Faces of Alzheimer’s Disease: Clinical and Imaging Phenotypes

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- Presentation includes the amyloid tracer $[^{11}\text{C}]$PIB and tau tracer $[^{18}\text{F}]$AV1451 which are not FDA-approved for clinical use
Dr. David Holtzman
Acclaimed neurologist, neuroscientist, Alzheimer’s researcher

Ken Holtzman
Accomplished MLB pitcher
W-L 174-150, 3.49 ERA
Chicago Cub 1965-71, 1978-79
Outline

• Diversity of Alzheimer’s clinical presentations
  – Early vs. late-onset AD
  – Focal cortical syndromes
• Neurodegeneration patterns
  – MRI and FDG-PET
• Molecular pathology
  – Amyloid and tau post-mortem and in vivo
• Putative mechanisms driving heterogeneity
  – Origin and spread of disease
  – Genetic and developmental vulnerabilities
Early-Onset AD (Age ≤ 65)

- 5% of all AD patients = ~250,000 in U.S.
  - Only ~5%-10% harbor APP/PSEN mutations
- Clinically distinct from late-onset AD
  - At presentation greater (sometimes focal) executive, language and visuospatial dysfunction; relatively spared episodic memory
  - More rapid disease progression
  - On MRI/FDG: greater cortical involvement, sparing of medial temporal lobes
- Likely enriched for novel genetic risk factors
  - Estimated heritability 92%-100%
  - Only ~50% carry ApoE4
Clinical Heterogeneity in AD

Behavioral/dysexecutive AD – 6%

AD-LANGUAGE – 18%
Logopenic Primary Progressive Aphasia

AD-VISUAL – 13%
Posterior Cortical Atrophy

AD-MEMORY – 63%
“Typical” AD
51 yo LHM with word-finding problems
51 yo LHM with word-finding problems
Primary Progressive Aphasia (PPA)

“Slowly progressive aphasia without generalized dementia” (Mesulam 1982)

Usually associated with FTLD pathology, but ~30% have AD

Gorno-Tempini et al. Ann Neurol 2004
Logopenic-variant PPA (lvPPA)

- Anomia, word finding pauses
- Impaired sentence/phrase repetition
- Phonologic errors
- Spared motor speech and grammar
- Spared single word and object knowledge

Gorno-Tempini et al., Ann Neurol 2004
Gorno-Tempini et al., Neurology 2011
Amyloid PET Links lvPPA to AD

MRI

FDG

Amyloid

nfvPPA (n=31)

svPPA (n=28)

lvPPA (n=26)

10% Aβ+

14% Aβ+

96% Aβ+

Rabinovici et al. Ann Neurol 2008; Santos et al., submitted
Series of five patients with progressive, higher order visual dysfunction; spared memory, insight and judgment

**Posterior Cortical Atrophy**

D. Frank Benson, MD; R. Jeffrey Davis, DO; Bruce D. Snyder, MD
Arch Neurol 1988

**Progressive posterior cortical dysfunction**

A clinicopathologic series

J.A. Renner, MD*; J.M. Burns, MD*; C.E. Hou, MD; D.W. McKeel, Jr., MD; M. Storandt, PhD; and
J.C. Morris, MD

**Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy**

D.F. Tang-Wai, MDCM; N.R. Graff-Radford, MBBCh FRCP (London); B.F. Boeve, MD; D.W. Dickson, MD;
J.E. Parisi, MD; R. Crook; R.J. Caselli, MD; D.S. Knopman, MD; and R.C. Petersen, PhD, MD

30 total patients with autopsy confirmation:
23 AD, 4 CBD, 2 prion disease, 1 DLB + subcortical gliosis
Posterior Cortical Atrophy (PCA)

- “Visual variant of AD” (80%-90%)
- Dorsal (“where”) visual stream
  - Spatial relationships, locating items
- Ventral (“what”) visual stream
  - Alexia, visual agnosia, prosopagnosia
- Balint syndrome
  - Ocular apraxia, optic ataxia, simultanagnosia
- Primary visual cortical dysfunction
  - Visual field deficit
- Dorsal > ventral visual stream, primary visual more rare

Benson et al., Arch Neurol 1988
Crutch et al., Lancet Neurol 2012
PCA: Non-Visual Features

- R parietal features
  - Environmental disorientation
  - Dressing apraxia
- L parietal features
  - Gerstmann syndrome
    - Acalculia, agraphia, L/R confusion, finger agnosia
  - Ideomotor apraxia
- Aphasia
  - Anomia, alexia
- Hemineglect (R or L)

Benson et al., Arch Neurol 1988
Crutch et al., Lancet Neurol 2012
National, open-label study on clinical utility of amyloid PET in ~18,500 Medicare beneficiaries with MCI or dementia of uncertain cause

- Eligible patients referred for PET by dementia experts
- Scans covered by CMS, performed and interpreted locally

Aim 1: Impact of scan on management plan at 3 months

Aim 2: Impact on major medical outcomes at 12 months

The primary hypothesis is that, in diagnostically uncertain cases, amyloid PET will lead to significant changes in patient management, and this will translate into improved medical outcomes
Neuropathology of Non-Amnestic AD

Posterior Cortical Atrophy

NFTs

Senile plaques

Tang-Wai et al. Neurology 2004

Frontal-Variant AD

NFTs

No difference in plaque distribution

Johnson et al. Arch Neurol 1999

Primary Progressive Aphasia

Gefen et al. Brain 2012
Diverging Amyloid and Hypometabolism Patterns in AD Variants

FDG - PET

- Controls $>$ EOAD
- Controls $>$ LOAD
- Controls $>$ lvPPA
- Controls $>$ PCA

PIB - PET

- EOAD $>$ controls
- LOAD $>$ controls
- lvPPA $>$ controls
- PCA $>$ controls

Lehmann et al., Brain 2013
[\textsuperscript{18}F]AV1451/T807: Tau-Selective PET Tracer

PHF tau IHC (AT8) \hspace{1cm} [\textsuperscript{18}F] AV1451 autoradiography \hspace{1cm} Amyloid β IHC

Xia et al., Alz and Dem 2013

PET tau

CDR0

CDR>0

Brier et al., Sci Transl Med 2016
Amyloid (PIB)

AD-MEM
MMSE 20

Atrophy (MRI)

IvPPA
MMSE 17

Tau (AV1451)

PCA
MMSE 22
Tau PET Patterns Correlate with AD Phenotype

LOAD (n=4)

EOAD (n=8)

LvPPA (n=7)

PCA (n=8)

Covaried for age, p(FWE)<0.05
Ossenkoppele et al., Brain 2016
AD Variants Target Distinct Brain Networks and Converge in DMN

AD-EXECUTIVE
Executive control network

AD-LANGUAGE
Language network

AD-VISUAL
Higher visual network

All AD Variants
Default mode network

Lehmann et al., PNAS 2013
Aβ aggregates in cortical hubs

Tauopathy develops in vulnerable epicenter/s

Trans-neuronal spread to inter-connected networks

Clinico-anatomic phenotype

Executive control

Higher-order visual

Memory

Language
Relationships Between Tau Patterns in AD and Normal Brain Connectivity

Seeds defined based on common and distinct atrophy

Selected peak atrophy voxels:
1. L posterior cingulate cortex (all AD variants)
2. R Middle occipital cortex (PCA)
3. L Superior temporal gyrus (lvPPA)
4. R Middle frontal gyrus (EO-AD)

Migliaccio et al., Neurology 2009

Ossenkoppele et al., HAI 2016
Generated covariance maps from seed regions

[^{18}F]AV1451 PET (36 AD patients)

Resting-state fMRI (1000 young controls, www.neurosynth.org)

“Resting” BOLD amplitude

Ossenkopelle et al., AAIC 2016
L Posterior Cingulate (Common) Seed

Seed region

Seed region

[18F]AV1451 covariance (AD patients)

Functional connectivity (Young adults)

<table>
<thead>
<tr>
<th>Network</th>
<th>GOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior DMN</td>
<td>3.76</td>
</tr>
<tr>
<td>Ventral DMN</td>
<td>1.76</td>
</tr>
<tr>
<td>R. Executive control</td>
<td>1.15</td>
</tr>
<tr>
<td>Language</td>
<td>0.96</td>
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<tr>
<td>Salience</td>
<td>1.04</td>
</tr>
<tr>
<td>L. Executive control</td>
<td>0.52</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>0.23</td>
</tr>
<tr>
<td>Higher-visual</td>
<td>-0.87</td>
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</table>

AV1451: p<0.05 FWE corrected;
R Middle Occipital Gyrus (PCA) Seed

Seed region

[18F]AV1451 covariance (AD patients)

Functional connectivity (Young adults)

Network GOF

<table>
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<tr>
<th>Network</th>
<th>GOF</th>
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<tr>
<td>Higher-visual</td>
<td>8.17</td>
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<tr>
<td>Ventral DMN</td>
<td>0.65</td>
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<tr>
<td>Language</td>
<td>0.35</td>
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<tr>
<td>Posterior DMN</td>
<td>0.10</td>
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<tr>
<td>Sensorimotor</td>
<td>-0.25</td>
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<tr>
<td>Salience</td>
<td>-0.38</td>
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<tr>
<td>R. Executive control</td>
<td>-1.60</td>
</tr>
<tr>
<td>L. Executive control</td>
<td>-1.76</td>
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AV1451: p<0.05 FWE corrected; fMRI: p<0.01 FDR corrected
**L Superior Temporal Gyrus (lvPPA) Seed**

<table>
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<tr>
<td>Language</td>
<td>5.88</td>
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<tr>
<td>Posterior DMN</td>
<td>2.56</td>
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<td>L. Executive control</td>
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<td>Salience</td>
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<td>Ventral DMN</td>
<td>1.17</td>
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<td>R. Executive control</td>
<td>0.43</td>
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<tr>
<td>Higher visual</td>
<td>-0.77</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>-1.85</td>
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</tbody>
</table>

AV1451: p<0.05 FWE corrected; fMRI: p<0.01 FDR corrected
R Middle Frontal Gyrus (EOAD) Seed

Seed region

[18F]AV1451 covariance (AD patients)

Functional connectivity (Young adults)

Network GOF

<table>
<thead>
<tr>
<th>Network</th>
<th>GOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Executive control</td>
<td>4.37</td>
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<tr>
<td>L. Executive control</td>
<td>2.29</td>
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<tr>
<td>Salience</td>
<td>1.41</td>
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<tr>
<td>Posterior DMN</td>
<td>1.12</td>
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<tr>
<td>Ventral DMN</td>
<td>0.79</td>
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<tr>
<td>Language</td>
<td>0.60</td>
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<tr>
<td>Sensorimotor</td>
<td>-1.27</td>
</tr>
<tr>
<td>Higher-visual</td>
<td>-2.90</td>
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AV1451: $p<0.05$ FWE corrected; fMRI: $p<0.01$ FDR corrected
PIB Covariance Patterns are Non-Specific

AV1451 covariance maps (p<0.05 FWE)

fMRI connectivity maps (p<0.01 FDR)

PIB covariance maps (p<0.05 FWE)
Aβ aggregates in cortical hubs

Tauopathy develops in vulnerable epicenter/s

Trans-neuronal spread to inter-connected networks

Clinico-anatomic phenotype
MRI Atrophy (VBM)
395 AD subjects from UCSF/VUMC
44% CDR 0.5 / 56% CDR 1.0

Ossenkoppele et al., Human Brain Mapping 2015
ApoE4 Associated with Amnestic/Medial Temporal Phenotype

ApoE4+ AD
63% amnestic
37% non-amnestic

ApoE4- AD
32% amnestic
68% non-amnestic

van der Flier et al. Lancet Neurol 2010; Lehmann et al., JNNP 2013
Featured Article

Genetic risk factors for the posterior cortical atrophy variant of Alzheimer’s disease

- 302 PCA patients from 11 centers
- Associations with APOE (weak), CR1, ABCA7, BIN1
- Exploratory GWAS
  - **SEMA3C**: Class III Semaphorin 3C (SEMA3C)
    - Chemotrophic molecule associated with maturation of visual system and development of septo-hippocampal connections
  - **FAM46A**: Family with sequence similarity 46
    - Expressed in neural retina
    - Cell signaling pathways related to retinal neurodegeneration
  - **CNTNAP5**: Contactin-associated protein-like 5
    - CNS Cell adhesion and intercellular communication
    - Risk factor for bipolar disorder and autism spectrum disorders

Schott et al. Alzheimer’s & Dementia 2016
Domain-Specific Learning Disabilities Associated with IvPPA and PCA

Developmental language disorders associate with IvPPA

High prevalence of non-language learning disabilities (acalculia, spatial) in PCA

Z Miller et al., Brain 2013; AAIC 2015
Aβ aggregates in cortical hubs

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Clinico-anatomic phenotype

Memory ApoE4

Executive control

Language learning disability

Higher-order visual
Non-language learning disability
CR1/ABCA7/BIN1 CNTNAP5, FAM46A, SEMA3C
Take Home Points

• Diverse clinical phenotypes associated with AD neuropathology
  – Diagnostic challenge
  – Model to study mechanisms of heterogeneity

• Phenotype in AD is tightly linked to NFTs
  – Amyloid PET useful diagnostically, but uptake patterns don’t distinguish variants
  – Evidence that spread of NFTs drives neurodegeneration and clinical deficits

• Much about AD heterogeneity remains unexplained
  – Early-onset and atypical patients may harbor clues about novel genetic, environmental and developmental vulnerabilities
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