1. **EXERCISE MATTERS: HOW TO CHANGE THE BRAIN TO IMPROVE FUNCTION**

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2. **OBJECTIVES: COGNITIVE LEVEL**

   By the need of this presentation clinicians will...
   1. Define neuroplasticity and how it can be affected by therapeutic intervention.
   2. Discuss the mechanisms of neuroplasticity and differentiate between adaptive and maladaptive neuroplasticity.
   3. Explore the principles of neuroplasticity and how to optimize therapy to induce neural plastic changes.
   4. Discuss how aerobic exercise produces Brain Derived Neurotrophic Factor which enhances brain function, driving neural plastic changes.
   5. Discuss contemporary interventions being researched to harness neural plasticity, such as Transcranial Magnetic Stimulation, Transcranial Direct Current Stimulation, Deep Brain Stimulation, and Neuropharmacology.

3. **OBJECTIVES: APPLICATION LEVEL**

   During this presentation clinicians will...
   1. Participate in group discussion to apply principles of neuroplasticity and motor learning principles to specific patient cases.
   2. Develop a treatment plan using these principles to provide the “just right challenge” to their patient population.
   3. Reflect upon current caseload of patients and discuss how to modify current interventions while applying knowledge of neuroplastic principles gained through this course.

4. **WHAT IS NEUROPLASTICITY?**

   • “The ability of the central nervous system (CNS) to undergo structural and functional change in response to new experiences” (Kleim, 2008)
   • Responsible for WHY adults can succeed with motor learning
   • Can be positive or maladaptive

5. **MECHANISMS OF NEUROPLASTICITY**

   1. Basic process driving Neuroplasticity relies on expression of genes
   • Direct versus Indirect Mechanisms
   • New neural connections (Unmasking silent synapses or reactive synaptogenesis)
   • Strengthen existing neural connections (regenerative synaptogenesis)
   • Pruning and focusing of preferential pathways

   2. Brain Derived Neurotrophic Factor
   • Neurotrophin family of proteins, reliant on genetics
   • Neuroprotective
   • Neurogenesis
   • Neuroplasticity
Mediator of motor learning during rehabilitation

6 INFLUENCES ON NEUROPLASTICITY
- Age
- Lesion demographics
- Pre-morbid and post-morbid life experiences
- Skilled and intense motor training

7 PRINCIPLES OF NEUROPLASTICITY

8 HOW IS NEUROPLASTICITY DETECTED?
1. Non-invasive brain stimulation (measures excitability of motor cortex maps): Transcranial Magnetic Stimulation
2. fMRI

9 TECHNIQUES THAT MAY “PRIME” MOTOR LEARNING
- TMS increase/decrease corticomotor excitability
- TDCS (transcranial direct current stimulation)
  - anodal depolarizes tissue increasing activity;
  - cathodal depolarizes tissue decreasing activity
- Aerobic exercise
- Deep brain stimulation
- Neuropharmacology
- Aerobic Exercise

10 RTMS VS TDCS
- TDCS: delivers low-intensity, direct electric current to the brain.
- Repetitive transcranial magnetic stimulation (rTMS) uses electromagnetic induction to generate electric currents in the brain.
- GOAL: Enhance neuronal excitability or to inhibit over-excitability of neuronal networks (affected brain vs less affected brain)
  - low-frequency rTMS and cathodal TDCS inhibit
  - high-frequency rTMS and anodal TDCS enhance excitability of targeted cortical neurons.
- TDCS is safer, more comfortable, easier to do, more affordable, and produces a more robust response.

11 FORMS OF DELIVERING TDCS

12 TARGETING THE AREA FOR RECOVERY

13 TMS

14 TMS: DIAGNOSTIC AND TREATMENT
- Detects Motor Evoked Potentials (MEP)
  - Integrity of the Cortical Spinal Tract (CST)
- Trains of low frequency (<1 hz) rTMS or Theta burst TMS lead to suppression of cortical excitability
- Trains of high frequency (>1 hz) rTMS lead to facilitation of cortical excitability
DEEP BRAIN STIMULATION
• Surgically implanted electrodes to provide electrical impulses to help with tremors, rigidity, slowness of movement, balance (block abnormal activity in the brain)

BDNF - BRAIN DERIVED NEUROTROPHIC FACTOR
• Neurotrophin family
• Involved in
  • Neuroprotection
  • Neurogenesis
  • Neuroplasticity
• Is a key mediator of motor learning and “priming the brain” for neuroplasticity
• Secreted by 2 mechanisms: constitutive and activity dependent pathways

NEUROPHARMACOLOGY

AEROBIC EXERCISE: WE GOT THIS!
• Indirect effects:
  • Improves general health and fitness
• Direct effects
  • Increase in neurotrophic factors (BDNF and others)
  • Increase in Neurotransmitters (dopamine, serotonin)

AEROBIC EXERCISE EFFECTS ON BRAIN FUNCTION
• Aerobic exercise can enhance BDNF levels and leads to increased BDNF gene expression in:
  • Hippocampus
  • Cerebellum
  • Cerebral cortex
  • Spinal cord

BDNF ROLE IN FACILITATING NEUROPLASTICITY AND MOTOR LEARNING
• BDNF facilitates long term potentiation through an activity-dependent secretion: vital to neuroplasticity
• Animal Studies:
  • If BDNF is disrupted with pharmacological interventions leads to impaired skilled motor performance and decreased cortical map plasticity.
  • If BDNF is then injected in primary motor cortex see improvement

EFFECTS OF INCREASED BDNF: EVIDENCE
• Evidence supports an increase in BDNF benefits cognitive functions
• Systemic levels of BDNF are increased for 10-60 minutes following a bout of aerobic exercise (Knaepen et al 2010)

EVIDENCE SUPPORTING AEROBIC EXERCISE TRAINING AND NEUROPLASTICITY
• Cognition
  • Meta analysis in older adults (Colcombe 2003) Aerobic exercise training improved cognition (executive control domain) most studies involved exercise at 3/wk, moderate intensity (70% MaxHR) *those that had sessions longer than 30 min for 6 mo or more and include combination of aerobic ex and resistance training had larger effects
• Mobility, balance and motor function
  • Quaney et al (several studies) 8 wk cycling – improved motor skill acquisition (not maintained 8 wks later after training stopped)
  • Meta analysis (Lambourne & Tomporowski 2010) analysis of 29 studies of healthy young adults
  single bout of aerobic ex significantly enhances information processing and memory (effect greater with cycling than treadmill).
  • Short bouts of high intensity aerobic exercise may enhance memory more than long duration low to moderate intensity exercise

“PRIME THE SYSTEM” WITH AEROBIC EXERCISE
• TIMING: Need to engage in aerobic exercise close in time to your behavioral training—pair exercise with motor practice—can be done before or after motor practice
  • Evidence by Roig: single bout of high intensity cycling 3X3 above ventilatory threshold immediately before motor task practice in healthy young adults—saw enhanced motor performance on retention tests 1 and 7 days post practice

EVIDENCE BASED RECOMMENDATIONS FOR PRACTICE: FITT PRINCIPLE
• Frequency: 4x/wk
• Intensity: 70 max HR
• Time: aerobic session of more than 30 min
• Type: combination of aerobic exercise and resistance training
  • Evidence that 30 min at 60% max HR is effective for increasing BDNF in pts with chronic disorders

DISCUSSION OF THE EVIDENCE: WHAT SAY YOU?
1 BARRIERS WITH APPLICATION?
3 SUPPORT WITH APPLICATION?

ASSESSING AEROBIC FITNESS/CAPACITY
• What do YOU do as clinicians?
• What does the evidence say?
  • Max testing
  • Submax testing
  • Billinger article, 2014:
    There is strong evidence to recommend low to moderate intensity aerobic activity, muscle strengthening, and a reduction of sedentary behavior for post stroke care (Billinger et al., 2014)

LET’S APPLY IT!
• CASE 1: A 65 yo male referred to outpt PT 6 mo post R MCA stroke. History of 2 falls and HTN. MD clearance for vigorous exercise.
  • BP: sitting 135/87, Standing 133/85, HTN controlled with Atenolol Resting HR: 75bpm
  • Gait: mod I with SPC for household distances. Mod I with SPC on level terrain, supervision / min A for curbs. During swing, intermittent foot drag occurs with reduced knee flexion during early swing. During stance the knee remains in 20d of flex from IC to thru mid stance
  • 10m walk test: 0.50m/s, 6min walk test: 395m
  • Fugl-Meyer Motor Function: UE 45/66, LE: 24/34
• **Sample strength testing for determination of 1RM:**
  • During LAQ with a 5 lb cuff weight on the more affected side the patient completed 6 reps but is unable to complete the 7th.
  • During unilateral leg press the patient can push 15 lbs on the more affected side 20 times and no more, and 50 lbs on the less affected side 16 times and no more.
• **Functional strength testing:**
  • Sit to Stand (18in chair): mod I without UE’s, slow, genu recurvatum at termination. Pt can do this 19x with good form (and no more)
  • Stair climbing: Pt requires UE assist to climb a full flight, L knee wobbles
  • Retrieve object from floor (squat): decreased wt acceptance on more affected LE

2. **CASE 2:** A 66 yo female is 3 weeks status post Right ACA stroke and is being seen in an inpt rehab. The patient is medically stable. The patient has a history of HTN and previous MI 6 years prior. The patient completed a cardiac rehab program post MI.
  • BP: sit 125/82, Stand 118/77, HTN controlled with Lozol (Indapamide), Resting HR: 75bpm
  • Gait: modA for 130 ft. The pt can initiate swing but with decreased force production and assist for initial contact. Pt has reduced knee flexion to 30 d during initial swing. Stance requires stability assist at both knee and hip.
  • BERG: 28/56 (high fall risk) Fugl-Meyer Motor Function: UE 35/66, LE: 15/34
  • Functional strength testing:
    • Sit to Stand (18in chair): pt accomplishes task with CGA to MinA with heavy reliance of the less affected UE & LE throughout. The patient is unable to complete a 6th repetition without physical lifting assistance.
    • Stair climbing: Patient requires UE assist for climbing a 6” step with the more affected LE. Patient is able to repeat this 4 times with good form and no more.

29 WHAT IS YOUR POC?
  • What are the barriers to applying the neuroplastic principles and/or exercise prescription to these patients?
    • How could we clinically measure neuroplastic changes?
    • Where would the evidence lead you when prescribing your plan of care?
    • What other considerations are you having about applying the evidence?

30 AND THERE’S MORE...
GENETICS!

31 GENETIC CONSIDERATIONS
  • Genetic variations may influence the efficacy of rehab
  • Common SNP (single nucleotide polymorphism) on the BDNF gene (Valine replaced by Methionine)

32 BDNF GENE VAL66MET POLYMORPHISM
  • 30-50% of population have this SNP
  • The presence of the MET allele results in a 25% reduction in activity dependent secretion of BDNF in the CNS
  • Associated with:
    • Decreased hippocampal activation
    • Decreased motor system activation
    • Increase gray matter atrophy
    • Poorer memory function
    • Poorer outcome after stroke
• Poorer learning and memory

**RESEARCH EXAMPLES**

• Kleim 2006 BDNF gene Val66Met polymorphism on plasticity associated with 30 minutes of fast finger movement training
  • Those without the polymorphism had greater expansion of motor maps and M1 excitability
  • Other studies: McHughen and Cramer 2013: similar study but with healthy elderly

**DRD2: POLYMORPHISM OF DOPAMINE D2 RECEPTOR GENE**

• May account for the large variability in motor learning outcomes

**REFERENCES**

• Cramer S et al. Harnessing neuroplasticity for clinical applications. Brain 2011: 134; 1591-1608
• Ries E. A growing concern. PT in Motion 2013
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**REFERENCES**

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