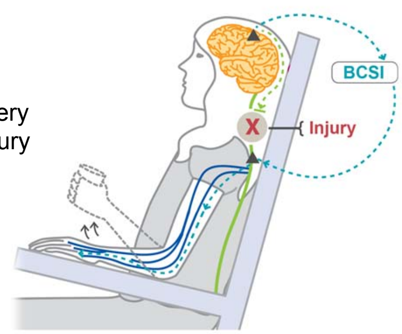
Restoring function after spinal cord injury:
New research in neural stimulation

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

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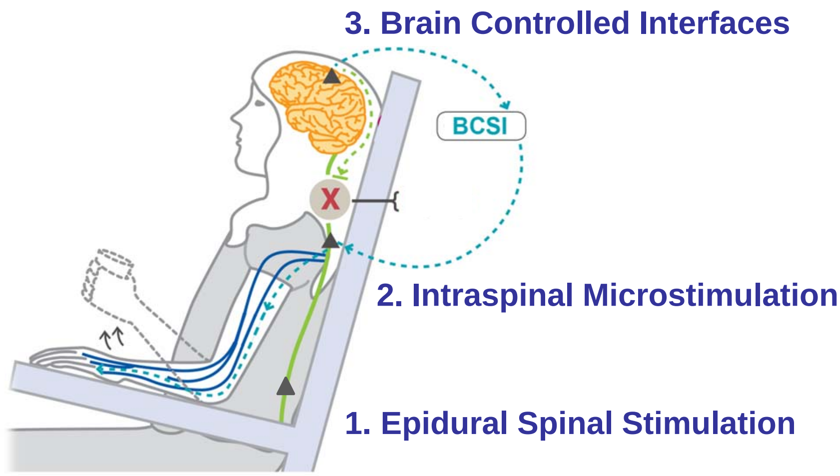
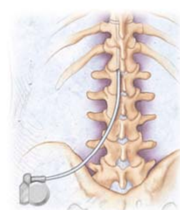
Three approaches to restore limb function after SCI

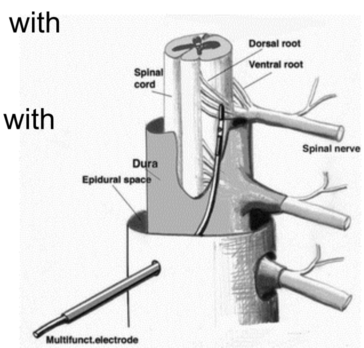


Epidural spinal stimulation to enable movement



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)



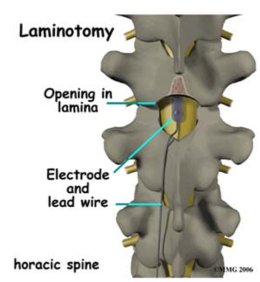
Epidural Stimulation

- 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-S1spinal 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.)



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***Harkema et al*, *Lancet* 2011**

Without Epidural Stimulation

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

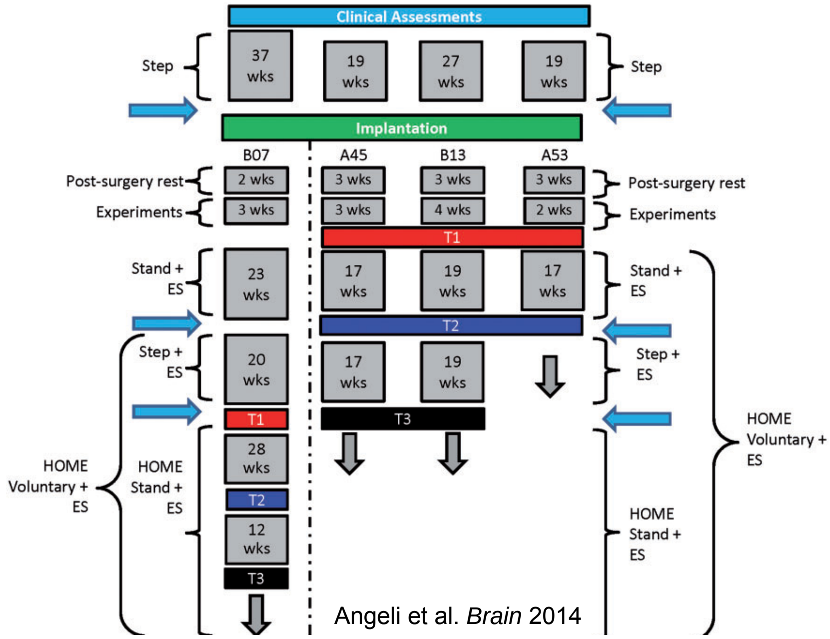
UNIVERSITY of WASHINGTON ***Harkema et al*, *Lancet* 2011**

With Epidural Stimulation ON

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

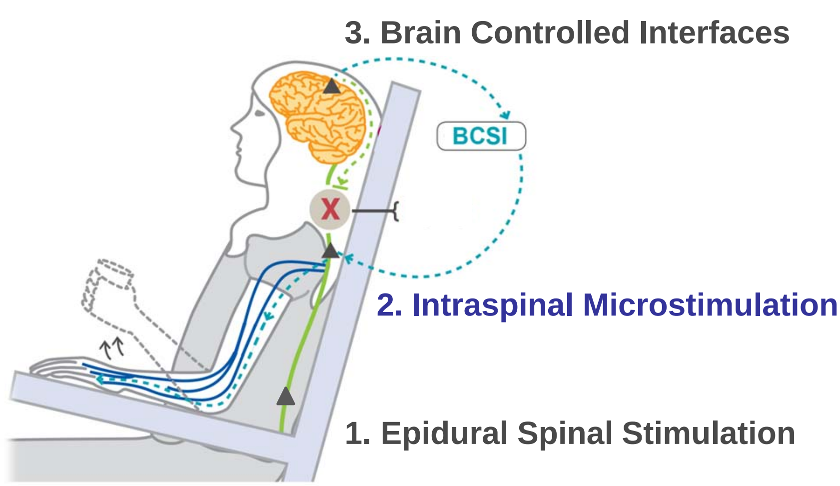
UNIVERSITY of WASHINGTON **Harkema et al., *Lancet* 2011, and Angeli et al., *Brain* 2014**

Epidural stimulation x4 subjects



Angeli et al. *Brain* 2014

Three approaches to restore limb function after SCI



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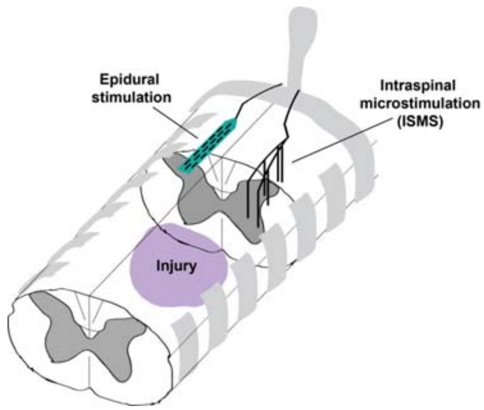
Therapeutic intraspinal stimulation

- 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?



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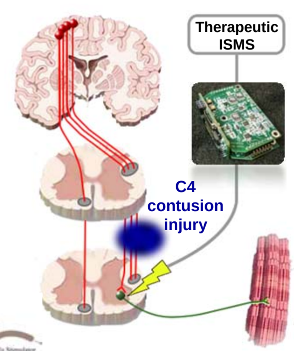
Mondello *et al*… Moritz *Frontiers in Neuroprosthetics* 2014

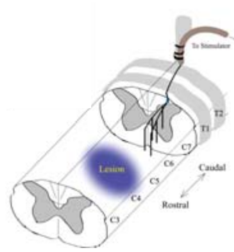
Therapeutic intraspinal stimulation

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

Forelimb reach task





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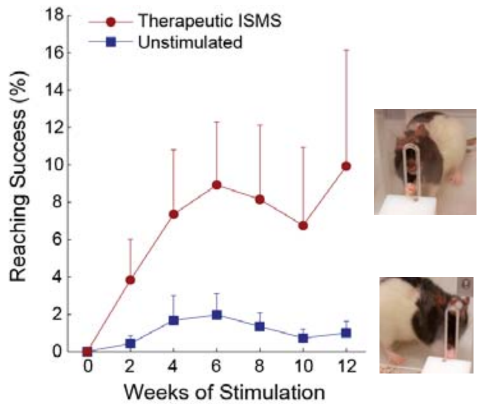
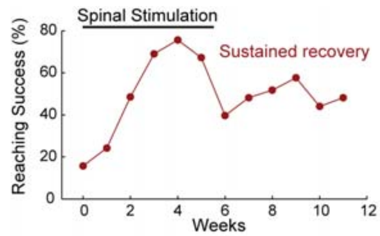
Kasten *et al*… Moritz, *Journal of Neural Engineering* 2013

Therapeutic intra-spinal stimulation improves function

Therapeutic ISMS promotes recovery after spinal contusion injury



Evidence of sustained recovery after stimulation is discontinued



Kasten *et al*… Moritz, *Journal of Neural Engineering* 2013

Mondello *et al…* Moritz *Frontiers in Neuroprosthetics* 2014

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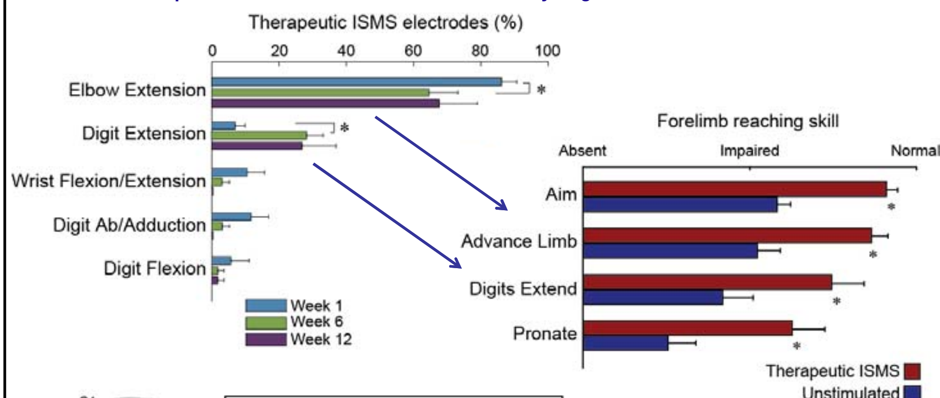
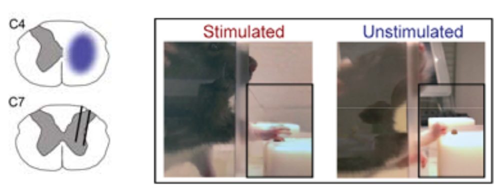
Therapeutic intraspinal microstimulation (ISMS) activates extensor synergies & reduces flexor tone (spasticity)

Therapeutic ISMS activates forelimb extensor synergies





Stimulated animals exhibit improved extension and durable reductions in flexor tone beyond ISMS

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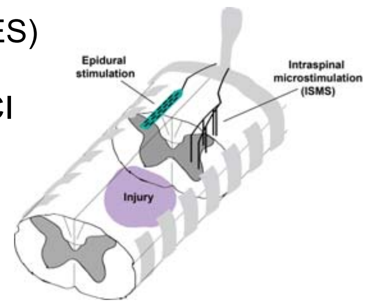
Kasten *et al*… Moritz, *Journal of Neural Engineering* 2013

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)



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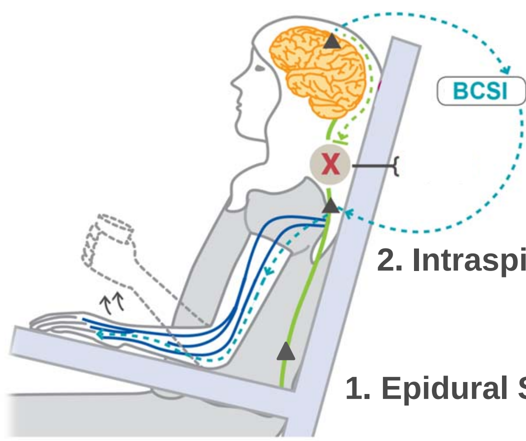
Three approaches to restore limb function after SCI



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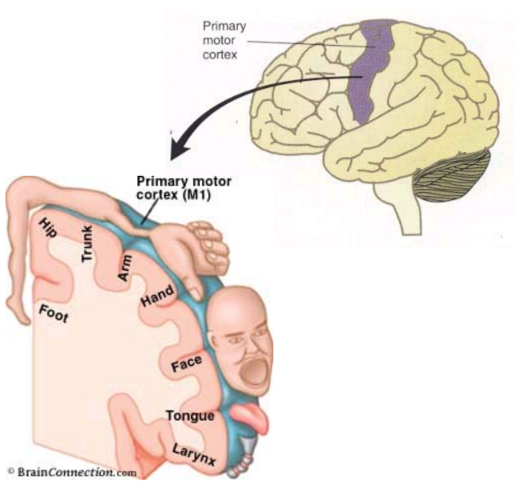
Brain-controlled interfaces to treat severe paralysis



Brain-computer interfaces typically focus on cortical motor areas

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Brain recording methods

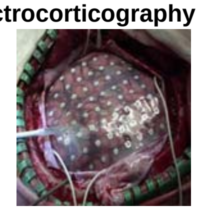
Signals recorded from outside or inside the brain

Scalp based EEG

Humans control cursors & robot's choices

Wolpaw, Birbaumer, Rao, et al

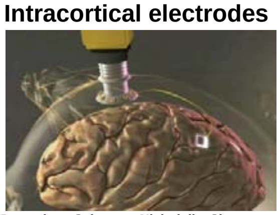
Electrocorticography (ECoG)



Epilepsy patients control 2D cursors and robotic hand

Ojeman, Birbaumer, et al

Intracortical electrodes



Monkeys & humans control cursors, robotic arms & hands

Donoghue, Schwartz, Nicholalis, Shenoy, et al

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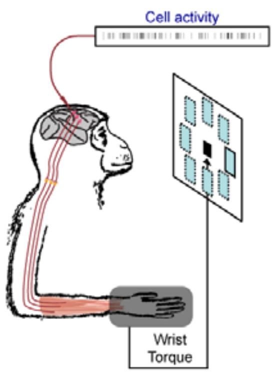
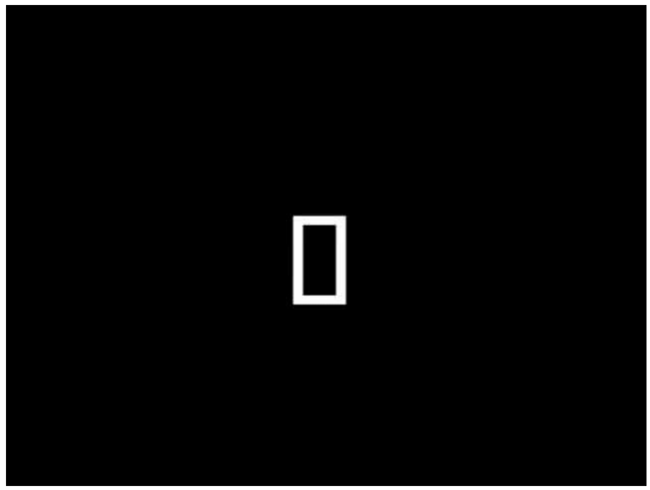
Brain cell activity during wrist movement





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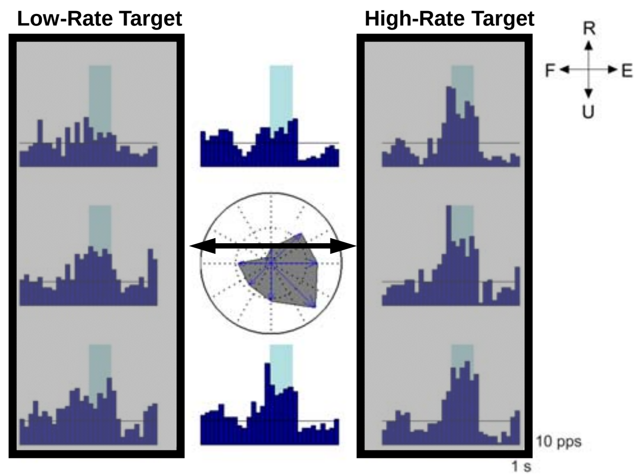
Brain cell directional tuning



Visual feedback of cell rate with targets oriented in preferred direction

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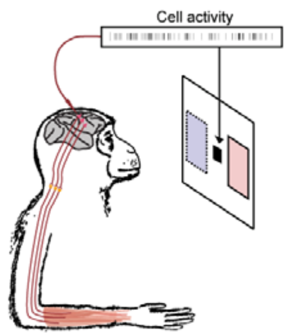
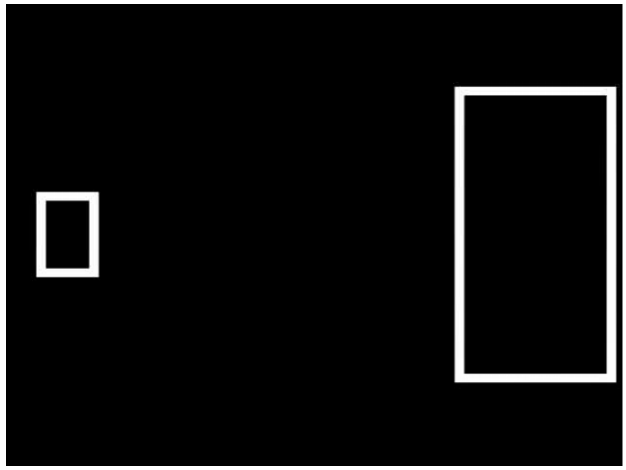
Monkey controls cursor with brain cell





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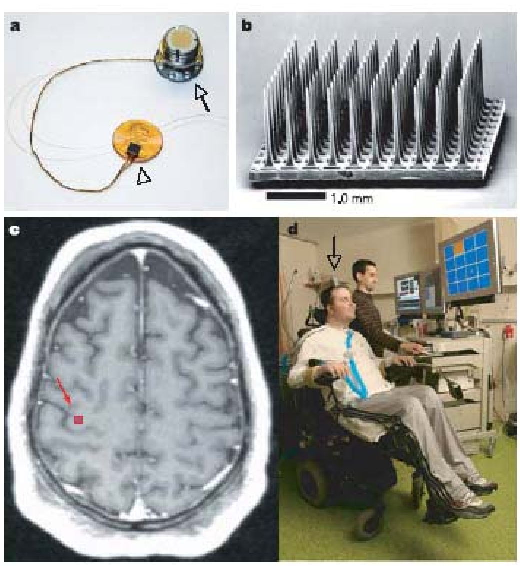
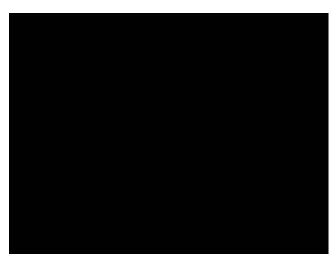
Decoding from human motor cortex



← 100-electrode array



30 neurons decoded for 2D cursor control

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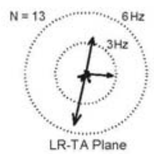
Hochberg et al… Donoghue, *Nature* 2006

Control robotic arm 5 years after implant



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

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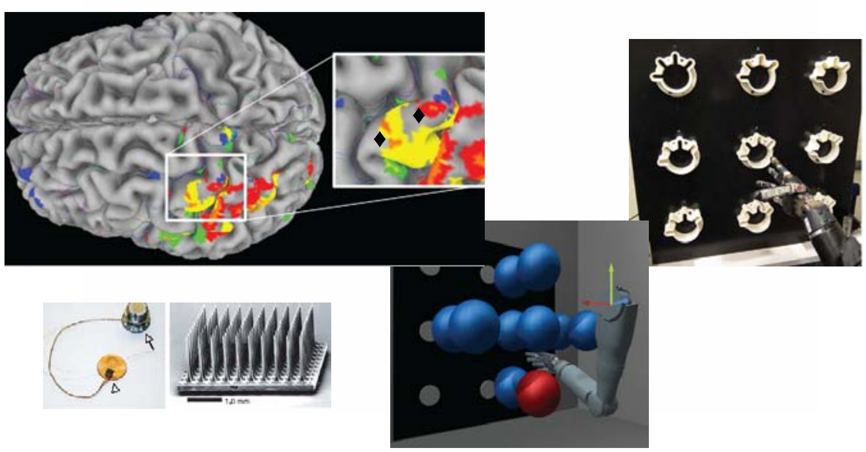
Hochberg et al… Donoghue, *Nature* 2012

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

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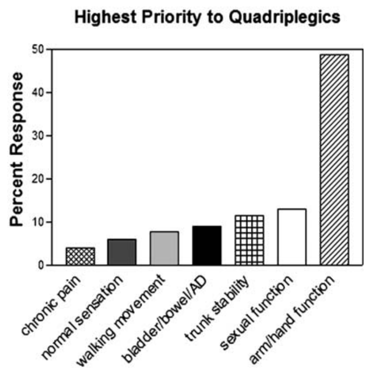
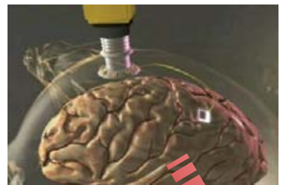
Collinger et al… Schwartz, *Lancet* 2012

Connecting cortical neurons to control muscle stimulation

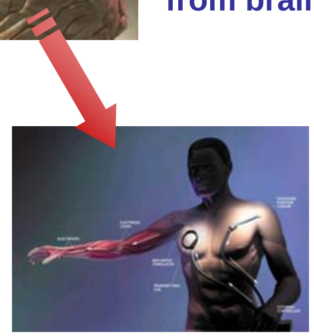


Anderson, *J Neurotrauma* 2004



Extract control signals from brain

Reanimate limbs using muscle stimulation (FES)



FreeHand*, Peckham *et al.

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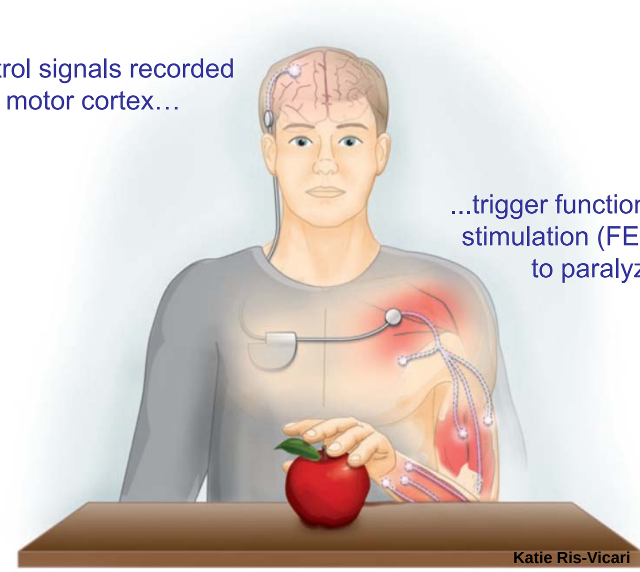
Brain control of muscle stimulation

Control signals recorded from motor cortex…

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



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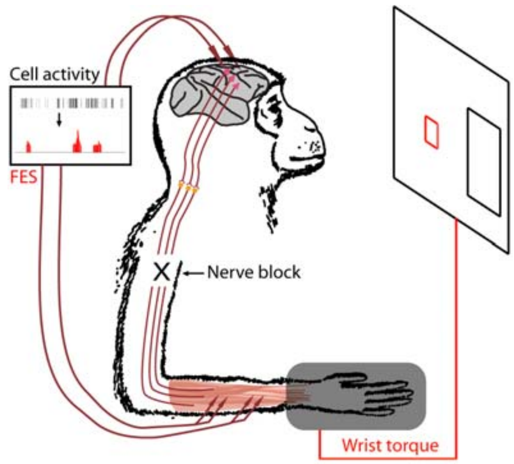
***News & Views* on Moritz *et al*; S. Scott, *Nature Neuroscience* 2008**

Brain-controlled muscle stimulation



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

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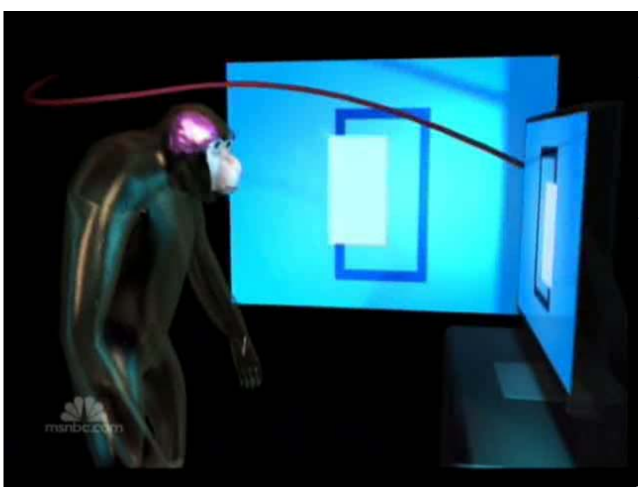
Moritz et al… Fetz *Nature* 2008

Cortical control of muscle stimulation



Cortical neurons move cursors on computer screen

Cortical neurons trigger FES of paralyzed muscles via standard or miniature computer

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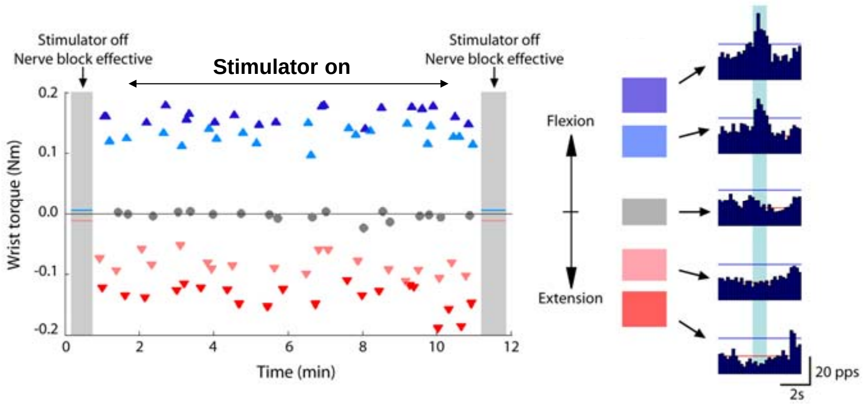
Moritz et al, *Nature* 2008

(c) Chet Moritz 2014

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

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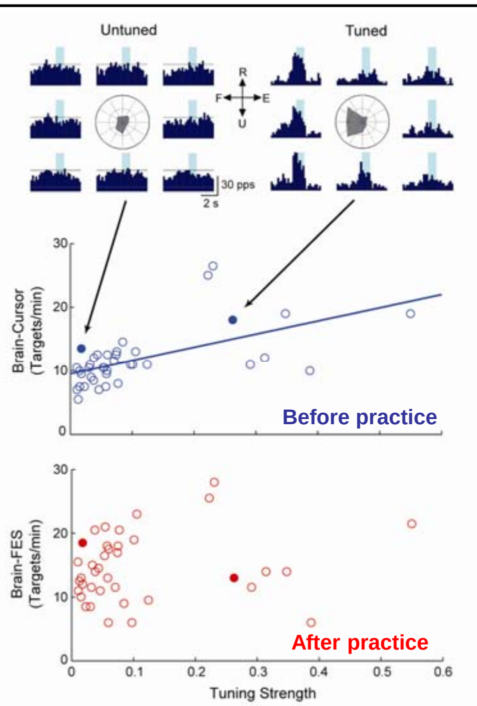
Moritz et al… Fetz *Nature* 2008

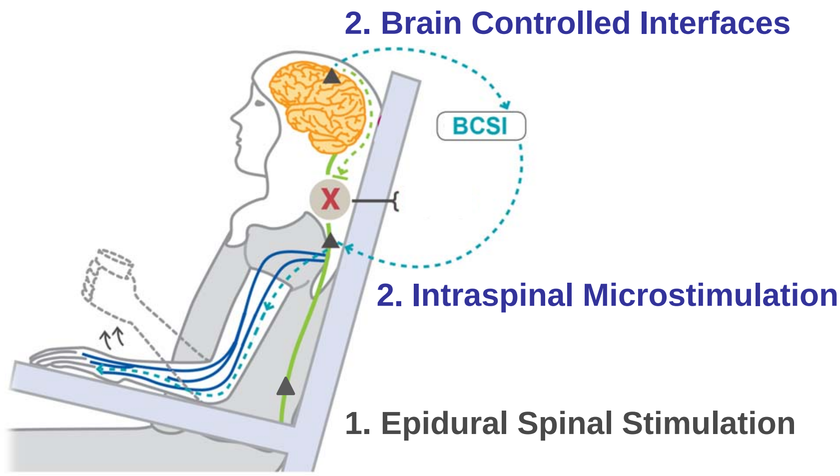
Cell tuning does not predict control of FES



- 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

Moritz et al… Fetz *Nature* 2008

Three approaches to restore limb function after SCI



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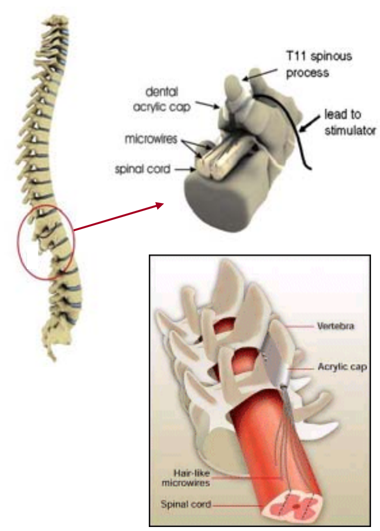
Advantages of intraspinal stimulation

- 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)



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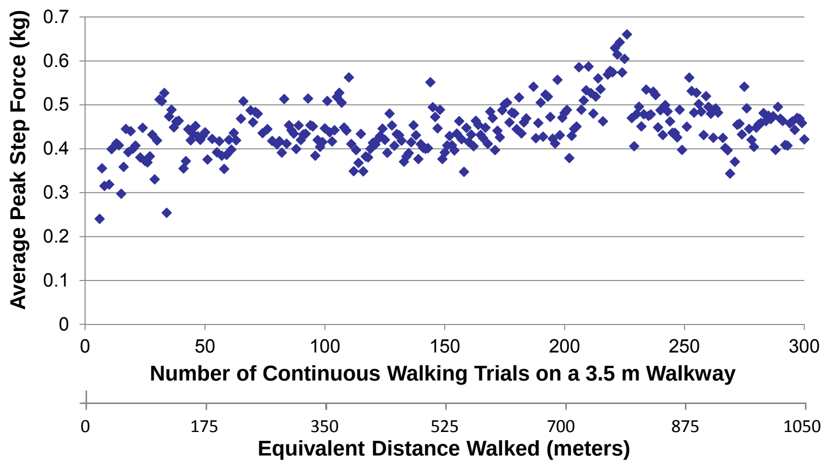
Mushahwar ***et al.*, *J Neural Eng*** 2007

Re-animate walking with ISMS for ~ 1kM



Lumbar intra-spinal microstimulation (ISMS) produces fatigue-resistant walking for ~10-fold longer distances than muscle FES

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Mushahwar *et al. In Review*

Cervical Intra-Spinal Micro-Stimulation (cISMS)

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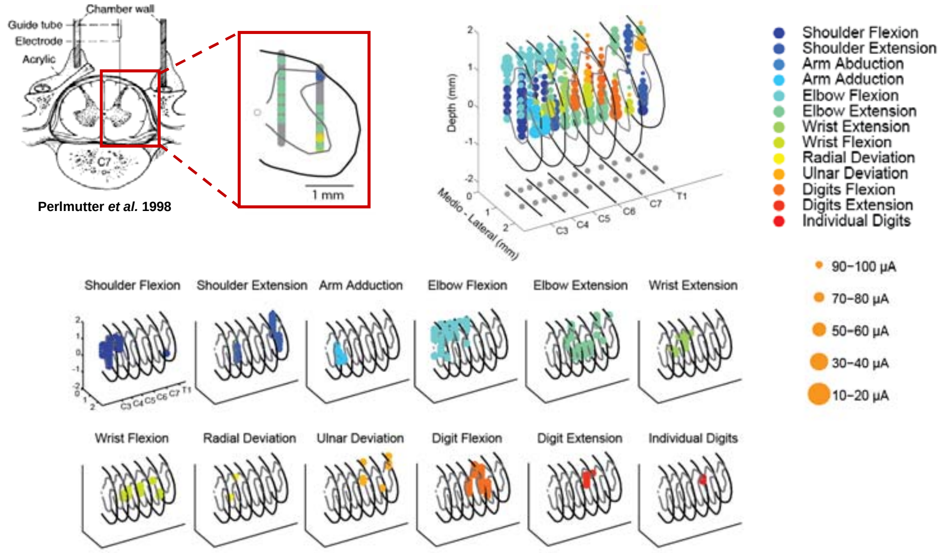
Moritz *et al… Fetz J Neurophysiol* 2007

Cervical spinal stimulation evokes hand & arm movements



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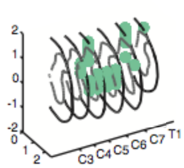
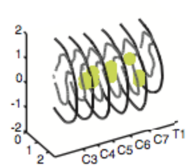
Sunshine et al… Moritz, *Journal of Neural Engineering* 2013

ISMS Evoked Movements

Elbow Extension



Wrist Flexion



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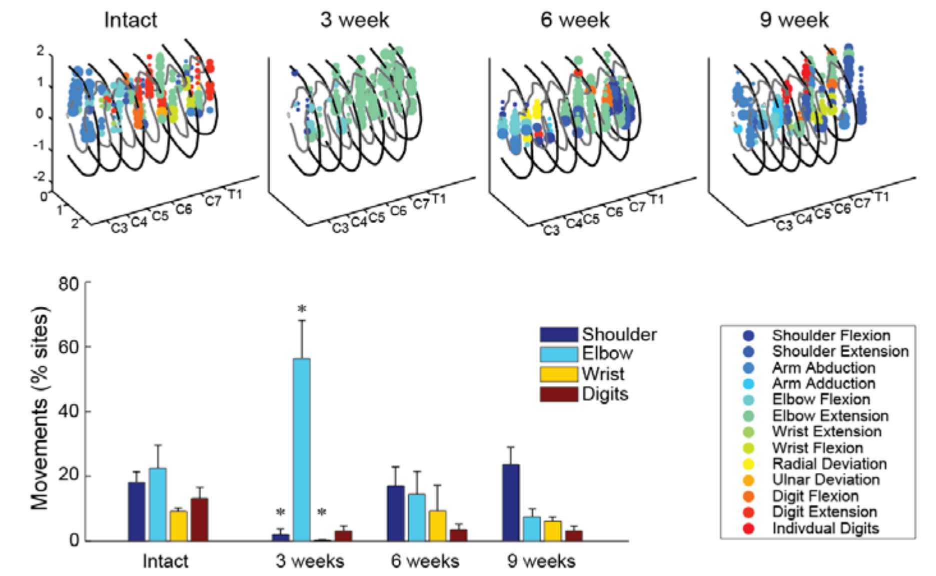
Sunshine et al… Moritz, *Journal of Neural Engineering* 2013

Transient change in movement post-injury



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Sunshine et al… Moritz, *Journal of Neural Engineering* 2013

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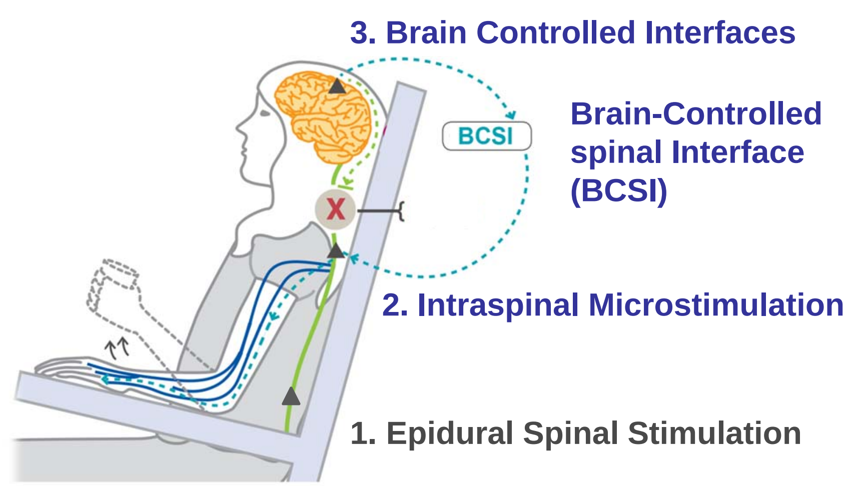

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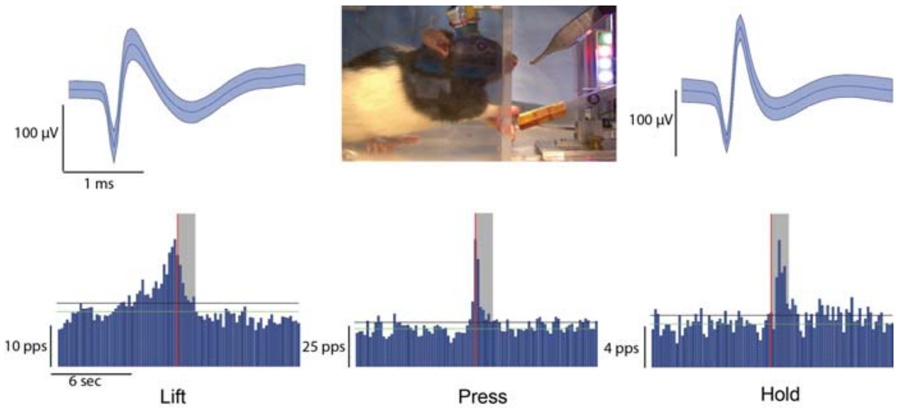
Brain cell activity correlates with reaching movement



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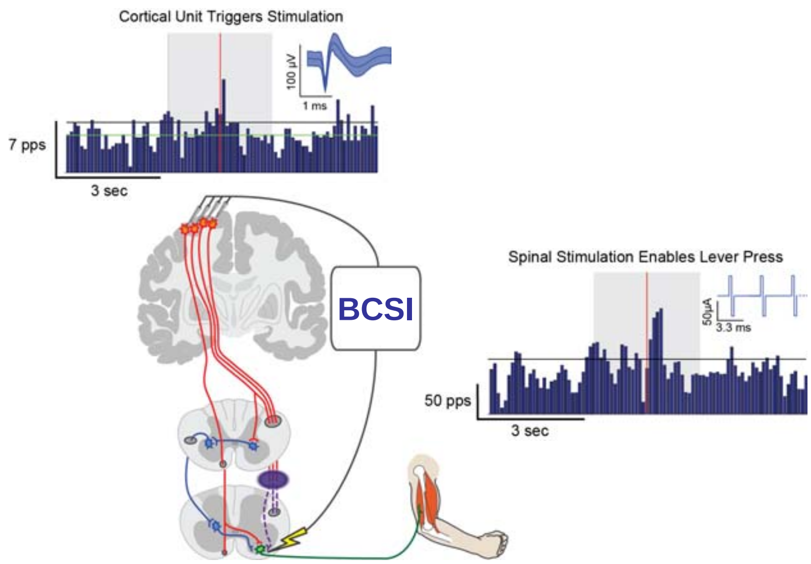
Ievins & Moritz, *In preparation*

Brain-Controlled Spinal Interface (BCSI)



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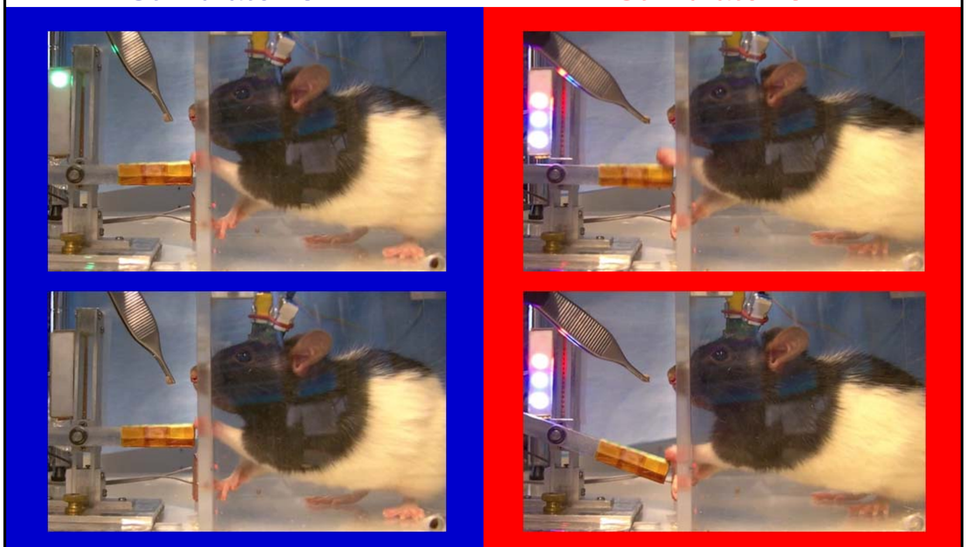
Ievins & Moritz, *In preparation*

BCSI operation permits lever deflection

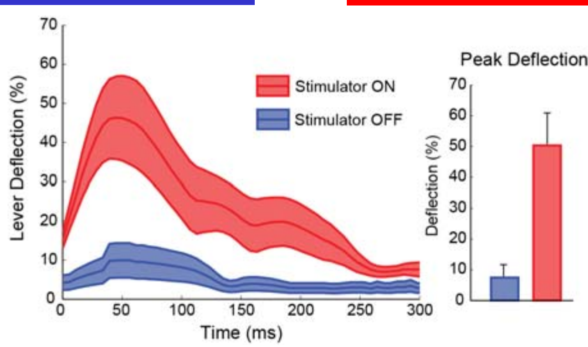
Stimulator OFF **Stimulator ON**



Ievins & Moritz, *In preparation*

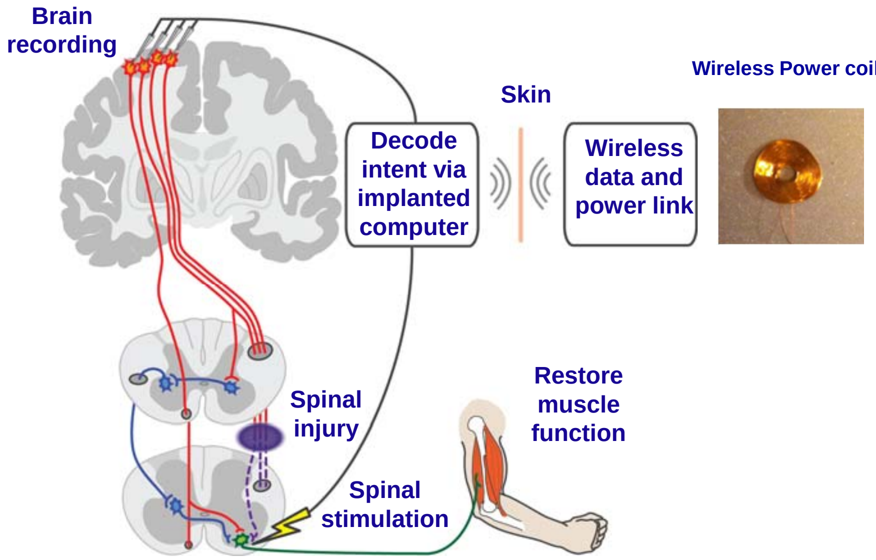
Restoration of function with BCSI

Stimulator OFF **Stimulator ON**



Ievins & Moritz, *In preparation*

Brain-Controlled Spinal Interface (BCSI)



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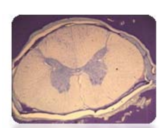
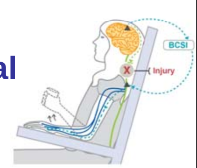
Collaboration with Josh Smith & Adrienne Fairhall

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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Acknowledgements

Eberhard Fetz
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Molly McCoy
Kendra Cherry

Phil Horner
Steve Perlmutter
Mike Kasten
Michael Sunshine
Aiva Ievins
Sam Nutt
Laura Schlosser
Eric Secrist
Alice Bosma-Moody
Ryan Carlson

Brian Otis
Sarah Mondello
David Boe
Dan Landeck
Anat Lubetzky-Vilnai
Elena Donoso Brown
Torey Gilbertson
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Reni Magbagbeola

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Jeremy Bilas
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John Burt
Behnum Habibi
Eliza Baird-Daniel
Nathaniel Cook
Jan Jimenez
Anand Kaul

Grad Students, Postdocs, *Undergraduates*

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