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Neuroplasticity: Putting principles into practice

Guest Editor: Mike Studer, PT, MHS, NCS, CEEAA, CWT

Apr 23: Neuroplasticity and Rehabilitation
Jim Lynskey, PT, PhD

Apr 24: Applying Cutting-edge Neuroplasticity Research for Functional Restoration after Spinal Cord Injury
Edelle Field-Fote, PT, PhD, FAPTA

Apr 25: Neuroplasticity in Stroke Across the Spectrum
Kelsi Smith, PT, DPT, NCS, and Erin McMullen, PT, DPT, NCS

Apr 26: Neuroplasticity in Vestibular Impairment: The Foundation and Facilitatory Techniques for Optimizing Healing
Janene M. Holmberg, PT, DPT, NCS

Apr 27: Neuroplasticity in Degenerative Diseases
Diane Huss, PT, DPT, NCS, and Herb Karpatkin, PT, DSc, NCS, MSCS

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Neuroplasticity in Degenerative Diseases

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Objectives

As a result of this course, participants will be able to:

- Define neuroplasticity and neuroprotection in people with Parkinson's disease
- Identify at least 3 potential strategies to provide intensity based treatments in home health care
- Identify three 3 maladaptive movement patterns typical of people with Parkinsons disease

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No Conflict of Interest

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Neuroplasticity

- Process by which the brain encodes experiences and learns new behaviors
  - Modification of existing neural networks by addition or modification of synapses
  - Mechanisms include synaptogenesis, neurogenesis, neuronal sprouting, potentiation of synaptic strength
  - Leads to strengthening, repair or formation of neuronal circuitry

Petzinger, Fisher, McEwen, et al, Neurology, 2013

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Neuroplasticity

- Positive –evidenced by intervention-induced increases in maximal cortico-motor excitability, exercise-induced changes in voxel-based gray matter volume changes and increases in exercise-induced serum levels of brain derived neurotrophic factor (BDNF).
- Negative –decreased activation with disuse or habituation of ineffective or inefficient movement patterns

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Neuroprotection

- Prevention (or rate reduction) of neuronal degeneration during the progress of the disease.
- With normal aging, Dopamine neurons are lost (5-8%/decade) in Parkinson's Disease the rate is accelerated
  - In both aging and PD oxidative stress induces degeneration

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Neuroprotective Trials in Humans

- Antioxidant
  - Coenzyme Q10 and Mitochondrialstabilizer (+ in phase II; futile phase III)
  - Pramipexole
  - Ropinirole
  - Rasagilne (not effective)
  - Inosine (diabetes)
- Mitochondria biogenesis/stabilizer
  - Creatine (not effective)
- Selegiline (delay need for levodpa)
- Caffeine Adenosine antagonist
- Estrogen
- Nicotine
- Isradipine Phase 3

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Neuroprotective Trials in Humans

Complicated by:

- Lack of effective animal models
- Heterogeneity of People with Parkinson's Disease (PWP)
- Identification of subject too late in disease process for efficacious treatment
- Biomarkers of disease/neuroplastic changes difficult to identify (beyond precursors to change i.e. performance)

Exciting opportunities exist to better focus intervention strategies by identification of homogeneous phenotypes through genetic typing

and

the determination of effectiveness through the evolving science in the discovery of readily accessible biomarkers of change

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Disease Modification

- Slowing of progression of disability independent of the impact on the course of neurodegeneration
  - Often through drugs that address symptoms
  - Levodopa reduces bradykinesia and is can be objectively measured as increased gait speed
  - As the neurodegeneration progresses, gait speed can be maintained with increasing doses for a period of time
- UPDRS outcomes (common marker)

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Disease modification and Neuroprotection in neurodegenerative disorders

- Disease modification is established by *slowing the progression of disability* independent of the course of neurodegeneration (symptomatic)
- Neuroprotection is the ability to *prevent the degeneration* of neurons

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Neuroplastic Interventions

- Antioxidant (drugs/exercise)
- Mitochondria biogenesis (drugs/exercise)
- Exercise
  - In early life
  - In mid life
  - After diagnosis
  - Targeted training
- Intensive Multidisciplinary Rehabilitation Treatment
- Transcranial Motor Stimulation
- Deep Brain Stimulation

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Impact of Physical Activity

Neuroprotective: Upregulates production of growth factors and receptors, attenuates dopaminergic neuron damage, reduces cellular inflammation and oxidative stress

- Previous evidence in animal studies, now demonstrated in humans; most with small subject numbers increases in:
  - BDNF
  - Dopamine receptors
  - Serum antioxidants

LaHue, Comella, Tanner, Movement Disorders 2016

Prepared by Diane S Huss, PT, DPT, NCS

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Physical Activity Demonstrates ***Risk Reduction*** for Parkinson's Disease

Longitudinal Population Health Studies

- Men who played sports in college and adult life
- Greater than 6 hrs of physical activity a week
- Some studies with greater risk reduction for men than women
- Physically fit PWP demonstrate better cognitive scores than unfit PWP

Ahlskog, Neurology. 2011

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Recreational Physical Activity in Middle Age

Participation in frequent (4-8 hrs) moderate to vigorous activities (bicycling, aerobics, tennis) associated with reduction in risk of PD

>18.5 to 23 MET/hrs/wk

But no activity, light (walking,dancing) and moderate activity at less frequency was not

>11.6 to 16 MET /hrs /wk

Reduction in PD risk through vigorous activity

or

perhaps decreased activity due to preclinical PD

Thacker, Chen, Patel, et al, Movement Disorders 2008

Prepared by Diane S Huss, PT, DPT, NCS

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Physical Activity

Physical Activity impact on Basal Ganglia

↑BDNF, GDNF, IGF
↑ Antioxidants
↑ Dopamine
↑ Dopamine Transporters
↓Glutamate Excitotoxicity

⇒

↑ Neuroprotection
↑ Synaptic Transmission
↓ Oxidative Stress
↓ Mitochondrial Dysfunction
↓ Apoptosis

⇩

Prevent or delay disease , or improve function

LaHue, Comella, Tanner, Movement Disorders, 2016

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Maladaptive

- Decline in hippocampal volume in control group of non-exercise while aerobic exercise group demonstrated 2% increase
- Repetition of low amplitude, slow velocity movement has musculoskeletal impact of ROM and strength impairment; which also leads to less activation of cortical structures

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Maladaptive

Dyskinesia-

Serotonin axon sprouting in response to dopamine depletion leads to Levodopa induced dyskinesia with dopamine depletion

Alterations in presynaptic dopaminergic function coupled to changes in the response of post-synaptic dopaminergic receptors cause alterations in striatal output with attempts at compensation

Eventually compensation fails and persistent changes in striatal function occurs

Dopamine receptor stimulation leads to altered signaling through D1 and D2 receptor systems and changes in striatal function causes abnormalities of LTP/LTD .

Iravani, McCreary, Jenner, Parkinsonism and Related Disorders. 2012

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Intensive Rehabilitation Treatment in Early Parkinson's disease

N-40 Newly dx people w/ PD treated with rasagiline

- Treatment Group (two 28-day) multidisciplinary intensive rehabilitation treatments

  [MIRT], at one year intervals-3 hrs-5 days week-balance, cardio, strength stretch, adl's
- Control Group (drug only)

2 year results

- MIRT Group: UPDRS II, UPDRS III, TUG, and PDDS were better than at baseline(all ps< .03), had lower L-dopa equivalents and more remained on monotherapy throughout (75% 2y).
  - Increase BDNF by 14% over baseline at 10 days through discharge
- Control Group: No changes in outcome measures, significant increase in L-dopa equivalent, fewer on monotherapy throughout (20% 2y)

Frazzitta G, Maestri R, Bertotti G,et al, Neurorehabilitation and Neural Repair, 2015

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The Effect of Exercise Training in Improving Motor Performance and Corticomotor Excitability in People With Early Parkinson's Disease

High-intensity exercise-body weight–supported treadmill training (BWSTT)

low intensity exercise-BWSTT 3xWx8w for both

zero-intensity education group 6 class over 6 wks

All had improvement in total and motor UPDRS

High-intensity group subjects only:

- increases in gait speed, step and stride length and hip and ankle joint excursion during gait and improved sit-to stand tasks. Improvements in gait and sit-to-stand measures
- Increased corticomotor excitability as measured through transcranial magnetic stimulation (TMS) indicating dose dependent cortical outcomes for exercise

Fisher, Wu, Salem, et al, Archives of Physical Medicine and Rehabilitation, 2008

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Aerobic Exercise

Aerobic Exercise Training (AET) with high-intensity, stationary recumbent bike-training program (3 times/wk for 12 wks). Exercise prescription started at 20 min (+5 min/week up to 40 min) based on participant's maximal aerobic power.

Twenty healthy controls (HC) 19 early PD individuals

Results: Significant improvement in aerobic capacity in all. Executive Function tests of cognitive inhibition and implicit motor sequence learning (MSL) capacity improved

Executive flexibility functions did not

Conclusion: Our results suggest that AET can be a valuable non-pharmacological intervention to promote physical fitness and better cognitive and procedural functioning.

Duchesne, Lungu, Nadeau, et al, Brain and Cognition 2015

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High Intensity Treadmill Training

- Increase in maximal corticomotor excitability and improved gait parameters
- Increase in Dopamine D2 receptor density in the dorsal striatum of the putamen
- Transfer of improved kinematics in untrained direction change task

Hirsch, Iyer, Sanjak , Parkinsonism Related Disorders, 2016

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Treadmill Training with Virtual Reality

- Treadmill training alone compared to treadmill training with virtual reality over obstacles over 6 wks
  - fMRI with participants imagining walking on clear path or with virtual obstacles
- Motor with cognitive had better performance in walking speed during obstacle negotiation, less falls over 6 months, and less reliance on frontal brain regions

Maidan, Rosenberg-Katz, Jacob, et al, Neurology 2017

25

Freezing of Gait

25 PD patients with freezing of gait 4 wk trial with 8 w follow-up

#1 Physical training (60 min) Action Observation + Practice of Observed Actions AOT)
#2 Physical training (60 min) Observed Landscape Video (Landscape)

Clinical Evaluation UPDRS, Berg Balance Scale and the 10 m walking test and fMRI @ 4wk and 8 wks

Both: ↑walking speed, ↑ QoL, ↓FOG @ 4 wks

Landscape ↓ fMRI activity of the left postcentral and inferior parietal gyri

AOT also ↓motor disability, ↑balance, increased recruitment of fronto-parietal areas

Only AOT: ↓motor disability, ↑balance, ↑walking speed, ↑ QoL @ 8wks

AOT-related performance gains are associated with an increased recruitment of motor regions and fronto-parietal mirror neuron and attentional control areas

Agosta, Gatti, Sarasso, et al, Journal of Neurology 2017

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High Intensity Cycling

- Increased BDNF
  - 5 minute bouts for 40 minutes
- Decreased UPDRS, rigidity, muscle stiffness and tremor
- Improved executive function

Hirsch, Iyer, Sanjak , Parkinsonism Related Disorders, 2016

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Dynamic Balance Training

Whole-body dynamic balancing task (DBT) 6 consecutive wks with 1 training day (TD)/wk for 45 min

20 PWP and 16 Healthy Controls

Balance testing and structural magnetic resonance imaging were performed before and after 2, 4, and 6 training weeks. Balance performance also at ~20 months

Performance improved in both groups with between group differences in rate and pattern of skill acquisition

Both showed reduction at 20 mos with better retention in PWP than in controls

Controls; Voxel-based morphometry revealed learning-dependent gray matter changes in the left hippocampus

PWP: Voxel-based morphometry revealed performance improvements correlated with gray matter changes in the right anterior precuneus, left inferior parietal cortex, left ventral premotor cortex, bilateral anterior cingulate cortex, and left middle temporal gyrus.

TIME × GROUP interaction analysis revealed time-dependent gray matter changes in the right cerebellum.

Training-induced balance improvements in PWP were be associated with specific patterns of structural brain plasticity that was different than healthy controls

Sehm, Taubert, Conde, et al. Neurobiology of Aging. 2014

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Effects of subthalamic nucleus stimulation on motor cortex plasticity in Parkinson disease

STN-DBS combined with dopaminergic medications restore LTP-like plasticity in motor cortex and long term depression of synaptic plasticity in the corticostriatal synapses

Result is improved motor function and decreased Levodopa Induced Dyskinesia

- Neither DBS alone or Dopaminergic medication alone had equitable effect

Kim, Udupa, Ni, et al. Neurology. 2015

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Transcranial Magnetic Stimulation (TMS)

Paired Associated Stimulation (PAS)-induced plasticity with Primary Motor Cortex (M1) and inhibitory Cerebellar stimulation On L-Dopa

- Daily sessions for 10 days:
  - Inhibitory stimulation of cerebellum demonstrated an anti-dyskinetic effect that was superior to sham stimulation.
  - Improved sensorimotor plasticity of M1
  - Sustained responsiveness of M1 more than 2 wks lost by 4 wks.

Kishore, Popa, Balachandran, et al. Cerebral Cortex. 2014

30

Deterrents to Physical Activity

- Apathy in PD has as prevalence of 20-36% in newly diagnosed and up to 60% after 5-10 yrs
- Fatigue present in at least 1/3 to 1/2 of PWP
- Lack of motivating person-spouse, personal trainer
- Low outcome expectation from exercise—subjects reported feeling the same whether physically active or not
- Lack of time to exercise—difficulty prioritizing and planning activities, potential cognitive changes
- Fear of falling--leads to increasing inactivity; is an independent risk factor for falls in PD

Ellis, et al, Physical Therapy 2013 ;
Pagonabarraga , et al, Neurology 2015;
Elbers , et al, Cochrane Database of Systematic Reviews 2015

31

Interference with Neuroplasticity

- Chronic Stress and Glucocorticoid
- REM Sleep Disorder

PET study positron emission tomography (PET) and regional cerebral blood flow measurements, we show that waking experience influences regional brain activity during subsequent sleep.

Several brain areas activated during the execution of a serial reaction time task during wakefulness were significantly more active during REM sleep in subjects previously trained on the task than in non-trained subjects.

These results support the hypothesis that memory traces are processed during REM sleep in humans

Vyas, Rodrigues, Silva, et al. Neural Plasticity 2016
Maquet, Laureys, Peigneux, et al. Nature Neuroscience. 2000

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Motivators

Exerciser Profile:

High self efficacy shown as greater influence than degree of disability

- individual's belief in his or her capacity to execute behaviors necessary to produce specific performance attainments (reach goals)
- reflects confidence in the ability to exert control over one's own motivation, behavior, and social environment.
- belief in their ability to overcome personal, social, and environmental barriers to exercise

Participate in higher intensity exercise regimens

More likely to start exercising after being diagnosed

Significant other or a personal trainer to motivate

College educated

Ellis, Cavanaugh, Earhart, et al, Physical Therapy 2011
Afshari, Yang, Bega, Journal of Parkinson Disease 2017

33

PD is correlated with Metabolic Syndrome

- suggested relationship between insulin resistance, *diabetes*, obesity, and dyslipidemia with development and severity of PD progression

- Physical exercise:
  - Reduces chronic oxidative stress
  - Stimulates mitochondria biogenesis
  - Up-regulates of autophagy in PWP
  - Increases activity and effectiveness of antioxidant enzymes
- Exercise
  - Stimulates synthesis of dopamine and trophic factors (BDNF, GDNF, FGF-2, IGF-1, among others) which promote neuroplasticity,
  - Decreases neural apoptosis

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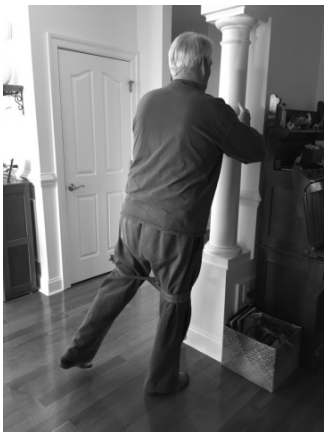
Intensity/Repetition Theraband



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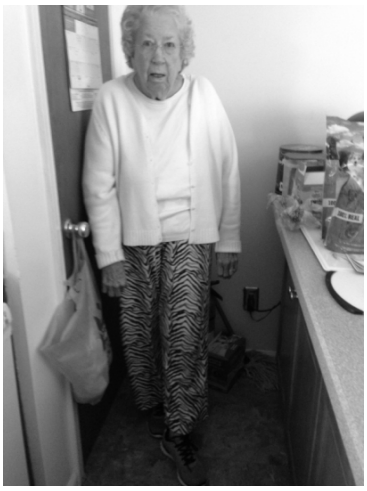
Intensity/Repetition Balance



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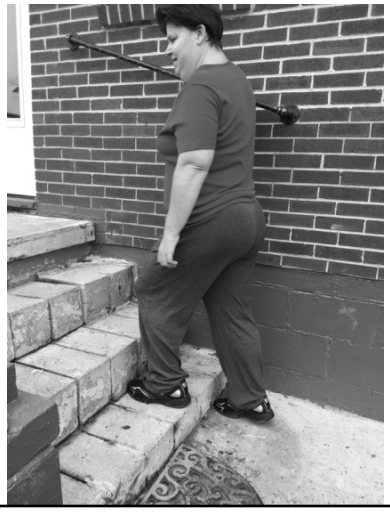
Intensity/Repetition Aerobic



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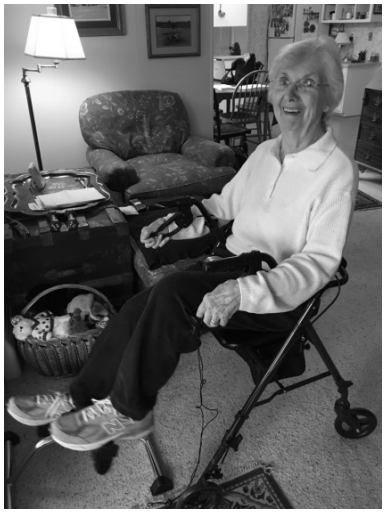
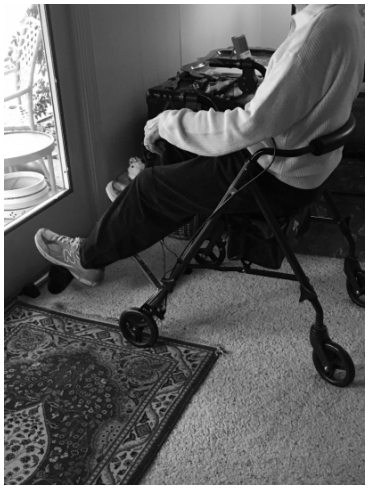
Intensity/Repetition Aerobic





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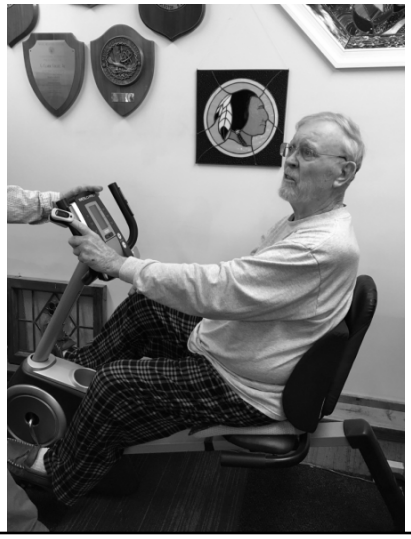
INTENSITY IN HOME HEALTH



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Intensity/Repetition Aerobic

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Principles of Exercise

- Goal-based: patient's goal-*salience*
- Experience-dependent neuroplasticity, include: *intensity, repetition, specificity, attention, and complexity*
- Practice activities that lead to improved (correct) performance
  (high reps-1200? with optimized mvmt pattern; increased amplitude – ON meds)
- Aerobic training: vigorous and sustained activity to increase cardio-pulmonary function, oxygen consumption, cortical blood flow, neuroprotection and neural plasticity
- Enhance cognitive engagement: feedback (verbal or proprioceptive), attentional demand (cueing or dual tasking, virtual reality), facilitate motivation
- Feasibility: Optimize medication status, identify and avoid barriers and realistic objectives

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