



NEUROPROTECTIVE EFFECTS OF EXERCISE

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СПЕЦИАЛИСТ ПО ФИЗИЧЕСКОЙ ТЕРАПИИ
ОТДЕЛЕНИЕ РЕАБИЛИТАЦИОННОЙ МЕДИЦИНЫ
УНИВЕРСИТЕТ ВАШИНГТОНА
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США



THE AGING BRAIN

- Human brain begins to atrophy in 3rd decade of life
 - Alterations in structure and function
 - Frontal
 - Parietal
 - Temporal regions

THE AGING BRAIN

- Alterations in activity of neurons
 - Hippocampus
 - Frontal cortex
- Alterations in synaptic morphology
- Chronic inflammatory changes of immune system
 - Microglia/monocytes
 - Astrocytes
- Neurovascular Unit
 - Provides structural and functional basis for blood brain barrier
 - Changes associated with cerebrovascular alterations

THE AGING BRAIN

- Changes in cerebrovascular function
 - Cerebral microvascular pathology
 - Reductions in cerebral blood flow
 - Reductions in glucose metabolism
 - Reductions in oxygen metabolism
 - Vascular leakage per high-resolution MRI and electron microscopy
 - Begins in hippocampus

NEURODEGENERATIVE DISEASES

- Disease processes affecting cognition
 - Mild cognitive impairment (MCI)
 - Dementia
 - Alzheimer's disease (AD)
- Alterations in brain structure and function exceed those expected for age and educational level
 - Frontal
 - Parietal
 - Temporal
 - Most profound atrophy of hippocampus

Kirk-Sanchez & McGough, 2014
Pedersen et al, 2014

EXERCISE EFFECTS ON BRAIN

- Exercise is essential to maintenance of
 - Physical function and physiologic health
 - Brain health and cognitive performance
- Human brain responds to moderate aerobic exercise
 - Regions vulnerable to age- and disease-related atrophy
 - Alterations in structure and function
- Epidemiological studies report reduced risk for MCI and dementia in older adults who maintain higher levels of physical activity

EXERCISE EFFECTS ON BRAIN

- Strong association of physical exercise with age-related declines in
 - Cognitive function
 - Sensorimotor function
- Exercise is associated with
 - Improved cardiovascular function
 - Improved blood flow within the CNS
 - Angiogenesis
 - Neurogenesis
- Molecular events responsible for this protective effect are not completely understood.

EXERCISE EFFECTS ON BRAIN

Animal Studies

- Exercise strongly protects against neurovascular decline in aged mice
 - Improved behavioral outcomes
 - Improved markers of neuroplasticity
 - Reduced inflammation
 - Reduced complement induction
- Potential molecular mechanisms
 - Astrocytic ApoE decreases in aged mice
 - Associated with age-related neurovascular decline
 - Risk factor for Alzheimer's disease
 - Exercise protects against this reduction in ApoE levels

EXERCISE EFFECTS ON BRAIN

Animal studies

- Exercise preconditioning exhibits neuroprotective effects after cerebral ischemia in rats
 - 3 groups with 7 rats each
 - Control, Ischemia, Exercise + ischemia
 - Run on treadmill 10-15 minutes at 5-7m/min, 5 days per week for 4 weeks
- Induced transient global cerebral ischemia
- Exercise + ischemia group demonstrated
 - Reduced rate of apoptotic and necrotic cell death in hippocampal CA1 neurons
 - Amelioration of ischemia-induced memory loss

EXERCISE EFFECTS ON BRAIN

- Potential mechanisms by which preconditioning protects neurons
 - Alleviate over-activation of glutamate, which aggravates neuronal damage
 - Improved anti-oxidant capacity by blocking free radical formation
 - Tumor necrosis factor (TNF)- α mediates inflammation
 - Up-regulation of heat shock protein (HSP)-70 exerts effects through over-expression of anti-apoptic (pro-survival) proteins
 - Up-regulation of neurotrophic factors
 - Brain-derived neurotrophic factor (BDNF)
 - Nerve growth factor (NGF)

CARDIOVASCULAR RISK FACTORS

- Risk factors include
 - Hypertension (HTN)
 - Elevated cholesterol
 - Metabolic syndrome
 - Type 2 diabetes
 - Inflammation
 - Insulin resistance
- Cardiovascular risk factors are associated with
 - Cognitive decline
 - Brain atrophy

CARDIOVASCULAR RISK FACTORS

HYPERTENSION

- Hypertension (HTN) is associated with
 - Reduced cerebral blood flow and metabolism
 - Frontal, temporal and subcortical regions
 - White matter disease and atrophy
- HTN is associated with
 - Midlife reduction in cognitive performance
 - Later life mild cognitive impairment (MCI) and dementia

CARDIOVASCULAR RISK FACTORS

HYPERTENSION

- Pharmacologic management of HTN
 - Associated with neuroprotective effects
 - Less white matter disease
 - Elimination of increased risk for cognitive decline
- Prevention and management of HTN with exercise
 - Enhanced cerebral blood flow
 - Reduced brain tissue pathology
 - Protective effect
 - Brain health
 - Cognitive performance

CARDIOVASCULAR RISK FACTORS METABOLIC SYNDROME

- Associated with significantly increased risk for cognitive impairment among older adults
 - 23% increased risk per unit increase in number of abnormal factors
 - Body mass index (BMI)
 - Elevated triglycerides
 - Low levels of high-density lipoprotein cholesterol (HDL)
 - Hypertension (HTN)
 - Hyperglycemia

CARDIOVASCULAR RISK FACTORS METABOLIC SYNDROME

- High levels of inflammatory markers associated with cognitive decline
 - Interleukin-6
 - C-reactive protein
- Lower levels of inflammatory markers associated with exercise in older adults
 - Interleukin-6
 - C-reactive protein

CARDIOVASCULAR RISK FACTORS

INSULIN RESISTANCE

- Insulin resistance in older adults is associated with reduced
 - Brain health
 - Cognitive performance
- Elevated plasma insulin levels associated with
 - Increased inflammatory agents

CARDIOVASCULAR RISK FACTORS

INSULIN RESISTANCE

- **Aerobic exercise** associated with improvements in
 - Cardiorespiratory fitness
 - Glucose tolerance
 - Function within several cognitive domains
- Positive effects of exercise may be related to
 - Improved cardiovascular function
 - Improved cerebral vascular function
 - Reduced inflammation
 - Enhanced insulin-dependent energy metabolism

CARDIOVASCULAR RISK FACTORS AND EXERCISE

- Well-established relationship
 - Exercise
 - Reduction of cardiovascular risk factors
- Unclear relationship
 - Exercise
 - Cognitive performance
- Not clear which cardiovascular factors serve as mediators

NEUROTROPHIC FACTORS AND EXERCISE

- Neuroprotective neurotrophins influence select regions of the brain, including the hippocampus
 - Facilitate plasticity
 - Enhance neurovasculature

NEUROTROPHIC FACTORS AND EXERCISE

- Exercise associated with increased release of neuroprotective neurotrophins
 - Brain-derived neurotrophic factor (BDNF)
 - Regulate growth, maintenance, and survival of neurons in adult brain
 - Short-term and long-term aerobic exercise
 - 3 months aerobic endurance training → 4-fold increase in BDNF
 - Insulin-like growth factor (IGF-1)
 - Promotes neuronal growth, survival and differentiation
 - 6 months moderate to high level resistance training
- Majority of data comes from studies including young adults
 - Carry-over to older populations is not known

SPECIFICITY OF TRAINING

- Animal models reveal that different types of training produce different changes in the brain
 - High-demand acrobatic training
 - Synaptogenesis – new circuits in response to novel learning experiences
 - Forced exercise
 - Increased angiogenesis in cerebellum
 - Voluntary exercise
 - Increased angiogenesis in cerebellum
 - Control group

INTENSITY & VARIETY OF TRAINING

- Doetinchem Cohort Study, n=1,927, 6- and 11-year follow-ups
 - Intensity and variation, but not duration, of physical activities positively associated with cognitive function
 - Processing speed
 - Memory
 - Mental flexibility
 - Overall

CARDIORESPIRATORY FITNESS AND BRAIN HEALTH

Cochran review of 11 randomized controlled trials (RCTs)

- Physical activity intended to improve cardiorespiratory fitness in order to improve cognitive function
 - Average 14% increase in maximal oxygen consumption (VO_2 max)
 - Large effects on
 - Motor function
 - Auditory attention
 - Moderate effects
 - Cognitive speed
 - Visual attention

CARDIORESPIRATORY FITNESS AND BRAIN HEALTH

- Cardiovascular fitness (VO_2 max) in individuals with early Alzheimer's disease compared to non-demented controls is associated with
 - MRI-measured whole brain volume (Burns et al, 2008)
 - Gray and white matter volume of medial temporal and parietal regions (Honea et al, 2009)
- Findings suggest that cardiorespiratory fitness may offer a protective effect by modifying Alzheimer's disease-related changes in brain structure

CARDIORESPIRATORY FITNESS AND BRAIN HEALTH

- Brain regions characterized by reduced gray matter and white matter volume with age
 - Closely mirror brain regions preserved with exercise (Colcombe et al, 2003)
- Higher cardiorespiratory fitness levels are associated with
 - Preservation of hippocampal volume
 - Better spatial memory task performance (Erickson et al, 2009)
- Higher estimated VO_2 max is associated with
 - Greater brain activation in regions associated with executive control
 - Less brain activation in areas believed to interfere with executive control (Colcombe et al, 2004)

CARDIORESPIRATORY FITNESS AND BRAIN HEALTH

- Optimal exercise dosage is not known
 - Positive relationship among older adults between
 - Higher dose
 - Cognitive health
- Higher exercise intensity (7.8 ± 3.9 MET versus 0.63 ± 7.4 MET hours per week) is associated with preservation of brain volume
 - Exercise volume seems to moderate brain volume, especially in the medial temporal lobe (key area for executive function and memory)
- Exercise volume found to be protective
 - Approximates recommendations for all older adults
 - 7.8 MET is roughly equivalent to moderate exercise for 30 minutes 5 days per week

CARDIORESPIRATORY FITNESS AND BRAIN HEALTH

- Research findings from cross-sectional and prospective longitudinal studies (Kirk-Sanchez & McGough, 2014)
 - higher levels of physical activity
 - Provide protective benefit against cognitive decline
- Positive effects of aerobic exercise training have been demonstrated in diverse populations
 - Frail older adults (Hayes et al, 2014)
 - Post-stroke survivors (Hayes et al, 2014)

EXERCISE AND COGNITIVE PERFORMANCE

- Large **observational studies**- examine associations between midlife and late life activity and cognitive impairment
 - Lower risk for global cognitive decline
 - Lower risk for incident dementia
- Honolulu-Asia Aging Study
 - 2,257 men followed for 3 decades
 - Men who walked <1 mile per day were at significantly greater risk (1.7-1.8) of dementia than men who walked >2 miles per day
- Nurses' Health Study
 - 18,766 women followed for 10-15 years
 - Women ages 70-81 at time of follow-up who walked 90 minutes per week demonstrated higher cognitive scores than those who walked <40 minutes per week

EXERCISE AND COGNITIVE PERFORMANCE

- **Randomized controlled trials (RCTs)** using **aerobic exercise** as an intervention demonstrate effects on cognitive performance in individuals with MCI
 - N=138, 24-week home **walking** program **versus educational** control (Lautenschlager et al, 2008)
 - Modest improvement in global cognition
 - Alzheimer's Disease Assessment Scale- Cognitive Subscale
 - N=29, 6 months **high intensity aerobic** exercise **versus stretching** control (Baker et al, 2010)
 - Improvements on tests of executive function
 - N=50, 12 month **aerobic** exercise program, 90 min per day, 2 times per week **versus education** control (Suzuki et al, 2012)
 - Better general cognitive function
 - Immediate memory
 - Language ability

EXERCISE AND COGNITIVE PERFORMANCE

- **Randomized controlled trials (RCTs)** using **aerobic exercise** as an intervention demonstrate effects on cognitive performance that can be related to
 - Changes in regional brain volume
 - White and gray matter in prefrontal and temporal cortices
 - Anterior hippocampal volume (2% ↑ vs 1.4% ↓)
 - Neurotrophin levels
 - Increased levels of brain-derived neurotrophic factor (BDNF)
 - Brain activation patterns
 - Increased activation in executive control regions
 - Decreased activation in other regions
 - Improved functional connectivity

EXERCISE AND COGNITIVE PERFORMANCE

- **Resistance training** has also demonstrated positive effects on cognitive performance
 - N=63 men, 24-week, **moderate- and high-intensity** resistance exercise group (50% and 80% one repetition maximum for upper and lower body) **versus stretching** control (Cassilhas et al, 2007)
 - Improvements in several cognitive domains
 - Increased levels of insulin growth factor (IGF-1)
 - N=155 women, 12-month 1-2 times weekly **resistance** training **versus balance and toning** control (Lui-Ambrose et al, 2010)
 - Selective attention
 - Conflict resolution

EXERCISE AND COGNITIVE PERFORMANCE

- Few studies have investigated the effect of **multicomponent exercise** interventions on cognitive function
 - N=74, 6 months, home balance and strengthening program intended to reduce falls
 - Improved executive function, especially response inhibition
 - N=389, 1 year, Tai Chi versus stretching and toning control
 - Modest differences in memory and global cognition
 - High drop out rate
 - Tai Chi
 - Multiple physical components
 - Incorporates engagement across several cognitive domains
 - Older adults who performed Tai Chi and aerobic exercise demonstrated better memory performance than controls performing one or the other, or no exercise

EXERCISE FOR PEOPLE WITH DEMENTIA

- Results of meta-analyses of exercise interventions for people with dementia
 - Do not consistently produce significant improvements in cognition
 - Do consistently produce improvements in
 - Physical performance
 - Behavior
 - Mood
- Dose may be a primary factor in effectiveness
 - Frequency
 - Intensity
 - Duration

EXERCISE SUMMARY

- Results of observational studies support a dose-dependent neuroprotective relationship between physical exercise and cognitive performance in older adults.
- Longitudinal studies provide evidence that higher levels of physical exercise are protective against cognitive decline.
- Physical function likely improves prior to cognitive performance
 - Provides a stronger foundation for progression of exercise dose
 - Intensity
 - Frequency
 - Duration
- Duration of exercise programs
 - 16-20 weeks to improve cardiorespiratory fitness in older adults
 - 6-12 months may be necessary for cognitive changes to be measurable

EXERCISE RECOMMENDATIONS

- **Aerobic exercise-** American College of Sports Medicine Guidelines (2009)
 - Frequency
 - Minimum 150 minutes moderate aerobic exercise per week (30 minutes, 5 days/week)
 - OR**
 - 60 minutes of vigorous exercise per week (20 minutes, 3 days per week)
 - Benefits can be achieved with 6-10 minute bouts of exercise, especially for individuals with limited capacity
 - Intensity
 - $\geq 60\%$ of pretraining VO₂ max
 - Duration
 - Minimum 16 weeks

EXERCISE RECOMMENDATIONS

- **Resistance exercise-** American College of Sports Medicine Guidelines (2009)
 - Frequency
 - 2 days per week for major muscle groups
 - Intensity
 - Resistance equivalent to 60%-80% of one repetition maximum
 - Older, deconditioned, frail may begin at 40%-50%
 - Strengthening- adjusted to allow completion of 8-12 repetitions/set
 - 2-3 sets per exercise
 - 2-3 minutes rest between sets
 - Recovery period 48-72 hours
 - Endurance
 - Decrease intensity to 40%-50% one repetition maximum
 - Increase repetitions to 15-20 /set

EXERCISE RECOMMENDATIONS

- **Neuromuscular fitness**- 2 days per week
 - Balance
 - Agility
 - Coordination
- **Flexibility**- 2 days per week



EXERCISE RECOMMENDATIONS

- Structured training better than advice alone
- Individually designed program to accommodate physical and cognitive impairments
 - Promotes compliance and safety

SUMMARY

- Human brain atrophies with age
 - Accelerated in presence of neurodegenerative diseases
 - Accelerated in presence of cardiovascular disease
- Exercise has been shown to
 - Reduce symptoms of cardiovascular disease
 - Protect neural structures
 - Increase brain volume
- Effectiveness of exercise appears to be dependent
 - Dose- intensity, frequency and duration
 - Type- aerobic, resistance, high demand coordination
- Exercise can be safely prescribed in diverse populations
 - Frail, post stroke



THANK YOU

Questions?

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