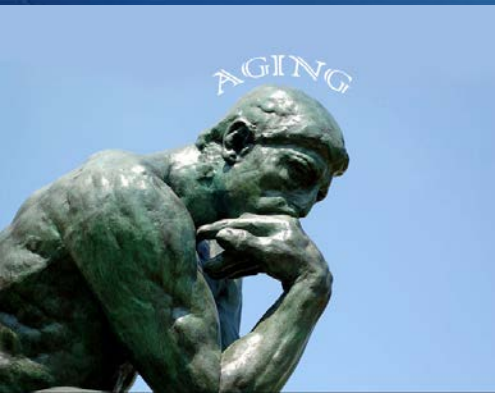


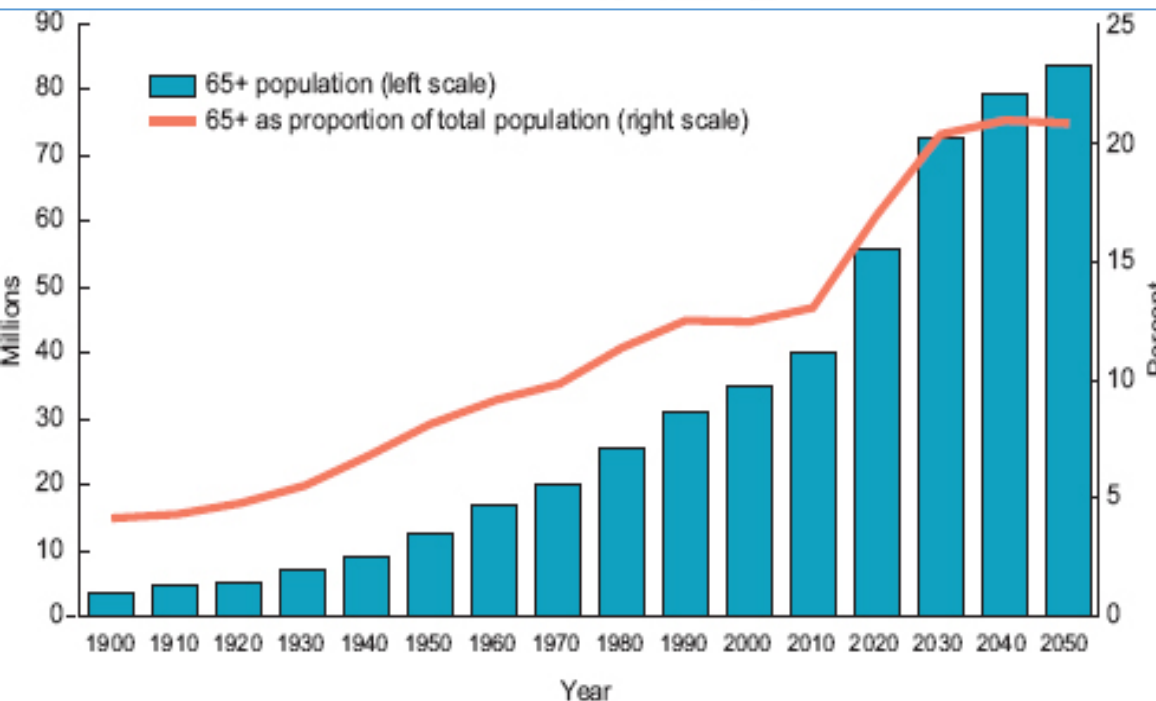
Alzheimer's Disease Pathology & Mechanisms

Heather A. Boger, PhD
Associate Professor, Dept. of Neuroscience
Director, College of Medicine Senior Mentor Program
Interim Director, Center on Aging
Medical University of South Carolina
Charleston, SC



Senior Statistics

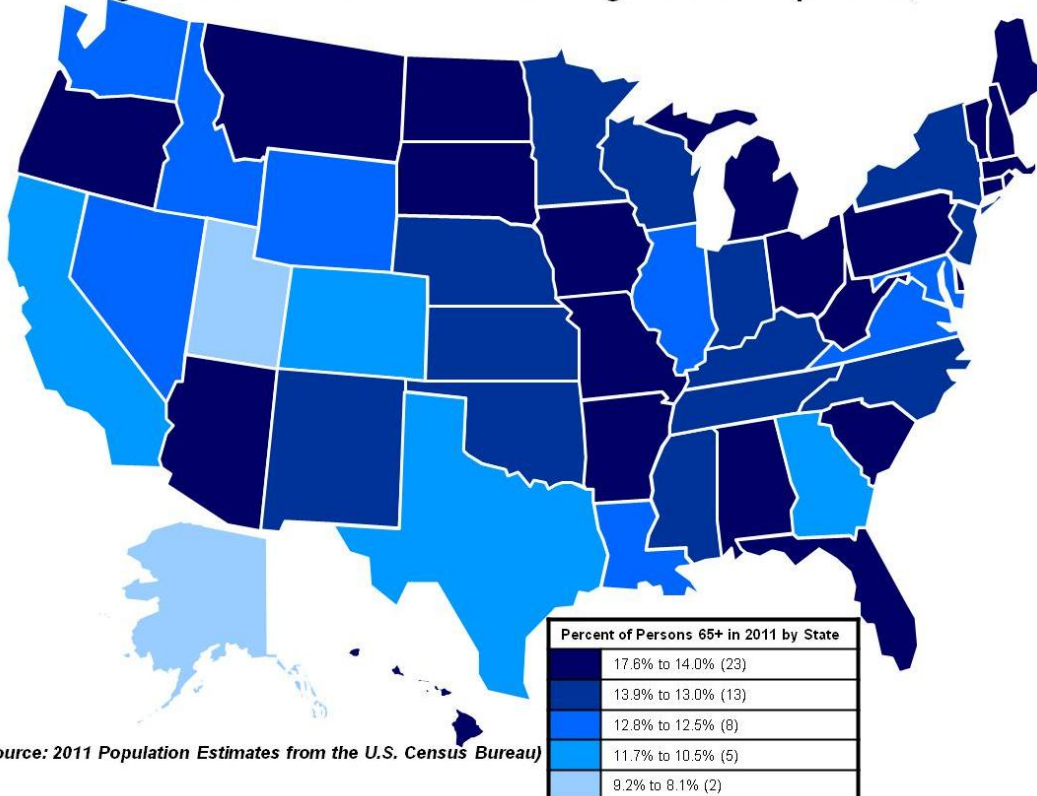
Population age 65+, 1900-2050



Senior Statistics

Percentage of Total Population

Figure 4: Persons 65+ as a Percentage of Total Population, 2011



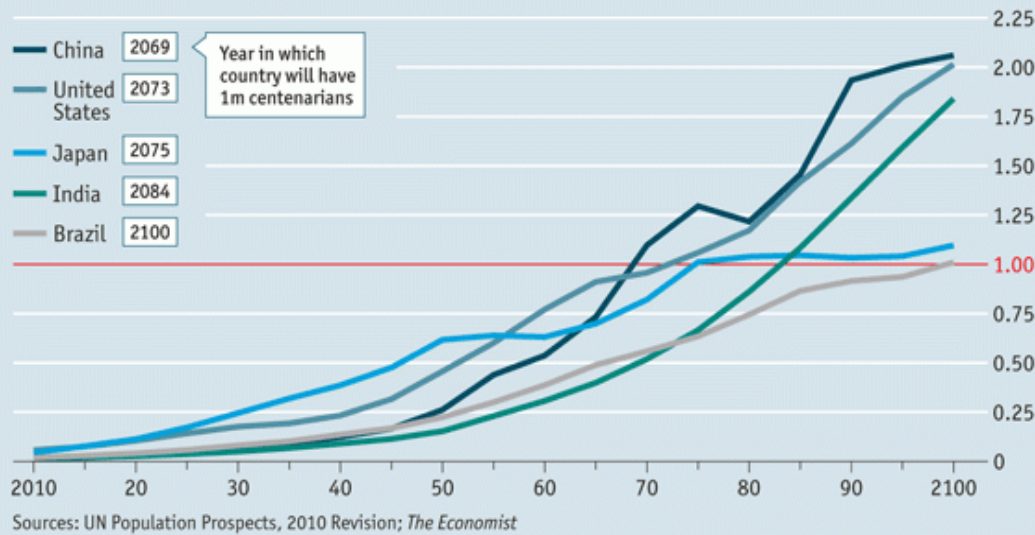
The geriatric population in South Carolina is growing even more quickly than other areas because of an influx of retirees from other parts of the country.

Senior Statistics

Project Number of People Over 100 Years of Age

Number of centenarians

Forecast, m



THE OFFICIAL
GUINNESS WORLD RECORD
**LARGEST GATHERING
OF CENTENARIANS**

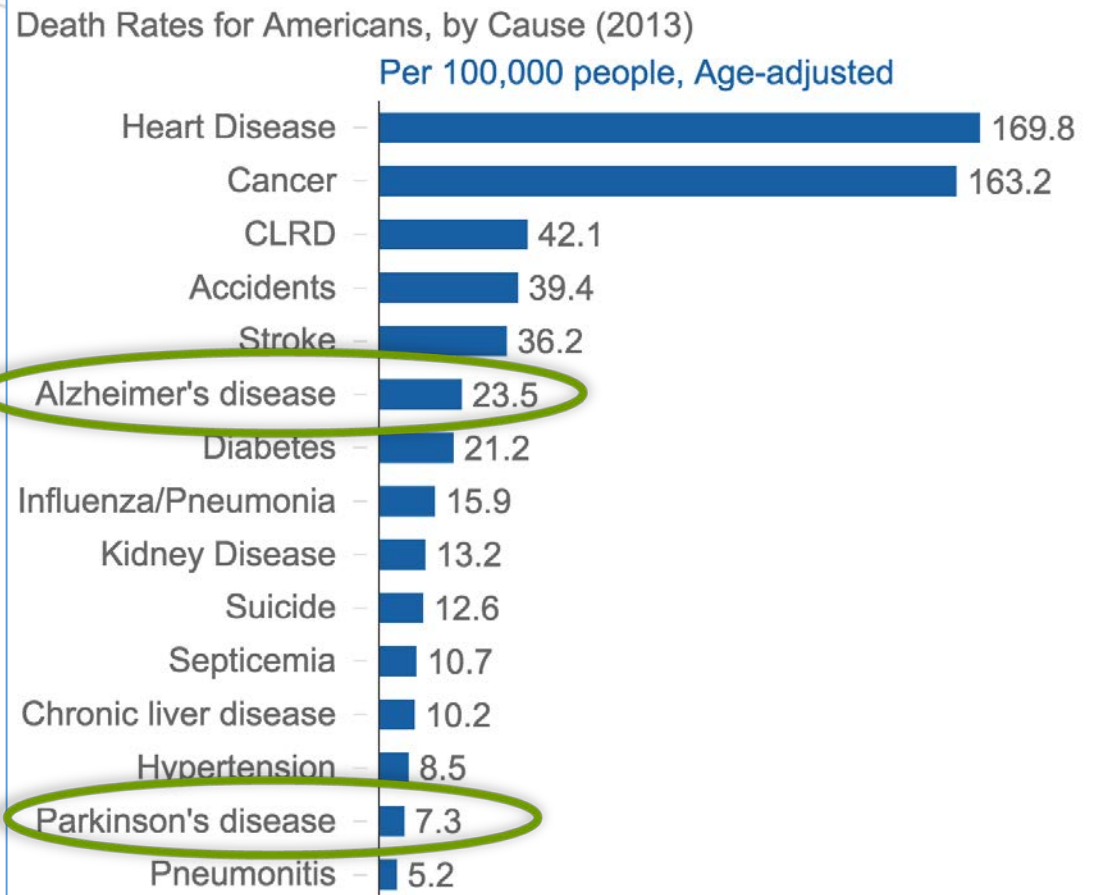
100

www.APlaceforMom.com/blog

The economist, 2010

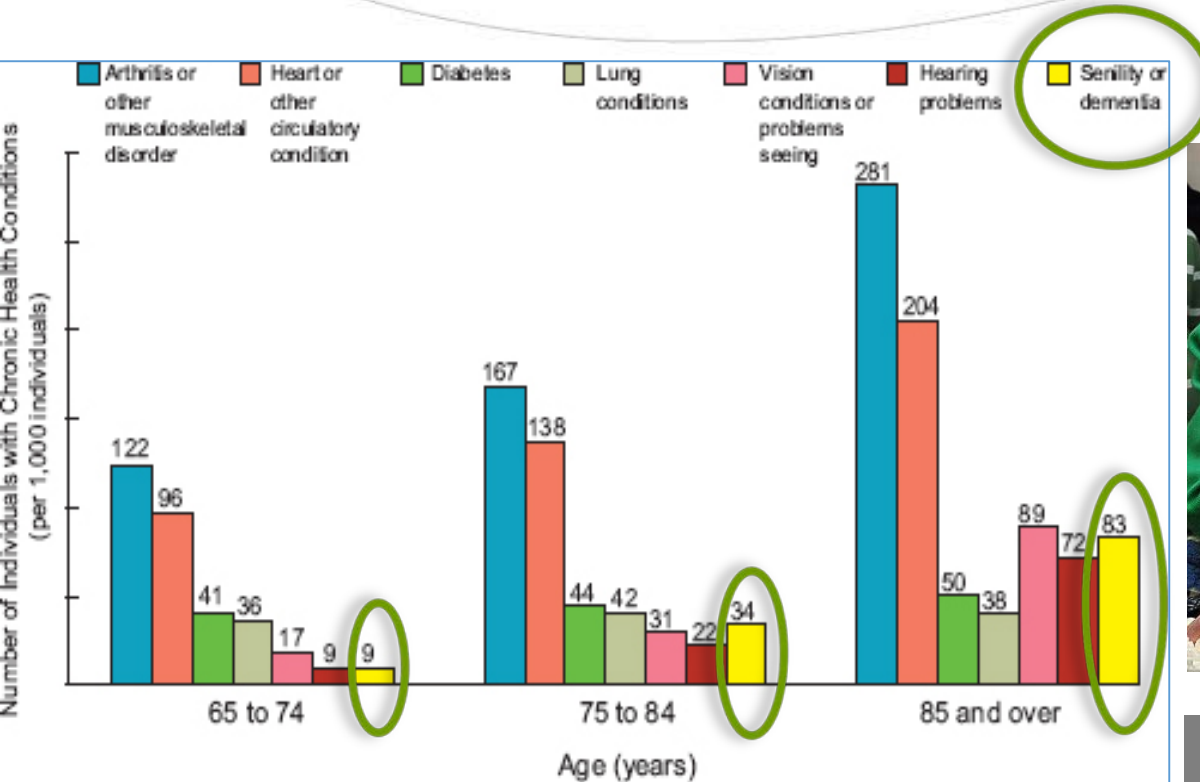
Senior Statistics

Leading Causes of Death



Senior Statistics

Chronic Health Conditions by Age



*World's Oldest Sisters (2012):
Marjorie Ruddle, 105,
and Dorothy Richards, 108.*

The Basics of a Healthy Brain

- ◆ Manages body functions
 - ◆ Breathing
 - ◆ Blood circulation
 - ◆ Digestion
- ◆ Directs functions we carry out consciously
- ◆ Due to mix of chemical and electrical processes that take place, we can
 - ◆ Speak
 - ◆ Hear
 - ◆ See
 - ◆ Move
 - ◆ Remember
 - ◆ Feel emotions
 - ◆ Make decisions

Brain's Vital Statistics

Adult Weight

- ◆ About 3 pounds

Adult size

- ◆ A medium cauliflower

Number of neurons

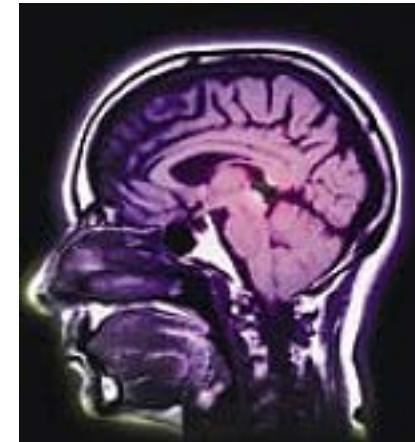
- ◆ 100 billion

Number of synapses

- ◆ 100 trillion

Number of capillaries

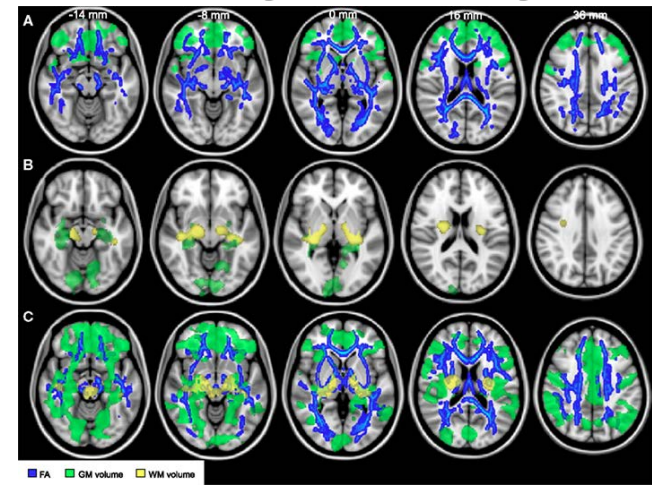
- ◆ 400 billion



The Changing Brain in Normal Aging

As a person gets older, changes occur in all parts of the body, including the brain:

- ◆ Certain parts shrink, especially the prefrontal cortex and hippocampus (regions important for learning, memory, & planning)
- ◆ Communication between neurons can be reduced because white matter (myelin-covered axons) is degraded or lost
- ◆ Blood flow can be reduced due to arteries narrowing and less growth of new capillaries
- ◆ For some, plaques and tangles develop
- ◆ Damage by free radicals increases
- ◆ Inflammation increases



Symptoms of Normal Brain Aging



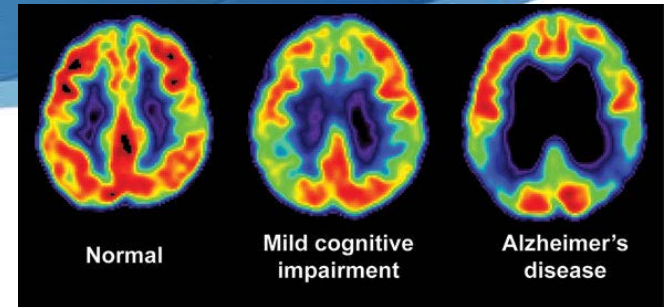
Cognitive Abilities Decline, such as:

- ◆ Difficulty recalling a word or name
- ◆ Trouble understanding the “jabbering” of a child or the “mumbled” conversation of a friend when in background noise
- ◆ Difficulty remembering verbal instructions
- ◆ Slower mental processing
- ◆ Keeping up with quick firing speech
- ◆ Better at dealing with the familiar, but worse at dealing with the new
- ◆ More forgetful

Normal vs. Accelerated Brain Aging

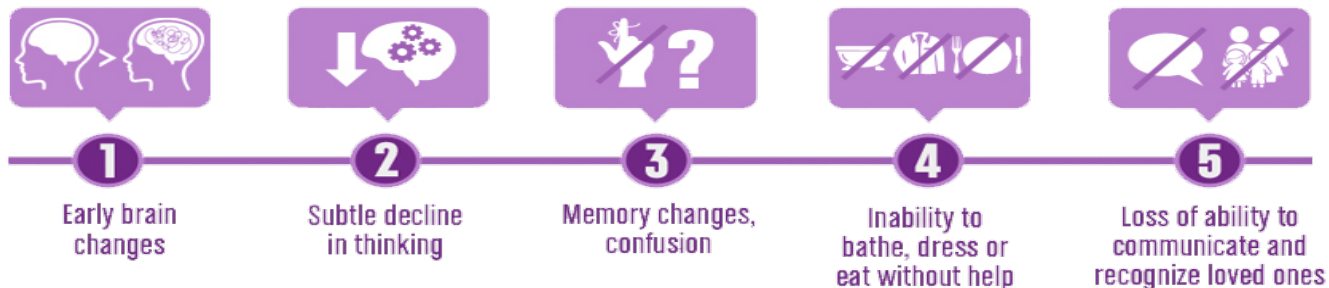


Accelerated Brain Aging: Alzheimer's Disease

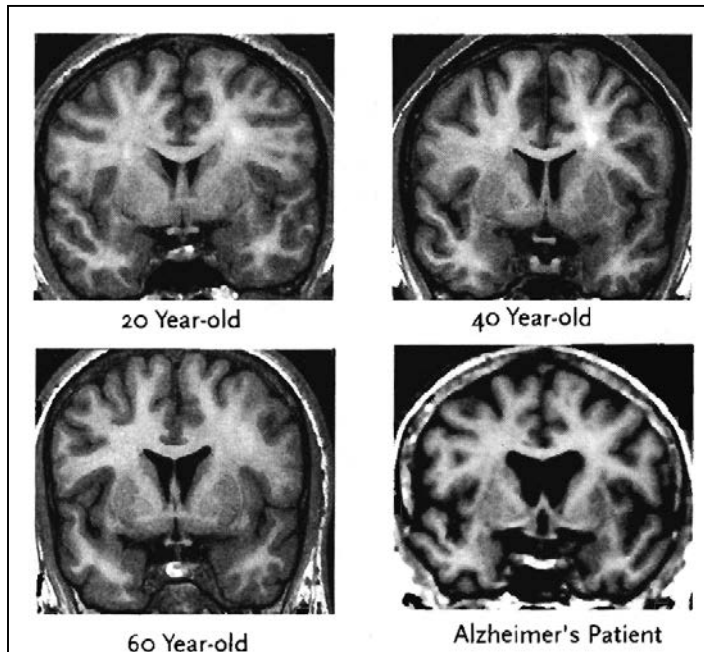
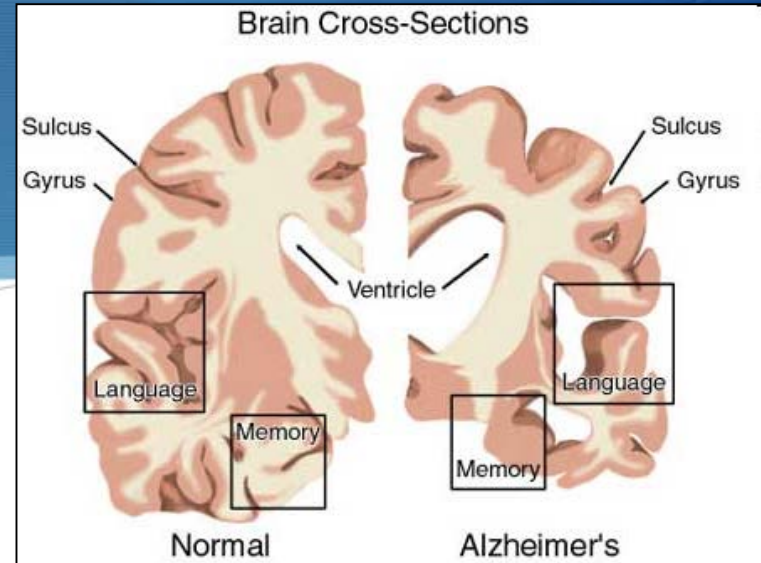
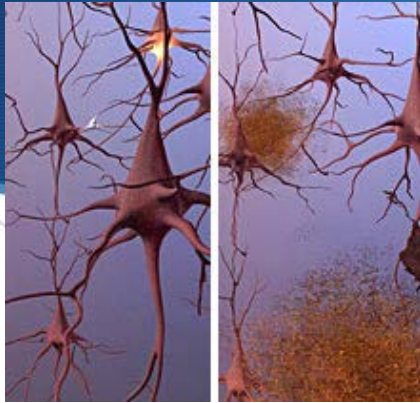


- Irreversible, progressive brain disorder
- Most common cause of dementia in older adults
- Slowly destroys memory and thinking skills, eventually ability to carry out the simplest tasks
- Average age of onset mid-60s
- Estimated to affect more than 5 million Americans

THE ALZHEIMER'S TIMELINE



Alzheimer's Disease Pathology



Plaques-brown
Tangles-black

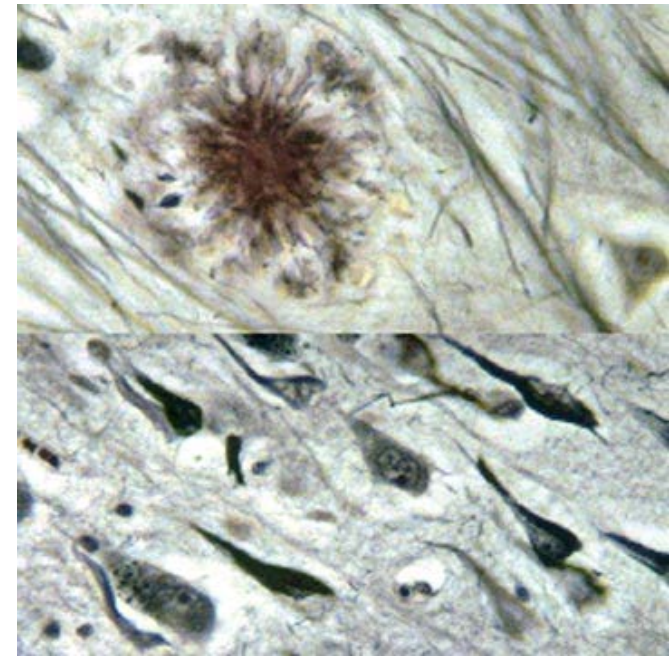


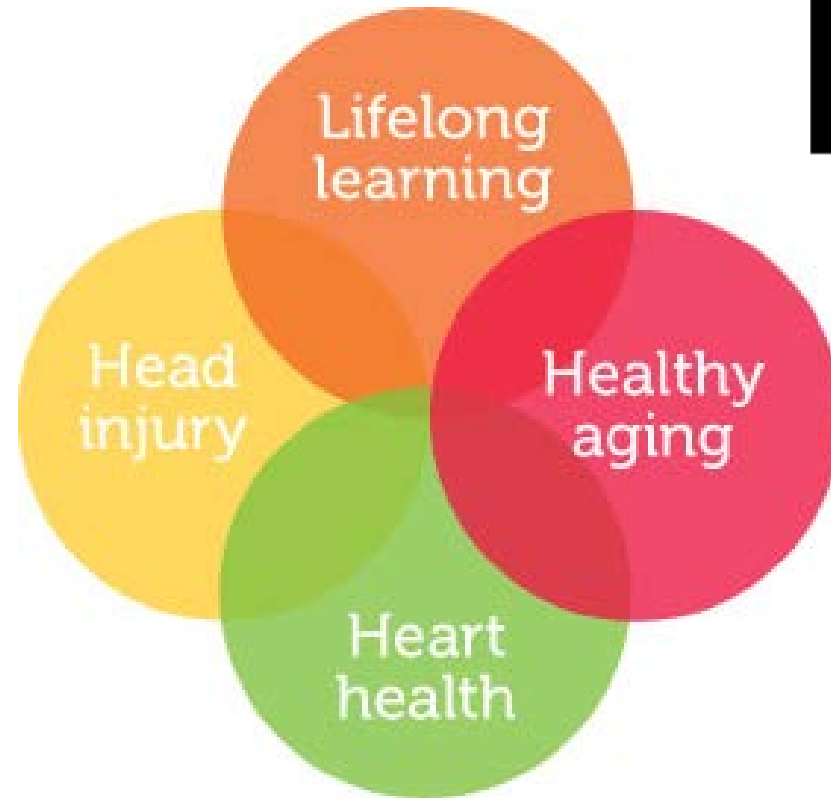
Figure 10-1: MR Scans Illustrating Changes as a Consequence of Aging and Disease

Non-Modifiable Risk Factors for Alzheimer's Disease

- ◆ Age
- ◆ Family History
- ◆ Genetic Factors
 - ◆ Early onset
 - ◆ Presenilin-1 mutation (30-70%)
 - ◆ APP mutation (10-15%)
 - ◆ Presenilin-2 mutation (<5%)
 - ◆ Late onset
 - ◆ APOE-4



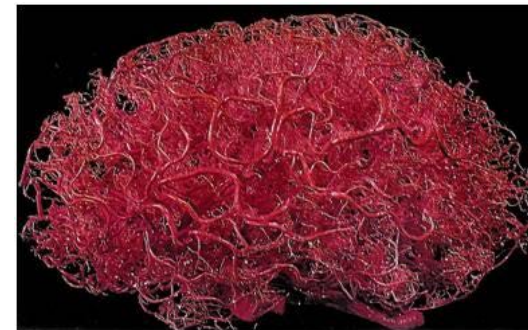
Modifiable Risk Factors for Alzheimer's Disease



- ◆ Hypertension
- ◆ Diabetes mellitus
- ◆ Hyperlipidemia
- ◆ Smoking
- ◆ Alcohol use
- ◆ Head Trauma
- ◆ Depression

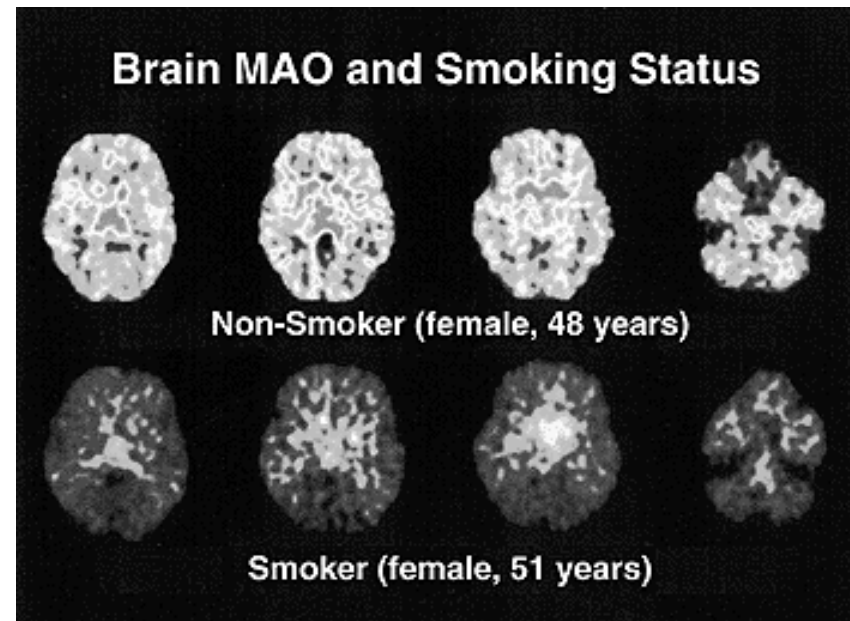
Diabetes: A Risk Factor for Cognitive Dysfunction and Alzheimer's Disease

- ◆ Diabetes raises the risk of heart disease and stroke, which hurts the heart and blood vessels.
- ◆ Damaged blood vessels in the brain may contribute to AD by reducing or blocking blood flow to the brain.
- ◆ Mechanisms associated with diabetes which result in metabolic changes that could affect neuropathology include:
 - ◆ Oxidative stress
 - ◆ Inflammation
 - ◆ Alteration in glucose and fatty acid metabolism
 - ◆ Accumulation of oxidatively altered and glycated proteins



Cigarette Smoking As a Risk Factor for Alzheimer's Disease

- Increases total plasma homocysteine, a known risk factor for stroke, cognitive impairment, AD, and other dementia
- Accelerates atherosclerosis in the heart and brain, depriving cells of oxygen and nutrients
 - Arterial stiffness is associated with build-up of beta-amyloid in the brain
- Causes oxidative stress, excitotoxicity, neural death, and inflammation
- Reports demonstrate the same link between secondhand smoke and dementia



Moderate Alcohol Intake is Associated with Lower Dementia Incidence

- Moderate consumption (1-2 drinks/day) associated with 37% lower risk of dementia in study participants with normal cognition at baseline, not MCI

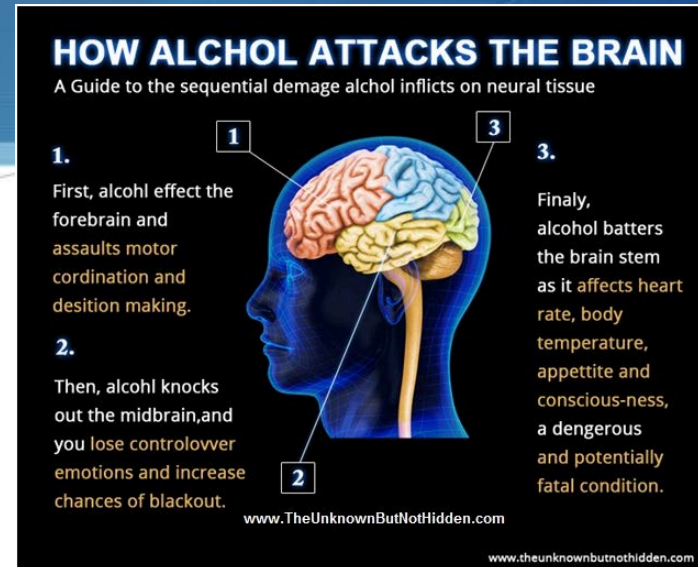
- Heavy drinking accelerates atrophy of the brain

- Chronic consumption causes degeneration of cholinergic neurons

- For those with MCI at baseline:

- Any alcohol intake was associated with a faster rate of cognitive decline

- Heavy drinkers (>14 drinks/week) were nearly twice as likely to develop dementia compared to non-drinkers with MCI



Magnetic Resonance Imaging of the Brain

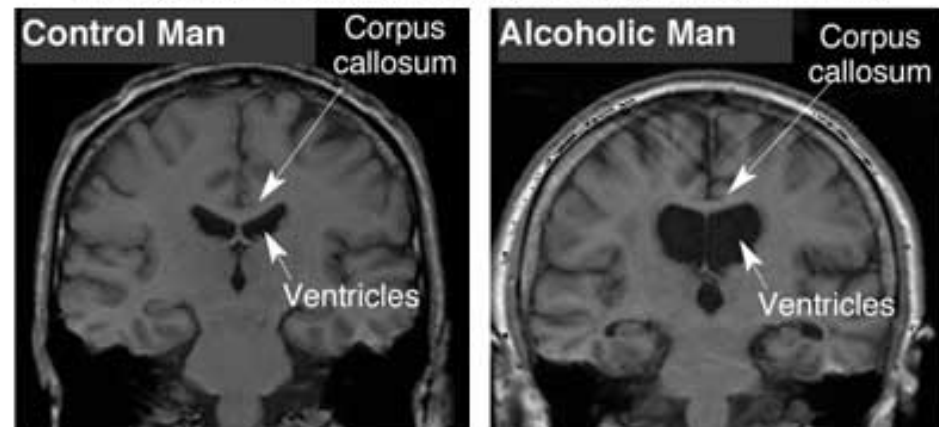


Image courtesy of the National Institute on Drug Abuse

Head Trauma Increased the Risk for Alzheimer's Disease

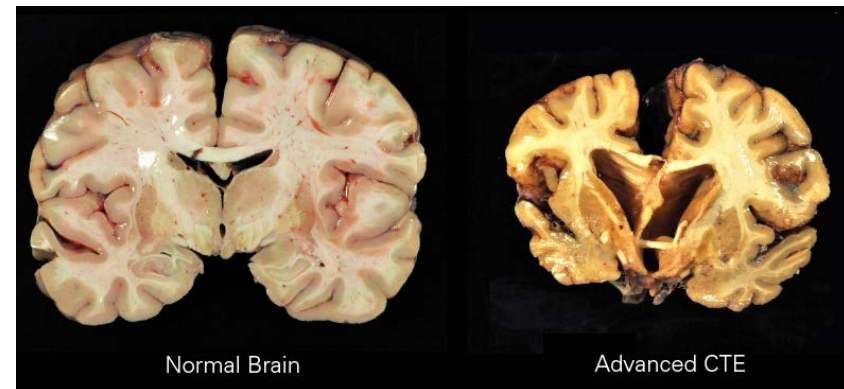
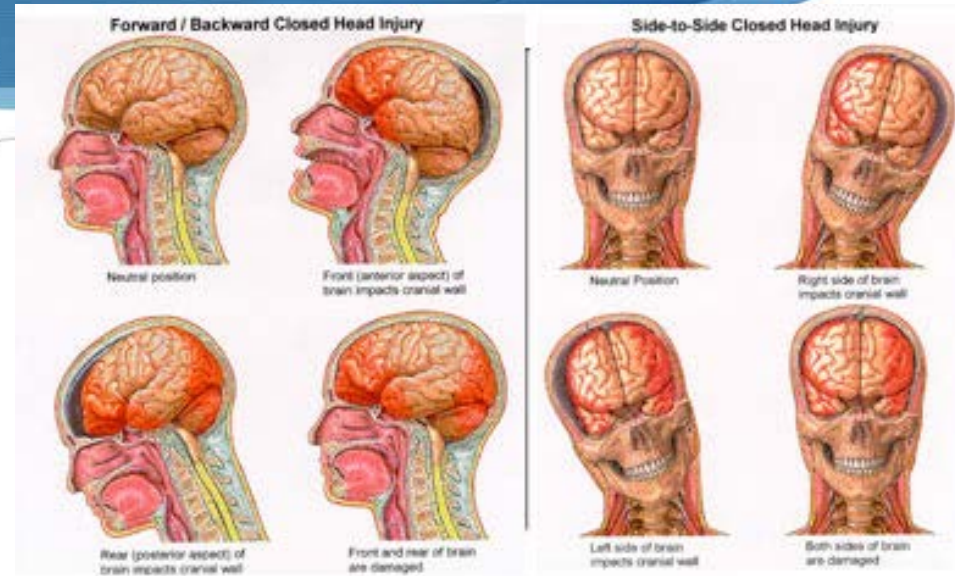
- Moderate to severe TBI, as well as a single concussion, even early in life increases the risk for AD

- Immediately after traumatic injury, the brain produces large amounts of beta amyloid, however the deposit of beta amyloid into plaques does not occur following TBI

- The formation of neurofibrillary tangles is a long-term consequence of TBI

- First described in boxers who became “punch drunk” in midlife, these tau neurofibrillary tangles are increasingly being found in the brains of football players and other athletes who have suffered repeated concussions from head trauma.

- Properly called Chronic Traumatic Encephalopathy



Depression As a Risk Factor for Alzheimer's Disease

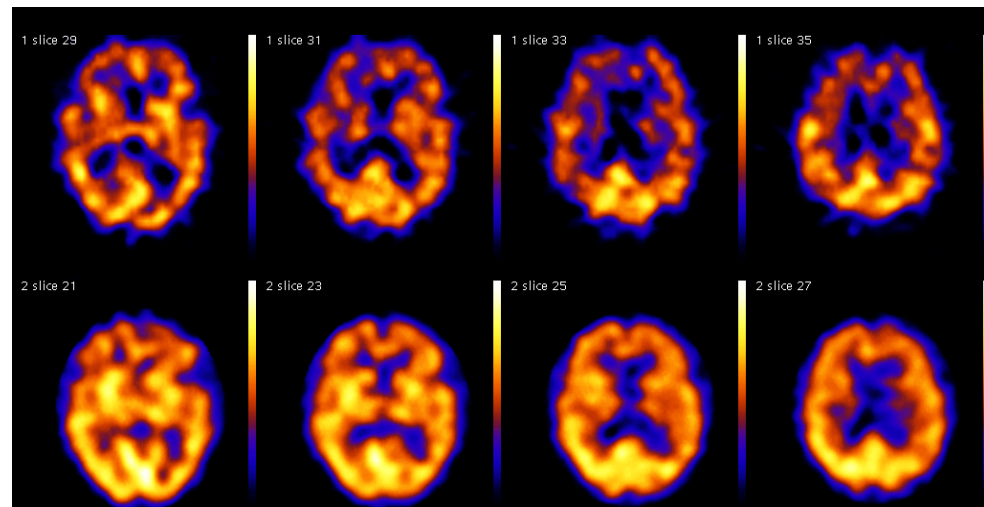
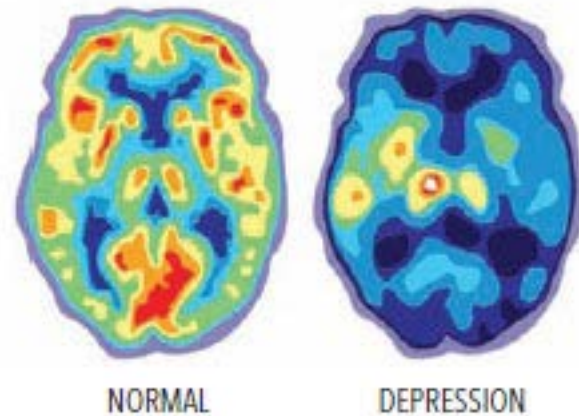
Wilson et al., 2014

- 1750 older persons without CI
- Followed for approximately 8 years
- 600 persons died and underwent neuropathologic examination

Depressive symptoms were associated with rate of cognitive decline

After adjustment for postmortem markers of 6 types of dementia-related pathology, higher level of depressive symptoms during study period remained associated with faster rate of cognitive decline

Depressive symptoms have an association with cognitive decline that is independent of the neuropathologic conditions most strongly linked to late-life cognitive decline and dementia



What About the Protective Factors Against Alzheimer's Disease?

How to protect your brain:

- ◆ Nutrition/Diet
- ◆ Physical Activity
- ◆ Social Activity
- ◆ Spiritual Activity
- ◆ Meditation
- ◆ Control of Stress
- ◆ Humor/Attitude



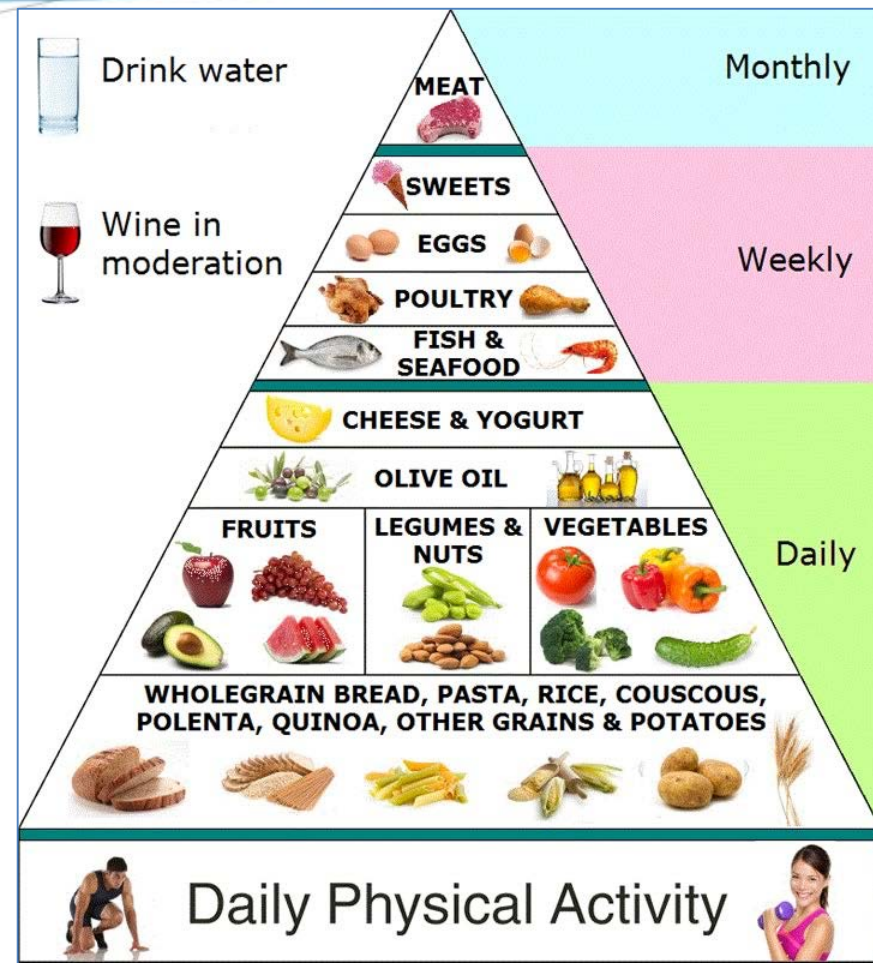
Mediterranean Diet Decreases the Risk of Mild Cognitive Impairment and Alzheimer's Disease

High Consumption of:

- ◆ Fruits (4-6 servings daily)
- ◆ Berries (flavanoids, phytochemicals)
- ◆ Vegetables (4-6 servings daily)
- ◆ Beans (4-6 servings daily)
- ◆ Nuts (3-5 pieces)
- ◆ Whole Grains (3-6 servings daily)
- ◆ Olive Oil (monosaturated fatty acids)
- ◆ Fish-broiled not fried!
- ◆ Alcohol-red
- ◆ Spices (turmeric, ginger, garlic)

Low Consumption of:

- ◆ Saturated Fat
- ◆ Dairy Products
- ◆ Red meat and poultry



Scarmeas et al., 2009

Get Up and Get Active to Reduce The Risk of Dementia

Yu et al. *Trials* 2014, **15**:394
<http://www.trialsjournal.com/content/15/1/394>



STUDY PROTOCOL

Open Access

Effects of aerobic exercise on cognition and hippocampal volume in Alzheimer's disease: study protocol of a randomized controlled trial (The FIT-AD trial)

Fang Yu^{1*}, Ulf G Bronas¹, Suma Konety², Nathaniel W Nelson³, Maurice Dysken⁴, Clifford Jack Jr⁵, Jean F Wyman¹, David Vock⁶ and Glenn Smith⁷

Neurotox Res
 DOI 10.1007/s12640-012-9373-0

ORIGINAL ARTICLE

Neuroprotective Effect of Physical Exercise in a Mouse Model of Alzheimer's Disease Induced by β -Amyloid₁₋₄₀ Peptide

Leandro C. Souza · Carlos B. Filho · André T. R. Goes · Lucian Del Fabbro · Marcelo G. de Gomes · Lucieli Savegnago · Mauro Schneider Oliveira · Cristiano R. Jesse

Moderate Treadmill Exercise Protects Synaptic Plasticity of the Dentate Gyrus and Related Signaling Cascade in a Rat Model of Alzheimer's Disease

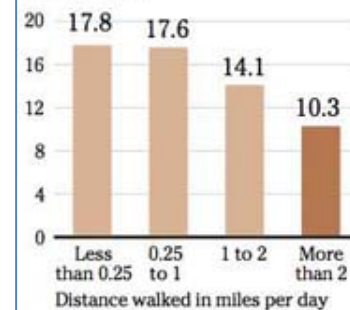
An T. Dao · Munder A. Zagaar · Karim A. Alkadhi

Received: 12 August 2014 / Accepted: 28 September 2014
 © Springer Science+Business Media New York 2014

Walking reduces dementia risk

A study involving 2,257 retired men ages 71 to 93 found that those who walked less than a quarter-mile a day were almost twice as likely to develop Alzheimer's or other forms of dementia as men who walked more than two miles daily.

Incidence of dementia per 1,000 person-years (Age-adjusted)



Source: American Medical Association

ASSOCIATED PRESS

Review

Open Access

Exercise and cognitive function: a hypothesis for the association of type II diabetes mellitus and Alzheimer's disease from an evolutionary perspective

Gilberto NO Brito^{1,2}

Address: ¹Sector de Neurociências, Departamento de Pediatria, Instituto Fernandes Figueira, FIOCRUZ, Rio de Janeiro, RJ, Brasil and ²Departamento de Psiquiatria e Saúde Mental, Instituto de Saúde da Comunidade, Universidade Federal Fluminense, Niterói, RJ, Brasil
 Email: Gilberto NO Brito - ccsgnob@vm.uff.br

Published: 18 September 2009

Received: 4 May 2009

Study protocol

Open Access

Effectiveness of balance training exercise in people with mild to moderate severity Alzheimer's disease: protocol for a randomised trial

Keith D Hill^{*1,2,3}, Dina LoGiudice⁴, Nicola T Lautenschlager^{5,6}, Catherine M Said^{7,8}, Karen J Dodd^{1,9} and Plaiwan Suttanon^{3,9}



The Benefits of Physical Activity

YOUR BRAIN LOVES THE GYM (OR SIDEWALK, BIKE TRAIL, POOL,...)

WHEN YOU EXERCISE....

Norepinephrine is released, improving attention, perception and motivation.

Endorphins are released, dulling the sensation of pain.

Brain-derived neurotrophic factor (BDNF) is released, protecting and repairing neurons from injury and degeneration.

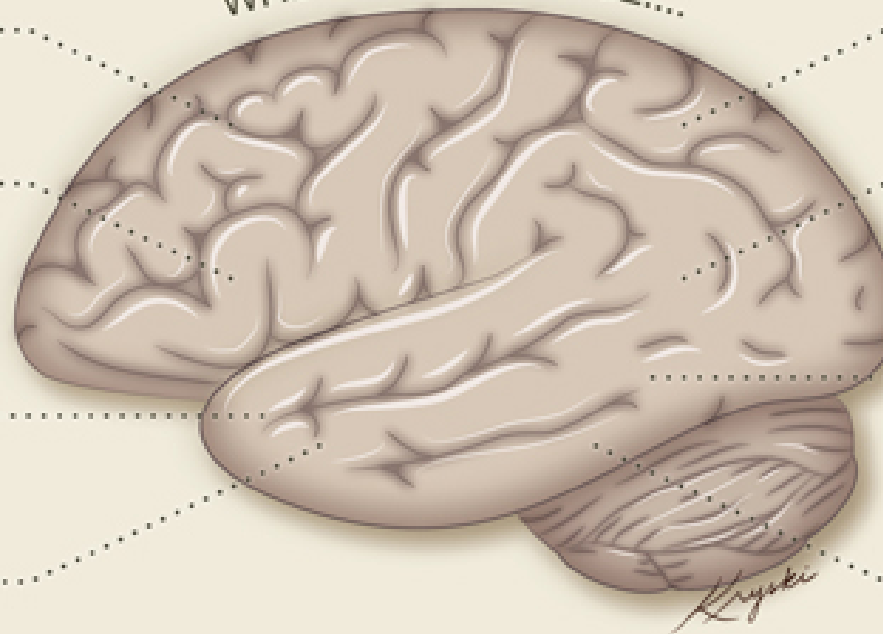
Serotonin is released, enhancing mood.

Hormones combine with BDNF to grow brain cells, regulate mood and provide mental clarity.

Blood flow to the brain increases, delivering more oxygen and nutrients and improving waste removal.

The hippocampus, a part of the brain concerned with learning and memory, grows in size with regular exercise over time.

Dopamine is released, improving motivation, focus and learning.



Road to Successful Aging: Use It, Don't Lose It!

Social Activity

- join groups, discuss topics, travel with friends

Spiritual Belief System

- Enables elderly people to cope with and overcome emotional and physical problems more effectively, leading to a heightened sense of well-being late in adulthood
- Less depression

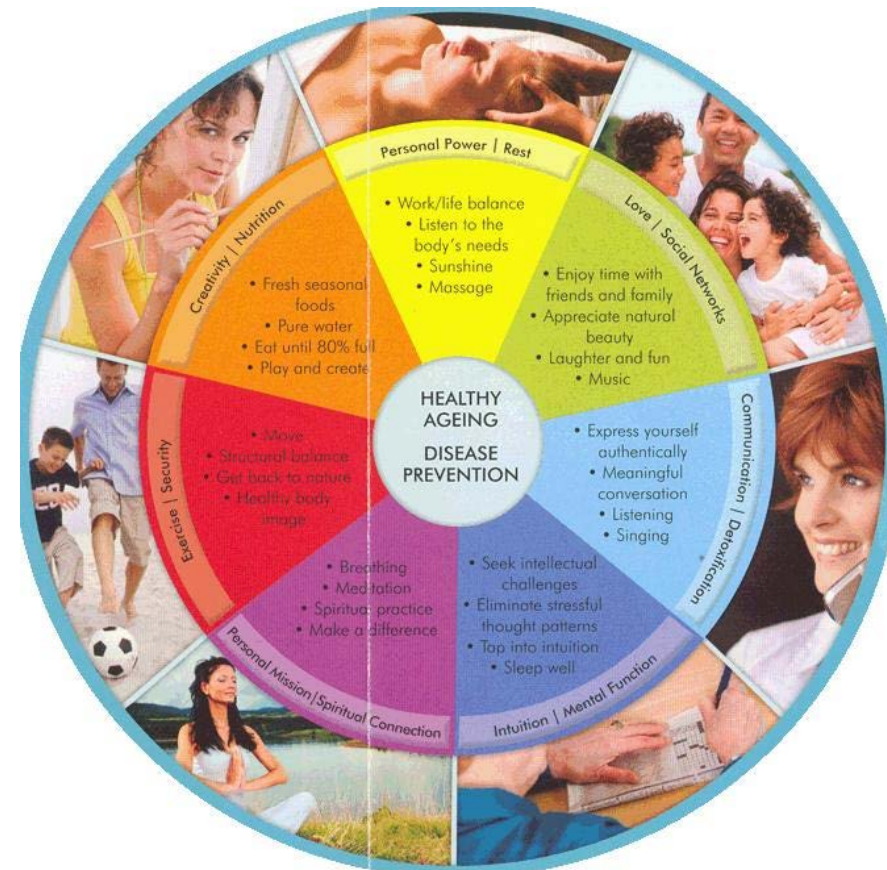
Mental Activity

- learn something new (language, game, music, instrument, dance, video games, computers, etc)

Meditation (Mindfulness, Transcendental)

- reduces stress, reduced inflammation

Yoga, Tai-chi



Information on AD Research

Drug
Development

Biomarker
Studies

Care
Interventions

Aerobic
Exercise
Training

Combination
Therapies

Cognitive
Training

Diet

The screenshot shows the NIH National Institute on Aging website. The URL is https://www.nia.nih.gov/research/ongoing-AD-trials. The page title is 'Ongoing Alzheimers and Related Clinical Trials and Studies'. The page was last updated on November 28, 2018. The page lists six tables of ongoing clinical trials and studies:

- Table 1: Early-stage Clinical Drug Development (Phase I and Phase II Clinical Trials)
- Table 2: Late-stage Clinical Drug Development (Phase II/III and Phase III Clinical Trials)
- Table 3: Non-Pharmacological Interventions
- Table 4: Clinical Therapy Development for the Neuropsychiatric Symptoms of AD/ADRD
- Table 5: Care Interventions
- Table 6: Delirium/Post-Operative Cognitive Decline

Thank you!



**“Growing Old is Mandatory,
Growing Up is Optional” –Chili
Davis**

How do you repay someone who was your Living Donor?
We established the Roseann Richards-Hines Education and
Research Fund within MUSC's Living Donor Institute to help others.
Passing it forward.

*-Kathy and Bob Richards
Bob is a living donor kidney recipient*



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To learn more about how you can help us
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muscd.edu/giving

Thank You!



Neurovascular Coupling in the Normal Brain and in Hypertension, Stroke and Alzheimer's Disease

- ◆ Regulation of cerebral blood flow (CBF) involves coordinated interaction of neurons, glia, and vascular cells
- ◆ Neurons and glia generate signals → vascular change → increased CBF
- ◆ Pathological conditions such as AD, hypertension, ischemic stroke disrupt neurovascular coupling → CBF not matched to metabolic needs
- ◆ Cerebrovascular dysregulation mediated by the enzyme, NADPH oxidase, a major source of cerebral vascular free radicals (oxidative stress)

Physical, Mental, and Social Activity Stave Off Dementia!

- ◆ Study after study has demonstrated that staying physically active is one of the best ways to protect your brain.
- ◆ Mental activity is equally important to brain health. Use It, Don't Lose It!
- ◆ Research has also shown that socially connected people are less likely to develop dementia than their isolated peers.