“So, What’s Wrong With a Little Memory Loss: Facts About Mild Cognitive Impairment”

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Objectives:

✓ Distinguish normal age related memory loss from incipient cognitive decline in the form of MCI

✓ Review diagnostic modalities for evaluating MCI

✓ Discuss treatment potions for MCI

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So What Is Wrong With A Little Memory Loss?

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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

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)
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Memory in Normal Aging

Issues in Aging Research:
- What is "Normal" vs Early Disease in the Chronologically Gifted?

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"Normal" Memory vs Dementia

- Problem 1: What is "Normal" loss vs Sign of Early Disease in the Chronologically Gifted?

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"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
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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.

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How do we conceptualize Memory?

- Verbal
- Visual / Spatial
- Tactile / Somatosensory
- Olfactory
- Motor
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**How do we conceptualize Memory?**

- Episodic
- Semantic
- Declaritive
- Perceptual-motor
- Priming
- Classical Conditioning
- Operant Conditioning
- Non-Declarative Memory

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**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

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**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
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**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.

**Interference with function**
- Multiple attempts to add numbers correctly, even with calculator.
- Can't calculate tip.
- Can't track finances.

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**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.

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**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.

- Suspicious and fearful accuse others of theft
- Rapid Mood Swings with no apparent cause or disproportionate.
Why it matters:

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

“Normal” Memory vs Dementia

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

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

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

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Course of Aging, MCI and AD
Some abilities naturally decrease as we get older.

- However, what is “Normal” may not be Optimal.
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**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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**Syndrome of MCI**

- Mild cognitive decline that is worse than typical for age but less severe than 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 early "AD" inclusion/exclusion criteria

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**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
Dementia

• Dementia
  • Compare to similar age and education
  • May or may not impact on daily function
  • May be a warning sign of incipient dementia

• MCI
  • Compare to young subjects
  • More than problematic
  • Probably stable or minimal decline

Ombrella

HD

PD (Lewy Body Dementias)

AD

Other (PSP, CBGD, Pick's, CJD, etc.)

Depression (?)
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**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


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**Risk Factors for Cognitive Decline**

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

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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)

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Non-Neurological Factors Affecting Performance with Age

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

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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)
Risk Factors for Alzheimer's Disease:

Psychological/Psychosocial Factors

+ ? Of Brain Vulnerability in
+ Aging
+ Dementia

Risk Factors for Cognitive Decline:

Lifestyle Choices

+ Smoking
+ Substance abuse, including alcohol and illicit drugs

Course of Aging, MCI and AD

Brain AD
MCI
Clinical AD

AAMI / ARCD
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Evaluation of Cognitive Decline

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Evaluation of Patients with Dementia

Routine
- 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
- Urinalysis
- Drug Levels
- HIV testing
- Lyme Serology
- EEG
- PET/SPECT
- Apo E genotyping
- CSF (Aβ42/tau or 14-3-3 for CJD)

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Memory Assessment

Verbal
- Word Lists
- Stories

Visuo-Spatial
- Drawings
- Pictures

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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

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Figure 7 Clock-Drawing Test. Clock faces show examples of distractibility difficulties.

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Eg Allen's Risk for AD by Age 80 in Dementia Patients
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MRI in Cognitively Normal Elderly

Hippocampal atrophy: Precedes and predicts AD
(Adapted from de Leon et al., 1997)

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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 hippocampus
- Only 60% showed decline in cognition
- MRI is more consistent than behavioral measures
- Jack et al. 2003, Neurology
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So how do we achieve "Optimal" Aging?
- what is the best oil, maintenance, etc.

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“Treatment” of Aging Memory

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

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“Treatment” of Aging Memory

- Mental Strategies:
  - Increase Active Encoding
  - Semantic (meaning)
  - Imagery (visual encoding)
  - Organization / Linking
  - Cueing for Recall
    - Mnemonics (Pie of pie)
    - Episodic to cue Semantic
    - Practiced Recall
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“Treatment” of Aging Memory

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

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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)

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Symptomatic Effects versus Slowing Disease Progression

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<th>Treatment</th>
<th>Severe</th>
<th>Mild</th>
<th>Baseline</th>
<th>End</th>
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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

Objections to Treating AAMI / ARCD

1) Normative reference group should be age peers, not young normals
   > Does it reflect a meaningful decrease in function?

2) Should not “mess” with the brain
   > Why risk, if favorable risk/benefit ratio?
   > Huge potential market

3) FDA will not accept this treatment target
   > No regulatory barriers if follow established rules
   > Trial design – define condition, subjects, outcomes

Mild Cognitive Impairment: Treatment data

1) Multicenter clinical trial with conversion as primary endpoint
   > Numerous age-censored and un-censored endpoints in the Aricept and placebo groups. Significant difference in conversion at each time point up to 20 months (Petersen et al 2005)

2) Meta analysis clinical benefit in preventing conversion to AD.
   > Study robustness 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)

3) Unpublished placebo study negative and may increase risk
   > Unpublished dopaminergic and rivastigmine studies reportedly negative in primary endpoint and all internal timepoints
Benefit of Cholinesterase Inhibitors

- AChEI
- Placebo

Ferris, 10/16/01

6 months

Cognition
Global change
Functioning
Behavior

Global change
Functioning
Behavior