Exercise Interventions Targeting Neuroplasticity and Neuroprotection in Adults with Neurodegenerative Diseases

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COURSE DESCRIPTION:
Exercise interventions targeting neuroprotective mechanisms in adults with neurodegenerative diseases will be presented including mode, frequency, intensity and duration. Potential mechanisms and evidence related to exercise interventions for Alzheimer's disease (AD), Parkinson's disease (PD) and Multiple Sclerosis (MS) will be discussed. Innovative approaches that address barriers and challenges to exercise implementation will be described.

OBJECTIVES:
Upon completion of this course, participants will be able:
1. To discuss potential neuroplastic and neuroprotective mechanisms of exercise in neurodegenerative disease processes, including Alzheimer's disease, Parkinson's disease and Multiple Sclerosis.
2. To describe evidence-based exercise interventions including mode, frequency, intensity, and duration of exercise interventions for individuals with neurodegenerative disease.
3. To describe considerations for evaluating exercise capacity (e.g. aerobic capacity) in adults with neurodegenerative disease.
4. To describe characteristics of delivery systems that address cognitive, physical and environmental barriers to exercise in adults with neurodegenerative disease.
Part 1: Neuroprotective Mechanisms of Exercise in Neurodegenerative Disease

I. Alterations in structure and function occur in the aging brain
   a. May be unrelated to neurodegenerative disease
   b. Nervous system changes with neurodegenerative disease
      i. Neurodegenerative dementias (AD and MCI)
      ii. Multiple sclerosis
      iii. Parkinson’s disease (Petzinger, 2010)

II. Executive function is most affected in the aging brain – and most prone to neurological insult by neurodegenerative disease
   a. Executive function
   b. Processes that show greatest rates of decline remain highly plastic (Colcombe 2004; Honea 2010)

III. Older adult brains have some capacity for plasticity – a natural capacity that can be modified by aerobic exercise
   a. Electrical, synaptic, and morphologic properties of neurons change constantly throughout their lifespan (Erickson and Kramer 2008)
   b. Functional re-organization of sensory and motor pathways following injury is a widely documented phenomenon (Pantano, Mainiero, Caramia, 2006)

IV. Neuroprotection and neurodegeneration occur via many mechanisms
   a. Vascular and cardiovascular
      i. HTN (Waldstein, 2003)
      ii. DM (Roberts 2008) and insulin resistance (Craft 2005; 2006)
      iii. Cardiovascular risk factors and exercise
   b. Inflammatory factors (Yaffe 2003; 2004)
      i. Inflammation and hyperinsulinemia (Craft 2006)
      ii. Inflammation and MS (White and Castellano 2008)
      iii. Inflammation and exercise
   c. Neurotrophins
      i. Neurotrophins and exercise in animal studies (Ahlskog 2011; Cotman and Bechtold 2007)
      ii. Neurotrophins and MS (White and Castellano 2008; Gold 2003)
      iii. Neurotrophins and exercise (Seifert 2010)
   d. Neurotransmitters
i. Neurotransmitters and PD (Hirsch and Farley 2009; Vuckovic 2010)
ii. Neurotransmitters and exercise
e. Synaptogenesis and neurogenesis
   i. Brain volume (Bugg and Head 2009; Erickson 2009; Burns 2008)
   ii. Cortical connectivity
      1. Young vs. old brains (Colcombe 2004)
      2. Cortical connectivity and MS (Prakash 2007; 2010)
f. Sensory-Motor input
   i. Information processing: a common causal factor in motor and cognitive decline
   ii. A potential pathway for interventions that target both physical and cognitive performance.

Part 2. Evidence: Neuroprotective Effects of Exercise in Adults with Neurodegenerative Disease

I. Theoretical Model: Exercise, Physical Performance & Cognitive Health

II. Relationships between Physical and Cognitive Function

   (McGough 2011; Aggarwal 2006; Waite 2005; Marquis 2002)

III. Measures of Neuroprotective Effects
   a. Brain structures
   b. Cognitive function
   c. Physical function
   d. IADL/ADL function

IV. Effects of Exercise in Older Adults

   (Coulcombe 2006; Erickson 2010; Smiley-Oyen 2008; Hill 1993; Voss 2010)
   a. Neuroplastic effects
      i. Increased brain volume & function
      ii. Improved cognitive function
      iii. Improved motor function
      iv. Improved complex tasks & daily function
   b. Neuroprotective effects
      i. Reduced brain volume & function
      ii. Less cognitive function decline
      iii. Less motor function decline
iv. Less decline in complex tasks & daily function

V. More Physical Activity Associated with Lower Incident Neurodegenerative Disease
   a. Less global cognitive decline (MMSE) \((Yaffe 2001; \text{van Gelder} 2004)\)
   b. Less incident mild cognitive impairment \((Geda 2010; \text{Middleton} 2008)\)
   c. Less incident dementia \((Larson 2006; \text{Rovio} 2005)\)
   d. Lower risk for Parkinson’s disease \((Chen 2005; \text{Thacker} 2008; \text{Xu} 2010)\)
   e. Preliminary evidence between PA & MS risk \((Motl \& \text{Fernhall} 2011)\)

VI. More Physical Activity Associated with Better Cognitive Function
   \((Clarkson-Smith \& \text{Hartley} 1989; \text{Hillman} 2006; \text{Bixby} 2007; \text{Angevaren} 2007)\)
   a. Global cognitive function
   b. Spatial memory
   c. Reasoning
   d. Executive function & mental flexibility
      i. Working memory
      ii. Reaction time
      iii. Processing speed

VII. Cardiorespiratory Fitness & Cognitive Function
   a. Older adults without cognitive impairment: Higher \(V O_2^{\text{peak}}\) associated with higher accuracy on a spatial memory task, after adjusting for age, sex and education. \((Erickson 2009)\)
   b. Older adults with early Alzheimer’s disease: Higher \(V O_2^{\text{peak}}\) associated with better delayed memory, attention & executive function. \((Burns, 2008)\)

VIII. Evidence of Neuroplasticity with Aerobic Exercise in Older Adults
   a. Brain Structure & Function
      i. Neuroplasticity in selected brain structures
      ii. Moderate intensity aerobic exercise enhances brain volume in frontal and anterior hippocampus regions of the brain in healthy older adults. \((Colcombe 2006; \text{Erickson} 2010)\)
      iii. Increased cortical connectivity \((Voss 2010)\)
   b. Cognitive Function: Preservation or enhancement of cognition, especially executive function and spatial memory.
      i. Resistance exercise enhances cognitive function \((Casilhas 2007; \text{Liu-Ambrose} 2010)\)
ii. Aerobic exercise enhances spatial memory and executive function (Colcombe 2006; Erickson 2010)

IX. Associations between Cardiorespiratory Fitness and CNS Health in Neurodegenerative Disease
   a. Alzheimer's disease (Burns 2008)
   b. Parkinson's disease (Ahlskog 2011)
   c. Multiple Sclerosis (Prakash 2010)

X. Dementia: Effects of Exercise
   a. Outcomes:
      i. Cognitive function - small gains in global cognitive function
      ii. Mood & behavioral symptoms - improved
      iii. Physical performance improved in mild-moderate dementia
         a. Gait speed
         b. Balance
         c. Endurance
      iv. IADL/ADL - Improved ADL all stages of dementia
   b. Interventions:
      i. Exercise + behavioral management
      ii. Multicomponent exercise programs - most effective in enhancing function
      iii. Functional training + progressive resistive exercise
      iv. Activity-specific exercises

XI. Parkinson's Disease: Effects of Exercise
   a. Outcomes:
      i. Cognitive function (Rigdel 2010)
         i. Walking economy
         ii. Gait speed
         iii. Upper extremity motor function
         iv. UPDRS - motor
      iii. IADL/ADL
      iv. Mood & quality of life
b. Exercise Interventions
   i. Walking
   ii. Augmented
      1. Treadmill training - body weight-supported
      2. Tandem bicycles
      3. Electric-assist bicycles
   iii. Balance training
   iv. Multicomponent programs

c. Factors Associated with Exercise Behavior (Rimmer 2010, Ellis 2011)
   i. Personal factors: Self-Efficacy, preference, ability
   ii. Environmental factors

XII. Multiple Sclerosis: Effects of Exercise (Molt & Pilutti, 2011)
   a. Cognitive function: limited evidence
   b. Physical performance (Dalga 2008)
   c. Aerobic capacity
      i. Disability status (EDSS scores)
      ii. Sample population in most studies included subjects with EDSS scores < 7.
      iii. Relationship between degree of training adaptation and disability (EDSS) is inconclusive:
         1. Low group (EDSS < 3.5-4.5) showed a larger increase in exercise time and VO2 max (Shapiro, 1988, Ponicthera-Mulcare, 1997)
         2. High function group experienced largest improvement (Mostert, 2002)
         3. Equal improvement in VO2 max (Petajan1996)

XIII. Addressing Barriers in Effort to Sustain Effective Exercise Dosage
   a. Alzheimer’s disease
      i. Structured & supervised exercise
      ii. Activity-specific (Roach 2011)
      iii. Multicomponent exercise
   b. PD & MS:
      i. Structured & supported exercise (physical + cognitive impairment)
      ii. Augmented exercise (Rigdel 2009, Alberts 2011)
      iii. Self-efficacy (Ellis 2011)
iv. Environment & social support are important

XIV. Factors Impacting Neuroprotective Response to Exercise

a. Pathology type (e.g. vascular, AD pathology)
b. Exercise type
c. Dose-response relationship
   i. Intensity, frequency & duration
   ii. Total exercise time
d. Personal & Environmental Factors
   i. Age matters, but neuroprotective at all ages
   ii. Sex – females benefit more
   iii. Education
   iv. Self-efficacy
   v. Social support

XV. Summary: Neuroprotective Effects of Exercise in Adults with Neurodegenerative Disease

i. We have evidence of neuroprotective effects of exercise from animal and human studies.
ii. Exercise interventions designed to achieve an effective dosage may enhance both motor and non-motor functions in people with neurodegenerative diseases.
iii. Exercise interventions designed to target neuroprotective effects must address physical, cognitive, personal and environmental barriers.
iv. Further research is needed to identify optimal exercise parameters.

Part 3. Considerations for Exercise Capacity Testing in Adults with Neurodegenerative Disease

I. Special Considerations for Exercise Testing (Protas EJ, 1997)

a. Is maximal testing necessary for accurate exercise prescription for people with neurodegenerative disease?
b. Can it be achieved?
c. Is it accurate and reliable?
d. Can it be done safely?
e. Uniform exercise testing guidelines assume no health condition that would influence HR and BP response (see ACSM: 70-85% of age predicted heart rate)
f. Multiple studies demonstrate abnormal cardiac responses to exercise in people with PD
II. Exercise Testing Decision Making
   a. Choose appropriate mode relative to degree of impairment, safety
      i. Treadmill (free movement vs. body weight supported)
      ii. Various cycle ergometers (standard/recumbent)
      iii. Upper extremity ergometers
   b. Special Considerations for Exercise Testing in People with AD *(Rimmer 1997)*
      i. Formal lab testing may be impossible (cognitive status, agitation)
      ii. Consider AM testing if possible
      iii. Refer to ACSM testing guidelines for elderly populations
      iv. Limited support in literature for advanced disease
      v. Disease effect on exercise response
      vi. Limited literature especially in advanced disease
      vii. Deconditioning associated with depression
      viii. Consider side effects of medication
      ix. Orthostasis
      x. Balance impairment
      xi. Cardiac arrhythmia
   c. Maximal Exercise Testing in People with Early Stage AD: Modified Bruce protocol *(Billinger 2011)*
      i. VO2 peak was lower than that of non-demented peers
      ii. ACSM normative values of fitness
      iii. 10th-15th percentile for women with AD
      iv. 15-20th percentile for men with AD
   d. Alternative Methods for Estimating Exercise Capacity in People with Advanced Dementia
   e. Special Considerations for Exercise Testing in People with PD *(Protas 1997)*
      i. Physical mobility constraints
      ii. Physiologic limitations
      iii. Chronotropic incompetence
      iv. Lower absolute maximal heart rate
      v. Orthostatic hypotension
      vi. Compromised cardiovascular reflexes
vii. Patients with PD represent age groups having higher likelihood of cardiovascular disease

viii. Anti-parkinsonian medication contribution to cardiac arrhythmia (Stanley 1999)

ix. Pharmacotherapy Considerations:
   1. Consider testing on and off medication to establish ranges of performance
   2. Test at peak dose when possible
   3. Peak effect may increase incidence of tachycardia and dyskinesias
   4. Ask about recent changes in medication – results may be unpredictable
   5. Medication levels can influence exercise performance

f. Disease Effect on Exercise Response in PD
   i. PD exercisers may demonstrate great variability in heart rate response to the same activity
   ii. HR performance should be closely followed
   iii. Exercise performance stability may depend on consistent exercise time relative to last medication dose
   iv. Exercise may alter drug absorption or metabolism rates causing changes in symptomology
   v. Baseline symptoms behavior should be documented across medication levels

g. Maximal Exercise Testing in People with Early Stage PD: Cardiorespiratory fitness (VO$_2$$_{peak}$) testing - Treadmill testing highly reliable in mild to moderate PD (Hoehn & Yahr 1.5-3.0) (Katzel 2011)

h. Special Considerations for Exercise Testing in MS
   i. Spasticity
   ii. Incoordination
   iii. Balance impairment
   iv. Fatigue
   v. Muscle weakness
   vi. Sensory loss
   vii. Cardiovascular dysautonomia
   viii. Heat sensitivity

i. Marked Reductions in Exercise Capacity with Mild Degree of Disability in Patients with MS (Kuspinar 2010)
i. Chose submaximal testing
ii. Indicated good predictor of exercise capacity
iii. Motl et al (2012) developed regression formula predicting VO2 peak
iv. Within 10% of true value in 95 of 100 patients with MS (mild disability)

j. Disease Effect on Exercise Response in MS
i. Attenuated HR and BP response during exercise in patients with MS
   1. Cardiovascular dysautonomia
   2. Many Patients with MS will experience fatigue before attaining age predicted maximal heart rate
   3. Inadequate rise in systolic BP during exercise may lead to insufficient perfusion of brain or muscles
   4. Premature exertion – lightheadedness, muscle fatigue
ii. Estimate of functional aerobic capacity - use actual HR response from graded exercise test to prescribe target HR range for training
iii. DMA and pharmacological management of symptoms (i.e., Baclofen, tizanidine, amantadine, fluoxetine, prednisone) may have side effects that alter exercise response, exercise tolerance or both.

k. Mode for Clinical Exercise Testing on MS
   i. Upright or recumbent leg cycle ergometer
      • Safety due to LE sensory loss, weakness (foot drop), spasticity, and/or clonus
      • Toe clips, heel straps
   ii. Combination arm-leg ergometer
      • Increase activated muscles and improve test results – greater cardiopulmonary stress achieved
   iii. Arm crank ergometer
      • More severely impaired individuals, UE fatigue before cardiopulmonary maximal response achieved
iv. Treadmill
   • Low EDSS scores, safety not an issue

l. Exercise Testing and Training Conditions for Patients with MS
   i. Morning optimal time
   ii. Use a fan for cooling
   iii. Monitor HR and BP
iv. Testing
v. Continuous or discontinuous protocol of 3 to 5 minute stages
vi. Begin with warm-up of unloaded pedaling/cranking
vii. Increase work rate for each stage by approximately 12 to 25 W (legs) and 8 to 10 W (arms)
viii. Use category – ratio RPE scale to estimate stress level
ix. Test termination:
   - Volitional fatigue
   - Reached MHR
   - Decrease or plateau in O2 consumption (VO2) with increasing work rate.
m. Considerations for Exercise Test Interpretation in MS
   i. Psychological dimension
   ii. Cognitive deficit
   iii. Memory loss
   iv. Increased processing time
   v. Disease progression
   vi. Variation in symptoms daily
   vii. Medication
   viii. Sleep
   ix. Temperature
   x. Exacerbation
   xi. Stop exercise until full remission
   xii. Reassess
   xiii. Temperature
   xiv. Attenuated or absent sweating
   xv. Utoff’s phenomena
   xvi. Hydration
   xvii. Urinary incontinence may cause individual to reduce fluid intake

III. Exercise Recommendations: Targeting Neuroprotective Mechanisms
   a. Foundational assumptions
      i. Exercise prescription must be tailored to the individual
ii. Best prescriptive “power” requires exercise testing
iii. Individuals with NDD exhibit altered exercise responses that have to be accounted for in Rx
iv. Goal – attain brain-beneficial effects of exercise while maintaining safety

b. Foundational assumptions (Cotman 2007)
i. Overall brain health
ii. Brain resilience
iii. Improved learning and memory
iv. Growth factor cascade stimulating
v. Plasticity
vi. Neurogenesis and cerebrovascular perfusion

c. Foundational assumptions
i. Protective effects of exercise
ii. Reduces risk factors for cognitive decline
iii. Slows the rate decline in established disease
iv. Reduces inflammation which interferes with growth factor signaling
v. Improved oxygen transport systemically
vi. Pulmonary efficiency
vii. Cardiovascular efficiency
viii. Increased glucose sensitivity

d. What level of metabolic challenge best produces neuroprotective effects?
i. What percentage of VO2 peak is that for
ii. Healthy adults, older adults
iii. Adults with neurodegenerative disease (NDD)
iv. Older adults with NDDs
v. Advanced stages of NDDs

e. Targeting Cardiovascular Fitness (Colombe & Kramer 2003)
i. Combined aerobic & strengthening greatest effect
ii. Longer duration (> 30 min) had greater effect
iii. Greatest effect on executive function
iv. PA is beneficial to all cognitive functions
v. Ages 60-70 benefitted the most
vi. Studies with > 50% female reported greater benefit than studies with >50% male
f. Targeting Glycemic Control (Karstoft 2012; Umpierre 2011)
   i. Interval training more effective in improving VO$_2$max and glycemic control in people with type 2 diabetes than steady paced walking
   ii. Interval training: 3 min low intensity/3 min high intensity
   iii. Steady Pace: continuous moderate walking x 60 min.
   iv. Structured exercise training that consisted of aerobic, resistance, or both for $\geq 150$ min/wk associated with improved glycemic control in type 2 diabetes.
   v. Structured exercise training more effective than physical activity advice alone.

g. Implementation: Addressing Barriers Using the ICF Model
   a. Health Condition
   b. Personal Factors
   c. Environment
   d. Body Systems
   e. Activity
   f. Participation

h. Exercise Interventions Designed to Accommodate:
   i. Body systems barriers
      i. Slowed motor function
      ii. Gait & balance impairments
   ii. Cognitive barriers
      i. Executive function deficits
      ii. Memory impairment
   iii. Social & environmental barriers

i. Implementation: Addressing Cognitive Impairment (Teri 2008)
   1. Easy-to-remember increments
   2. High repetition and lots of practice
   3. Cognitively intact “study partner”
   4. Written instructions (laminated, small magnets attached to the back of the page)
   5. Visual memory cue
   6. Handy reminder of how to do exercises
   7. Make it fun and Individualized

i. Health Condition: Pathology

ii. Body Systems:
   a. Communication – exertion level, discomfort
   b. Heart rate monitor
   c. Cognitive-behavioral interventions

iii. Environment (room temperature, distractions)
   a. Staff Training
   b. Supervision- safety on equipment, cues/strategies to maintain intensity, task-specific training
   c. Structure and routine
   d. Storage place for equipment
   e. Fun

iv. Personal Factors
   a. Self-efficacy
   b. Preferences
   c. Dyad model
   d. Opportunity social interaction
   e. Circuit Training, Virtual Reality Training

k. Prevention of Chronic Disease: ACSM/AHA Physical Activity Recommendations
   i. ≥150 min/wk of physical Activity
   ii. ≥ 30 min of moderate PA at least 5 days/wk,
   iii. OR ≥ 20 minutes of vigorous PA at least 3 days/wk.
   iv. Supervised by professional
   v. Individually designed and tailored
   vi. Behaviorally-base interventions & change strategies
   vii. Education on progression
   viii. Enjoyable

l. Prevention of Chronic Disease: Aerobic Exercise Dose - Intensity/Frequency/Duration
   i. Moderate: 5-6/10, 5x/wk, 30-60 min/session (≥150 min/wk)
   ii. Vigorous: 7-8/10, 3x/wk, 20-30 min/session (≥75 min/wk)
   iii. Can be accrued in 10-min bouts

m. Prevention of Chronic Disease: Resistance Ex Dose: Frequency/Intensity/Duration
   i. Moderate: 5-6/10, 2x/wk, 8-10 Ex, 8-12 reps
ii. Vigorous: 7-8/10, 2x/wk, 8-10 Ex, 8-12 reps
iii. Type: Progressive weight training or weight bearing Ex

n. Prevention of Chronic Disease: *Flexibility Exercises: Major Muscle Groups*
   i. Moderate Intensity: 5-6/10
   ii. Duration: 60 seconds/exercise
   iii. Frequency: 2x/wk

o. Prevention of Chronic Disease: Neuromuscular Fitness - Balance/agility/coordination
   i. *Neuromuscular Fitness: Balance/agility/coordination*
   ii. Moderate Intensity: 5-6/10
   iii. Frequency: 2x/wk
   iv. *Balance Exercises:* Progressively difficult postures and gradually reduce base of support

p. Increasing Exercise Dose in Neurodegenerative Disease: Innovative Strategies
q. Tandem Biking in PD: Augmented (or forced) Exercise (*Alberts 2010, Rigdel 2009*)
   i. Forced exercise via tandem biking facilitates increased quantity of pedaling (higher rate) and greater consistency (quality of pedaling).
   ii. People with PD have slowed motor function making it difficult to sustain *higher pace and consistency to achieve aerobic exercise that meets the Surgeon General's Guidelines*

r. Innovative Interventions & Programs
s. Considerations for Exercise Recommendations in People with MS
   i. Core body temperature
   ii. Exercise has been reported to trigger symptom exacerbation in more than 40% of individuals with MS
   iii. Effects normalized within 30-60 minutes after termination in most
   iv. Resistance training is not accompanied by the same increase in core body temperature as endurance training
t. Recommendations: Strengthening Exercises in MS
   i. Mode
   ii. Initial phase – machines, elastic bands (i.e. Theraband ®), use of body weight as load
   iii. 4-8 exercises, whole body program
   iv. LE exercises priority
   v. Intensity
   vi. 8-15 repetition maximum, 1-3 sets
vii. Rest periods between sets and exercises (2-4 minutes)
viii. Frequency
ix. 2-3 days per week
u. Aerobic Exercise Recommendations in MS
i. Mode
   a. Bicycle ergometry
   b. Arm-leg ergometry
   c. Aquatic exercise
d. Treadmill walking
ii. Intensity - initial training intensity 50-70% VO2 max corresponding to 60-80% of MHR
iii. Duration - 10-40 minutes
iv. Frequency - 2-3 sessions per week, progress by increasing training duration or adding an additional day
v. Combined Training Recommendations
   i. Equal proportions of resistance- and endurance training should be performed on alternate days
   ii. Frequency
   iii. 4 days/week – 2 resistance and 2 endurance
w. Summary: Exercise Recommendations
   i. Exercise programs should be developed and monitored by a professional
   ii. Consideration disease effect on exercise response
   iii. Design exercise programs to target neuroprotective mechanisms
   iv. Innovative strategies
   v. Creative programs
   vi. Supportive environment
   vii. Focus on increasing self-efficacy
   viii. Educate patients

Part 4: Innovative Exercise Approaches to Target Neuroprotective Effects of Exercise in adults with neurodegenerative disease

a. Clinic-based vs. community-based implementation

b. Model programs
References


