The Message

- A brain-healthy lifestyle can reduce the risk of milder and serious cognitive decline.
- Promote graceful, optimal brain aging!

Join the “DANCERS”:

Our Older Population Is Growing!

>40 million ≥ 65 years old in US
13.0% of population

We are here!
The Prevalence of AD Is Increasing

Even Small Progress Will Help!

What The Biomarker Findings Tell Us: “Dementia” Is The Tip Of A Clinical Iceberg

Subjective Memory Impairment (SMI):
Definition and Prevalence

Evidence Is Growing For Neurodegenerative Basis of SCD

DSM 5 Mild Neurocognitive Disorder

A. Evidence of modest cognitive decline in one or more domains based on concern AND objective assessment.
B. Not sufficient to interfere with independence (instrumental activities of daily living (IADLs)) preserved but may require greater effort and compensatory strategies or accommodation

Exclusions: C) Not delirium, or D) another Axis I disorder.

*Specify whether due to AD, FTLD, LBD, VD, TBI, SUD, HIV, prion, PD, HD, other, multiple, unspecified; with or without behavioral disturbance

MCI Has Many Possible Etiologies, But aMCI is Often Prodromal Alzheimer’s Disease

- Hypoxemia (COPD, OSA, s/p cardiac arrest)
- Autoimmune disorders (SLE, Sjogren’s)
- Neurological disorders (MS)
- Metabolic disorders (dialysis)
- Endocrine (thyrotoxicosis, cortisol deficit)
- Cancer (paraneoplastic, chemotherapy)
- Infectious (HIV, Lyme, syphilis)
- Toxins, Substances, Pollutants

The Spectrum Of Cognitive Changes With Aging

Asymptomatic
Normal Cognitive Aging (may be earliest preclinical)
Subjective Cognitive Impairment
Mild Neurocog. Disorder
Major Neurocog. Disorder
Progressive impairment in cognitive functioning

In Autosomal Dominant AD, Cognitive Decline Is Preceded by Decades of Physical Changes

A Brain-Healthy Lifestyle Can Help Optimize Cognitive Aging

- Disease Management
- Activity
- Nutrition
- Cognitive Stimulation
- Engagement with others and sense of purpose
- Relaxation
- Successful Sleep

Keys to Optimal Cognitive Aging:

Remember This List

- Diabetes
- Midlife hypertension
- Midlife obesity
- Physical inactivity
- Smoking
- Hearing loss
- Depression
- Medication-related effects
- Sleep disorders
- Neurological disorders
- Infectious/inflammatory
- Post-surgical and post-anesthesia impairment
- Nutritional/Metabolic/Endocrine Disorders
- Autoimmune/Collagen Vascular Diseases
- Normal Pressure Hydrocephalus
- Head Injury/Subdural Hematoma
- Neoplasms

Disease Management: Treat Exacerbating Disease and Lifestyle Factors


Stop Smoking!

Prevalence of Cigarette Smoking in US Adults by Age and Sex (2016)


Recommendations re Smoking

- Earlier inference that cigarette smoking protected against AD was erroneous.
  - Selective survival bias may have accounted for lower rate of AD among older smokers.
- Prospective studies have found increased AD risk with cigarette smoking.
  - Especially among APOE ε4 noncarriers
  - Overall OR = 1.79 (CI 1.43-2.23)
- Recommendation: No Smoking


Control Blood Pressure!

Prevalence of Hypertension by Age in US Adults


Age-Specific Control of HT Among Adults with Hypertension in the US (2009-2010)


Treatment of Hypertension (1 of 2)

- Uncontrolled midlife high BP linked with late-life AD in observational studies\(^1\)
- Antihypertensives may have effects in addition to lowering BP, e.g. neuroprotective effects and/or direct effects on pathophysiology\(^2\)
- ACE inhibitor and diuretics have best-documented preventive effects on cognitive decline\(^3\)


Treatment of Hypertension (2 of 2)

- Evidence suggests that antihypertensive drugs reduce risk of dementia with early and continuing treatment of HT\(^1,2,3,4\)
- Effects of treatment on established cognitive impairment? Not demonstrated.
- Overtreatment can be dangerous: Target no less than 150/90 for 80 years and older.\(^5\)
- Recommend: Early and sustained treatment but avoid overtreatment.

SPRINT MIND Preliminary Results (AAIC 2018)

• Large study – 9,361 participants, mean age 68, followed for an average of 5 years.
• Cognitively healthy intervention group goal SBP<120 mm Hg vs control group SBP <140 mm Hg.
• Intervention group – 15% fewer people developed MCI or dementia of any cause. WMD also reduced with aggressive treatment.
• US POINTER study will follow up on this.


Treatment of Dyslipidemia

• Midlife high total cholesterol linked with late life AD1,2
• Most recent metanalysis:3
  _25 studies included
  _Statin use significantly associated with reduced risk of all-cause dementia
  _Stronger effect measured with lipophilic statins for reduced AD risk
  _Statin use significantly associated with reduced risk of MCI
  _No meaningful effects shown for prevention of VaD
  _Anticholesterol, anti-inflammatory, and endothelial effects hypothesized
• Recommend: Treat early – especially with high baseline cholesterol, ApoE4 genotype


Treatment of DM

• Diabetes increases risk for AD and VaD1
• Effect may be primary or secondary (e.g. HT, dyslipidemia)2
• Longer duration of DM increases AD risk3
• Even in later life, impaired glucose tolerance is linked to AD onset4
• Treatment reduces vascular and other complications.
• Recommendation: Treatment even after onset of AD is important.

Physical Activity: Strongly Evidence-Based

- Disease management
- **Activity**
- Nutrition
- Cognitive stimulation
- Engagement (social / purpose)
- Relaxation
- Successful Sleep

Total Activity Includes Exercise

Exercise

Activity

Four Types of Exercise

- Endurance
- Flexibility
- Strength
- Balance

Exercise’s Benefits

- Improves lipid profile
  - Increase HDL
  - Reduce LDL
  - Reduce plasma triglycerides
- Reduces blood pressure
- Reduces intra-abdominal and total body fat
- Improves insulin sensitivity
- Improves energy metabolism
- Improves balance and reduce fall risk
- Increases neurogenesis
- Increase Aβ metabolism and reduce deposition in mouse AD model
- Improves mood


Preparing for The Rat Race: Cognitive Aging in Rodents

Studies have demonstrated:

- Improved learning and memory
- Reversal of age-related impairment
- Resistance to damaging cognitive effects of stress:
  - Cortisone administration
  - Immobilization

Exercise And Cognitive Aging In Humans

Data come from from several types of studies. Each has advantages/disadvantages:

- Cross sectional studies
- Longitudinal studies
- Interventional studies

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Human Cross-Sectional And Longitudinal Studies

- Increased physical activity is associated with better cognitive performance.
  - Effect size varies among studies
  - Methodology of studies may be responsible
- More active individuals have reduced risk of cognitive impairment and dementia.
- These study types identify ASSOCIATION rather than CAUSAL RELATIONSHIP.

High Physical Activity and Cognitive Decline: Meta-analysis of Longitudinal Studies

The association between high physical activity and cognitive decline.

Blondell et al. BMC Public Health 2014, 14:510

High Physical Activity and Dementia: Meta-analysis of Longitudinal Studies

The association between high physical activity and cognitive decline.

Blondell et al. BMC Public Health 2014, 14:510

English Longitudinal Study of Ageing

- N=10,652 older adults
- Self-reported physical activity and neuropsychological testing followed over 10 yr
- Physically inactive women experienced:
  - Greater decline in memory and executive function
- Decline in executive function seen between inactive and vigorously active men.


Human Interventional Studies

- Metaanalysis\(^1\) (29 studies) shows improved:
  - Processing speed
  - Executive function
  - Memory (less consistent evidence)
- Balancing / Stretching not so consistently associated with cognitive improvement

Metaanalysis of Intervventional RCTs: Effect of Exercise on Attention and Processing Speed in Cognitively Normal Older Adults

Smith et al. Psychosomatic Medicine 2010;72:239-252

Exercise Also Helps Cognition After The Onset of “Memory Complaints”

- RCT in older adults with memory complaints:
  - 24 week exercise program
  - 3x50 min exercise/wk
  - Modest improvement in
    - ADAS-Cog
    - CDR Sum of Boxes (CDR-SOB)
  - Gains maintained over 18 month follow up.
  - Consistent with other recent findings.


Exercise Even Helps Persons with “Dementia”

- A meta-analysis of 30 trials in older adults with dementia (2020 subjects) found that exercise improved:
  - Physical fitness
  - Physical function
  - Cognitive function
  - Positive behavior

- Recommendation: Appropriate activity is valuable through life regardless of cognition.


ACSM/AHA Recommendations: Exercise for Healthy Adults over age 65

1. Aerobic exercise (endurance)
   - 55-90% of maximum Heart Rate
   - Moderate level of intensity, 30 min/day, 5 days/wk
   - Or vigorous intensity level, 20 min/day, 3 days/wk

2. Resistance training (strength)
   - 8 to 10 exercises, 10-15 reps of each, 2-3x/wk

3. Flexibility training

4. Balance exercises as appropriate


Physical Activity Recommendations For Cognitive Fitness

- Frequency:
  - 3 days/week is the standard for studies reviewed

- Intensity:
  - Moderate is better than low or extreme

- Duration
  - Moderate duration (31-45 min) better than <30 min
  - Effects requires adherence (at least 6 months)

What We Say vs What We Do: Self-Report vs Actigraphy in US

How Many U.S. Adults Meet Federal Guidelines for Suggested Physical Activity?


Healthcare Counseling Needed!

DATA SOURCE: 2003–2005 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey data files. Available at http://www.cdc.gov/nchs

Keys to Optimal Cognitive Aging:
You Are What You Eat!

CLUES
Down
1. You are what you eat.
2. You are what you eat.
3.

Nutrition:
Brain Healthy Diet

- Brain health is affected by diet
- Typical western diet is:
  - High in saturated fats, low in “good fats”
  - Low in vegetables, fiber, antioxidants
  - Increasing in TEI, carbohydrates
- This eating pattern increases:
  - Risk for chronic medical diseases
  - Insulin resistance
  - Systemic inflammation
  - Metabolic syndrome now 28% in US adults


Brain Tissue Volume and Diet Quality

- 4,213 participants in Rotterdam Study subjected to dietary assessment and MRI scanning.
- Better diet quality - more vegetables, fruit, whole grains, nuts, dairy, fish; less sugary beverages
- This was associated with larger:
  - Brain volume
  - Gray matter volume
  - White matter volume
  - Hippocampal volume


Mediterranean Diet

- Olive oil is main dietary fat
- Focus on vegetables, fruits, wine, legumes, fish/shellfish, nuts, poultry, sauces made with tomatoes/onions/leeks/garlic/olive oil
- De-emphasize red meat, butter, margarine, cream, sweet beverages, pastries

MIND Diet
• Hybrid of Mediterranean and DASH
  – Whole grains, green leafy and other vegetables, berries, fish, poultry, beans, nuts, olive oil,
  – Low in red meats, butter, margarine, cheese, sweets
• Associated with:
  – Slower cognitive decline
  – Diminished association with Alzheimer’s Disease
• Prospective study of 923 subjects, age 58-95
• Higher adherence to MIND diet decreased risk for onset of AD
Morris et al. Alzheimer’s & Dementia 2015:1-8

Dietary Recommendations
• Control **caloric intake**
• Increase intake of **antioxidants** (such as flavonoids and polyphenols) with proven cardiovascular benefits
• Emulate the **Mediterranean Diet**, associated with reduced risk of cognitive decline1,2,3
• Associations with:
  – Decreased white matter hyperintensities4
  – Greater brain volume5
  – Increased leukocyte telomere length6


Brain Healthy Supplements?
• We need sufficient:
  – Folate, B₁₂
  – Vitamin E
  – Vitamin D
• We don’t want excessive:
  – Vitamin E
  – Vitamin D
  – Coconut oil
  – Ginseng

The Jury’s Still Out On:
• Berries
• Curcumin
• Cocoa
• Green tea
• Omega 3 fatty acids
• Ginkgo
• Bacopa
• Walnuts
• Phosphatidyl serine

See for example Varteresian and Lavretsky Curr Psychiatry Rep (2014) 16:456
Alcohol?

• Multiple studies find dementia risk reduction (40 – 80%) with mild-moderate alcohol use
  – Most applicable to non-ApoE4 carriers
  – In ApoE4 carriers even moderate alcohol use increases dementia risk.
• Benefits of wine have not been shown with beer or spirits.


ApoE4 Genotype Determines Relationship Between Alcohol Consumption in Midlife and Dementia Risk


Keys to Optimal Cognitive Aging: Cognitive Stimulation

• Seaside Magenta Men
• A Tipsy Civil Yacht
• Ruin It Not
• Incite A Vomiting Lotus
• Elegiac Gents Moan
• I alter axon
• Feel success plus

Behavioral Strategies Improve Cognitive Functioning

• New learning requires time and space
• Use aids
• Try mnemonic strategies
  • Chunking/Associations
  • Rehearsal
  • Method of loci
  • Peg words

Use It or Lose It?

• Greater cognitive activity is linked with maintenance/improvement of cognitive function.¹
• In transgenic mice, cognitive stimulation reduces amyloid pathology.²
• Various approaches:
  – Strategy training³
  – Cognitive training/practice
  – Computerized cognitive training (see next slide)
• More high quality intervention studies needed¹

Do Cognitive Exercises Improve Memory?

• ACTIVE Study: 2832 adults (age 65 – 94) randomized to:
  – Memory training
  – Problem solving training
  – Training processing speed
  – No training (control group)
• Relative to control group, improvement seen in speed and problem-solving groups.
• Memory gains not maintained at 2 years
• Speed/Problem Solving gains were maintained at 2 years

ACTIVE At Follow Up

Advanced Cognitive Training for Independent and Vital Elderly

- 2832 “normal” older adults, mean age 73, participated
- 10 sessions (each 60–75 minutes) for 5-6 wk
  - Control vs Memory vs Reasoning vs Speed
- After 10 years:
  - Gains in trained Reasoning and Speed (best result) but not Memory were maintained
  - Self-reported (though not functionally tested) Instrumental Activities of Daily Living were at or above baseline

Rebok et al. JAGS 2014

Speed of Processing Training Gains

Computer-Assisted Cognitive Training

- Benefits of computerized cognitive training remain under discussion
- Key issues:
  - Maintenance of gains
  - Effect size
  - Generalization non-trained tasks


What Can A Computer Add?

- Variety
- Interactivity
- Individualization
- Standardization

Lumosity
- Brain HQ
- CogMed
- AARP

IADLS, Computerized SOPT

- IHAM (Iowa Health and Active Minds) Study
- n=226 adults aged 65 and older
- SOP Software similar to ACTIVE
  - Training = 10 hr, delivered in 2 hr blocks
  - Follow up at 1 year
  - Outcomes = IADLS, depressive symptoms
- Control = crossword puzzles
- Results: Depressive symptoms diminished, and IADLS declined less at 1 year followup

Wolinsky et al. Journal of Aging and Health 2015, Vol. 27(2) 334–354

Lumosity
- Widely-advertised suite of cognitive games targeting multiple cognitive functions.
- Confronted by FTC regarding:
  - Testimonials that were not spontaneous
  - Unsubstantiated claims, direct or indirect, that Lumosity training improves performance on:
    - everyday tasks
    - School
    - Work
    - Athletic performance

accessed 01/09/16
BrainHQ

- A suite of cognitive games targeting multiple cognitive functions — cites more extensive evidence base for its claims.
- Includes "speed of processing" gain associated with benefits in ACTIVE study
- IMPACT study found RBANS score improvement\(^1\) but this primary outcome lost significance at 3 month followup\(^2\).


Expert Consensus 2014

- A consensus on the brain training industry from the scientific community
  - Cautions acceptance of unsubstantiated claims
  - Acknowledges plasticity and existence of some evidence supporting cognitive training
  - Cites need for further study
  - Encourages prioritization of meaningful cognitive engagement and physical activity

http://longevity3.stanford.edu/blog/2014/10/15/the-consensus-on-the-brain-training-industry-from-the-scientific-community/, accessed 01/09/16

Sharing Games Adds The Social Dimension

- Scrabble
- Jigsaw puzzles
  - Various levels of difficulty
- Multi-player computer games
  - SCRAMBLE
  - WORDS WITH FRIENDS

The Combined Approach

- Cognitive training plus physical training in combined format exceeds benefits of either intervention alone\(^1,2\)
- Diet, relaxation exercises, cardiovascular conditioning, and cognitive training have synergistic effect — shown to increase efficiency of working memory\(^3\)


Keys to Optimal Cognitive Aging: Social Engagement!

- Eeeiaadmmngntss
- Ciittvay
- Ttrouinn
- Aeiiioouctttsgnnlvm
- Esgghhoppssu
- Aaelontxr
- Cceeefllpssuu

Social Engagement

- Isolation is a risk factor for health decline:
  - Increases risk for breast cancer in women
  - Impairs immune function
  - Boosts inflammation
  - Increases risk for arthritis, type II diabetes, and heart disease
  - Reduces survival after cardiac surgery.
  - Isolated elderly adults are twice as likely to die prematurely. The mortality risk of isolation is comparable to that of smoking.

How Does Engagement Help?

- Promotes healthier self-care.
- Is associated with lower levels of stress.
  - Lower levels of anxiety, negative mood, perceived stress
  - Higher levels of optimism, happiness, satisfaction
  - Lower activation of sympathetic nervous system
  - Lower stress hormone levels
  - Better wound healing
  - More restorative sleep
- Social engagement is linked with “active coping”, while “passive coping” is linked with stimulation of alpha-adrenergic mechanisms and increased peripheral vascular resistance, setting the stage for HT and cardiac disease.


Do Social Media’s Virtual Communities Reduce Loneliness?

- Facebook
- Linked In
- Vimeo
- Twitter
- Tumblr
- YouTube

Social Media Effects Depend On How They are Used

- Passive use
- Investment of time
- Envy of others
- Feelings of inferiority
- Active use
  - Posting
  - Liking
  - Messaging
- Sharing is rewarding

Keys to Optimal Cognitive Aging: Relaxation

- Disease Management
- Activity
- Nutrition
- Cognitive Stimulation
- Engagement
- Relaxation
- Successful Sleep

Relaxation / Meditation / Yoga

- Benson RR improved attention but not other measures, small trial in older adults.¹
- Several forms of meditation improved attention and executive function.²
- Yoga, a form of meditation, is well-suited. Hatha Yoga classes (3x/wk x 8 wk, n=118) were associated with improvement in working memory, set-shifting, mental flexibility.³

Keys to Optimal Cognitive Aging:

- Disease Management
- Physical Activity
- Nutrition
- Cognitive Stimulation
- Engagement
- Relaxation

Older Adults typically

• Take longer to fall asleep
• Awake more frequently during the night (sleep fragmentation)
• Spend more time in bed
• Feel less rested
• Feel drowsier in the day time
• Nap more during the day time Increased daytime drowsiness
• More daytime napping

Consequences of Poor Sleep in older adults

• Difficulty sustaining attention
• Slowed response time
• Decreased ability to accomplish daily tasks
• Impaired memory and concentration
• Increased use of health care resources
• Higher incidence of depression and anxiety symptoms

Consequences of Poor Sleep (cont.)

• Increased risk of falls
• Increased risk for institutionalization
• Diminished enjoyment of social relationships
• Increased cognitive decline
• Increased pain

Bottom Line: Decreased quality of life and shorter survival

Chronic Sleep Deprivation and AD Risk?

• One night of unrestricted sleep lowered morning Aβ42 level in healthy men by 6%.1
• In aMCI, sleep deficits (e.g. disrupted slow wave sleep, shortened REM sleep) are associated with increased plasma amyloid-β levels and cortical thinning.2

Address These Factors To Improve Sleep

• Assure adequate exposure to natural light
• Make sure that the sleep environment is pleasant/relaxing/dark.
• Associate your bed with sleep, not with tension.
• Establish a regular relaxing bedtime routine.
• Avoid these:
  – Daytime napping
  – Stimulants (caffeine, nicotine, alcohol, TV?) near bedtime
  – Aerobic exercise near bedtime, but a relaxing practice such as yoga can facilitate sleep.
  – Excessive eating just before sleep.

What About Sleeping Pills?

- Less effective than cognitive/behavioral strategies!
- Potential hazards for cognition, balance, and daytime alertness
- Dependency risk
- In some cases, herbals may suffice.

Put Them All Together, They Spell DANCERS...or FINGER

- The FINGER study combined disease management (vascular), activity, nutrition, cognitive stimulation, social engagement.
- 2 yr RTC, n>1000, age 60-77 with HC/MND
- Control = health advice
- Memory, executive function, processing speed, and composite evaluated at baseline and several subsequent visits.

FINGER Points The Way!

Related Ongoing Studies: Mixed Outcomes

- ASPIS
  - Austrian RTC of 202 post-CVA patients randomized to 24 month intervention of physical activity, weight loss, dietary goals. No benefit shown on ADAS-cog or prevention of cognitive decline
- Prevention of Dementia by Intensive Vascular Care (Pre-DIVA)
  - Netherlands RCT of 6 yr, n=3700 older adults, 70-78, intervention=nurse-led groups focus on HT, cholesterol, DM, overweight, smoking, exercise. Did not reduce all-cause dementia in whole group, but reduced risk in hypertensive subgroup.

A Model Programs: BIDMC Brain Fit Club

- Personalized initial assessment / coaching
- Transcranial Magnetic Stimulation (TMS)
- Gait and balance assessment
- Targeted cognitive training / Computer
- Nutrition Assessment
- Tai-chi
- Sleep and nutrition education
- Mindfulness meditation

Smart Drugs: Pharmacotherapy For Cognitive-Enhancement?

- Caffeine
- Stimulants
- Energy drinks
- New pharmaceuticals

Not Yet, But Stay Tuned!
On the Horizon

- CAM supplements (antioxidants, anti-inflammatory)
- Cholinergic agonists
- Omega-3 fatty acid (DHA)
- Calcium channel blocker
- Testosterone
- VIP
- Glutamate receptor antagonist
- PDE inhibitor
- GABA B receptor antagonist
- 5HT6 antagonist
- Anti-amyloid agents (SALAs, immunotherapies)


The Message: DANCERS have The Answers!
A brain-healthy lifestyle can reduce the risk of milder and more serious cognitive decline.

- Disease management
- Physical activity
- Nutrition
- Cognitive stimulation
- Engagement (social/purpose)
- Relaxation
- Successful Sleep

QUESTIONS/COMMENTS