Dementia the Brain Eraser

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Financial Disclosure

I have financial relationships to disclose:

- Employee of Oklahoma State University
- VA WOC Researcher
- Consulting
- Research funding: National Institute on Aging Resource Center for Minority Aging Research /Native Elder Research Center

Outline

- 1. Cognitive Decline
- 2. AD Dementia
- 3. Updates on the state of research
- 3. Environmental Risk Factors of Cognitive Decline
- 4. Cognitive Reserve
- 5. Building Cognitive Reserve

Dementia

- Dementia is not a specific disease
- A general term for a syndrome
- Impaired ability to remember, think, or make decisions that interferes with doing everyday activities.
- Mostly affects older adults, it is not a part of normal aging. It may also occur in children (HAD, Huntington's disease)
- The syndrome is not attributed to any current active neurological or systemic illness

Healthy Ageing

- Slight decrements in:
  - Sensory and motor loss (hearing, visual acuity, smell, motor speed)
  - Change in sleep patterns; shorter and more fragmented sleep
  - Mild decline in the brain volume , increase of the ventricles
  - Cognitive
    - Sustained and divided attention
    - Slower rates of learning new information (more proactive required)
    - Reduced spontaneous recall of older information
    - Reduced mental flexibility

Cognitive Resilience

- Language and Knowledge
- Verbal skills and vocabulary
- Simple attention and concentration
- Basic math
- Recognition memory and recall or the gist of the events
- Remote memory

Mild Cognitive Impairment

- Prodromal to Dementia
- Relatively isolated decline
  - Amnestic (most commonly verbal memory)
  - Nonamnestic (e.g., executive function)
  - Multiple domain
- Does not affect the activities of daily living
- Not all MCI progress

Beyond Ageing

- The most common types of dementia:
  - Alzheimer's disease
  - Vascular dementia
  - Frontotemporal dementia
  - Dementia with Lewy Bodies

Alzheimer's Disease

- Most common form of dementia in the elderly
- 60 to 80 percent of cases
- 5% of people over the age of 65 have AD, prevalence doubling every 4-5 years
- In the United States 6.7 million by 2025

(Hebert, Scherr et al. 2003; Alzheimer's Association, 2012 Alzheimer's disease facts and figures)

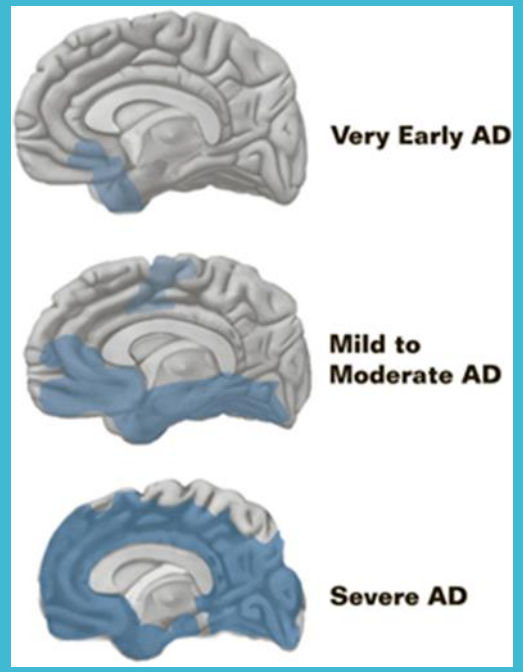
Alzheimer's Disease

- The trademark symptom is trouble remembering recent events, such as a conversation that occurred minutes or hours ago and word finding difficulties
- Family history is the most important risk factor. Having a first-degree relative with Alzheimer's disease increases the risk of developing it by 10 to 30 percent.
- Progressive global dementia characterized by:
  - anterograde amnesia
  - progressing to deficits in visuo-spatial abilities, mental processing speed, attention and executive function

Alzheimer's Disease

- Average age of diagnosis is 74.7 years (70-79)
- 5% have familial form of the disease
  - an earlier onset, more rapid decline
- Length of the disease ranges 5-15 years (mean of 7)
- In early stages, patients often unaware of the decline
  - Personality changes
  - Social withdrawal
  - Decreased interest in hobbies
  - Problems sequencing, problem solving at home/work

Alzheimer's Disease



- The hallmark neuropathologic changes:
  - diffuse and neuritic plaques, marked by extracellular amyloid beta deposition
  - neurofibrillary tangles, comprised of the intracellular accumulation of hyperphosphorylated tau (p-tau) protein.
- Acetylcholine (ACh)
  - a neurotransmitter essential for processing memory and learning
  - decreased in both concentration and function in patients with Alzheimer's disease.

Diagnosis and Treatment

- Referral to neuropsychology and neurology
  - MRI, PET, SPECT
- Medications:
  - Acetylcholinesterase inhibitors used in all stages of AD
    - donepezil (Aricept)
    - rivastigmine (Exelon)
    - galantamine (Razadyne)
  - NMDA inhibitors (mementine-Namenda) introduced at moderate stage
  - Variable efficacy
  - Modest benefit in helping to stabilize and delay the progression by 12-18 months in some individuals

Updates on Research into Possible Treatment

Amyloid Plaques: IMMUNE SYSTEM

Several drugs — known as **monoclonal antibodies** — may prevent beta-amyloid from clumping into plaques or remove beta-amyloid plaques from the brain.

Monoclonal antibodies mimic the antibodies

The monoclonal antibody **solanezumab** did not demonstrate benefits in Phase III clinical trials for mild or moderate AD.

It's possible that solanezumab may be more effective when given earlier in the course of the disease. The drug seemed safe in recent studies, and continues to be evaluated in the preclinical stage of the disease.

Amyloid Plaques: PREVENTING DESTRUCTION

Beta-amyloid interacts with another protein called Fyn.

When combined with beta-amyloid, Fyn is over-activated, which triggers a destruction of connections between nerve cells (synapses) in the brain.

Studies are currently in progress for drugs that inhibit the Fyn protein.

A drug initially developed as a possible cancer treatment — **saracatinib** — is now being tested in Alzheimer's disease.

Amyloid Plaques: PRODUCTION BLOCKERS

- New therapies **to reduce the amount of beta-amyloid formed in the brain.**
- Research has shown that beta-amyloid is produced from a "parent protein" in two steps performed by different enzymes.
- Several experimental drugs aim to block the activity of these enzymes.
- They're known **as beta- and gamma-secretase inhibitors**.
- However, in studies showed that the beta-secretase inhibitor **verubecestat** did not slow down cognitive decline and was associated with several side effects in those with mild or moderate Alzheimer's.

Tau Protein: TAU TWISTING

- Tau supports transport withing the brain cells
- In AD, Tau transport collapses because of twists and microscopic tangles
- This is a hallmark brain abnormality of Alzheimer's.
- Researchers are looking at a way to prevent tau from forming tangles.
- Tau aggregation inhibitors and tau vaccines are currently being studied in clinical trials.

INFLAMMATION

- Alzheimer's causes chronic, low-level brain cell inflammation.
- Treating this inflation may address Alzheimer's disease.
- The cancer drug **sargramostim (Leukine)** is currently in research.
- It's thought that the drug may stimulate the immune system to protect the brain from harmful proteins.

- Researchers studied the diabetes drug **pioglitazone (Actos)** because it may lessen beta-amyloid and inflammation in the brain, but this trial was negative.

INSULIN RESISTANCE

- A trial testing an insulin nasal spray to determine whether it slows the progression of Alzheimer's was recently reported as negative

HORMONES

- Estrogen-based hormone therapy for at least a year during perimenopause or early menopause appeared to protect thinking and memory in women with a higher risk of Alzheimer's disease.
- Based on a singular study
- But further research has been conflicting, with some studies indicating that estrogen didn't offer any benefit

VASCULAR FACTORS

- Brain health is closely linked to heart and blood vessel health.
- The risk of developing AD increases with high blood pressure, heart disease, stroke, diabetes and high cholesterol.
- A number of studies are exploring how best to build on this connection. Strategies under investigation include:
  - Current drugs for heart disease (i.e., blood pressure medications) in reduction of the risk of developing AD.
- Lifestyle choices. Research suggests that lifestyle choices with known heart benefits, such as exercising on most days and eating a heart-healthy diet, may help prevent Alzheimer's disease or delay its onset.

Environmental Risks

WELL KNOWN RISKS

- **Age**: After age 65, the risk of Alzheimer's doubles every five years. After age 85, the risk reaches nearly one-third.
- **Family history**: Having a parent, brother or sister with AD are more likely to develop the disease. May be due to genetic or lifestyle/environmental factors.
- **Genetics**: Less than 1% of Alzheimer’s cases are caused by deterministic genes (genes that cause a disease, rather than increase the risk of developing a disease).

HEART-HEAD CONNECTION

- The brain is nourished by one of the body's richest networks of blood vessels
- Cardiovascular Health is directly linked to AD development

HEAD INJURY

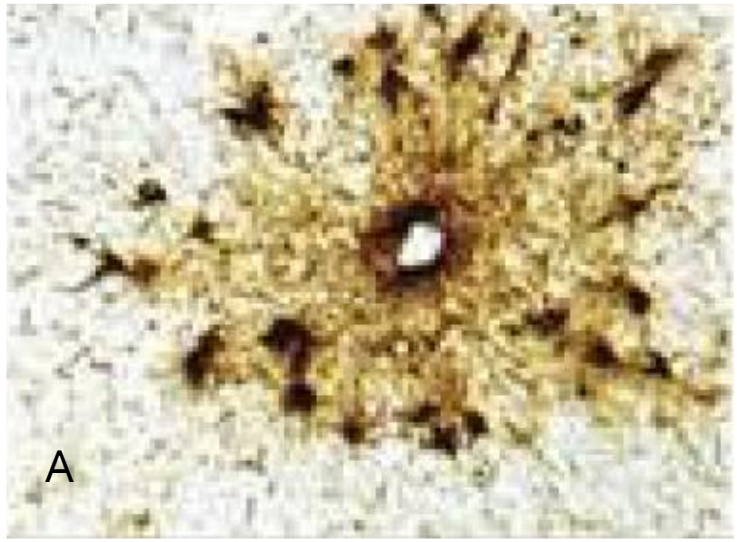
- Singular Severe TBI may contribute to earlier AD
- Repeated Concussions and Subconcussive Injuries are shown to lead to Chronic Traumatic Encephalopathy

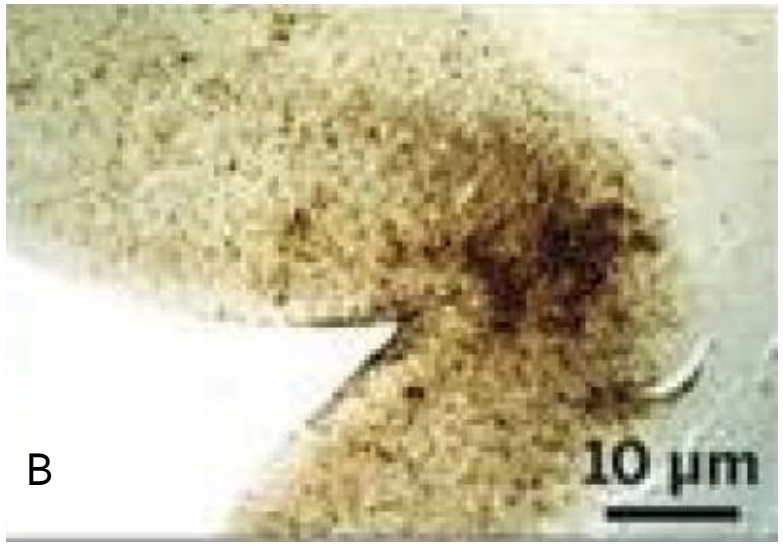
Chronic Traumatic Encephalopathy

- Degenerative brain disease found in athletes, military veterans, and others with a history of repetitive brain trauma.
- Traditionally though to be a result of repetitive concussions (mTBI)
- Most of what we have learned about CTE has come from the research of Dr. Ann McKee, director of the VA-BU-CLF Brain Bank, who has revolutionized our understanding of CTE.
- In CTE, a protein called Tau forms clumps that slowly spread throughout the brain, killing brain cells.

Chronic Traumatic Encephalopathy

- Shares some similarities with Alzheimer's disease
- Unlike in Alzheimer's disease, in ECT, *tau protein tangles* first accumulate in the brains cortex. In addition, the tau protein collects:
  - around the blood vessels (Picture A)
  - Deep in the cortical sulci of the brain(Picture B)





Stages

- **Stage I:** Hotspots of tangled tau pop up in isolated areas of the cortex
- **Stage II:** Multiple hotspots of tangled tau in the cortical sulci, tau begins to migrate
- **Stage III:** Tau hotspots blend with one another. Tangles are diffuse throughout the brain.

Tau begins to collect in the hippocampus and amygdala.

- **Stage IV:** Dense tau tangles cover the brain's cortex and appear in the most other regions including the spinal cord

TREATMENT: NONE

NOTE: Stages proposed by Ann C. McKee, Boston University, still need to be validated by other research groups. Based on *Brain* 2013, DOI: 10.1093/brain/aws307.

ECT

- CTE has been seen in people as young as 17, but symptoms do not generally begin appearing until years after the onset of head impacts.
- ECT is not cost necessary by concussions, but is relevant to subconcussive impact
- Children and youth with history of **subconcussive sports impact** have more risks for neurocognitive decline and CTE as adults

WHAT IS A SUBCONCUSSIVE IMPACT?

- Impact to the brain with adequate force to have an effect on the function of neurons.
- This includes neurometabolic cascade, neuro immune response, breakdown of blood-brain barrier, neurovascular recapping, and release of toxic proteins.
- However, in subconcussive impact, there is no immediate signs or symptoms of concussion
- Some sports and positions are very prone

Concussion vs Subconcussive Impact

- Concussions: caused by hits to the head, and shaking of the brain, so violently that the brain cells become damaged. The brain cells become damaged to the point where they don't work properly, causing immediate symptoms associated with concussion.
- Subconcussive hits are milder, and below the threshold for concussion. However the brain is still shaken, but not so violently to cause immediate symptoms.
  - Potholes in the road: if you hit a big one, you can damage your tire. Subconcussive hits like are like smaller potholes: You will not pop your tire right away, but drive over repeatedly, and the damage will start to add up.

How Often Do They Happen

- Using helmet accelerometers, high school football players received an average of 652 hits to the head in excess of 15 g of force. One player received +2,235 hits (Broglio et al 2011). Higher in college players.
- Growing evidence that even after one season, repetitive subconcussive trauma can lead to cognitive, emotional, physiological, metabolic, and structural brain changes across all levels of play, and across multiple sports.

JOURNAL OF NEUROTRAUMA 34:328–340 (January 15, 2017)

DOI: 10.1089/neu.2016.4413

Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players

Philip H. Montenigro,[1,2] Michael L. Alosco,[1] Brett M. Martin,[3] Daniel H. Daneshvar,[1] Jesse Mez,[1,4] Christine E. Chaisson,[1,3,5] Christopher J. Nowinski,[1,6] Rhoda Au,[4,7] Ann C. McKee,[1,4,8,9] Robert C. Cantu,[1,6,10,11] Michael D. McClean,[12] Robert A. Stern,[1,2,4,10,*] and Yorghos Tripodis[1,5,*]

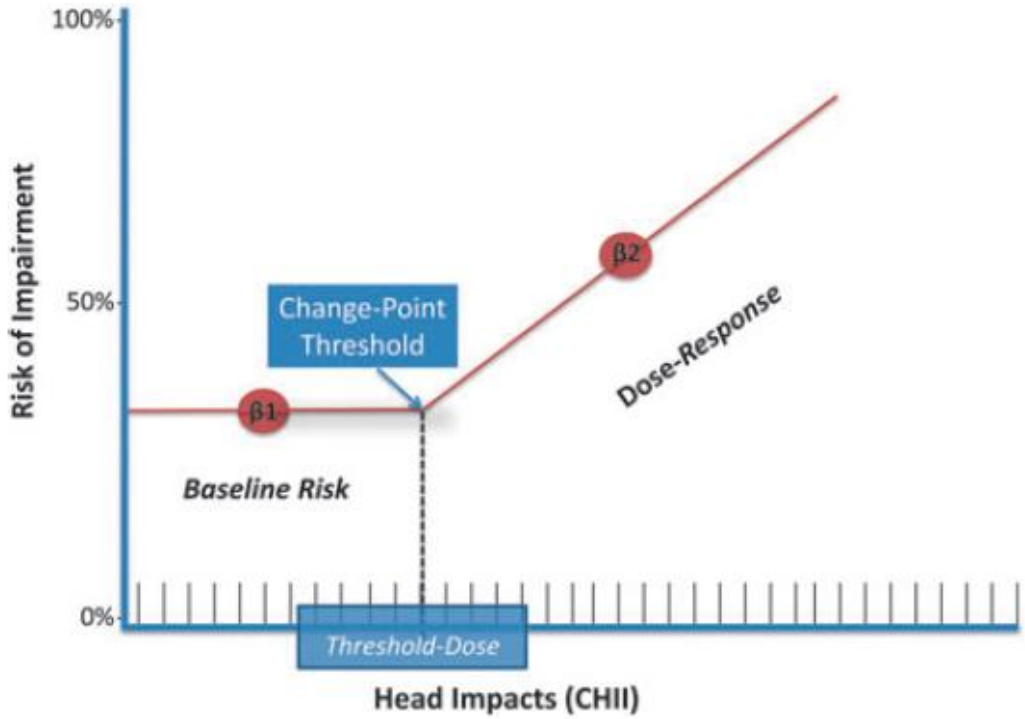
Long Term Impact

93 former high school (n=17) and college (and 76) football players from the BU Legend study.

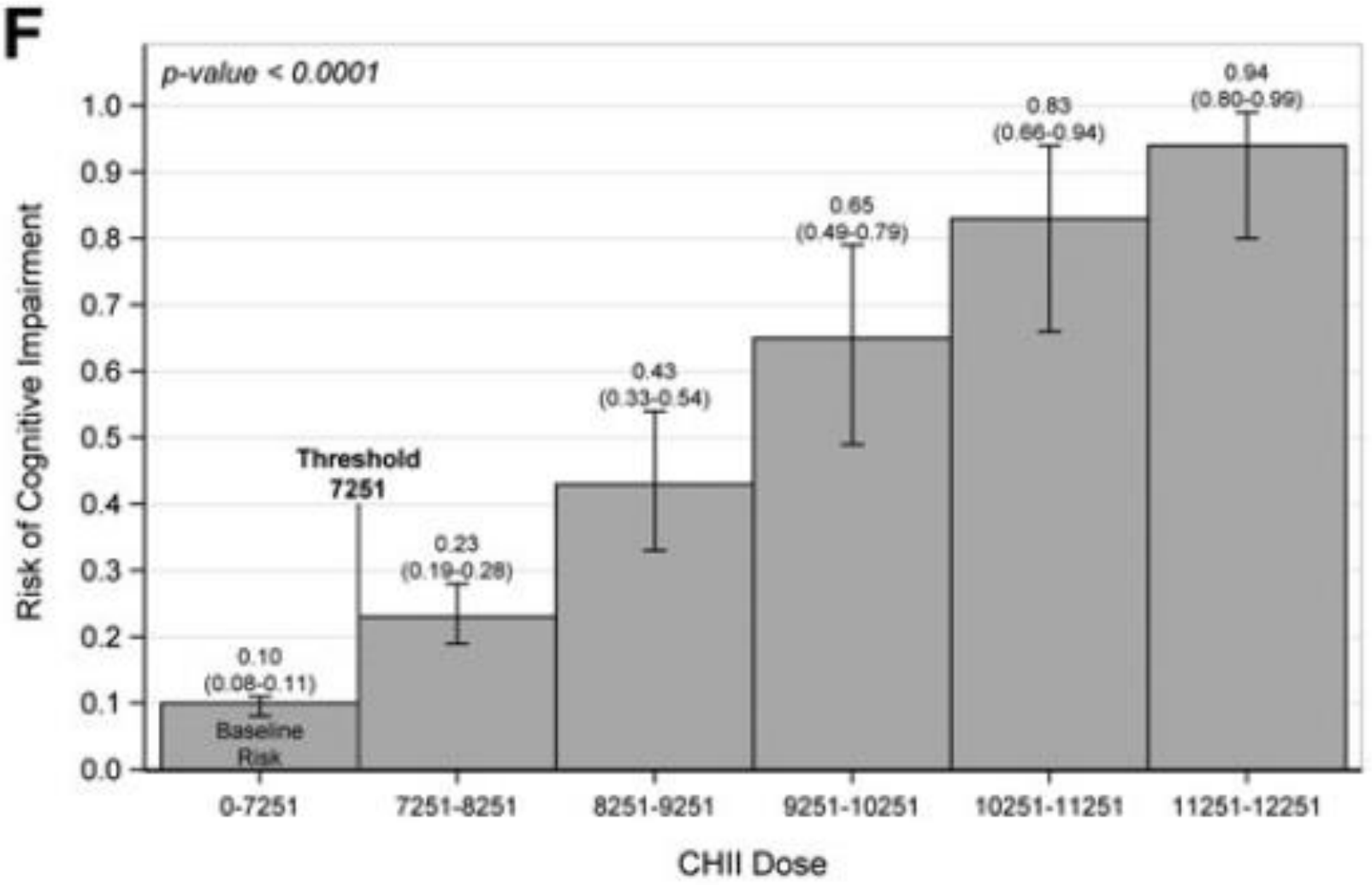
Mean age of 47.3

Dose response relationship between cumulative head impact and later cognitive, mood, and behavioral impairment

With each additional 1000 heads, the risk of later life impairments increased significantly



Risk of Cognitive Impairment



Reserve and Dementia

Reserve

- Approximately 25% of individuals who have post-mortem neuropathological evidence of AD did not demonstrate dementia during their lives

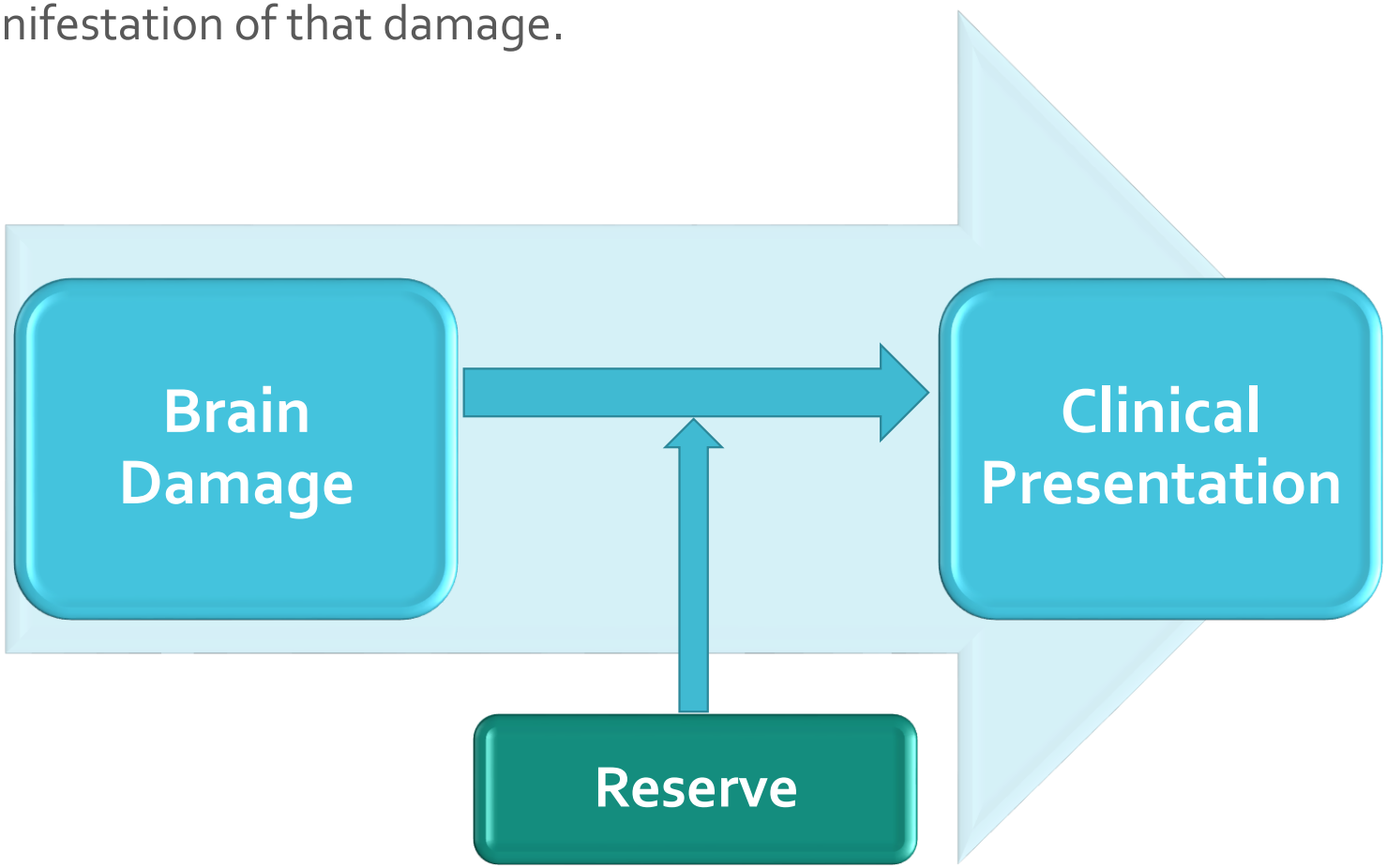
Aging
dependency

(US Census Bureau News, May 20, 2010, population: aging boomers will increase ratio, census bureau projects)

- This discrepancy leads to questions about brain structure, brain function, and possible mediating factors between these two
- Reserve model suggests that brain tries to actively cope with damage by enlisting compensatory strategies

Cognitive Reserve

Cognitive Reserve may explain the difference that sometimes occurs between the degree of brain damage and the clinical manifestation of that damage.



Increasing the Brain Reserve

Early life bilingualism

Early music education

Healthy cardiovascular system

Avoiding substances including alcohol

Exercise, mental stimulation, socialization are shown to increase:

- Brain vascularization (exercise)
- Neurogenesis in the dentate gyrus of the hippocampus
  - The dentate gyrus (DG) is a region in the mammalian brain critical for memory
  - Dentate gyrus generates new principal neurons that are continuously integrated into a fully functional neural circuit throughout life.

Thank you!

Questions?