Mechanisms of Spinal Neuromodulation And Plasticity Post Paralysis

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Kessler Foundation

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BRAIN RESEARCH INSTITUTE UCLA

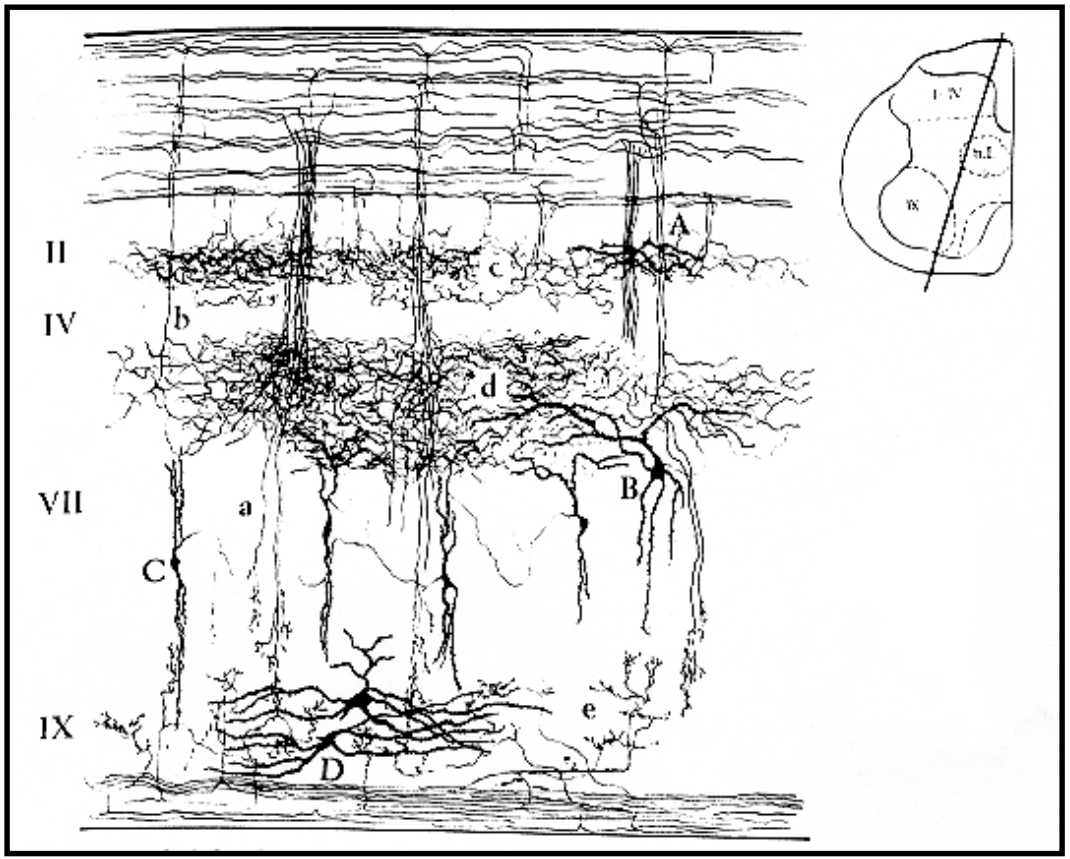
Frazier Rehab Institute

A service of Jewish Hospital & St. Mary's HealthCare

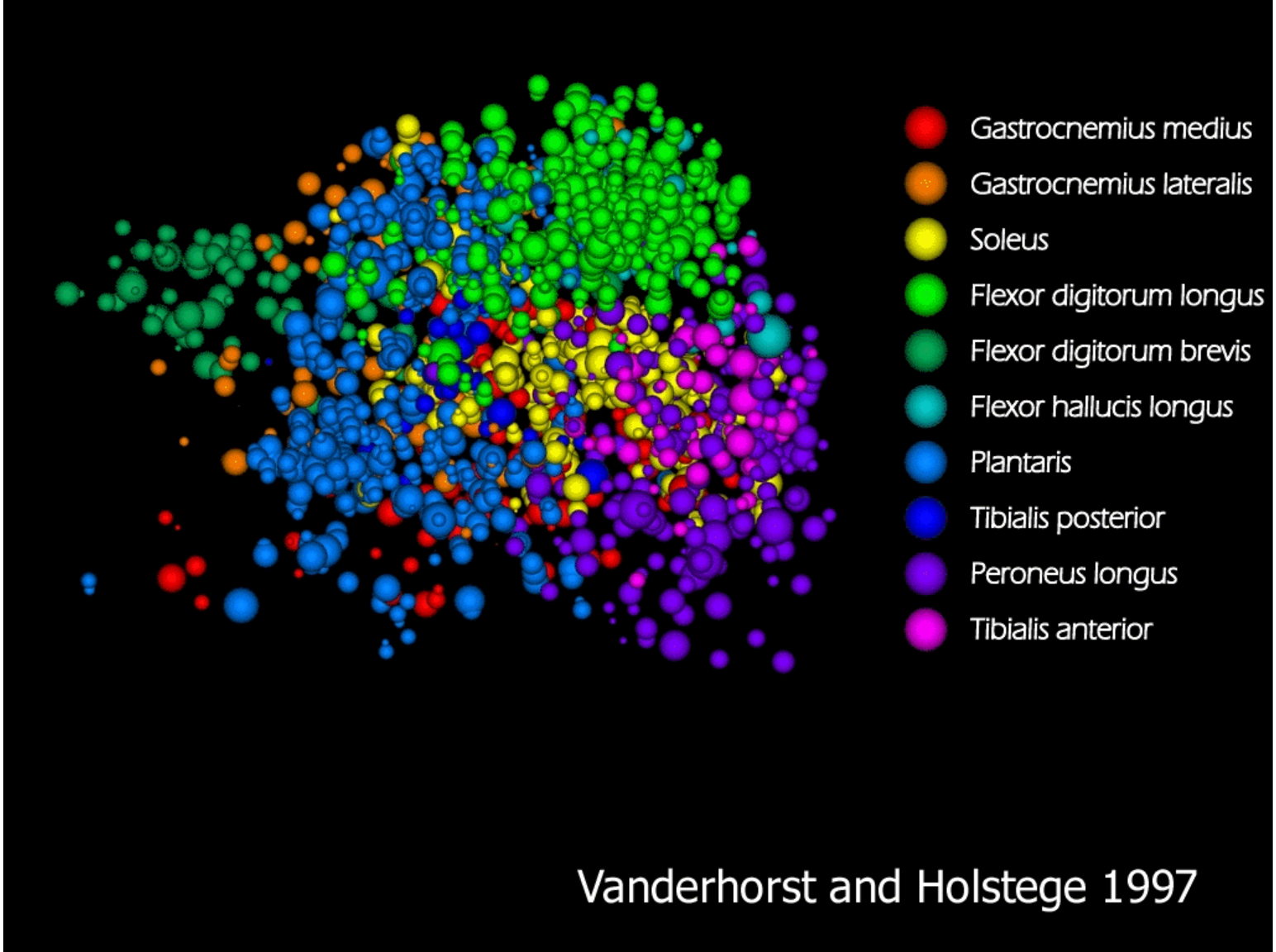
Disclosure

I hold shareholder interest in NeuroRecovery Technologies. I hold certain inventorship rights on intellectual property licensed by The Regents of the University of California to NeuroRecovery Technologies and its subsidiaries.

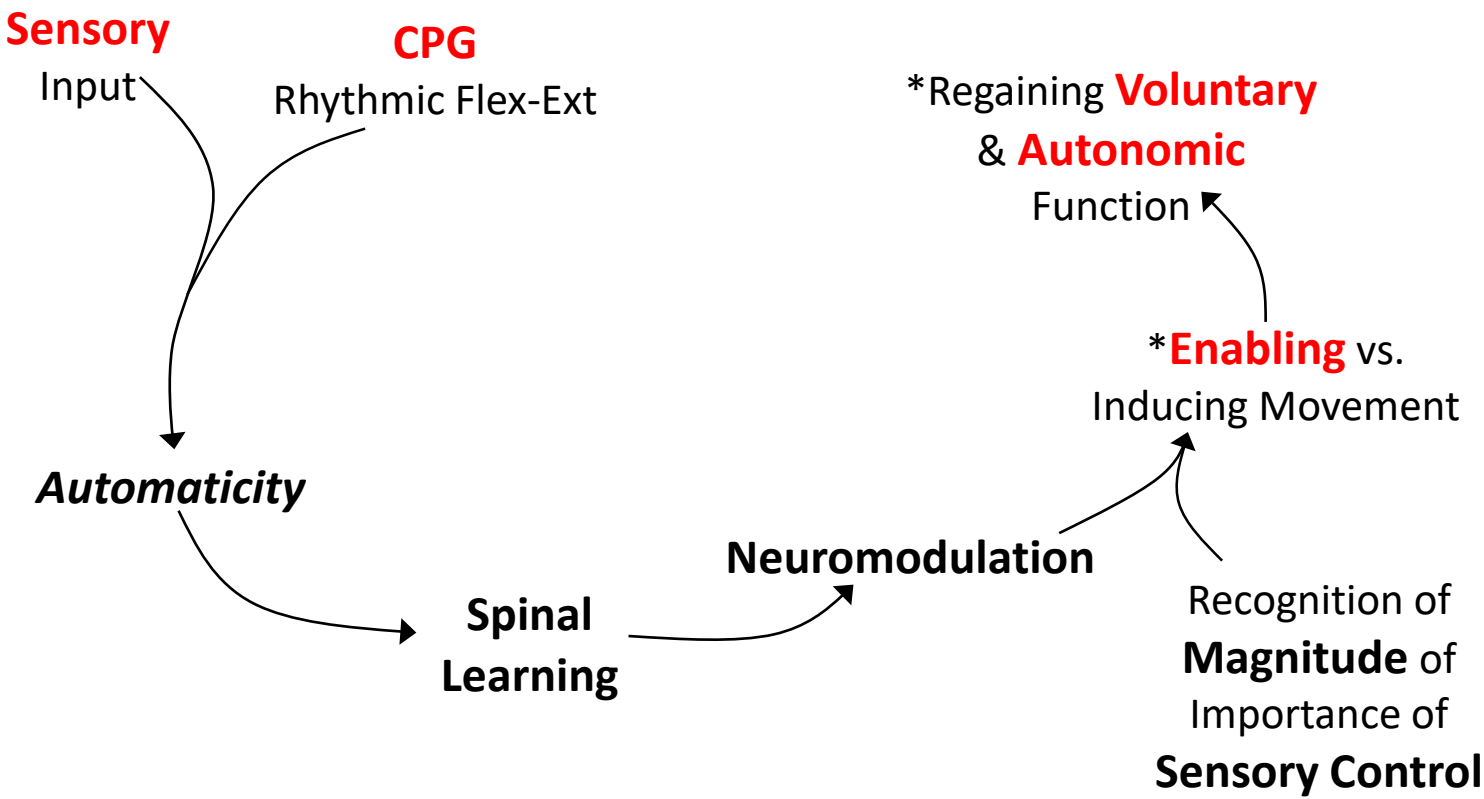
Specificity of Connectivity



From: Scheibel, M.E. and Scheibel, A.B., A Structural Analysis of Spinal Interneurons and Renshaw Cells, The Interneuron,

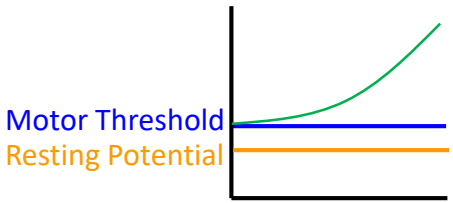

Gastrocnemius medius
Gastrocnemius lateralis
Soleus
Flexor digitorum longus
Flexor digitorum brevis
Flexor hallucis longus
Plantaris
Tibialis posterior
Peroneus longus
Tibialis anterior
Vanderhorst and Holstege 1997

Principles Underlying Recovery of Function

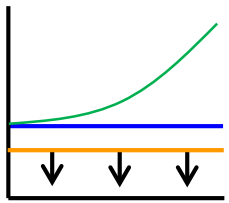


Plasticity

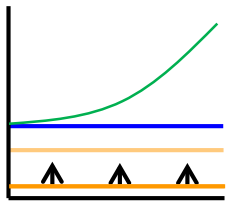
Recruitment



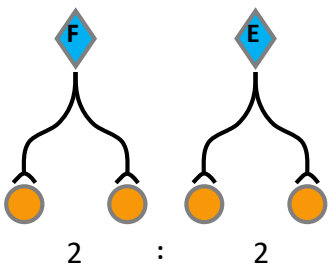
INJURY

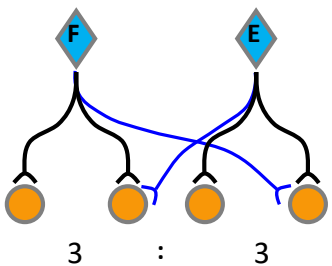


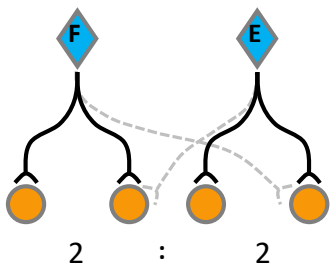
eEmc + Training + Pharma



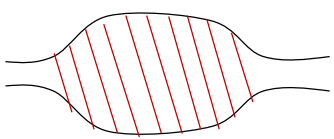
Coordination

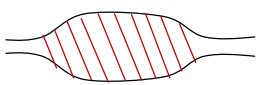




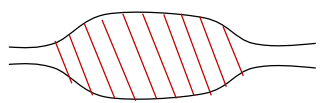


Torque / Metabostasis





Atrophy



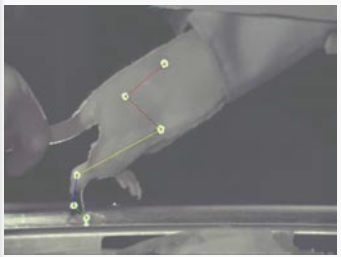
Hypertrophy

4 Remodeling of lumbosacral circuits through use-dependent mechanisms

c-fos

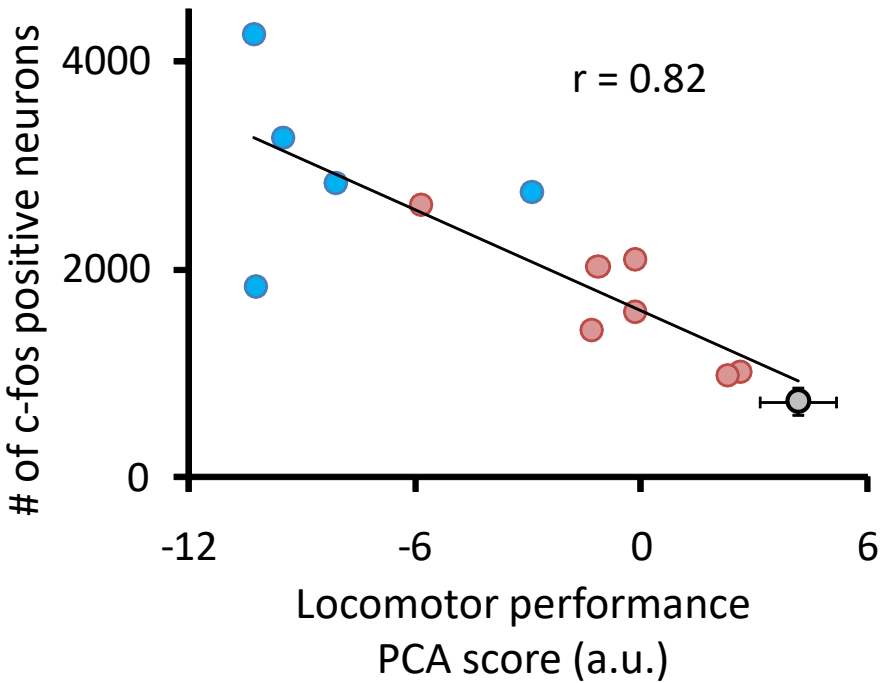
Neural Plasticity and Repair
National Center of Competence in Research

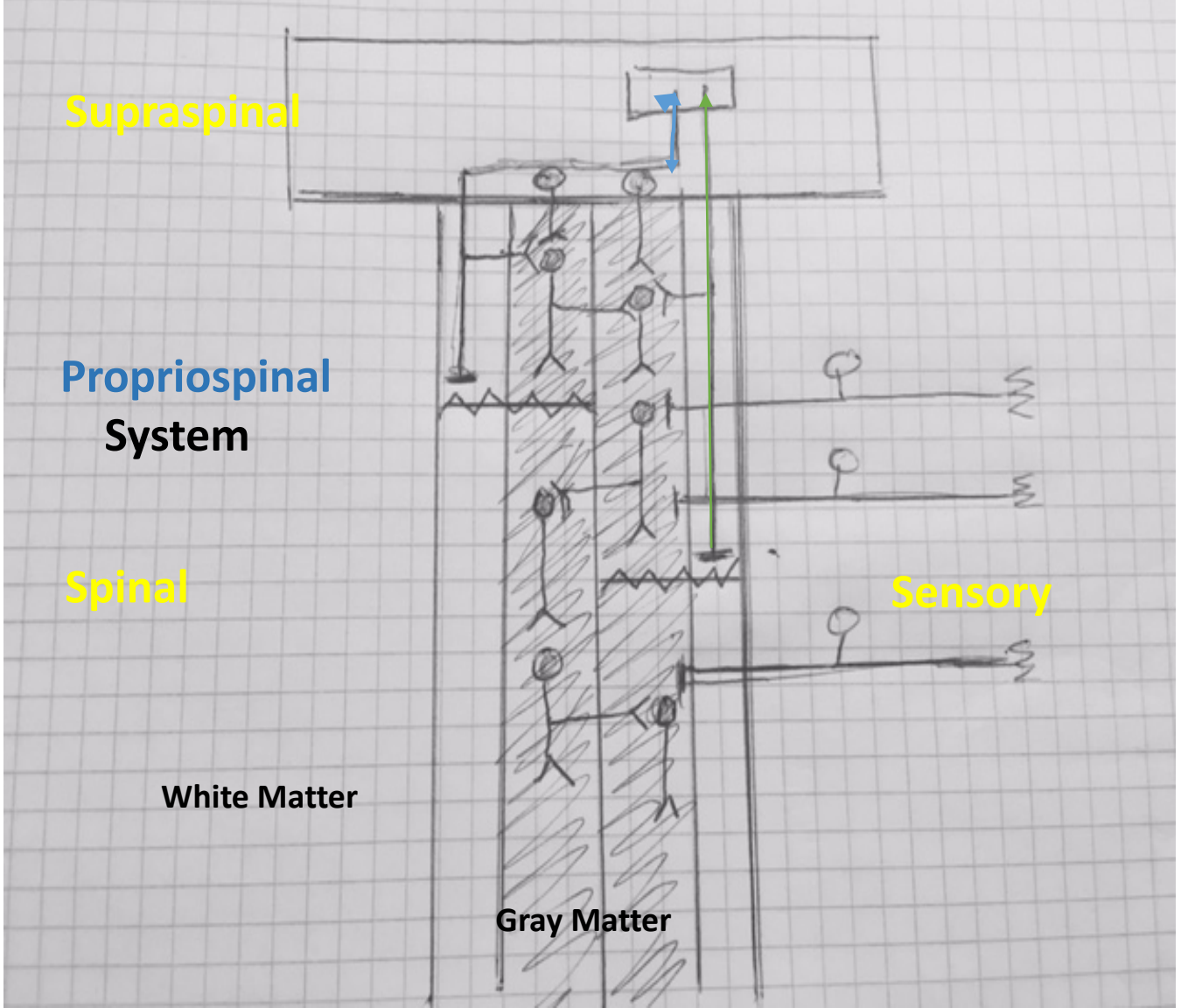
NO INJURY



NO REHABILITATION

REHABILITATION




Supraspinal
Propriospinal
System
Spinal
Sensory
White Matter
Gray Matter

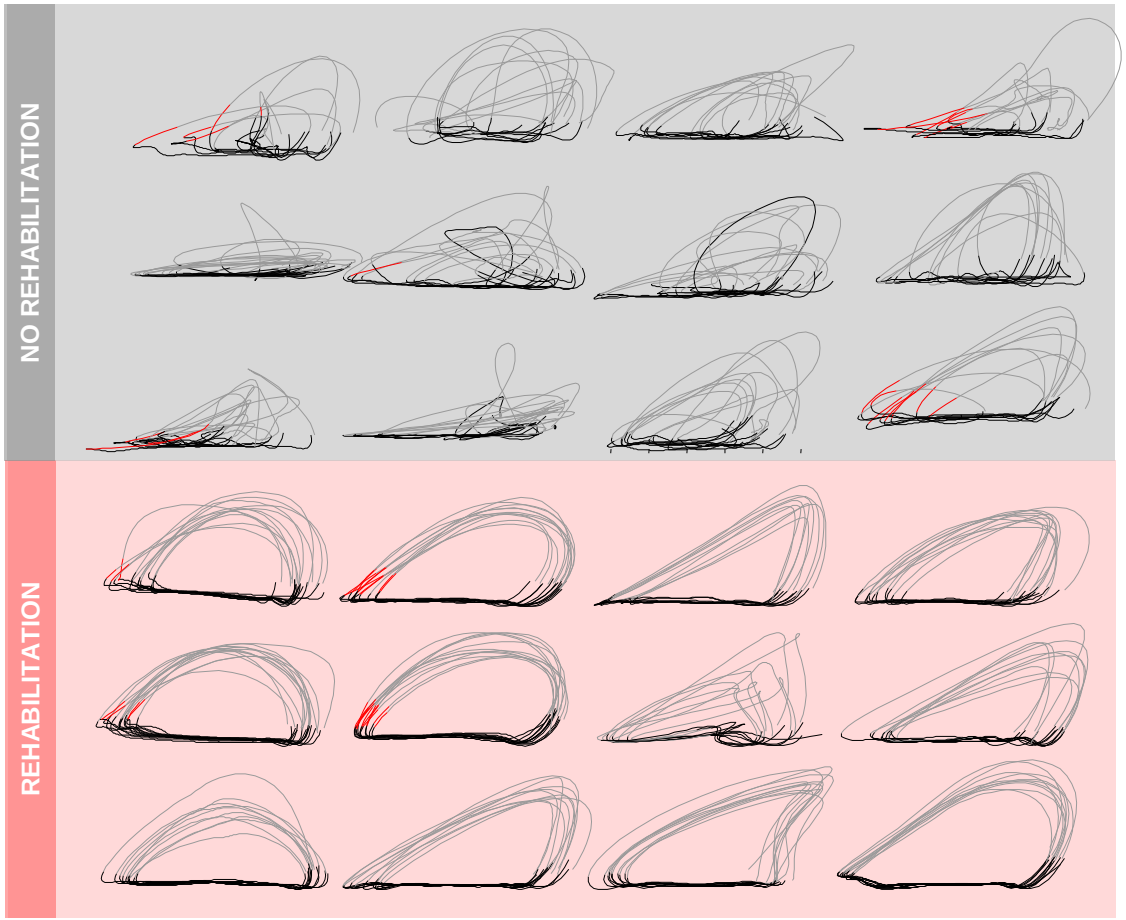
Automaticity in Movement

(You don’t have to think about the details)

Spinal Learning
And
Sensory Control

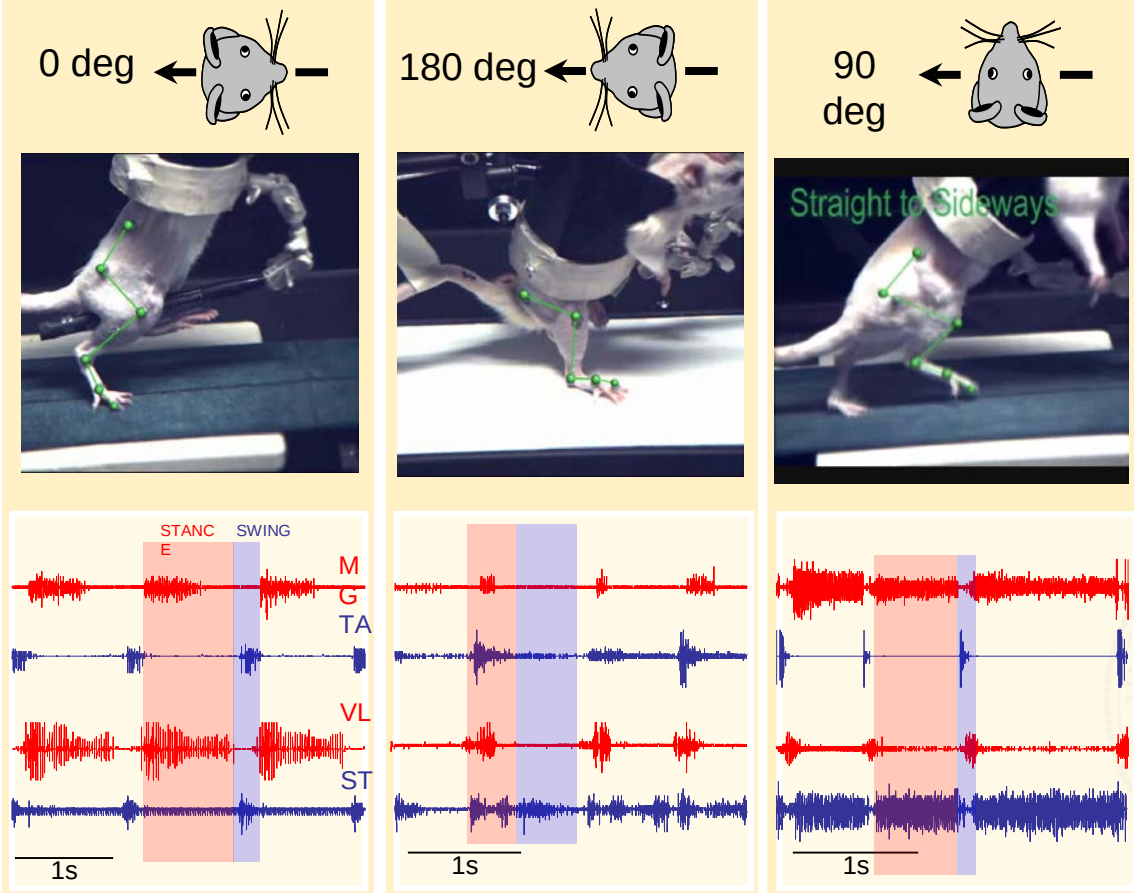
CHRONIC

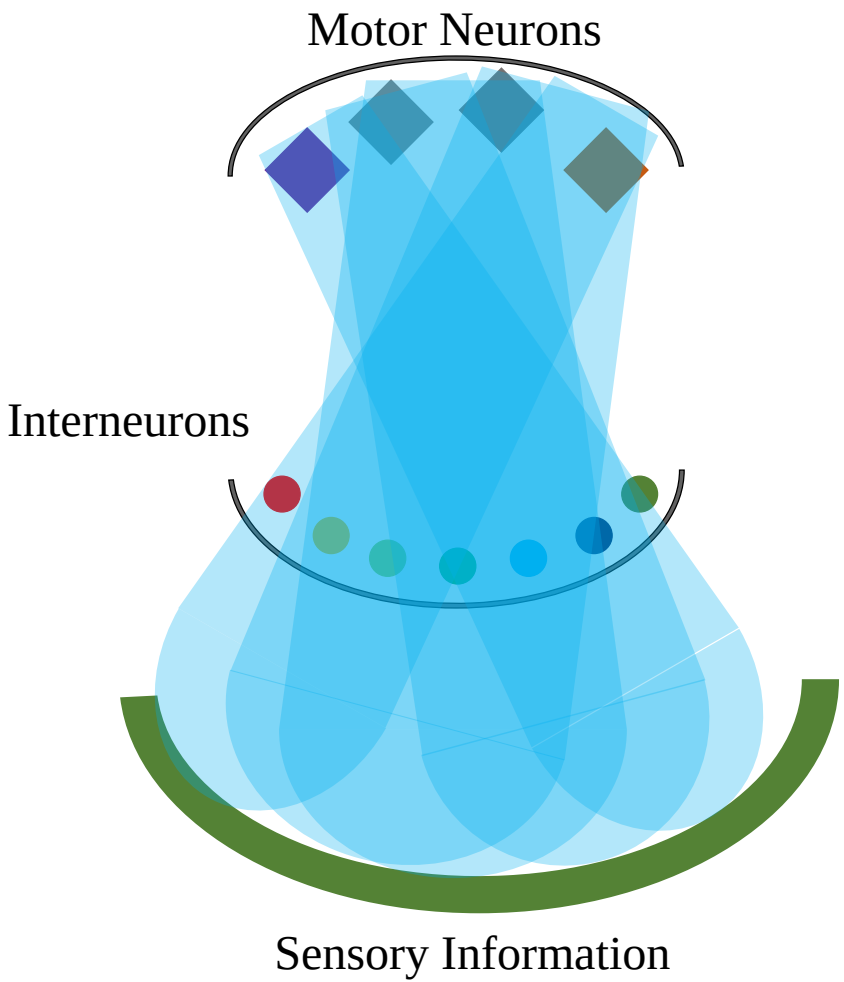
NEUROREHABILITATION UNDER COMBINATORY STEPPING-ENABLING INTERVENTIONS



Direction-dependent afferent input
Determines the features of locomotor patterns

UCLA




Motor Neurons
Interneurons
Sensory Information

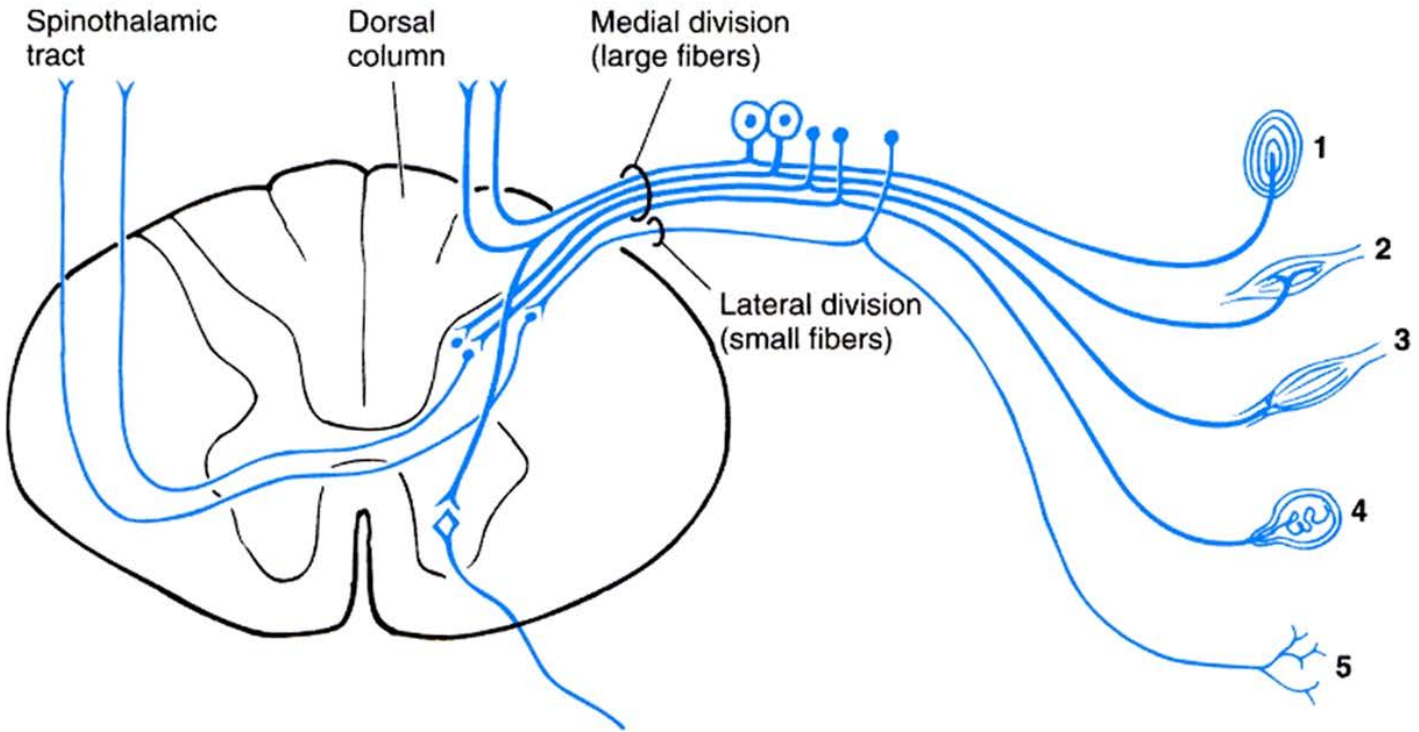
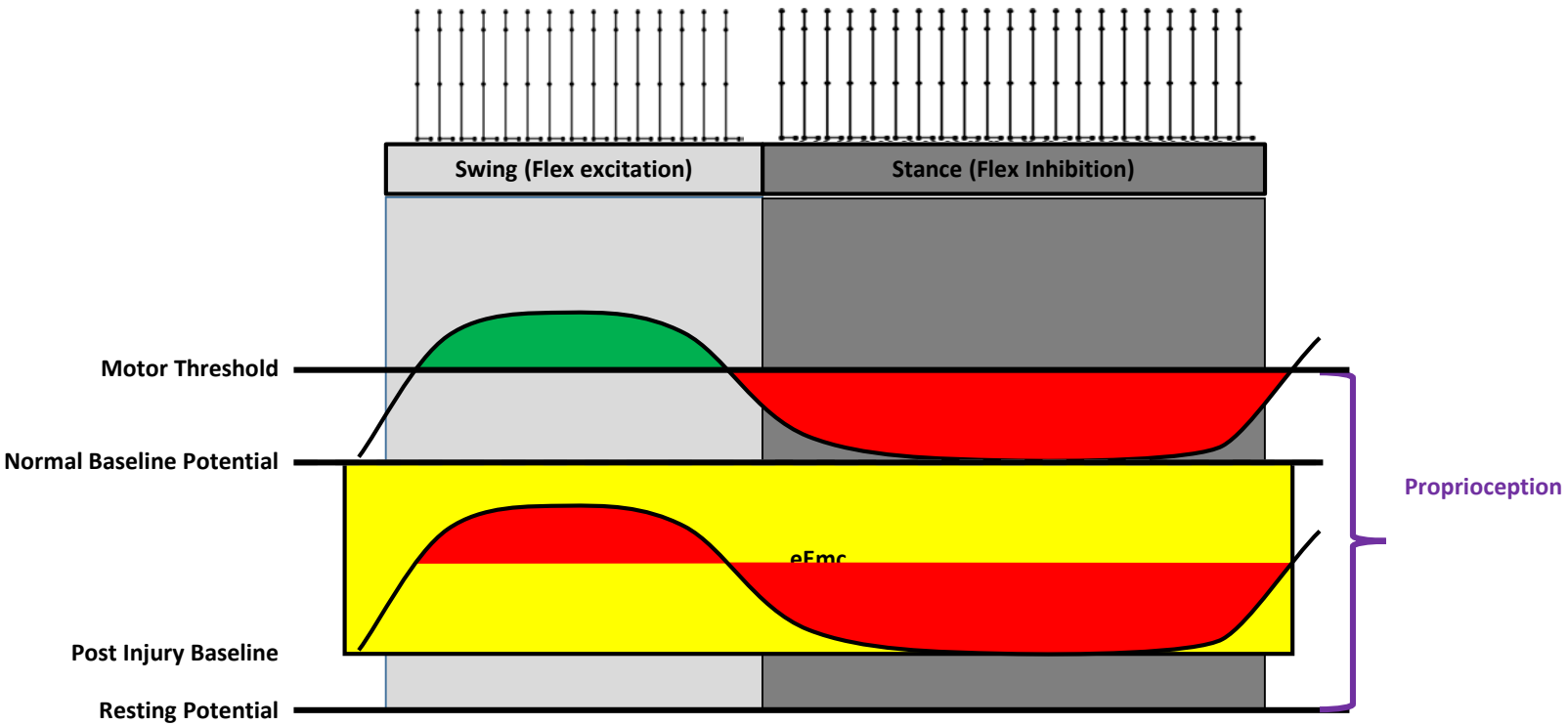
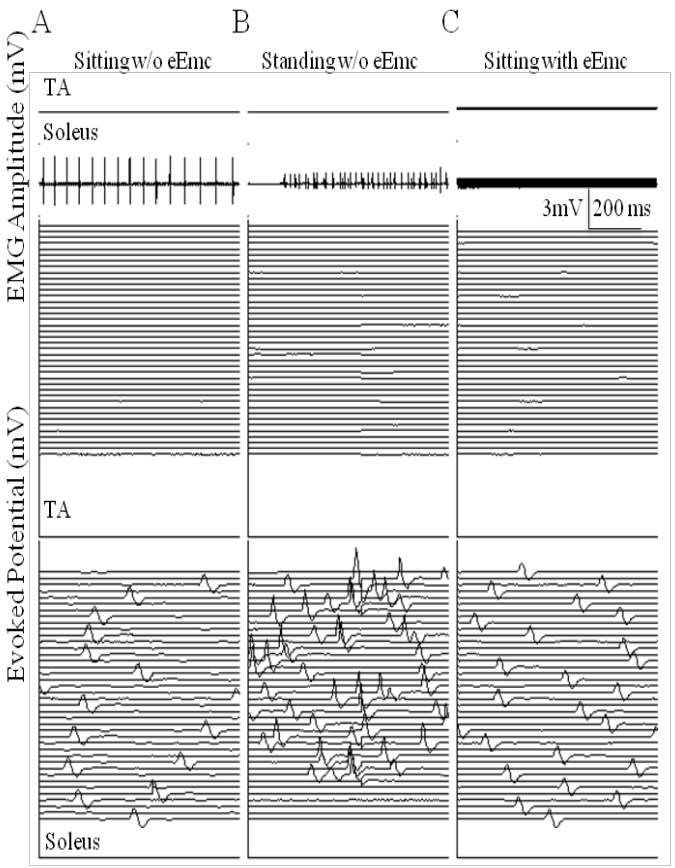


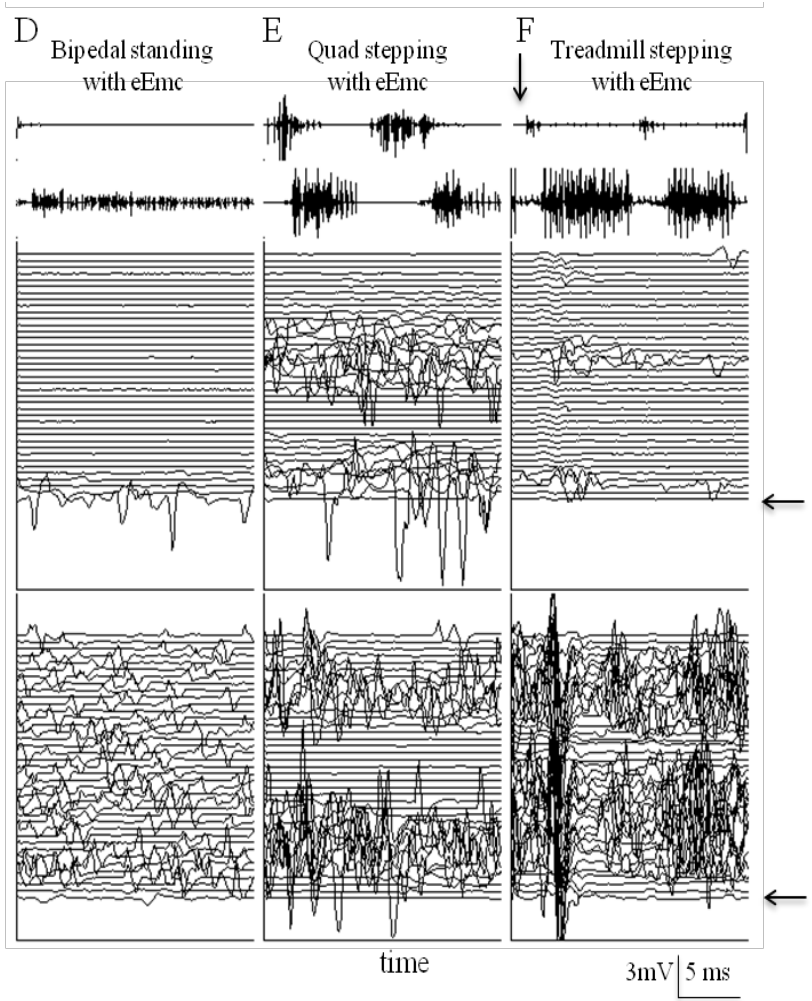
Figure 5–7. Schematic illustration of a cord segment with its dorsal root, ganglion cells, and sensory organs. 1: Pacinian corpuscle; 2: muscle spindle; 3: Golgi tendon organ; 4: encapsulated ending; 5: free nerve endings.

Traditional Injured Action Potential

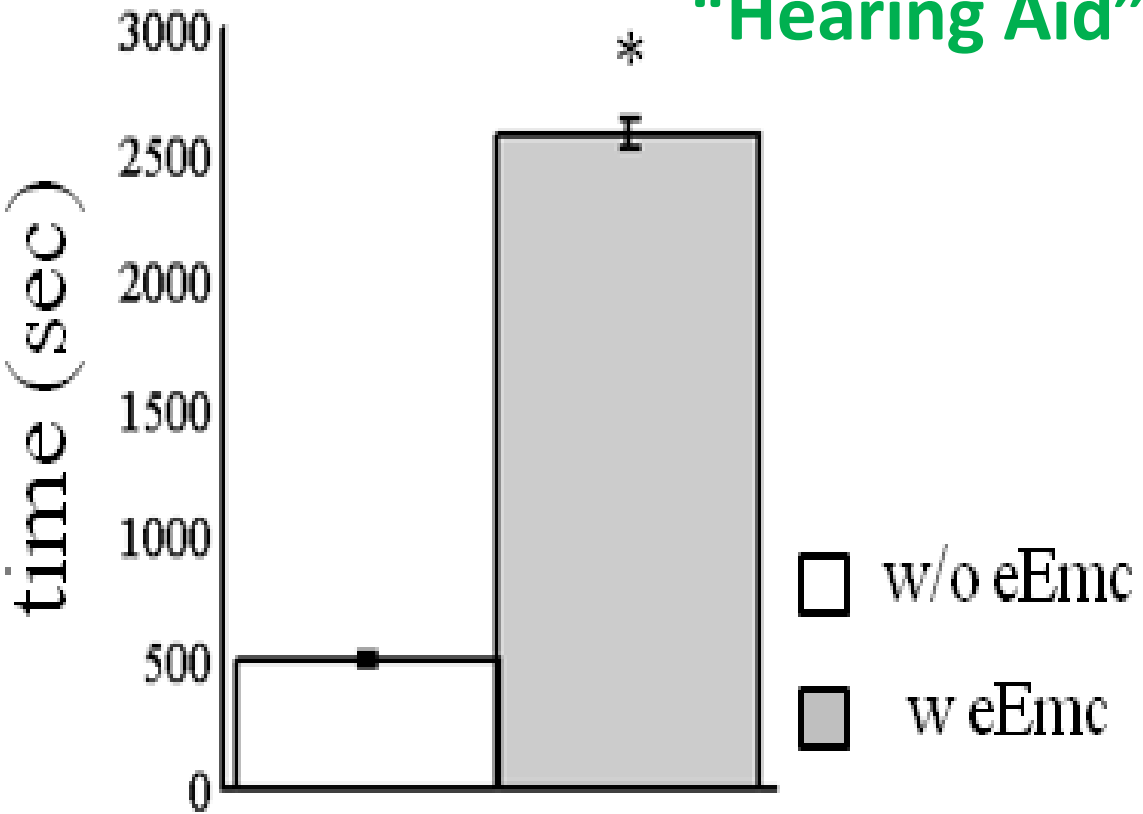


Spontaneous EMG after Spinal Transection




D
Bipedal standing
with eEmc
E
Quad stepping
with eEmc
F
Treadmill stepping
with eEmc
time
3mV
5 ms

“Hearing Aid”



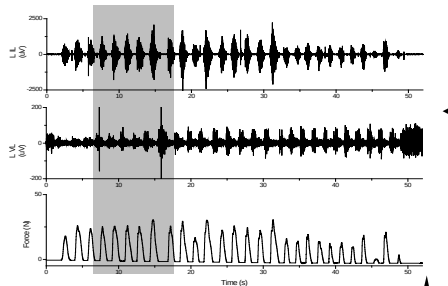
Epidural Stimulation in humans (N=4)

AIS-A: Motor and sensory complete

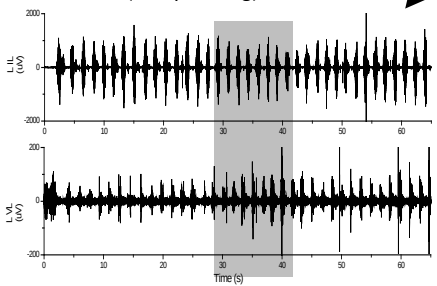
Neurological Level: T4

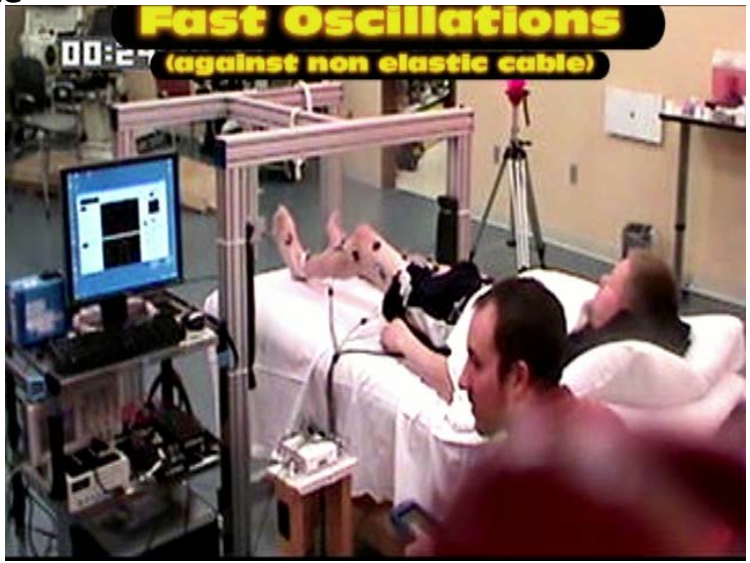
Fast Oscillations of Left Leg

(with non compliant cable measuring force generation)



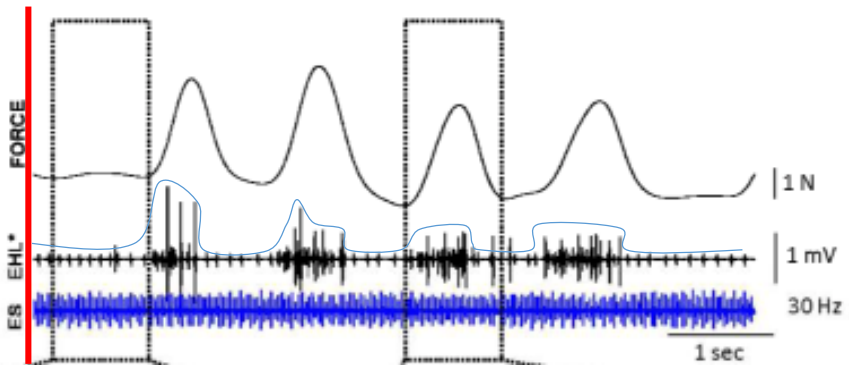
(freely moving)

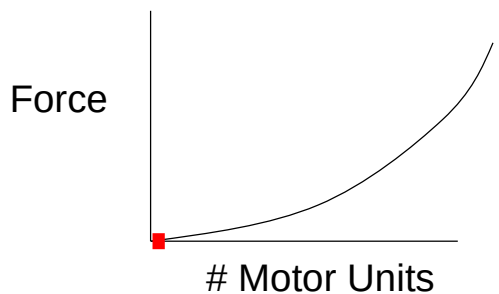


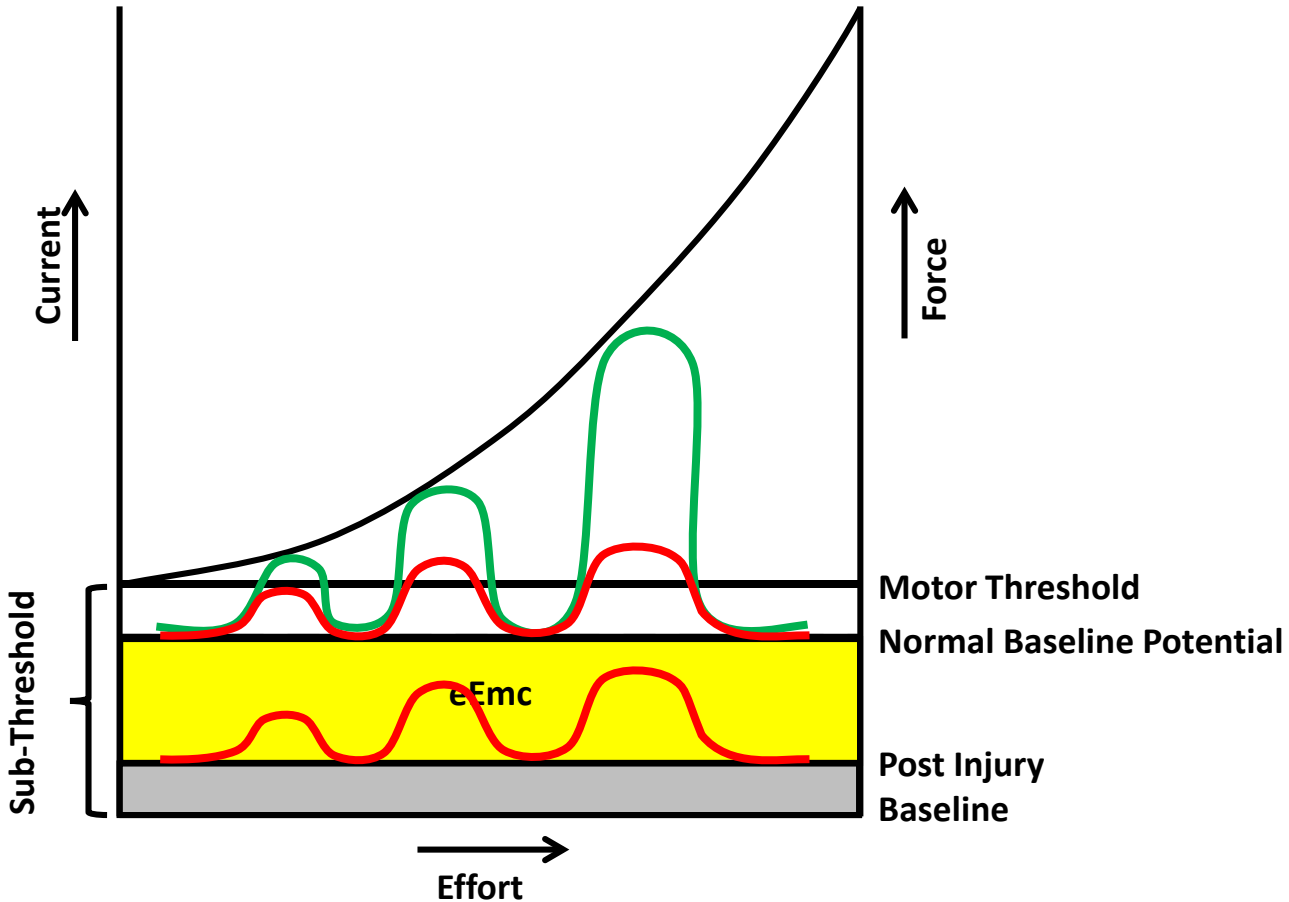


Standing while throwing and catching a ball

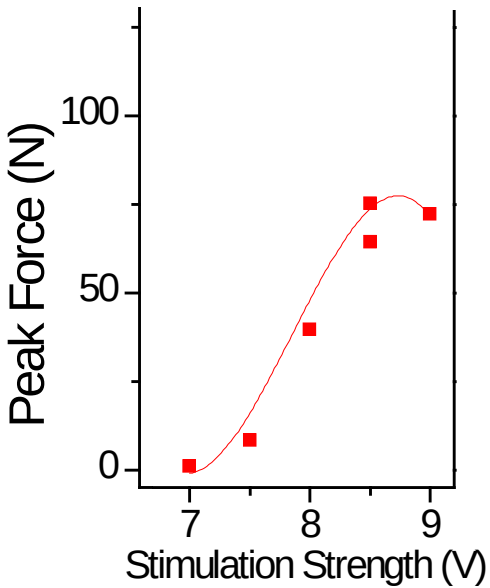
(left hand on elastic band to challenge posture)


FORCE
EHL*
ES
1 N
1 mV
30 Hz
1 sec


Force
Motor Units

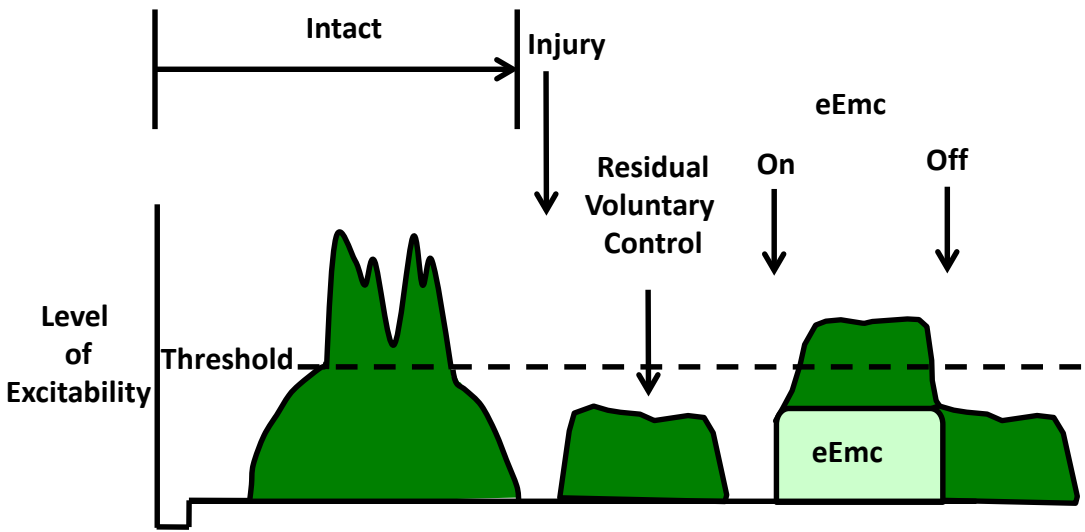

Current
Force
Sub-Threshold
Motor Threshold
Normal Baseline Potential
eEmc
Post Injury
Baseline
Effort

Network Excitability Amplification



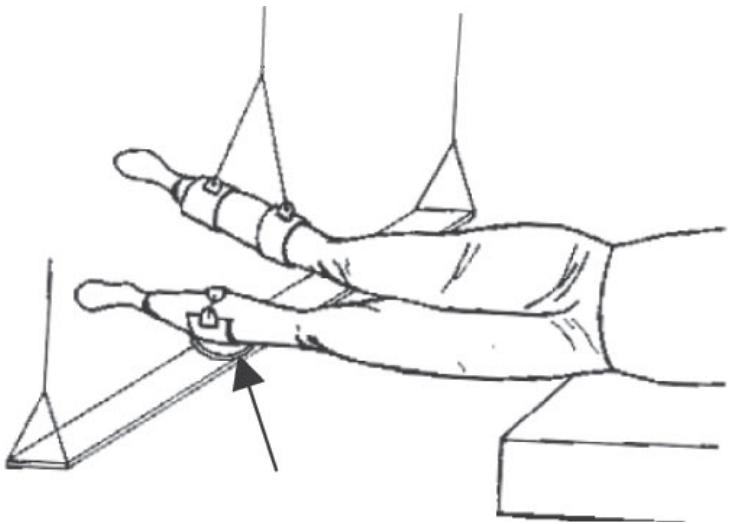
BRAIN
RESEARCH
INSTITUTE
UCLA

electroEnabling motor control (eEmc)



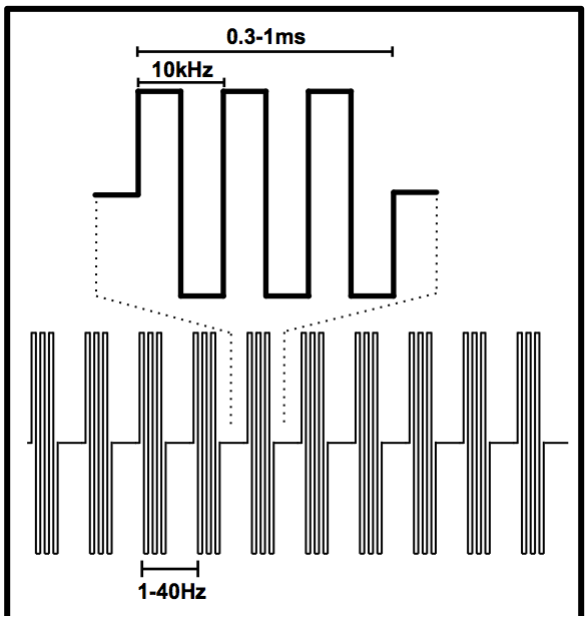
Lumbosacral Neuromodulation after Chronic SCI (N=5)

Experimental design for percutaneous electrical spinal cord stimulation (PTES) in normal individual



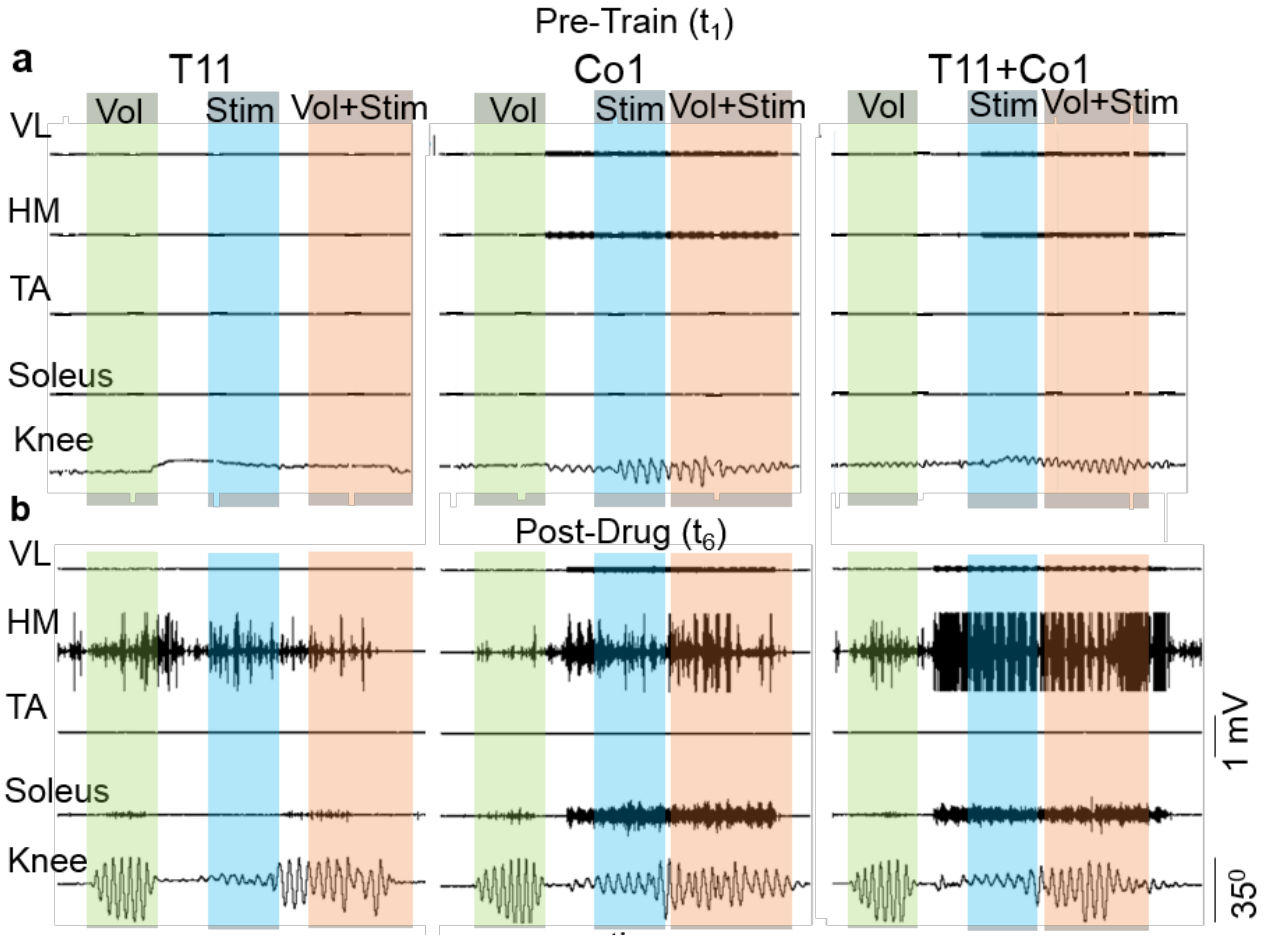
Гурфинкель и др. 1998; Selionov et al. 2009

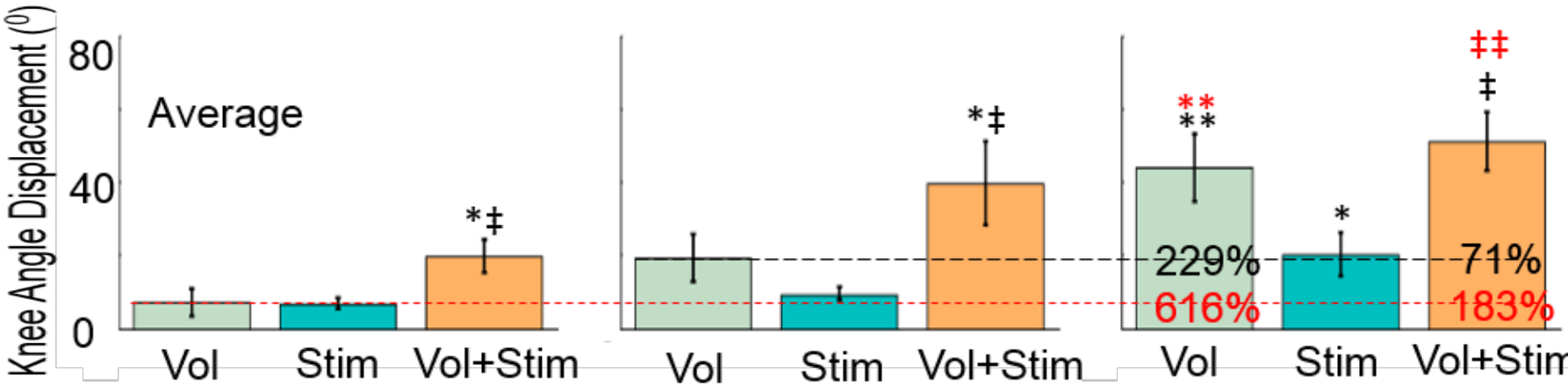
“Russian” current



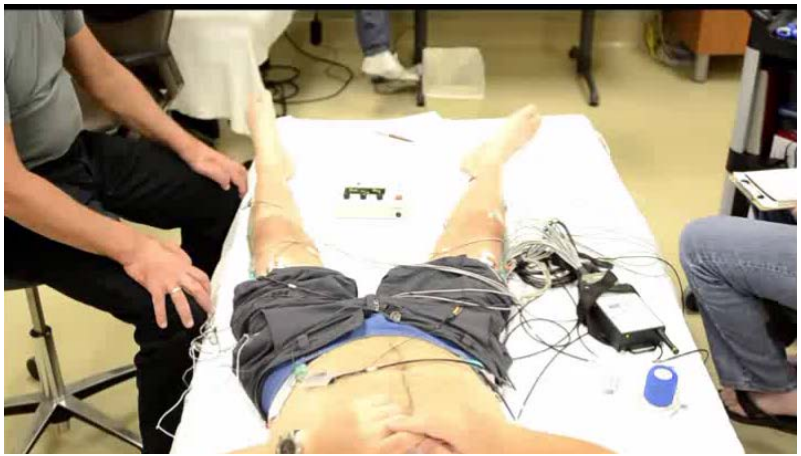
A 10kHz biphasic stimulation is delivered in 0.3 to 1ms bursts. These pulses are delivered at 1-40 Hz.

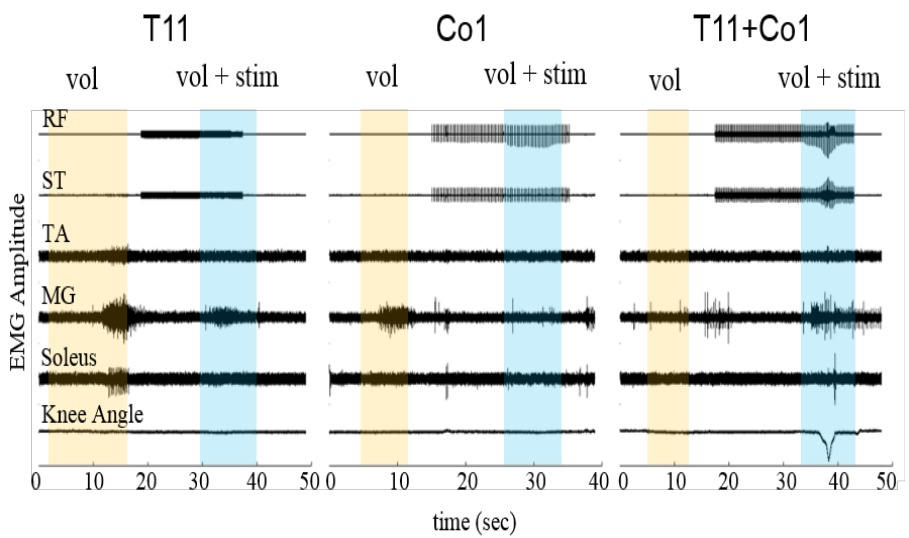
Non-invasive Neuromodulation to regain voluntary leg movements after complete paralysis

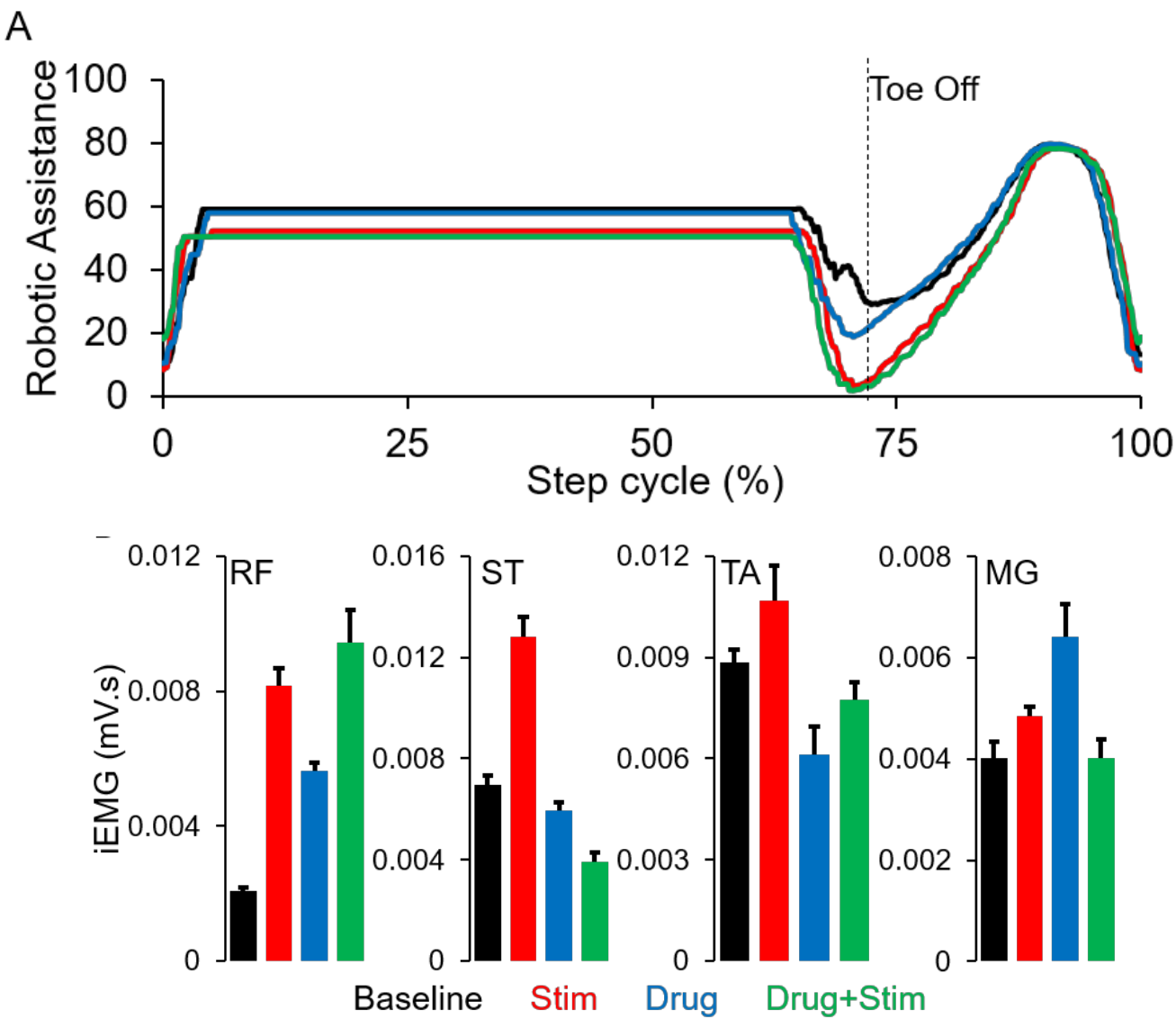

Pre-Train (t_1)
a
T11
Co1
T11+Co1
Vol
Stim
Vol+Stim
VL
HM
TA
Soleus
Knee
b
Post-Drug (t_6)
1 mV
35^0


Knee Angle Displacement (°)
80
40
0
Average
*‡
*‡
**
**
*
‡‡
‡
229%
616%
71%
183%
Vol
Stim
Vol+Stim
Vol
Stim
Vol+Stim
Vol
Stim
Vol+Stim

Combining pcEmc and Exoskeletal Assistive Devices (Ekso)




T11
Co1
T11+Co1
vol
vol + stim
vol
vol + stim
vol
vol + stim
RF
ST
TA
MG
Soleus
Knee Angle
EMG Amplitude
0 10 20 30 40 50
0 10 20 30 40
0 10 20 30 40 50
time (sec)

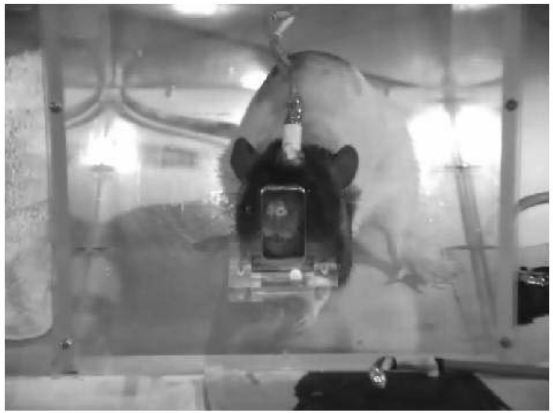

A
Robotic Assistance
100
80
60
40
20
0
Toe Off
0
25
50
75
100
Step cycle (%)
iEMG (mV.s)
RF
0.012
0.008
0.004
0
ST
0.016
0.012
0.008
0.004
0
TA
0.012
0.009
0.006
0.003
0
MG
0.008
0.006
0.004
0.002
0
Baseline
Stim
Drug
Drug+Stim

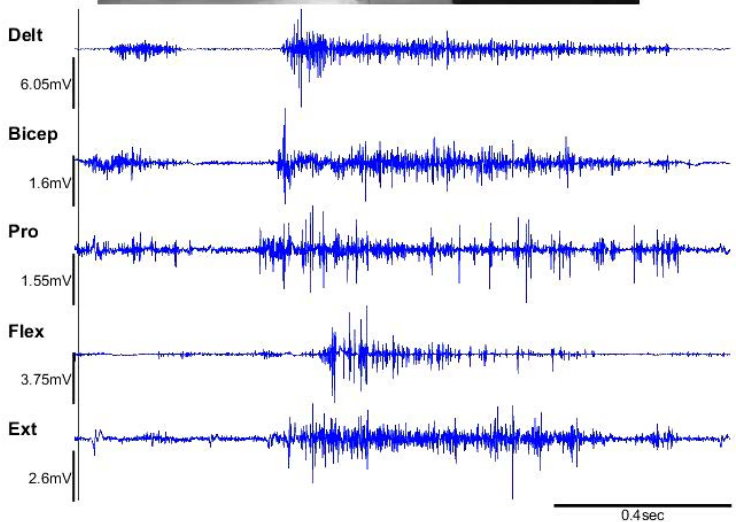
Cervical Spinal Neuromodulation

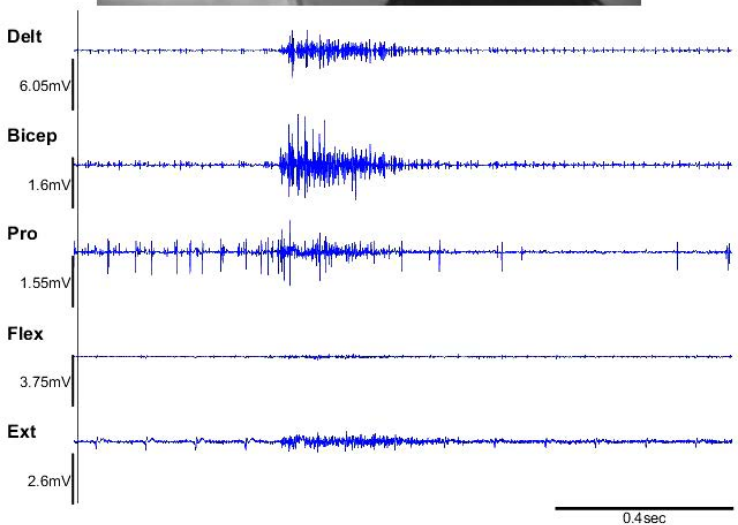
Before Injury

Post-Injury (1 week)

Left Paw Dominant



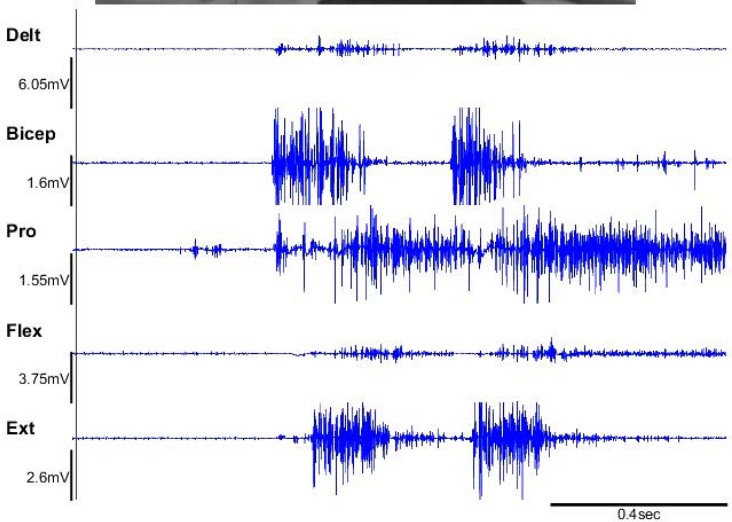




Same Representative Animal & Scale (amplitude, time)

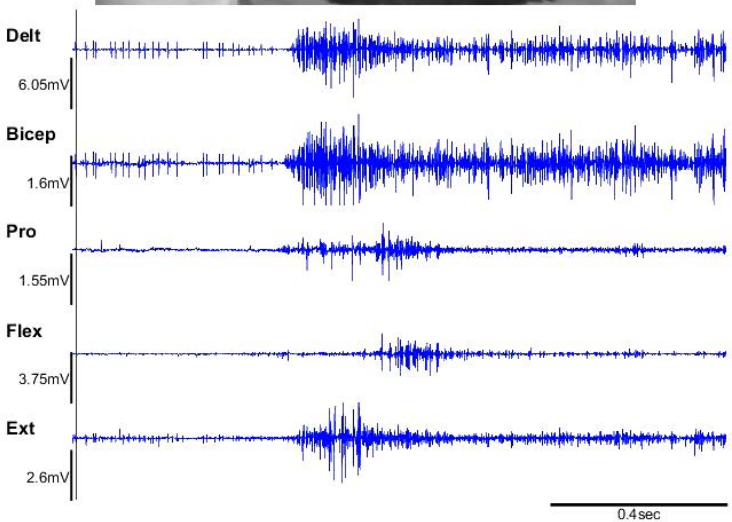
Post-Injury (6 weeks) **Sham Treatment**

Right Paw Dominant

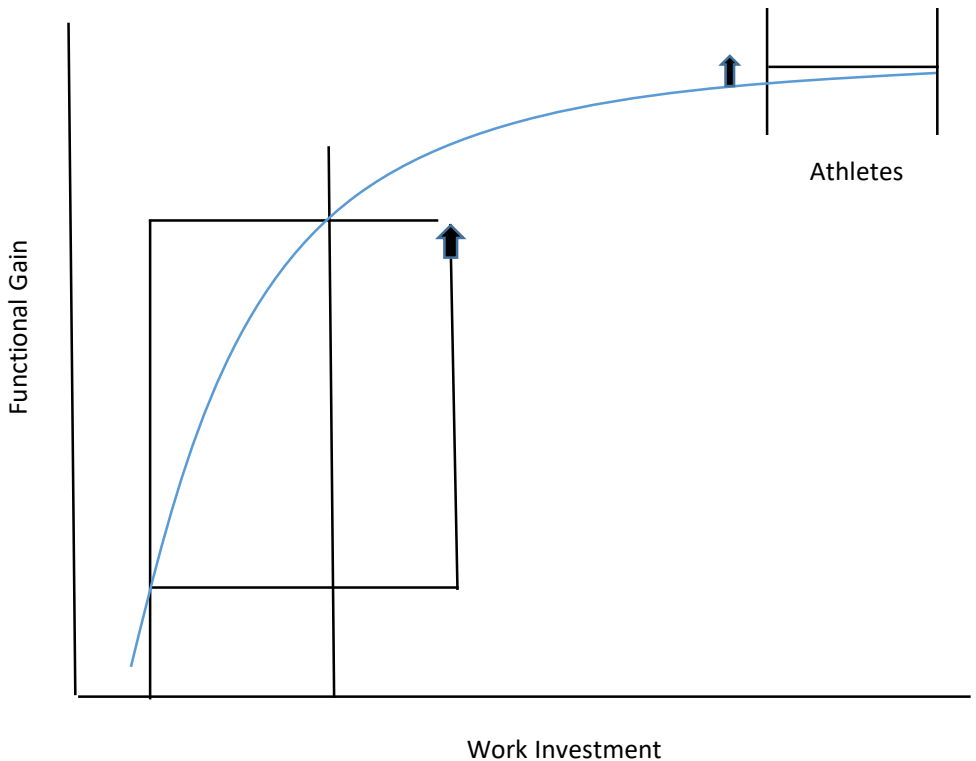


Buspirone Treatment

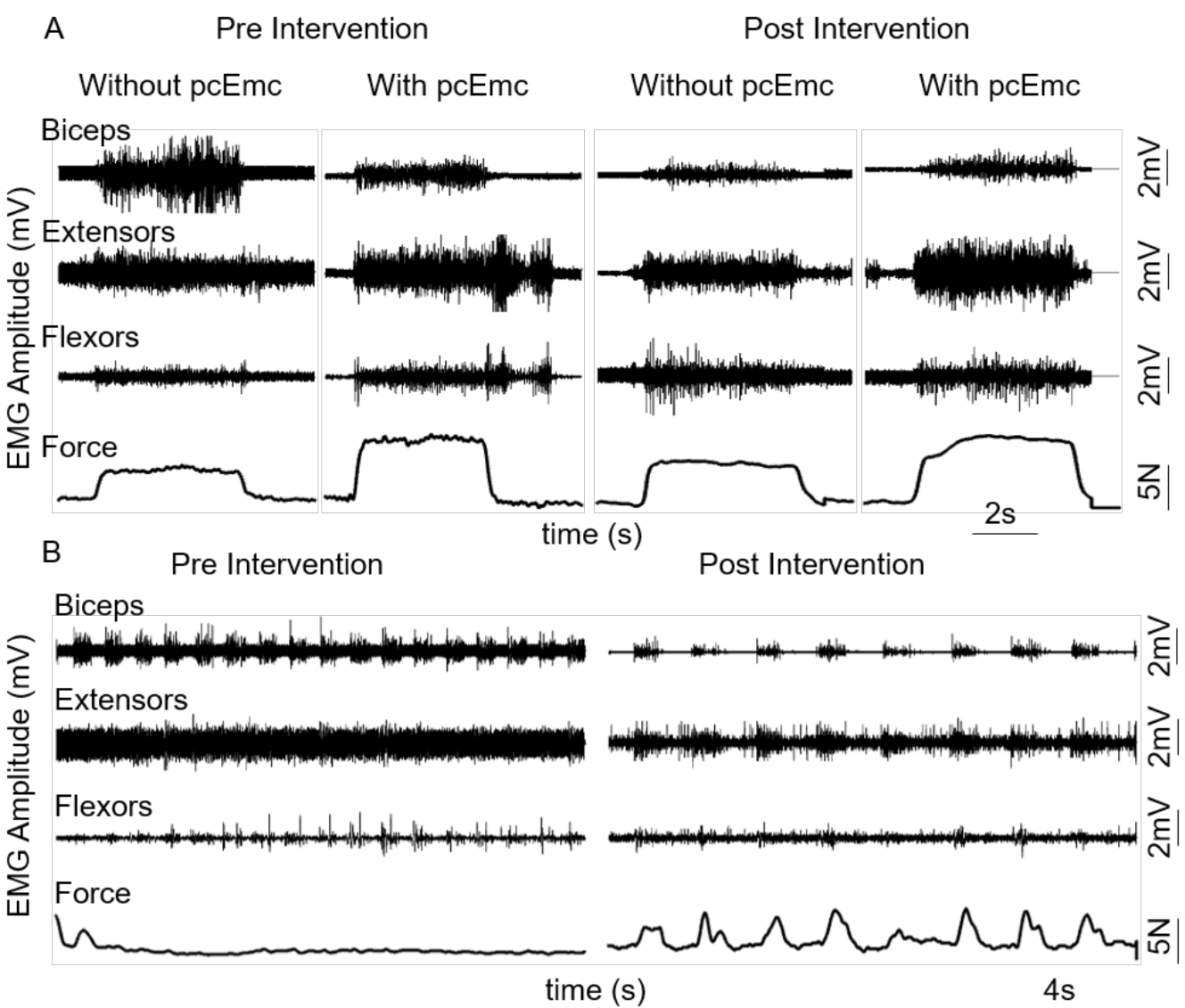
Left Paw Dominant



Same Representative Animals as Previous Slide

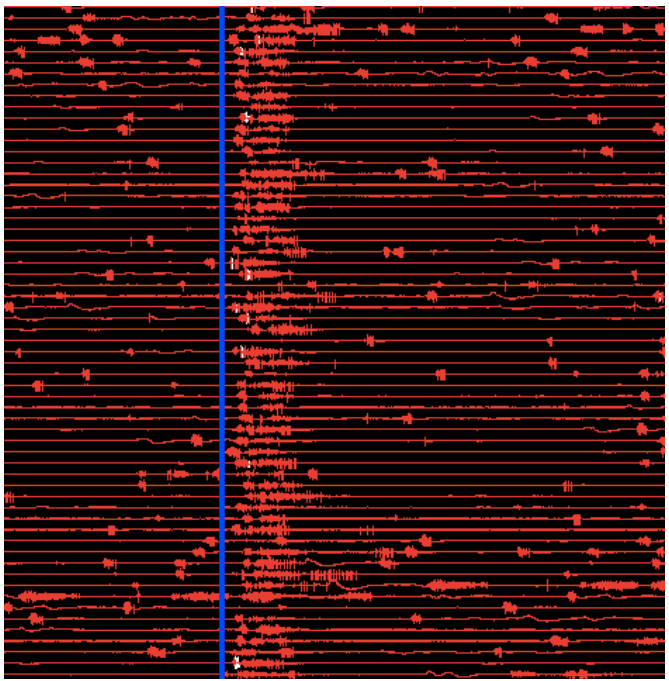

Athletes
Functional Gain
Work Investment

Non-Invasive Neuromodulation to regain hand grip function after paralysis

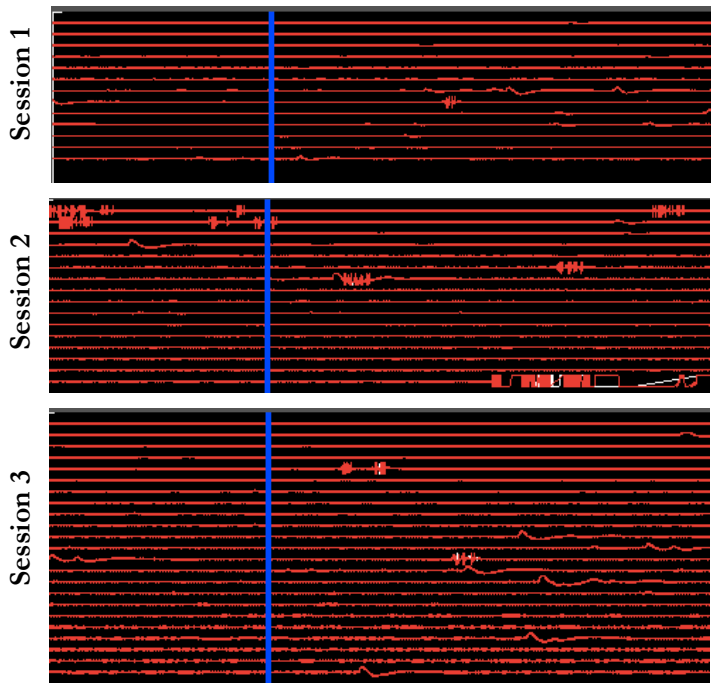

A
Pre Intervention
Post Intervention
Without pcEmc
With pcEmc
Without pcEmc
With pcEmc
Biceps
Extensors
Flexors
Force
EMG Amplitude (mV)
2mV
2mV
2mV
5N
2s
time (s)
B
Pre Intervention
Post Intervention
Biceps
Extensors
Flexors
Force
EMG Amplitude (mV)
2mV
2mV
2mV
5N
time (s)
4s

CONTROL ANIMAL

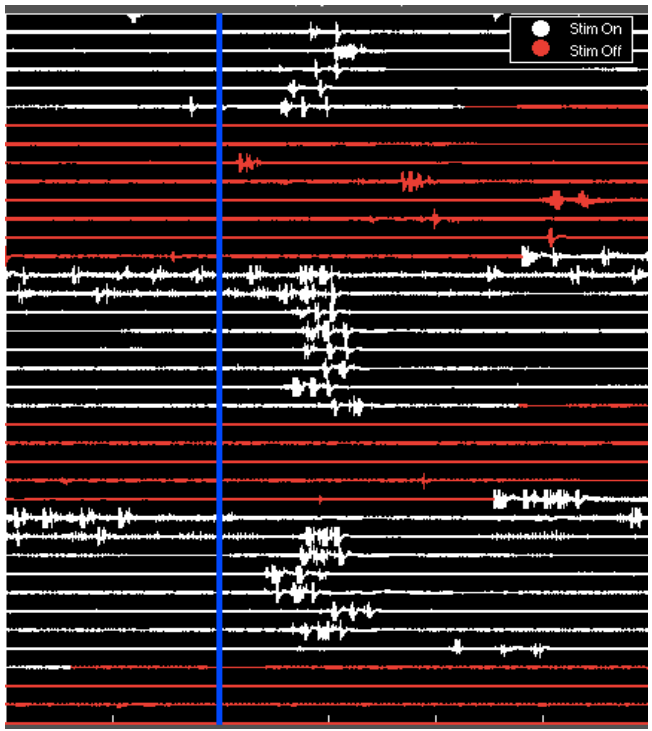
Pre-injury

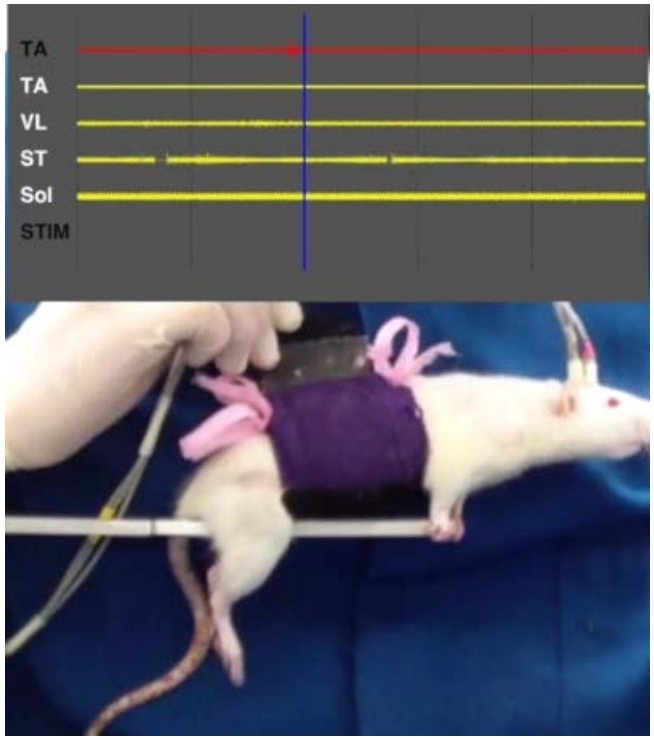


Post Injury

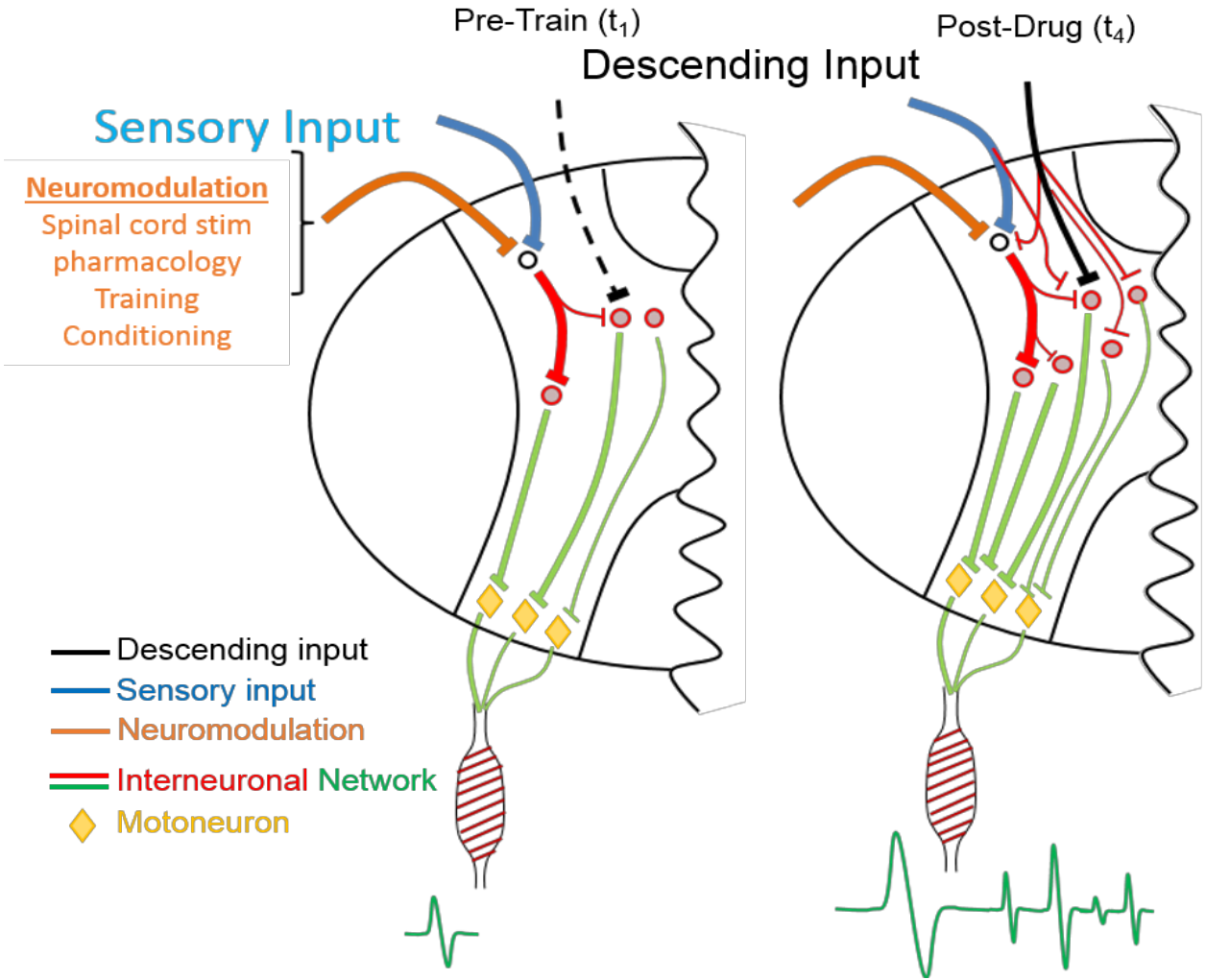


STIM ON/OFF



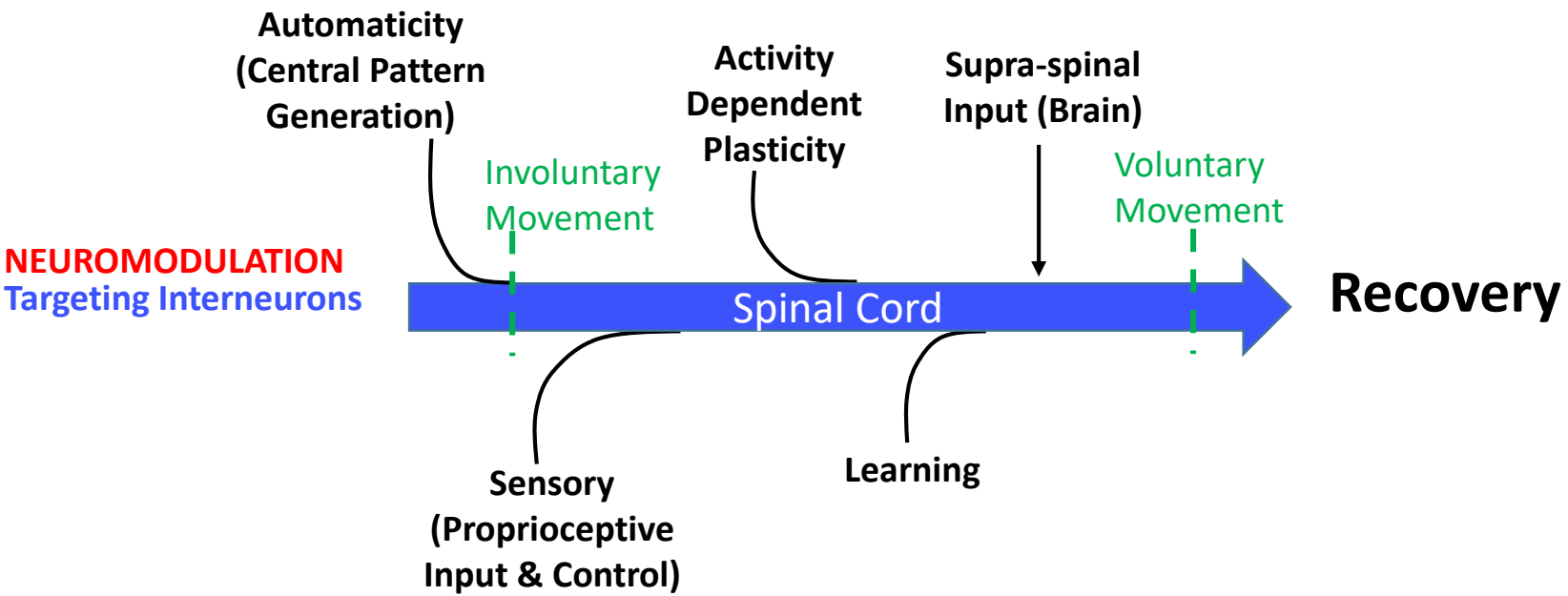


Neuromodulation of Bladder Function


Pre-Train (t_1)
Post-Drug (t_4)
Descending Input
Sensory Input
Neuromodulation
Spinal cord stim
pharmacology
Training
Conditioning
Descending input
Sensory input
Neuromodulation
Interneuronal Network
Motoneuron

Principles Underlying Recovery of Function

You don't have to think about the details
the spinal cord knows what to do

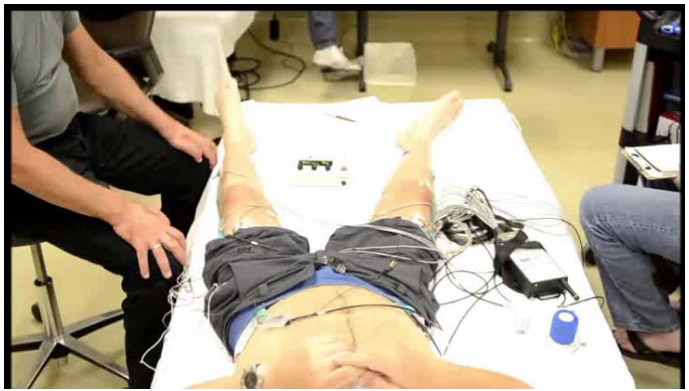


To relearn there must be re-engagment of the circuits

This can be accomplished pharmacologically and via electrical neuromodulation when combined with training

Previously unrecognized potential levels of recovery of motor function via neuromodulation and neural plasticity

New clinical horizons



Voluntary Control

SCI

Individual movements
Facilitate Standing
Facilitate Stepping
Facilitate Trunk Control
Facilitate Upper Limb Function

Ventilation Dependence

Neuromodulation

Improved Sensory Function

SCI

Muscle Mass

Skin Lesion

Health Cost?

eEmc(O)
pcEmc
eEmc(N)
sEmc
fEmc

SCI

Sexual Function

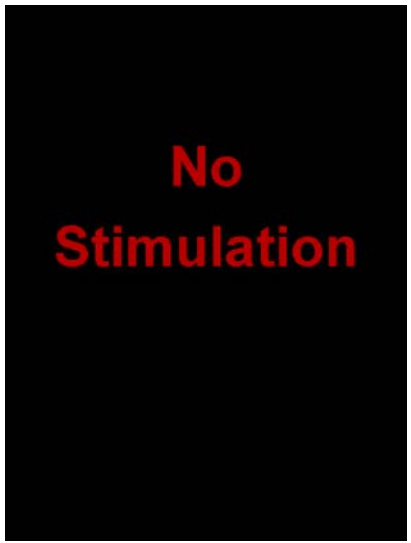
Bladder Control

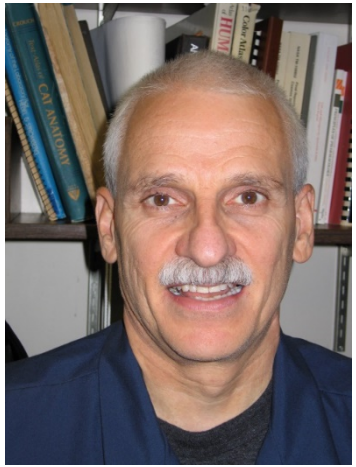
Improve Metabolic Homeostasis

Blood Pressure

Temperature Control

Hand Function





Roland Roy

Yury Gerasimenko

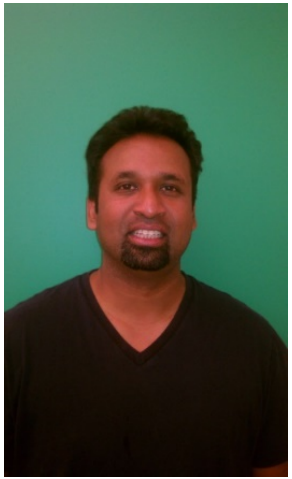
Parag Gad

Joel Burdick

Ruslan Gorodnichev

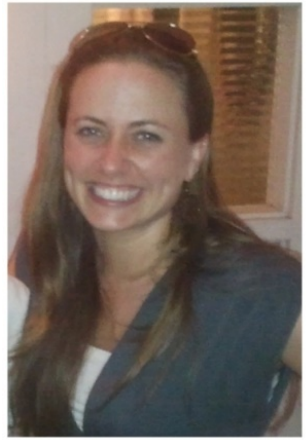
Wentai Liu

Mandy Turner



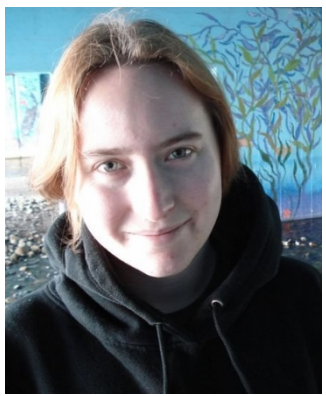
Michael (Selvan) Joseph

Niranjala Tilakaratne



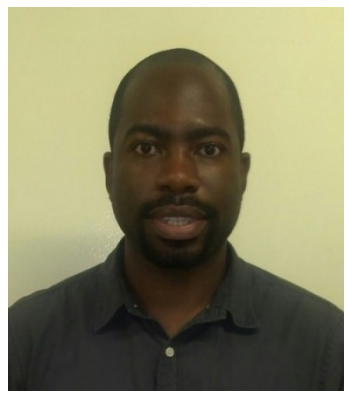
Erica Dale

Jaehoon Choe



Lisa Moore

Mrinal (Neil) Rath



Paul Duru

Susan Harkema

Jonathan Hodes

Claudia Angeli

Acknowledgments

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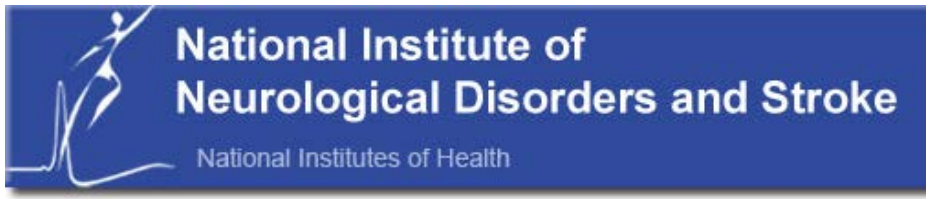
Biomedical Imaging and Bioengineering



NASA

US Congress

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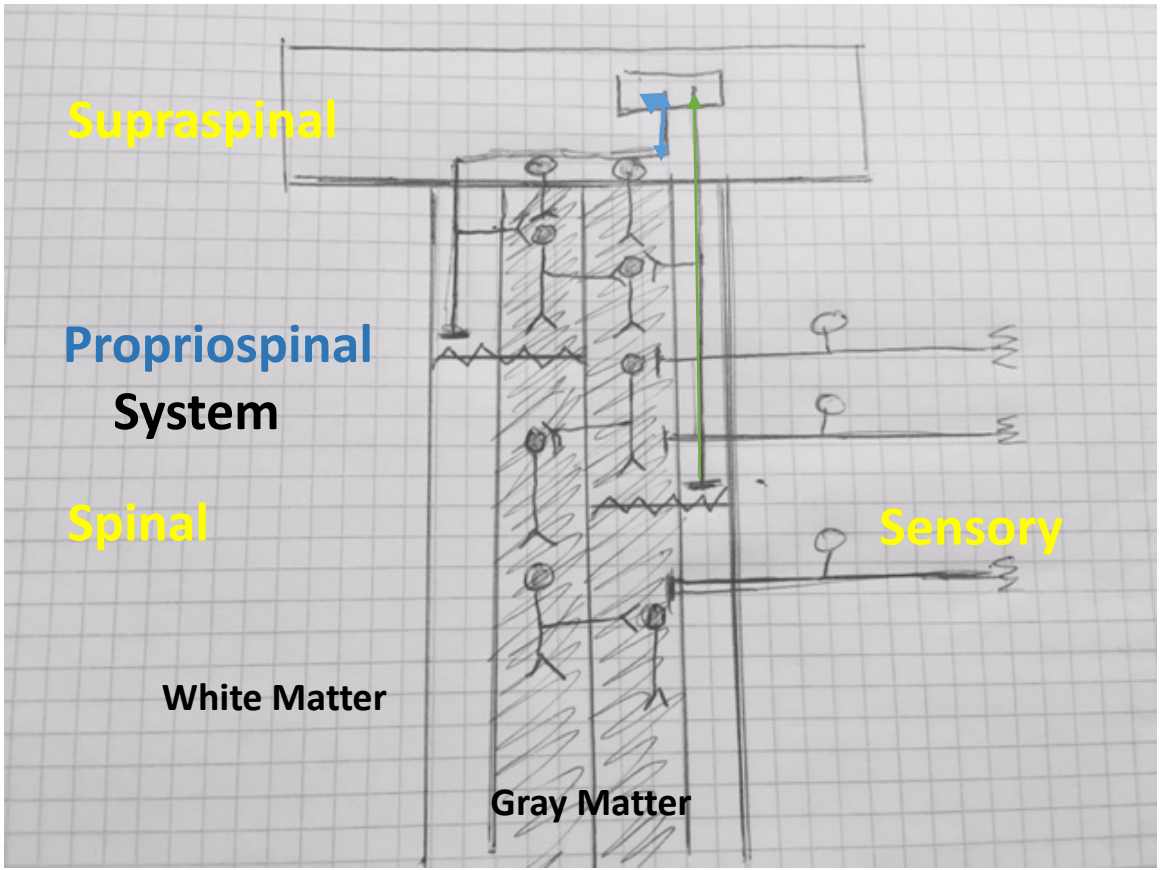
Al Mann Foundation

Jonathan & Marilyn Palo Family


Supraspinal
Propriospinal
System
Spinal
Sensory
White Matter
Gray Matter