Is there a Distinct Phenotype to Memory Loss in Alzheimer's Disease?

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ALTHEIMER
POP. 5 Million
# Clinical and Pathological Course of AD

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Cognitive State</th>
<th>Pathologic State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>No Symptoms</td>
<td>No Disease</td>
</tr>
<tr>
<td>Pre-Clinical AD</td>
<td>No Symptoms?</td>
<td>Early Changes</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild Symptoms</td>
<td>Mild Mod Changes</td>
</tr>
<tr>
<td>AD</td>
<td>Mild-Severe Symptoms</td>
<td>Mod-Severe Changes</td>
</tr>
</tbody>
</table>

- **Plaques**:
- **Tangles**

![Brain Images](brain_images.png)
Aging Versus AD

I may have alzheimer's, but at least I don't have alzheimer's.
Age-Associated Cognitive Impairment

Performance declines with increasing age for Speed of Processing, Working Memory, and Long-Term Memory.

Performance is preserved over age for World Knowledge.

Aging Versus Preclinical/Prodromal AD

• Quantitative differences
  – E.g. Face-name memory test
  – Specificity dependent of degree of age-related and AD-related change

• Qualitative differences?
Topographic Selectivity of AD

Mesulam, 1990
“Doctor Who”
“Downton Abbey”

Sir Richard Carlisle (Ian Glenn)
Dual Process Models of Recognition Memory

- Two distinct memory processes
  - Familiarity (item memory)
    - Acontextual sense of prior encounter
    - Quantitative
    - Relatively *automatic* process
  - Recollection (associative, relational)
    - Detailed retrieval, including spatial and temporal context – “mental time travel”
    - Qualitative
    - *Controlled* Process
Proposed Spatial and Temporal Dissociation of Recollection and Familiarity

• Neuroanatomy
  – Recollection: Hippocampus, Frontal control networks
  – Familiarity: Perirhinal cortex/lateral entorhinal area

• Timing
  – Recollection: Slower
  – Familiarity: Faster
Binding of Items and Context Model

Eichenbaum et al., *Ann Rev Neurosci*, 2007
What Drives Memory Loss with Normal Aging?

**Buckner, Neuron, 2004**

Small et al., *Nature Neuroscience*, 2012
Is Familiarity Selectively Impaired in MCI (prodromal AD)?

- Normal aging: recollection impaired, familiarity intact
- MCI: Predict familiarity (and recollection) should be impaired
- Alternative:
  - If familiarity and recollection on strength continuum, expect relative sparing of familiarity
Table 1
Demographic and neuropsychological data

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>a-MCI</th>
<th>Norms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.2 (8.9)</td>
<td>72.2 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>16.1 (3.2)</td>
<td>16.9 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Female:Male</td>
<td>13:8</td>
<td>6:10</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>29.6 (.9)</td>
<td>28.1* (1.8)</td>
<td>28.9 (1.3)</td>
</tr>
<tr>
<td>Trails A</td>
<td>28.4 (9.1)</td>
<td>34.8 (11.2)</td>
<td>40.6 (13.1)</td>
</tr>
<tr>
<td>Trails B</td>
<td>60.6 (15.7)</td>
<td>77.1 (32.9)</td>
<td>87.2 (31.6)</td>
</tr>
<tr>
<td>Digits forwards max.</td>
<td>6.9 (1.1)</td>
<td>7.0 (1.0)</td>
<td>6.7 (1.4)</td>
</tr>
<tr>
<td>Digits backwards max.</td>
<td>5.7 (1.1)</td>
<td>4.6** (1.0)</td>
<td>5.2 (1.4)</td>
</tr>
<tr>
<td>CERAD encoding</td>
<td>22.7 (3.4)</td>
<td>16.6** (3.3)</td>
<td>22.3 (3.8)</td>
</tr>
<tr>
<td>CERAD recall</td>
<td>7.2 (1.8)</td>
<td>2.4** (2.0)</td>
<td>7.4 (2.1)</td>
</tr>
<tr>
<td>Category fluency (animals)</td>
<td>21.9 (4.9)</td>
<td>16.3** (3.6)</td>
<td>19.0 (5.1)</td>
</tr>
<tr>
<td>COWAT (FAS)</td>
<td>47.9 (15.8)</td>
<td>38.3* (11.8)</td>
<td>43.5 (13.1)</td>
</tr>
</tbody>
</table>

Note: Standard deviations are in parentheses.
* $p<0.05$.
** $p<0.01$, compared to the control group.
In Process-Dissociation Paradigms

\[ p_R = p(\text{"Old"}|\text{Intact}) - p(\text{"Old"}|\text{Rearranged}) \]

\[ p_F = \frac{p(\text{"Old"}|\text{Rearranged})}{1 - p_R} \]
Wolk et al., *Neuropsychologia*, 2008
Recollection and Familiarity Impaired in MCI
(NC: n=81; MCI: n=65)

Recollection

\[ p < 0.001 \]

Familiarity

\[ p < 0.001 \]

Control-Referenced z-scores

\[ p < 0.001 \]

Wolk et al., *Neuropsychologia*, 2013
Is Familiarity Spared in “Normal Aging”? (YC: n=18; OC: n=81)

Recollection

Familiarity

Wolk et al., *Neuropsychologia*, 2013
“Petersen Criteria” for MCI
(now referred to as amnestic-MCI)

• Memory complaint (preferably corroborated by informant)
• Episodic Memory impairment for age and education
• Largely intact general cognitive function
• Essentially preserved activities of daily living
• Do not meet criteria for dementia
Amnestic MCI

- Enriched in patients with AD pathology
  - Specialty Clinics
    - 10 to 15% “Conversion” to clinical AD per year
      - 1-3% in cognitively normal adults
    - 50-80% over 5 years
  - Community Studies (PAQUID, MoVIES)
    - Lower conversion rate (4 to 8%/year)
    - Reversion to normal (10 to 40% over 2 years)
Amyloid Imaging

55-65% PiB positive in most studies of MCI

Wolk and Klunk, 2009
Does Familiarity Discriminates MCI Based on Amyloid Status (n=22)?

**Recollection**
- Amyloid Negative
- Amyloid Positive

**Familiarity**
- Amyloid Negative
- Amyloid Positive

$p < 0.05$
Limited Neuropsychological Data

- Familiarity
- Recollection

Rugg and Yonelinas, *TICS*, 2002

Bowles et al., *PNAS*, 2007

Guedj et al., *Neuropsychologia*, 2010
Relationship to MTL Volumes

- Examined relationship of recollection and familiarity estimates with structure
  - Hippocampus
  - Extrahippocampal MTL (PRC, ERC, PHG)
  - Automated Labeling Pathway (Wu et al., 2006; Andreeescu et al., 2007)

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**Demographic and Memory Data for Older Adults, Amnesic-Mild Cognitive Impairment Patients, and Alzheimer’s Disease Patients**

<table>
<thead>
<tr>
<th></th>
<th>OA (n = 21)</th>
<th>a-MCI (n = 14)</th>
<th>AD (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>29.7 (0.7)</td>
<td>28.0 (1.7)a</td>
<td>24.0 (1.9)a,b</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.7 (9.1)</td>
<td>71.2 (8.0)</td>
<td>77.8 (4.4)b</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.7 (2.9)</td>
<td>16.6 (3.1)</td>
<td>15.0 (3.0)</td>
</tr>
<tr>
<td>Recollection</td>
<td>0.36 (0.23)</td>
<td>0.21 (0.12)a</td>
<td>0.10 (0.09)a,b</td>
</tr>
<tr>
<td>Familiarity (d')</td>
<td>1.86 (0.50)</td>
<td>1.12 (0.42)a</td>
<td>0.73 (0.40)a,b</td>
</tr>
<tr>
<td>Source/total studied</td>
<td>0.58 (0.17)</td>
<td>0.37 (0.16)a</td>
<td>0.30 (0.15)a</td>
</tr>
<tr>
<td>Source/hits</td>
<td>0.73 (0.15)</td>
<td>0.54 (0.19)a</td>
<td>0.36 (0.13)a,b</td>
</tr>
<tr>
<td>Item (d')</td>
<td>2.93 (0.57)</td>
<td>2.13 (0.60)a</td>
<td>1.74 (0.75)a</td>
</tr>
</tbody>
</table>

OA, older adult controls; a-MCI, amnesic-mild cognitive impairment; AD: Alzheimer’s disease.

a P < 0.05 relative to controls.
b P < 0.05 relative to a-MCI.

Wolk et al., *Hippocampus*, 2011
Wolk et al., *Hippocampus*, 2011
Correlates of Memory in AD Patients from ADNI

• ADNI participants with clinical AD diagnosis
  – Mean MMSE: 23.3 ± 2.0 (SD)
  – MRI of sufficient quality (n=146)

• MRI analysis
  – Disease specific ROI’s (hippocampus, PRC/ERC)
  – Correlate with standard memory measures differentially dependent on recollection/familiarity
Memory Measure

• Rey Auditory Verbal Learning Test (AVLT)
  – 15 words
  – 5 Immediate memory (learning) trials
  – List B immediate memory
  – 5-minute delayed recall
  – 30-minute delayed recall
  – Recognition memory test
AD Cohort from ADNI (n=146) – AVLT Delayed Memory Measures

Recollection \rightarrow \text{Recall}

Familiarity \rightarrow \text{Recognition}

Recollection

Wolk & Dickerson, *NeuroImage*, 2011
Pure Familiarity – Recognition discrimination controlled for free recall

Wolk and Dickerson, *NeuroImage*, 2011
Interim Summary

• Familiarity-based memory is spared as part of normal age-associated cognitive decline
• Familiarity is dependent on integrity of perirhinal cortex (ERC?)
• Consistent with early involvement of PRC in AD pathologic process, familiarity-based memory appears sensitive and specific to prodromal AD
• Is familiarity-based memory sensitive to preclinical AD?
Preclinical Alzheimer’s Disease

- 25-30% of CN adults with AD molecular biomarker profile
- Consistent with autopsy data

Morris et al., *Annals of Neurology*, 2010
Cortical Signature of AD

Dickerson et al., *Cerebral Cortex*, 2011
Abnormal Function

Amyloid (PiB)  
Function  
Psychometrics

Normal

Modified from Jack et al., 2010
Abnormal Function Amyloid (PiB)

Psychometrics

Brain Structure (MRI)

Normal MCI Dementia

Clinical disease stage

Modified from Jack et al., 2010
Modified from Jack et al., 2010
Does Evidence of AD-Specific Atrophy Predict Decline in CN Adults

• ADNI healthy controls with adequate 1.5 T MRI (n=159)
• Mean AD signature measure converted to z-score
  – > 1 SD below mean – ADsig “thin” (high risk group)
  – Within 1 SD of mean – ADsig “Average”
  – > 1 SD above mean – ADsig “thick” (lowest risk group)
• 3 year follow-up
  – *a priori* cutoffs of functional (> 1.0 increase in CDR Sum of Boxes) and cognitive decline (> 1 SD decline)
Cortical Thinning in Signature of AD regions predicts decline and CSF AD profile in Cognitively Normal Adults

Dickerson and Wolk, *Neurology*, 2012
Relationship of AD Cortical Signature with Recollection/Familiarity

$\beta = 0.55, p < 0.001$

$\beta = 0.37, p < 0.05$

Wolk et al., *Neuropsychologia*, 2013
Summary

• Biomarkers of neurodegeneration may be valuable in temporal prediction in preclinical phases beyond amyloid status

• Preclinical disease may be associated with subtle cognitive change
  – Familiarity as possible screening measure?
  – Familiarity as cognitive outcome measure in preclinical trials
Collaborators

• Penn
  – Paul Yushkevich
  – Sandy Das
  – John Detre
  – Steve Arnold
  – Lauren Mancuso
  – Dasha Kliot
  – Katie Manning

• MGH/Harvard
  – Brad Dickerson

• Pitt
  – Steve DeKosky
  – Howard Aizenstein
  – Eric Signoff
  – Kathryn Dunfee

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