Maximizing Cognitive Health and Memory in Normal Aging, Mild Cognitive Impairment, and Alzheimer's Dementia

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Overview

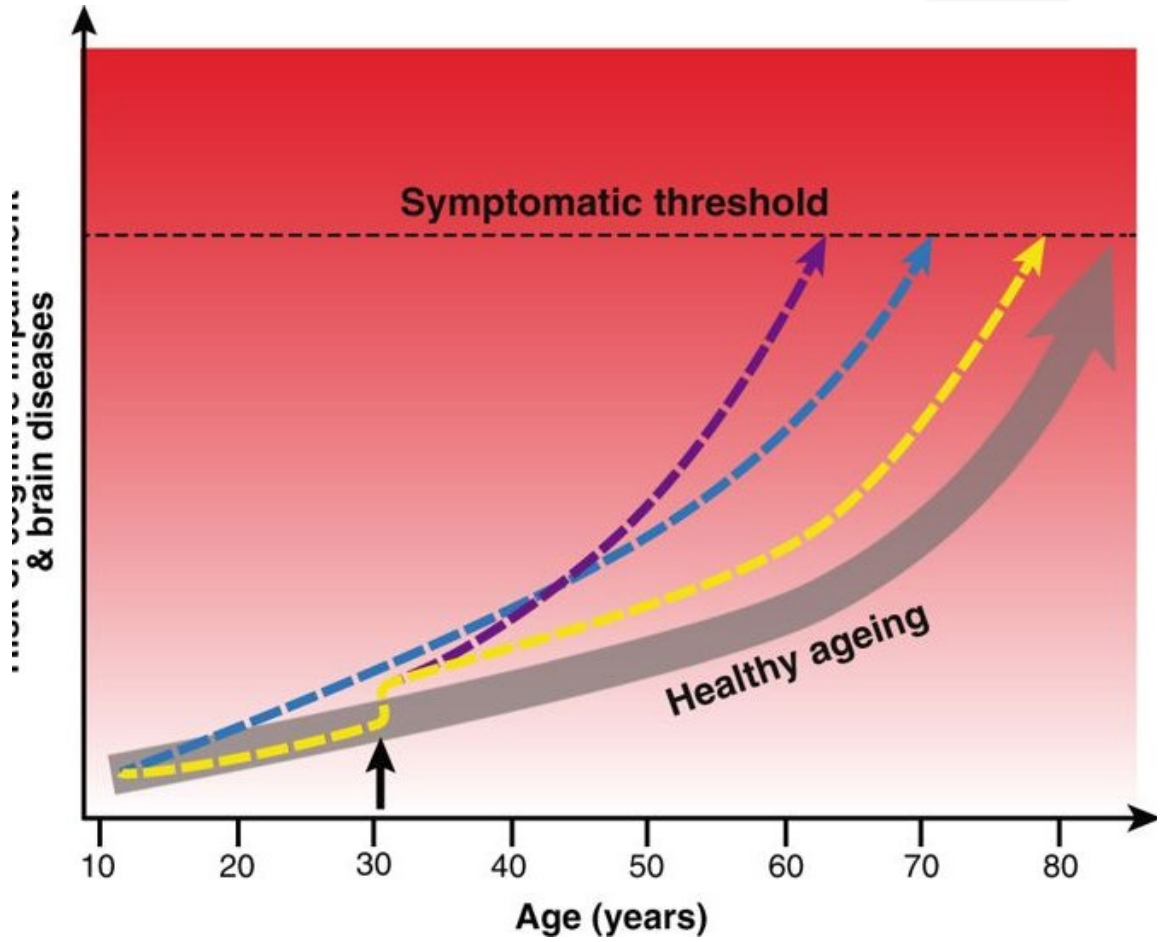
Learning objectives:

- 1. Discuss top strategies to maximize cognitive health and minimize memory impairment in normal aging, and tips to maximize engagement in health-promoting behaviors.
- 2. Summarize scientifically-backed interventions to slow the potential progression of mild cognitive impairment.
- 3. Identify the top strategies to slow the rate of cognitive decline in Alzheimer's.

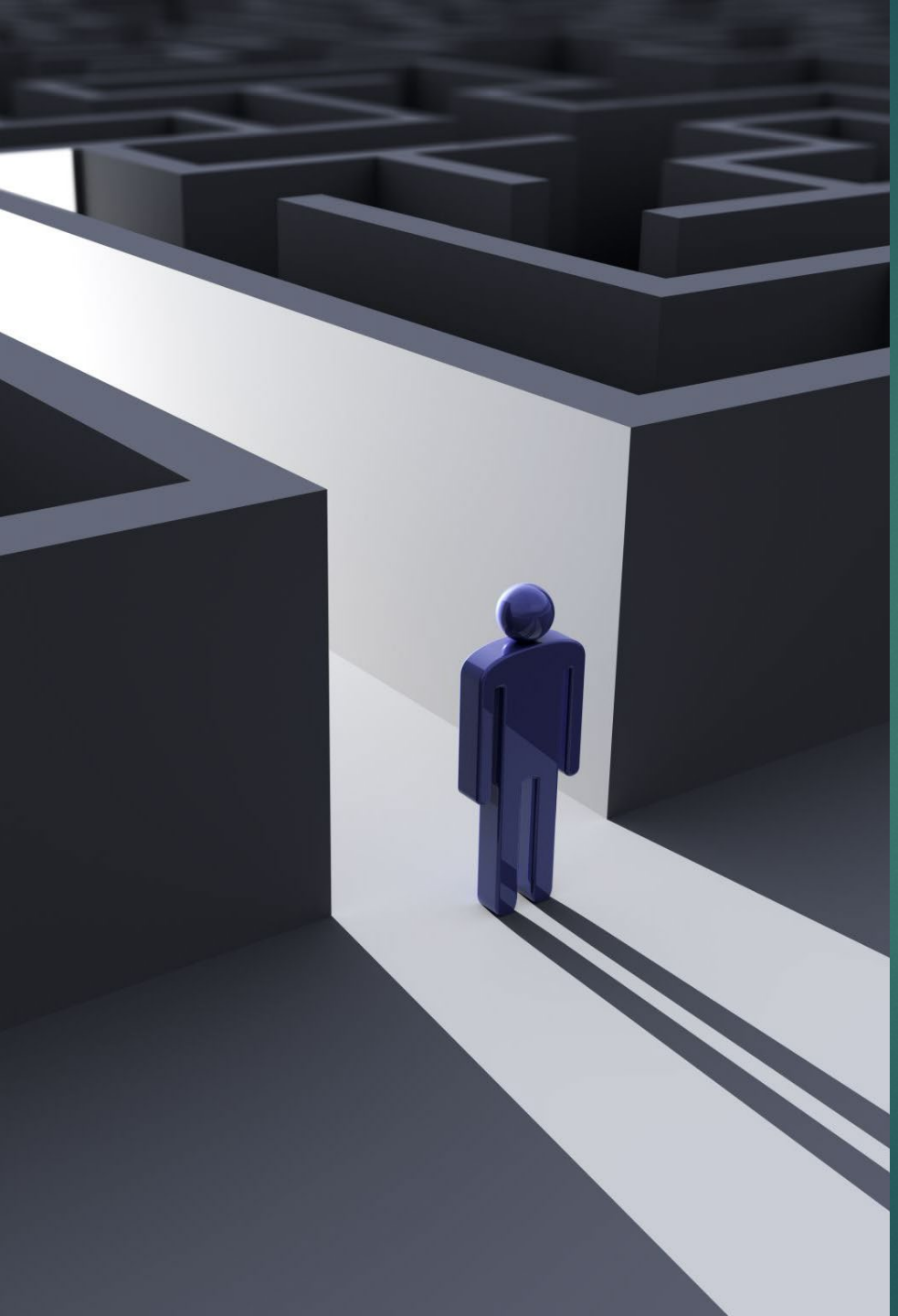
Brain Health is a worldwide priority

Aging	Aging population (the "Silver Tsunami") •75% of adults are worried their brain health will decline, and want to improve it (AARP 2015 survey on brain health) •More people fear Alzheimer's than any other disease
New Perspectives	Shifting paradigm for treating Alzheimer's and optimizing cognitive functioning •Significant, growing evidence of the power of lifestyle factors for many years, with recent randomized controlled trials •No new Alzheimer's medications since 2003 until Aducanumab was approved in 6/2021 •99.6% of drug trials fail, and several pharmaceutical companies have exited the Alzheimer's market

Variable brain health trajectories



COLE ET AL., 2019; MOLECULAR PSYCHIATRY, 24, 266–281



Brain Health in Action: Identify hurdles and personalize strategies

Common barriers to engagement in brain healthy behaviors

Myths about time

Brain aging begins in middle age or later

Alzheimer's begins to develop in older adulthood

Habits and activities in childhood, young adulthood, and middle adulthood don't impact the future risk of Alzheimer's

Myths about risk

1. Alzheimer's is highly hereditary

2. If you have a genetic risk for Alzheimer's, lifestyle factors will be less effective

3. Alzheimer's occurs equally in men and women, and in different ethnic groups

“Fragmented science” - Strategies that are partially (but not **maximally**) helpful

- Crosswords
- Sudoku

→ Fuels misperception that cognitive exercise is the **most** protective factor

- Generic understanding that “exercise” and “diet” are important

→ A lack of knowledge re: mechanisms of action often decreases engagement

Popular Pseudoscience Methods

Supplements

Most on-line brain games

Restrictive ”brain health” diets

Inspiration

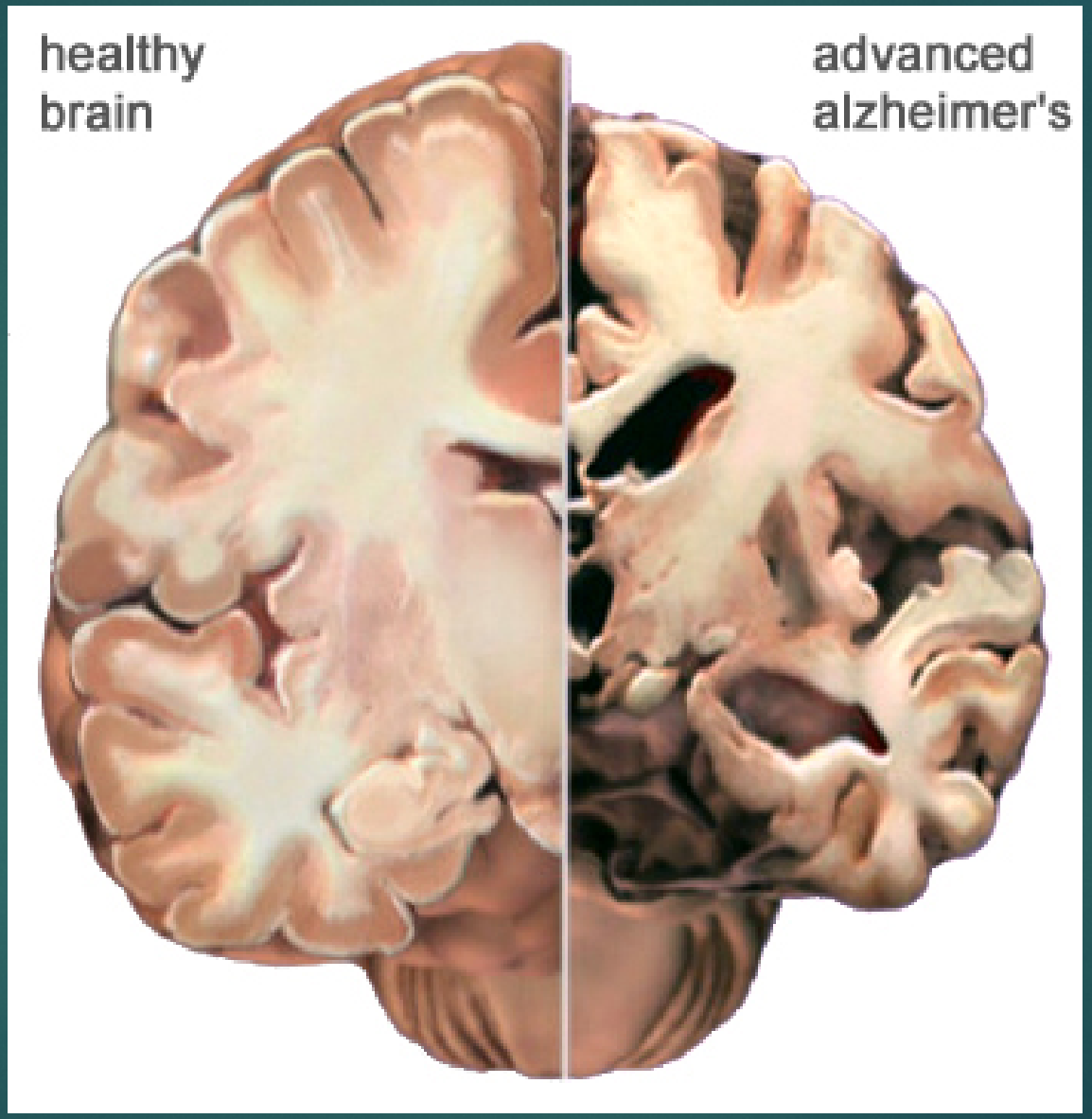
Sister Matthias

"Gold standard" for healthy aging

104 years old

Moderate Alzheimer's pathology but not symptoms

Cognitive reserve


healthy
brain
advanced
alzheimer's

FINGER Study

FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability); randomized controlled trial

- Exercise, brain-healthy diet, cognitive training, and vascular risk management = 30% reduction in cognitive decline after just two years
- Benefits continued for two more years and are still being tracked
- People with APOE-4 had the same 30% reduction in cognitive decline
- FINGER even more effective for people with other cognitive impairment risk factors!

U.S. Pointer study

U.S. POINTER (U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk) is led by the Alzheimer's Association to investigate whether lifestyle modification helps to decrease the risk of cognitive impairment in a diverse U.S. population

Worldwide fingers (WW-fingers)

- In addition to U.S. POINTER, similar interventions are underway in:

  Singapore, Australia, Sweden, Finland, France, Germany, China, and Basque
- Alzheimer's Association co-leading network to harmonize data and establish joint international initiatives for prevention of cognitive decline

Super Agers

Science-Backed Strategies

5 Top Tools to Slow Brain Aging and Minimize the Risk of Alzheimer's

- EXCELS
  - EX: Exercise
  - C: Consume brain-healthy foods
  - E: Engage and Learn!
  - L: Lower stress to boost well-being
  - S: Sleep to boost brain health

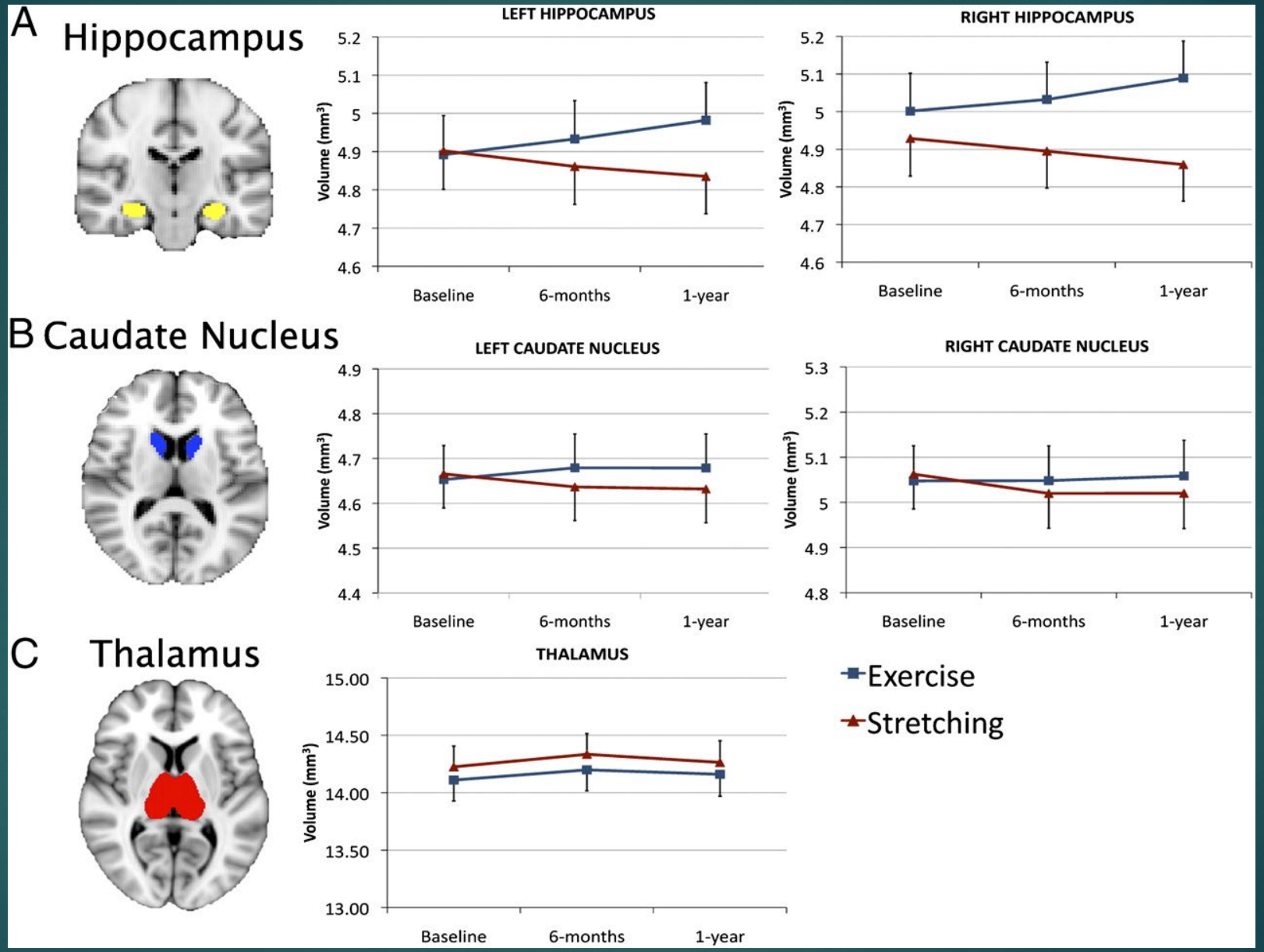
- Synergistic impact from multiple techniques

EXCELS – Exercise

- Evidence of **dose-dependent relationship** between fitness level and later dementia
  - 44-year study on 191 Swedish women found dose-dependent relationship between mid-life fitness and later dementia;
    - Low, medium, and high fitness groups: 32%, 25%, 5% likelihood of developing dementia
    - 44 women developed dementia, including 2 women in the high fitness group (who developed it 11 years later at age 90 – vs medium fitness group – age 79)
  - 32% reduced risk of dementia for men exercising 3x/wk vs. <3x/wk
  - Meta-analysis of 17 studies: highest level ex group 38% less likely to develop dementia than lowest ex group
  - Men 71 to 93 who walked 2 mi/day had 77% reduced risk of Alzheimer's vs. <1/4 mi/day
  - **Hundreds of studies show exercise is related to a reduced risk of dementia and increased volume in brain regions related to memory, attention, & mental flexibility**

Rapid & sustained impact of exercise

- Link between increased brain volume and exercise is rapid
  - Older adults showed more efficient use of brain networks after 12 weeks of exercise
  - Aerobic ex for 6 mos = increased volume of FL and WM tracts vs. non-aerobic exercise
- Exercise is linked to healthy brain changes many years later
  - Adults 65 and older who walked 6 to 9 mi/wk had larger brain volumes 9 years later and reduced risk of MCI and dementia
  - Higher levels of ex linked to reduced beta amyloid 13 years later and lower cog impairment
- Exercise also synergistically increases the benefit from Omega 3 fatty acids



(Erickson, et al., PNAS 2011,108,3017-3022)

Hippocampus visualization

Optimal exercise "dose"

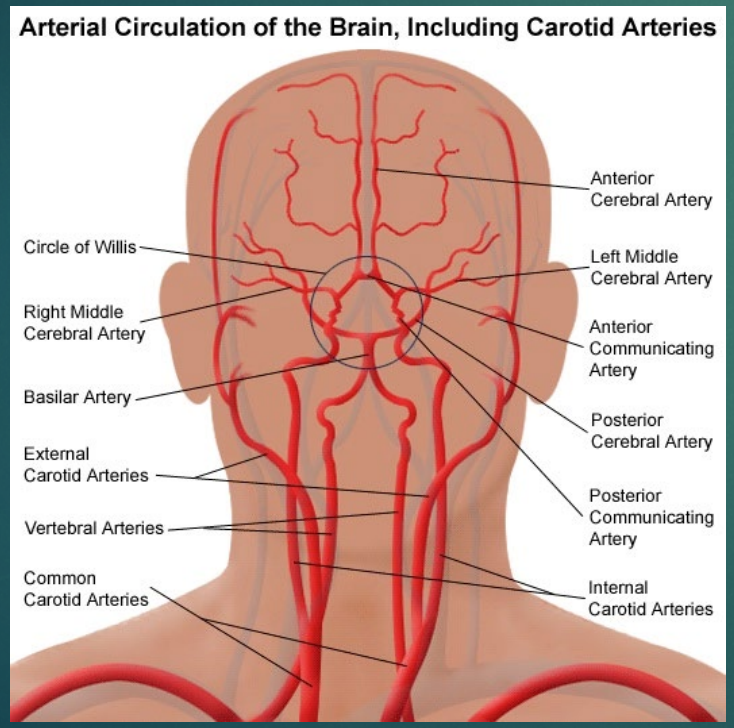
- Cardiovascular exercise, 150 minutes/week (22 minutes daily) for moderate intensity; 75 min/week for vigorous intensity
  - Intensity level
    - Moderate
      - Talk Test = talk but not sing
      - 64-76% of max HR (220-age = max HR)
    - Vigorous
      - Talk Test = can't way more than a few words
      - 77-93% of max HR (220-age = max HR)
- Some evidence that yoga, tai chi, and strength training enhance brain health, but the evidence is not as strong, possibly bc the research is not as mature as cardiovascular training

Personalize approach to maximize engagement in exercise

- Reframe exercise as "movement with joy" and inquire about preferences
- Identify components that increase joy
  - Social support, belongingness, classes
  - Pets
  - Nature
  - Learning (reading, watching programs)
- Identify "bonus benefits"
  - "Brain health homerun": enhances **memory**, **sleep**, **mood**, and **cardiovascular health**
- Acute exercise boosts (10-15 minutes aerobic sessions) appeal to busy schedule and immediate performance enhancement
- Set proximal initial goal, and increase when goal is attained

Minimize vascular risk factors

- Vascular risk factors (hypertension, diabetes, high cholesterol) and excess weight linked to Alzheimer's



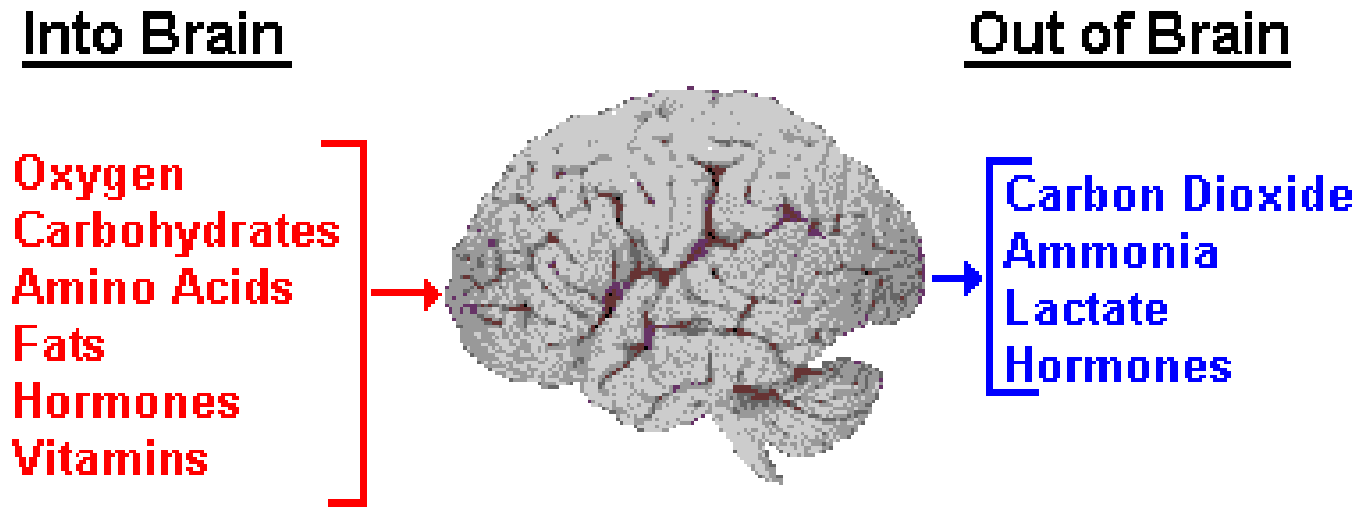
EXCELS: Consume Brain-Healthy Foods

- Mediterranean and DASH diets
- MIND Diet – Rush University
  - People who followed for 4 years had a 53% reduced risk of Alzheimer's!
  - People who followed for 10 years had a 7.5 year reduced rate of aging
  - 10 brain-healthy foods: Green leafy vegs, other vegs, nuts, berries (especially blueberries), beans, whole grains, fish, poultry, olive oil, red wine
    - Green leafy vegetables especially powerful (11 years of slowed cognitive aging)
  - 5 foods to minimize: red means, butter and stick margarine, cheese, pastries and sweets, fried or fast food

Supplements

- Projected sales by 2023 = $5.8 billion
- Most popular = fish oil, omega 3, turmeric/curcumin, green tea
- 73% of adults believed supplements could improve brain health, 61% said could delay dementia; 48% said could reverse dementia
- No support that supplements improve brain health unless there is a nutrient deficiency in Vitamins B12 or B9 (folate); this includes insufficient evidence for multivitamins

What enters and leaves the brain?



- *http://faculty.washington.edu/chudler/vessel.html*

The MIND Diet

Mediterranean-DASH diet Intervention for Neurodegenerative Delay

WHAT TO EAT

Every day	• 3 servings of whole grains • 1 serving of vegetables • 1 glass of wine (5 oz)
Most days	• Leafy green vegetables (6x) • Nuts (5x)
Every other day	• Beans (3x)
Twice a week	• Poultry • Berries
Once a week	• Fish

WHAT TO LIMIT

Less than 1 T. a day	• Butter and stick margarine
Less than 5x/week	• Pastries and sweets
Less than 4x/week	• Red meat
Less than 1x/week	• Whole-fat cheese • Fried fast food

MIND Diet components and scoring

MIND diet component servings and scoring

Diet component	0	0.5	1
Green leafy vegetables	≤2 servings/wk	>2 to <6/wk	≥6 servings/wk
Other vegetables	<5 serving/wk	5 to <7 wk	≥1 serving/d
Berries	<1 serving/wk	1/wk	≥2 servings/wk
Nuts	<1/mo	1/mo to <5/wk	≥5 servings/wk
Olive oil	Not primary oil		Primary oil used
Butter, margarine	>2 T/d	1–2/d	<1 T/d
Cheese	7 + servings/wk	1–6/wk	<1 serving/wk
Whole grains	<1 serving/d	1–2/d	≥3 servings/d
Fish (not fried)	Rarely	1–3/mo	≥1 meals/wk
Beans	<1 meal/wk	1–3/wk	>3 meals/wk
Poultry (not fried)	<1 meal/wk	1/wk	≥2 meals/wk
Red meat and products	7 + meals/wk	4–6/wk	<4 meals/wk
Fast fried foods	4 + times/wk	1–3/wk	<1 time/wk
Pastries and sweets	7 + servings/wk	5–6/wk	<5 servings/wk
Wine	>1 glass/d or never	1/mo–6/wk	1 glass/d
Total score			15

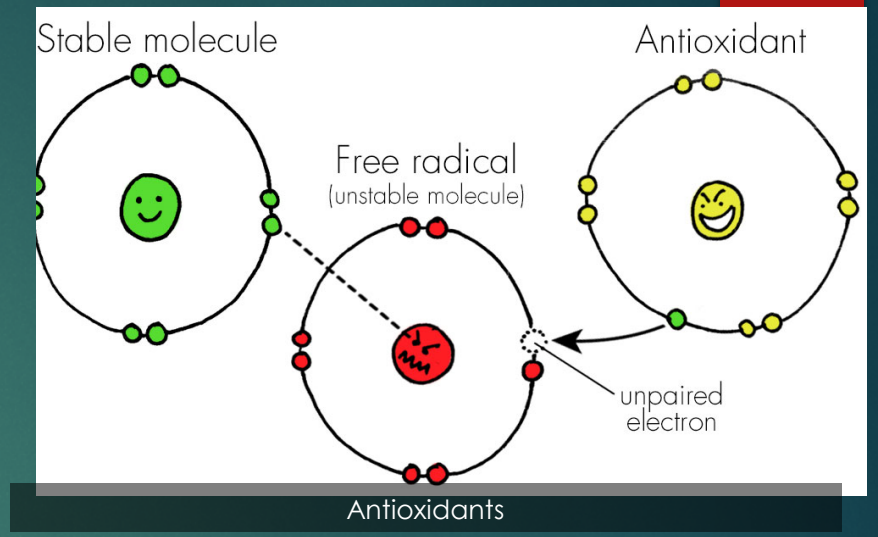
Fueling Your Best Self

A personalized approach to making dietary changes “stick”

Visualize Your Ideal Future Self

Harness the power of mindfulness and visualization

- Mindful eating exercise
  - Boost this exercise by visualizing how one of your favorite foods with **antioxidants** serves as a "cellular decoy" for free radicals and decreases oxidative stress and brain aging.
  - Visualize how one of your favorite foods with **omega 3 fatty acids** strengthens your cellular membrane and the ability of cells to function.



Antioxidants


Omega 3 fatty acids

Hurdle: "It doesn't really matter what I eat"

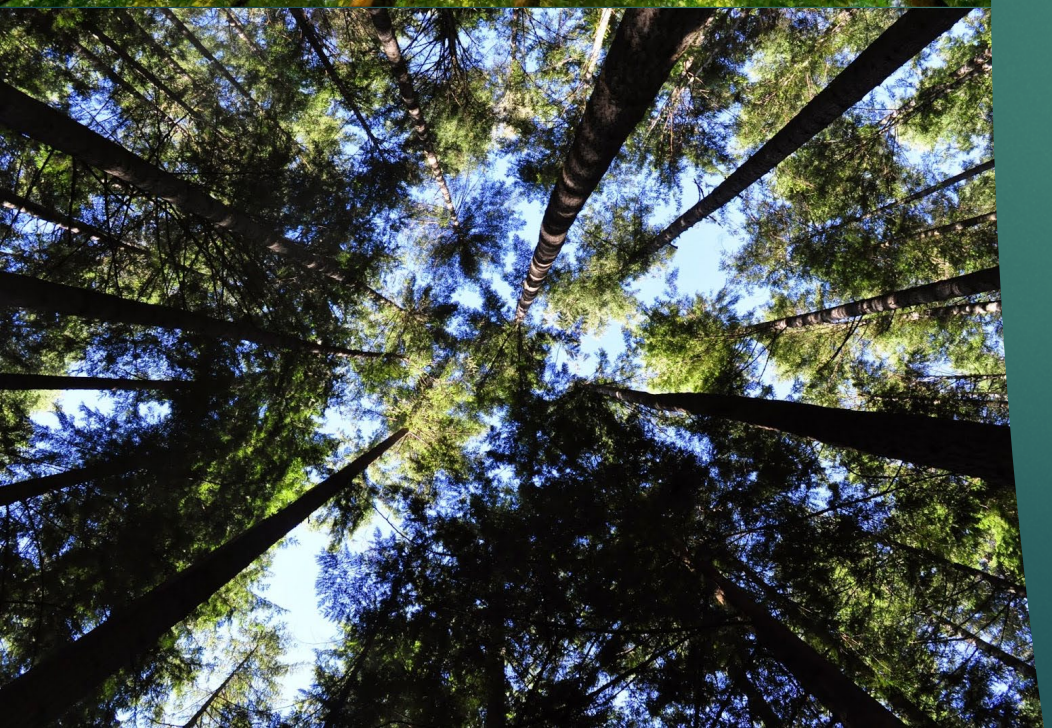
- Strategies:
  - Highlight research on how healthy diet slows cognitive aging
  - Record how you feel after you eat healthy vs. unhealthy food
  - Focus on "bonus benefits" of healthy diet, in addition to brain health, including:
    - Decreased rate of aging
    - Weight maintenance
    - Improved muscle tone and mobility

Hurdle: "I don't have enough time to eat healthy"

- Strategies:
  - Batch cooking
  - "Nutrient bullet"
  - Pack food ahead of time
  - "Go-to" foods
  - Check out simple on-line recipes (also works for hurdle "I don't know what to make")

Hurdle: "I don't like how healthy food tastes"

- Strategies
  - Create healthy substitutes in favorite recipes
  - Add a healthy food to a loved recipe
  - Expect it will take time for taste buds to adjust (6-8 tries)
  - Change the appearance of food



EXCELS– Engage and Learn!

Cognitive Reserve is fueled by engagement

- Cognitive Reserve (CR): Increased neuronal capacity, communication, and efficiency. Higher CR linked to significantly lower risk of Alzheimer's, and a delayed expression of Alzheimer's symptoms
- Meta-analysis of 22 studies w/29,000 people = mentally stimulating leisure activities = 50% reduced risk of Alzheimer's
- Chicago Health & Aging Project: Engagement in cognitive leisure activities (e.g., reading, radio, TV, games) several times/year = twice as likely to develop Alzheimer's as those engaging several times/wk
- 19 studies across multiple cultures = mentally stimulating leisure activities ass'd w/ reduced cog decline and better memory, EF
- 800 women studied over 40 years: greater engagement in arts, intellectual info, religion = significantly lower risk of Alzheimer's
- Bronx Aging Study: 11 or more activities/wk linked w/63% lower risk of dementia

There is no "best" cognitive engagement activity

Supported by findings of Nun study, several other studies

Several studies support a wide variety of CR activities

- Reading
- Social engagement
- Games (cards checkers)
- Puzzles (crosswords, jigsaws)
- Writing
- Radio & TV learning
- Arts, Crafts
- Visiting museums
- Playing musical instrument
- Attending religious services
- Participating in discussions w/others
- Learning another language

Brain games/"computerized cognitive training"(CCT)

- Most brain games lack transfer of benefit to real world
- One notable exception: ACTIVE Study (Advanced Cognitive Training for Vital and Independent Elderly)
  - First large RCT showing CCT improves cog function in older adults
  - Initial training 10-14 weeks, then booster sessions
  - Benefits to daily fxg, memory 5 years later; enhanced daily fxg, reasoning, processing speed 10 years later
  - Participants 33% less likely to develop dementia over 10 yrs; 48% reduced risk for those who completed the most PS training
- Rec: If desire to use CCT, choose an effective platform, and use as one of multiple components of brain healthy program

SAVE method

- **S**lightly challenging
- **A**bsorbing
- **V**aried
- **E**nlarge your knowledge

EXCELS = Lower Stress to Boost Well-Being

High perceived stress linked to lower cog performance and higher risk of MCI, dementia

In 10,000 participants, high perceived stress at mid-life = highest rates of dementia 13 years later

Chronic stress linked to factors in Alzheimer's and depression, including

- Higher cortisol levels
- Smaller hippocampus
- Chronic inflammation

Stress reduction tools

- Exercise
- Mindfulness
- Resilience
- Positive stress management tools (social engagement, changing stressful situation, CBT, positive activities)The power of mindfulness

EXCELS Sleep for Better Brain Power

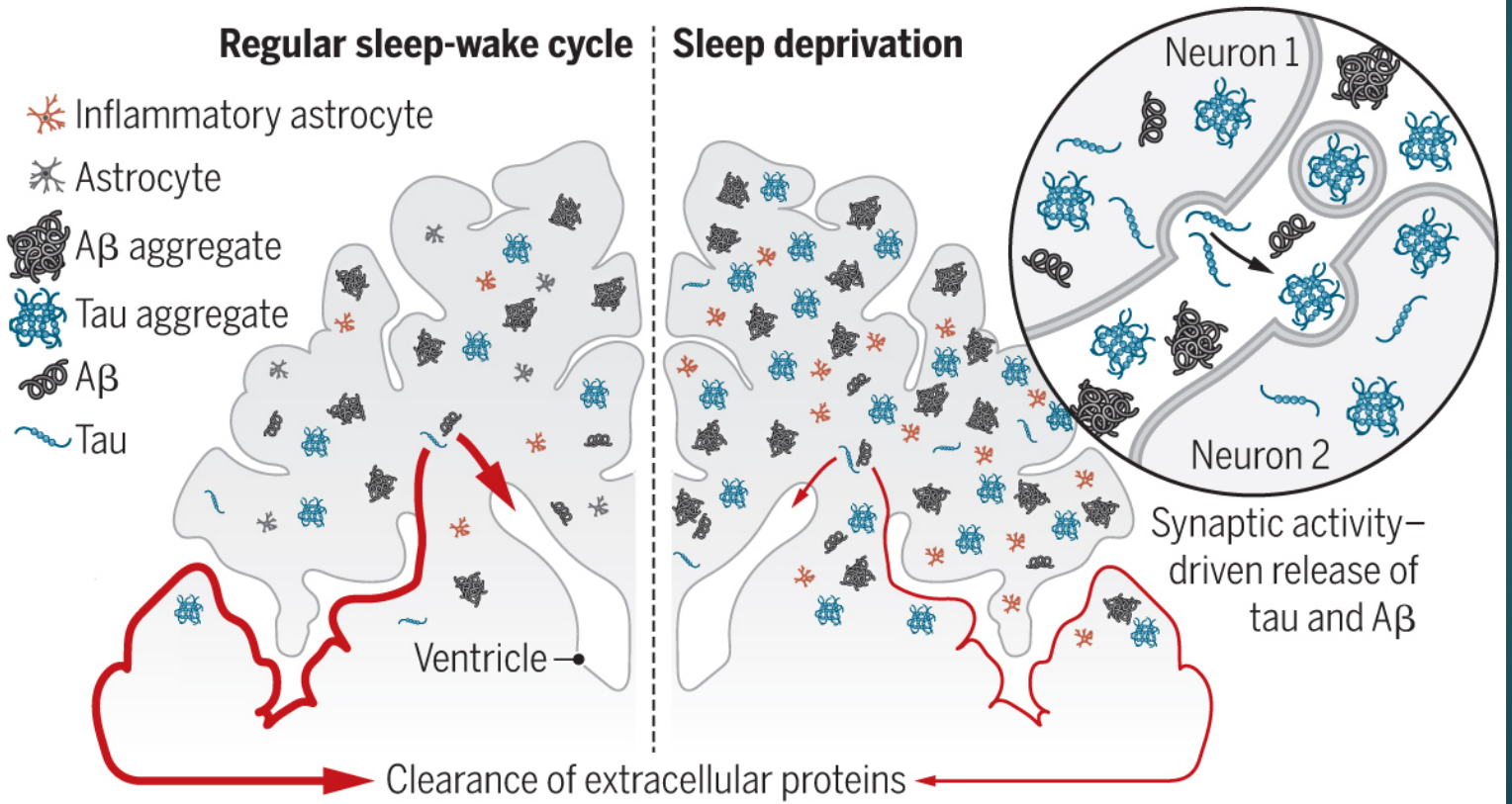
- Alzheimer's related protein deposits may occur in insomnia
- Tips
  - Figure out how much sleep you need to feel well rested
  - Schedule "downtime" prior to bedtime
  - Get up and do something relaxing if you can't fall asleep after 10-15 minutes

Sleep and cognitive functioning

- Cross-cultural studies support relationship between poor-quality sleep and cognitive symptoms
- Increased risk of dementia with <5 and >9 hours
- 15% of cases of Alzheimer's may relate to sleep px
- Potential bi-directional relationship between poor sleep and Alzheimer's

Sleep deprivation promotes Alzheimer's pathology

Sleep is accompanied by lowered activity-driven release and heightened clearance of Aβ and tau from the brain. Sleep deprivation reduces aggregate clearance and promotes astrogliosis, network activity–driven tau and Aβ release, further protein aggregation, and the spread of Alzheimer's disease pathology.



Science 22 Feb 2019:
Vol. 363, Issue 6429, pp. 813-814

Strategies to enhance sleep

- Identify untreated sleep disorders
- Sleep hygiene for insomnia
- CBT for Insomnia (CBT-I)
- Physical exercise
- Mindfulness
- Volunteering
- Minimize blue light exposure
- “Wind down” routine before bedtime

How to ***rapidly*** boost cognitive functioning

ACUTE EXERCISE BOOSTS (10-15 MINUTES OF CARDIOVASCULAR EXERCISE LEADS TO IMMEDIATE IMPROVEMENTS IN MEMORY!)

MINDFULNESS (ENHANCES WORKING MEMORY)

QUALITY SLEEP (ENHANCES ATTENTION)

RAPID COGNITIVE BOOSTS CAN BE USED STRATEGICALLY PRIOR TO MEETINGS, PRESENTATIONS, AND OTHER IMPORTANT EVENTS

Mild Cognitive Impairment

Historical development of "Mild Cognitive Impairment"

1980's

Staging of Alzheimer's/AD symptoms on rating scales led to categorization of pre-Alzheimer's stage

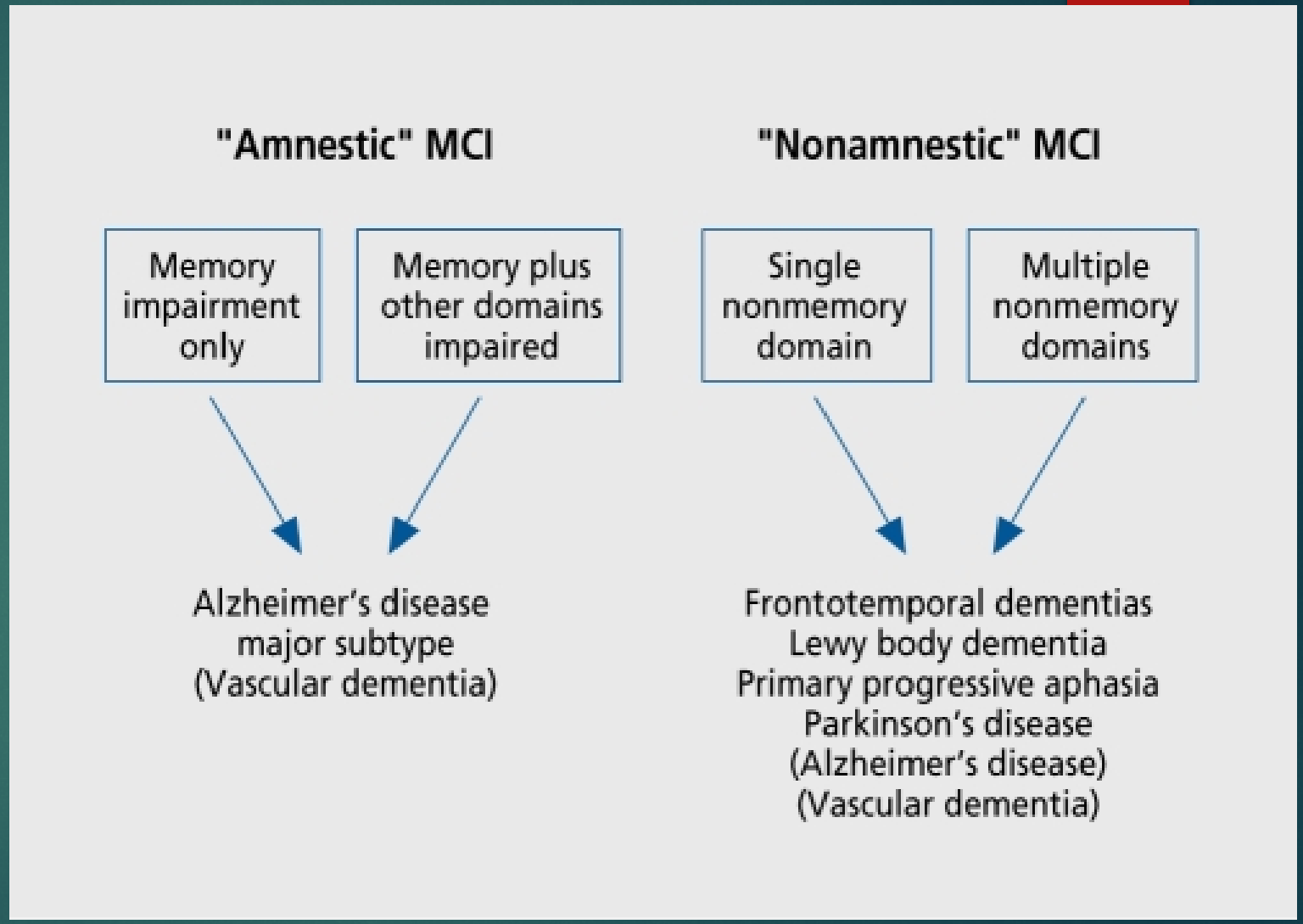
1988

First use of term "Mild Cognitive Impairment" to classify mild deficits on a rating scale

1995

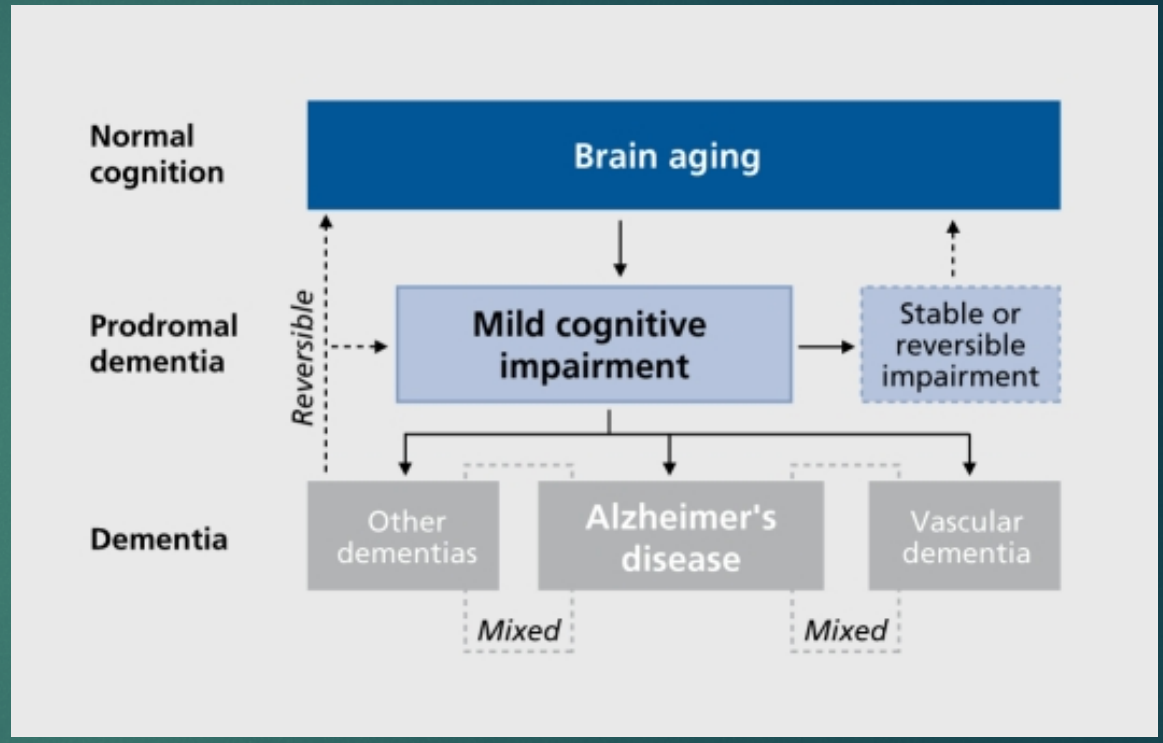
Dr. Ronald Petersen (Mayo) first used the term as an independent diagnostic category not linked to a rating scale

MCI Classification



MCI Conversion to Dementia

- Annual conversion rate to Alzheimer's: 3–23% in community settings and 10–31% in specialty clinics
- 2006 study: 50% of amnestic multiple domain MCI pts converted to Alzheimer's in 3 yrs vs. 10% of amnestic single domain MCI
- 2021 study in national sample 65 and older: 4% of population had MCI (greater with age); 24% of MCI pts converted to dementia per year
  - African Americans more likely to convert from MCI to dementia than Caucasian Americans
  - Hispanic Americans more likely to develop MCI and dementia, and more likely to revert from MCI to normal cognitive functioning



Scientifically supported strategies to slow progression of MCI to AD

Exercise:

Aerobic exercise decreases levels of tau and decreases shrinkage of the cortex across the entire brain

Yoga and Tai Chi = better memory and daily functioning

Brain healthy diet

Mindfulness (“moment to moment nonjudgmental awareness”) = better memory and daily functioning

DASH + Aerobic exercise reversed 10 years of brain aging

- 2018 Study; 160 older adults with MCI and or or more cardiovascular disease risk factors (e.g. high cholesterol)
- Group 1: Aerobic ex
- Group 2: DASH Diet
- Group 3: Aerobic ex + DASH Diet
- Group 4: Weekly heart health education
- Results: Group 1 had a small improvement in executive functioning skills (planning, organizing), but Group 3 had largest improvement in executive functioning (reversed 10 years of brain aging)

EXERT Clinical Trial for MCI is ongoing

- EXERT Trial = Exercise in Adults with MCI EXERT Trial = Exercise in Adults with Mild Memory Problems (ages 65-89)
- Investigating impact of exercise on:
  - Brain atrophy
  - Blood flow
  - Cellular markers of Alzheimer's
  - Cognitive ability
  - Daily functioning d Memory Problems (ages 65-89)
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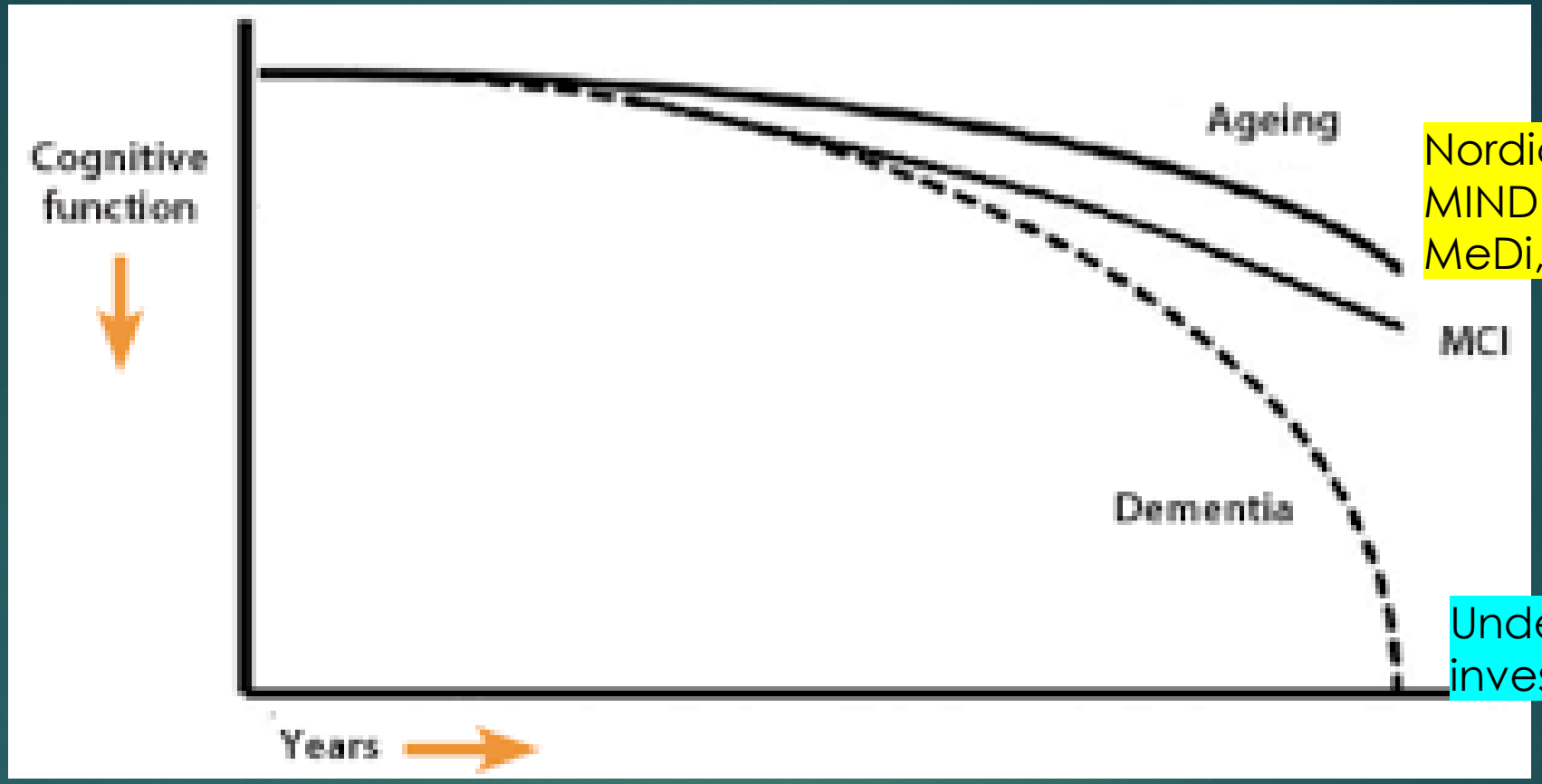


Nordic Diet, MIND Diet, MeDi, DASH

MeDi , DASH

Under investigation

Different cognitive stages = Support for different diets

2014 Meta-analysis: MeDi

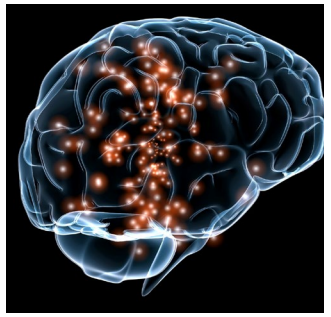
Reduced risk of MCI and Alzheimer's (varied based on adherence to MeDi)

Reduced risk of progression from MCI to AD

Mediterranean Diet:

- Varies by country
- Diet is part of overall lifestyle (which includes daily exercise and sharing meals with others)

Why is MeDi therapeutic in MCI?



Reduces inflammation and oxidative stress via

lower levels of C-reactive protein

lower interleukin levels

high ratio of monounsaturated fats to saturated fats

Cardio-protective effects

improved blood pressure

Improved cholesterol levels

Reduced coronary artery disease

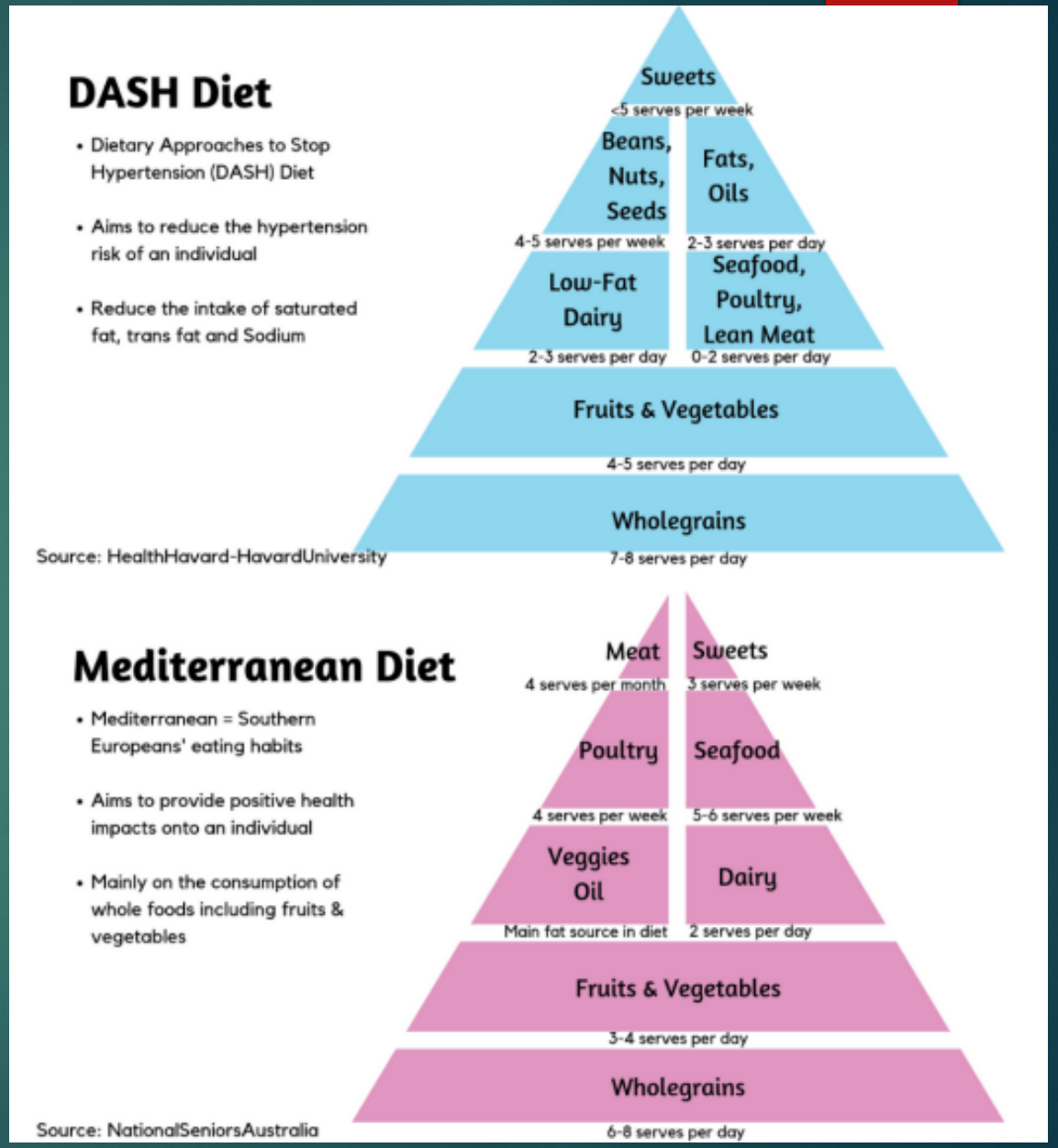
Improved plasma glucose level and insulin levels

Healthier weight

Differences between MeDi and DASH Diets

- MeDi :
  - High consumption of healthy fats (olive oil)
  - Includes wine
  - Fewer servings of sweets
  - Doesn't include a daily recommendation for dairy foods
  - Doesn't emphasize reduced sodium intake
  - Lower in red meat consumption

Mediterranean & DASH Diets



Alcohol and MCI

1 drink per day has been shown to decrease the rate of progression to dementia

- Some research shows wine drinkers have slower progression than other alcohol types
- Some research shows no difference between abstainers and having >1 drink/day

Serving sizes based on alcohol type and percent of alcohol content:

- **Wine:**
  5 fluid oz of wine (12.0% alcohol content):
- **Beer:**
  12 fluid ounces (5.0% alcohol content):
- **Liquor:**
  1.5 fluid oz of **40% alcohol** (**80 proof**)

HABIT Program for MCI

- HABIT Program at Mayo (Healthy Action to Benefit Independence and Thinking) includes:
  - Memory training (www.brainhq.com)
  - Cognitive exercise
  - Yoga
  - Wellness education
  - Support groups for individuals with MCI and care partners

Enlist a "Brain Health Champion"

Brain health coaching study

6-month study of 40 patients with either MCI, mild dementia, or subjective cognitive impairment

Intervention:

- Weekly motivational interviewing phone calls
- 3 visits with Brain Health Champion, who personalized goals (short, medium, long range)
- Results: Increased physical activity, adherence to MeDi, cognitive and social activity, and quality of life
- Provides support for a health coaching model to augment clinical care delivery in individuals with cognitive decline

Alzheimer's Dementia

Aerobic exercise improves brain structure and function in Alzheimer's

- Moderate to high intensity aerobic exercise is disease modifying, and can improve the underlying cellular abnormalities of Alzheimer's
  - Decreased hippocampal shrinkage as a function of increased cardiorespiratory fitness (peak VO2)
- Meta-analysis of 18 RCTs showed aerobic ex or aerobic + non-aerobic ex slowed the rate of cognitive decline, but not non-aerobic exercise alone

Other strategies that can slow cognitive decline in Alzheimer's

- Cognitive engagement (e.g., discussion of current events)
  - Over 7 weeks, stable MMSE, better cog fxg, mood, and QOL
- Religion and spirituality
  - May relate to social engagement and development of coping strategies to accept the disease, maintain hope, and find meaning
- Music therapy
  - Over 6 weeks, significant improvement in memory, orientation, depression, anxiety in mild to moderate Alzheimer's; also improvement in beh symptoms in moderate group (hallucinations, agitation)

MIND-ADmini Pilot Trial for Alzheimer's

- MIND-AD Trial = Multimodal Preventative Trial for Alzheimer's Disease
- Investigating impact of 3 interventions on individuals with Alzheimer's:
  - Regular health advice
  - Multidomain lifestyle intervention (nutritional guidance, exercise, cognitive training and monitoring and management of vascular and metabolic risk factors)
  - Multidomain lifestyle intervention + Medical Food (based on synergistic effects of omega 3 + physical activity)
- Outcomes from cognitive and functional assessments will inform estimates of change for larger study (MIND-ADmaxi)

Enhancing quality of life and functioning

- **Caregiver education and support**
- Maintain a ROUTINE that includes positive events
- Find something to CARE FOR that needs you (pet, plant, grandchild, etc)
- Look for and SAVOR beautiful moments (sunrise, loved one's laugh)
- Create a COUNT DOWN to special days and holidays (creates sense of anticipation as time passes)
- ENGAGE socially (even if across the room, across the yard, or virtually); consider engaging with others who have Alzheimer's

Other strategies to enhance quality of life

- **Aim to increase smiles with all interactions**
  - Seek harmony rather than factual correctness
  - Questions should be about personal opinion, not facts
  - Listen/see the message behind the words, and respond to the emotion of the intended message
  - Minimize stressful situations
  - Maximize positive events
  - Help simplify favorite tasks
  - Streamline the environment
  - Incorporate environmental reminders
  - Engage the senses
  - Follow your instincts
  - **Engage in the arts!**

Research on the arts…

- Salient improvements when individuals with cognitive changes were engaged in art, including :
  - Increased smiling
  - Increased social engagement
  - Improved moods
  - Decreased agitation
- TimeSlips program focuses on asking “Beautiful Questions “(emphasizing imagination rather than memory)

Other benefits of artistic engagement

- Increases ability to make choices in the moment; to be "self propelled"
- Sharpens sensory attention
- Provides a sense of engagement, efficacy
- Empowers one to be a communicator
- Encourages novel interaction that is personally meaningful
- Enlarges scope of communication to include non-linguistic methods (especially important if language abilities are declining)

Music

- One of the most well-studied art forms
- Consistently linked with reduced agitation
- Innovative study combining medical, functional, and cognitive measurements showed decreased irritability, improvement in language, and decreased stress hormones

Dance

- In one study, after nine weekly sessions of ‘Dance and Movement Therapy’, individuals with dementia showed slightly improved self-care abilities and performance on the Clock Drawing


Música para Despertar

Willem de Kooning

1964 - Woman, Sag Harbor

1988 – No Title

Danae Chambers

Portrait of Giller Prize-winning novelist, Austin Clarke, painted in 1978.

Self portrait, 1988

Aducanumab (Aduhelm)

Recently approved as an Alzheimer's treatment

First drug approved since 2003; first disease-modifying medication

Reduces beta-amyloid

Concerns

- No consistent evidence that it decreases cognitive and functional decline
- Cost
- Risk
- Generalizability of clinical trial data
- Approved to treat Alzheimer's of any severity

Next steps

- Awaiting guidelines from Medicare (CMS), American Academy of Neurology and other groups
- Highlight cardiovascular exercise as an existing disease-modifying treatment
- Highlight other treatments that slow Alzheimer's: memory medication, cognitive engagement, music therapy, religion & spirituality

"The best time to plant a tree was 20 years ago. The second best time is today."

-Chinese proverb

Questions?

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