Untangling The Tau Of Memory Loss: New Hopes For The Diagnosis And Treatment Of Alzheimer’s Disease

Dan Mungas, Ph.D.

U.C. Davis Alzheimer’s Disease Center

On the web: alzheimer.ucdavis.edu
Outline of today’s talk

• Diversity in how people age cognitively
• Alzheimer’s disease
  – Advances in understanding the biology
  – Early diagnosis
  – Treatment initiatives
• Promoting brain health - a lifelong process
THE MEMORY TRAINING CLASS? ... GO DOWN TWO FLIGHTS OF STAIRS, MAKE A RIGHT AND TWO LEFT TURNS AND TAKE THE THIRD ELEVATOR TO PAVILION SIX AND TURN LEFT AT THE COFFEE SHOP, THEN GO DOWN CORRIDOR THREE TO...
Cross-sectional memory performance and age

Wilson et al, Arch Neuro, 1999
Cross-sectional and longitudinal memory performance

Wilson et al, Arch Neuro, 1999

Wilson et al, Psychology and Aging, 2002
Dementia

- Loss of mental ability sufficient to impair day to day function
- Symptoms
  - Memory Loss
  - Loss of other mental abilities
  - Behavior change
  - Impairment of independent function
Pathways influencing cognition

- Genes
- Aging
- Disease
- Environment
- Brain
- Cognition
Causes of dementia in older persons

- Degenerative Dementias
  - Alzheimer’s disease
  - Cerebrovascular disease
  - Lewy body disease
  - Frontal-temporal degeneration
  - Parkinson’s disease
  - Many more . . .
What is Alzheimer’s disease (AD)?

- AD is a progressive, neurodegenerative disease and the most common cause of age-related dementia
- The dementia syndrome is the result of loss of brain cells and synapses
1906 - Dr. Alois Alzheimer first describes "a peculiar disease"

51 year old patient who had profound memory loss, unfounded suspicions about her family, and worsening psychological changes

In her brain at autopsy, he saw dramatic shrinkage and abnormal deposits in and around nerve cells
Neurofibrillary tangles and neuritic plaques
Senile plaque development
Neurofibrillary tangles
Model of AD progression

Jack et al., 2010
Diagnosis of AD

- Definitive AD can only be diagnosed with a clinical history of dementia and pathological evidence of plaques and tangles in the cortical areas of the brain.
- Recent advances hold promise for diagnosis before irreversible brain injury and clinical impairment.
  - Especially important as effective treatments become available.
New Diagnostic Criteria for AD

- **Preclinical AD**: AD pathology is present but the patient does not display symptoms.
- **MCI secondary to AD**: the patient has cognitive symptoms, but still functions independently.
- **Alzheimer’s dementia**: the patient has both cognitive and functional impairments.
AD biomarkers and early diagnosis

- Structural Imaging – MRI
- Functional Imaging – FDG PET
- Amyloid Imaging – PIB, Florbetapir
- Cerebrospinal fluid – beta-amyloid, tau
Brain shrinkage (cerebral atrophy)
Atrophy of the hippocampus

- normal
- mild
- moderate
- severe

Assymetry is common
Brain Metabolism

FDG PET scan with hypometabolism in temporal lobes

FDG PET scan with hypometabolism in parietal lobes
Amyloid imaging
Pittsburgh Imaging Compound B
a new amyloid imaging technique

Klunk et al, Ann Neuro, 2004
CSF testing

- Measures the amount of beta-amyloid, tau and phospho-tau in the CSF
- Amyloid levels drop as AD progresses
- Tau levels increase as AD progresses
Biomarkers and Diagnosis

- Brain imaging and CSF biomarkers are sensitive to early biological changes of AD
- Some measures are not specific to AD
  – brain atrophy especially
- Direct measures of beta-amyloid and tau offer potential for early diagnosis
  - Makes effective treatment a priority
If you can’t put toothpaste back in the tube, how did it get there in the first place?
Treatment Outcomes in AD

- Slowing of progression
- Maintenance of function
- Cure
- Symptomatic benefit
- Untreated
Cognitive Enhancers

- Cholinesterase inhibitors
  - Donepezil (5mg and 10mg)
  - Rivastigmine (6 and 12 mg, also patch form)
  - Galantamine (16mg and 32mg)
- Memantine (NMDA receptor antagonist)
  - For moderate to severe AD
AD - Disease-Modifying Strategies

APP → β-secretase → Aβ → Neuron death

- secretase modulators
- amyloid binders
- immunotherapy
- anti-inflammatories
- antioxidants
- neuroprotectants
- inflammation
- oxidative stress
- excitotoxicity
- direct toxicity
Anti-Amyloid Therapies

- Alter APP metabolism/cleavage (↓Aβ deposition)
  - γ-secretase inhibitors
  - α-secretase agonists
- Increase amyloid clearance
  - Immunization (active, passive)
  - Intranasal insulin and PPAR γ agonists (rosiglitazone)
  - Statins
  - RAGE (Receptor Advanced Glycation Endproducts) inhibitors – transport A beta across BBB
- Anti-Oligomer therapy
- Reduce amyloid-related neurotoxicity
  - Mitochondrial agents - dimebon
  - Anti-inflammatories
Drug Development for Alzheimer Disease Therapies is Very Difficult

- AD agents that failed in late-stage development
  - Tramiprosate – antifibrillar agents
  - Tarenflurbil - gamma secretase modulator
  - Atorvastatin
  - Curcumin (low bioavailability)
  - Conjugated estrogens
  - B6, + B12, + folate (in AD with normal homocysteine levels)
  - Anti-inflammatory agents (prednisone and NSAIDs)
  - Gingko biloba
  - Solanezumab, bapineuzumab
New directions in AD clinical trials

- Treatment target in previous trials may have been too late in AD progression
- Earlier treatment might prevent irreversible brain injury
- Increased interest in targeting preclinical stage
  - Early diagnosis critical to this process
Alzheimer’s Prevention Initiative

- Extended family in Antioquia, Colombia, with familial (inherited) AD
- Clinical trial will test monoclonal antibody targeting beta-amyloid (crenezumab) in individuals with AD gene who have not yet experienced symptoms
- Important test of amyloid hypothesis with potential for showing ability to prevent AD
Cognitive decline is multiply determined
Cerebrovascular disease can make Alzheimer’s disease worse

Schneider et al., 2004
Heart healthy is brain healthy
Maintaining vascular health

- Lower fats (lipids) in the bloodstream
  - Lower cholesterol, triglycerides, LDL
  - Raise good lipids (HDL)!
- Control diabetes and blood sugar
- Maintain normal blood pressure normal
- Weight control (body mass index or BMI)
- Regular exercise and good diet
Now that you have a heart, you really should switch to polyunsaturated oil.
Life experience might protect against Alzheimer’s disease and cognitive decline
Use it or lose it: Maintaining an active mind & body

- Social activities and involvement
  - Family, friends, church, other groups etc…

- Mental stimulation
  - New hobbies, cross-word puzzles, musical instrument, new language etc…

- Exercise
  - Benefits of regular walking
  - Tailor to physical limitations/health
Well, I think I've heard it all now.

Reading the paper while soaking your feet is not multitasking.
Brain health is a lifelong process

- Early life experience can affect late-life cognitive and functional ability
- Substantial brain injury and disability may have occurred by the time a disease is diagnosed
  - e.g. Alzheimer’s disease
- But it’s never too late to promote brain health