Distinguishing Normal vs. Abnormal Aging

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Disclosures

Speakers:
Ryan Townley, MD, Alzheimer's Clinical Trials Consortium Associate PI; Cognitive and Behavioral Fellowship Program Director; Assistant Professor has no financial relationships to report in the last 24 months with an ineligible company.

Dr. Townley has indicated the presentation may include discussion of off-label uses of a product.

Planners and other Administrative Support:
Jeffrey Burns, MD and Kristi Day have no financial relationships to report in the last 24 months with an ineligible company.
Objectives

• Aging is a broad topic, and we will focus only on cognition
  • What is normal aging?
  • What is abnormal aging?

• What is Subjective Cognitive Impairment?
  • Is it meaningful?

• What is cognitive resilience?

• Discuss research opportunities at KU ADC for cognitively normal and “At Risk” preclinical Alzheimer’s disease

• Note: In two weeks we will discuss broader mild cognitive impairment workup
What is normal aging?

- Aging is a natural process
  - Begins with birth and ends with death
  - Not all individuals age at a similar rate
What is normal aging?

• Having troubles thinking of a name ~83%
  • “As we get older, we build up a larger library, and it takes us longer to find the book (name) we are looking for.”

• Misplacing items around the house ~ 53%
  • “I should put a tracker on my keys”

• Walking into rooms and forgetting why you walked in there ~ 41%

• More difficulties multitasking

• Difficulties paying attention
The Turret on Alert

• These symptoms happen to all of us
  • Even my children!

• When it happens to children we don’t say: “Is this early Alzheimer’s?”

• As we age, our radar goes up and can be overly sensitive
  • Concept of “the worried well” – not great terminology
  • Some people have subjective cognitive decline/impairment
    • Normal objective cognitive testing would help support this
What is normal aging?

• Memory recall on a 12-15 word list decreases with age
  • Different norms for ages 50-59, 60-69, 70-79, and 80+ for this reason

• Brain changes with age:
  • Hippocampus (red box):

![Image of brain MRI with atrophy grades](https://radiologyassistant.nl/neuroradiology/brain-dementia-role-of-mri#assessment-of-mr-in-dementia-mta-scale-for-medial-temporal-lobe-atrophy)

Frederik Barkhof, Marieke Hazewinkel, Maja Binnewijzend and Robin Smithuis
Alzheimer Centre and Image Analysis Centre, Vrije Universiteit Medical Center, Amsterdam and the Rijnland Hospital, Leiderdorp, The Netherlands
What about abnormal aging?

• Difficulty with everyday tasks
  • Keeping track of monthly bills, following a recipe, troubles finishing tasks, troubles with the familiar remote/electronics (unfamiliar = grey zone)
  • Frequently forgetting appointments

• Repetition
  • Telling the same story, repeating questions

• Communication problems
  • Troubles joining and following conversations
    • Rule out hearing loss as well!
  • Abruptly stopping mid thought
  • Defers to caregivers to answer questions
What is abnormal aging?

• Getting lost
  • Navigational place cells are right next to the hippocampus
  • Visuospatial difficulties may also contribute

• Personality changes
  • Less interest in people, places, and activities
    • Withdrawing from hobbies/social activities
    • Increased irritability, depression, anxiety

• Orientation
  • Losing track of days, time, place

• Judgment problems
  • Poor financial decisions, vulnerable to scams, neglecting hygiene
Clinical Case

• 72 yo F with concerns about changes in memory
  • Forgetting names and why they went into rooms
  • More difficulties multi-tasking and completing tasks
• Retired dentist 5 years ago
• Other family members are not concerned
  • Important to establish this from an informant!
• Still managing all iADLs
• Increased daytime sleepiness, doing less hobbies than in the past
• MoCA of 26/30 – gets all 5 of delayed recall correct
What are your thoughts on this case?

• Should we just offer reassurance?
  • The score is technically normal
  • Does the prior education background/occupation sway your opinion?
  • Does the pattern of points she missed matter?
    • What if all 4 points were on delayed recall? = Red flag

• What if she has a first-degree family history of Alzheimer’s?

• Does the patient have depression?
  • Withdrawing from hobbies/activities

• Should we investigate sleep apnea?
  • Daytime sleepiness and/or snoring

• Should we get more detailed cognitive testing?
Detailed neuropsychological testing

• Thoroughly tests verbal memory, visual memory, sequential processing, encoding, delayed memory, language ability, executive functions, and visuospatial construction

• Normative databases for age and education
  • Our screening tools are not as sensitive for high education patients

• Establishes a baseline for someone with subjective cognitive impairment
  • “I may be 30th percentile in verbal memory but I am a college level English professor – this is not normal!”
Subjective cognitive decline

Subjective cognitive decline (SCD): indicating compensation and subtle decline in cognitive performance

Onset of decline in cognitive performance

Impairment on a cognitive test

Age-, sex- and education adjusted normal performance range

progression of disease pathology and clinical states

preclinical AD
MCI / prodromal AD
dementia
Harvard Brain Aging Study

- 279 clinically normal (mean age = 74 years)
- Baseline amyloid status measured by amyloid PET
- Followed for 5+ years with subjective memory questionnaires

Untreated Sleep Apnea

- Risk factor for atrial fibrillation, heart attack and stroke
- Suspected risk factor for vascular disease in the brain
- Risk factor for Alzheimer’s disease and related dementias
- Associated with amyloid positivity
- Treatment may reduce risk of all cause dementia (OR 0.65)


Spinal fluid and Alzheimer’s disease

- Spinal fluid flows through spaces between brain cells
  - Helps clear bad proteins and protein waste built up throughout the day

- What disrupts this flow?
  - Vascular disease, sleep apnea, amyloid plaques, and neuroinflammation - to name a few

Depression and Anxiety

• Are early behavioral symptoms part of early neurodegeneration?
  • Depression/anxiety should be treated
• Often linked to sleep abnormalities
  • In a circular manner
• Difficulty falling asleep or getting back to sleep
  • Often a mind racing phenomenon
  • “Solving the world’s problems at 2AM”
  • Often underlying anxiety driving this
• Poor sleep then feeds depression/anxiety symptoms
  • It leads to chronic inflammation, poor diet, chronic pain, reduced drive for exercise
Cognitive Severity Spectrum

Normal Aging

Mild Cognitive Impairment

Dementia

- SCI in the green/yellow overlap
- Overlapping spectrum
- Reasonable debate in the field for exact cut offs
AD Timeline

- Amyloid Phase = 10-20 years
- In some = Subjective Cognitive Impairment
- We are enrolling patients in a trial targeting Amyloid at this phase- AHEAD study

Research Studies at KU ADC

• Studies targeting the preclinical phases of Alzheimer's disease
  • Amyloid positive, cognitively normal – at risk for Alzheimer's disease
  • AHEAD A3-45
    • 55 or older, family history of AD, cognitively normal, amyloid positive
    • 65 or older, cognitively normal, amyloid positive
    • BAN2401 = Anti-amyloid monoclonal antibody

• Normal Cognition trials:

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PI</th>
<th>Population</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHEAD</td>
<td>Ryan Townley, MD</td>
<td>Normal Cog</td>
<td>Phase 3 trial, Anti-Amyloid MAB in healthy adults with elevated Brain Amyloid</td>
</tr>
<tr>
<td>NICE</td>
<td>Debra Sullivan, PhD</td>
<td>Normal Cog</td>
<td>1 yr Mediterranean diet</td>
</tr>
<tr>
<td>SIESTA</td>
<td>Catherine Siengsukon, PhD</td>
<td>Normal Cog</td>
<td>Sleep &amp; Brain Amyloid</td>
</tr>
<tr>
<td>STATINS</td>
<td>John Thyfault, PhD</td>
<td>Normal Cog</td>
<td>Statins &amp; Aerobic Capacity</td>
</tr>
<tr>
<td>IGNITE</td>
<td>Jeffrey Burns, MD</td>
<td>Normal Cog</td>
<td>1 yr exercise</td>
</tr>
<tr>
<td>LEAP Rx</td>
<td>Jeffrey Burns, MD</td>
<td>Normal Cog</td>
<td>Lifetime Enrichment for Alzheimer's Prevention</td>
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</tbody>
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A Word on Cognitive Resilience

• Patients can have Alzheimer’s disease pathology (amyloid and tau) in the brain but still test normally on cognitive exams
  • Preclinical stage or “At Risk for Alzheimer’s disease”

• Lifestyle factors play a large role in delaying onset of symptoms
  • Baseline education (earliest intervention at a population level)
  • Improved cardiorespiratory fitness results in improved vascular brain health
  • Aerobic exercise, proper sleep, diet, cognitive and social engagement
  • Challenging your brain with novel tasks – a diverse cognitive diet

• Will come back to this in a later talk on prevention
Summary

• Defined the difference between normal aging and abnormal aging
  • May require detailed cognitive testing with age-based norms
• Defined subjective cognitive decline/impairment
• Discussed the concept of novelty and lifestyle implications on building cognitive resilience
• Discussed KU ADC studies for preclinical AD and prevention trials