WHAT IS NORMAL IN THE MEMORY SPECTRUM?

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Objectives:

• Explain criteria for mild cognitive impairment and dementia.

• Review risk factors for cognitive to decline.

• Discuss cognitive aspects of different dementias.

DISCLOSURE
Marwan Sabbagh, MD, FAAN does have a significant financial interest or other relationship with manufacturer(s) of commercial product(s) and or provider(s) of commercial services discussed in the presentation.

Abbott, Eisai, Elan, Eli Lilly, Forest, GSK, Novartis, Pfizer, Wyeth
Slide 1

What is Normal in the Memory Spectrum?

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Slide 2

TOPICS

• I. The BRAIN and MEMORY?
• II. Does it change with Age?
  ➢ How does it change?
• III. Aging vs Dementia(s)
• IV. Research:
  ➢ Levels of Evidence
  ➢ Clinical Trials
• V. Treatments / Suggestions

Slide 3

The Brain’s Vital Statistics

• Adult weight: About 3 pounds
• Adult size: a medium cauliflower
• Number of neurons: 100,000,000,000 (100 billion)
• Number of synapses (the connections between neurons):
  • 100,000,000,000,000 (100 trillion)
Memory in Normal Aging

Issues in Aging Research:
• What is “Normal” vs Early Disease in the Chronologically Gifted?

“Normal” Memory vs Dementia

• Problem 1: What is “Normal” loss vs Sign of Early Disease in the Chronologically Gifted

• Problem 2: Early Decline is Different for Everyone.
  » Different starting points
  » Different levels of “reserve” (and injuries)
  » Life Styles
Slide 7

What is the Problem?

- Swings away and remembers it was a stick.
  - Anxiety, stress, normal
- Sees stick and remembers that was it.
  - Still normal or ??
- Sits on stick and still can’t remember it.
  - Might be a real problem.

Slide 9

How do we conceptualize Memory?

- Verbal
- Visual / Spatial
- Tactile / Somatosensory
- Olfactory
- Motor
Slide 10

How do we conceptualize Memory?

- Episodic Memory
- Semantic Memory
- Perceptual-motor Priming
- Classical Conditioning
- Operant Conditioning

Slide 11

Normal Aging vs Warning Signs

Memory
- "Senior moments"
  - where you parked
  - what you came into a room for
  - harder to get around town
- Interfere with function
  - not recognizing your car
  - forgetting how to cook a favorite meal
  - getting lost in a familiar area

Slide 12

Normal Aging vs Warning Signs

Language
- "Tip-of-your-tongue"
  - takes longer to come up with a word or familiar name
  - May need directions, etc. written out.
- Interfere with function
  - Being unable to name familiar objects or substituting incorrect words.
  - Difficulty following spoken or written directions.
Slide 13

Normal Aging vs Warning Signs

Finances

- Everything is more complex
  - A bit harder to organize bills and balance checkbook
  - May rely on accountant, but able to organize finances.

- Interfere with function
  - Multiple attempts to add numbers correctly, even with calculator
  - Can’t calculate tip
  - Can’t track finances.

Slide 14

Normal Aging vs Warning Signs

Misplaces Objects

- “I know they were here a minute ago”
  - May misplace keys, wallet, etc. in a drawer or on counter.
  - Usually able to easily retrace steps and find them.

- “Somebody took them.”
  - May put thing in inappropriate places (e.g. wallet in Freezer)
  - Very hard to “retrace steps” to find them.

Slide 15

Normal Aging vs Warning Signs

Mood and Personality

- Cranky and Irritable
  - Minor due to frustration, etc.

- Depression or Anxiety due to medical, loss of loved one, etc.

- “Not like himself”
  - Suspicious and fearful accuse others of theft

- Rapid Mood Swings with no apparent cause or disproportionate.
Slide 16

Why it matters:
• Is it safe for someone with “mild” Alzheimer’s dementia to drive a car?

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Slide 17

“Normal” Memory vs Dementia

• "I forgot where I put my keys."
• "I forgot what my keys are for."
  – Pick wrong key at first (MCI ?)

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Slide 18

Memory: The Basics

• Getting it in - “Encoding”
• Keeping it in - “Storage”
• Getting it out - “Retrieval”

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Course of Aging, MCI and AD

Age

Cognitive Decline

Brain AD

MCI

Clinical AD

AAMI / ARCD

All this leads to a greater range of what is "Normal" as we age.

Course of Aging, MCI and AD

Age

Cognitive Decline

Brain AD

MCI

Clinical AD

AAMI / ARCD
Some abilities naturally decrease as we get older.
- However, what is “Normal” may not be Optimal.

Aging: AAMI (ARCD), MCI, and AD


Healthy 30 year old
Healthy 76 year old
Healthy 76 year old
78 year old with Alzheimer’s Disease
**Slide 25**

**AAMI / ARCD Operational Criteria**

- Subjective complaint of decline in memory
  - Use a standardized metamemory instrument
- Objective confirmation of memory decline
  - Use standardized memory tests
  - > 1 SD below mean of Young normals
- Absence of dementia or MCI
- No clinically significant neurological, medical or psychiatric disorders

Adapted from Crook, et al., 1986

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**Slide 26**

**Syndrome of MCI**

- Mild cognitive decline that is worse than typical for age but less severe than in dementia (Flicker, et al., 1991)
  - Mild memory impairment – Other cognitive domains
- Common activities of daily living (ADL) are intact
  - May be subtle impairment in very complex ADL
- Often a very early stage of dementia
  - 5 - 15% / year progress to dementia – 80% over 10 years
- Prodromal AD if apply “AD” inclusion/exclusion criteria

(Ferris, 10/16/01)

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**Slide 27**

**MCI: Definitions and Categories**

- MCI
  - Amnestic Forms
    - Single Domain
    - Multiple Domain
  - Non-amnestic Forms
    - Single Domain
    - Multiple Domain
Clinical Criteria for MCI of AD Type

- Subjective memory complaint reported by subject or informant
- Global cognition intact (MMSE >25)
- Memory impairment confirmed objectively
- ADL impairment is insufficient for diagnosis of dementia; IADL may be effected (GDS = 3 or CDR = 0.5)
- No medical / other etiology for memory deficit.

AAMI vs MCI

<table>
<thead>
<tr>
<th>AAMI</th>
<th>MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compare to young subjects</td>
<td>Compare to similar age and education</td>
</tr>
<tr>
<td>Annoying more than problematic</td>
<td>May or may not impact on daily function</td>
</tr>
<tr>
<td>Probably stable or minimal decline</td>
<td>May be a warning sign of incipient dementia</td>
</tr>
</tbody>
</table>

Model of MCI as Prodromal Dementia

Normal Cognition

Unexpected Decline for AGE

Mild Cognitive Impairment

Brain Aging

Dementia

Alzheimer's Disease

Vascular Dementia

Mixed Dementia

Mixed Alzheimer's Disease
### Slide 31

**Dementia**

*Umbrella* Term

- Head injury
- Stroke
- AD
- PD (Lewy Body Dementias)
- HD
- Other (PSP, CBGD, Pick’s, CJD, etc.)
- Depression (?)

### Slide 32

**Clinical Characterization of Alzheimer’s Disease**

- Impairment in memory
- Impairment in at least one other area of cognition
  - Language, Praxis, Executive, etc.
- Activities of daily living affected
- Other possible cause of dementia excluded

### Slide 33

**Risk Factors for Cognitive Decline**
Slide 34

Risk Factors for Cognitive Decline

- Age
- Genetic influences
- ApoE status
- Female gender
- Medical comorbidities

Slide 35

Risk Factors for Alzheimer's Disease:

Medical Comorbidities

- Hypertension
- Heart disease
- Diabetes
- Elevated low-density lipoprotein cholesterol
- High homocysteine levels
- Transitory ischemic attacks (TIAs)
- Head trauma
- Environmental exposure to toxins (particularly lead)

Slide 36

Non-Neurological Factors Affecting Performance with Age

- Acute - Medications
  - Nutritional (B12, Dehydration)
  - Metabolic (endocrine, hypothyroid)
  - Psychological (anxiety, depression)
  - "Pseudodementia"
- Chronic - Different Genetics
  - Accumulated Damage / Disease
Slide 37

Risk Factors for Alzheimer's Disease:
Psychological/Psychosocial Factors

- Low educational achievement
- Lack of physical activity
- Lack of social interaction/leisure activities
- Excessive response to stress (excessive cortisol levels)

Slide 38

Risk Factors for Alzheimer's Disease:
Psychological/Psychosocial Factors

- Of Brain Vulnerability in
  - Aging
  - Dementia

Slide 39

Risk Factors for Cognitive Decline:
Lifestyle Choices

- Smoking
- Substance abuse, including alcohol and illicit drugs
**Slide 40**

**Course of Aging, MCI and AD**

![Graph showing the progression of cognitive decline from Age to Clinical AD](Image)

**Slide 41**

**Evaluation of Cognitive Decline**

- History
- Mental Status Exam
- Neurological Exam
- Chemistry Panel
- Complete Blood Count
- Vitamin B12 level
- Thyroid function studies
- CT/MRI

**Optional**
- Syphilis serology
- Sedimentation Rate
- Chest X-Ray
- Electrocardiogram
- Urine tests
- Drug Levels
- HIV testing
- Lyme serology
- EEG
- PET/SPECT
- Apo E genotyping
- CSF (Aβ42/tau or 14-3-3 for CJD)

**Slide 42**

**Evaluation of Patients with Dementia**

- History
- Mental Status Exam
- Neurological Exam
- Chemistry Panel
- Complete Blood Count
- Vitamin B12 level
- Thyroid function studies
- CT/MRI

**Optional**
- Syphilis serology
- Sedimentation Rate
- Chest X-Ray
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- HIV testing
- Lyme serology
- EEG
- PET/SPECT
- Apo E genotyping
- CSF (Aβ42/tau or 14-3-3 for CJD)
Slide 43

Memory Assessment

Verbal:
• Word Lists
• Stories

Visuo-Spatial
• Drawings
• Pictures

Slide 44

Memory Changes with Normal Aging

• Verbal and Visual Memory usually tested.

• Declarative Memory is usually most affected
  › Episodic - some encoding, mostly retrieval
  › Semantic - mostly retrieval

• Crystallized vs Fluid Intelligence

Slide 45

Figure 7 Clock Drawing Test. Clock faces show examples of abstraction difficulties.

[Image of a clock drawing test]
Slide 46

![Graph showing the distribution of a specific allele as a risk factor for AD by age 60 in dementia patients.](image)

Slide 47

![Decision tree for cognitive decline and dementia classification.](image)

Slide 48

**MRI in Cognitively Normal Elderly**

- **“Normal”**
- **“Moderate Atrophy”**

Hippocampal atrophy: Precedes and predicts AD

(Adapted from de Leon et al., 1997)
Slide 49

MRI Hippocampal volume

Annual rate of decline in AD vs Aging
- 4.9% decline in hippocampus vs 1.4% (3.5x)
- 16% increase in temporal horn volume vs 4%
- 99% of subjects showed decline in hippo volume
  - Only 60% showed decline in cognition
  - MRI is more consistent than behavioral measures (?)

Jack et al. 2003, Neurology

Slide 50

So how do we achieve "Optimal" Aging?
- what is the best oil, maintenance, etc.?

Slide 51

"Treatment" of Aging Memory

- Mental Strategies:
  - Increase Active Encoding
  - Semantic (meaning)
  - Imagery (visual encoding)
  - Organization / Linking
Slide 52

“Treatment” of Aging Memory

- Mental Strategies:
  - Increase Active Encoding
    - Semantic (meaning)
    - Imagery (visual encoding)
    - Organization / Linking
  - Cueing for Recall
    - Mnemonics (Slice of pie)
    - Episodic to cue Semantic
    - Practiced Recall

Slide 53

“Treatment” of Aging Memory

- Mental Strategies:
  - Effect of Context
  - Complex Encoding
  - Effortful Encoding
  - Retrieval Cues

Slide 54

Treatment Approaches

1) Symptom therapy (Cholinesterase Inhibitors)
2) Slow it (Statins, Vitamin E?)
   “Disease Modification therapy”
3) Stop it (beta-secretase inhibitors?)
4) Cure it (another vaccine?)
5) Prevent it (Anti-inflammatories; Antioxidants; Neurotropics)
Slide 55
Symptomatic Effects versus Slowing Disease Progression

Impairment

<table>
<thead>
<tr>
<th>Time</th>
<th>Severe</th>
<th>Mild</th>
<th>Placebo</th>
<th>Symptomatic</th>
<th>Disease modifying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>End</td>
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</tr>
</tbody>
</table>

(Rev. 10/16/01)

Slide 56
Objections to Treating AAMI / ARCD

1) It is not a disease
   - Define “disease”
2) It is not an accepted condition
   - But, evidence for age-related cognitive decline is significant and widely accepted (DSM IV)
3) Should not treat what is “normal”
   - Numerous age-related, “normal” changes are treated (presbyopia, hair color/loss, wrinkles, etc.)
   - AD primary prevention trials are AAMI/ARCD trials

(modified from Ferris, 10/16/01)

Slide 57
Objections to Treating AAMI / ARCD

4) Normative reference group should be age peers, not young normals
   - Does it reflect a meaningful decrease in function?
5) Should not “mess” with the brain
   - Why not, if favorable risk/benefit ratio?
   - Huge potential market
6) FDA will not accept this treatment target
   - No regulatory barriers if follow established rules
   - Trial design – define condition, subjects, outcomes

(modified from Ferris, 10/16/01)
Slide 58

Mild Cognitive Impairment: Treatment data

- Multi-center clinical trial with conversion as primary endpoint reveals that Aricept delayed conversion by 6 months compared to placebo. Significant difference in conversion at each time point up to 26 months [Poter et al 2005]
- Vitamin E no clinical benefit in preventing conversion to AD.
- Most robust predictor of conversion to AD is ApoE genotype
- Clinical trial with cognition as primary outcome measure demonstrated that Aricept reached statistical significant superiority to placebo on secondary endpoints [Salloway et al 2004]
- Unpublished rofecoxib study negative and may increase risk
- Unpublished galantamine and rivastigmine studies reportedly negative in primary endpoint and all interval timepoints

Slide 59

Benefit of Cholinesterase Inhibitors

<table>
<thead>
<tr>
<th>Improve</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td>Placebo</td>
</tr>
<tr>
<td>Global change</td>
<td>Behavor</td>
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</tbody>
</table>

(AChEI) 

Ferris, 10/16/01