Non-invasive Brain Stimulation for Neurorehabilitation after Spinal Cord Injury:
what we know and where we're going

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Outline

Introduction

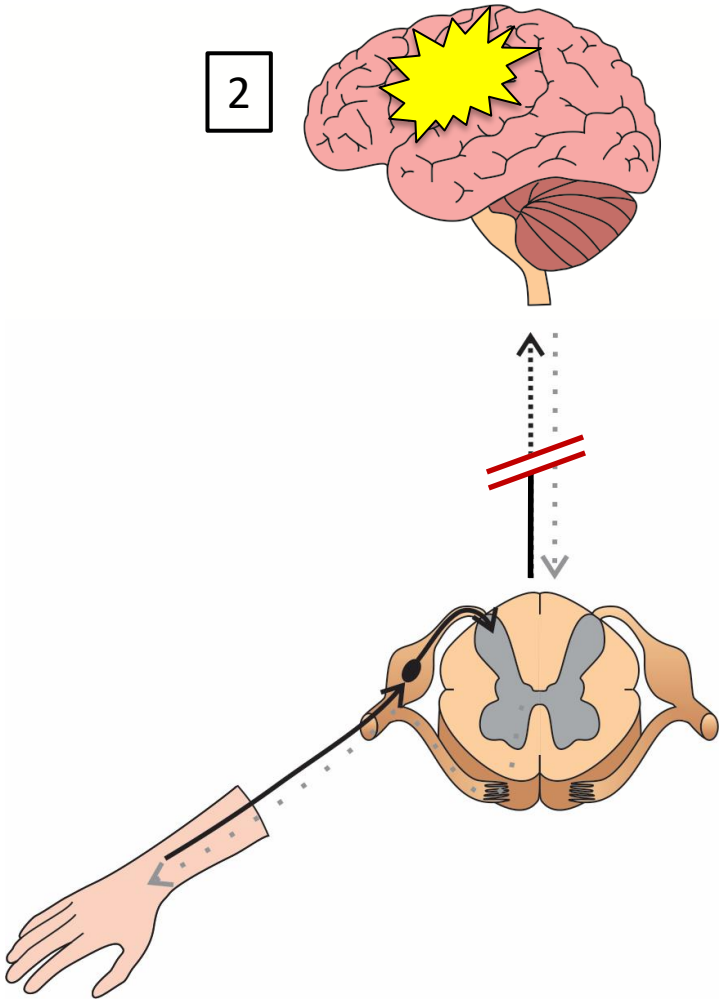
- Maladaptive cortical plasticity after SCI
- Reversing maladaptive cortical plasticity
- Using NIBS as a neuromodulation tool
  - Type of stimulation
  - Stimulation montage

Neilsen SCIRTS Fellowship Project

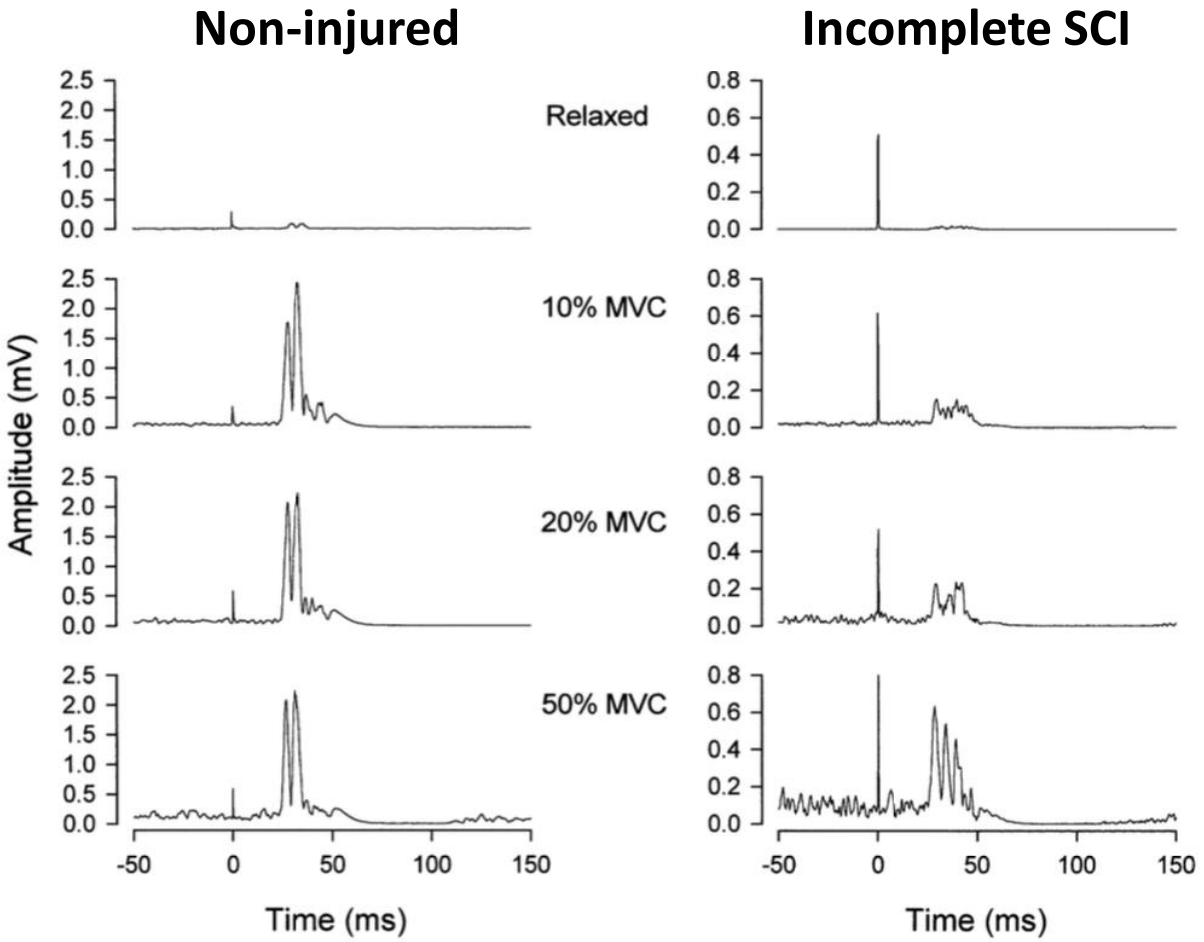
- Design
- Results to date
- Variability
- Challenges measuring corticospinal excitability

Moving forward

Maladaptive Cortical Plasticity Post-SCI



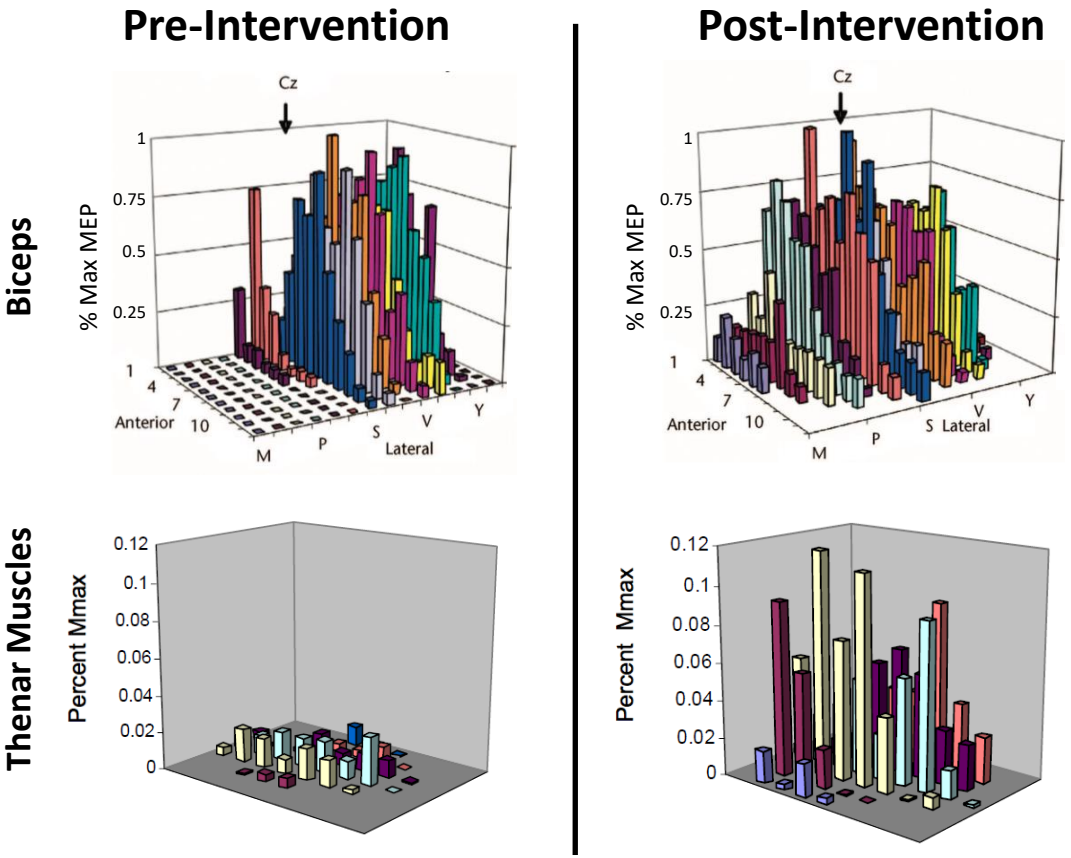
Reduced Corticospinal Excitability Post-SCI



Davey et al., Exp Brain Res,1999

Reversing Maladaptive Cortical Plasticity

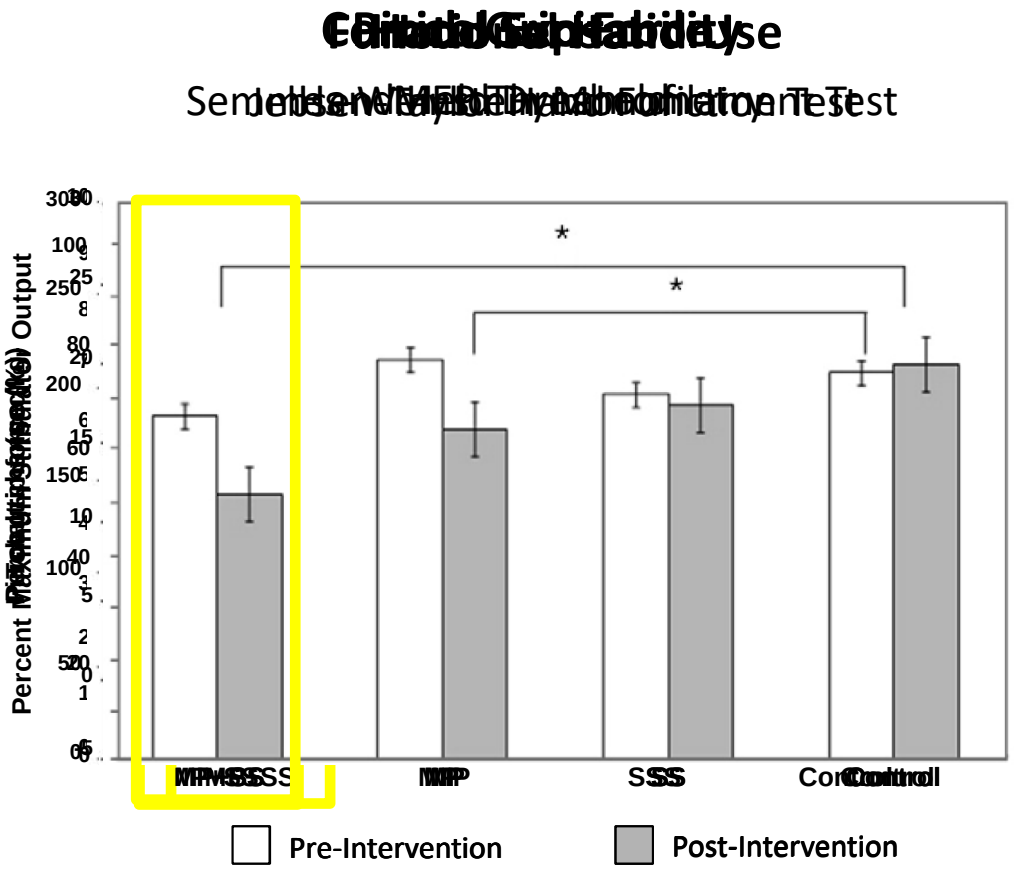
- Chronic, cervical SCI
- Upper extremity massed practice + somatosensory stimulation
- 3 weeks: 2 hrs/day, 5x/week



Hoffman & Field-Fote: Phys Ther, 2007 (top), Top Spinal Cord Rehabil, 2013 (bottom)

Efficacy of Combined Interventions

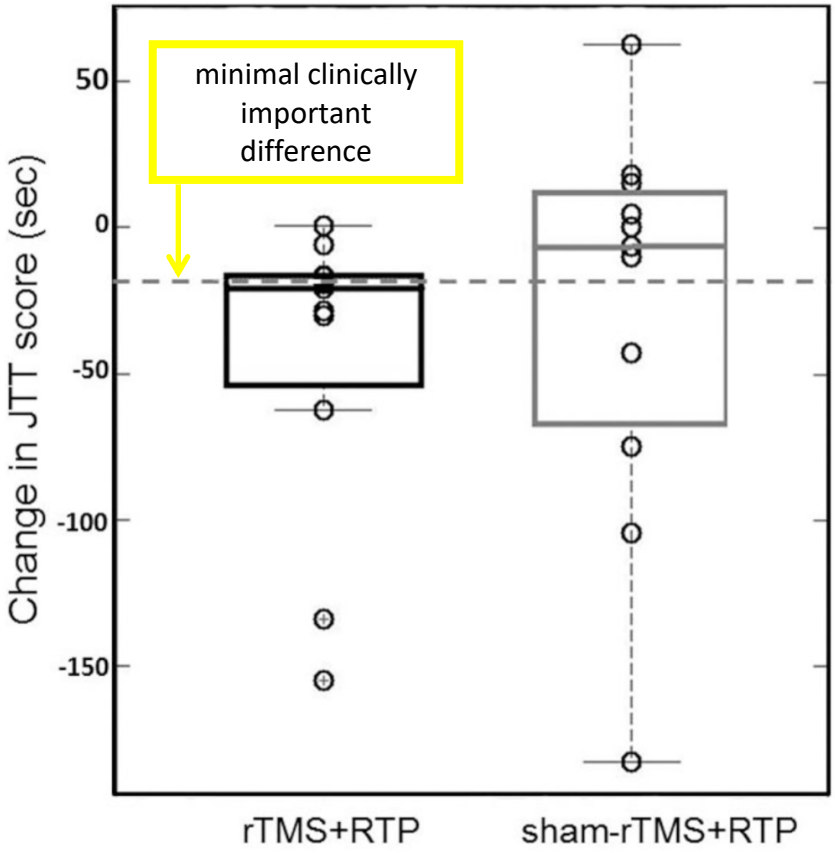
- Chronic, cervical SCI
- 4 groups:
  - massed practice + somatosensory stimulation (MP+SS)
  - Massed practice (MP)
  - Somatosensory stimulation (SS)
  - No intervention (control)
- 3 weeks: 2 hrs/day, 5x/week



Beekhuizen & Field-Fote, Arch Phys Med Rehabil, 2008

Cortical Stimulation Improves Motor Function

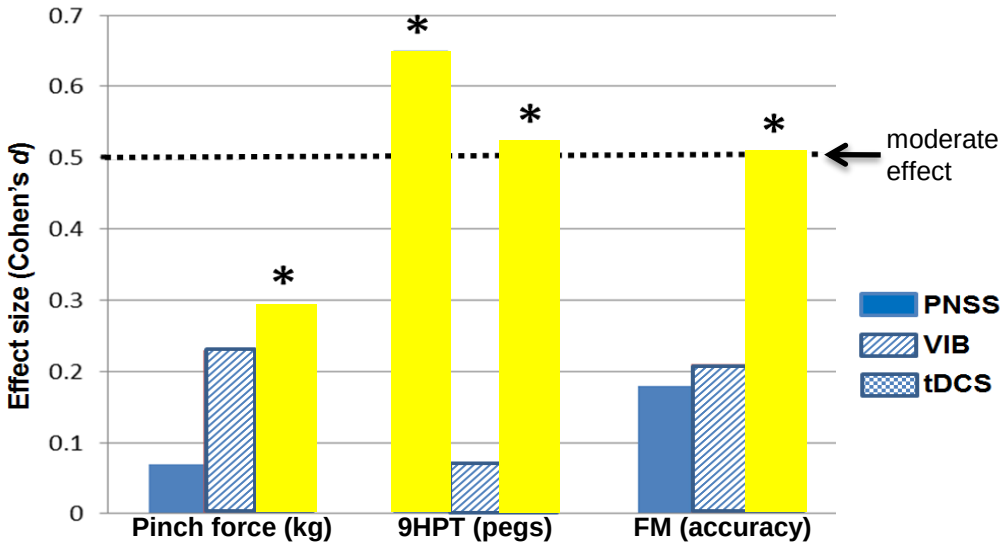
- Chronic, cervical SCI
- Randomized crossover
- rTMS or sham-rTMS + upper extremity repetitive task practice
- 3 days: ~11 min/day



Gomes-Osman & Field-Fote, J Neurol Phys Ther, 2015

Cortical vs. Peripheral Stimulation for Improving Motor Function

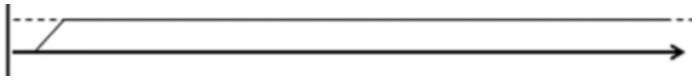
- Chronic, cervical SCI
- Randomized crossover
- Clinically accessible stimulation + upper extremity massed practice
  - PNSS of median nerve
  - Vibration over distal tendon of flexor carpi radialis
  - tDCS of corticomotor area controlling weaker hand
- Single 30-min session



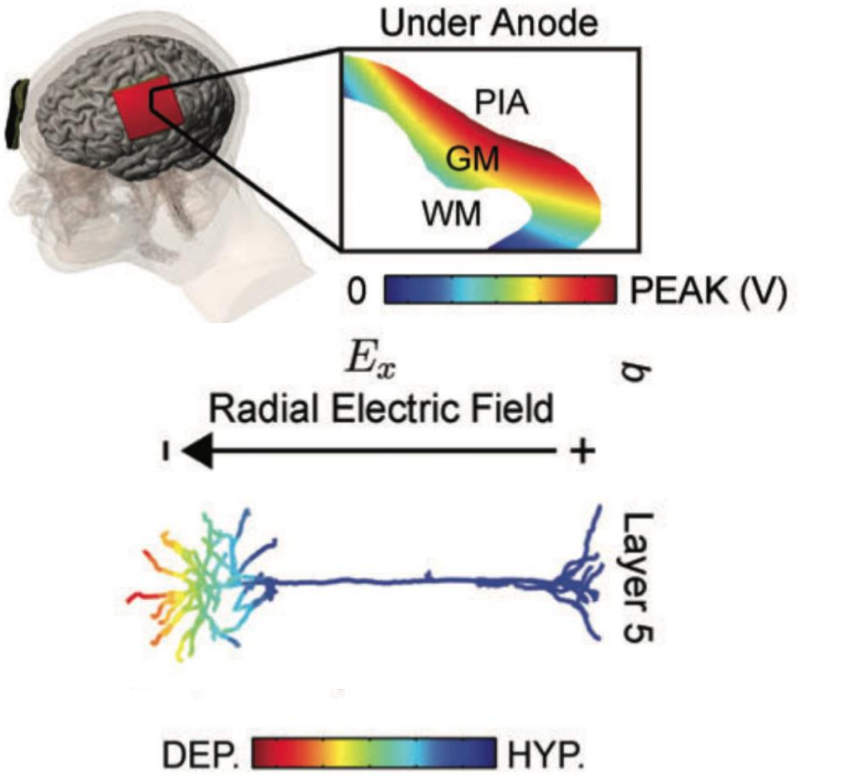
Gomes-Osman & Field-Fote, Clin Rehabil, 2014

Transcranial Direct Current Stimulation (tDCS) for Enhancing Cortical Excitability

- Monophasic, continuous stimulation

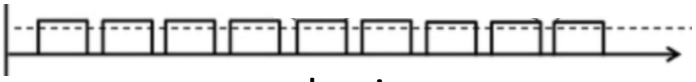


- Anode placed over target region
- **Somatic** depolarization of layer V cortical neurons
  - Ca^{2+} and Na^{+} channel dependent
- Enhanced glutamateric & reduced gabaergic neurotransmission



Rahman et al., J Physiol, 2013

Moving Beyond tDCS:
Other Clinically-Accessible Forms of NIBS

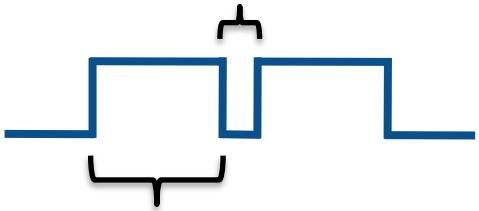
NIBS type	Waveform	Parameters
tDCS	 monophasic, continuous	✓ stimulus intensity ✓ **polarity (anodal/cathodal)**
tACS	 biphasic, sinusoidal	✓ stimulus intensity ✓ **frequency**
tRNS	 biphasic, random	✓ stimulus intensity range ✓ **frequency range**
tPCS	 monophasic, square	✓ stimulus intensity ✓ polarity (anodal/cathodal) ✓ **pulse duration** ✓ **inter-pulse interval**

Waveforms adapted from: Jaberzadeh & Zoghi, Basic Clin Neurosci, 2013; Jaberzadeh et al., PLOS One, 2015

tPCS Effects on Corticospinal Excitability

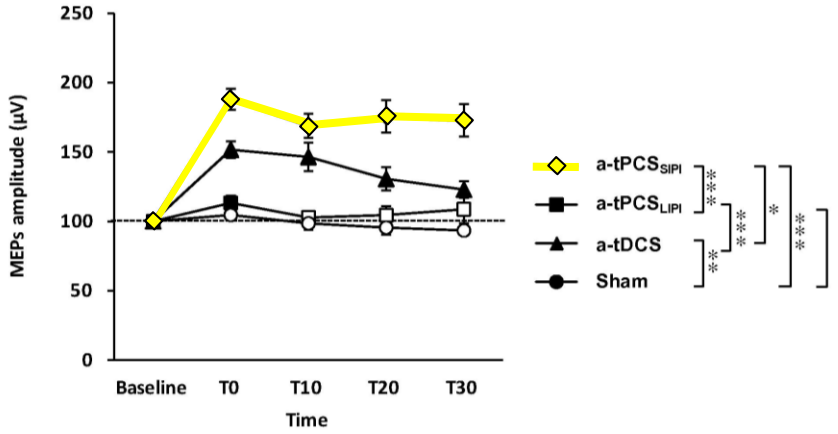
Inter-pulse interval (IPI):

- **short – 50 ms**
- long – 650 ms

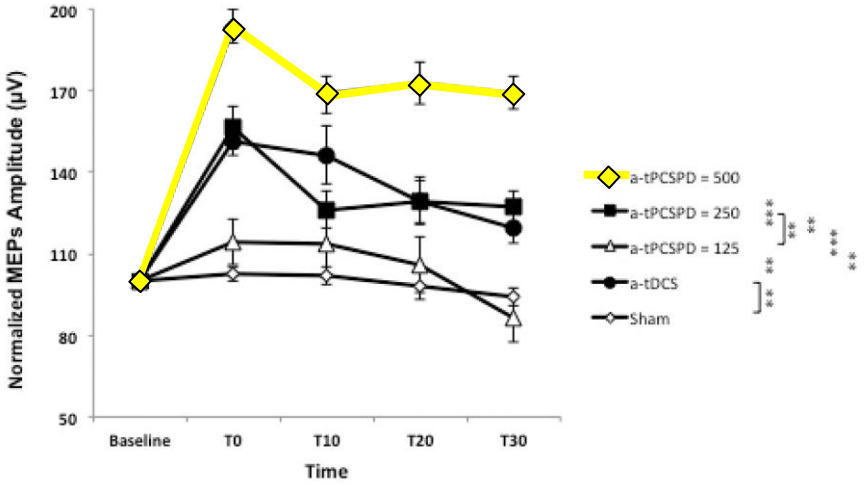


Pulse duration (PD):

- **500 ms**
- 250 ms
- 100 ms

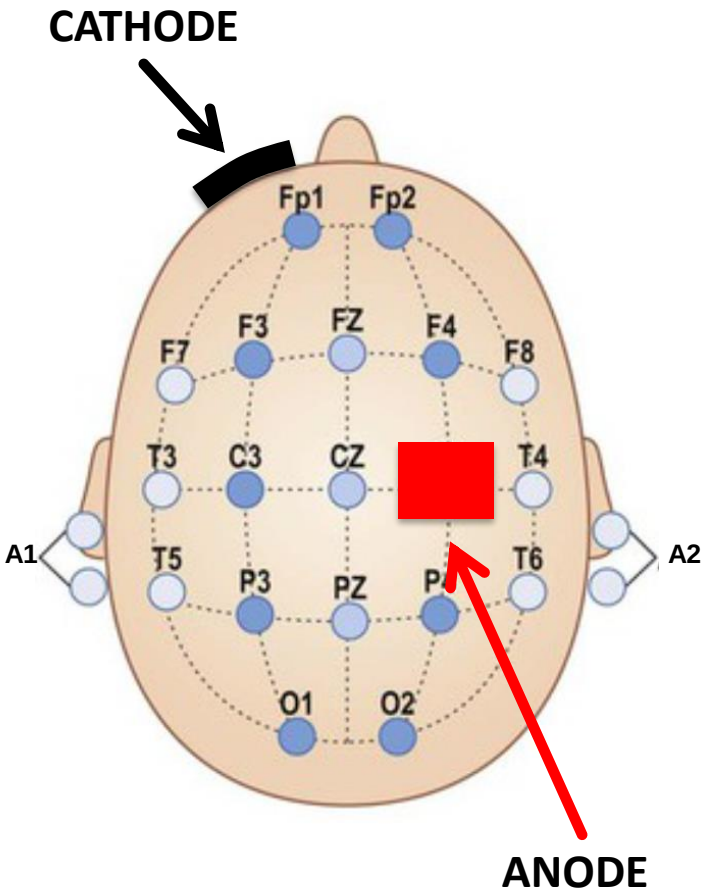


Jaberzadeh et al., Clin Neurophysiol, 2014



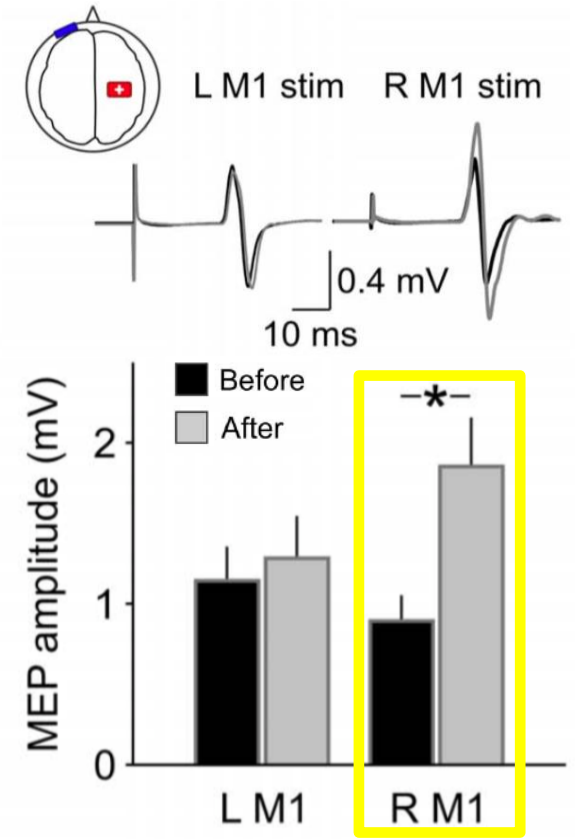
Jaberzadeh et al., PLOS One, 2015

NIBS: Importance of Electrode Montage



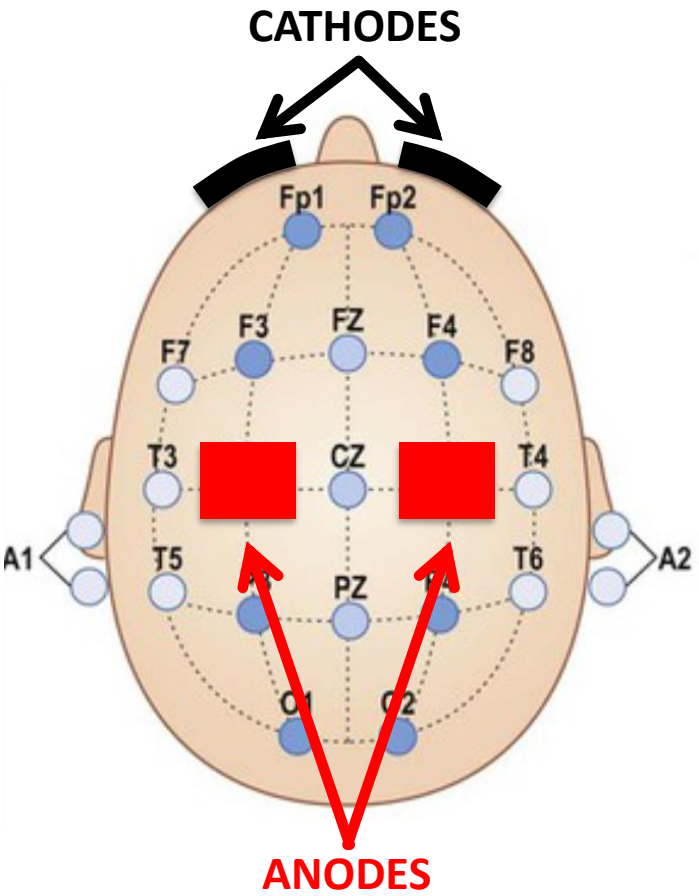
Adapted from www.clinicalgate.com/epilepsy-8

a-tDCS: 1.5 mA, 15 min



Tazoe et al., PLOS One, 2014

NIBS: Importance of Electrode Montage



Adapted from www.clinicalgate.com/epilepsy-8

Optimizing NIBS for SCI Neurorehabilitation: Neilsen SCIRTS Postdoctoral Fellowship

Stimulation type:

Specific Aim 1. Quantify the effects of two different forms of non-invasive brain stimulation (tDCS, tPCS) and a sham-control on ***strength and motor control*** in persons with tetraplegia.

Specific Aim 2. Quantify the effects of two different forms of non-invasive brain stimulation (tDCS, tPCS) and a sham-control on ***corticospinal excitability*** in persons with tetraplegia.

Montage:

Specific Aim 3. Determine the effects of two non-invasive brain stimulation electrode montages, **uni-and bihemispheric**, on strength, motor control and corticospinal excitability in persons with tetraplegia.

Project Design

Design	Randomized, crossover study
Intervention	Unihemispheric tDCS → **Functional Task Practice** Bihemispheric tDCS → Unihemispheric tPCS → Bihemispheric tPCS → Sham stimulation →  
Assessments	Upper extremity motor control, strength and corticospinal excitability

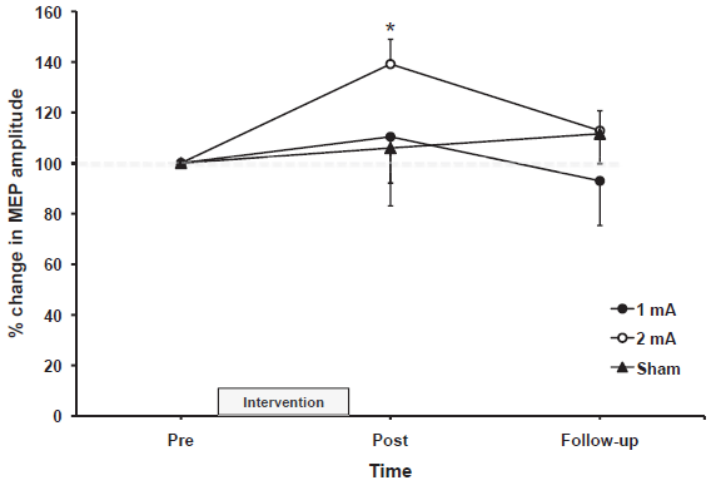
Study Recruitment

- Participants with cervical SCI, >3 months post-injury
- Bilateral impairments in hand function
- Minimal (trace) intrinsic hand function

Participant No.	Gender	Age (Years)	Time Since Injury	AIS	Neurological Injury Level	More Impaired UE
1	M	59	4 Years, 4 Months	D	C4	L
2	M	50	30 Years, 1 Months	D	C5	R
3	M	71	11 Years, 0 Months	C	C4	L
4	F	21	1 Years, 1 Months	D	C4	L
5	M	57	8 Years, 6 Months	D	C5	L
6	M	50	23 Years, 2 Months	D	C5	L
7	M	44	19 Years, 10 Months	D	C5	L
8	F	39	0 Years, 4 Months	B	C7	L
9	F	53	1 Years, 1 Months	C	C7	R
10	M	46	2 Years, 2 Months	D	C4	L

Stimulation Parameters

- Electrode size: 35cm^2
- Stimulation intensity: 2 mA
- Stimulation duration: 20 min
- Unihemispheric stimulation
  - anode placed over the motor cortex area controlling more impaired UE (C3 or C4)
  - cathode placed over contralateral supraorbital area
- Bihemispheric stimulation
  - two anodes placed over C3 and C4
  - two cathodes placed bilaterally over the supraorbital areas



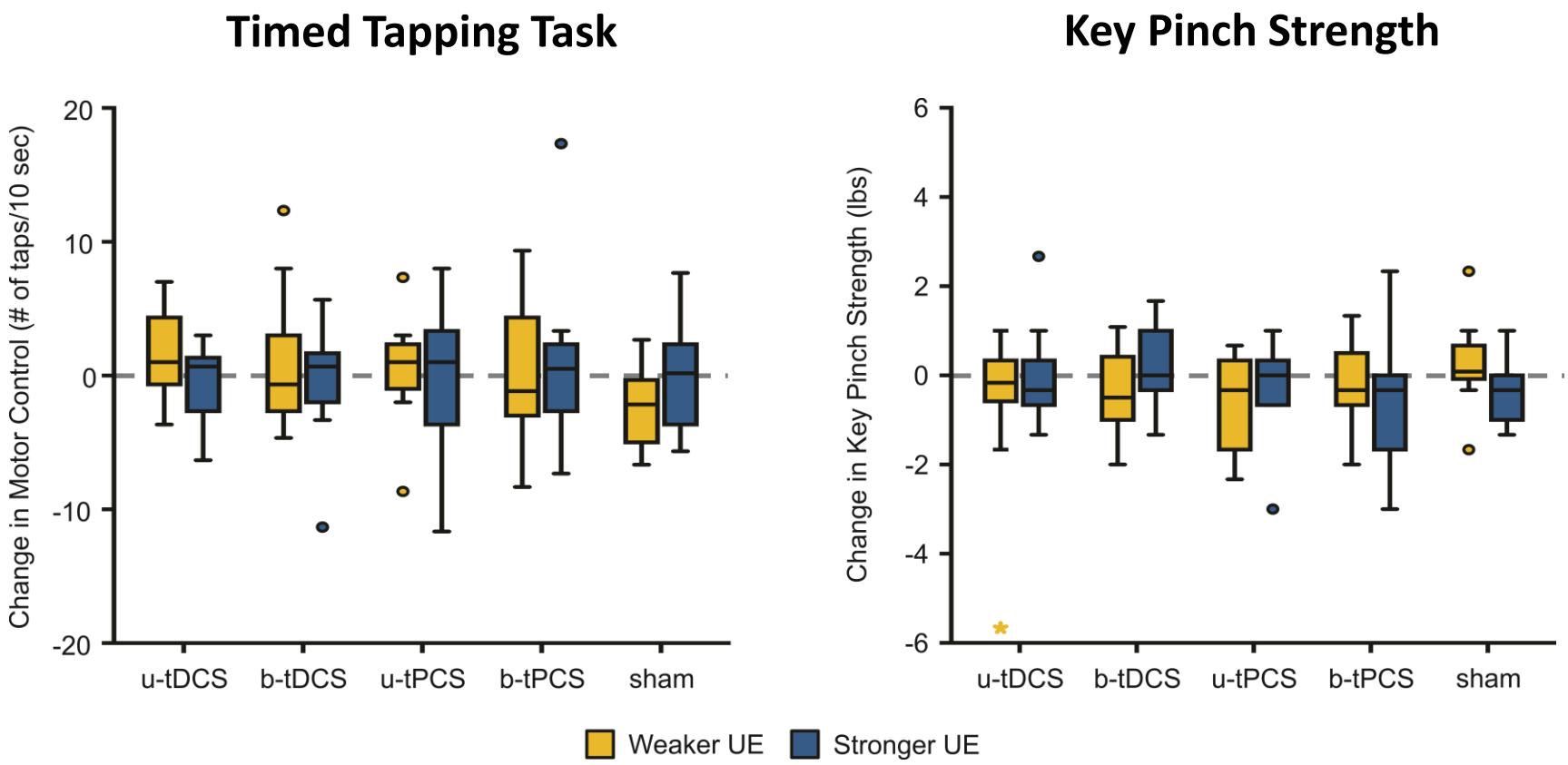
Murray et al., Arch Phys Med Rehabil, 2015

Stimulation Tolerance

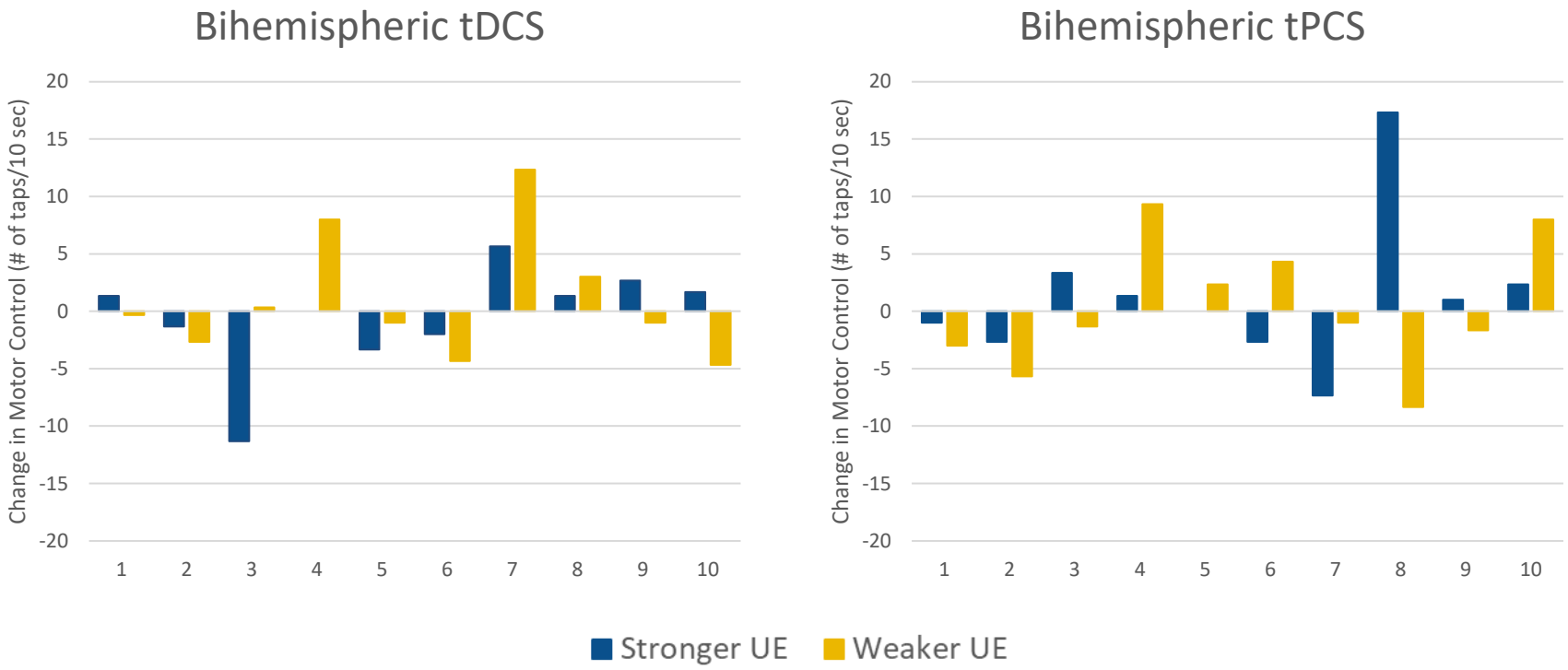
- Stimulation was well-tolerated by all participants
- Most commonly reported sensations: itching, tingling and burning
- Phosphenes (flashing/bright spots) are a known potential side effect of tPCS due to activation of the retina/visual cortex or associated pathways

	u-tDCS	b-tDCS	u-tPCS	b-tPCS	sham
Itching	8	4	5	5	7
Tingling	2	2	4	3	2
Warmth/Heat	0	1	2	2	2
Headache	0	0	0	0	0
Burning	3	2	1	3	1
Pain	0	0	0	0	0
Flashing/Bright spots	0	0	3	5	1
Metallic/Iron Taste	0	0	0	2	0
Fatigue/Decreased Alertness	0	0	0	0	0
Distracted Attention	2	0	2	1	1

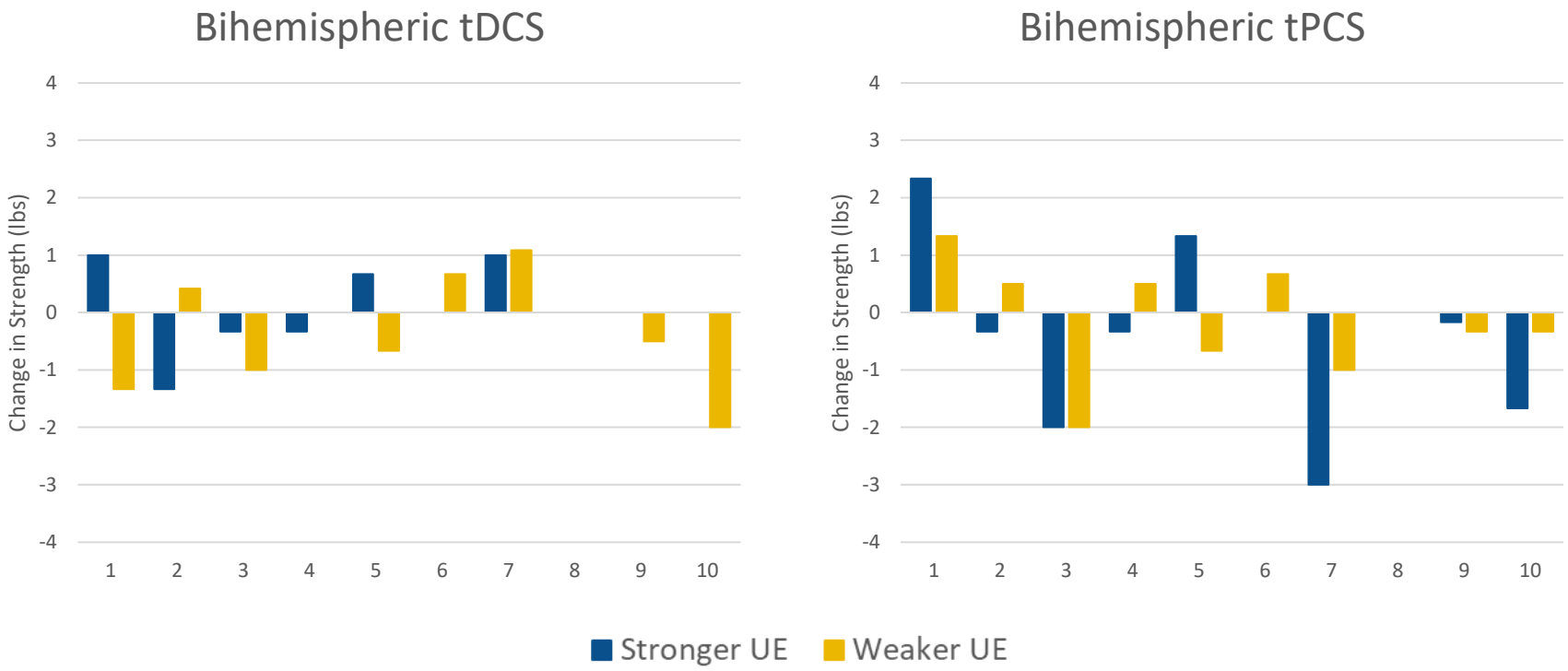
Changes in Motor Control and Strength



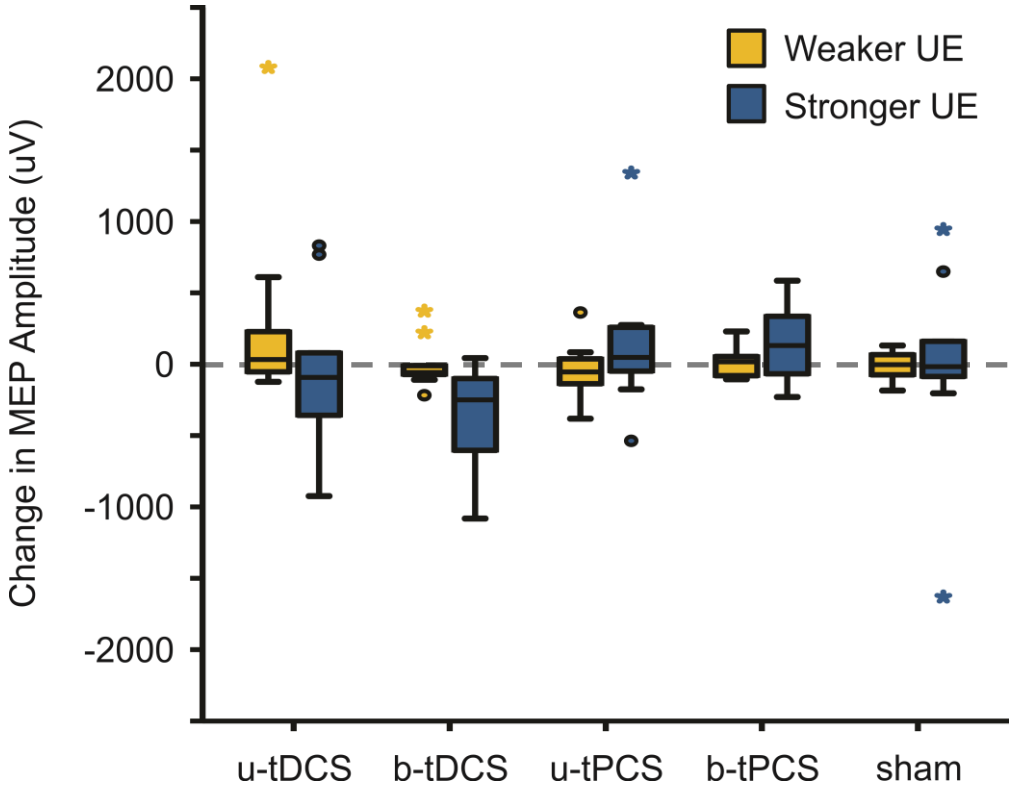
Changes in Motor Control: Interindividual Variability



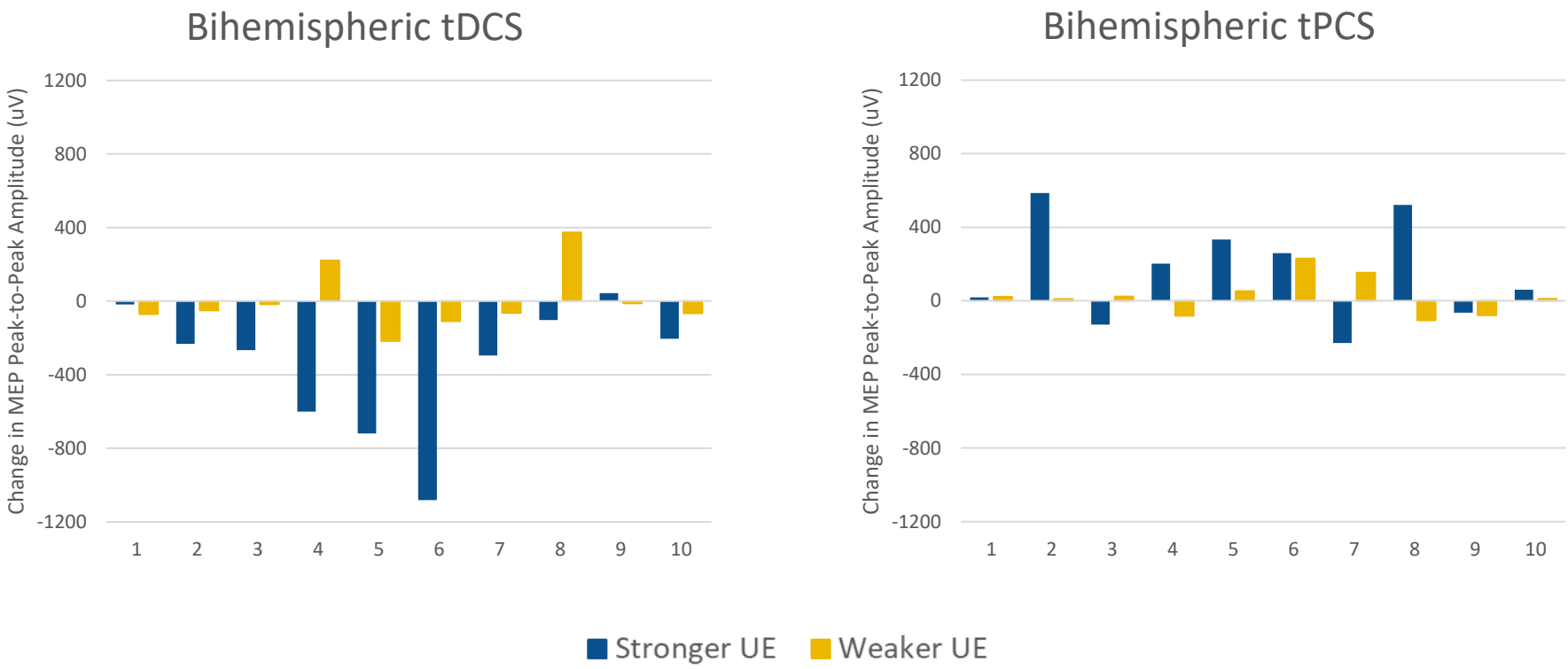
Changes in Strength: Interindividual Variability



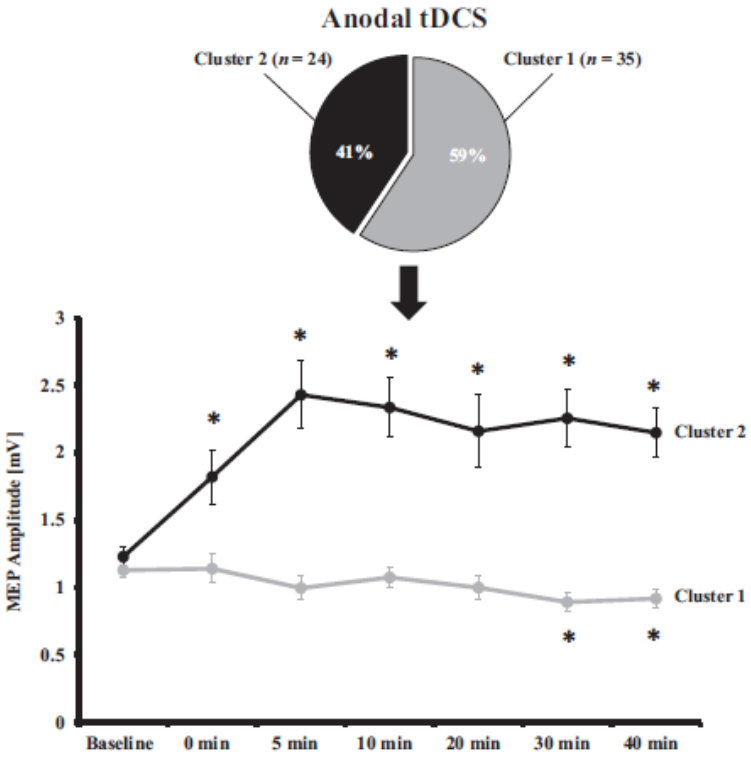
Changes in Cortical Excitability

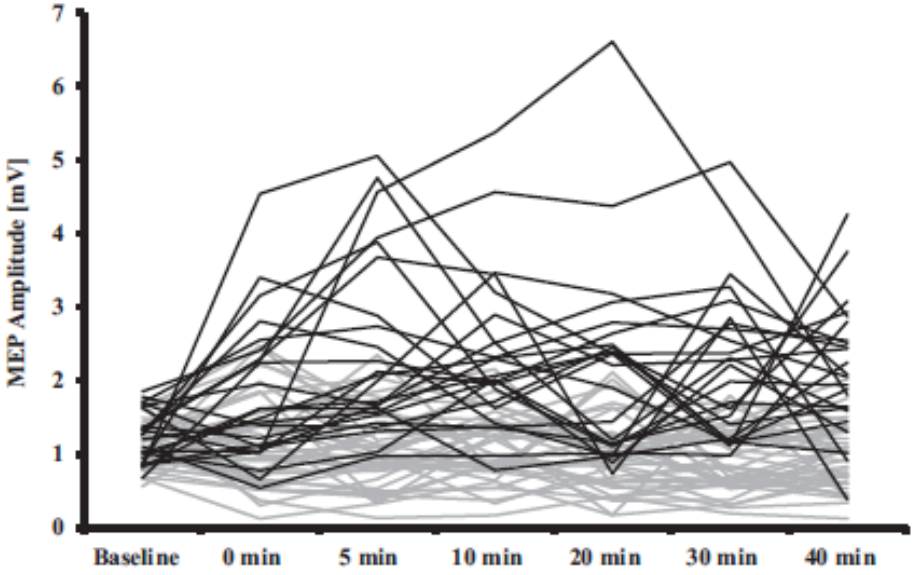


Changes in Cortical Excitability: Interindividual Variability



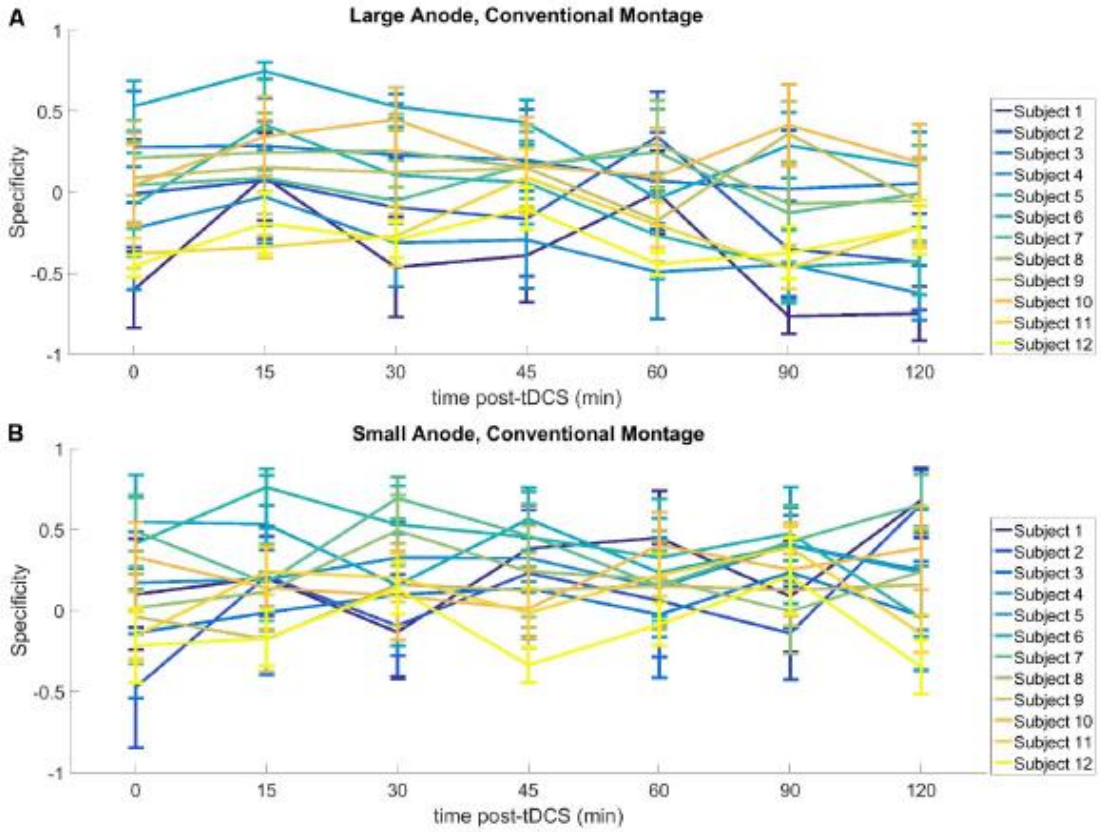
NIBS Responsiveness: Interindividual Variability (non-injured participants)





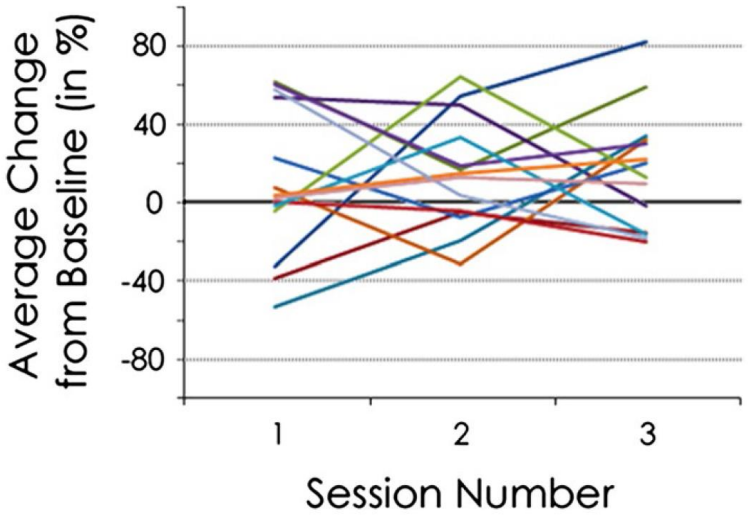
Strube et al., Physiol Rep, 2016

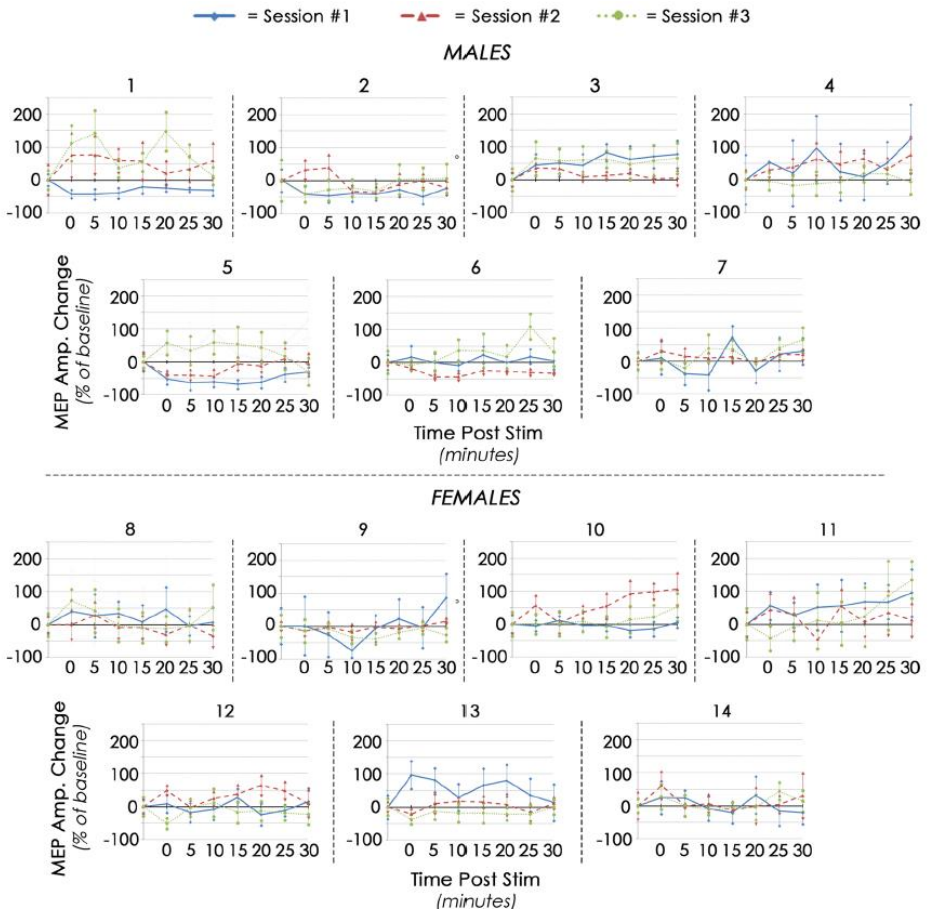
NIBS Responsiveness: Interindividual Variability (non-injured participants)



Foerster et al., Front Neurosci, 2018

NIBS Responsiveness: A Dichotomy or More Complex Phenomenon? (non-injured participants)

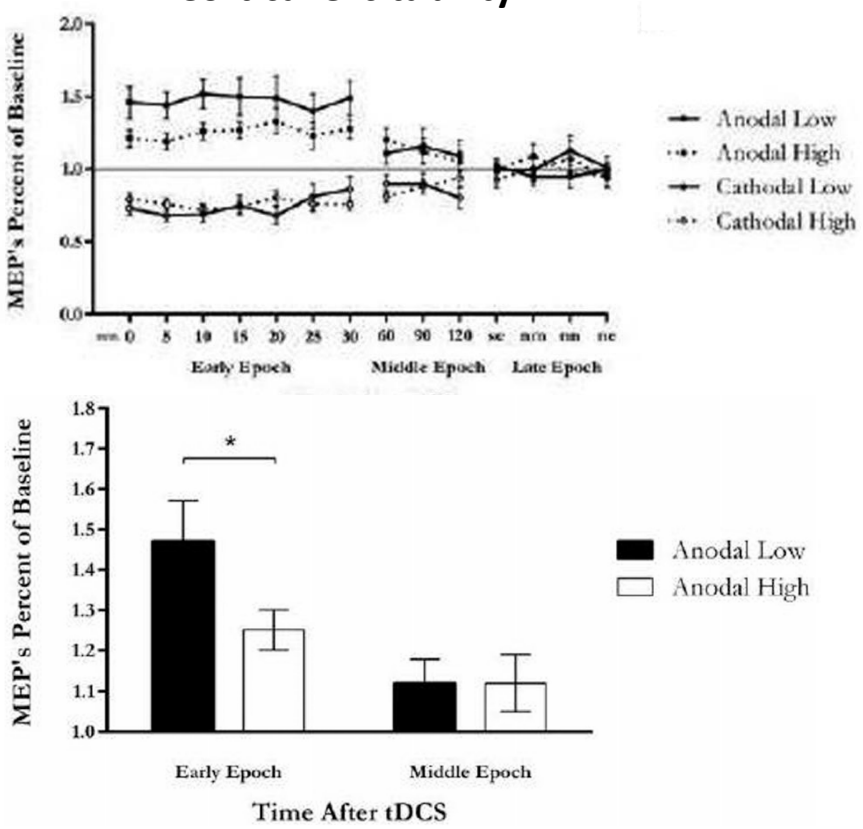




Horvath et al., Exp Brain Res, 2016

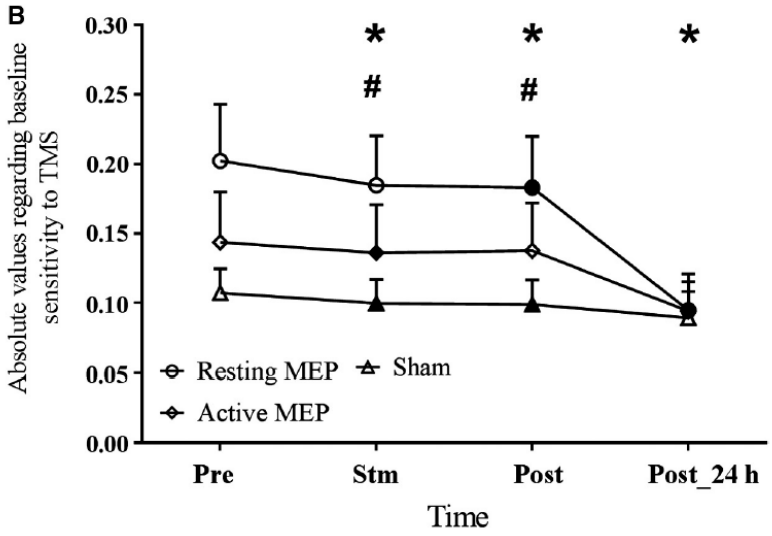
Using TMS Responsiveness to Address Interindividual Variability (non-injured participants)

Cortical excitability



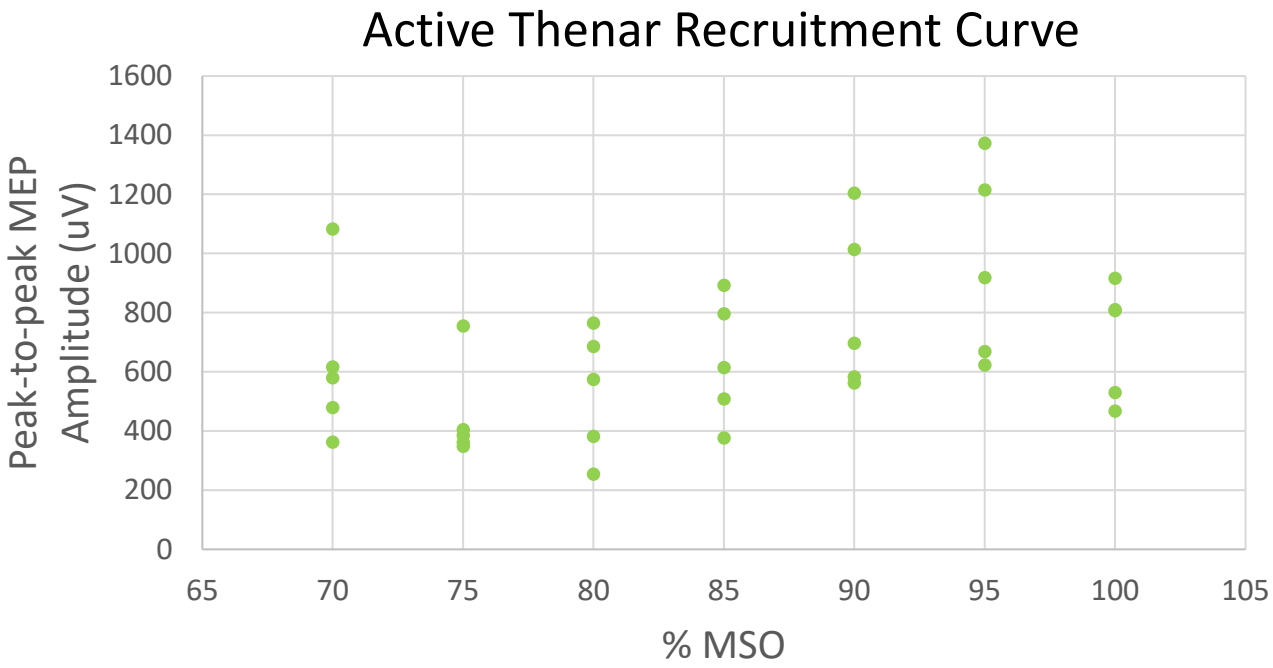
Labruna et al., Brain Stimul, 2016

Visuo motor task performance

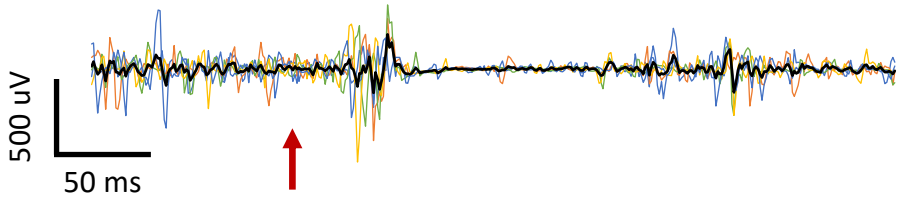


Foerster et al., Eur J Neurosci, 2018

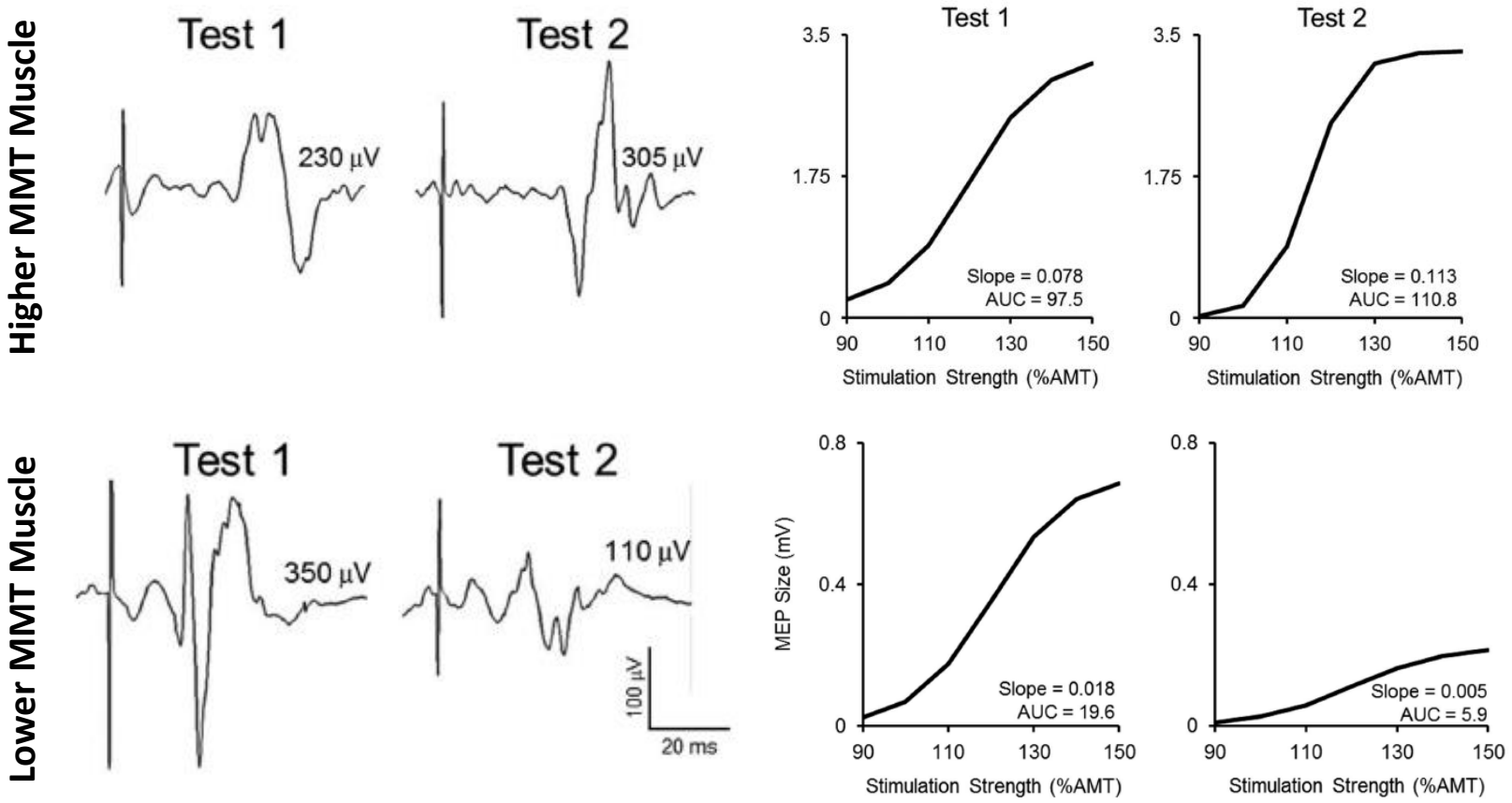
Measuring Cortical Excitability in Persons with SCI: MEP Variability & Amplitude



Active Thenar MEPs, 100% MSO

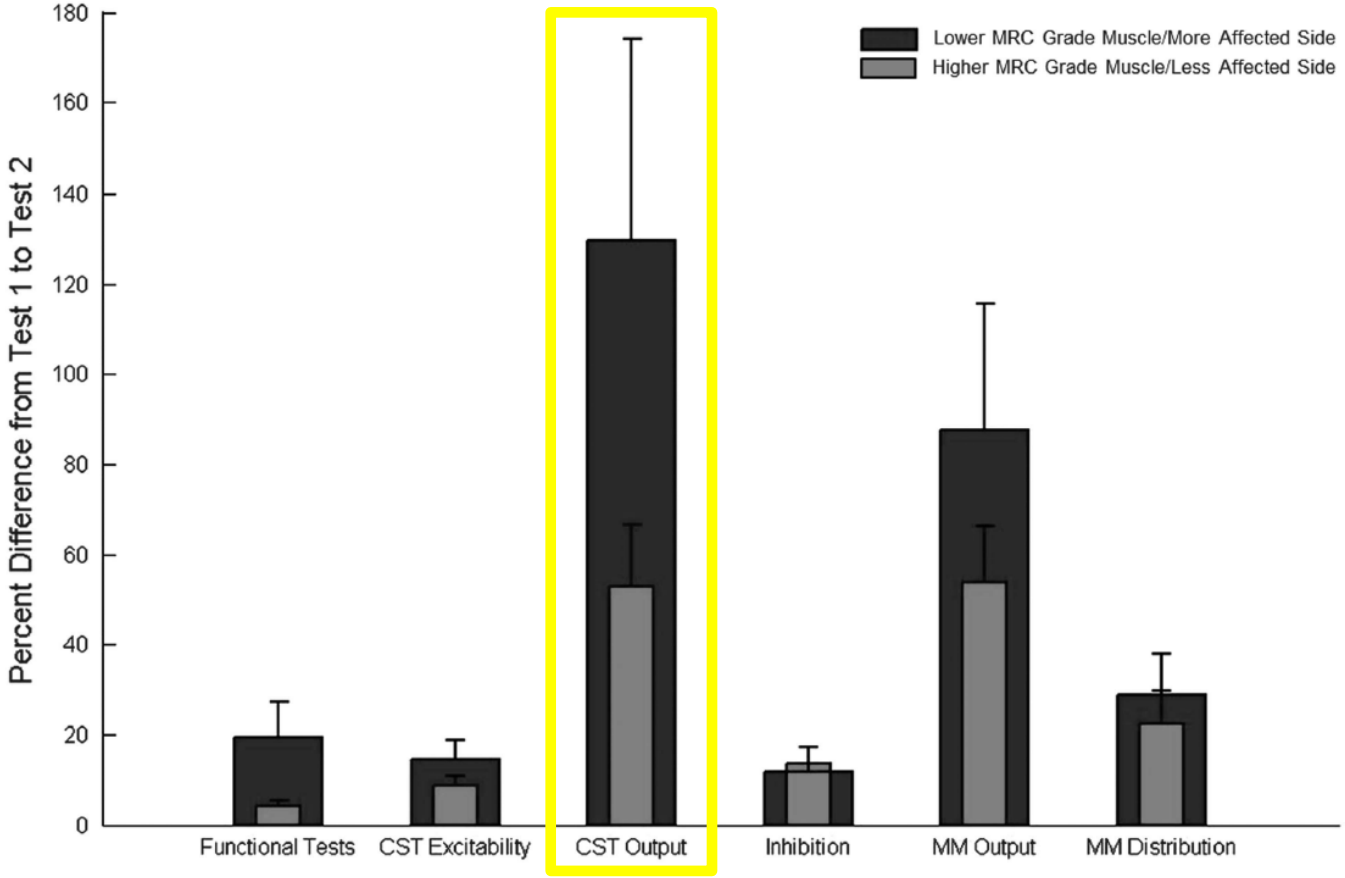


Measuring Cortical Excitability in Persons with SCI: MEP Variability



Potter-Baker et al., Spinal Cord, 2016

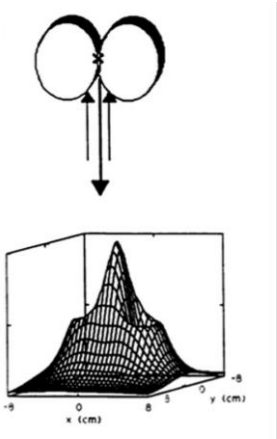
Measuring Cortical Excitability in Persons with SCI: MEP Variability



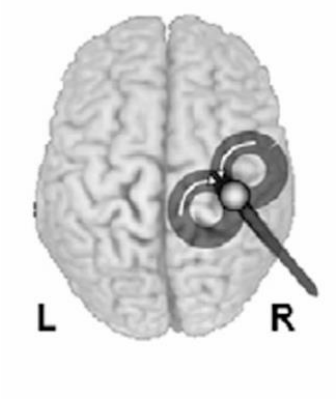
Potter-Baker et al., Spinal Cord, 2016

Measuring Cortical Excitability in Persons with SCI: Choosing a Coil

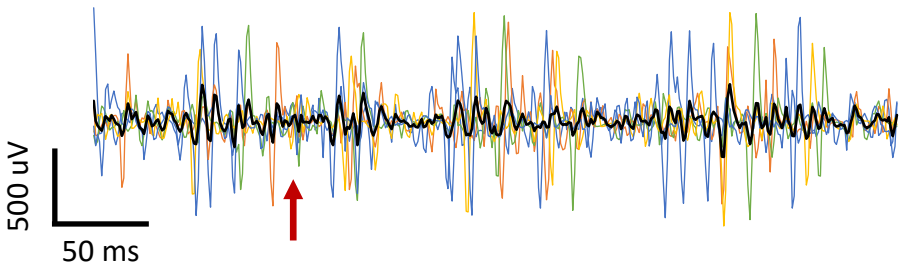
Figure of Eight Coil



Hallett, Neuron, 2007

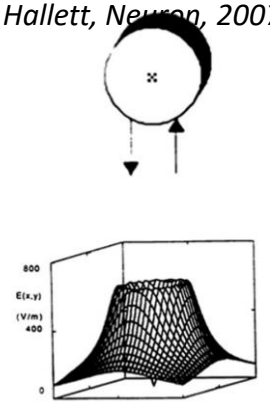


Groppa et al., Clin Neurophysiol, 2012

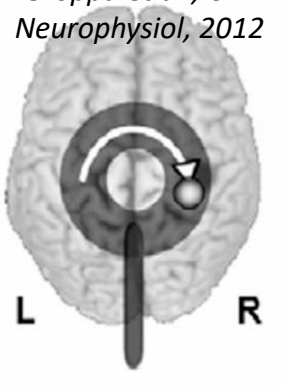


Active Thenar MEPs, 100% MSO

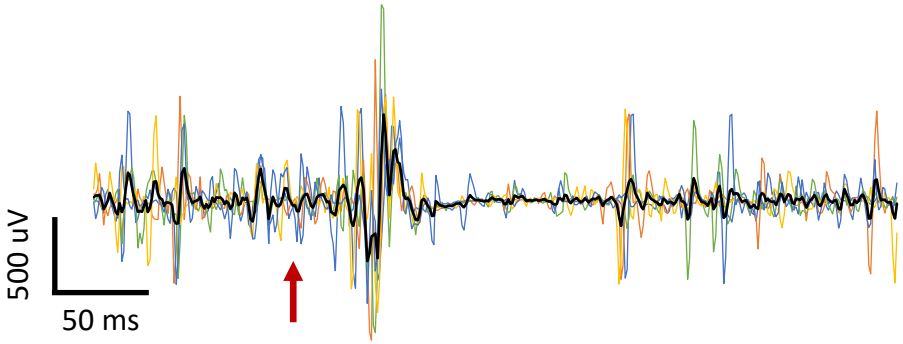
Round Coil



Hallett, Neuron, 2007



Groppa et al., Clin Neurophysiol, 2012



Future Directions

- Identifying NIBS responders among participants with SCI
  - TMS sensitivity
- NIBS dosage studies in participants with SCI
  - Stimulation intensity
  - Number of sessions
- TMS methodology study
  - Determine which coil & placement is best for eliciting MEPs for participants with SCI

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