Strong bodies-Strong Minds: The Role of Physical Activity and Exercise in the Cognitive Function of Older Adults

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Purpose & Description of Course

A. Purpose: The purpose of this presentation is to describe current research related to physical activity, fitness, and exercise in older adults with and without cognitive impairment. The course will also review parameters of physical activity programs, which aim to improve cognitive function in older adults.

B. Description: This course will focus on a summary of exercise and physical activity research related to cognitive function and brain health in aging adults with and without cognitive impairment. Measures of cognitive function and how exercise affects different types of cognitive function will be discussed. Epidemiological studies as well as cross-sectional studies and randomized clinical trials will be reviewed. Research on non-human animals and its implications for the role of exercise and physical activity in humans will also be discussed. Recommendations for exercise and physical activity programs, which are thought to be beneficial for cognitive function and brain health will be covered. Finally, directions for future research by physical therapist researchers will be explored.

Course Objectives

A. To describe typical cognitive decline in the older adult
B. To describe the possible mechanisms by which exercise, physical activity, and fitness can impact cognitive function and brain health
C. To discuss research related to exercise and physical activity in the management and prevention of cognitive decline in the cognitively intact adult and in those with mild cognitive impairment and dementia
D. To provide evidence-based recommendations for exercise and physical activity programs for physical therapists working on health promotion, prevention, and/or interventions to enhance cognitive function and brain health in older adults.

I. Introduction

Our population is growing older!

The U.S. population of those aged 65 years of older is expected to double from 35 million to 70 million by 2030.

The prevalence of dementia and other cognitive impairment is also expected to increase incrementally.

Assumptions

Alterations in brain structure and function occur in the aging brain
Changes in cognition occur in normal human aging
Not all changes in cognition are precursors of dementia
Mapping between brain and behavior is extremely difficult

Brain tissue loss with age

Human brain begins to lose tissue in the third decade of life
- 15% of the cerebral cortex
- 25% of the cerebral white matter
- 35% in the hippocampus

Disproportionate losses in the frontal, parietal, and temporal cortices
Loss is closely matched by declines in cognitive performance

Changes in attention

Significant impairments on attentional tasks that require dividing or switching of attention among multiple tasks (difficulty multi-tasking), difficulty with ADLs, especially driving
Slower in responding to targets, but not differentially affected by distractions
Vigilance not impaired

Changes in working memory

Reduction of attentional resources
Reduced speed of information processing
Lack of inhibitory control
Difficulty in tasks that involve active manipulation, reorganization or integration of the contents of memory
- Decision making
- Problem solving
- Planning of goal-directed behaviors

Changes in long-term memory

Many types of memory

Aging mostly effects episodic memory – for specific events or experiences that occurred in the past

Other cognitive changes

Speech and language do not decline in normal aging

Comprehension may decline as it related to working memory (especially for complex text)

Executive control (planning, organization, coordination) reliant on the frontal cortex, whose volume and function appears to decline with normal aging

Cognitive function

Normally aging older adults appear to activate different brain structures than young people when performing cognitive tasks.

There is huge variability related to cognitive function and decline.

Scope of the problem

Aging, Demographics and Memory study sample (n=856) people 71 years and older, part of the Health and Retirement Study assessed using an in-home assessment. Identified as normal cognition, cognitive impairment, not dementia, or dementia (with subtype.)

Prevalence of dementia – 13.9%, 3.4 million individuals AD – 9.7% (2.4 million individuals)

Dementia increased with age from 5% of those 71-79 to 37.4% of those 90 and older.

Other predictors of dementia included:

- More years of education decreased risk
- African Americans have increased risk
- Presence of one or two APOE e4 allele increased risk

Prevalence of cognitive impairment not dementia (CIND)

- 22.2% of people age 71 years or older had CIND
- 5.4 million people
- This includes prodromal AD and CVD
- 11.7% progress to dementia annually

Categories of cognitive impairment

Age associated memory impairment – normal age related changes in memory

Aging - associated cognitive decline – gradual cognitive decline for at least 6 months with difficulties in one of memory in absence of dementia or other condition affecting cognition.

CIND – presence of cognitive impairment in the absence of dementia (regardless of cause)

Age-consistent memory impairment

Late life forgetfulness

Questionable dementia (CDR)

Mild cognitive impairment

A stage of cognitive impairment beyond what is considered normal for age, but not of sufficient magnitude as to warrant the diagnosis of dementia or AD

Nomenclature is used by NIA sponsored Alzheimer's disease research center programs and Alzheimer's Disease Neuroimaging Initiative

Amnestic MCI

Progression to AD at rate of 10-12% per year (compared to 1-2% of general population)
Some people with MCI improve to normal (<5%)
Some improve then decline
Risk increased with:
- APOe4 carrier
- More severe impairment
- Multiple domain
- Atrophy of hippocampus, brain volume

Dementia of Alzheimer's type

Development of multiple cognitive deficits manifested by both memory impairment and at least one of:
- Aphasia
- Apraxia
- Agnosia
- Disturbance in executive functioning

Causes significant impairment in social or occupational functioning
Characterized by gradual onset and continuing decline
Not due to other CNS conditions

II. Measures of Cognitive Function in Older Adults

Brain Imaging

MRI Volumetric Measures

Whole brain

Region of Interest

Measures of Brain Pathology

Dimensions of Cognitive Function

- Attention
- Memory & learning
- Executive function
- Language
- Visual Spatial

Attention

Functions:
- Attention Span
- Auditory
  - Visual
  - Sustained attention
- Processing speed

Common Neuropsych Test:
- Trail-Making A

Memory & Learning

Functions:
- Immediate & Delayed Recall
- Verbal
- Nonverbal

Stages of Learning:
- Encoding
- Retention
- Retrieval

Neuropsychological Tests:
- Weschler Memory Scale-III
- Logical Memory I
- Logical Memory II

Considerations:
- Task Complexity
- Task Length
- Linguistic demands

Executive Function

Functions:
- Selective Attention
- Capacity to resist interference
- Initiation/inhibition
- Cognitive Flexibility
- Decision-Making
- Planning
- Abstract thinking

Common NeuropsychTests:
- Trail-Making B Test
- Stroop Color-Word Interference
- Wisconsin Card Sorting Test

Language

Functions:
- Fluency
- Confrontation naming
- Word retrieval speed
- Comprehension
- Written language

Common Neuropsych Tests:
- Boston Naming Test
- Controlled Oral Word Association
- Boston Diagnostic Aphasia Examination

Visual Spatial

Functions:

Visual perception
Scanning
Visual integration

Common Neuropsych Tests:

Clock and cube drawing
Benton facial recognition
Benton judgment of line orientation

Rating Severity of Cognitive Impairment

Common Multi-Domain Tests:

Clinical Dementia Rating (CDR) *(Hughes et al., 1982)*
Global Deterioration Scale (GDS) *(Reisberg et al., 1982)*
Mini-Mental Status Exam *(Folstein et al.,1975)*
Montreal Cognitive Assessment (MoCA) *(Nasreddine et al., 2005)*
ADAS-COG *(Rosen,1984)*

III. Mechanisms by which physical activity & fitness effect cognitive health

Relationship between cardiovascular risk and cognitive impairment

Hypertension – risk factor for stroke

Prior to clinical event has a more subtle impact on cognitive function
Hypertension related to poorer performance on tests of attention, learning and memory, executive functions, visuospatial skills, psychomotor abilities, and perceptual skills

Hypertension

Known risk factor for stroke, but prior to clinical event has a more subtle impact on cognitive function related to poorer performance on tests of attention, learning and memory, executive functions, visuospatial skills, psychomotor abilities, and perceptual skills.

Related to reduced cerebral blood flow and metabolism, particularly in the frontal and temporal lobes and subcortical regions
Reduced blood flow during memory tasks
Damage to smaller blood vessels leads to white matter disease
People with hypertension have more brain atrophy
People who are medicated have less white matter disease than those who are not
Correlated to high insulin and cholesterol levels, enhanced cortisol reponses

Higher midlife blood pressure seems to be more strongly related to cognitive decline than concurrent blood pressure
Systolic hypertension seems to be more risky than diastolic hypertension
Antihypertensive therapy seems to have a strong protective effect, in fact people on hypertensive therapies for 12 years had a risk similar to normotensives

Dyslipidemia

Higher HDL is associated with decreased risk and lower LDL is associated with increased risk.

Supported by several large epidemiological studies

Diabetes

Persons with diabetes decline in cognitive function 1.2-1.5 times faster than controls.

OR for dementia is 1.6

Hyperinsulinemia increases risk even in those who do not have overt diabetes

Inflammation

Among high-functioning elders without cognitive impairment, those with metabolic syndrome and elevated inflammatory markers have an increased risk of developing cognitive impairment over four years. (RR 1.66)

Serum markers (IL6 and CRP) are also prospectively related to decline in cognitive function

Predictors of maintaining cognitive function (vs minor decline) over 8 years
In 2509 high functioning elders, measured by MMSE

Age
white race
High school education or higher
Ninth grade literacy level or higher
Weekly moderate/vigorous exercise*
Not smoking*

Exercise programs and cognitive function

Older sedentary adults without cognitive impairment were either assigned to a walking group (aerobic exercise) or a stretching group.

Subjects who walked improved their fitness and improved their executive function, while subjects who only stretched had no improvements in ability to organize thoughts and activities

- prioritize tasks
- manage time efficiently
- make decisions

Mouse research

Access to exercise equipment (running wheels) help neurons to grow and strengthens the connections in the systems involved in learning and memory

Exercise in mice

- Increases hormones in the brain associated with brain health
- Increased blood supply in the brain, nerve growth and nerve function
- Changes are especially apparent in the hippocampus, area associated with memory and learning
- Gene expression and neurogenesis
- Learning and memory
- Theoretical frameworks

Speed hypothesis – Fitness improves simple reaction times, as it taps low-level CNS function uncontaminated by subject strategies or high level cognition

Visuospatial hypothesis - Because visuospatial processes are more susceptible to decline with aging, these cognitive tasks will be more modifiable by fitness training. (ability to transform or remember visual and spatial information

Controlled-processing hypothesis - Tasks that require more effortful processing will be more likely to be effected by fitness

Executive control hypothesis - Tasks that require executive control (that do not become automatic over time) are likely to be improved by fitness training (also decline more with normal aging.) I.e. coordination, inhibition, scheduling, planning, and working memory

Brain health

Brain function – fMRI shows evidence of increased activity in the frontal and parietal regions (involved in attentional control and performance) and decreased activity in the areas thought to be sensitive to behavioral conflict in aerobically trained individuals vs controls

Brain structure - observational
Older adults with higher levels of aerobic fitness have less grey matter loss in the frontal, temporal, and parietal lobes, and less tissue loss in the anterior and posterior white matter tracts.

Physical activity
Brain tissue loss in older adults who engaged in less than the average physical activity

No brain tissue loss in older adults who engaged in more than the average

Brain structure - RCT
Six month training regimen led to a significant increase in gray matter volume in regions of the frontal and temporal lobe (increased in cell body size?, increased dendritic connections?, increased vascularization? or increased glial size or number?)

IV. The role of physical activity on cognitive function in older adults

Cognitive Function & Cardiorespiratory Fitness

Whole Brain Volume & Cardiorespiratory Fitness (VO_2^{peak})
(Burns, et al., *Neurology*, 2008,v. 71)

Hippocampal Volume & Cardiorespiratory Fitness (VO_2^{peak})
(Erickson et al., *Hippocampus*, 2009, v.19)

Cognitive Function & Cardiorespiratory Fitness (VO_2^{peak})
In early AD:
Higher VO_2^{peak} was associated with delayed memory (LM II), Attention (Trails A) &

Executive Function (Trails B , Stroop-Interference), but not after controlling for age. (*Burns, et al., 2008)*

In older adults without cognitive impairment:
Higher VO_2^{peak} was associated with higher accuracy on a *spatial memory task*, after adjusting for age, sex and education.
(Erickson, et al., 2009)

Summary:
Protective effect of cardiorespiratory fitness:
Whole brain volume
Prefrontal cortex
Hippocampus/medial temporal lobe structures

Cognitive Function & Physical Performance
Gait speed and dimensions of cognitive function
Gait speed and incident dementia

Key Findings;
Slower gait speed associated with lower cognitive function
Slower gait speed and increased incident dementia
Physical frailty and increased incident MCI

Cognitive Function & Physical Activity: *Cross-sectional studies*
Higher physical activity associated with better cognitive performance on:
Reasoning
Working memory
Reaction time
Accuracy
Executive function
Global cognitive function
(Clarkson-Smith & Hartley,1989; Hillman et al., 2006; Bixby et al., 2007; Angevaren et al., 2007)

Physical Activity Dose
In 1,927 adults (ages 45-70), the weighted average intensity of weekly PA significantly positively associated with:
Memory
Processing speed
Mental flexibility
(Angevaren et al., 2007)

Cognitive Function & Physical Activity: *Longitudinal studies*
People who are physically active in mid- and late life have lower risk for:
Global cognitive decline (MMSE) *(Yaffe 2001; van Gelder 2004)*
Incident MCI *(Geda 2010; Middleton 2008)*
Incident dementia *(Larson 2006; Rovio 2005)*

Women vs. Men
Association between cognitive function & physical activity differs in women vs. men

Protective effect is greater in women
(*Laurin et al., 2001; Middleton et al., 2008)*

Across the life course

Older women physically active as teenagers had the highest cognitive performance & lowest rates of CI.
Older women physically active at age 30, 50, or in late life (inactive as teenagers): 50% lower rate of late-life CI compared to women who remained inactive.
Older women physically active at any age were less likely to have CI.
(Middleton et al., 2010)

Exercise Dose

Differences based on physical activity dose
PA dose matters:
Frequency, Duration, Intensity *(van Gelder 2004)*

Women (≥ 65) in the lower quartile of blocks walked/wk at baseline had the highest odds of cognitive decline over 6-8 yrs, after adjusting for age and age-related factors.
(Yaffe et al., 2001)

Summary: Cognitive Function & Physical Activity

Physical activity plays a protective role in the cognitive function of older adults.
- Brain structure preservation
- Preservation of global & dimensions of cognitive function.
- Lower incident MCI & dementia

Early-life physical activity associated with lower risk for CI in old age.

Protective effect of physical activity moderated by*:*
- Dose-response relationship
  - Women > Men
  - Pathology – type of CI

Exercise Intervention Studies: Older adults without known cognitive impairment

Brain Volume & Aerobic Exercise Training

Sedentary community-dwelling ages 60-79, n=59
Intervention: 6-mos**.** aerobic Ex vs. stretching & toning

Aerobic Ex group: Increased gray and white matter
Volume increased in pre-frontal and temporal cortical regions particularly in regions implicated for higher order attentional control and memory processes.
(*Colcombe et al., Gerontol: Med Sci, 2006, v. 61A)*

Exercise RCT: Older adults without known cognitive impairment

Meta-Analysis*:* 18 RTC of aerobic fitness training studies, sedentary, ages 55-80
Effect of Exercise on Cognitive Function:
- Combined aerobic & strengthening greatest effect
- Longer duration (> 30 min) had greater effect
- Greatest effect on executive function

PA is beneficial to all cognitive functions
Ages 60-70 benefitted the most
Studies with > 50% female reported greater men than studies with > 50% male
(Colombe & Kramer, 2003)

16-wk Aerobic Ex (n=85)
Cognitive outcomes: No diff aerobic vs. non-aerobic Ex groups
(*Madden et al., 1989)*

9 to 12-mos Aerobic Ex (n=121)
Cognitive Outcomes: No change in Ex grp
, Decreased cognitive function in control grp.
(*Hill et al.,1993)*

10-mos Aerobic Ex (n=57)
Cognitive Outcomes: Increase on Stroop only
(*Smiley-Oyen et al., 2008)*

Summary:
Exercise slows the decline of cognitive function
Exercise played a protective role in cognitive function
Improved in selected dimensions of cognition – mostly executive function
Strengthening + aerobic EX was most beneficial combo
Protective effect may vary by age & sex
Exercise dose matters – duration, frequency, and intensity

Exercise Interventions Studies (RCTs) in Older Adults With Cognitive Impairment and Dementia

Exercise RCTs in persons with MCI

Low Intensity Exercise Interventions:
24-wk home-based walking *vs*. usual care
n=170, community-dwelling, age >= 50 , MCI
Cognitive Outcomes: ADAS-Cog (1.3;SD 2.38-0.03) improved score for Ex grp. (signif. 6 & 18 mos.)
(Lautenschlager et al., 2008)

12-mos mod walking *vs*. non-aerobic ex + vit B_{12} B_6 *vs.*
placebo n=152, aMCI
Cognitive Outcomes: No diff b/w intervention groups.
(*van Uffelen et al., 2008)*

Moderate - High Intensity Exercise Intervention:
6-mos. high intensity aerobic Ex *vs*. stretching control
(supervised by fitness trainer) n=33, aMCI, ages 55-85
Cognitive Outcomes: Improvement on Trails B in HI Ex grp, but not control.
(*Baker et al., 2010)*

Exercise Intervention studies in persons with <u>dementia</u>

Physical Function: *Exercise RCTs in Older Adults with Dementia*
Cognitive Function – small increase in MMSE
Physical Performance - Improved gait speed, balance, & endurance
ADLs – improved at all stages of dementia
Behavioral symptoms improved
Multicomponent program (walking, strengthening & balance) most effective in improving function.
(Blankevoort et al., 2010; Kwak et al.; 2010; Heyn et al., 2004)

Caregiver and Emotional Health: *RCTs in Older adults with Dementia*

Adherence with caregiver assistance
Improvements in mood and behavior
Persons with dementia
Caregivers of persons with dementia

Summary

Dose-response relationship
Intensity matters
Session duration matters
Total exercise time matters
Age matters
Protective effect differs in men vs. women
Protective effect differs based on pathological mechanism (e.g. vascular, AD pathology)
Protective effect impacted by age, but slowing of cognitive decline and improvement reported in the oldest adults.

V. Exercise parameters for the prevention of cognitive decline and the maintenance of cognitive and physical function

The good news

- Exercise recommendations for dementia and cognitive impairment are the same as for other chronic diseases such as diabetes, heart disease, and osteoarthritis.

Maintain a physically active lifestyle

- Exercise through the life span. Younger is better, but it's never too late!
- Focus should be on both regular physical activity and decreasing time spent in sedentary activities.
- Transgenerational programs may be an effective way to encourage physical activity.

Aerobic (endurance) activity

- Minimum of 30 minutes of moderate physical activity at least five days per week, OR
- Minimum of 20 minutes of vigorous physical activity at least three days per week.

- Relative to one's level of fitness

- Can be accrued in 10 minute bouts

- Moderate physical activity
  5-6 on a 10 point scale
  Moderate increase in HR and breathing

- Vigorous physical activity
  7-8 on a 10 point scale
  Marked increase in HR and breathing

- 50 sedentary adults randomized
  30 minutes continuous PA, 4-5 days per week
  5 bouts of 6 minutes PA, 4-5 days per week.
  Similar improvements in max VO2 measured aerobic fitness
  Take home message, be creative with how to encourage and prescribe endurance activity.

Training characteristics

- Combined strength + aerobic showed greater improvement than aerobic alone.

- Long-term training showed the greatest improvement.

- Short bouts of ex (< 30 min) had little impact on cognitive function.
  (normal aging, not cognitively impaired)

Compliance basics

- Keep it simple
- Limit number of exercises – choose carefully
- Visual cues and reminders
- Practice the motor tasks
- Incorporate family (spouse, children, grandchildren)
- Partners
- Community based programs

Seattle Protocol (*Teri et al. 2008)*

- Designed in a series of easy-to-remember increments
- Repeated several times during training sessions in order to help participants' initial learning and facilitate subsequent recall.
- Participants have a cognitively intact "study partner" who attends classes and assists them with their exercises throughout the week
- Written instructions for all exercises are laminated and have small magnets attached to the back of the page, so participants can put them on their refrigerator doors. This provides a visual cue for participants to remember to do the exercises each day, as well as providing a handy reminder of how to do them. These memory aides and cues are incorporated throughout training.
- Incorporate lessons learned from earlier implementations to insure that exercise is

targeted in such a way as to maximize its enjoyability (and thereby insure sustainability) as well as problem-solve obstacles to initiation and maintenance.

VI. Directions for physical therapy practice and research

Physical Therapy Practice

A. Prevention

B. Early Intervention (MCI)

C. Interventions at all stages of dementia

Opportunities for physical therapists

A. Involvement in community-based programs:
- Exercise programs
- Public education
- Residential programs
- Senior Day Activity Centers

B. Develop exercise guidelines for older adults:
- At risk for cognitive impairment
- Early stages of cognitive decline
- Dementia

C. Become team members
- Community-based advisory and planning committees
- Multidisciplinary patient care teams
- Interdisciplinary research collaborations

D. Development of new models for prevention and intervention

Future Research Directions

A. Identify biological mechanisms in pathway: exercise <-> cognition

B. Identify functional markers
- Early indicators of functional decline
- Responsive to physical therapy intervention

C. Identify exercise parameters for guidelines
- Types of exercise
- Intensity
- Frequency

- Duration

D. Effective implementation strategies for persons with:
- Cognitive impairments
- Physical impairments
- Medical comorbidities (e.g. CVD, DM)

E. Effective adaptation programs:
- Neurodegenerative disease processes (e.g. MS, Parkinson's)
- CVA

F. Timing:
- Effect of exercise across the life span
- Effect of exercise at various stages of cognitive decline

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