Mild Cognitive Decline/ Memory Loss/Dementia

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Lecture 3
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Age-Related Memory Changes

- The magnitude of age-related memory deficits varies across different forms of memory.

- Semantic memory, primary memory, procedural memory, and various forms of priming are relatively spared.

- Episodic memory (e.g., forgetting names and faces, misplacing objects, forgetting phone numbers, missing appointments, losing train of conversation) is often impaired.
Episodic Memory

• Deals with conscious retrieval of information that is encoded in a particular place at a particular time (Tulving, 1983)

• Typically assessed by having subjects recall or recognize information acquired in a laboratory (e.g., a list of words, series of faces)

• Attempts to change memory have primarily focused on this type of memory
## Percent Age 65 or Older with Moderate or Severe Memory Impairment, by Age Group and Sex

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Moderate or Severe Memory Impairment</th>
<th>Severe Memory Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Men</td>
</tr>
<tr>
<td>65 to 69</td>
<td>4.4</td>
<td>5.3</td>
</tr>
<tr>
<td>70 to 74</td>
<td>8.3</td>
<td>10.1</td>
</tr>
<tr>
<td>75 to 79</td>
<td>13.5</td>
<td>16.2</td>
</tr>
<tr>
<td>80 to 84</td>
<td>20.1</td>
<td>22.8</td>
</tr>
<tr>
<td>85 or older</td>
<td>35.8</td>
<td>37.3</td>
</tr>
</tbody>
</table>

*Source: Health and Retirement Study*
Moving Toward Prevention of AD: Rise of Mild Cognitive Impairment

- Often a preclinical stage of progressive dementias, such as AD and now, Vascular Dementia
- How to identify subclinical cognitive impairment?
- Varying definitions and prevalences
  - Age-associated Memory Impairment (Crook, 1986). More than simply memory loss
  - MCI (Petersen, 1989). Emphasis on memory
  - Differential reliance on presence of objective as well as subjective memory problems
  - Differential reliance on presence of IADL difficulties, by self-report
Spectrum of Cognitive Impairments

- Normal aging
- Asymptomatic Alzheimer’s disease
- Subjective cognitive complaints
- MCI Objective impairment
- Dementia Usually caused by Alzheimer’s disease

Increasing risk of developing dementia
Function

Mild cognitive impairment

Probable AD

Definite AD

Age
Symptomatic Course of AD

• AD is characterized by a gradual onset with a continual cognitive decline
• Personality changes may include
  – Increased irritability
  – Depression, perhaps as a prodromal feature
• Generalized cortical atrophy on CT/MRI
ALZHEIMER DETERIORATION ON THE MINI-MENTAL STATE EXAM OVER TIME

SCORE

AVERAGE TIME OF ILLNESS (years)
Changes in Brain Metabolism with AD

PET Scan of Normal Brain

PET Scan of AD Brain

Predictors of Cognitive Decline and Alzheimer’s Disease

- Raised systolic blood pressure
- High cholesterol
- Impairments on tests of memory and executive function
- White-matter lesions on MRI scans
- Possession of \textit{APOE-}ε4 allele
Criteria for MCI Amnestic Type (MCI-AT)

- Memory complaints preferably corroborated by an informant
- Impaired memory function for age and education
- Preserved general cognitive function
- Intact activities of daily living
- No evidence of dementia
Criteria for MCI Multiple Cognitive Deficits-Type (MCI-MCOT)

- Deterioration in at least one cognitive domain
- May or may not affect IADLs
From MCI to Dementia of the Alzheimer’s type

• Rates of conversion from MCI to AD vary greatly
• Most studies have annual rates between 10-15%
• Rates are higher where domains in addition to memory loss are affected and where there is evidence of associated vascular or parkinsonian disease
• Possible to delineate degrees of severity within MCI (mild, moderate, severe)
Mild Cognitive Impairment (MCI)

<table>
<thead>
<tr>
<th></th>
<th>Initial exam</th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
<th>48 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MCI → AD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control → AD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symptomatic Course of AD - MCI

- MCI first operationally defined by Flicker et al. (1991), later redefined by Petersen et al. (1999)
- Is Mild Cognitive Impairment (MCI) early/ prodromal AD or a distinct diagnostic entity?
  - Morris JC et al. argues MCI represents early-stage AD
  - Petersen RC et al. argues MCI is distinct entity, can transition back to normal or AD
- MCI – Amnestic Type (MCIa) is most common form
  - Characterized by isolated memory impairment and subjective memory complaint, but no IADL impairment (IADLs not well operationalized)
## Prevalence of MCI

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>age</th>
<th>Diagnostic Criteria</th>
<th>Prevalence Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frisoni 2000</td>
<td>1,435</td>
<td>75-95</td>
<td>MCI</td>
<td>15</td>
</tr>
<tr>
<td>Ritchie 2001</td>
<td>833</td>
<td>≥60</td>
<td>MCI</td>
<td>3</td>
</tr>
<tr>
<td>Hanninen 2002</td>
<td>1,150</td>
<td>60-76</td>
<td>MCI</td>
<td>5.3</td>
</tr>
<tr>
<td>Busse 2003</td>
<td>1,045</td>
<td>≥75</td>
<td>MCI</td>
<td>3.1</td>
</tr>
<tr>
<td>Busse 2003</td>
<td>1,045</td>
<td>≥75</td>
<td>MCI w/o SMC</td>
<td>5.1</td>
</tr>
<tr>
<td>Fisk 2003</td>
<td>1,790</td>
<td>≥65</td>
<td>MCI</td>
<td>1.03</td>
</tr>
<tr>
<td>Fisk 2003</td>
<td>1,790</td>
<td>≥65</td>
<td>MCI w/o SMC</td>
<td>3.02</td>
</tr>
<tr>
<td>Lopez 2003</td>
<td>3,608</td>
<td>≥65</td>
<td>MCI</td>
<td>19</td>
</tr>
<tr>
<td>Lopez 2003</td>
<td>927</td>
<td>≥65</td>
<td>MCIa</td>
<td>6</td>
</tr>
<tr>
<td>Ganguli 2004</td>
<td>1,248</td>
<td>≥65</td>
<td>MCI</td>
<td>3.2</td>
</tr>
<tr>
<td>Solfrizzi 2004</td>
<td>2,963</td>
<td>65-84</td>
<td>MCI</td>
<td>3.2</td>
</tr>
</tbody>
</table>
## Conversion from MCI to AD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Source</th>
<th>Mean Age</th>
<th>N</th>
<th>Conversion To:</th>
<th>Mean follow-up (months)</th>
<th>Annual Conversion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tierney 1996</td>
<td>Clinic</td>
<td>73.9</td>
<td>138</td>
<td>NINCDS-ADRDAD AD</td>
<td>24</td>
<td>10.9</td>
</tr>
<tr>
<td>Huang 2000</td>
<td>Clinic</td>
<td>61.2</td>
<td>31</td>
<td>NINCDS-ADRDAD AD</td>
<td>26</td>
<td>22.5</td>
</tr>
<tr>
<td>Li 2001</td>
<td>Community</td>
<td>68.7</td>
<td>19</td>
<td>Clinical Dx of AD CDR &gt;= 1</td>
<td>44</td>
<td>13.5</td>
</tr>
<tr>
<td>Morris 2001</td>
<td>Community</td>
<td>76.4</td>
<td>53</td>
<td>DSM-III R</td>
<td>61</td>
<td>4.0</td>
</tr>
<tr>
<td>Ritchie 2001</td>
<td>Community</td>
<td>&gt;65</td>
<td>308</td>
<td>DSM-III R</td>
<td>24</td>
<td>5.6</td>
</tr>
<tr>
<td>Amieva 2004</td>
<td>Community</td>
<td>50-85</td>
<td>90</td>
<td>DSM-III R</td>
<td>24</td>
<td>16.1</td>
</tr>
<tr>
<td>Tabert 2006</td>
<td>Clinic</td>
<td>&gt;65</td>
<td>148</td>
<td>NINCDS-ADRDAD AD</td>
<td>36</td>
<td>10.1</td>
</tr>
</tbody>
</table>

(16.6 MCIa)
MCI Clinical Trials

- MCI cases studied in most centers and currently being sought for clinical trials represent the most severe end of spectrum of MCI
- Milder cases take much longer to progress to diagnosis of AD (or decline or remain stable)
- Other factors influence rate of conversion from MCI to AD in addition to severity of impairment (e.g., ApoE-4)
MCI: Conversion to Dementia

APOE 4 noncarrier

APOE 4 carrier

Years

%
Remaining Challenges for MCI Clinical Trials

• Identify homogeneous population at high risk for conversion to AD
• Select variables sensitive to progression over time in domains central to pathophysiology of disease (identify optimal tests)
• Select time interval over which change can be measured
• Why try?
Evolving Concept of MCI

• MCI relevant to disorders other than AD
  - Other dementing disorders most likely to present with non-memory impairments (e.g., fronto-temporal dementia, vascular dementia)
Mild cognitive impairment
- Amnestic

Mild cognitive impairment
- Multiple domains slightly impaired

Mild cognitive impairment
- Single non-memory domain

Alzheimer’s disease

Alzheimer’s disease
- ? normal aging

Frontotemporal dementia
- Lewy body dementia
- Primary progressive aphasia
- Parkinson’s disease

Alzheimer’s disease
An Updated Model of Dynamic Biomarkers in AD

Jack et al., 2013, Lancet Neurology