Targeted neuromodulation of interhemispheric circuits post-stroke

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MAKING A CONNECTION

EMORY UNIVERSITY SCHOOL OF MEDICINE

Neural Plasticity Research Laboratory
Division of Physical Therapy

Acknowledgements

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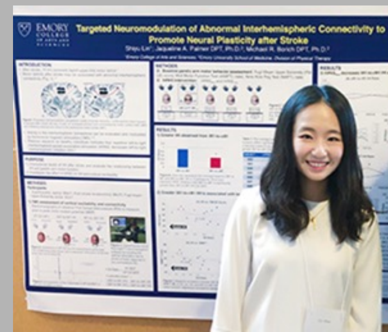
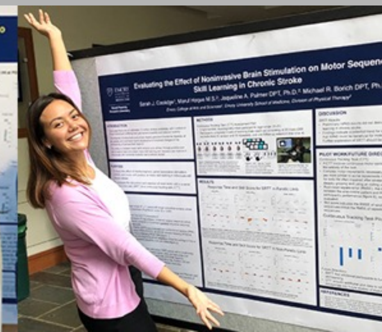
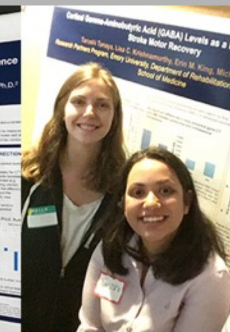
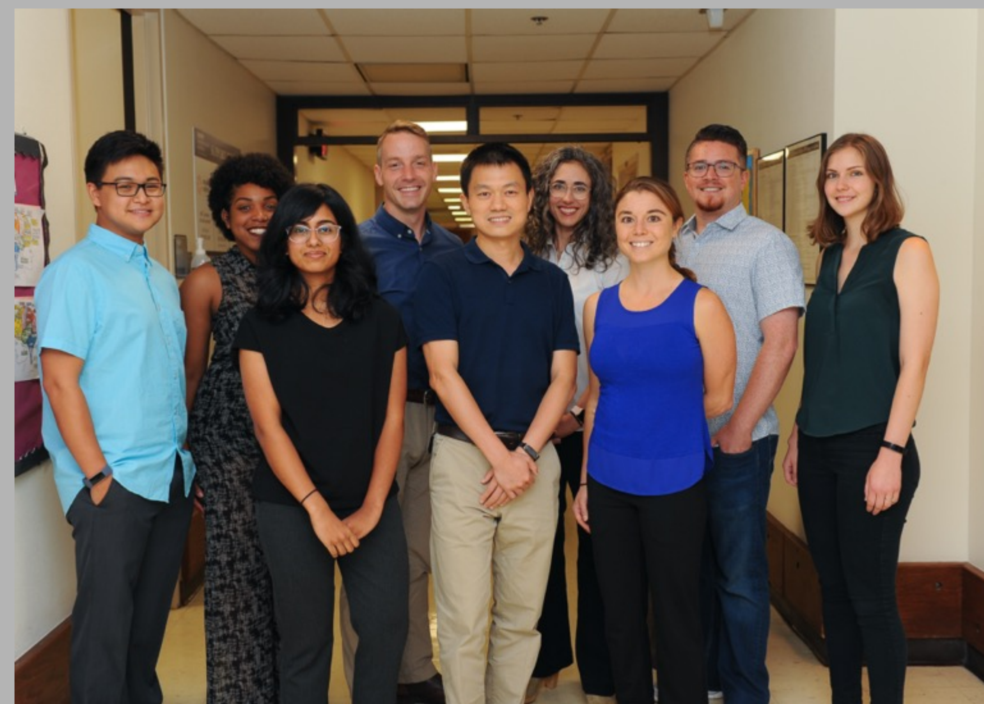
-Members of the NPRL
-Emory Center for Systems Imaging
-Research participants
-Funding sources: NIH, CORRT, AHA, NC NM4R, Foundation for PT









Members of the NPRL at Emory/Ga. Tech

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?

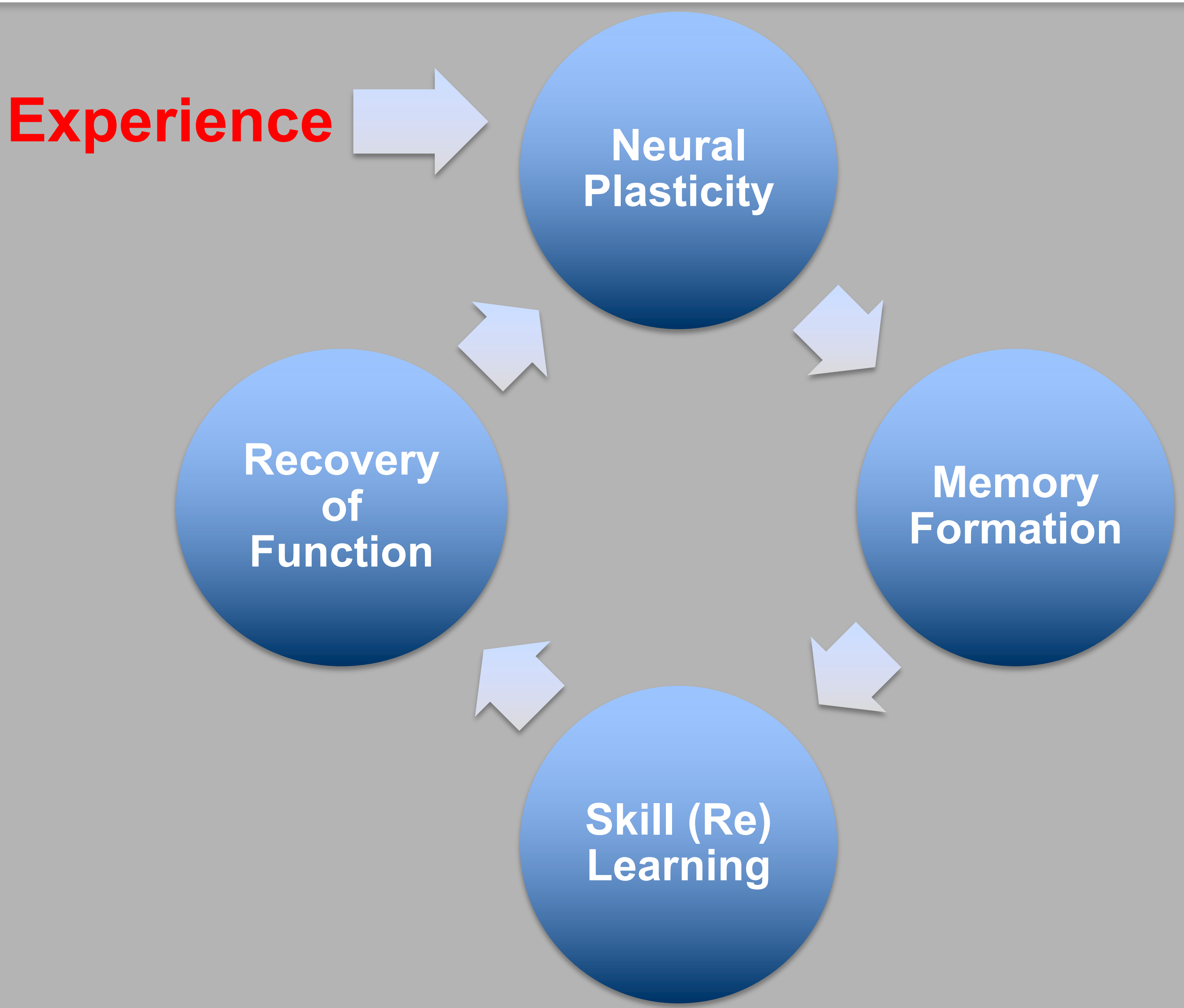
Scope of the problem

- Stroke is the leading cause of serious adult disability
- Up to 80% of have persistent motor impairment of the paretic arm
- In the next 20 years:
  - Prevalence of stroke expected to increase 20%
  - Direct medical costs projected to triple
- Stroke mortality decreasing since 2001
- Advances in rehabilitation failing to keep pace

Increasing numbers of stroke survivors with unmet rehabilitation needs

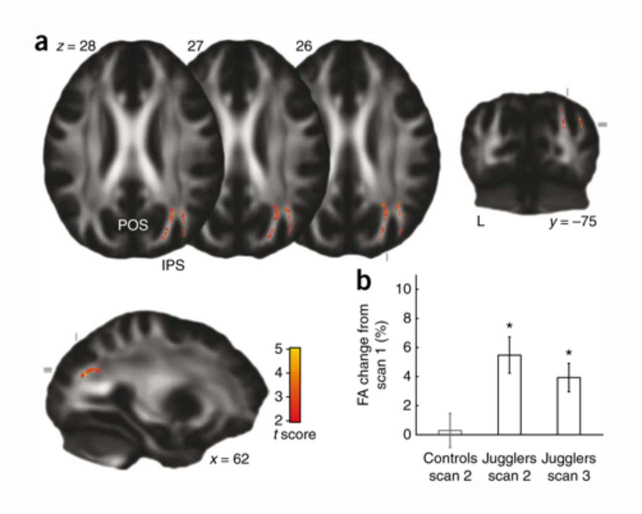
Langhorne et al., 2009; Mozaffarian et al., 2015

Organizing principle – Mechanisms underlying recovery of function

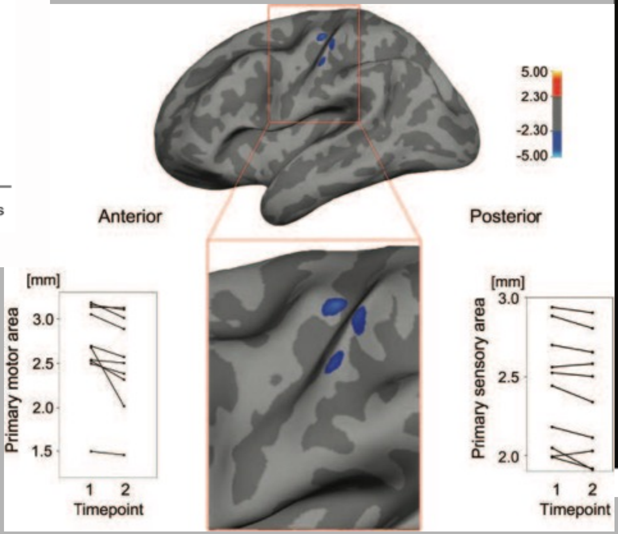


Neuroplasticity underlies (re)learning

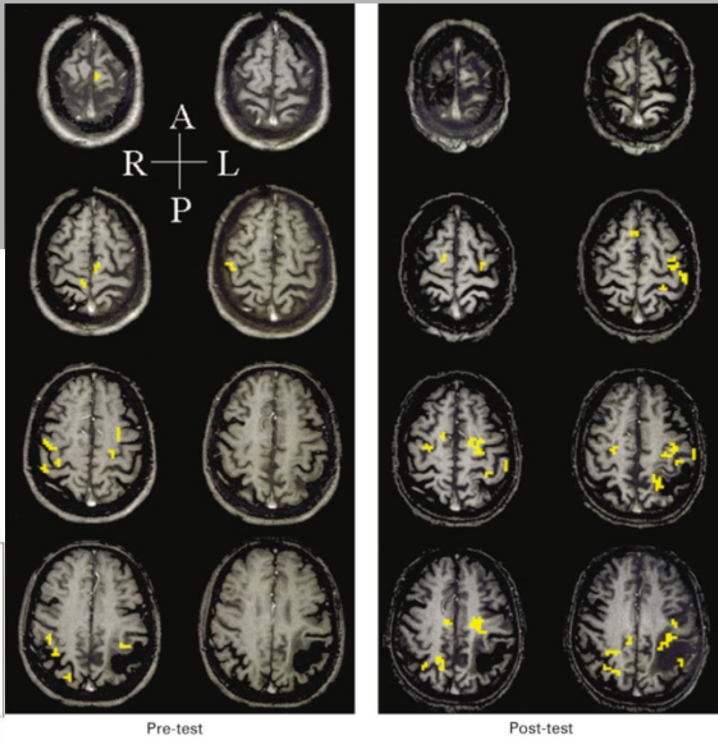
- The brain adapts and reorganizes in response to experience
- Structural and functional plasticity occurs in the human brain after injury or in the context disease



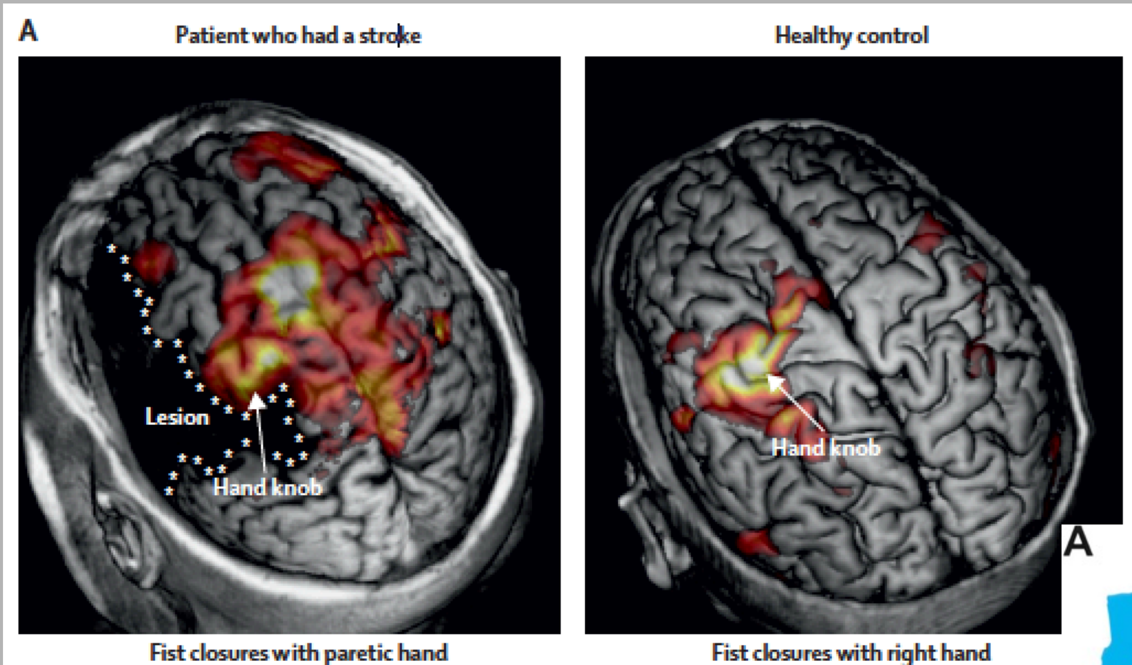
Scholz et al., 2009



Langer et al., 2012



Carey et al., 2002

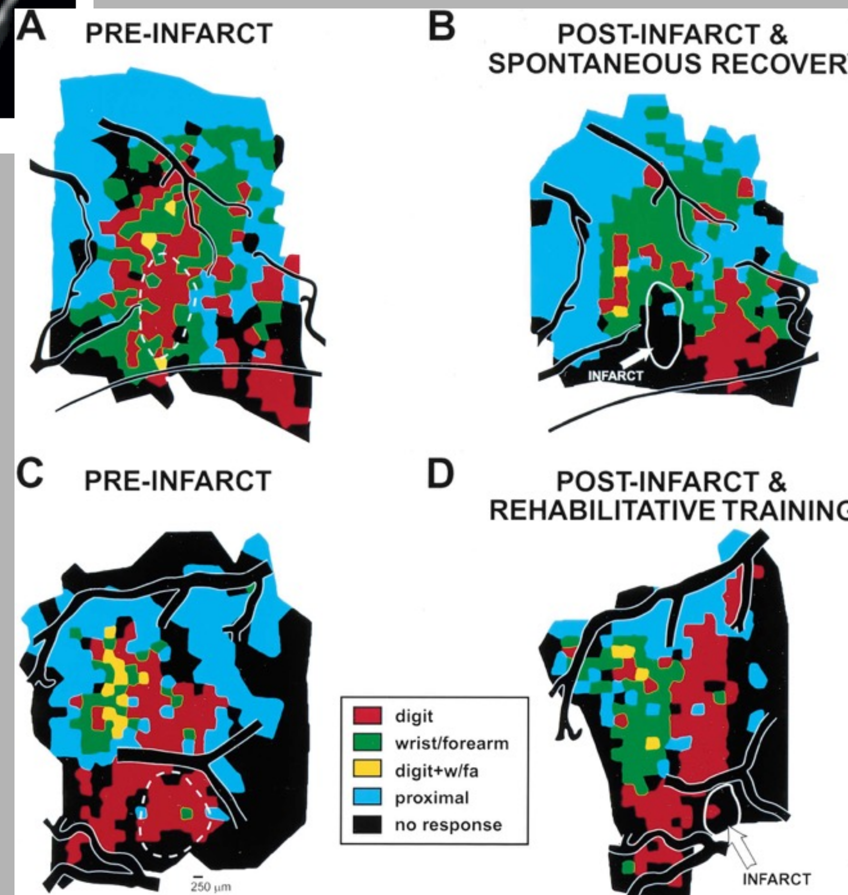


Grefkes and Fink, 2014 (adapted from Ward et al., 2007)

Stroke triggers peri-infarct and distant changes in neural activity

Rehabilitation can shape post-stroke neural activity

Nudo et al., 1997



How can we drive neural plasticity?

Table 1. Principles of experience-dependent plasticity.

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

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)

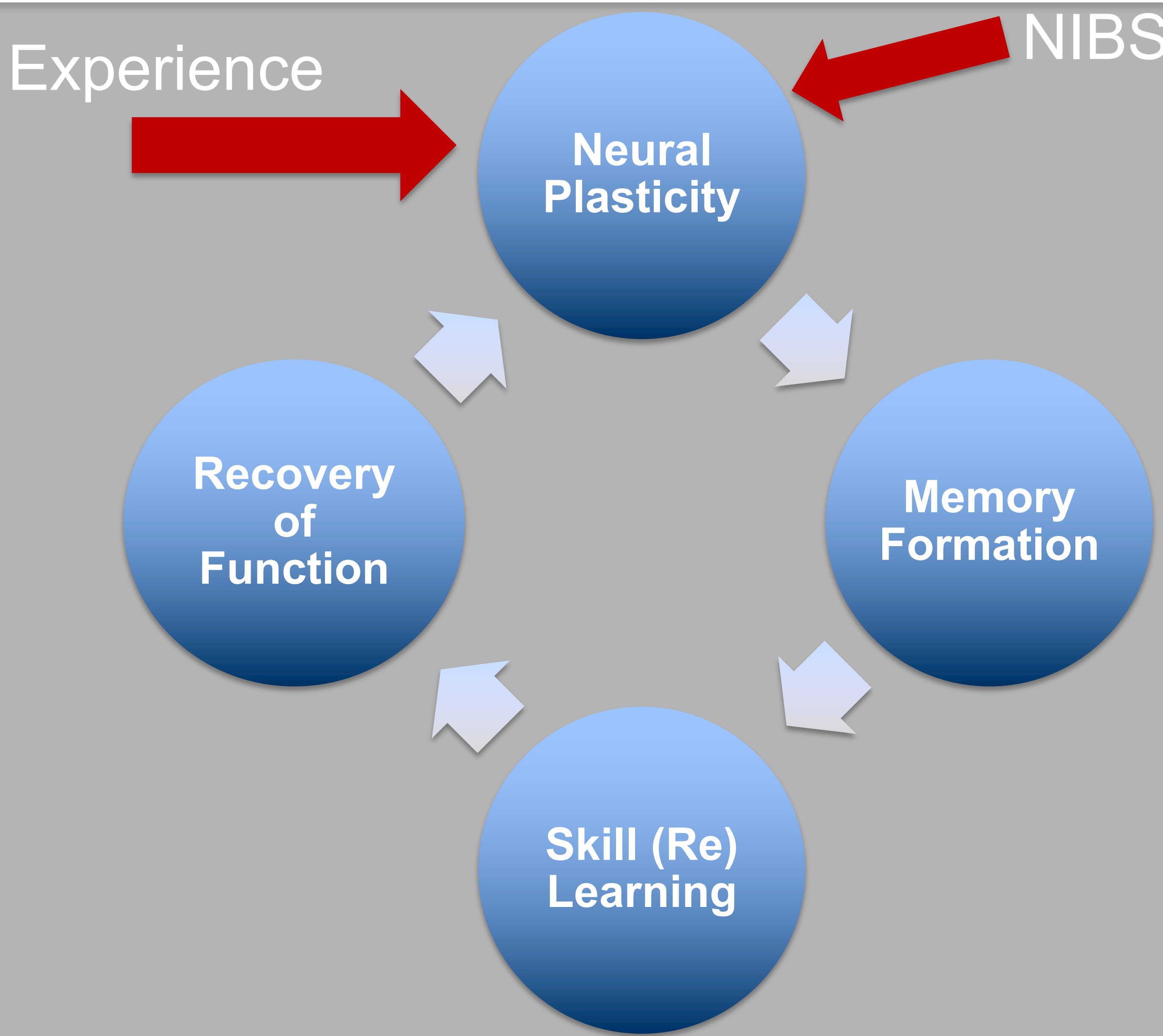
31,500 repetitions of a finger sequence over 35 days (Karni et al., 1995)

12-14 hrs x 14 days = 196 hrs of opportunity to use affected arm/hand (Taub et al., 1993; Wolf et al., 1989)

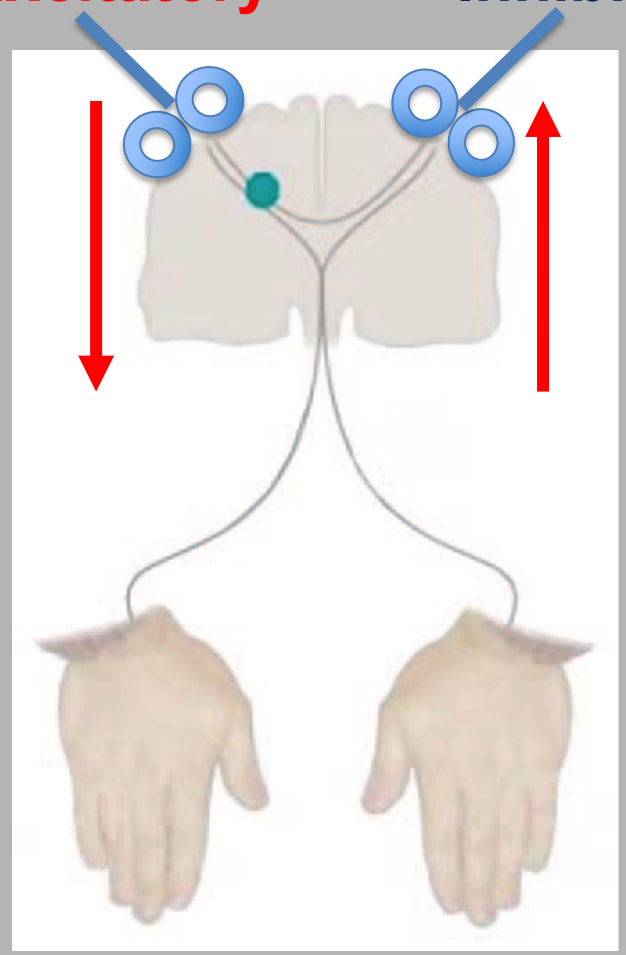
How might therapies be optimized and/or augmented?

- Novel rehabilitation technologies
  - e.g. virtual reality environments, robotics
- **Neuromodulation approaches to modify excitability and capacity for plasticity**
  - **Non-invasive brain stimulation (NIBS)**

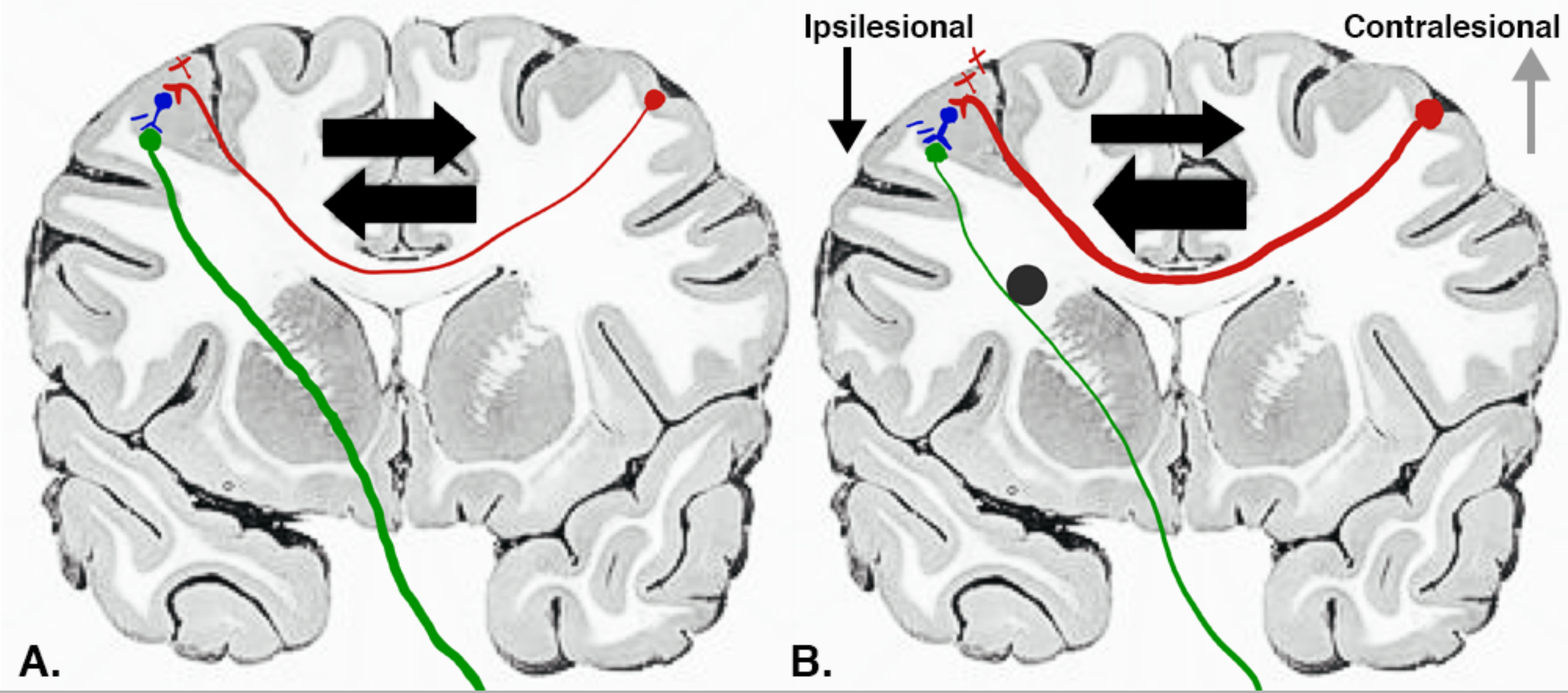
Organizing principle – Mechanisms underlying motor recovery after stroke



NIBS modulation of abnormal cortical excitability post-stroke

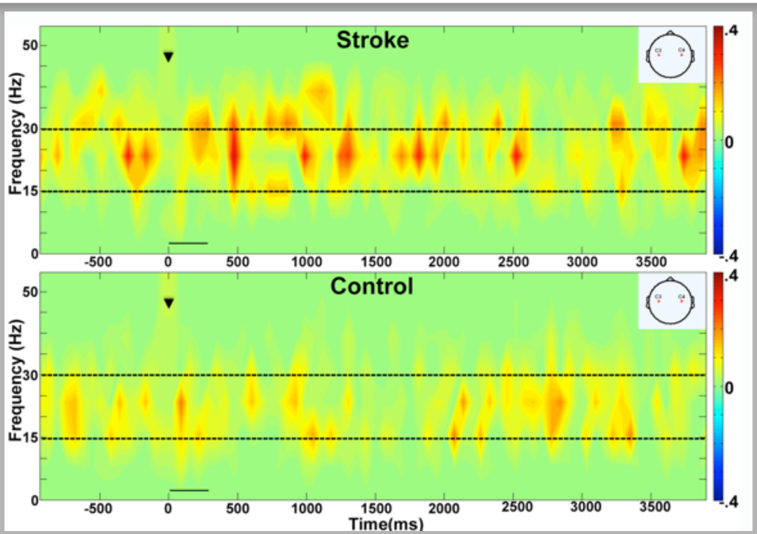


Interhemispheric imbalance model of stroke recovery

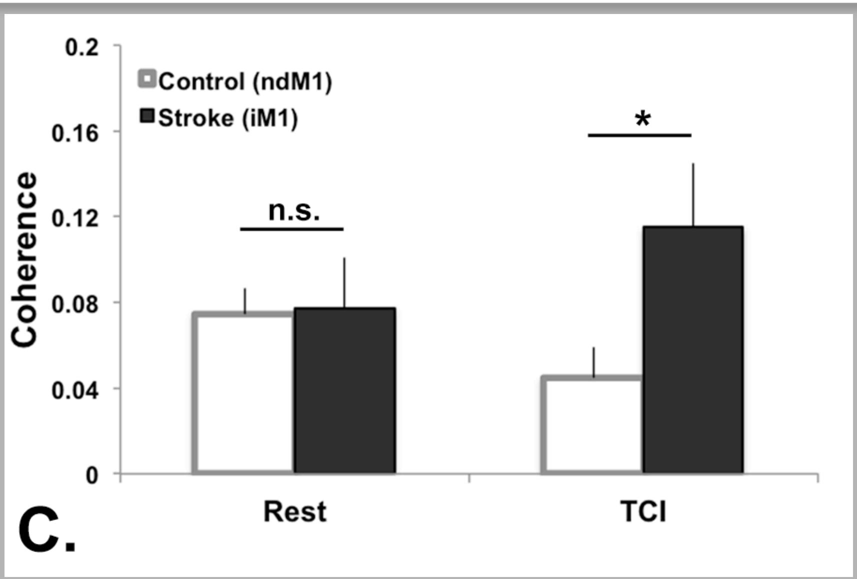


- Stroke induces local and global cortical reorganization
- *Decreased* ipsi and *increased* contralesional cortical excitability
- Mediated directly by transcallosal projections
- Depends on level of impairment, structural connectivity*

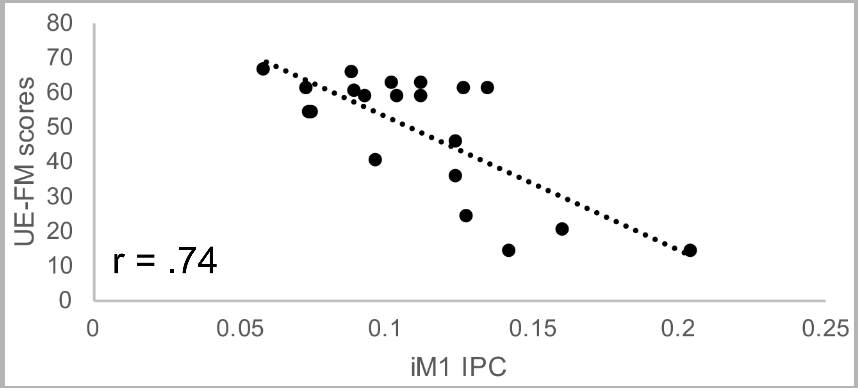
Interhemispheric interactions are abnormal in chronic stroke



1. **Greater** interhemispheric coherence in stroke



2. Only observed during an **active motor state** (TCI)



3. Those with **greater TMS-evoked** coherence had **more severe** arm motor impairment

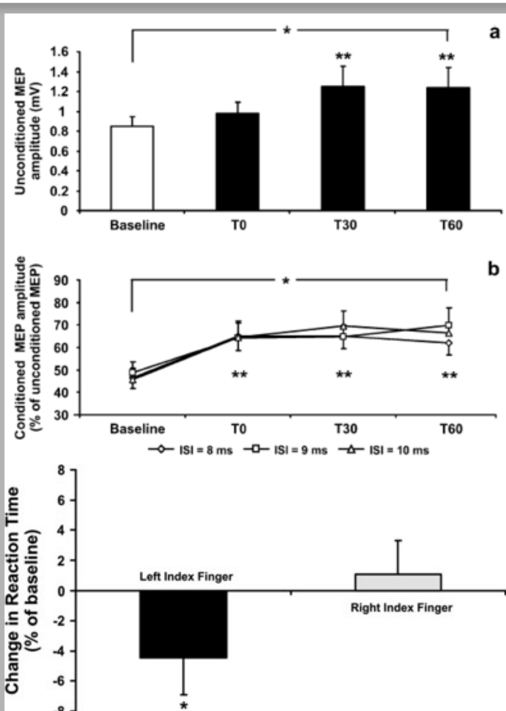
Borich, Wheaton et al., 2016; Palmer et al. 2019

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 strategies?

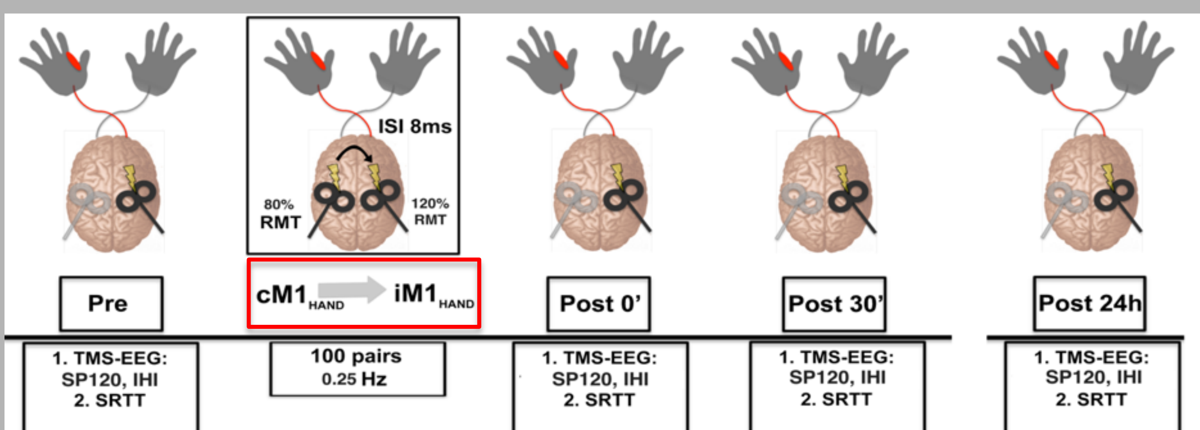
Di Pino et al., 2014, Hao et al., 2013, Elsner et al., 2013

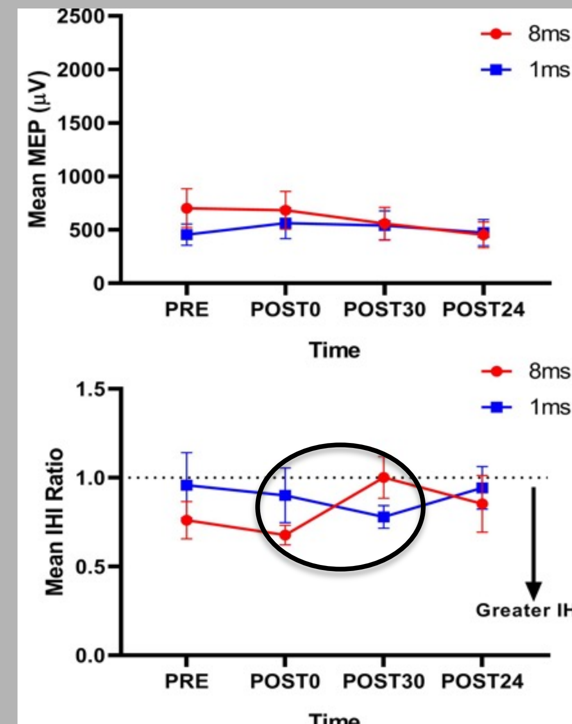
Targeting interhemispheric connections post-stroke with cortico-cortical (cc)PAS



Rizzo et al., 2009

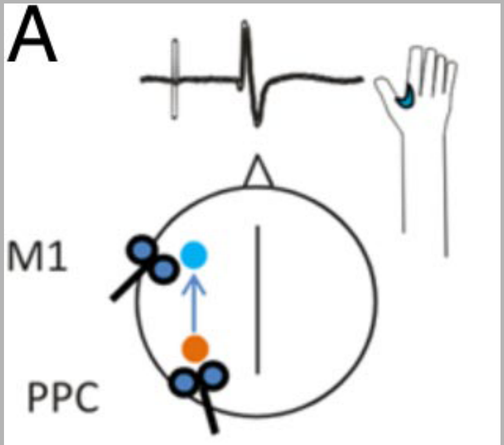
Participants (n=13):
All MEP+
Mean age (y): 65±11
Mean PSD (mo): 65±56
Mean UEFM (/66): 52±10



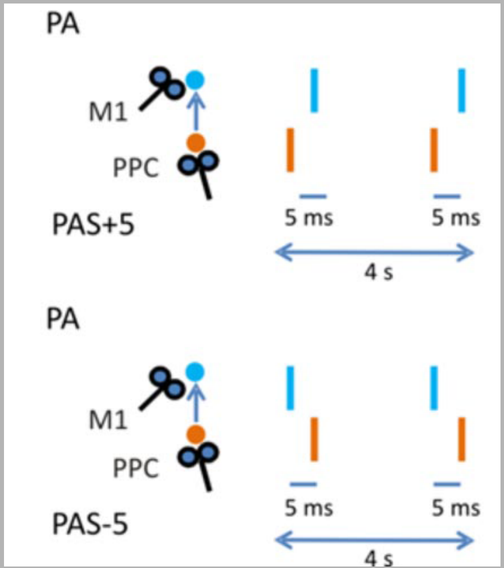


Borich et al., 2018, Lin, in prep

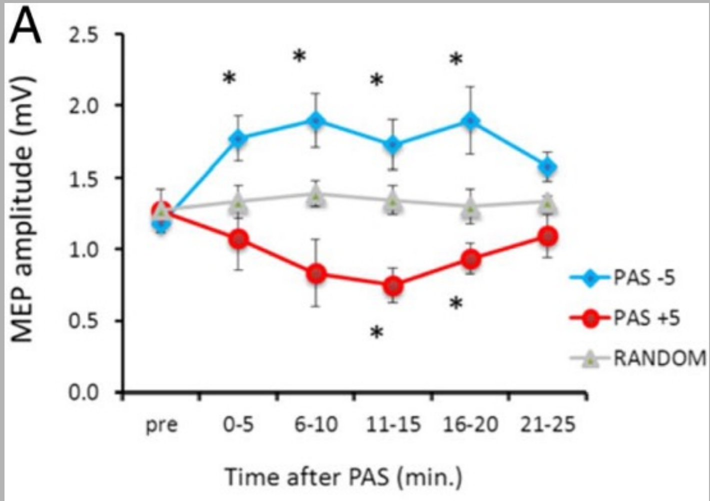
Plasticity induction in cortico-cortical circuits is time-dependent

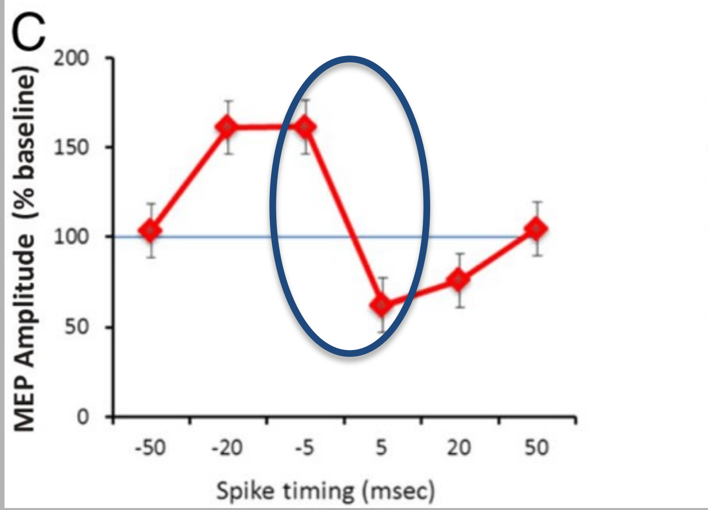


M1 excitability modulated by stimulation of a directly connected cortical region (PPC)



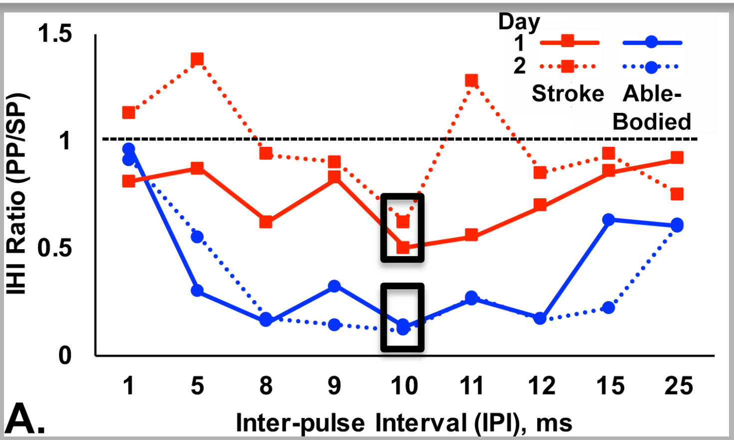
****Sign of excitability change dependent on interstimulus interval**

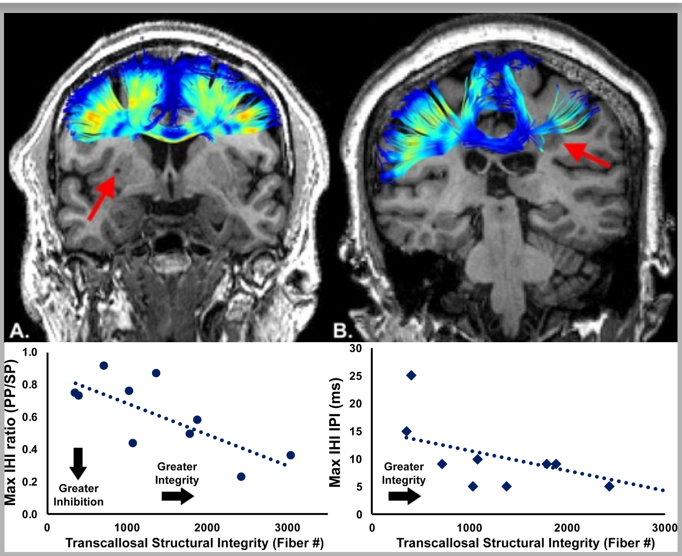


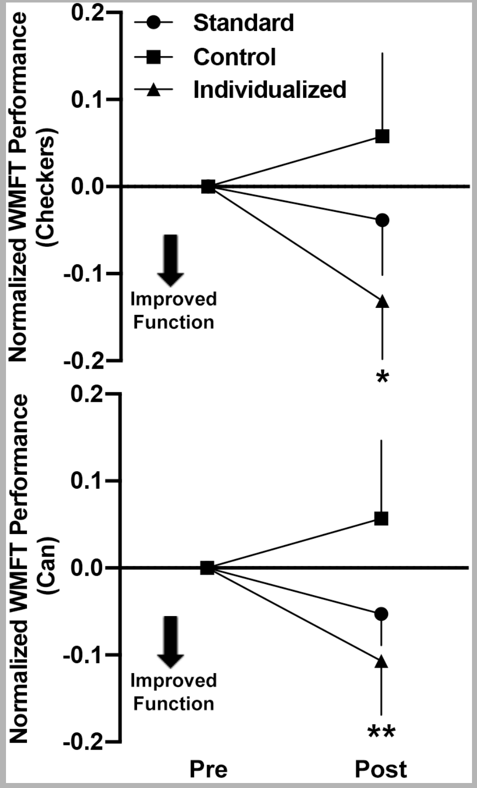


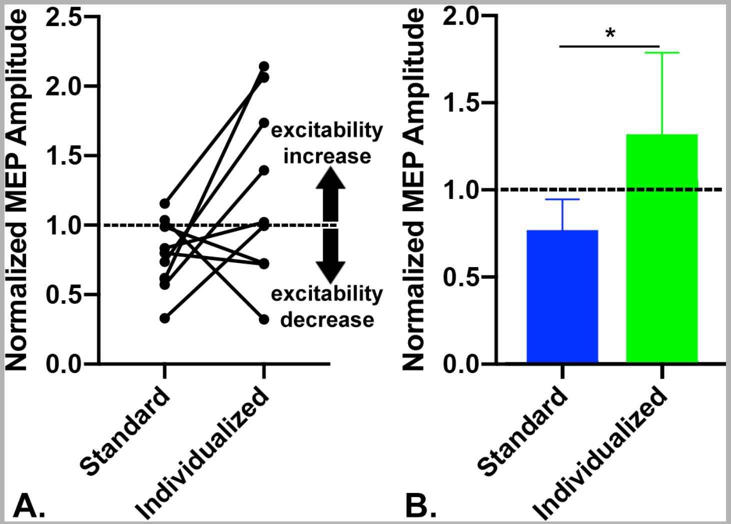
Koch et al., 2013

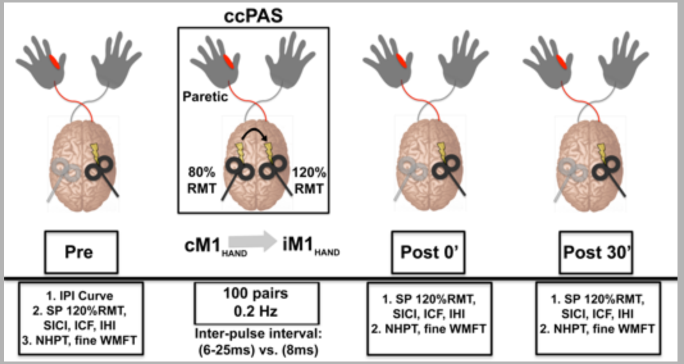
Individualizing ISI to increase ccPAS effects in stroke











Borich, Lin, Palmer, in prep

Summary

- Characterizing and targeting neuroplastic change is important to the recovery of function post-stroke
- PAS can induce systems-level LTP/LTD-like plasticity
- Cortico-cortical PAS can target plasticity induction in specific circuits
- Important to account for inter-individual variability using relevant biomarkers to optimize NIBS delivery

Acknowledgements

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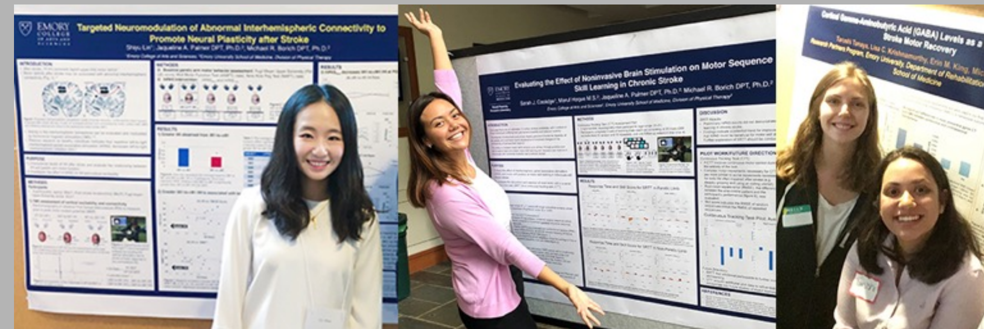

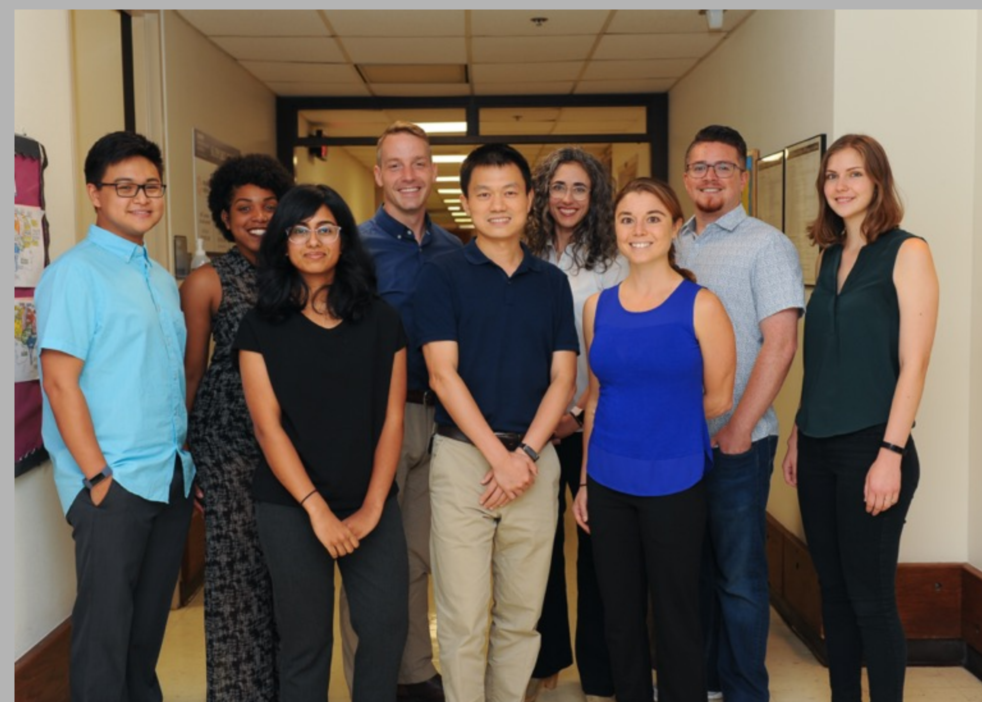

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Thank you

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