Neuropsychological Assessment of Early Cognitive Impairment in the Elderly

David Loewenstein PhD, ABPP/CN
Professor of Psychiatry and Behavioral Sciences
Department of Psychiatry, Miller School of Medicine, University of Miami
PI, Co-PI and Co-Investigator on Several Funded NIH GRANTS

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The United States population is growing older

- In 2000 the number of older adults (age 65 or above) in the United States was estimated to be 35 million
- In 2030 it is estimated that there will be greater than 72 million older adults
- Age is the greatest risk factor for cognitive impairment and for conditions such as Alzheimer’s disease (AD)
Number of Persons 65+, 1900-2030 (numbers in millions)

<table>
<thead>
<tr>
<th>Year (as of July 1)</th>
<th>Number Persons 65+</th>
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<tbody>
<tr>
<td>1900</td>
<td>3.1</td>
</tr>
<tr>
<td>1920</td>
<td>4.9</td>
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<tr>
<td>1940</td>
<td>9.0</td>
</tr>
<tr>
<td>1960</td>
<td>16.6</td>
</tr>
<tr>
<td>1980</td>
<td>25.5</td>
</tr>
<tr>
<td>1990</td>
<td>31.2</td>
</tr>
<tr>
<td>2000</td>
<td>35.0</td>
</tr>
<tr>
<td>2010</td>
<td>40.2</td>
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<tr>
<td>2020</td>
<td>54.8</td>
</tr>
<tr>
<td>2030</td>
<td>72.1</td>
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Age-Related Cognitive Changes

Z-scores vs Age Groups

- Perceptual Speed
- Spatial Ability
- Working Memory
- Memory - Recall
- Verbal Ability

Park Lab n = 350
THREE COGNITIVE STATES THAT CLINICIANS NEED TO CONSIDER WHENEVER AN ELDERLY PERSON IS BEING EVALUATED

• SUBJECTIVE MEMORY COMPLAINTS (No Cognitive or Functional Deficits)

• MILD COGNITIVE IMPAIRMENT (MCI) (Memory Complaints, Cognitive Deficits, but No Functional Deficits)

• DEMENTIA (Cognitive + Functional Deficits)
CASE Study

- The patient states that his memory is fine but his wife interjects that he has become forgetful.
- She states that he is “terrible with dates and numbers. That was the main reason that we had to sell the business”.
DSM-IV Criteria for Dementia

• A. The development of multiple cognitive deficits manifested by both
  • 1) memory impairment
  • 2) one or more cognitive disturbances (aphasia, apraxia, agnosia, disturbance in executive function)
• B. Cognitive deficits cause significant impairment which represents decline in social and occupational function
• C. Deficits do not occur exclusively during the course of a delirium
Potential Clinical and Research Contributions of Neuropsychological Assessment

• Detection of subtle dysfunction in areas such as memory, language, visual-spatial skills, executive function, attention, psychomotor speed, information processing

• Can serve as a useful baseline to evaluate changes longitudinally

• Can be related to neuroimaging and other biomarkers of brain function
Dementia: Scope of the Problem

• In 2010 35.6 million older adults across the globe are living with dementia (predominantly Alzheimer’s disease)

By 2030- estimated 65.7 million cases
By 2059- estimated 115.4 million cases

• The total estimated worldwide costs of dementia in 2010 are US $604 billion

Alzheimer’s disease

Over 5.5 million people in the United States are currently afflicted with Alzheimer’s Disease

Greatest risk factor is age (Risk at 85 Years of Age as High as 35%-50%)

There is presently no cure, only mild amelioration of symptoms
Alzheimer’s Disease

• Progressive cognitive decline – symptoms worsen over time
• Additional behavioral features
  – Agitation
  – Wandering
  – Emotional distress
• Characteristic neuropathology
  – Amyloid plaques (deposits of abnormal protein – beta-amyloid)
  – Neurofibrillary tangles (tau protein)
• No single test can show if a person has AD
  – Thorough medical history
  – Mental status testing
  – Neurological examination and tests (e.g., brain imaging)
Beta-amyloid Plaques

1. APP sticks through the neuron membrane.

2. Enzymes cut the APP into fragments of protein, including beta-amyloid.

3. Beta-amyloid fragments come together in clumps to form plaques.

In AD, many of these clumps form, disrupting the work of neurons. This affects the hippocampus and other areas of the cerebral cortex.
Neurons have an internal support structure partly made up of microtubules. A protein called \textit{tau} helps stabilize microtubules. In AD, \textit{tau} changes, causing microtubules to collapse, and \textit{tau} proteins clump together to form neurofibrillary tangles.
**Beta Amyloid Pathogenic Pathways**

- **β-amyloid (Aβ)**
  - Leads to **Free Radicals**
  - Causes **Oxidative Damage**
  - Results in **NFTs**
  - Contributes to **Loss of brain cells and their connections**
  - Leads to **Cognitive Impairment**
  - Generates **Microglia Activation**
  - Triggers **Astrocyte Activation**
  - Promotes **Inflammatory Proteins**
  - Induces **Cholinergic Damage**
  - Enhances **Aβ Deposit**
MILD COGNITIVE IMPAIRMENT IN THE OLDER ADULT

- What is mild cognitive impairment (MCI) in the elderly?

- What are the causes of mild cognitive impairment?

- Is MCI a risk factor for progression of symptoms?

- What evidence suggests that MCI may represent early Alzheimer’s Disease?
Why Elephants Never Forget...
MILD COGNITIVE IMPAIRMENT CRITERIA
(Petersen et al., 2001 – Neurology)

1. Memory complaint, preferably corroborated by an informant
2. Objective memory impairment
3. Normal general cognitive function
4. Intact activities of daily living
5. Not demented
The Concept of Mild Cognitive Impairment

- Definite impairments in more than one cognitive domain
  - Memory
  - Executive functioning
  - Attention
- Subjective awareness of impairment
- Less efficient and more error prone when performing common activities (e.g., bill paying).
- Risk is present for development of other conditions
- Not all people with MCI convert to AD
Not all Cognitive Impairment Represents Alzheimer’s Disease

• There are a number of reasons that a person might present with cognitive impairments
  – depression
  – anxiety
  – medical conditions
  – medication interactions
  – neurological conditions

• Causes may be reversible
MILD COGNITIVE IMPAIRMENT
CONVERSION TO DEMENTIA

Conversion to Dementia

Year
1 2 3
0 10 20 30 40 50
Normal
MCI

Year
WHEN IS MCI EARLY ALZHEIMER’S DISEASE?

- Morris (2001) 100% of MCI patients in memory disorders clinic progressed to dementia over a 9.5 year period (84% met neuropathological pathological criteria for AD)
- Reviewing of epidemiological studies, reversion rate of MCI to normal is as much as 30% (see Brooks and Loewenstein, 2010; Ganguli et al., In Press)
MCI was expanded by Petersen (2003) to include non-amnestic and multiple cognitive domains.

The number of persons with MCI in the US age 70 and above is estimated to be between 5 and 6 million.

Among older adults with MCI, reversion to normal is less likely and progression to dementia is more likely if multiple memory tests impaired or a combination of memory and non-memory tests impaired.

- Alexopolus et al., 2006
- Loewenstein et al., 2006
- Manley et al., 2008
- Loewenstein et al., 2009
• Risk of Alzheimer’s by age 80:
  ▪ $\varepsilon_3/\varepsilon_3$ - 3%
  ▪ $\varepsilon_3/\varepsilon_4$ - 8%
  ▪ $\varepsilon_4/\varepsilon_4$ - 55%

• APOE genetic testing not recommended for asymptomatic persons

• APOE testing may help in diagnosis of persons with dementia
CURRENT TREATMENTS FOR ALZHEIMER’S DISEASE

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Dosage*</th>
</tr>
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<tbody>
<tr>
<td>Aricept / Donepezil</td>
<td>AChE Inhibitor</td>
<td>5 → 10 mg (daily)</td>
</tr>
<tr>
<td>Exelon / Rivastigmine</td>
<td>AChE Inhibitor</td>
<td>1.5 → 6 mg (2 x daily)</td>
</tr>
<tr>
<td>Reminyl / Galantamine</td>
<td>AChE Inhibitor</td>
<td>4 → 12 mg (2 x daily)</td>
</tr>
<tr>
<td>Namenda / Memantine</td>
<td>Neuroprotection</td>
<td></td>
</tr>
</tbody>
</table>

* With food
Neuropsychological Assessment The Evaluation of Early Cognitive Impairment

• Must capture be **reliable** and **valid** and have adequate **sensitivity** and **specificity**.

• the most robust and important effects in the most economical period of time (cost-effective)

• Provide sufficient information for intended purpose (the need for further testing, provide information necessary for the diagnostic process)
Hallmark Feature of Medial Temporal Lobe Deficits

• Deficits in Delayed Recall and Rate of Forgetting

• Newer Findings in AD (Inability to Profit From Cues at Acquisition and Retrieval- Buschke, 1999;2002)

• Vulnerability to Proactive and Retroactive Semantic Interference Loewenstein and Acevedo,2003; 2004)
Issues with Commonly Used Neuropsychological Tests

• Subtle cognitive changes may occur years before a clinical diagnosis of MCI or dementia

• Many neuropsychological measures developed for head injury and used with dementia subjects - not developed to be used with MCI or pre-MCI conditions
Memory Function

1) Should always include a list-learning test (i.e., CVLT-II, HVLT-R, Fuld OME with Semantic Memory Test)

2) Should include verbal as well as nonverbal learning and memory tests (BVMT-R, WMS-IV Visual Reproduction)

3) Include Delay Recall and/or Rate of Forgetting
Language Function

1) Expressive- Category Fluency, Letter Fluency, Confrontation Naming

2) Receptive Language Function- Following simple and more complex commands
Executive Function

1) Concept Formation and Set Shifting - Wisconsin Card Sorting Test
2) Complex Visual Scanning and Shifting Sets (Trails B)
3) Abstract Reasoning Abilities (Similarities - WAIS-IV)
Perceptual/ Visuospatial Skills

1) Perceptual Non-Motor (Hooper Visual Organizational Test, Judgment of Line Orientation)

2) Visuoconstructive-Block Design WAIS-IV
Processing Speed

• Digit Symbol, Coding, Trails A
Summary of Domains that Should be Assessed

• Memory
• Language
• Visuospatial Skills
• Executive Function
• Processing Speed
Can we construct a Cognitive Stress Test?

Vulnerability to Semantic Interference as an Early Marker of Alzheimer’s Disease
Semantic interference deficits and the detection of mild Alzheimer’s disease and mild cognitive impairment without dementia

DAVID A. LOEWENSTEIN,1,2 AMARILIS ACEVEDO,1,2 CHERYL LUIS,1,2 THOMAS CRUM,1,2 WARREN W. BARKER,1 AND RANJAN DUARA1,2
1Wien Center for Alzheimer’s Disease and Memory Disorders, Mount Sinai Medical Center, Miami Beach, Florida
2Department of Psychiatry and Behavioral Sciences, University of Miami School of Medicine, Miami, Florida
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Abstract
Impairment in delayed recall has traditionally been considered a hallmark feature of Alzheimer’s disease (AD). However, vulnerability to semantic interference may reflect early manifestations of the disorder. In this study, 26 mildly demented AD patients (mild AD), 53 patients with mild cognitive impairment without dementia (MCI), and 53 normal community-dwelling elders were first presented 10 common objects that were recalled over 3 learning trials. Subjects were then presented 10 new semantically related objects followed by recall for the original targets. After controlling for the degree of overall memory impairment, mild AD patients demonstrated greater proactive but equivalent retroactive interference relative to MCI patients. Normal elderly subjects exhibited the least amount of proactive and retroactive interference effects. Recall for targets susceptible to proactive interference correctly classified 81.3% of MCI patients and 81.3% of normal elderly subjects, outperforming measures of delayed recall and rate of forgetting. Adding recognition memory scores to the model enhanced both sensitivity (84.6%) and specificity (88.5%). A combination of proactive and retroactive interference measures yielded sensitivity of 84.6% and specificity of 96.2% in differentiating mild AD patients from normal older adults. Susceptibility to proactive semantic interference may be an early cognitive feature of MCI and AD patients presenting for clinical evaluation. (JINS, 2004, 10, 91–100.)
Semantic Interference Test (SIT)
SEMANTIC INTERFERENCE TEST (SIT) (Loewenstein, Acevedo and Duara et al, 2003; 2004)

• Ten common objects are presented and recalled over three learning trials
• Introduce 10 additional objects for recall which are semantically related to items on 1\textsuperscript{st} list (e.g., fork for spoon; comb for brush)
• **Proactive Interference**- Old learning interferes with new List B learning
• **Retroactive Interference**- New List B Learning interferes with recall of original targets
Interference Effects In Learning and Memory

• Proactive Interference- Old Learning Interferes with New Learning

• Retroactive Interference- New Learning Interferes with Old Learning
Sensitivity and Specificity of the SIT in the early Detection of MCI-AD

MCI-AD      Sensitivity= 84.6%
Normal Elderly Specificity= 96.2%
SIT Longitudinal Findings

• Relative to a wide array of neuropsychological measures Bag B recall was more highly predictive of decline from MCI to dementia over an average 30 month period

NEWER TESTS DEVELOPED IN OUR LABORATORIES- LASSI-L (Crocco et al, In Press)

• 1) Subject is told up front that they will need to recall 15 targets that are either fruits, clothing and musical instruments (sets up more active encoding)

• 2) Free and Cued Recall then an additional learning trial

• 3) A second list if 15 targets from the exact same categories as List 1 (free recall, cued and second learning trial.

• 4) Subsequent short delay and cued recall of the target list
ADVANTAGES OF LASSI-L

• More active encoding of the to-be-remembered target
• Can look control for initial degree of memory performance and examine a) ability of MCI-AD subjects to a) benefit from cues; b) cued recall format tends to produce semantic errors; c) proactive and retroactive interference can be examined independently of general retrieval deficits
• Most sensitive test to date for picking up earliest impairments of MCI-AD or Pre-MCI
• Developed for use with multi-cultural populations
NOT ALL MCI REPRESENTS ALZHEIMER’S DISEASE

• Neuropsychologist Must Insure That Sensory Deficits (Hearing and Vision Loss) Are Not Mistaken for MCI

• Anxiety/Depression/Stress and Cultural Factors Need To Be Accounted For With Regards To Impact On Cognitive Performance

• Degenerative: Lewy Body Disease; Fronto-Temporal Dementia

• Vascular: Strokes, TIAS, Vasculitis

• Toxic/Metabolic/Endocrine (Drugs, Alcohol, Thyroid)
• Space Occupying Lesions (Tumors, Subdural Hematomas Hydrocephalus)
FACTORS THAT INCREASE THE PROBABILITY THAT MCI REPRESENTS EARLY ALZHEIMER’S DISEASE

• Atrophy of the hippocampus and particularly the entorhinal cortex
• PET Scan amyloid imaging or FDG
• CSF levels of AB 42 and tau
• Homozygous for the ApoE allele (4/4) or Heterozygous for the ApoE allele
Progressive Atrophy of ERC & HPC

Young

Aged (control)

MCI

Mild AD
Sagittal MRI: Progressive HPC/Amygdala Atrophy

Time 0 18months  36months
MRI PREDICTION OF CONVERSION FROM MCI TO CLINAL AD

Meta –Analyses revealed that hippocampal atrophy on MRI could identify 73% of MCI subjects who progressed to AD

Similar progression could be predicted by FDG PET scans


PET IMAGING OF AMYLOID WITHIN THE BRAIN

• Pathologic diagnosis of Alzheimer’s disease (AD) requires β-amyloid plaques
• PET radiotracers can now detect amyloid plaques in vivo
• Applications of PET amyloid imaging in AD and aging may be enormous
[\textsuperscript{11}C] PIB and PET: 
In Vivo Imaging of β-Amyloid Plaques

PIB Scans in Normal and MCI Subjects

**Normal Subjects**
- **CDR 0**
  - 75 y/o man
  - MMSE = 30
  - PIB-negative

**Mild Cognitive Impairment Subjects**
- **CDR 0.5**
  - 74 y/o NC
  - MMSE = 25
  - PIB-negative
  - 77 y/o woman
  - MMSE = 27
  - PIB-positive
  - 82 y/o man
  - MMSE = 28
  - PIB-positive
CSF Amyloid and Tau

1) Unique beta-amyloid and tau profiles occur in 90% of AD patients, 72% of MCI patients and 36% of Normal Controls

2) 100% of MCI with CSF amyloid and tau markers progressed to AD and 94% of pathologically verified AD patients could be identified

3) Questions about the specificity to AD

ROC Analyses For CSF Biomarkers

Aβ-42 AUC=78; p-tau AUC=76; Total AU=.79


In meta analyses, episodic memory scores more predictive in detecting preclinical AD than CSF biomarkers

COULD THOSE WITH NORMAL COGNITION ACTUALLY HAVE EARLY AD DUE TO COGNITIVE RESERVE?

• Alzheimer’s Pathology is seen on autopsy among 30% of subjects who are not cognitively impaired in their lifetime.

• This raises the possibility that those with high cognitive reserve may be able to handle increased amyloid load and subsequent early neurodegeneration without exhibiting symptoms.
Large Sample of 800 Subjects In Miami and Tampa (Loewenstein et al., 2010)

Identified Subjects that did not meet stringent Criteria for MCI but were not normal

1) Pre-MCI Clinical  (Clinical History suggestive of memory decline but normal neuropsychological testing)

2) Pre-MCI amnestic+ (Normal clinical history and exam but one neuropsychological memory test 1.5 or more SD below expected levels)

3) Pre-MCI amnestic++ (Normal clinical history and exam but two or more neuropsychological memory tests 1.5 SD or more below expected levels)
Pre-MCI States and Progression To MCI or Dementia Over a 2-3 Year Follow-up (Loewenstein et al., 2010)

<table>
<thead>
<tr>
<th>Initial DX</th>
<th>No Progression</th>
<th>Progression to MCI</th>
<th>Progression to Dementia</th>
<th>Total Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>96.3%</td>
<td>3.7%</td>
<td>0%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Pre- Amnestic MCI+ (N=48)</td>
<td>83.3%</td>
<td>16.7%</td>
<td>0%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Pre-Amnestic MCI ++ (N=18)</td>
<td>61.1%</td>
<td>27.8%</td>
<td>11.1%</td>
<td>38.9%</td>
</tr>
<tr>
<td>Pre- Amnestic MCI Clinical (N=41)</td>
<td>78.0%</td>
<td>17.1%</td>
<td>4.9%</td>
<td>22.0%</td>
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Progression of Pre-MCI Over a 2-3 Year Follow-up (Loewenstein et al., 2010)
Has the Study of MCI Been Fruitful?

- Is MCI a useful concept in that it has generated interest in studying diseases their early stages (important implications for diagnosis and treatment)? **YES**

- Is MCI necessarily Alzheimer’s disease? **NO** MCI and etiological underpinnings must be established through comprehensive clinical evaluation and neuropsychological testing.

- Will certain cognitive profiles and biomarkers increase the probability that we are probably dealing with an underlying Alzheimer’s process? **Yes**

- Are we ready to make a research diagnosis of Alzheimer’s disease at the MCI stage based on cognitive and biomarker data? **Yes** Clinical Diagnosis of MCI-AD- Probably too early...
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