Restoring function after spinal cord injury: New research in neural stimulation

Chet Moritz, Ph.D.
Assistant Professor
Departments of Rehabilitation Medicine and Physiology & Biophysics
University of Washington

Goal: Restore limb function after SCI

Dual Outcome Goals
- Enable movements and promote recovery after incomplete injury
- Directly re-animate limb function after complete injury

Our Approach: develop a brain-controlled spinal interface (BCSI) to restore limb function after paralysis due to spinal cord injury
Three approaches to restore limb function after SCI

1. Epidural Spinal Stimulation
   - FDA approved for treatment of chronic pain
   - In animal models, stimulation at L2 segment below an injury results in coordinated stepping if combined with treadmill training.
   - Effect enhanced when combined with quipazine (5-HT agonist)

2. Intraspinal Microstimulation

3. Brain Controlled Interfaces (BCSI)
Epidural Stimulation

- A 23-year-old man with paraplegia from a C7–T1 subluxation
- MRI of the injury site revealed atrophy of cord segment adjacent to T1.
- ASIA - B (pinprick and light-touch sensation present below the lesion).
  - No motor function of trunk or leg muscles
  - Flaccid anal sphincter, no voluntary bladder contraction.
  - Sensation abnormal below C7

Harkema et al, Lancet 2011

Epidural Stimulation Methods

- Multisite epidural electrode array implanted over L1-S1 spinal segments
- Therapeutic stimulation duration 40-120 minutes using frequencies of 5-40 Hz
- 7 months of stimulation paired with physical therapy movement training (standing, stepping, etc.)

Harkema et al, Lancet 2011
Without Epidural Stimulation

Attempts of voluntary movements (leg, ankle, and toe) without epidural stimulation

With Epidural Stimulation ON

Voluntary movements (leg, ankle, and toe) with epidural stimulation (4 V, 30 Hz)
Epidural stimulation x4 subjects

Three approaches to restore limb function after SCI

1. Epidural Spinal Stimulation
2. Intraspinal Microstimulation
3. Brain Controlled Interfaces
Therapeutic intraspinal stimulation

- With rare exception, epidural stimulation only enabled movements during periods of stimulation.
- Intraspinal microstimulation directly activates circuits within the spinal cord.
- Can therapeutic intraspinal stimulation lead to sustained improvements in movement after injury?

Mondello et al... Moritz  Frontiers in Neuroprosthetics  2014

Therapeutic intraspinal stimulation

Examine Recovery benefit of ISMS that persist beyond the period of stimulation

- Rats trained at tested at precision forelimb reaching task (FRT)
- Receive lateralized C4 contusion injury
- Therapeutic ISMS 7 hrs/day for 12 weeks

Kasten et al... Moritz,  Journal of Neural Engineering  2013
Evidence of sustained recovery after stimulation is discontinued

Therapeutic ISMS promotes recovery after spinal contusion injury

Kasten et al... Moritz, Journal of Neural Engineering 2013

Mondello et al... Moritz Frontiers in Neuroprosthetics 2014

Therapeutic intraspinal microstimulation (ISMS) activates extensor synergies & reduces flexor tone (spasticity)

Kasten et al... Moritz, Journal of Neural Engineering 2013

Stimulated animals exhibit improved extension and durable reductions in flexor tone beyond ISMS
Potential mechanisms of therapeutic spinal stimulation

- Epidural stimulation: Bring networks closer to threshold so remaining descending drive can activate (Harkema et al. Lancet 2011)

- Intraspinal stimulation: re-regulate neural circuits below injury to improve tone/spasticity (e.g. 5-HT) (Kasten et al. J Neural Eng 2013)

- Muscle & nerve stimulation (e.g., FES) also improves tone/spasticity for animal and human subjects post SCI (Mirbagheri et al. IEEE Trans Neural Syst Rehabil 2002) (Jung et al. J Neural Eng 2009)

Three approaches to restore limb function after SCI

1. Epidural Spinal Stimulation
2. Intraspinal Microstimulation
3. Brain Controlled Interfaces
Brain-controlled interfaces to treat severe paralysis

Brain-computer interfaces typically focus on cortical motor areas

Brain recording methods

Signals recorded from outside or inside the brain

Scalp based EEG

Humans control cursors & robot’s choices

Wolpaw, Birbaumer, Rao, et al

Electrocorticography (ECoG)

Epilepsy patients control 2D cursors and robotic hand

Ojemann, Birbaumer, et al

Intracortical electrodes

Monkeys & humans control cursors, robotic arms & hands

Junghues, Schwartz, Nicholaus, Shenoy, et al
Brain cell activity during wrist movement

Brain cell directional tuning

Visual feedback of cell rate with targets oriented in preferred direction
Monkey controls cursor with brain cell

Decoding from human motor cortex

Hochberg et al… Donoghue, Nature 2006
Control robotic arm 5 years after implant

Serial 2D task + Grasp/Tilt using only 3 to 13 neurons

Hochberg et al... Donoghue, Nature 2012

Human brain-control of 7 DOF robotic arm

52 y/o woman with motor complete spinocerebellar degeneration implanted with two Utah arrays in motor cortex

Collinger et al... Schwartz, Lancet 2012
Connecting cortical neurons to control muscle stimulation

Extract control signals from brain

Reanimate limbs using muscle stimulation (FES)

Brain control of muscle stimulation

Control signals recorded from motor cortex...

...trigger functional electrical stimulation (FES) delivered to paralyzed muscles

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Brain-controlled muscle stimulation

- Cell activity directly converted to muscle stimulation (FES)
- Wrist muscles temporarily paralyzed by nerve block

Cortical control of muscle stimulation

Cortical neurons move cursors on computer screen

Cortical neurons trigger FES of paralyzed muscles via standard or miniature computer
Brain-control of muscle stimulation

Monkeys match 5 levels of wrist torque using cortically-controlled FES
Only 5-10% of torque can be produced without stimulator

Cell tuning does not predict control of FES

- Tuned neurons initially control cursor faster
- The brain learns to use all neurons equally well to control FES with practice
- Biofeedback triples population of useful neurons
Three approaches to restore limb function after SCI

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2. Intraspinal Microstimulation
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Advantages of intraspinal stimulation

- More natural recruitment order of motor units
  (Mushahwar & Horsch, 2000)
  - Smooth grading of force
  - Fatigue-resistant contractions
- Elicit functional muscle synergies or reflex circuits from single stimulating electrodes, reducing number of electrodes & controllers
  (Mushahwar et al. 2002)
Lumbar intra-spinal microstimulation (ISMS) produces fatigue-resistant walking for ~10-fold longer distances than muscle FES.

Cervical Intra-Spinal Micro-Stimulation (cISMS)

Mushahwar et al. In Review
Cervical spinal stimulation evokes hand & arm movements

Perlmutter et al. 1998

Sunshine et al… Moritz, Journal of Neural Engineering 2013

ISMS Evoked Movements

Elbow Extension  Wrist Flexion

Sunshine et al… Moritz, Journal of Neural Engineering 2013
Transient change in movement post-injury

Sunshine et al… Moritz, Journal of Neural Engineering 2013

Three approaches to restore limb function after SCI

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Brain-Controlled spinal Interface (BCSI)
Brain cell activity correlates with reaching movement

Brain-Controlled Spinal Interface (BCSI)
BCSI operation permits lever deflection

Stimulator OFF  Stimulator ON

Restoration of function with BCSI

Stimulator OFF  Stimulator ON

levins & Moritz, *In preparation*
Summary: Neural stimulation after SCI

1. Both epidural and intraspinal spinal stimulation enhance movement after injury. Can spinal stimulation lead to long-term recovery of human subjects after SCI?

2. Recorded brain activity can be used to control computers, robotic arms and muscle stimulation. Can brain computer interfaces improve quality of life after SCI?

3. Intraspinal stimulation evokes robust movements of the hand & arms after injury. Is brain-control of spinal stimulation an ideal method for reanimation of paralyzed limbs?
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