Functional neuroplasticity after stroke: clinical implications and future directions

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Objectives

- Explain the relationship between neural plasticity, memory formation, skill learning and recovery of function
- Discuss current barriers to improving patient outcomes in stroke
- Identify at least two potentially clinically viable approaches to measure and modulate brain activity
Why should you care about the brain as a PT?

According to Daniel Wolpert…

The only reason to have a *brain* is to produce adaptable and complex *movements*

Therefore, if you care about optimizing movement, you care about the brain

TED talk: ‘The real reason for brains’

Sea squirt
Guiding question in the lab

How can neuroplastic change in the human brain be measured and modulated non-invasively, *in vivo*, after injury or in disease?
Stroke is the leading cause of serious adult disability

In the next 20 years:
- Prevalence of stroke expected to increase 20%
- Direct medical costs projected to triple

Up to 80% of have persistent motor impairment of the paretic arm

Stroke mortality decreasing since 2001

Advances in rehabilitation failing to keep pace

Increasing numbers of stroke survivors with unmet rehabilitation needs

Langhorne et al., 2009; Mozaffarian et al., 2015
Organizing principle – Mechanisms underlying motor recovery after stroke

Experience → Neural Plasticity → Recovery of Function → Memory Formation → Skill (Re) Learning
Neuroplasticity underlies (re)learning

- The brain adapts and reorganizes in response to experience

- Structural and functional plasticity occurs in the human brain after injury or in the context of disease

Scholz et al., 2009

Langer et al., 2012

Carey et al., 2002
Stroke triggers peri-infarct and distant changes in neural activity

Rehabilitation can shape post-stroke neural repair

Grefkes and Fink, 2014 (adapted from Ward et al., 2007)

Nudo et al., 1997
Neuroimaging and neurostimulation approaches can be used to characterize neuroplastic change in the human brain.

Both approaches have the potential to influence experience-dependent neuroplastic change that supports recovery.
How can we drive neural plasticity?

Table 1. Principles of experience-dependent plasticity.

<table>
<thead>
<tr>
<th>Principle</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. Use It or Lose It</td>
<td>Failure to drive specific brain functions can lead to functional degradation.</td>
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<td>2. Use It and Improve It</td>
<td>Training that drives a specific brain function can lead to an enhancement of that function.</td>
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<td>3. Specificity</td>
<td>The nature of the training experience dictates the nature of the plasticity.</td>
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<td>5. Intensity Matters</td>
<td>Induction of plasticity requires sufficient training intensity.</td>
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<td>6. Time Matters</td>
<td>Different forms of plasticity occur at different times during training.</td>
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<td>7. Salience Matters</td>
<td>The training experience must be sufficiently salient to induce plasticity.</td>
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<td>8. Age Matters</td>
<td>Training-induced plasticity occurs more readily in younger brains.</td>
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<td>9. Transference</td>
<td>Plasticity in response to one training experience can enhance the acquisition of similar behaviors.</td>
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<tr>
<td>10. Interference</td>
<td>Plasticity in response to one experience can interfere with the acquisition of other behaviors.</td>
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Jones & Kleim, 2008
The Dose Problem

What amount of practice leads to relatively permanent behavioral and neuroplastic change?

- 9,600 retrievals over 4 weeks (Nudo et al., 1996)
- 100 retrievals/session, 19-24 sessions over 24 days (O’Bryant et al. 2014)
- 2,500 hand movement repetitions over 5 days in healthy controls and people with stroke (Boyd et al., 2003; 2004; 2008; 2009; 2010)
- 1000+ per day x 18 sessions finger tracking (Carey et al., 2002, 2004)
- 31,500 repetitions of a finger sequence over 35 days (Karni et al., 1995)
- 12-14 hrs x 14 days = 196 hrs of opportunity to use affected arm/hand (Taub et al., 1993; Wolf et al., 1989)
The Dose Problem

What is observed in the real-world:

32 task-specific repetitions/session (Lang et al., 2009)

Take-home: In the clinic, we are not optimally driving lasting neuroplastic change
Feasibility of High-Repetition, Task-Specific Training for Individuals With Upper-Extremity Paresis

Kimberly J. Waddell, Rebecca L. Birkenmeier, Jennifer L. Moore, T. George Hornby, Catherine E. Lang

OBJECTIVE. We investigated the feasibility of delivering an individualized, progressive, high-repetition upper-extremity (UE) task-specific training protocol for people with stroke in the inpatient rehabilitation setting.

METHOD. Fifteen patients with UE paresis participated in this study. Task-specific UE training was scheduled for 60 min/day, 4 days/wk, during occupational therapy for the duration of a participant’s inpatient stay. During each session, participants were challenged to complete ≥300 repetitions of various tasks.

RESULTS. Participants averaged 289 repetitions/session, spending 47 of 60 min in active training. Participants improved on impairment and activity level outcome measures.

CONCLUSION. People with stroke in an inpatient setting can achieve hundreds of repetitions of task-specific training in 1-hr sessions. As expected, all participants improved on functional outcome measures. Future studies are needed to determine whether this high-repetition training program results in better outcomes than current UE interventions.

How might therapies be optimized and/or augmented?

• Novel rehabilitation technologies
  – e.g. VR environments, telehealth, robotics
Virtual reality to increase paretic arm use
Experience-dependent myelin plasticity in humans

Lakhani et al., 2016

Current clinical trial in chronic stroke:
*Neuroplastic change in myelin in the brain*
[NCT 01937910]
How might therapies be optimized and/or augmented?

• Novel rehabilitation technologies
  – e.g. virtual reality environments, robotics

• Non-invasive brain stimulation approaches
  – paired associative stimulation (PAS)
  – repetitive transcranial magnetic stimulation (rTMS)
Organizing principle – Mechanisms underlying motor recovery after stroke

Experience → Neural Plasticity → NIBS

Neural Plasticity:
- Recovery of Function
- Memory Formation
- Skill (Re) Learning
TMS: How does it work?

Magnetic field, B

Electric field, E

Intracranial field

Pyramidal axons

Axon

Nucleus

Dendrites

Cell body

Synapse

Macroscopic response
- evoked neural activity (EEG)
- changes in blood flow and metabolism (PET, fMRI, SPECT)
- muscle twitch (EMG)
- behavioural changes

Microscopic response
- Local depolarization

Axon membrane

Distance from center in mm

Magnetic Field Strength
TMS can measure or modulate cortical activity

Non-repetitive or pulsed

Investigatory

Repetitive or patterned

Neuromodulatory

Frequency:
≤1Hz tends to inhibit
≥5Hz tends to excite

Rossi et al., 2009
Can plasticity be induced in vivo in the human brain?

Stefan et al., 2000

"LTP/LTD-like" plasticity - mimics in vitro synaptic effects:
1. Evolves quickly
2. Reversible
3. Persists beyond stimulation period
4. Follows temporal rules

Paired associative stimulation (PAS) modulates motor cortex excitability

Spike-timing-dependent plasticity (STDP)

Stefan et al., 2000
Greater skill learning but not performance after PAS

Palmer et al., in review
Interhemispheric competition model of stroke recovery

- Stroke induces local and global cortical reorganization
- *Increased* contra and *decreased* ipsi-lesional cortical excitability
- Mediated directly by transcallosal projections
- Depends on level of impairment, structural connectivity*
Increased ipsilesional M1 excitability after PAS application in chronic stroke

*No significant effects on skill performance or learning

Palmer et al., 2018
rTMS can modulate abnormal brain activity after stroke

Grefkes and Fink, 2014

Over-activity during paretic hand movement

Reduced after rTMS
rTMS to improve hand function in stroke

Excitatory

Inhibitory

Paretic hand
5Hz rTMS to ipsilesional S1

Excitatory

Improved motor function

AND

Paretic hand

Improved sensory function

Brodie, Meehan, Borich & Boyd, 2014
NIBS in chronic stroke

• Modulates cortical excitability
• Enhances motor skill learning
• Can translate into motor and sensory function improvements

But:
• Effect size is small
• Unclear who will benefit
• Response is variable within and across patients
• Optimal stimulation parameters unknown
• TMS measures of cortical excitability have limitations
Abnormal interhemispheric activity as a potential biomarker in stroke

1. Greater interhemispheric coherence between primary motor (M1) regions in stroke

2. Greater interhemispheric inhibition (IHI) from contra (c)M1-to-ipsilesional (i)M1

3. Poorer manual dexterity associated with more abnormal IHI

Borich, Wheaton et al., 2016; Palmer et al. in prep
Potential biomarker to target?

• Approaches to normalize interhemispheric interactions may facilitate recovery
• Non-invasive brain stimulation (NIBS) is an approach to modulate cortical excitability
• Traditional NIBS techniques have shown limited ability to enhance paretic arm and hand function
• Are there potentially more promising NIBS paradigms?

Di Pino et al., 2014, Hao et al., 2013, Elsner et al., 2013
Targeting interhemispheric connections in chronic stroke with NIBS

Interhemispheric ccPAS transiently reduces IHI

Borich et al., 2018, Lin, in prep
Plasticity induction in cortico-cortical circuits is time-dependent

**Sign of excitability change dependent on interstimulus interval**

M1 excitability modulated by stimulation of a directly connected cortical region (PPC)

Koch et al., 2013
Individualizing ISI to increase ihPAS effects in stroke

Borich, Lin, Palmer, in prep
Organizing principle – Mechanisms underlying motor recovery after stroke

Experience → Neural Plasticity → Recovery of Function → Memory Formation → Skill (Re) Learning → NIBS

- Brodie et al. 2014
- Palmer et al. in prep
- Palmer et al. 2018
How might therapies be optimized and/or augmented?

- **Novel rehabilitation technologies**
  - e.g. virtual reality environments, robotics

- **Non-invasive brain stimulation approaches**
  - paired associative stimulation (PAS)
  - repetitive transcranial magnetic stimulation (rTMS)

- **Identification of novel neural biomarkers**
TMS predicts proportional recovery after stroke

- MEP+ is a strong predictor of better functional recovery
- MEP- does not rule out a good outcome
- Identify those "proportional" (70%) recovery

Prabhakaran, 2008, Byblow, et. al., 2015
The Predict Recovery Potential (PREP2) Algorithm

Shoulder Abduction/Finger Extension @ 72 hours

Corticomotor Functional Integrity

Prognosis

- Complete or near complete use of paretic upper extremity (PUE) for daily tasks.
- Use of PUE for most activities with compensatory strategies. Expect some weakness and incoordination.
- Improvement will be made in PUE but will be limited in functional ability. Significant modifications will be necessary.
- Gross motion is possible but likely primarily at proximal joints. Functional motion in PUE is unlikely.


http://presto.auckland.ac.nz/
Limitations of standalone TMS for measuring and modulating cortical activity

- Infer cortical activity indirectly
- Stimulation sites primarily limited to those that evoke a peripheral response (e.g. M1, V1)
- Limited ability to characterize brain network connectivity

Hagmann et. al., 2008
Inability to elicit MEPs with significant motor output path disruption in stroke
Online approach: combining TMS with EEG

Siebner et al., 2009

Ilmoniemi & Kicic, 2010
EEG: How does it work?

EEG field potentials are a complex mixture of multi-scale neural dynamics.

Temporal resolution of 1ms or better.
Concurrent TMS-EEG approach

Simultaneous EEG recording during TMS delivery

Real-time targeting over motor representation of the hand
TMS-evoked EEG responses capture spatiotemporal cortical dynamics

Miyakoshi, Makeig, Borich in prep
Measuring cortical connectivity in stroke

Goal: probe spatiotemporal network dynamics at rest and during activity using TMS-EEG

Measure in the time domain or also in the frequency domain

Bortoletto et al., 2015
Translational potential

• Promoting and characterizing neuroplastic change is important to the recovery of function post-stroke:
  • NIBS-based neuromodulation as an adjuvant to standard therapies to promote functionally-relevant neuroplastic change
  • NIBS as an assessment tool to identify neuroplastic capacity/potential to inform clinical decision-making
Thank you

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