• If you are viewing this course as a recorded course after the live webinar, you can use the scroll bar at the bottom of the player window to pause and navigate the course.

• This handout is for reference only. It may not include content identical to the PowerPoint. Any links included in the handout are current at the time of the live webinar, but are subject to change and may not be current at a later date.
Neuroplasticity and Rehabilitation

Jim Lynskey, PT, PhD
Associate Professor
A.T. Still University

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

- Define neuroplasticity, activity dependent neuroplasticity, and motor learning
- Understand the factors that modulate neuroplasticity and motor learning
- Implement the principles of neuroplasticity and motor learning into clinical practice
Outline

- Introduction
- The Mechanisms of Neuroplasticity: Synaptic
- The Mechanisms of Neuroplasticity: Structural
- Principles of Activity-Dependent Neuroplasticity
- Principles of Motor Learning
- Theoretical Application of Principles
- Summary

Introduction
Neuroplasticity

- Definition:
  - Ability of neurons to change function, chemical profile or structure
  - A natural innate process within the nervous system underlying learning and adaptation
  - An essential function of the nervous system to recover from damage
  - Occurs throughout the lifespan
  - Not inherently “good”
  - Can be adaptive or maladaptive

Neuroplasticity

- Is the change that happens in the brain that results in changes in function (memory, movement, reaction time, skill improvement, skill reduction…)

- The idea of neuroplasticity was first proposed by William James in 1890
  - “Organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity…” The Principles of Psychology
Neuroplasticity

- Another important theory on neuroplasticity was proposed by Donald Hebb in 1949
  - “When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A’s efficiency, as one of the cells firing B, is increased.” The Organization of Behavior (1949)

- Cells that fire together, wire together

Neuroplasticity

- Without neuroplasticity, our nervous systems would not be able to:
  - Learn new facts or skills
  - Form memories
  - Adapt to new environments
  - Recover from injury
Measurement of Neuroplasticity

- Cellular
  - Intracellular and extracellular recording and stimulation
- Structural
  - MRI
    - DTI
- Functional
  - fMRI
  - PET
  - TMS
  - EEG

The Mechanisms of Neuroplasticity: Synaptic
Synaptic Efficacy

- Altered signal transmission between neurons
- Can involve presynaptic or postsynaptic changes
- Can increase or decrease efficacy
  - Increases are considered potentiation (think long-term potentiation – LTP)
  - Decreases are considered depression (think long-term depression – LTD)

Synaptic Efficacy: Presynaptic
Synaptic Efficacy: Presynaptic

- Increased synthesis and storage of neurotransmitter
- Increased release of neurotransmitter

Pre-synaptic

Post-synaptic

---

Synaptic Efficacy: Presynaptic

- Decreased synthesis and storage of neurotransmitter
- Decreased release of neurotransmitter

Pre-synaptic

Post-synaptic
Synaptic Efficacy: Postsynaptic

- Increased number and density of receptors
- Increased responsiveness of receptors
Synaptic Efficacy: Postsynaptic

- Decreased number and density of receptors
- Decreased responsiveness of receptors

Membrane Excitability

- Augmentation or depression of a neuron’s responsiveness to stimulation
- Can occur by changing:
  - Sodium channels activity
  - Potassium channels activity
  - Calcium availability / activity
  - Membrane proteins / genes
- Result in:
  - Changes in neurotransmitter release, time of activity, reabsorption
  - Changes in receptor responsivity to neurotransmitter
  - Changes in resting membrane potential (hyperpolarize, depolarize)
Synaptic Plasticity: Summary

- Plasticity at the synapse take the form of:
  - Alterations in amount of neurotransmitters
  - Alterations in number, density and type of receptors
  - Alterations in membrane excitability

- Taken together these plastic changes will increase or decrease the efficacy of current synapses
  - Think LTP and LTD
  - Sensitization and Habituation

The Mechanisms of Neuroplasticity: Structural
Synaptogenesis

- Definition: the formation of new synapses
- Normal process that occurs throughout a healthy person’s lifespan
- Synapses can also be pruned

Synaptogenesis

- Usually Involves:
  - Axonal sprouting and regeneration
  - Dendritic sprouting
  - Dendritic spine alterations
Synaptogenesis: Axonal Sprouting

Synaptogenesis: Axonal Regeneration
Synaptogenesis: Dendritic Sprouting

Magariños A M et al. PNAS 2006;103:18775-18780

Dendritic Spine Alterations

**Neurogenesis**

- **Definition:** new cell development from neural stem cells
- **Where:** subventricular zone (caudate), subgranular zone (hippocampus)
- **Process:**
  - Proliferation
  - Migration
  - Differentiation
  - Integration

**Angiogenesis**

- **Definition:** blood vessel proliferation
- **Stimulated by:** endothelial cells releasing growth factors
- **Correlates with amount of neurogenesis**
- **Serves as supporting pathway for new neuron migration**
Structural Plasticity: Summary

- Structural Plasticity can take the form of:
  - Axonal sprouting, regeneration, or atrophy
  - Dendritic sprouting or atrophy
  - Dendritic spine alterations
  - Alterations in number of neurons
  - Alterations in blood supply

- Taken together these structural plastic changes will:
  - Increase or decrease the number of synapses
  - Create new circuits or breakdown old one

Synaptic and Structural Plasticity Summary

- Functionally, these forms of neuroplasticity are the mechanisms underlying:
  - Habitation
  - Sensitization
  - Classical Conditioning
  - Learning and Memory
  - Motor Learning
  - Recovery from Injury
Factors That Affect Neuroplasticity

- Activity
- Sleep
- Mood
- Hormones
- Diet
- Cardiorespiratory Function/Fitness
- Genetics
- Sex
- Pharmaceuticals
- Stimulation
- Disease
- Injury

Stewart and Cramer 2017
Factors That Affect Neuroplasticity

- Stimulation
  - Noninvasive brain stimulation such as transcranial magnetic stimulation and transcranial direct current stimulation have been shown to alter excitability of the nervous system

Huang et al. 2018

Factors That Affect Neuroplasticity

- Activity
  - Activity has been shown to be a powerful mediator of neuroplasticity in both animals and humans.
  - It appears to be guided by certain principles

Kleim and Jones, 2008
The Principles of Activity Dependent Neuroplasticity

- Use it or Lose it
- Use it and Improve it
- Specificity
- Repetition
- Intensity
- Salience/Attention
- Timing
- Age
- Difficulty/Complexity

Use It or Lose It

- Description

‘Failure to drive specific brain functions can lead to functional degradation.’

Kleim and Jones, 2008
Use It or Lose It

- Massive negative reorganization was observed in somatosensory cortices of monkeys after complete sensory deafferentation of an upper limb

- Syndactyly experiments: The cortical map for receptive fields in two digits of the hand combine into one representation when those digits are surgically joined and used as one functional unit.

- Merzenich et al 1990
Use It and Improve It

- Description:

‘Training that drives a specific brain function can lead to an enhancement of that function.’

Kleim and Jones, 2008

Use It & Improve It

Note: post stroke, shrinkage of the area of the hand representation

With rehabilitation, expansion of the area of the hand representation

Nudo et al., 1996
Specificity

- Description:

‘The nature of the training experience dictates the nature of the plasticity.’

SAID Principle: Specific Adaptation to Imposed Demands

Kleim and Jones, 2008
Specificity

Pellet retrieval task: encouraged increased use of the digits

- Increase in representational area devoted to fingers (flexion and extension)
- Decreased representational area devoted to wrist (wrist abduction)

Nudo et al., (1996) J. Neurosci 16(2) 785-807

Repetition

- Description

‘Induction of plasticity requires sufficient repetition.’

Kleim and Jones, 2008
Repetition

- **Injured Animal**
  - 9,600 retrievals over 4 weeks (Nudo et al., 1996)
  - 7,000 trials food catch task over 35 days (Pavlides et al., 1993)
  - 1500-2500 repetitive squeezing movements daily in 1.5 hours over 3 months (deterioration in function) (Byl et al. 1996)

- **Healthy & Injured Human**
  - 2,500 hand movement repetitions over 5 days in healthy controls and people with stroke (Boyd et al., 2003; 2004; 2010)
  - 31,500 repetitions of a finger sequence over 35 days (Karni, 1995)
  - 1000+ per day x 18 sessions finger tracking (Carey et al., 2002; Kimberley et al., 2004)
  - 12-14 hrs x 14 days = 196 hrs of opportunity to use affected arm/hand (Taub et al., 1993; Wolf et al., 1989)
Intensity

- Description:

‘Induction of plasticity requires sufficient training intensity.’

Kleim and Jones, 2008

---

Intensity

- High Intensity interval training can increase serum BDNF levels in healthy humans (Saucedo Marquez et al., 2015)
- High Intensity interval training improves recovery and promotes upregulation of anti-inflammatory and pro-plasticity markers in the brain after ischemic stroke in rats (Pin-Barre et al 2017).
- A single bout of intense cardiovascular exercise may reduce interhemispheric imbalances in excitability in chronic stroke survivors (Nepveu et al 2017)
Salience/Attention

- Description:

‘The training experience must be sufficiently salient to induce plasticity

Kleim and Jones, 2008

Salience/Attention

- Evidence suggests that experience dependent plasticity is enhanced
  - when the patient is attending to the activity
  - the activity has significance for the patient
Salience/Attention

- Multiple studies have demonstrated that plasticity in response to non-invasive brain stimulation increases with attention.

[Graph showing plasticity changes with attention]

Conte et al 2007; Ridding and Ziemann, 2010

Salience/Attention

- Human and Animal
  - The Ventral Tegmental Area of the Brainstem is rich with dopaminergic neurons that project to many areas of the brain including the limbic system and hippocampus
  - This circuitry is thought to play a large role in motivation, attention, learning, memory, reward, and addiction
  - Research has demonstrated that stimulation of this circuitry via drugs, electrical stimulation and activity can produce lasting plastic changes and significantly alter behavior

Lüscher and Malenka, 2011; Marmeli and Lüscher, 2011
Timing

- Description:

The timing of pre and postsynaptic neuronal firing alters the connectivity of the neurons

Referred to as Spike Timing Dependent Plasticity

Feldman 2012

- High frequency pairing of pre and post synaptic firing (<20ms) tends to lead to LTP and a strengthening of the synapse
- Lower frequency pairing of pre and post synaptic firing (20-100ms) tends to lead to LTD and a weakening of the synapse
- Usually 60-100 repetitions of the stimulation are required to produce the changes.

Feldman 2012
Age

- Description:

‘Training-induced plasticity occurs more readily in younger brains’

However, plasticity can occur throughout the lifespan

Kleim and Jones, 2008

---

Age


Birch AM, Kelly AM (2018). Lifelong environmental enrichment in the absence of exercise protects the brain from age-related cognitive decline. Neuropharmacology. 2018 Apr 7;epub


Difficulty/Complexity

- Description:

There is an optimal amount of difficulty/complexity of a task that drives plasticity

“The Goldilocks Zone”

Kleim 2011

- In rats trained on auditory discrimination tasks, the maximal amount of cortical plasticity was observed during tasks of intermediate difficulty

Engineer et al. 2012
Activity Dependent Plasticity: Summary

- To date, research has identified principles that promote activity dependent plasticity in the normal and impaired nervous system

Using it or Lose it
Use it and Improve it
Specificity
Repetition
Intensity

Salience/Attention
Timing
Age
Difficulty/Complexity

Activity Dependent Plasticity and Motor Learning

- Activity dependent plasticity is thought to be the mechanism that underlies motor learning
- And, in fact, motor learning has been shown to drive plasticity

Plasticity  Motor Learning
The Principles of Motor Learning

Motor Learning

- Characteristics of Skill Learning
  - Improvement
  - Consistency
  - Stability
  - Persistence (Retention)
  - Adaptability (Transfer)
Motor Learning

- Gentile Stages:
  - Early
    - Develop the pattern
    - Requires cognitive processing
    - Involves trial and error
  - Late
    - Consistency
    - Adaptability to situation
    - Economy of effort


Motor Learning

- Feedback
  - Knowledge of Results (KR)
    - Information about the outcome of the movement in the environment
  - Knowledge of Performance (KP)
    - Information about the nature of the movement pattern

Schmidt & Lee 1999
Motor Learning

- Feedback
  - Faded Feedback
    - Frequency reduces as skills develop
  - Bandwidth Feedback
    - Given only when movement falls outside of a bandwidth of correctness

Schmidt & Lee 1999

Motor Learning

- Practice
  - Random vs. Blocked
  - Massed vs. Distributed
  - Part vs. Whole
  - Contextual Interference

Magill 2010
Motor Learning

- Challenge Point Framework

Performance vs Learning


Guadagnoli and Lee 2004

Motor Learning

- OPTIMAL Theory

Wulf & Lewthwaite 2016
Motor Learning: Summary

- Optimization of Motor Learning Depends Upon:
  - Initial Skill Level/Impairment
    - Novice, Intermediate, Skilled, Expert
    - Severely, Moderately, Mildly Impaired
  - Stage of Learning
    - Early vs. Late
  - Attention and Motivation
  - Practice
    - Schedule & Variability
  - Feedback
    - Type, Schedule and Variability
  - Interaction with Environment/Context
  - Task Orientation

Theoretical Application of Principles

- Incorporate principles of both neuroplasticity and motor learning into practice
  - Practice the task you want to improve
  - Training should be of sufficient repetition and intensity
  - Customize types of practice and feedback to patient
  - Find the “sweet spot” for difficulty/complexity
  - The task should be meaningful for the patient
  - Emphasize personal motivation and autonomy
  - Incorporate context into practice
Summary

- The human nervous system is plastic
- This ability is retained throughout the lifespan
- Activity dependent neuroplasticity is governed by specific principles
- Plasticity is an underlying mechanism for motor learning
- Motor learning drives neuroplasticity
- Incorporating the principles of both neuroplasticity and motor learning into practice should improve the effectiveness of therapy

References

References