Amyloid-related brain dysfunction: Evidence for a presymptomatic stage of AD

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Alzheimer’s Disease

Cognitive function

Presymptomatic

Prodromal

Normal Aging

Dementia

Years
Pathology of AD
Pathophysiological Process of AD

? 

Cognitive and Behavioral Symptoms of AD
What we know.....

Normal                      Mild AD
What we don’t yet know…

Sperling R et al. *NeuroMolecular Med* 2010
Linking pathology to cognitive impairment: Connundrums

- Anatomic distributions of amyloid and tangles do not always map well onto classical brain-behavior relationships.
- Amyloid plaque load does not correlate well with dementia severity, tangles somewhat better, synaptic loss correlates best.
- Individuals with a “head full of amyloid” are still cognitively normal.
Linking pathology to cognitive impairment: SPACE-TIME CONTINUUM

• SPACE: pathology =? domain localization
  – Networks rather than “lightbulbs” or regions
  – Oligomeric forms poorly localized

• TIME: pathology =? stage of impairment
  – Lag between development of pathology and appearance of symptoms
  – Threshold of pathological burden

• CAPACITY: brain and cognitive reserve
  – Capacity to tolerate pathology
  – Compensation
Linking anatomic distributions of pathology to brain-behavior systems and networks
Autopsy Series: Amyloid and Neurofibrillary Tangles

Braak and Braak Acta Neuropath 1991
PIB-PET Amyloid Imaging

Normal
Older Control

Alzheimer’s Disease

DVR = 1.0       2.0
Hippocampal Atrophy

Figure 2. Coronal T1-weighted MRI scans of control (left) and patient with AD (right). Both subjects are 75 years old. The patient with AD shows clear atrophy of the hippocampus.

Scheltens, P. Imaging in AD. Dialogues in Clinical Neuroscience (2009)
Memory Networks in Aging, MCI and AD

Celone K et al. J Neuroscience 2006
Face-Name Association

• Remembering proper names is the most common memory complaint of older individuals.

• Difficult paired associative memory task
  – Faces and names inherently unrelated
  – Requires the formation of a novel association across visual and verbal domains

• Likely requires the coordination of multiple brain regions, in particular the hippocampal formation
"Hi. I'm, I'm, I'm... You'll have to forgive me, I'm terrible with names."
Event-Related fMRI - Subsequent Memory
“Correctly Remembered vs. Forgotten” Face-Name pairs

Young Subjects (n=16)

MR Signal: Right Anterior Hippocampus (27, -15, -15)

Sperling et al. NeuroImage 2003
Decreased Hippocampal Activation in AD compared to Normal Aging

Mild AD patients < Normal Older Controls

Sperling R et al JNNP 2003
Hippocampal function fails during MCI

Early MCI
CDR-SB 0.5-1.5

Late MCI
CDR-SB 2.0-3.5

Celone K et al. J. Neuroscience 2006
Reciprocal relationship between hippocampal activation and parietal deactivation

Celone K et al. *J Neuroscience* 2006
Hippocampal and Precuneus/Post Cingulate fMRI during Successful Memory Formation

Miller S
PNAS
2008
Relationship of amyloid deposition to the “default network” in AD

Buckner R et al. J Neurosci 2005
Anatomic overlap of amyloid deposition with default network during memory formation

Sperling R et al Neuron 2009
Relationship of amyloid deposition to default network activity

Sperling et al. Neuron 2009
Relationship of amyloid deposition to default network failure

Sperling R et al, Neuron 2009
Failure of Default Network in Cognitively Normal Older ApoE ε4 carriers

L precuneus (-10,-68,44)

e4- vs. e4+, Z-score: 2.3 — 4.3
CDR 0.0 vs. 1.0, Z-score: 2.3 — 4.3

Pihlajamaki M et al  ADAD 2010
Potential mechanisms underlying increased activity

• Cholinergic (ChAT) upregulation in MCI
  – DeKosky *Annals Neurology* 2002

• Aberrant cholinergic or noradrenergic sprouting
  – Hashimoto and Masliah *Neurochem Res* 2003
  – Szot *J Neuroscience* 2006

• De-synchronization of neuronal firing
  – Stern *J Neuroscience* 2004

• Lower baseline metabolism or perfusion
  – Mosconi *Neurology* 2005

• Compensatory neuronal recruitment
  – Sperling *Ann NY Acad Sci* 2007

• Excitotoxicity – harbinger of neural system failure
Hyperactive neurons near amyloid plaques

Busche et al. Science 2008
What goes down must come up…

Encoding vs. Retrieval

P<.001, extent = 5 voxels

* F(1,38) = 5.19, p=.028

Vannini P et al Cerebral Cortex (In Press)
ICA-based detection of default-mode network in healthy aging (A) and AD (B).

Greicius et al., PNAS, 2004
Amyloid-related disruption of intrinsic connectivity among asymptomatic elderly

Hedden T et al J Neuroscience 2009
Default network connectivity predicts memory performance in older individuals

Wang L NeuroImage (In press)
TIME

Linking the pathophysiological sequence of Alzheimer’s disease to the progression of clinical impairment
Brain and Cognitive Reserve

Age Genetics

Amyloid-β Pathology

Synaptic Dysfunction

Neuronal Loss

Cognitive Impairment

PiB
CSF A-β

Task fMRI

Resting FDG

CSF tau

Volumetric MRI

Sensitive Cognitive Measures

Standard Clinical Measures
Dynamic Model of Biomarkers of the Alzheimer’s Pathological Cascade

- Aβ Amyloid
- Tau Mediated Neuron Injury & Dysfunction
- Brain Structure
- Memory
- Clinical Function

Clinical Disease Stage

- Normal
- Cognitively Normal
- MCI
- Dementia

Jack C. Lancet Neurology
2010
Heterogeneity of amyloid burden in asymptomatic elderly

Sperling R et al. *NeuroMolecular Med* 2010
Appearance of Plaques vs. Dementia

Figure courtesy of Mark Mintun and John Morris, Washington University
Dynamic Model of Biomarkers of the Alzheimer’s Pathological Cascade

Clinical Disease Stage

- Normal
- Cognitively Normal
- MCI
- Dementia

Abnormal

Aβ Amyloid

Tau Mediated Neuron Injury & Dysfunction

Brain Structure

Memory

Clinical Function

Jack C. Lancet Neurology 2010
Decreased metabolism with increased amyloid: FDG vs precuneus PiB

All CN (N=77)

J.A. Becker HAI 2010
Longitudinal Amyloid Accumulation and AD markers

Baseline PiB vs. Cortical thickness

Longitudinal PiB

Johnson K (in preparation)
CAPACITY

Brain and Cognitive Reserve Compensation?
Pre-symptomatic genetic at-risk for AD

Bookheimer et al., NEJM 2000
Increased hippocampal fMRI activation in early MCI

Dickerson et al. *Neurology* 2005
Longitudinal fMRI in MCI: Change in Hippocampal Activation Baseline vs. Two year follow-up

Baseline > Year 2
n = 51; p<0.001

O’Brien J et al Neurology (in press)
CAPACITY

What is “Normal”? 
$^{18}$F-AV-45 Representative Images: Healthy Controls

Amyloid Negative HC

Amyloid Positive HC
WMS-Immediate Recall

\[ R = -0.33 \]
\[ p = 0.003 \]

SUVr: partial \( r = -0.334 \)
\[ p = 0.027 \]

Age: partial \( r = 0.067 \)
\[ p = 0.562 \]
Cognition in Aβ Pos vs. Neg in HC > 70 years old

WMS Immediate      WMS Delayed                                   Digit-Symbol

Sperling et al. HAI 2010
Dang!... Now where was I going?

Superman in his later years
Cognitive Reserve mediates clinical expression of amyloid burden

Memory Capacity Test*
Delayed Recall

Rentz D et al *Annals of Neurology 2010*
Summary of what we know

• Anatomic overlap of AD pathology and critical nodes of brain networks subserving memory function
  – Amyloid (default network)
  – Neurofibrillary pathology (medial temporal lobe)

• Converging evidence from multiple imaging modalities that there are functional abnormalities in this network prior to symptoms

• Early evidence that amyloid is associated with very subtle memory impairment
Remaining questions?

• Is there a specific threshold of amyloid burden that will trigger downstream pathological cascade and eventual impairment?
• Is the anatomic location of amyloid pathology critical for predicting decline?
• Is fibrillar amyloid deposition (as assessed by imaging) a reasonable proxy for presence of oligomeric forms that may be responsible for the synaptic dysfunction?
Investigate amyloid-related alterations in neural function and structure at molecular, synaptic, network, and behavioral levels.
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