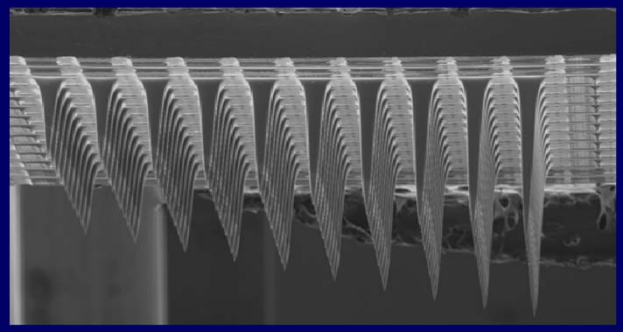
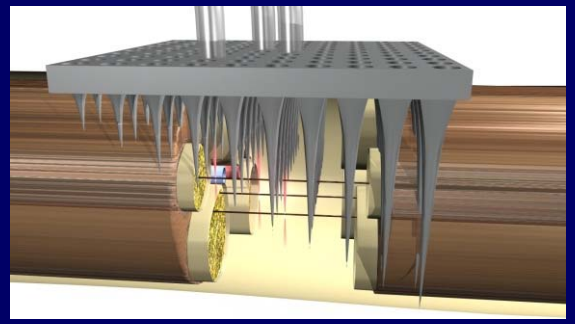
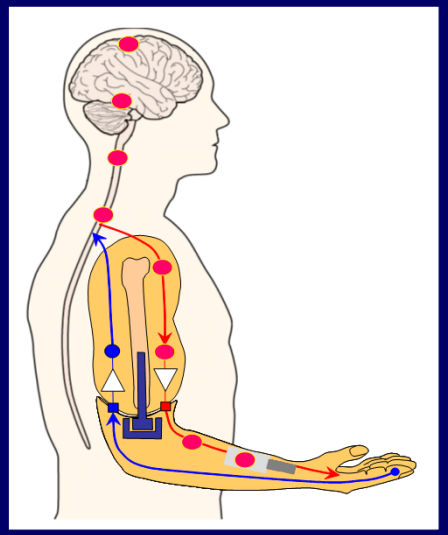




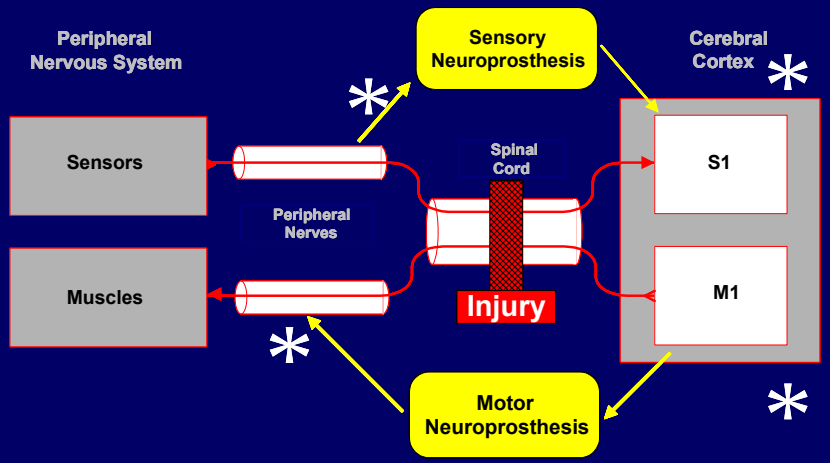
It Takes a Lot of Nerve: Using the Utah Slanted Electrode Array to Restore Sensorimotor Function

Gregory A. Clark

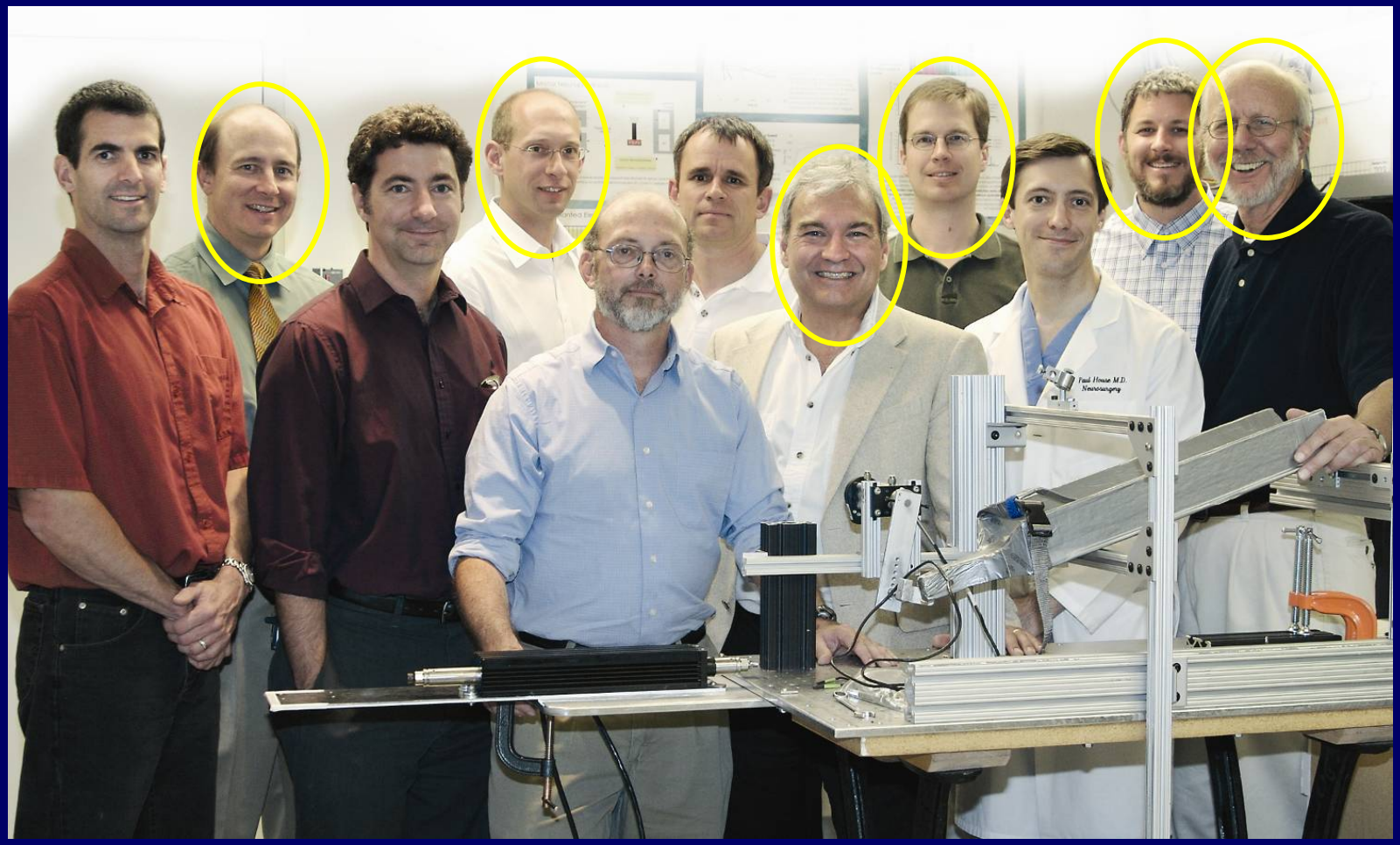
State of the Science Symposium
Regenerative Medicine and the Impact on Rehabilitation
Walter Reed National Military Medical Center
11 May 2012



(Kandel et al., 2000)



An Interdisciplinary Effort:
It Takes Not Only a Lot of Nerve—
But Also a Lot of Investigators!

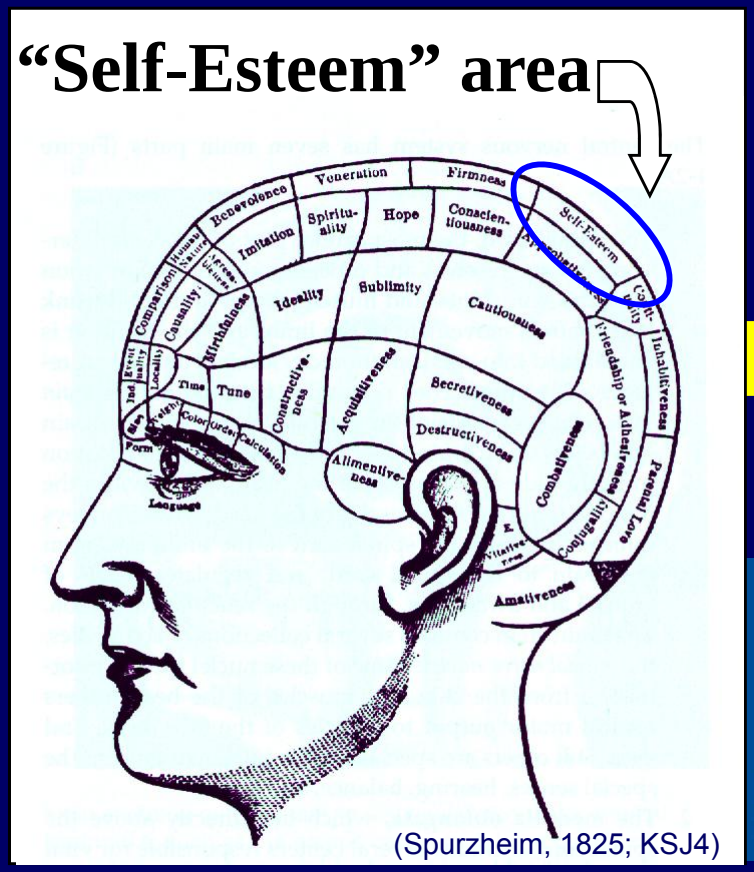


Nick Brown, Douglas “Hutch” Hutchinson, Shane Guillory (Ripple), Florian Solzbacher, Greg Clark, Michael Töpper (IZM), Patrick Tresco, Reid Harrison, Paul House, Bradley Greger, Richard Normann

Neuroprostheses:
Where?
How?

Central vs. Peripheral Interfaces?

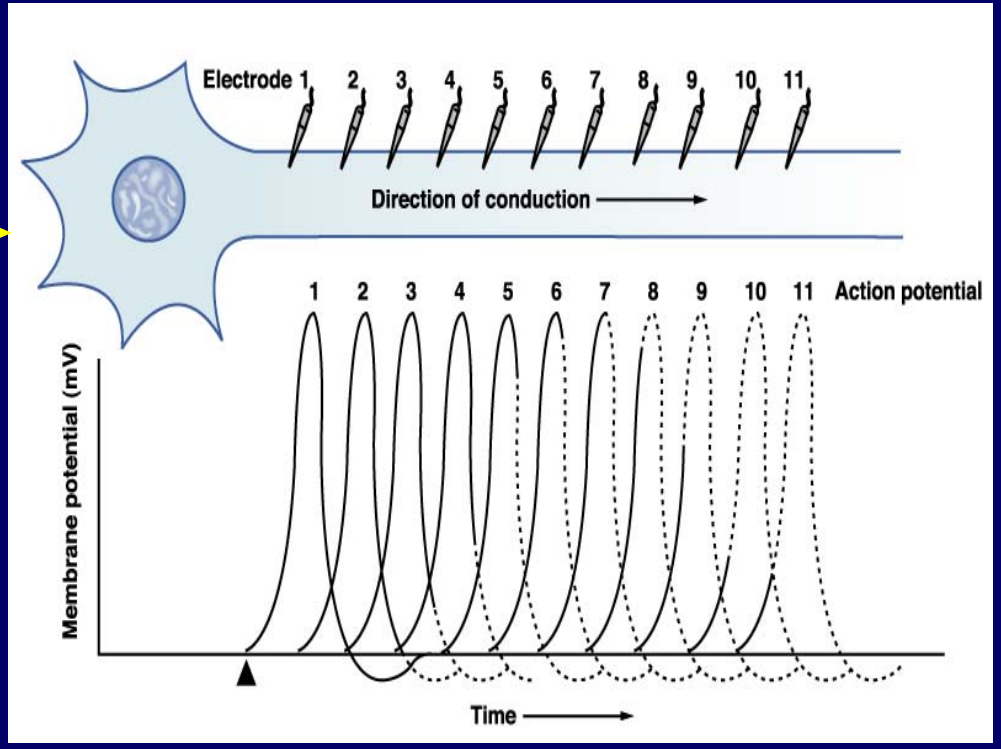
Brains are smart



(Spurzheim, 1825; KSJ4)

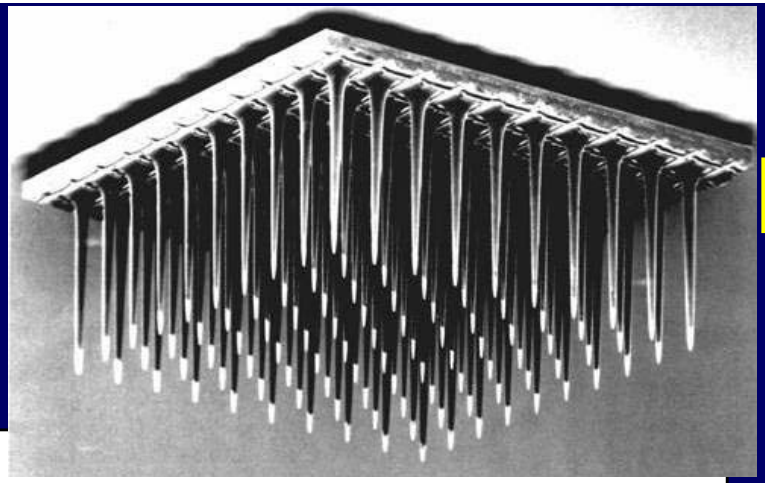
Nerves are dumb

(The axon doesn't think—
it only ax." -G. Bishop)

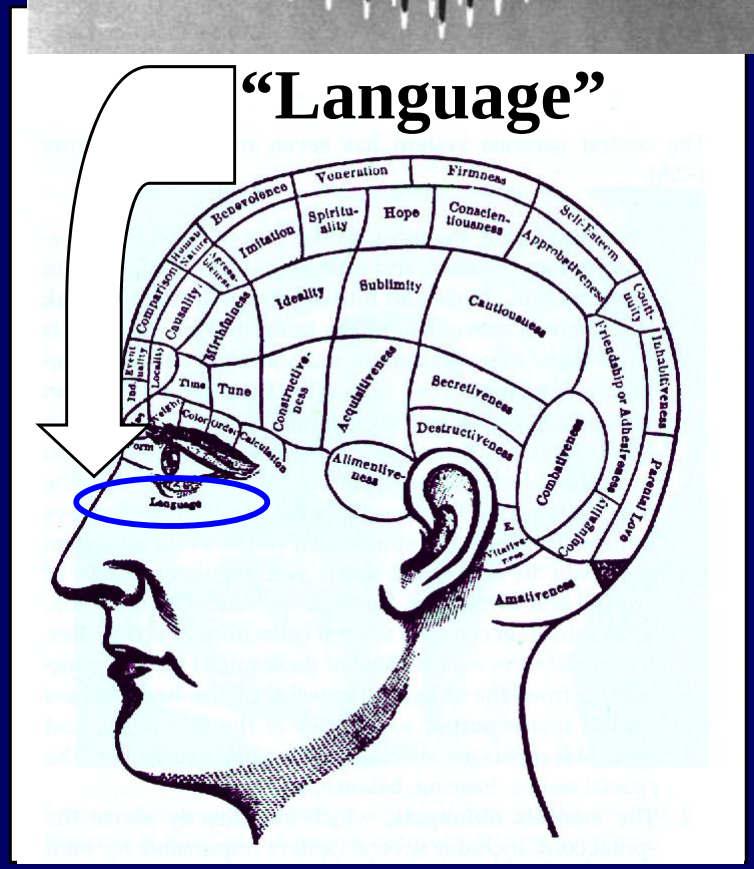


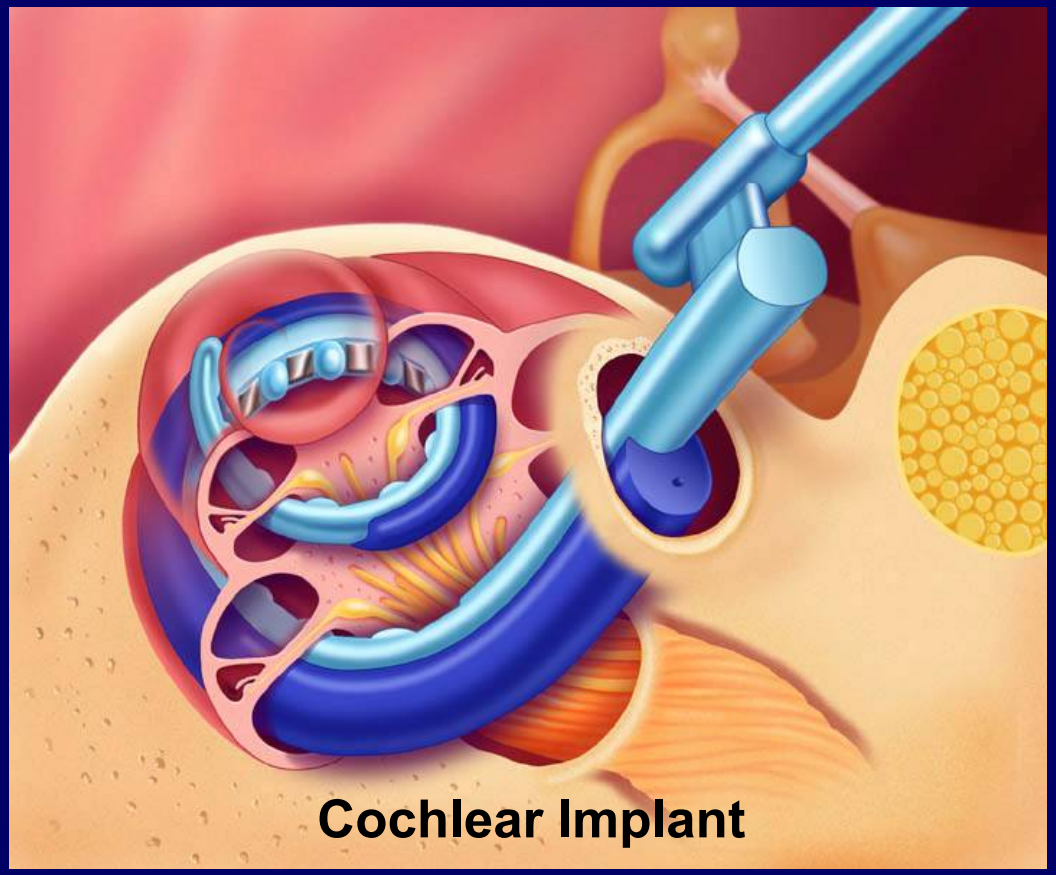
"Neuroprostheses" =
"BCIs", "BMIs"

FINAL COMMON PATHWAY
Motor: CNS → muscle
Sensory: CNS ← body



Do The Encode For Us





Successful speech perception without knowing the code!
Just provide the right pixels of information.

Safety & Patient Acceptance
"First, Do No Harm"

- ✓ PNS
  - "Go ahead and stick it in my nerve. I'm not using it anyway."
- ✓ CNS
  - "Go ahead and stick it in my brain. I'm not using it anyway."

Claudia Mitchell
Targeted Reinnervation Patient

What does the ***<u>customer</u>*** want?

"I told Doc he can do whatever he wants to my arm, but he ain't messing with my head."

Muscle Memory. Ben McGrath. *New Yorker,* July 30, 2007. Photograph by Martin Schoeller.

Motor and Sensory Neuroprostheses

Motor System

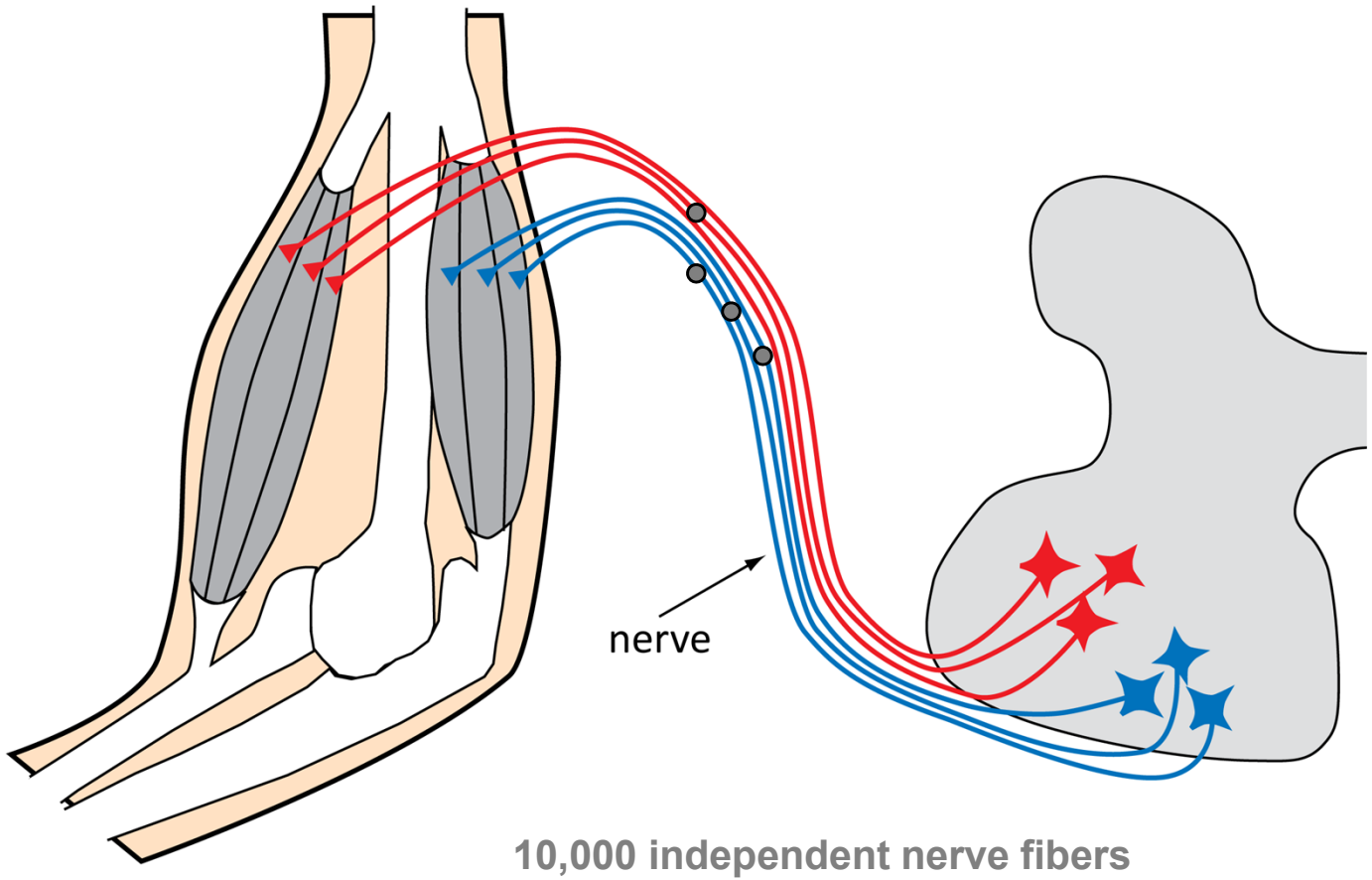
- A huge area of investigation

Somato-Sensory

- A huge area of investigation

- The good news: Nerves as bottlenecks
- The bad news: Nerves as bottlenecks

MOTOR. Multiple Muscles with Multiple Motor Units



We need to record *selectively*
with *multiple* electrodes *inside* the nerve

SENSORY. ~20 Somatosensory Receptor Types & Submodalites: We Need *Multiple* Signals and Sub-Fascicular *Selectivity*

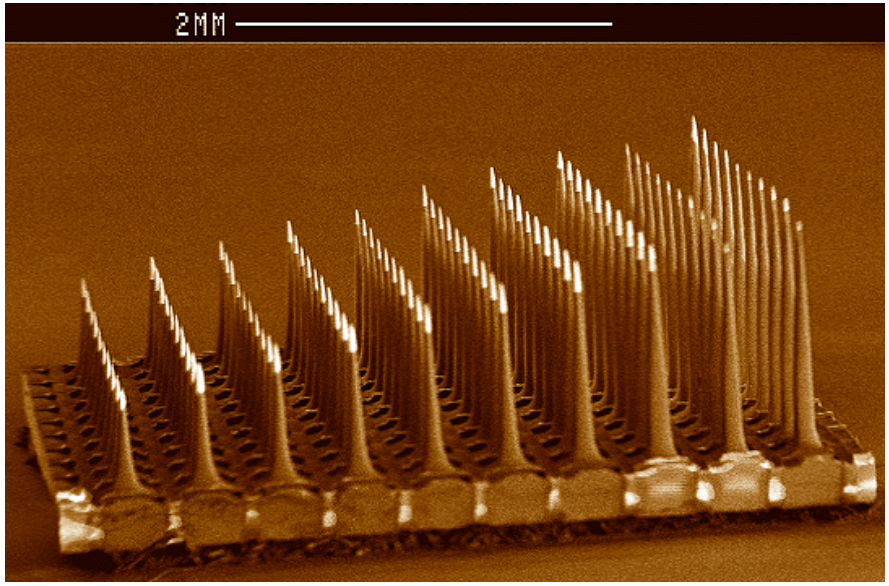
Table 22-1 Receptor Types Active in Somatic Sensation

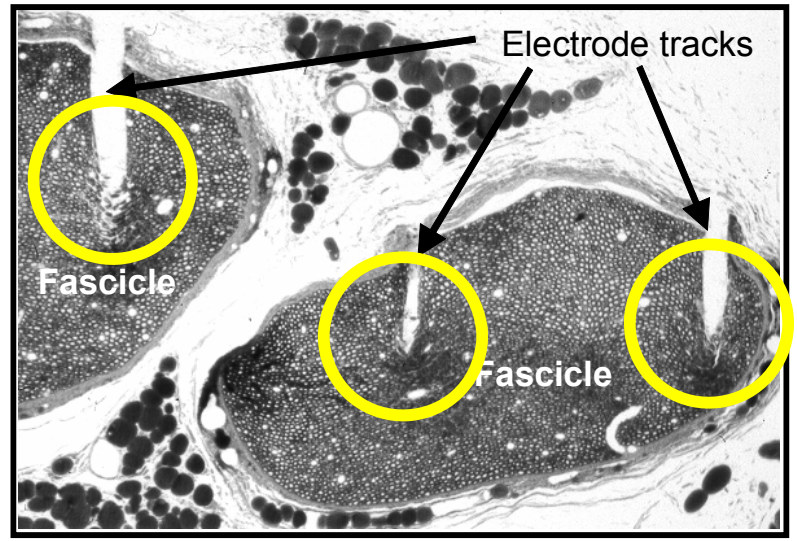
Receptor type	Fiber group[1]	Fiber name[1]	Modality
Cutaneous and subcutaneous mechanoreceptors			Touch
Meissner's corpuscle	Aα,β	RA	Stroking, fluttering
Merkel disk receptor	Aα,β	SAI	Pressure, texture
Pacinian corpuscle[2]	Aα,β	PC	Vibration
Ruffini ending	Aα,β	SAII	Skin stretch
Hair-tylotrich, hair-guard	Aα,β	G1, G2	Stroking, fluttering
Hair-down	Aδ	D	Light stroking
Field	Aα,β	F	Skin stretch
Thermal receptors			Temperature
Cool receptors	Aδ	III	Skin cooling (25°C)
Warm receptors	C	IV	Skin warming (41°C)
Heat nociceptors	Aδ	III	Hot temperatures (>45°C)
Cold nociceptors	C	IV	Cold temperatures (<5°C)
Nociceptors			Pain
Mechanical	Aδ	III	Sharp, pricking pain
Thermal-mechanical	Aδ	III	Burning pain
Thermal-mechanical	C	IV	Freezing pain
Polymodal	C	IV	Slow, burning pain
Muscle and skeletal mechanoreceptors			Limb proprioception
Muscle spindle primary	Aα	Ia	Muscle length and speed
Muscle spindle secondary	Aβ	II	Muscle stretch
Golgi tendon organ	Aα	Ib	Muscle contraction
Joint capsule mechanoreceptors	Aβ	II	Joint angle
Stretch-sensitive free endings	Aδ	III	Excess stretch or force

[1]See Table 22–2.
[2]Pacinian corpuscles are also located in the mesentery, between layers of muscle, and on interosseous membranes.

Kandel et al., 2000

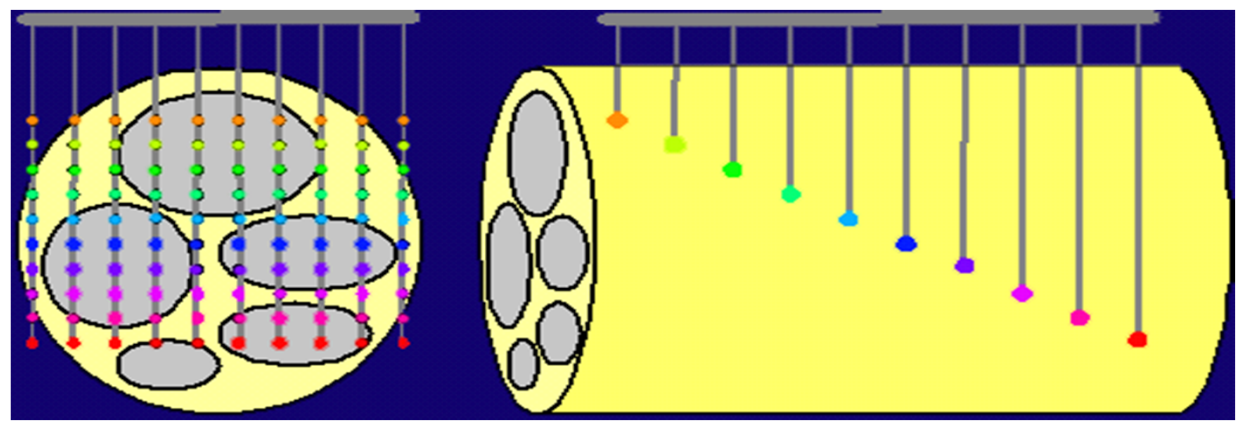
USEA: 100-Electrode Intrafascicular Array
The Willie Sutton Approach





USEA (10 x 10)

- Selective
- Comprehensive
  - ✓ Width
  - ✓ Depth
- Combinatorial
  - ✓ Multiple locations/modalities
- Simple decodes & encodes



A. Branner, R. Normann et al., 2004

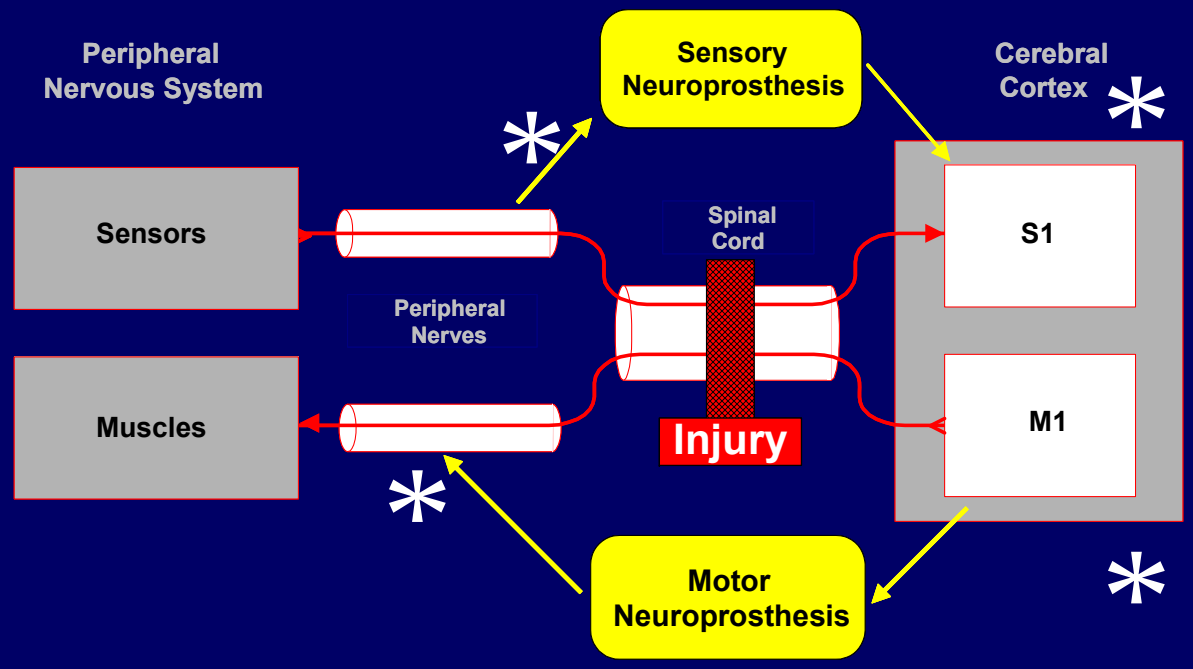
Cortical vs. Peripheral Interfaces?

Real (Non-facetious) Answer:

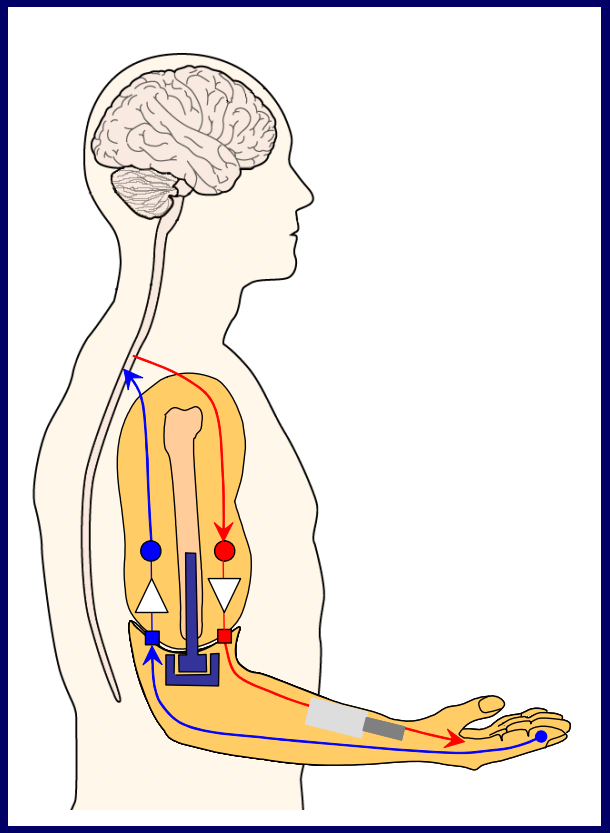
- ✓ Multiple, different approaches
  - Situation-specific
  - Patient preference
  - Also complementary and even synergistic
- ✓ Today: mostly what nerve can do

Sensorimotor Neuroprostheses

Spinal Cord Injury



Neuroprosthetic Limb



(Kandel et al., 2000)

Limb intact, pathways missing

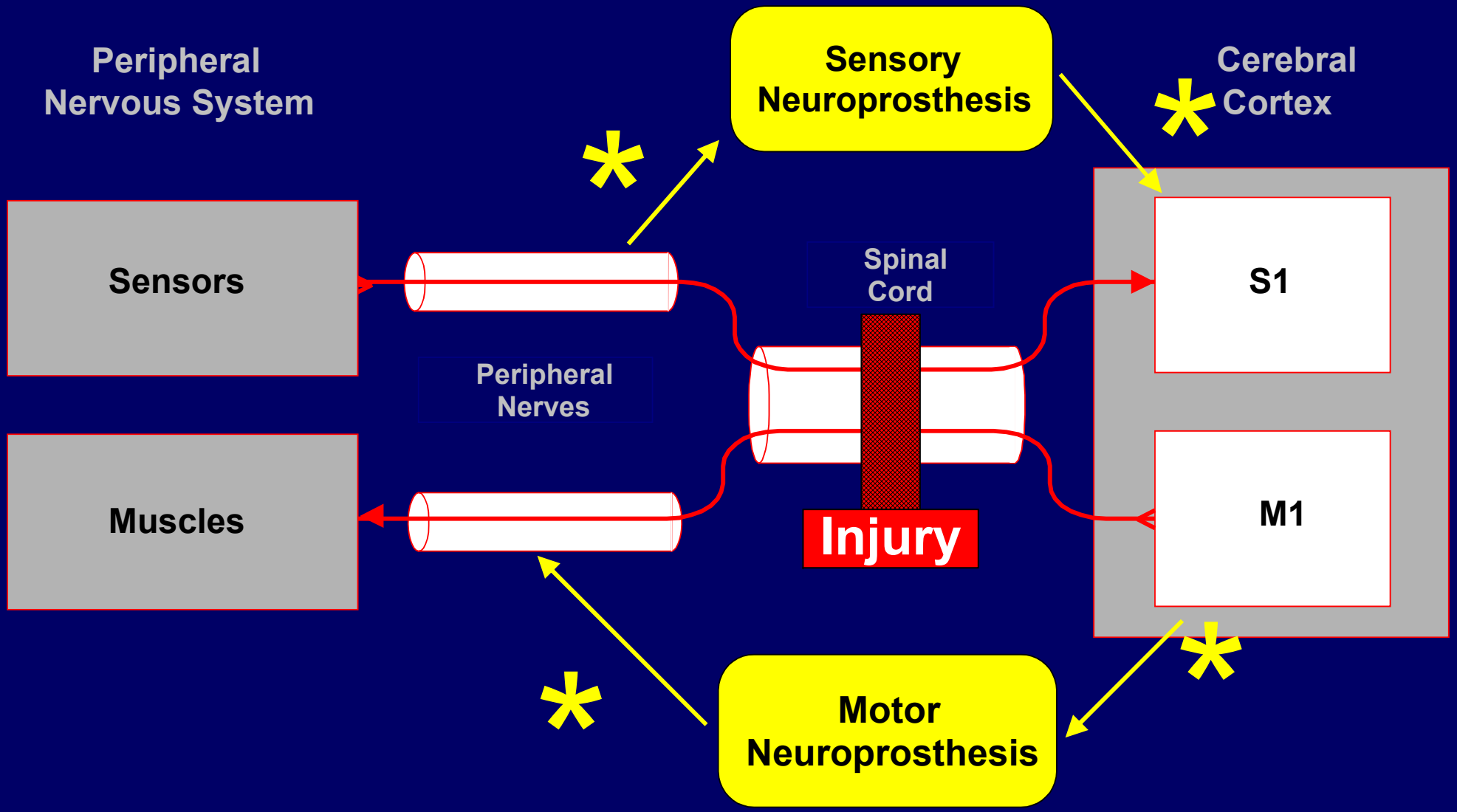
- ✓ Stimulate efferents
- ✓ Record afferents

Limb missing, pathways intact

- ✓ Record efferents
- ✓ Stimulate afferents

Both: Can we <u>record</u> from and <u>stimulate</u> nerve fibers?

Neuroprosthetic Interventions for SCI



Use of UEA & USEA has achieved success in all 4 stages

"To care for him [or her] who shall have borne the battle" – A. Lincoln

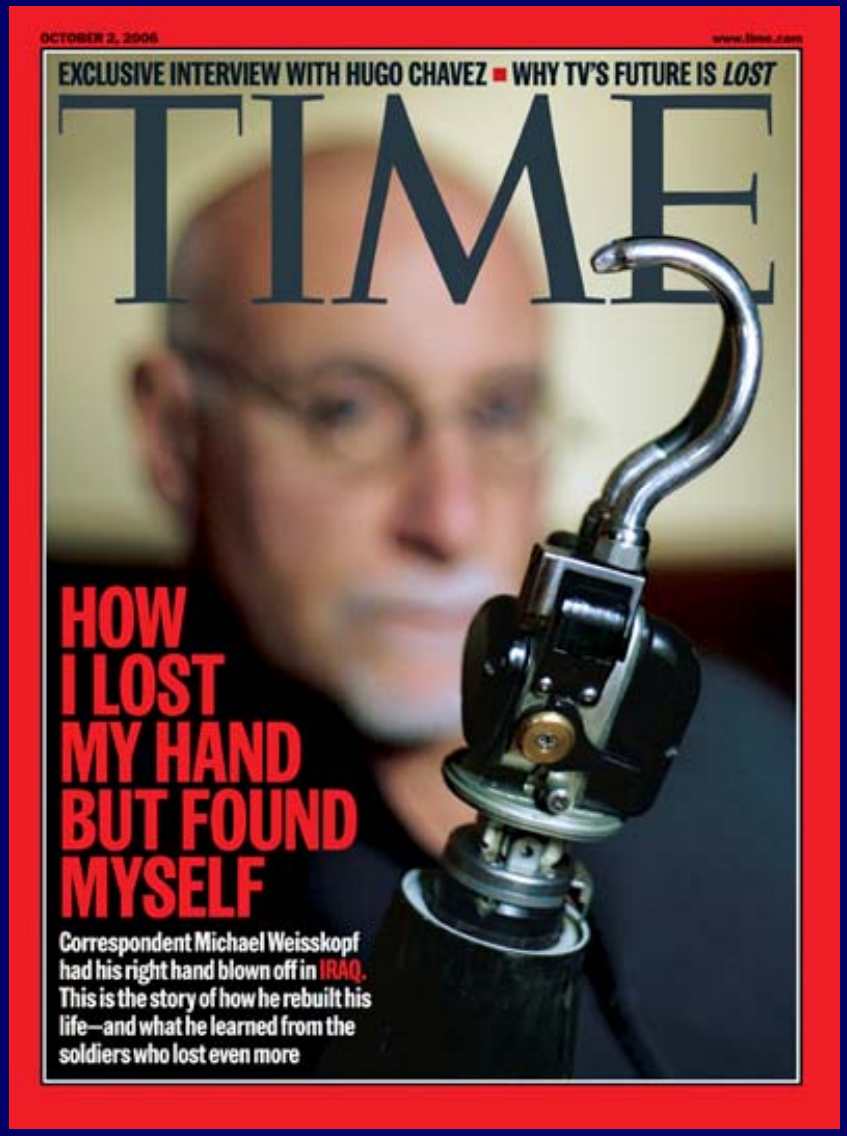
Lance Corporal James Crosby, paralyzed by a rocket attack outside of Baghdad

WWII *Comprehensive* Rehabilitation: Impacts on Spinal Cord Injuries

- ✓ WWI:
  - "[O]f the four hundred men who became paraplegics in World War I, a third died in France, a third died in within six weeks thereafter, and of the remaining third, 90 percent were dead within a year."
  - Total: 97% dead within a year
- ✓ WWII:
  - "In World War II there were 2500 American service-connected combat paraplegics, and…
  - three-fourths of them were alive twenty years later."
- ✓ Present:
  - Near-normal life expectancy
  - ~230,000 individuals, **~$250 billion** total cost
  - **QUALITY OF LIFE**: ***independence***

Lanska, DJ. Historical Perspective: Neurological Advances from Studies of War Injuries aear-nnd Illnesses. **Ann. Neuro.** 2009; 66:444-459.

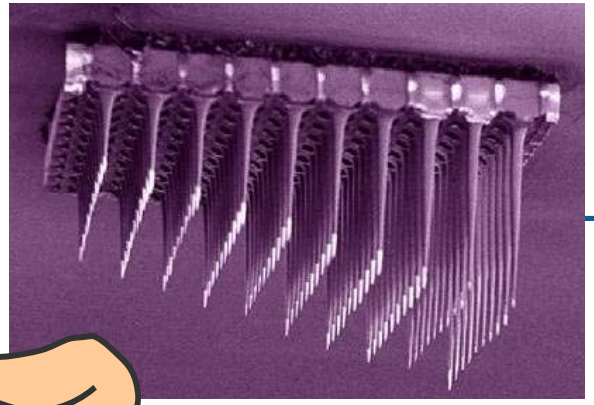
Present-Day Prosthetic Arms: Often ~Civil War Technology!

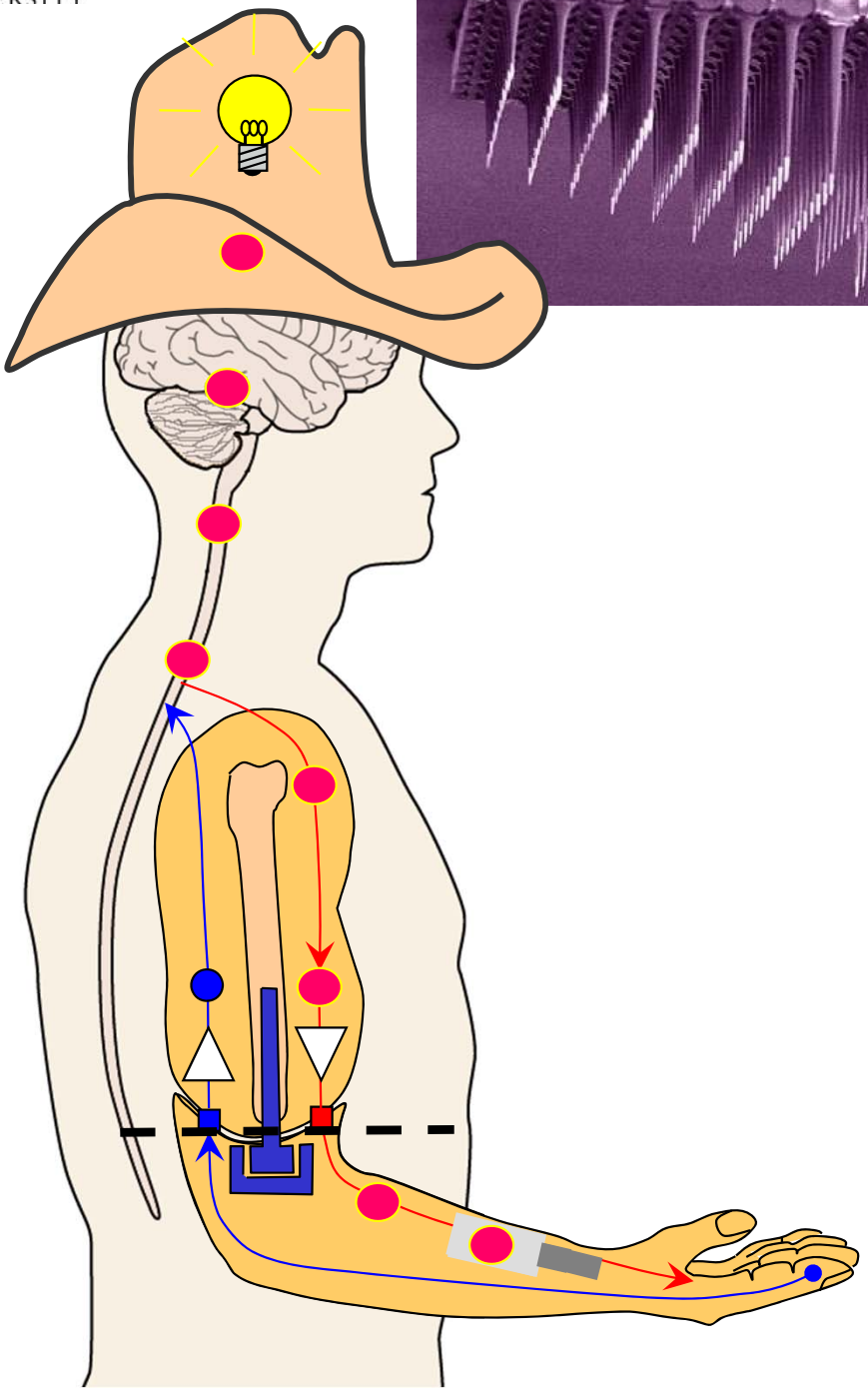


Michael Weisskopf
"Amputee Alley," Ward 57, Walter Reed

- ✓ The major limitation in control is *not* just the arm itself
- ✓ Lack of multiple different, intuitive control signals
  - The greater the amputation…
  - The *greater number* of control signals are needed, but…
  - The *fewer* are available
- ✓ No sensory feedback
- ✓ Neural interfaces a potential solution

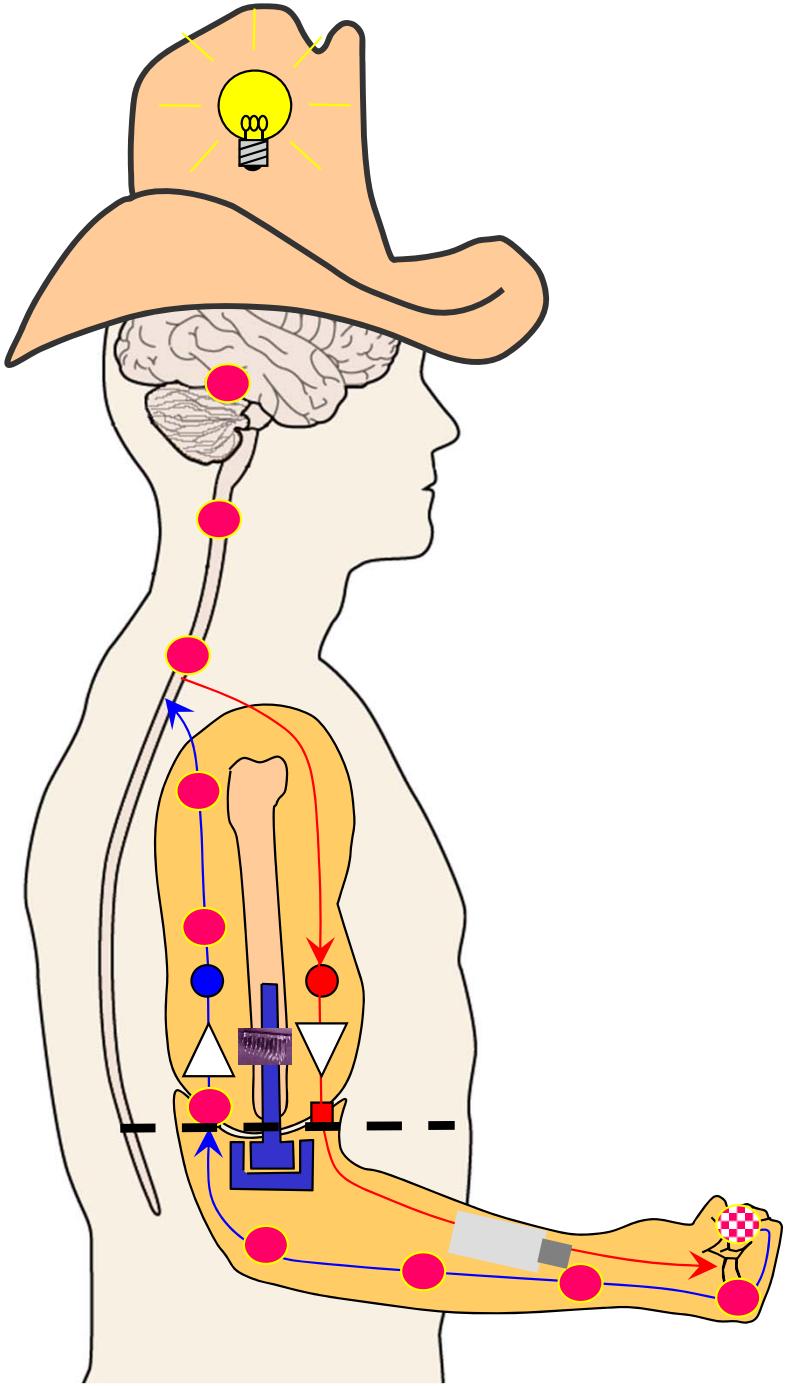
Neuroprosthetic Arm





- **Approach**
  - Implant USEA in residual nerve of amputated limb
- **Motor control**
  - Record motor signals with USEA
  - Control prosthetic limb

Neuroprosthetic Arm

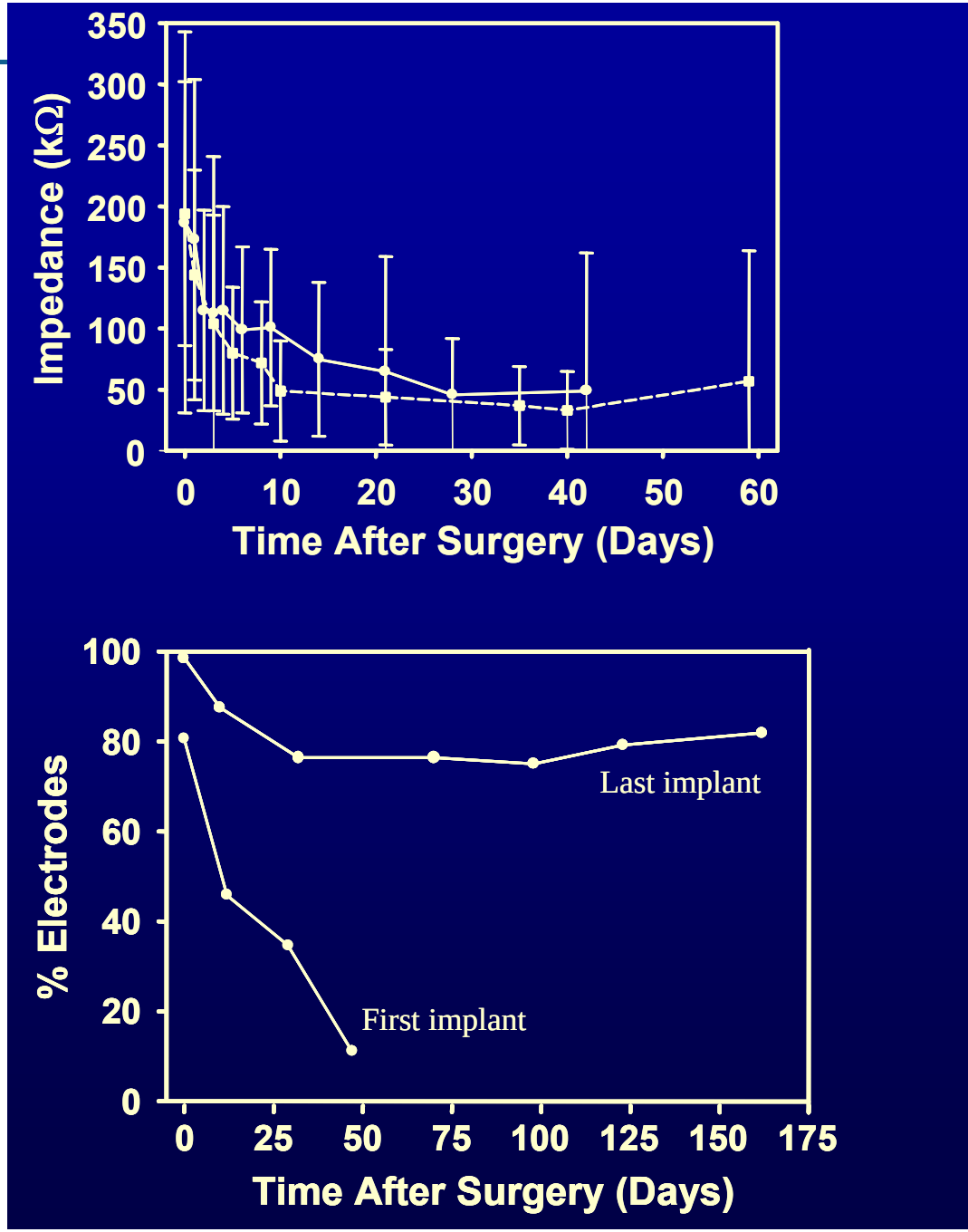


- **Approach**
  - Implant USEA in residual nerve of amputated limb
- **Motor control**
  - Record motor signals with USEA
  - Control prosthetic limb
- **Sensory feedback**
  - Artificial sensors provide signals
  - Stimulate sensory fibers with USEA
- **Advantages**
  - Straightforward neural codes
  - Low risk

Yeah, but…
Will USEAs work long-term?

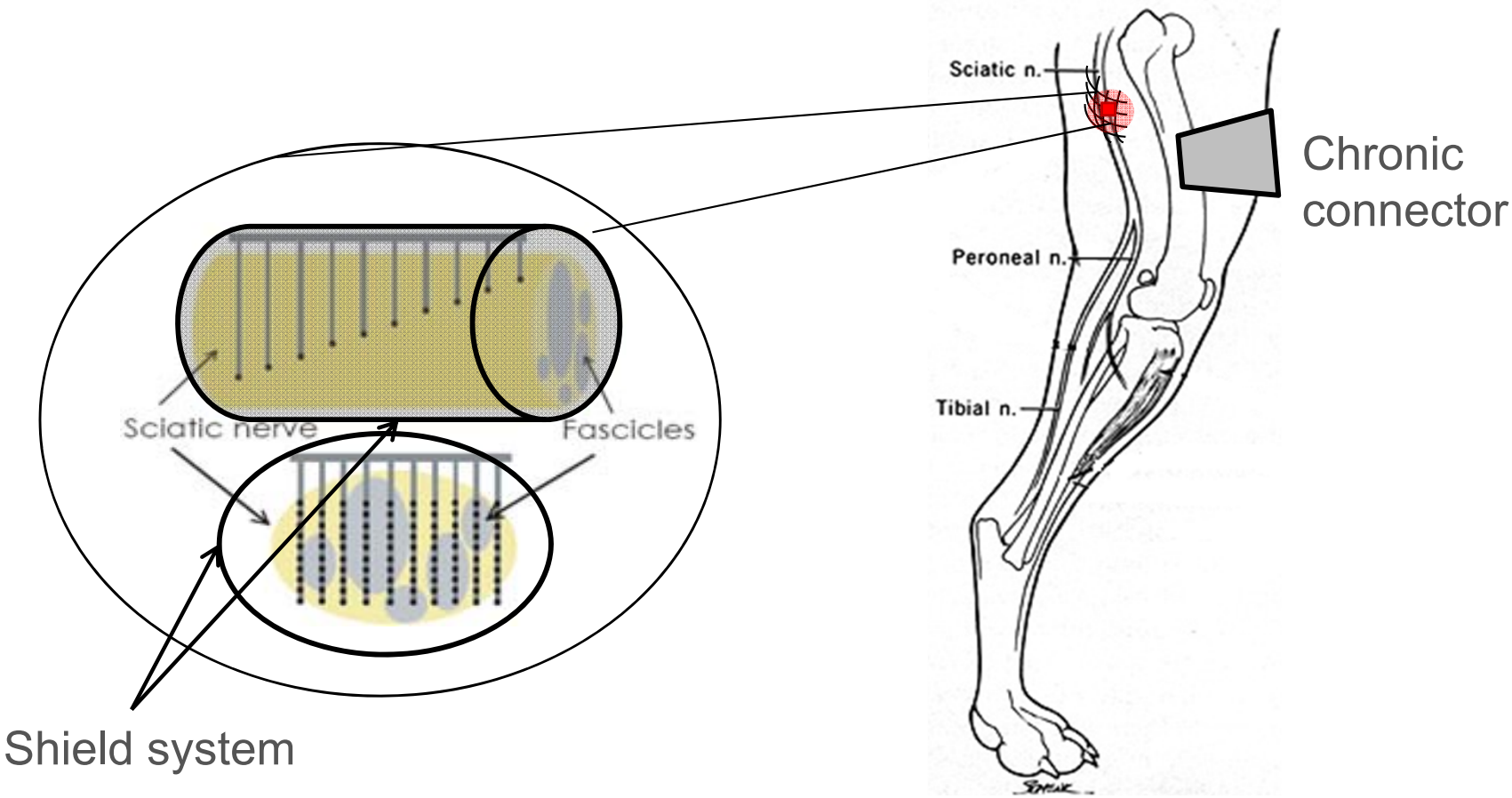
Initial Long-term USEA Investigations

- Successful behavior and stimulation, *but*...
- ✓ Impedances dropped precipitously
- ✓ Wires broke
- ✓ Unit recordings generally ***not*** successful (not shown)
- ✓ Recordings contaminated by EMG



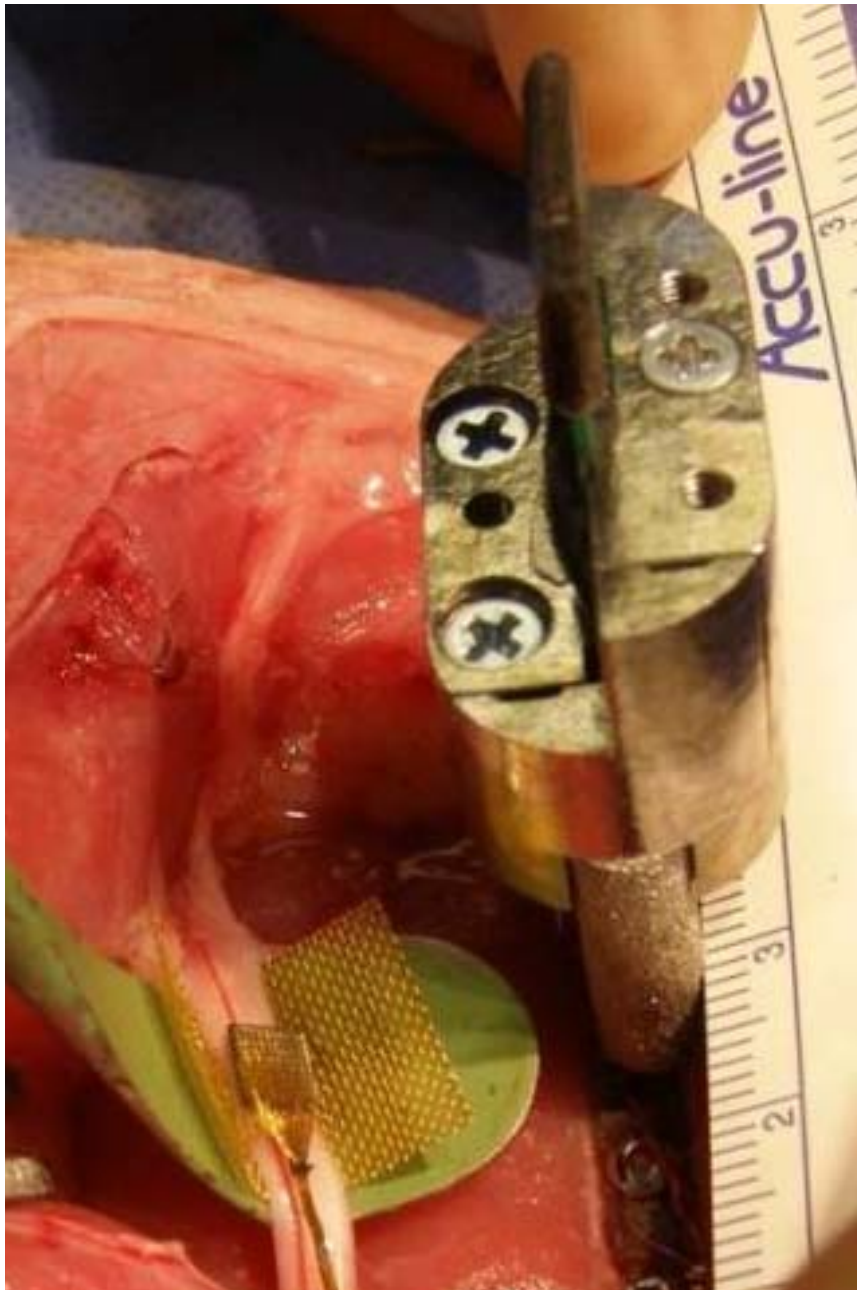
(Branner et al., 2004)

Long-Term Experimental Setup in Cat



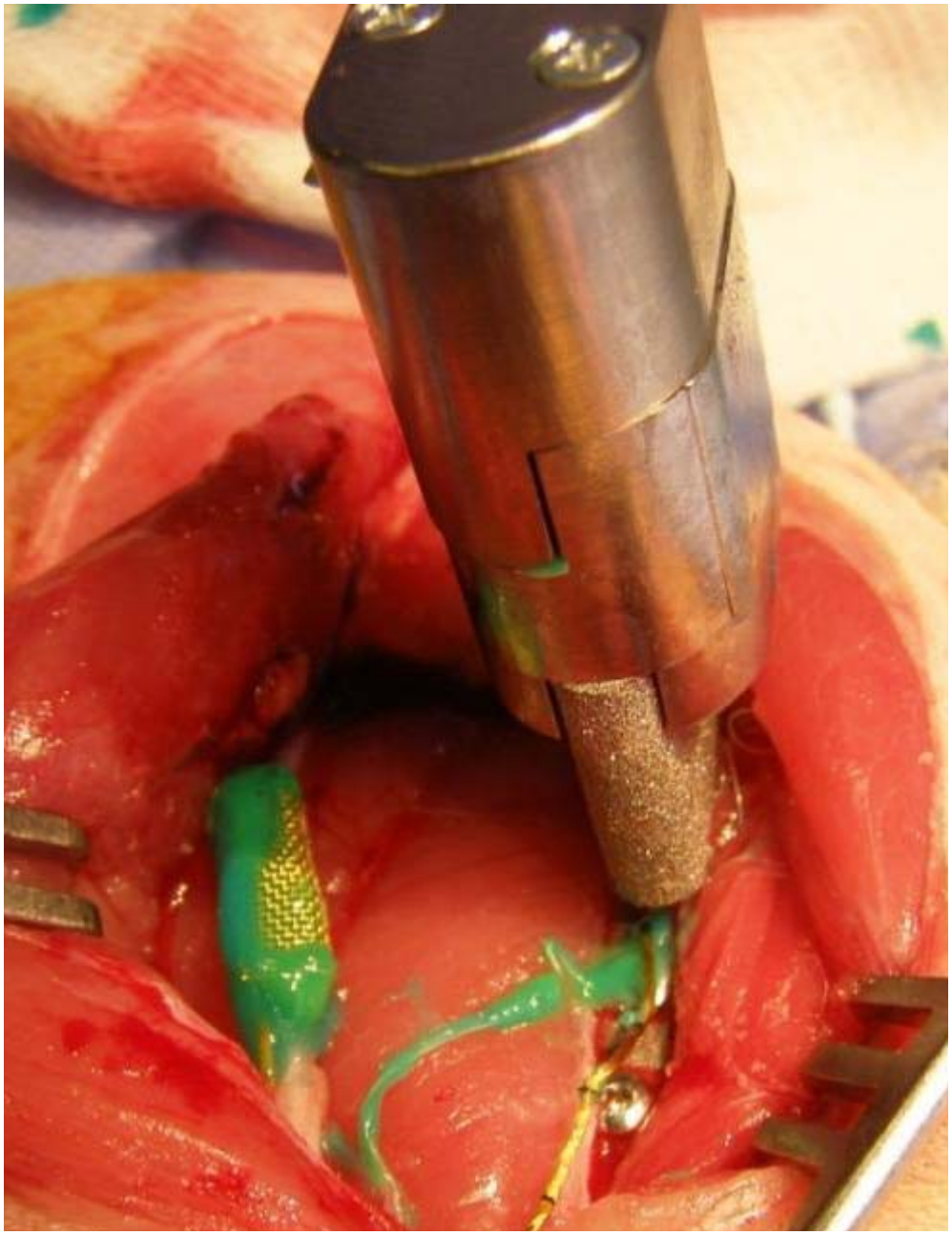
- USEA implanted in sciatic nerve of cat with shielding and bone-mounted 96-pin TDT transcutaneous connector
- Improved arrays, containment system, connector

Connector & Containment Systems, 1



- **96-pin Connector**
  - Surface-treated Ti
  - Small cross-sectional area
  - Secured to the femur with bone screws (1- or 2-stage surgery)
- **Wires**
  - Do not cross joints (unlike previous back-mounts)
- **Containment System (Shield)**
  - Gold mesh around the nerve
  - Grounded to the connector
  - Silicone fills voids & closes

Connector & Containment Systems, 2

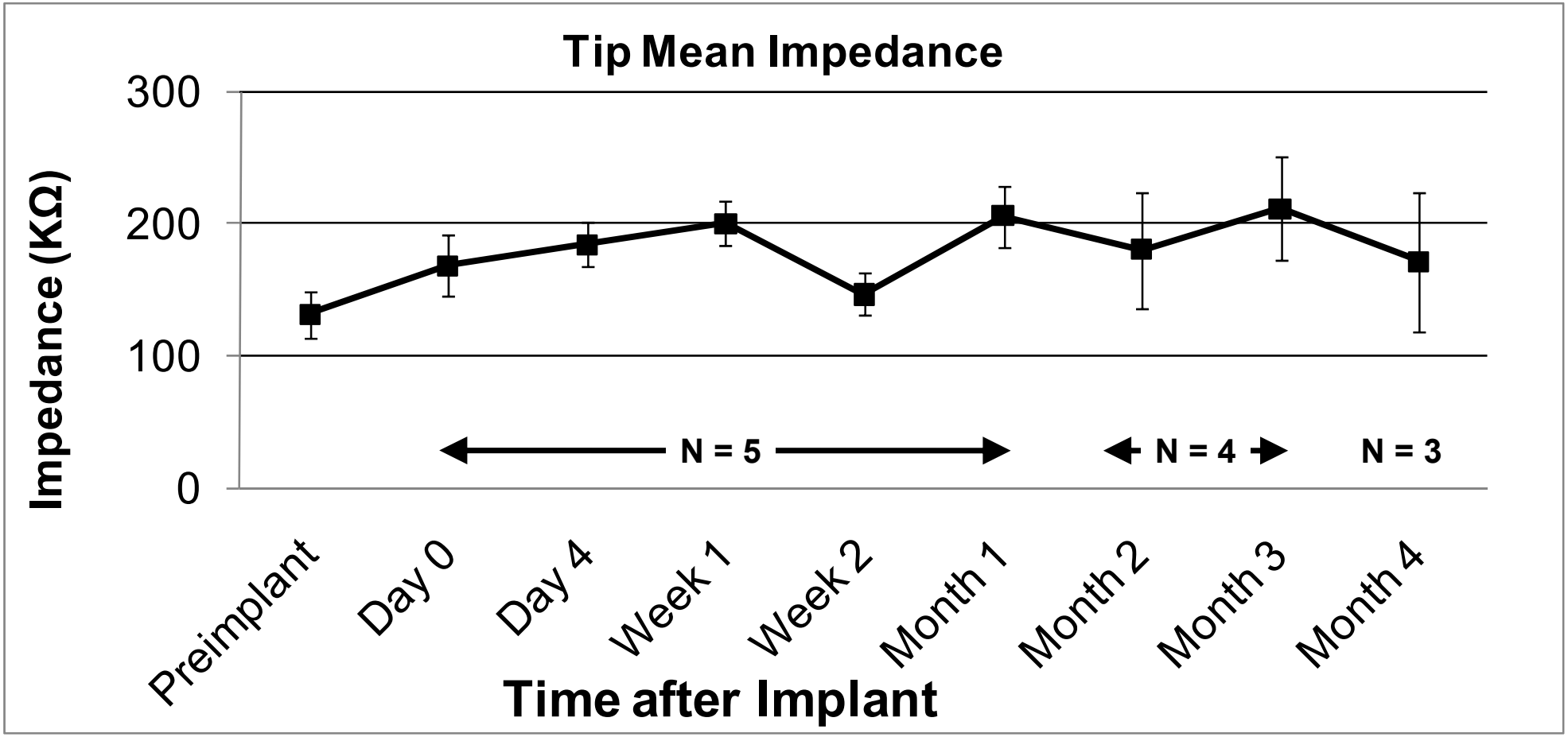


- **96-pin Connector**
  - Surface-treated Ti
  - Small cross-sectional area
  - Secured to the femur with bone screws (1- or 2-stage surgery)
- **Wires**
  - Do not cross joints (unlike previous back-mounts)
- **Containment System (Shield)**
  - Gold mesh around the nerve
  - Grounded to the connector
  - Silicone fills voids & closes

Chronic Implants 1: ***Behavior***

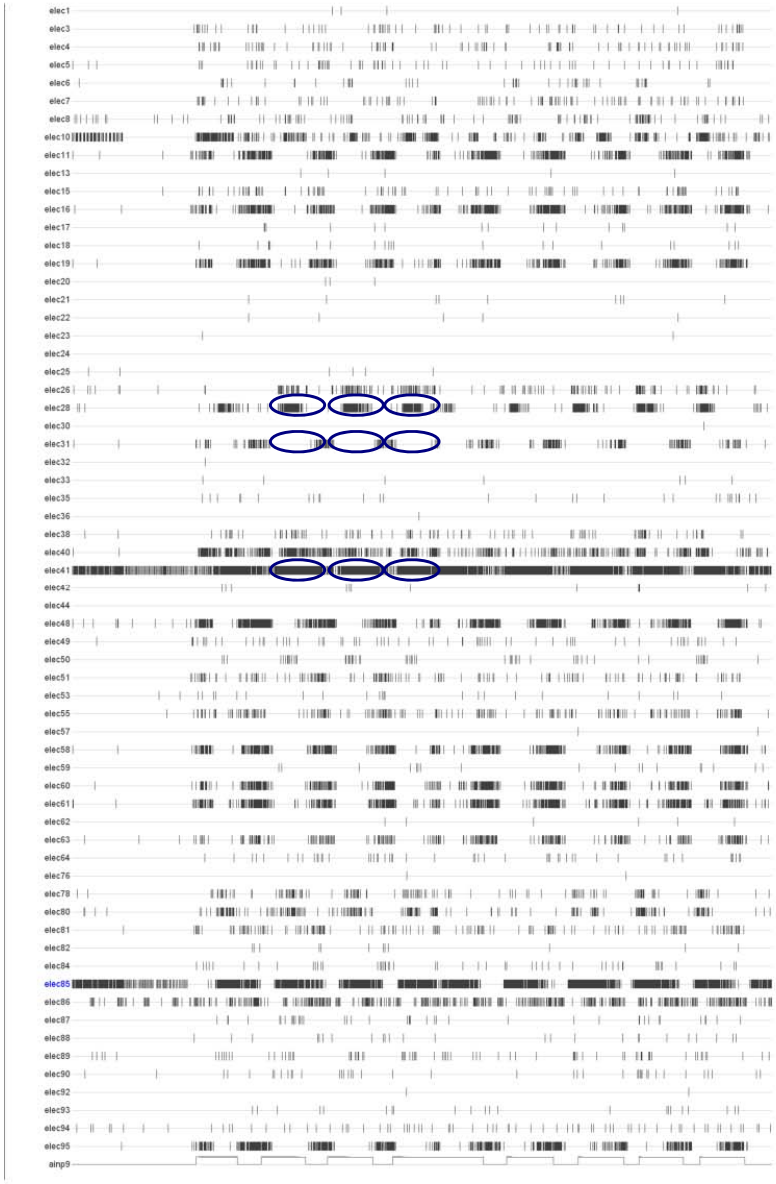
Locomotion excellent after implant

2: Stable Long-Term *Impedances*

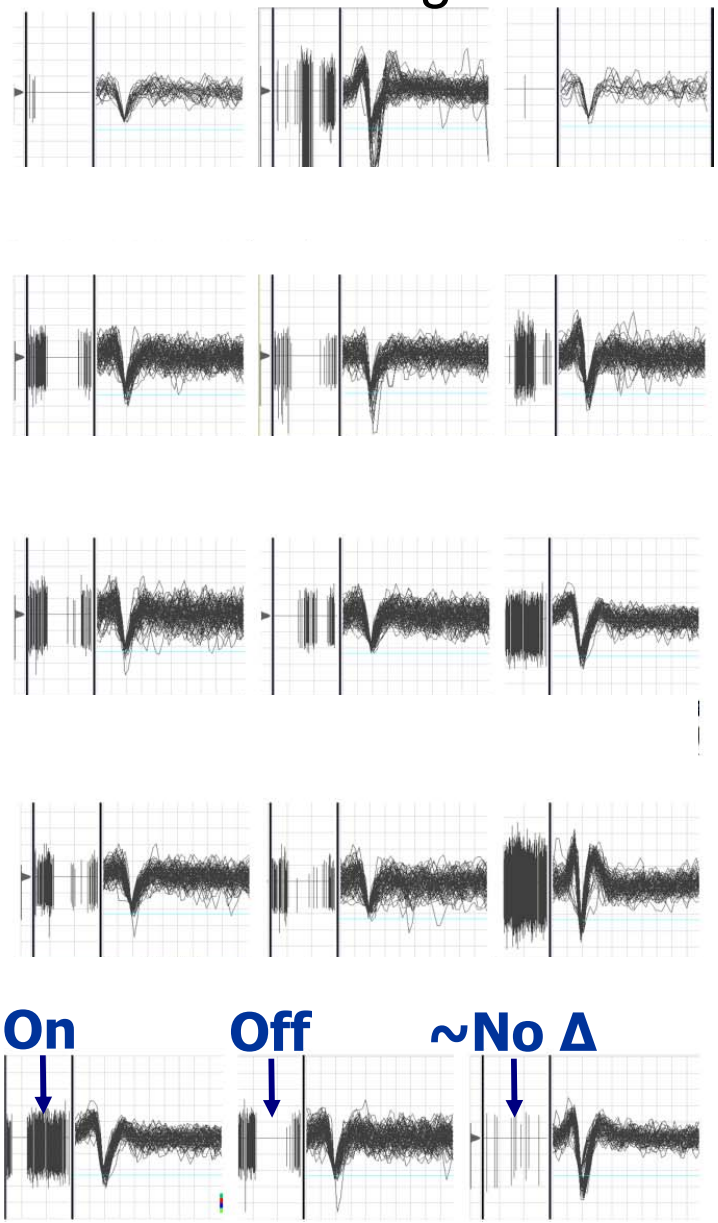


3a. Successful Long-Term *Recordings* (2.5 Mo)

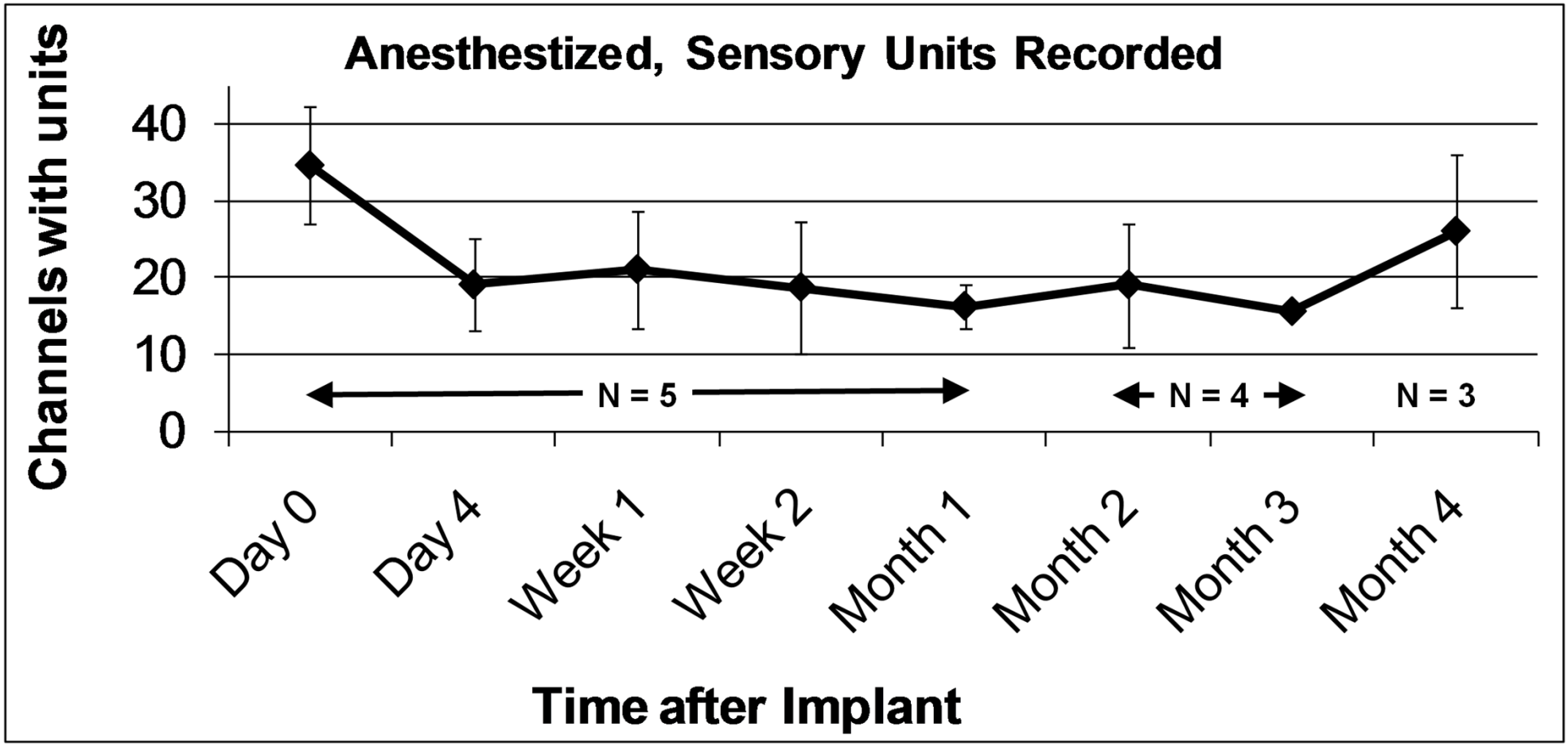
100-Channel Raster



Isolated Single Units



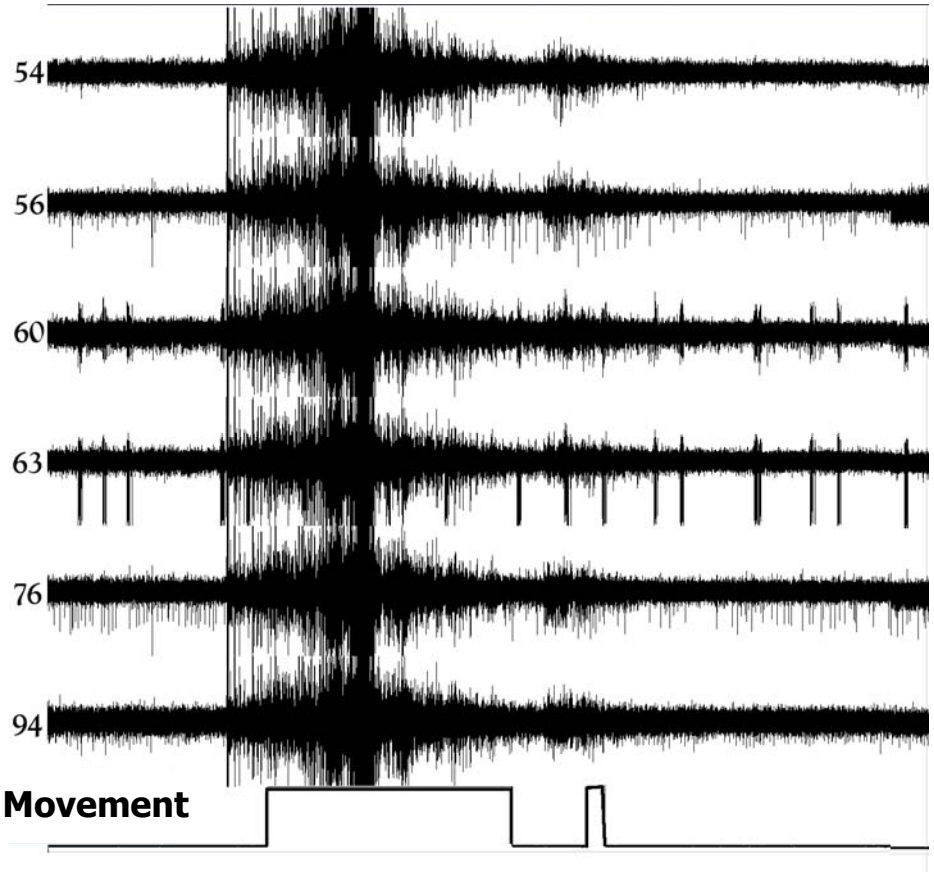
3a: Long-Term *Recordings*



- Typical
  - "Noise": ~±10 uV, 0 to peak (3 x SD)
  - Spike threshold settings: ~-20 uV, 6 x –RMS
- Underestimate; sensory only
  - More channels (motor) active in awake animals

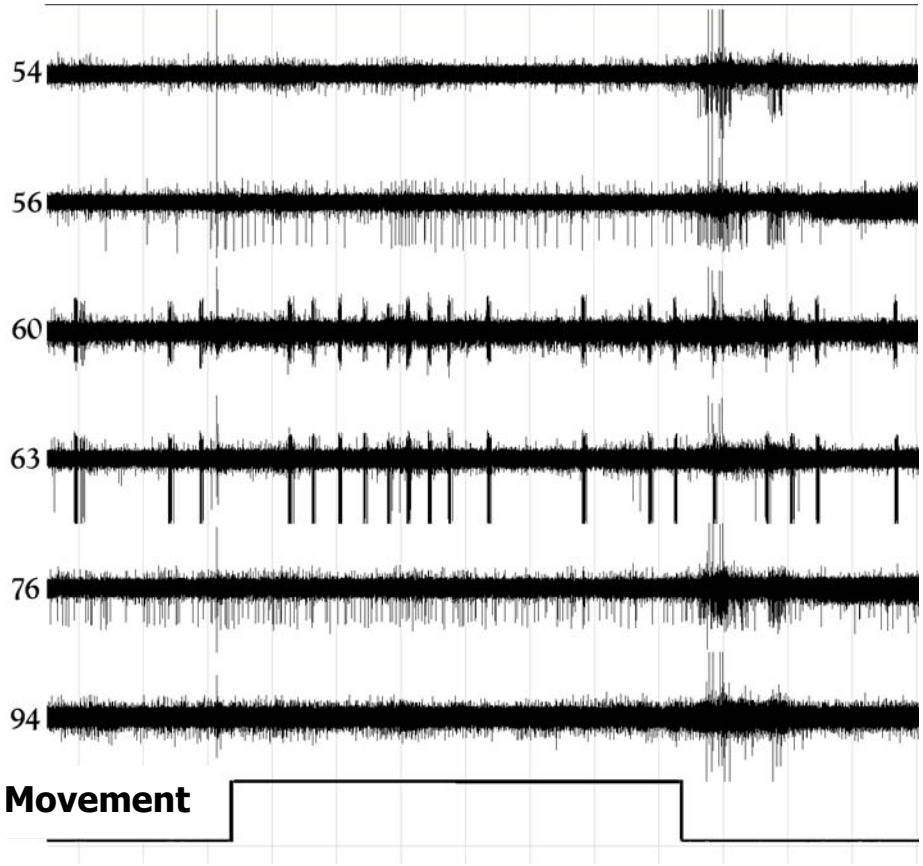
3b: EMG-Free Recordings in Behaving Animal

With*out* Protection from EMG



- Extensive EMG contamination
- Neural recordings obscured

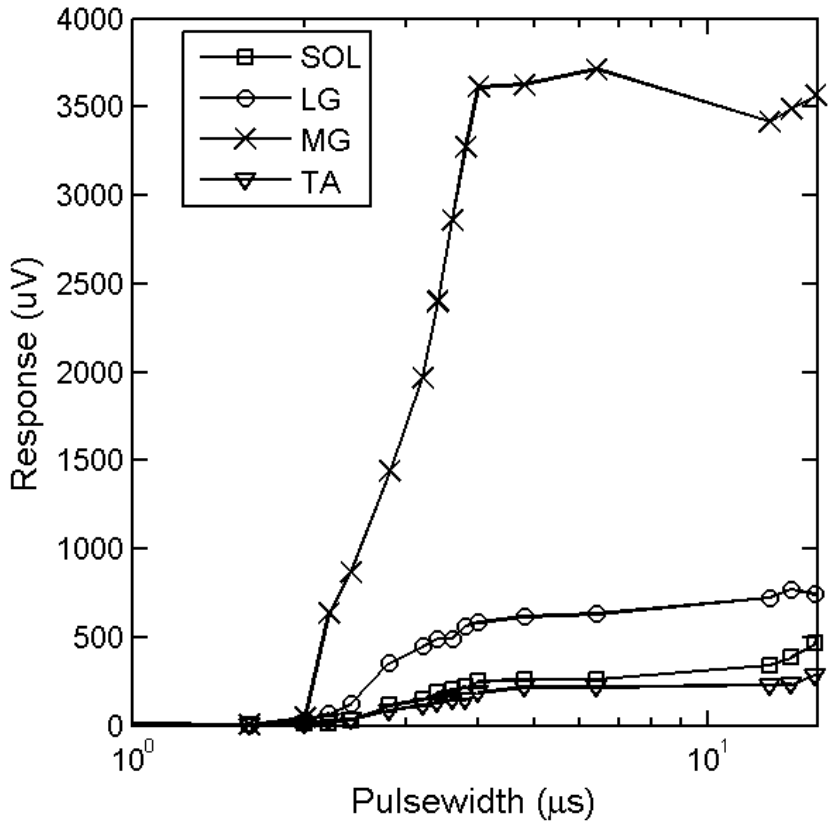
With Protection from EMG



- Little EMG contamination
- Neural recordings possible

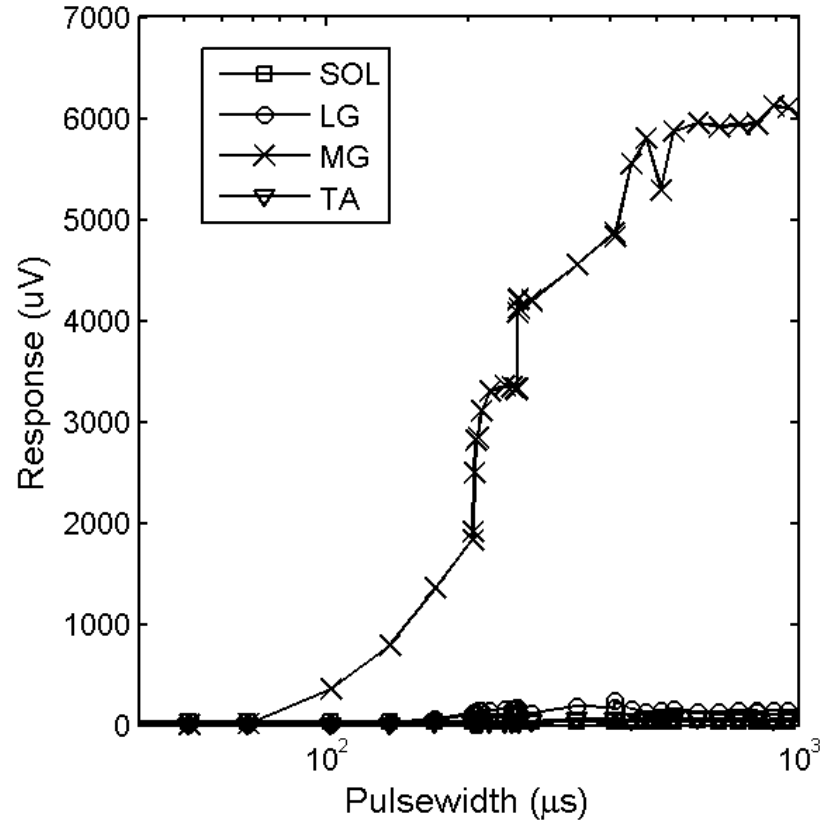
4: Long-Term Stable, Selective (Motor) ***Stimulation***

Day 0



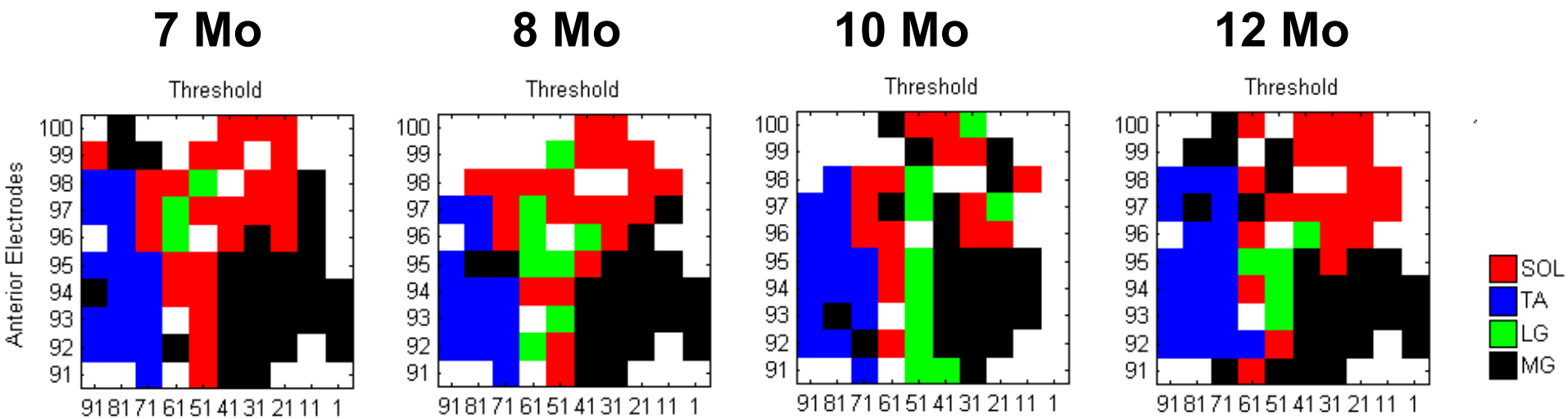
- **Highly Selective**
  - Activates MG
  - Little activation of other hind limb muscles

Day 33 (Same Electrode)



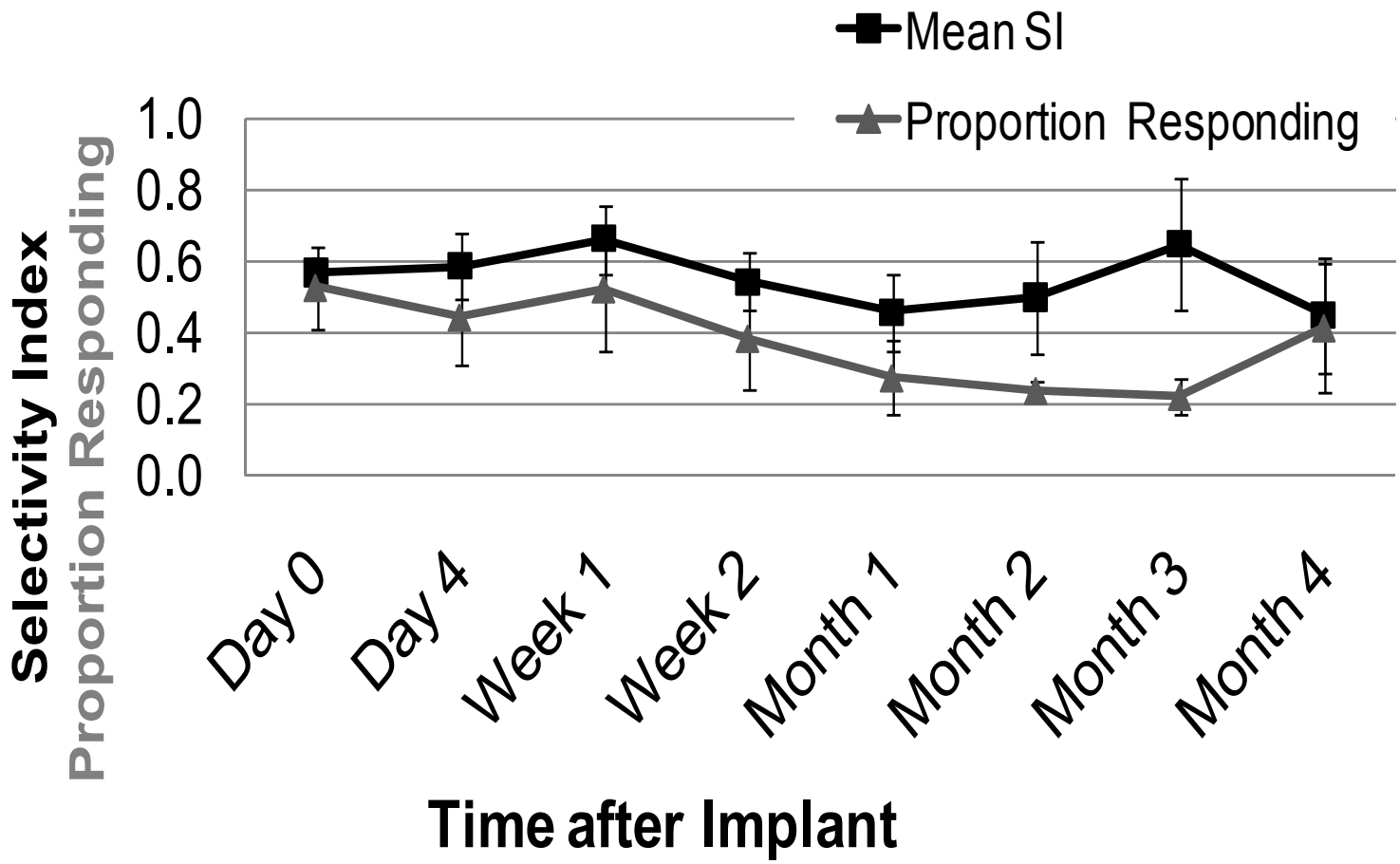
- **Stable**
  - Increased threshold, but selectivity maintained
  - Activation of MG maintained
  - Weeks, but not months
  - Should generalize to afferents

4: Long-Term Stable, Selective (Motor) ***Stimulation***



- Musculotopic maps show reasonable stability

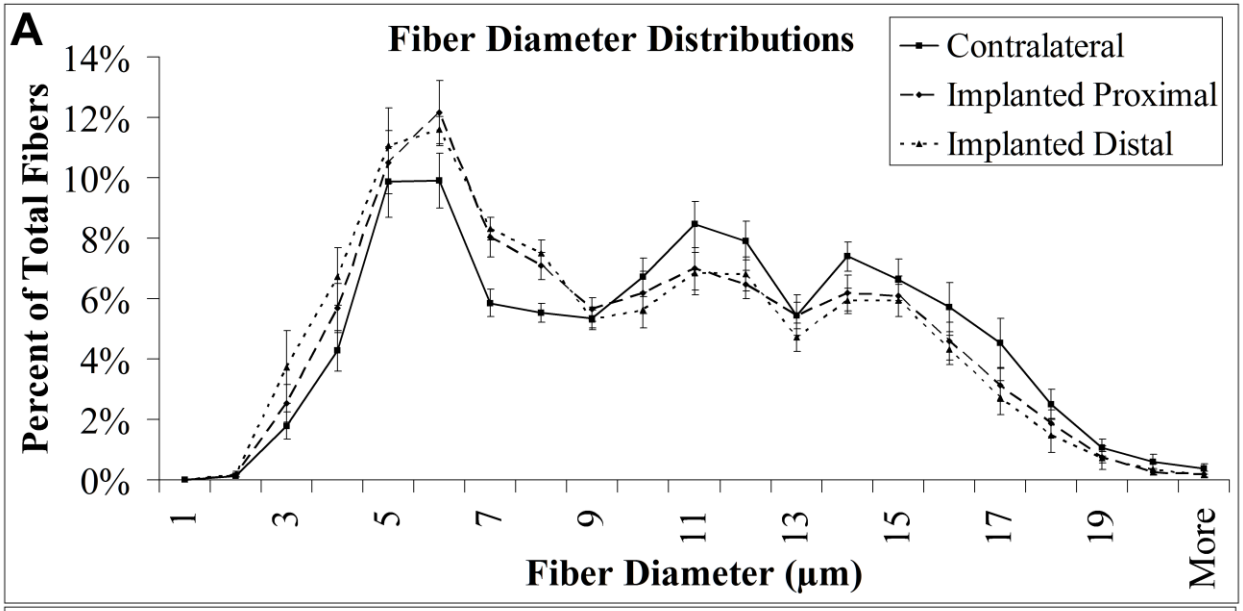
4. Long-Term Stimulation Maintains Viability & Selectivity

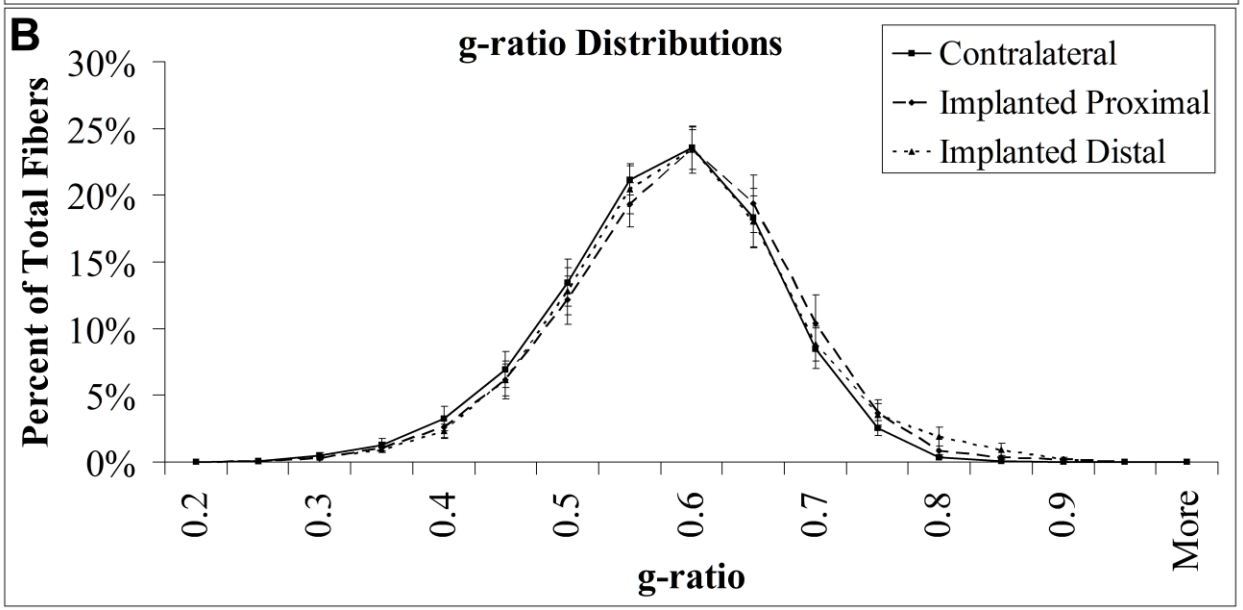


$$SI = 1 - \frac{2^{nd}\text{ Largest EMG}}{\text{Target EMG}}$$

- 1 = Perfect selectivity
- 0 = No selectivity

5: *Quantitative Histology* Reveals Only Modest or Not-Significant Changes (Tresco Lab)





- ✓ **Nerve Fiber Diameter**
  - Trimodal distribution maintained
  - Modest shift from larger to smaller fibers
- ✓ **G-ratio (myelin thickness)**
  - Axon D/Total D
  - No significant differences
- ✓ **Fiber counts (not shown)**
  - No significant differences:
    - Unimplanted: 19551 ±567
    - Proximal:18300 ±828
    - Distal: 19099 ±1011

Christensen, M.B., Pearce, S.M., Ledbetter, N.M., Warren, D.J., Clark, G.A., Tresco, P.A. Submitted

Success Mode Analysis: (Tentative) Lessons Learned

More a magic "machine gun" than a single "magic bullet"

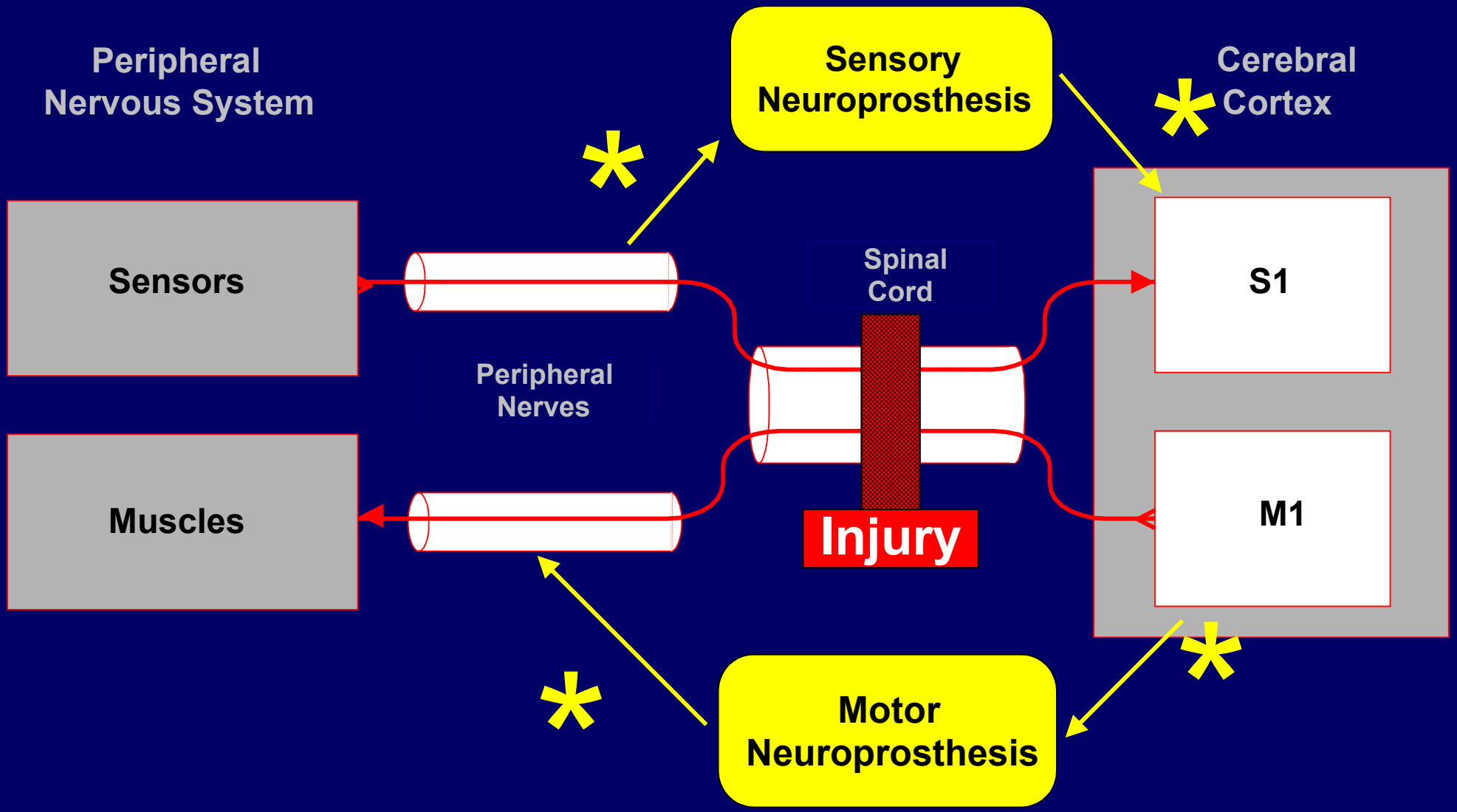
- **Arrays:** Better testing → better USEAs (Solzbacher et al.)
  - General
    - Improved insulation → ↓ shunting on arrays, wires, connectors
    - Multiple other improvements (SIROF, etc.)
  - Pre-use selection
    - Impedance tests ("infant mortality")
    - Visual inspection
- **Containment system**
  - Conformal silicone elastomer cuff: ↑ mechanical stability & ↓ connective tissue ingrowth (and associate macrophage aggregation)
  - Shield: ↓ EMG contamination
- **Connector system**
  - 96-pins
  - 2-stage surgery, first with bone-plate alone → ↑ osseointegration
    - (Alternatively, locking head screws may help)
  - Ti-surface treatment and form factor → ↑ tissue adhesion, ↓ infection

CONCLUSIONS

- Intrafascicular USEAs may provide multiple, selective sites for
  - Recording
  - Stimulation
- Improved long-term capabilities
  - (Behavior)
  - Long-term recordings
  - EMG-free recordings
  - Stimulation

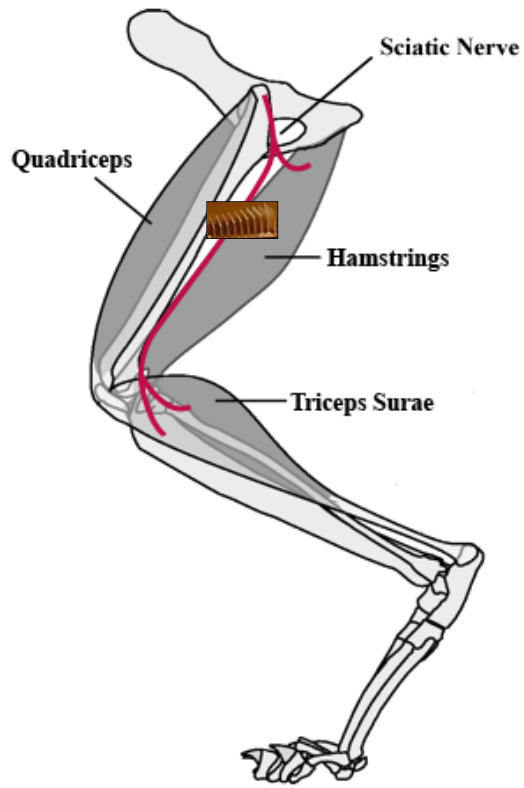
“Cat Standing”: Steps Toward Restoring Stance (and Gait)

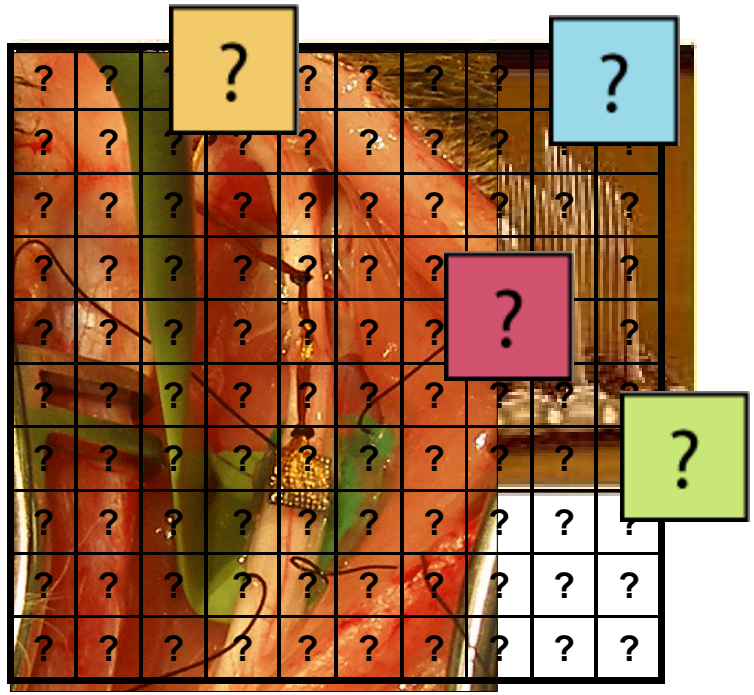
Neuroprosthetic Interventions for SCI

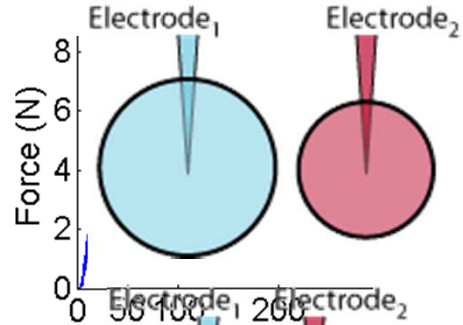


Use of UEA & USEA has achieved success in all 4 stages

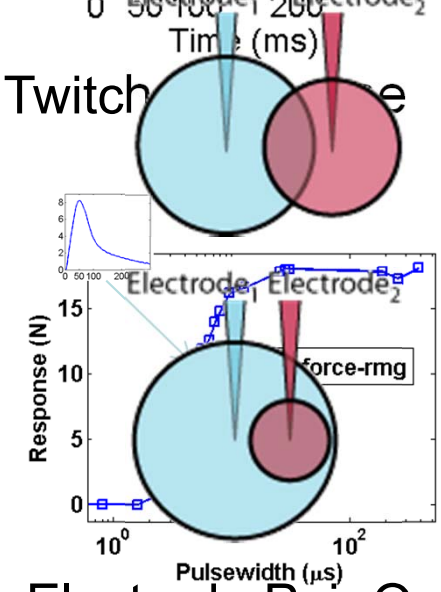
Parameter Setting for Single & Multiple Electrodes



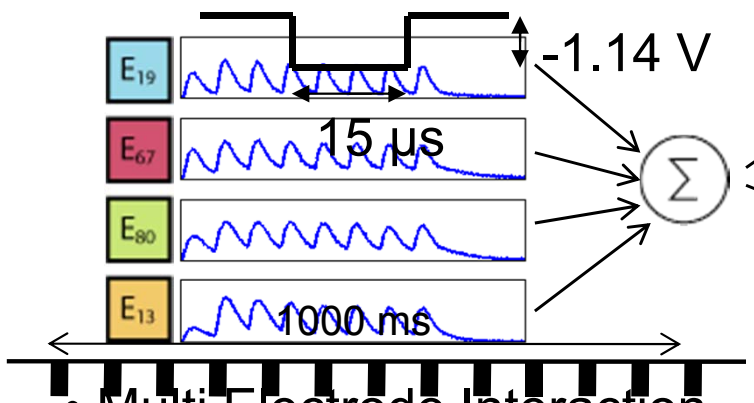




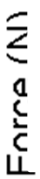
- Twitch



- Electrode Pair Overlap
- Recruitment Curve

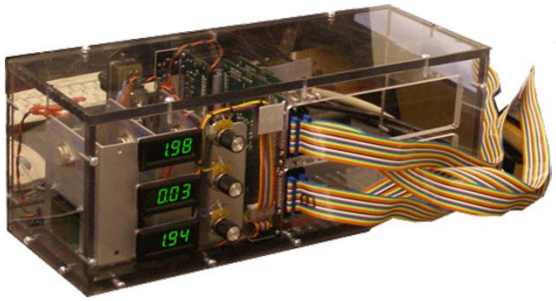


- Multi Electrode Interaction

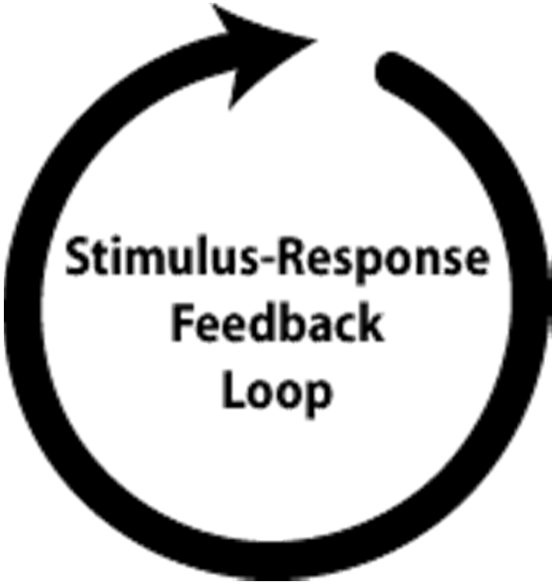


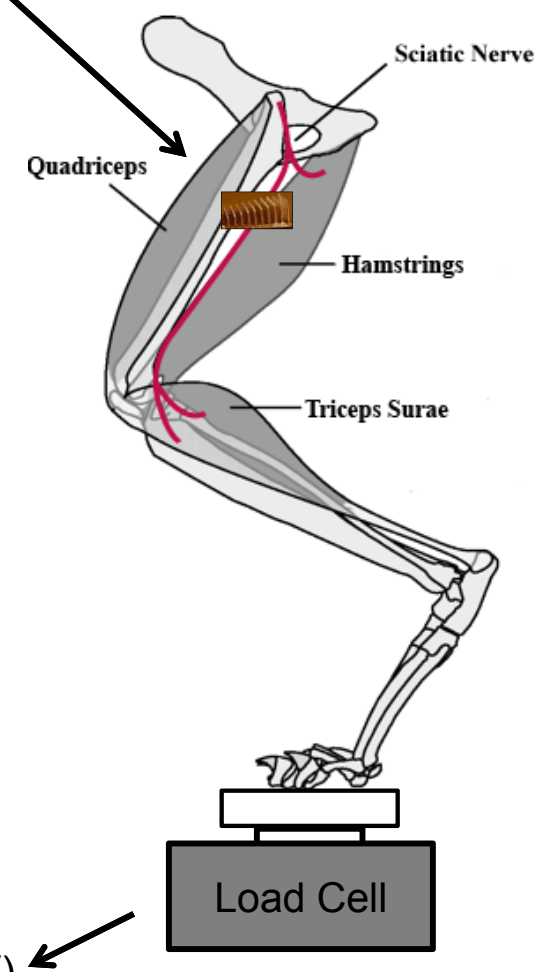
- Pu

Closed-Loop FES Platform



Custom Stimulator
- 1100-Channels
- Constant Voltage
- Pulsewidth Modulated
- 0.2 μs resolution

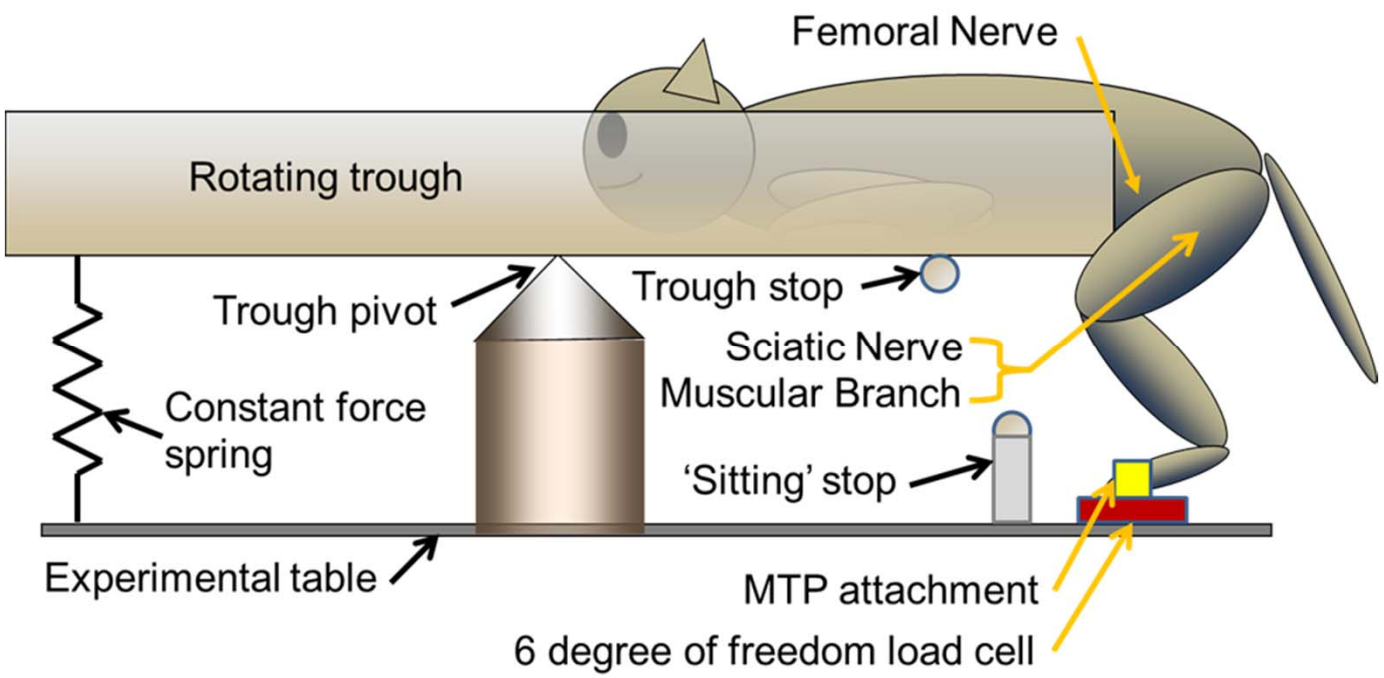




Control Module
- USEA Calibration
- Single-Electrode Algorithms
- Multi-Electrode Algorithms
- Control Stimulator
- Trigger Data Acquisition Unit
- User Interface

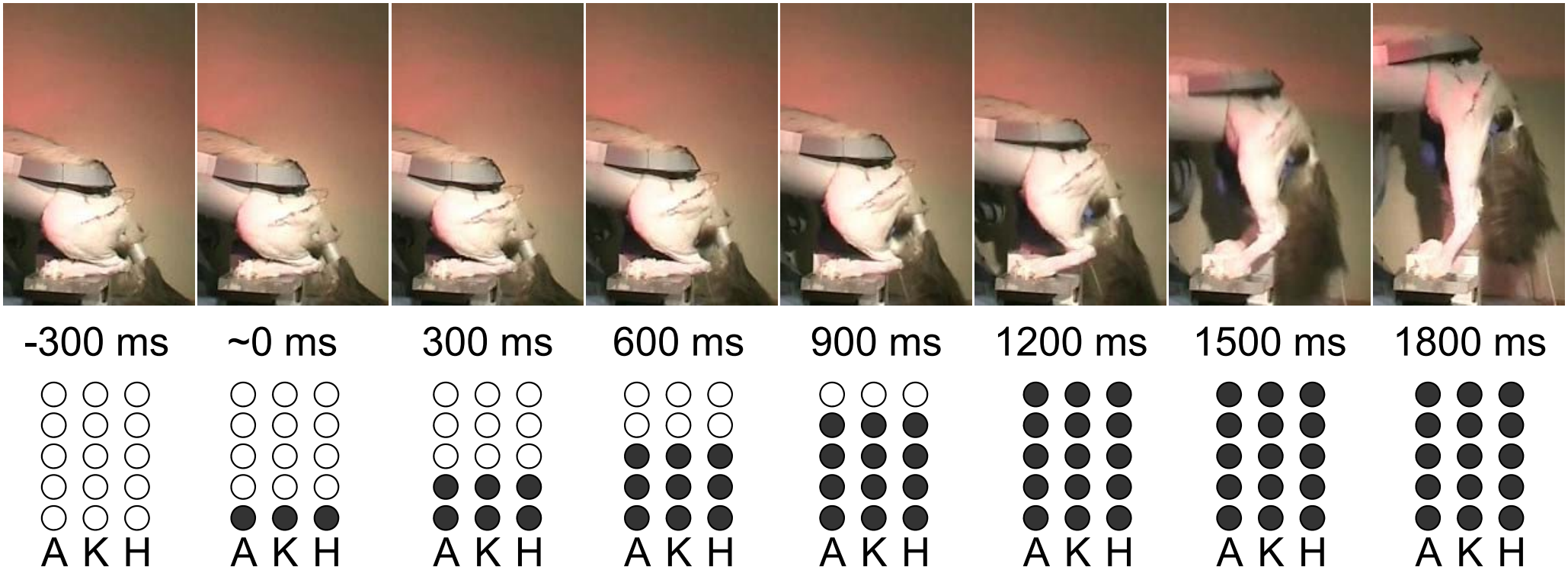
Data Acquisition Unit
- 128 analog inputs (1 μV – 8.9 mV)
- 16 analog inputs (1 – 5 mV)
- 16 digital inputs
- 30 ks/s continuous sample rate

Cat Stance: Experimental Arrangement



- ✓ 3 USEAs
  - Ankle, knee, hip
- ✓ Sit-to-Stance-to-Sit
  - Change in trough angle; ground reaction forces
- ✓ Kinetics, Kinematics, and Fatigue Resistance

Three-Joint Stance: Concurrent Activation of Ankle, Knee, & Hip

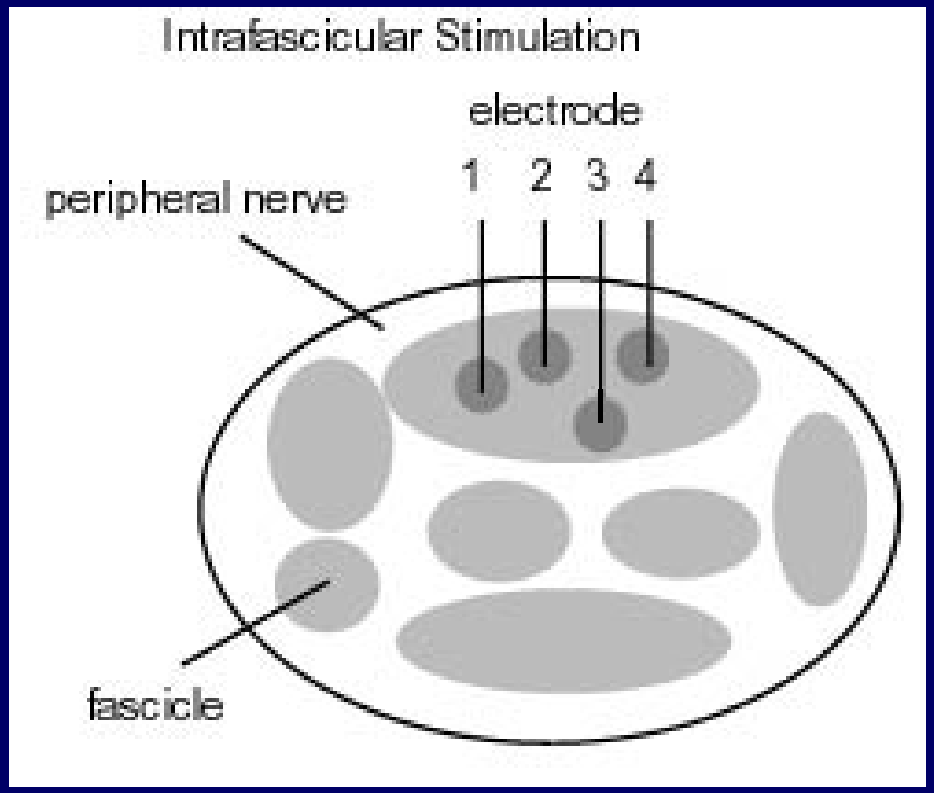


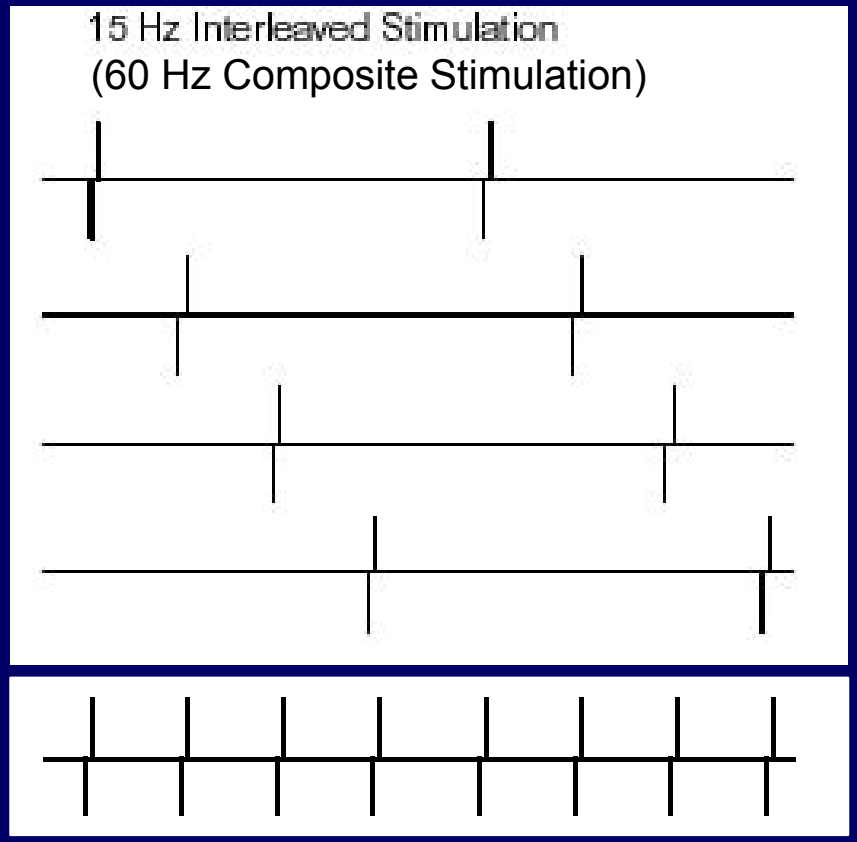
- Graceful, controlled sit-to-stance(-to-sit)
- Reasonably parameter tolerant
- *Multiple* electrodes
- In appropriate *combinations*

Three-Joint Stance:
Concurrent Activation of Ankle, Knee, & Hip

Advantages of *Interleaved* Multi-Electrode Intrafascicular Stimulation

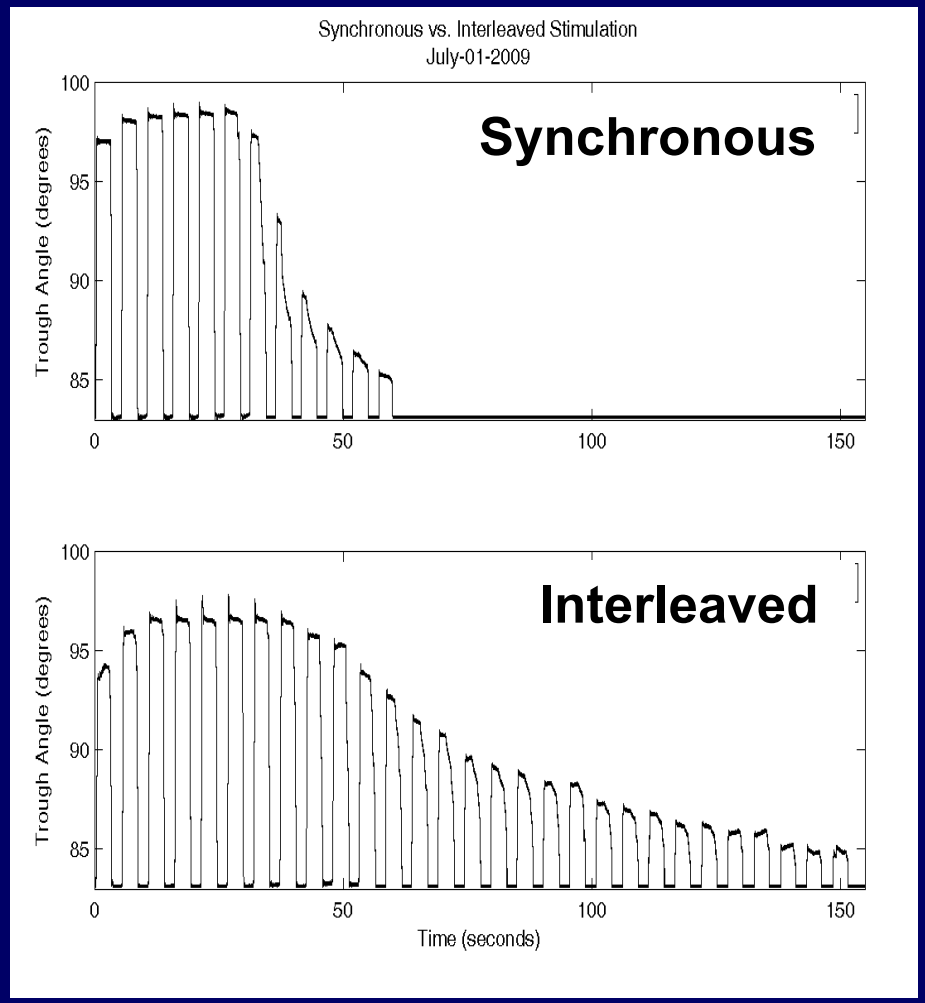
Increased Fatigue Resistance via *Interleaved* Stimulation





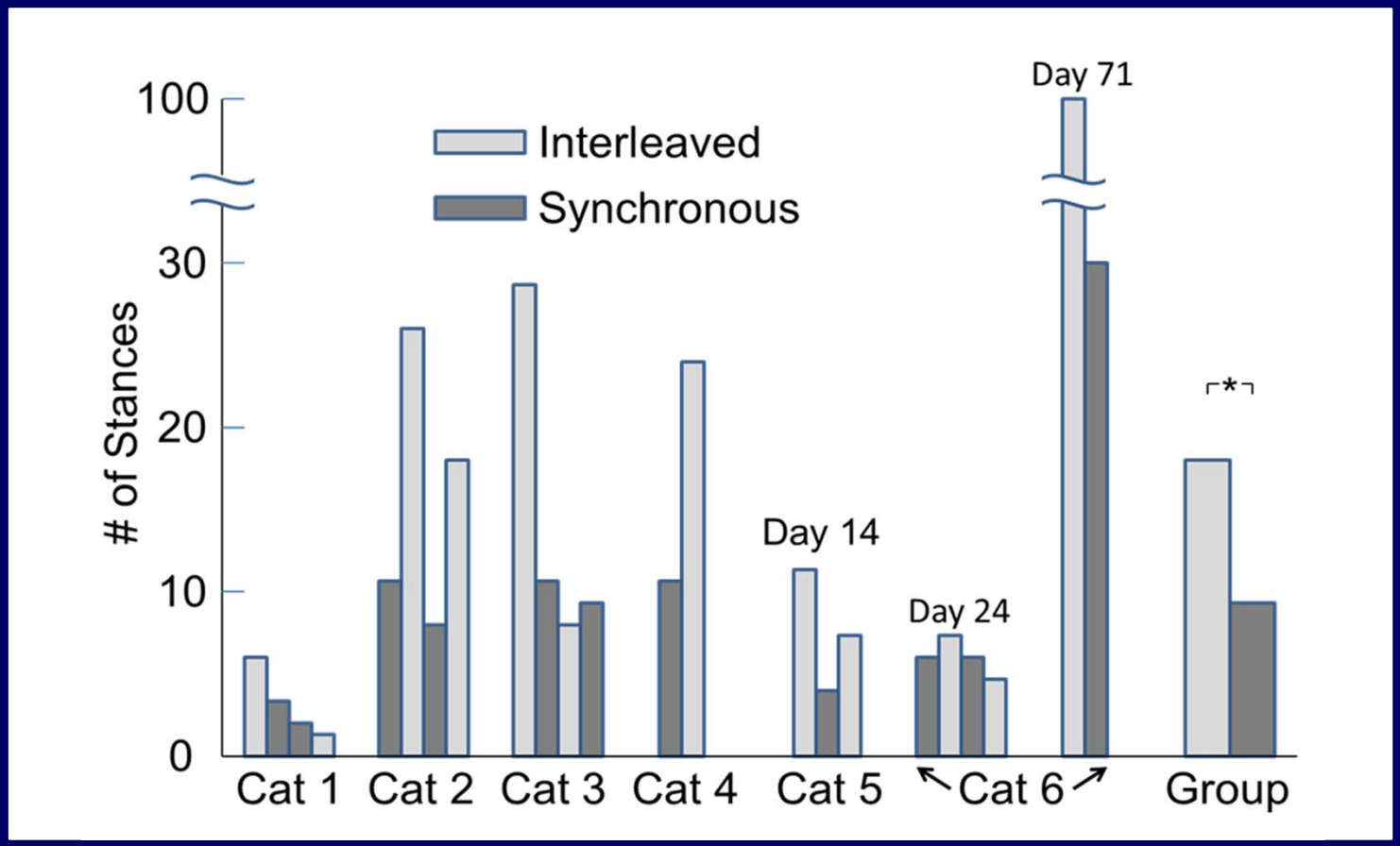
- ✓ Asynchronous, interleaved stimulation of independent motor units
- ✓ Physiologically realistic
- ✓ Best of both worlds:
  - – Decreased ripple (like high-frequency stimulation)
  - – Decreased fatigue (like low-frequency stimulation)

Interleaved Stimulation Promotes Fatigue-Resistant Stance



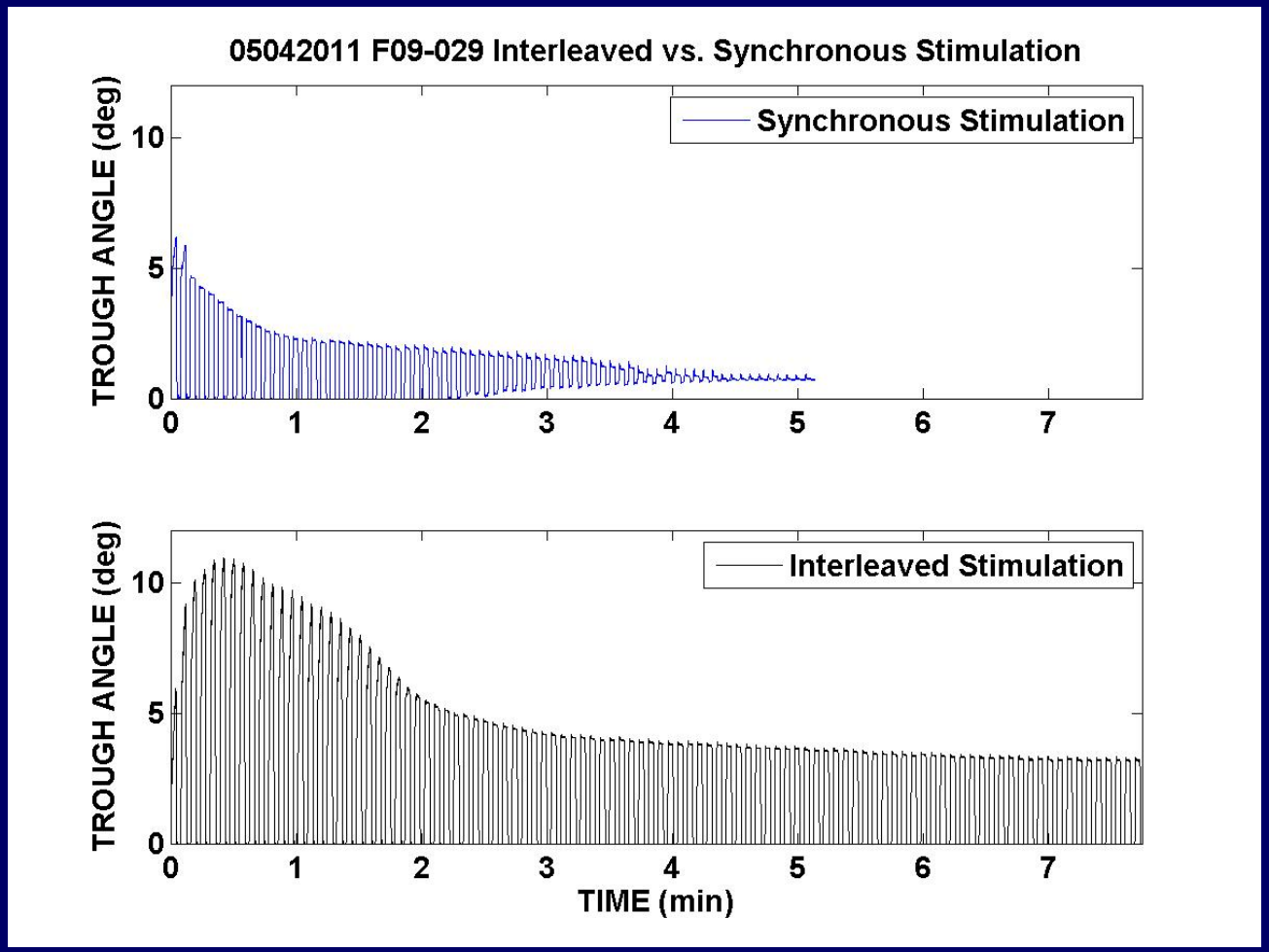
Multi-Electrode Interleaved Stimulation Promotes Fatigue Resistance in 3-Joint Stance (01-July-2009)

Interleaved Stimulation Promotes Fatigue-Resistant Stance: *Group Data*



- ✓ **Interleaved is more fatigue-resistant**
  - **Every animal (n = 6)**
  - **Overall $p < .05$**
  - **Note 2 chronic animals**

Interleaved Stimulation Promotes Fatigue-Resistant Stance: *Chronic Cat*



- ✓ **Interleaved is more fatigue-resistant**
  - **Chronic cat, 71 d post–implant of 3 USEAs**

What About *Sensory* Stimulation?

(Acute; prosthetic limb)

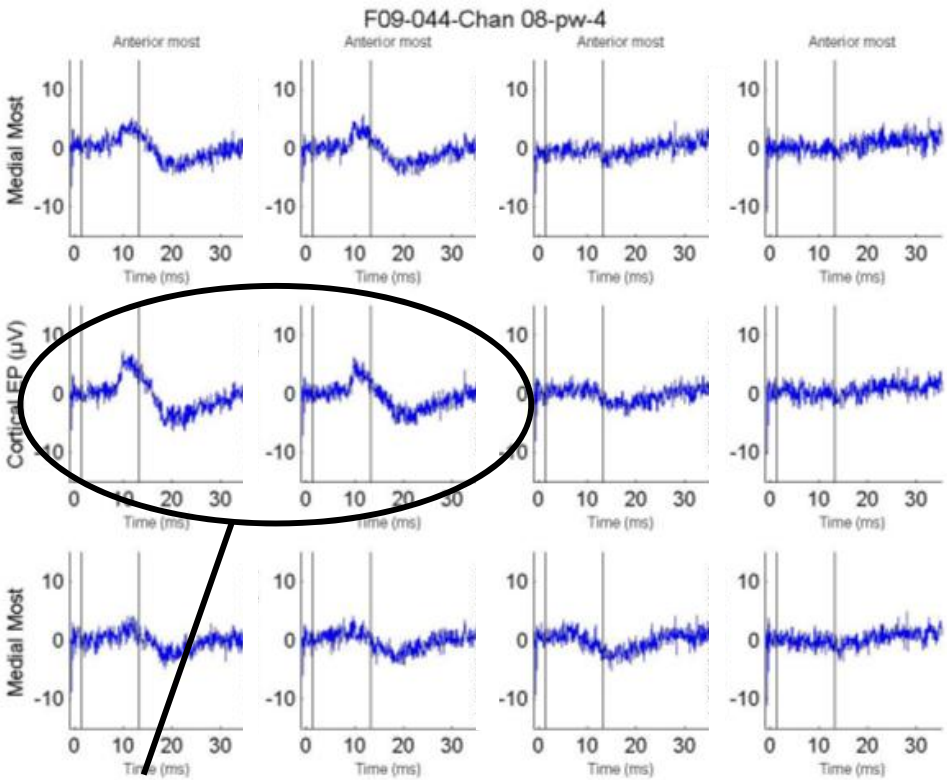
Sensory **Stimulation Paradigm**

- Stimulate: sciatic nerve with implanted USEA
  - Cut sciatic nerve distal to implanted USEA (at end of experiment)
  - To prevent sensory feedback from muscle twitches (unlike Warwick)

- Record: EPs over primary somatosensory cortex and other regions

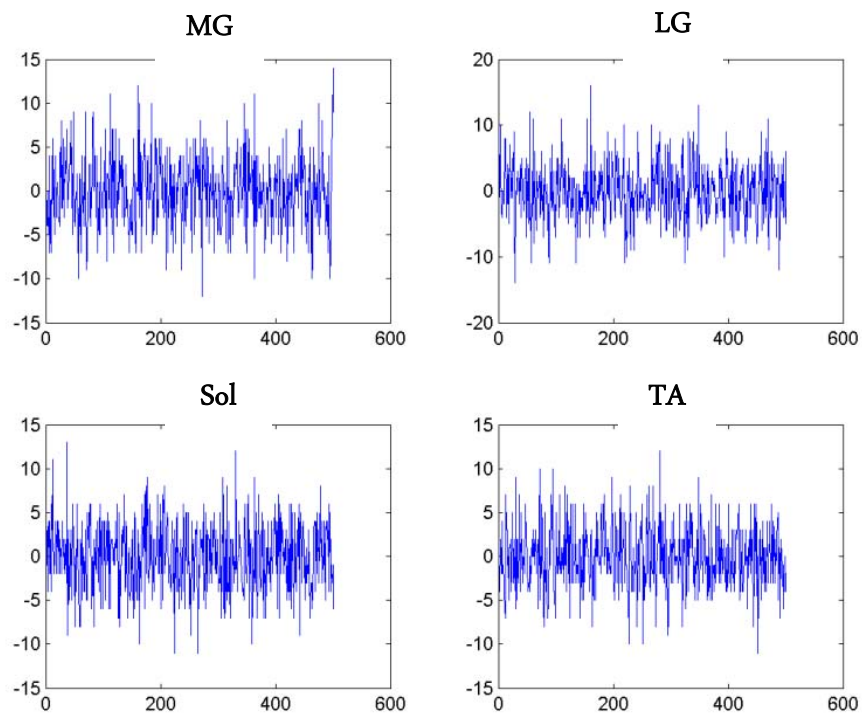
Sensory Responses Without EMG (Uncut Nerve; Acute; Prosthetic Limb)

SS Cx EPs



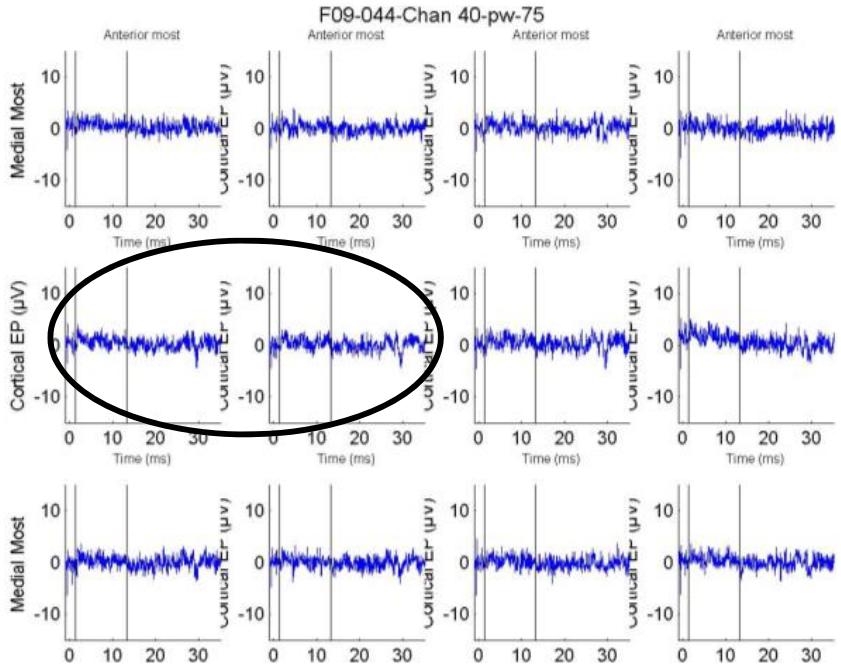
S1 Cortex

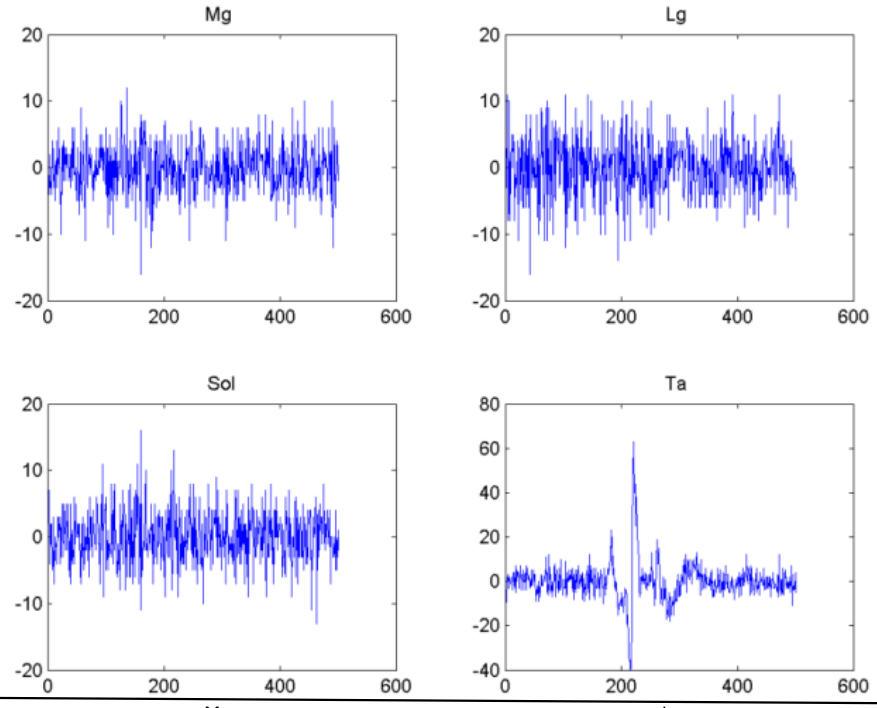
Hindlimb EMGs

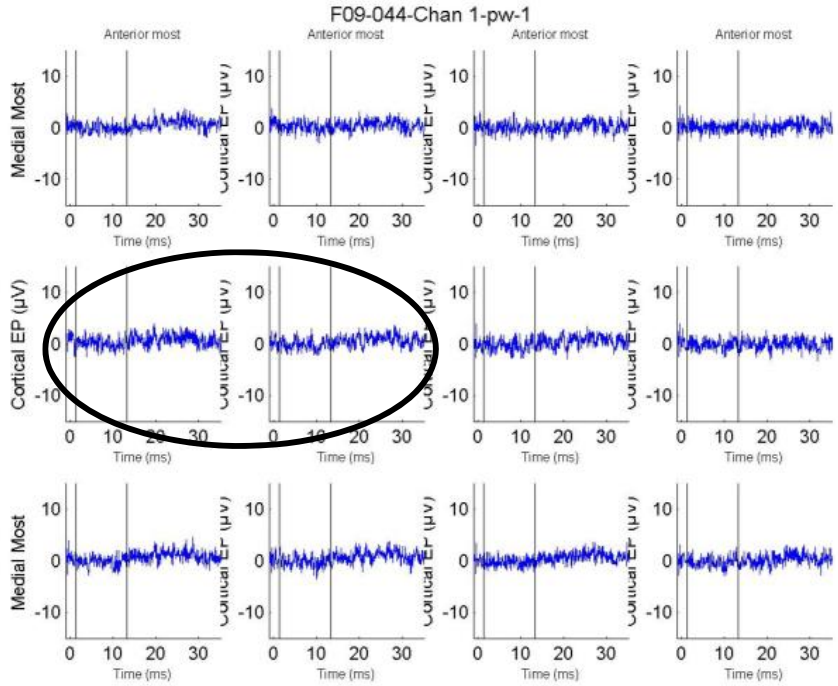


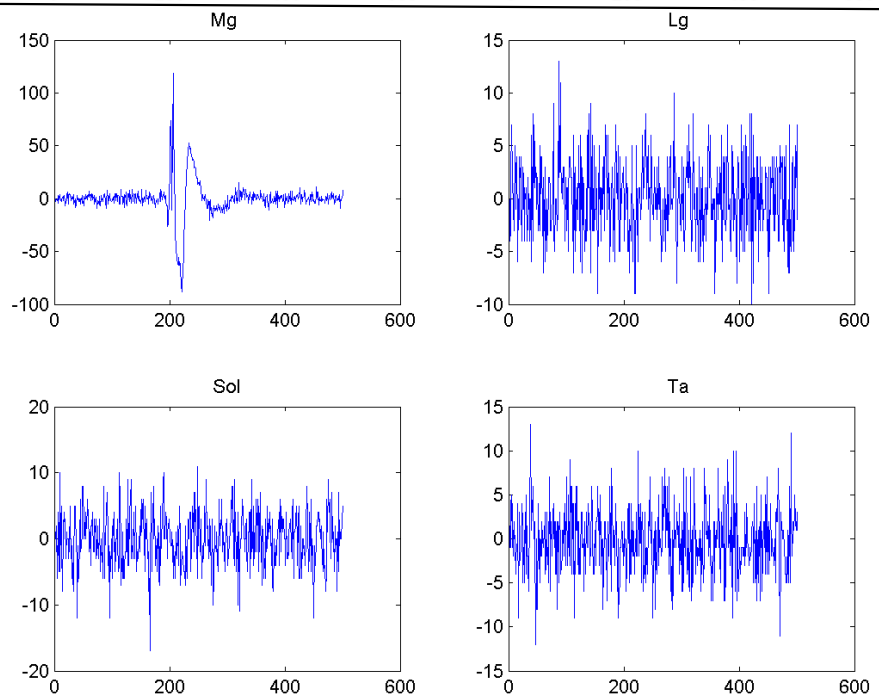
- **74%** of electrodes evoke SS Cx EPs; 62% evoked motor responses
  - Sensory fibers first: **41%** of 29 effective electrodes
  - Motor fibers first: 47% of 29 effective electrodes
- Implication: Could evoke SSEPs/percepts without also evoking movement of residual muscles

EMG Without Sensory Responses (cat; SCI)









Selective Activation of and Recording from Motor and Sensory Nerve Fibers via USEAs in Arm Nerves of Non-Human Primates

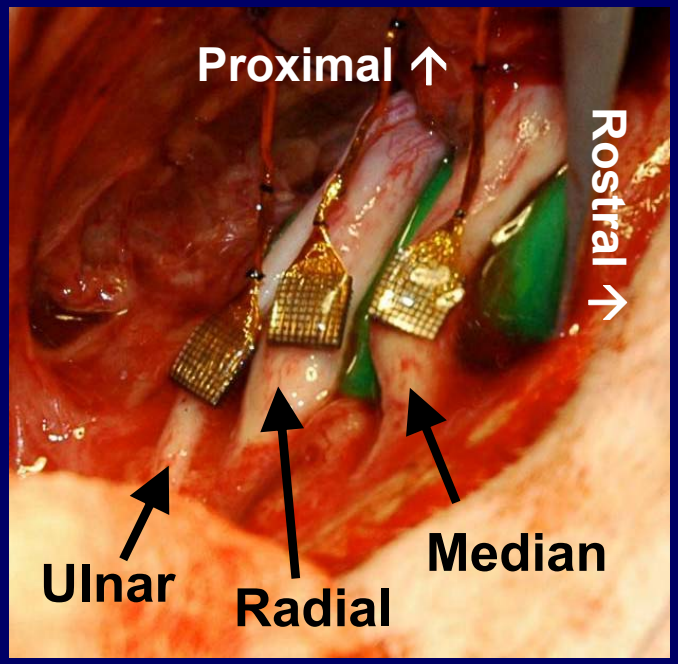
With Lee Miller and colleagues

NM Ledbetter[1], C Ethier[2], ER Oby[2], NM Sachs[2], SD Hiatt[1], AM Wilder[1], JH Ko[2], JM Souza[2], LE Miller[2], and GA Clark[1]

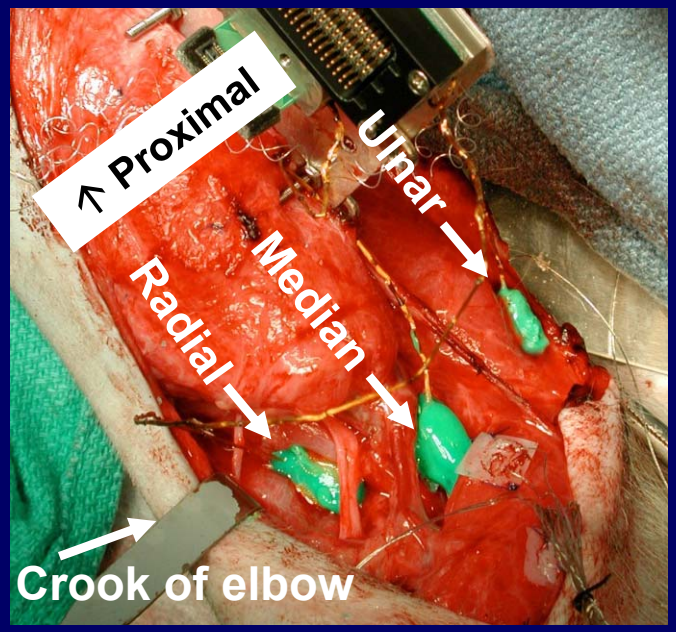
[1]Univ. of Utah, [2]Feinberg School of Medicine, Northwestern University

First-Ever (and *Only*-Ever): USEAs in Arm Nerves of Non-Human Primates

3 Arrays, Near Plexus



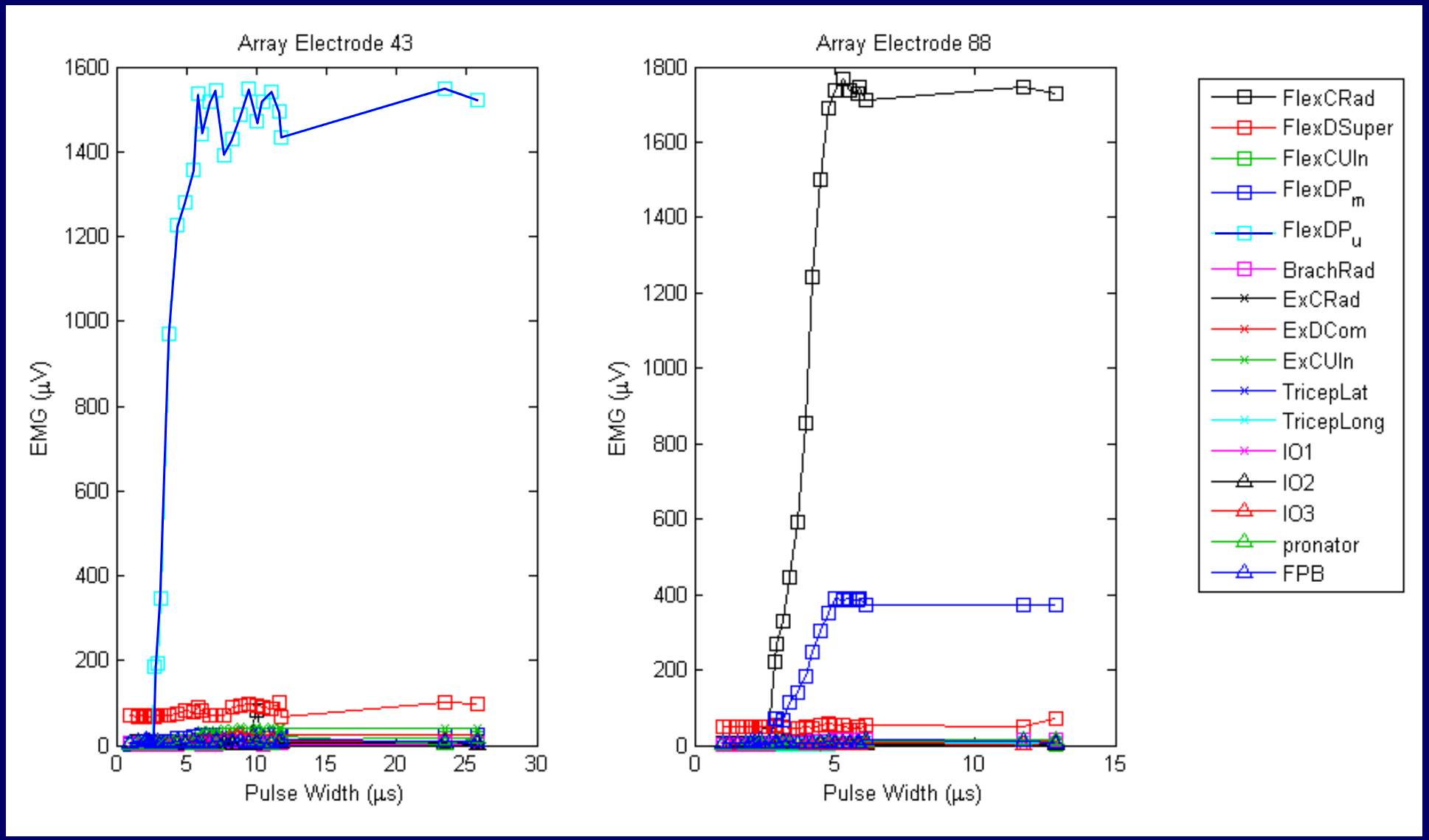
3 Arrays, Near Elbow
(with containment systems)



- ✓ **Stimulation**
  - Efferent fibers (record EMG & movements)
  - Afferent fibers (record S1 Cx EPs)
- ✓ **Recording**
  - Unit discharges to sensory stimulation & imposed movements

Selective Finger and Wrist Movements

Finger (FDP) Wrist (FCR)



6 Hand Movements Evoked by USEA Median N. Stimulation

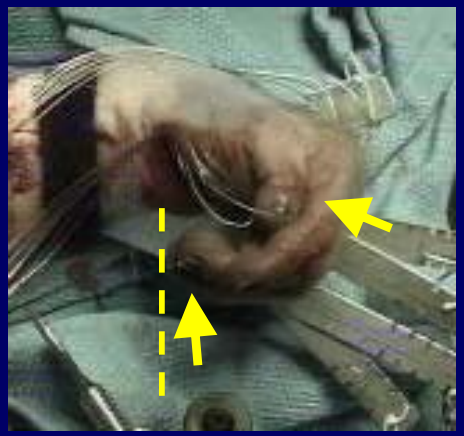
Rest

4 Finger Flexions

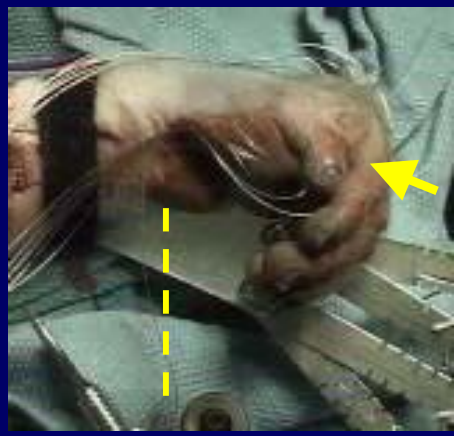
D2,3 Tip Flex

D3-5 Tip Flex

D2-5 Base & Tip Flex



D2-5 Base Flex, Tip Ext



2 Wrist Actions

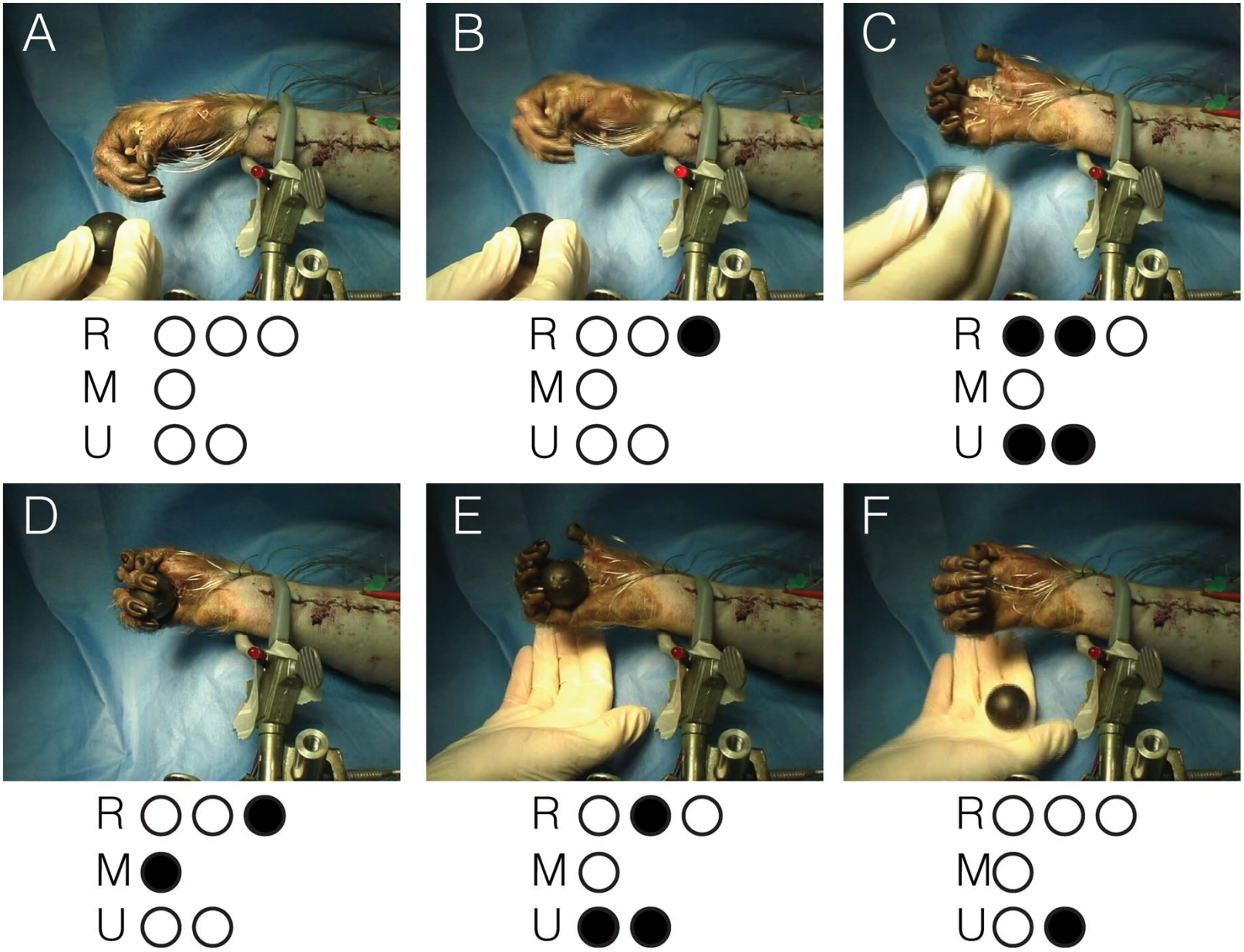
Wrist Flex

Wrist Pronation

- 79 of 96 electrodes (82%)
- 6 different movements
- Selective

With Miller et al.

Coordinated Grasp & Release via Multi-Electrode, Multi-USEA Stimulation



Coordinated Reach-Grasp-Release

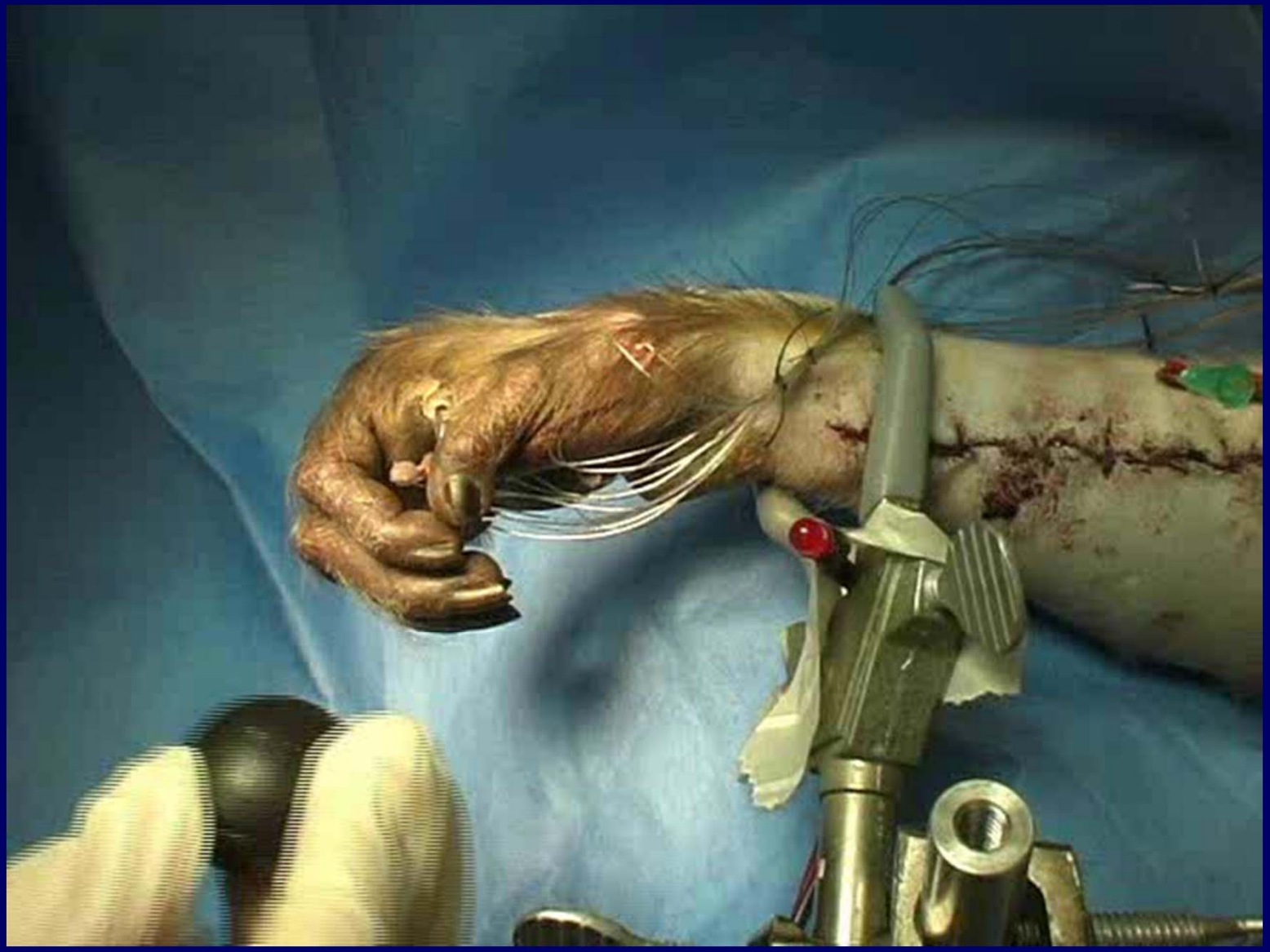
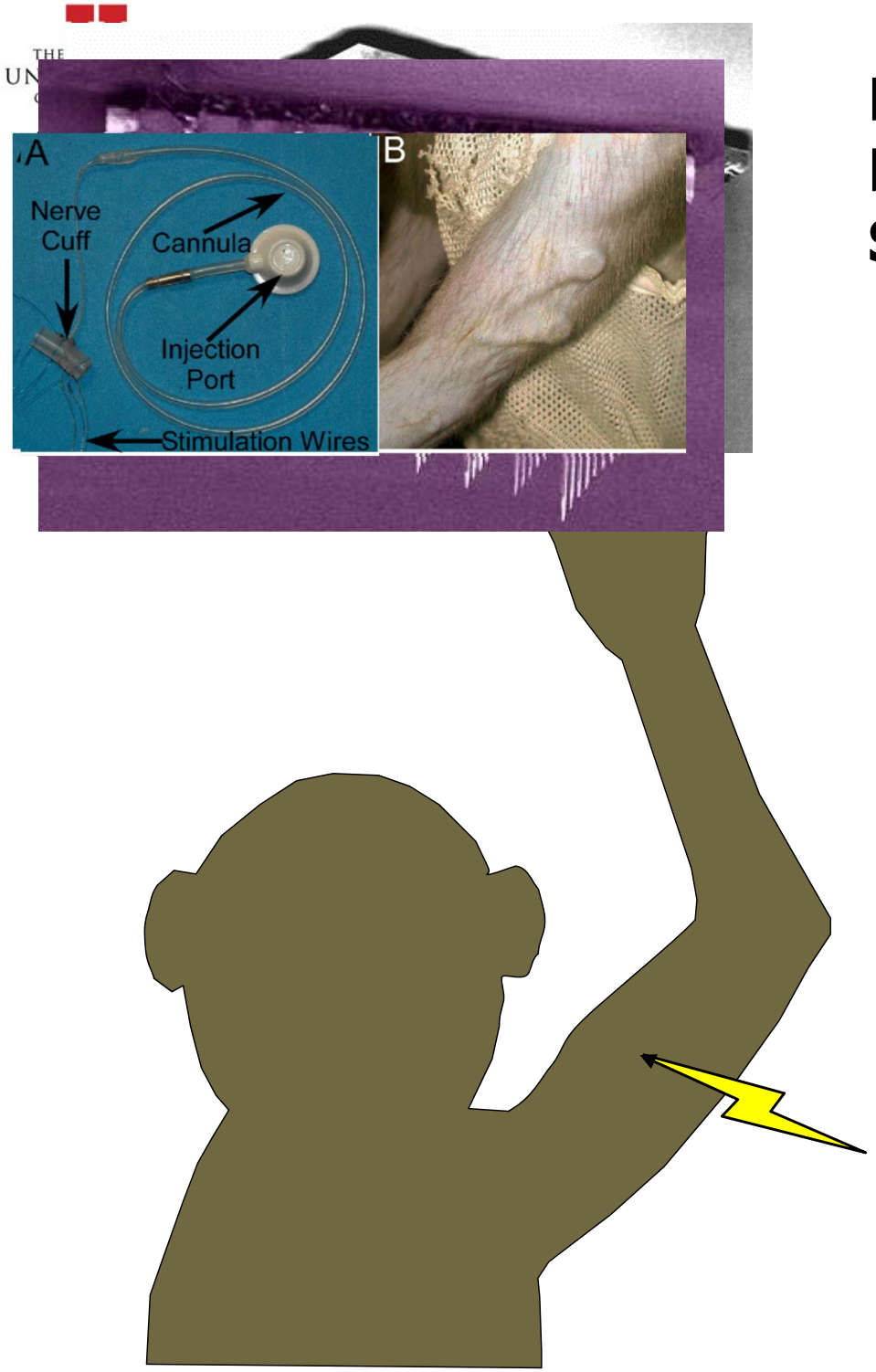


Figure S3 - ball hold no sound.wmv, Or NHP4_09-08-18 13;31;16_Ball.dv



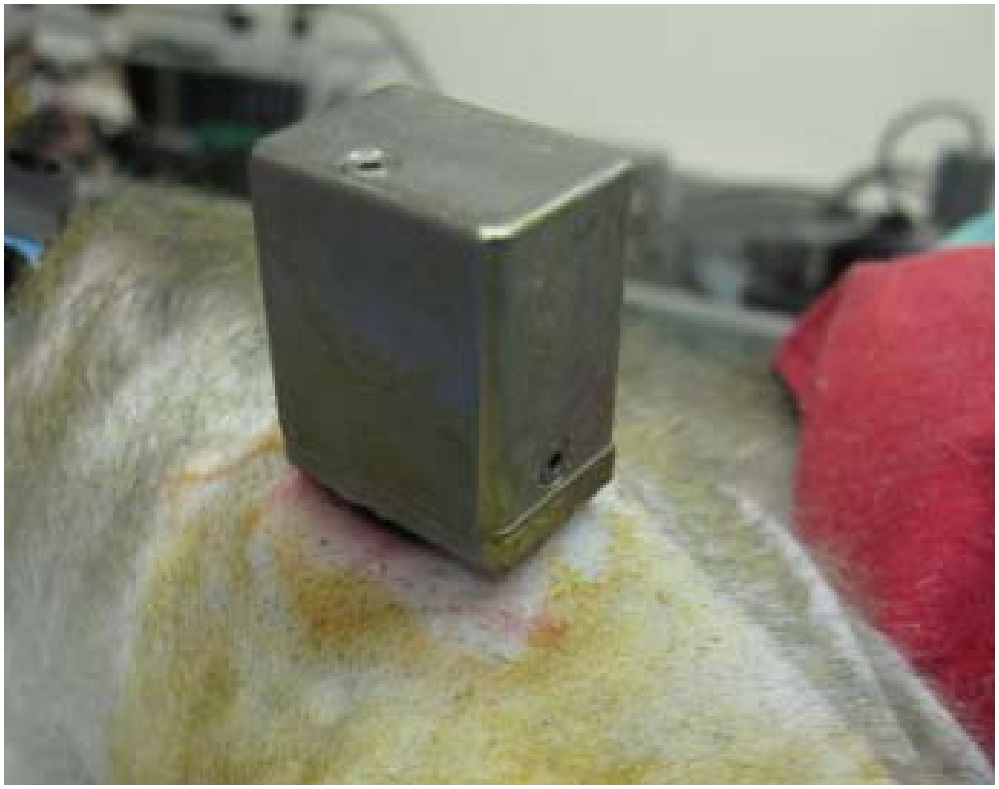
Brain-Controlled Coordinated Hand Grasps Evoked by USEAs in SCI Model

- **Cortical Recording & Decode**
  - Determine relationship between Cx and muscles to determine “intent”
- **USEA in arm nerves**
  - Evoke movements
- **Nerve block spinal cord injury model**
  - Temporary paralysis
  - Attempt to evoke “intended” movements as inferred from decode of brain activity

Chronic USEA Implants

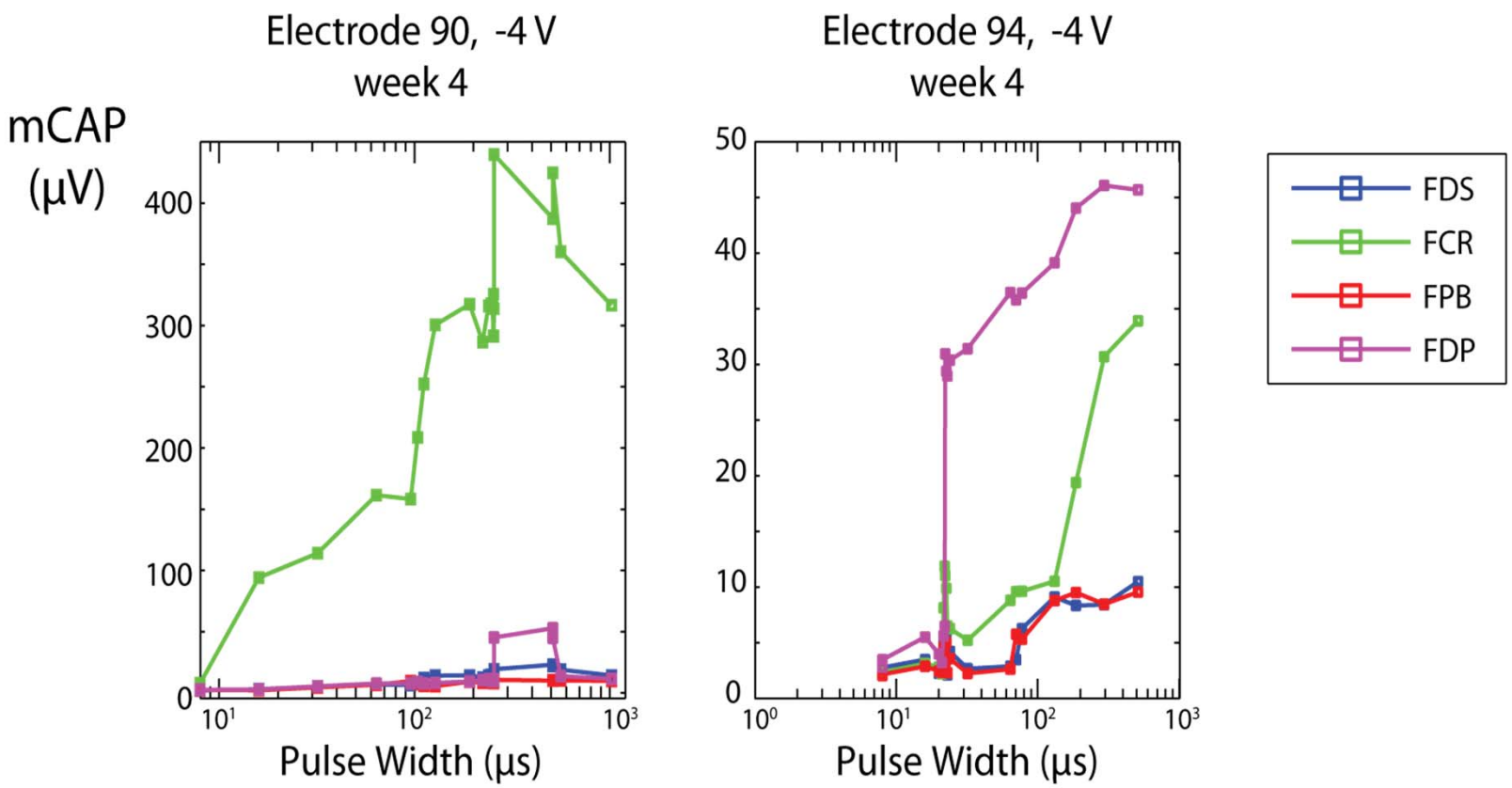
Bone Plate (Stage 1)

USEA & Connector (Stage 2)
4 weeks post USEA implant

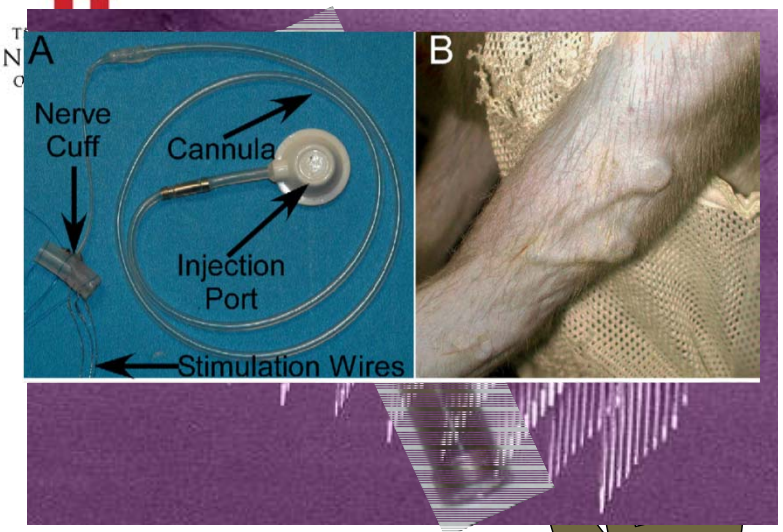


- Connector good for a few months, but...
- Need greater access for cleaning

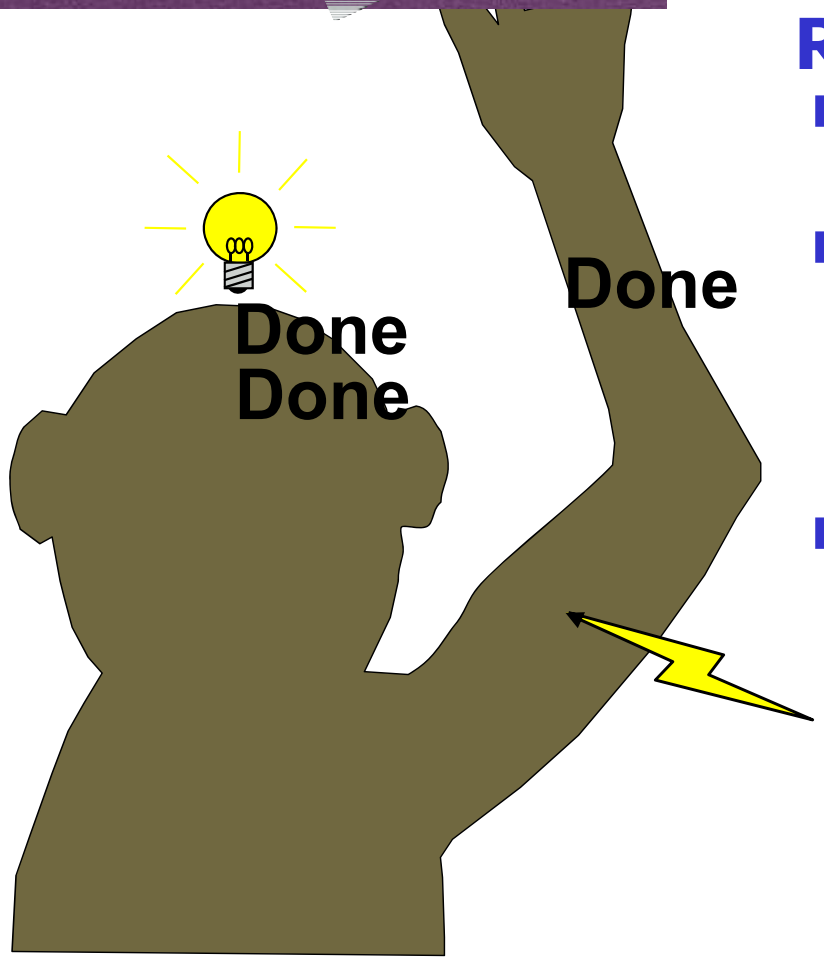
Chronic USEA Implants: Physiology



- Stimulation remains possible, but desire
  - More electrodes that evoke responses
  - Greater selectivity



PNS Control of a Prosthetic Hand (with Bradley Greger)



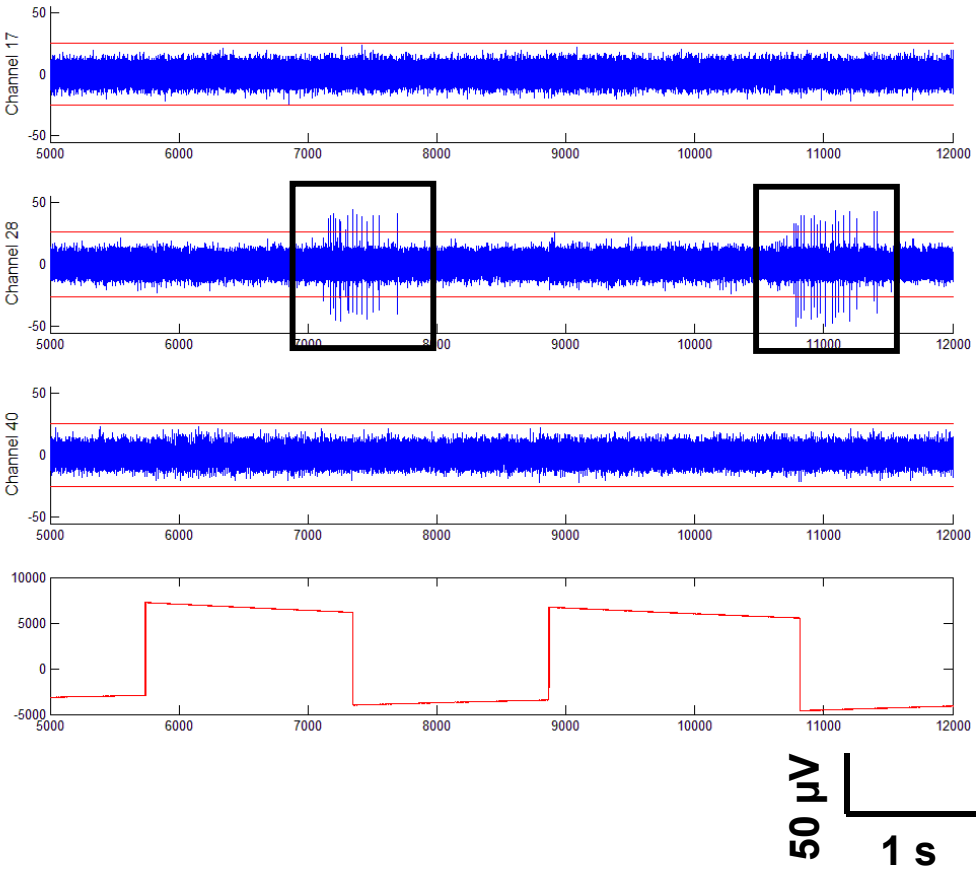
- **Motor Control: 3 sites**
  - Muscle: EMG via IMES
  - Motor cortex: via UEA & ECoG
  - *Peripheral nerve: via USEA*

RPI

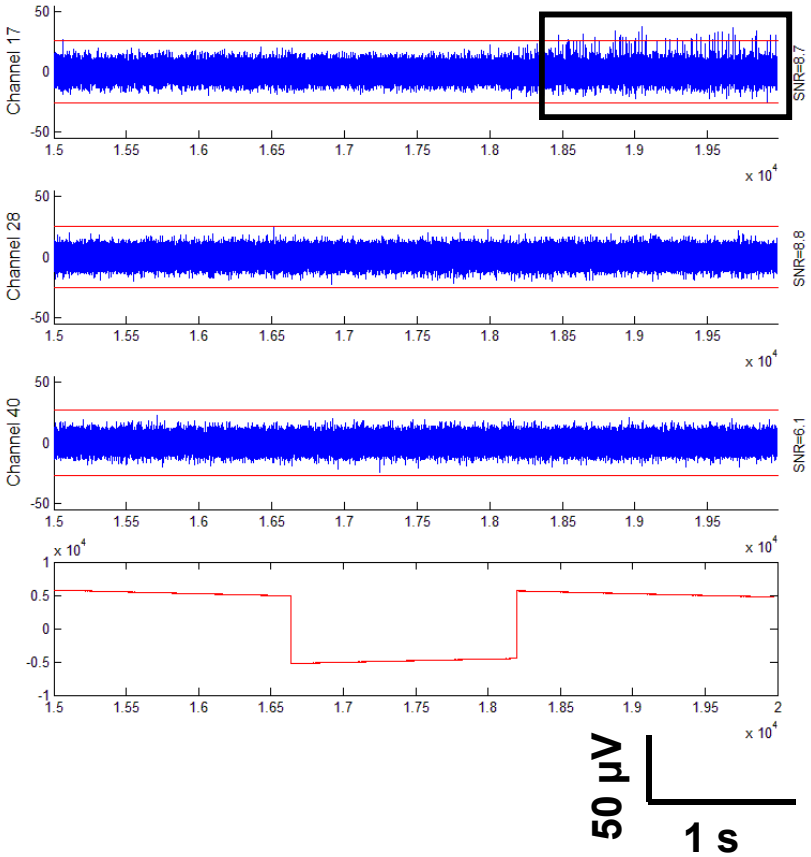
- Sensory feedback(?)
  - Can stimulation of peripheral nerve afferents substitute for natural stimuli?
- Amputation model
  - Distal nerve block (w/ Lee Miller)
    - No nerve to muscle activation
    - No natural sensory feedback

Sensory Recordings from Median N.

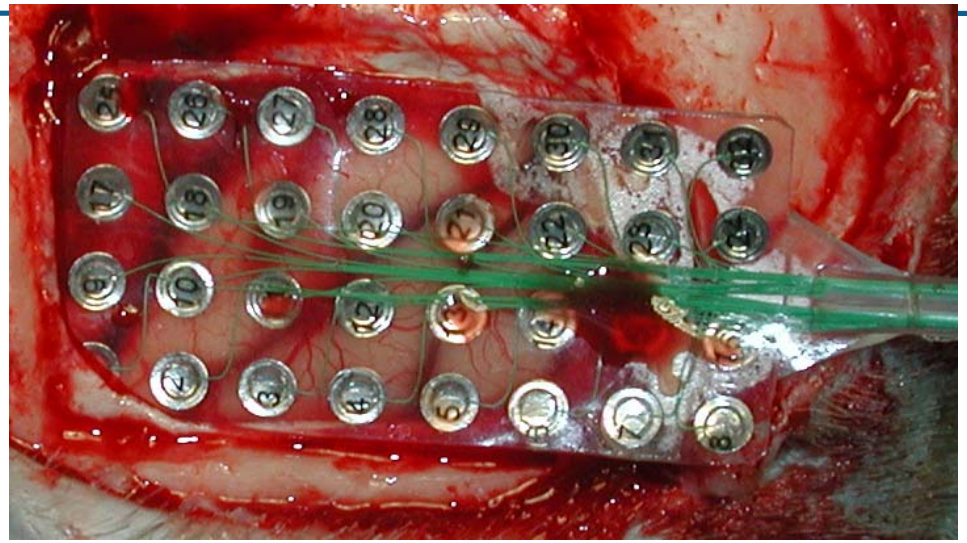
Thumb Flexion

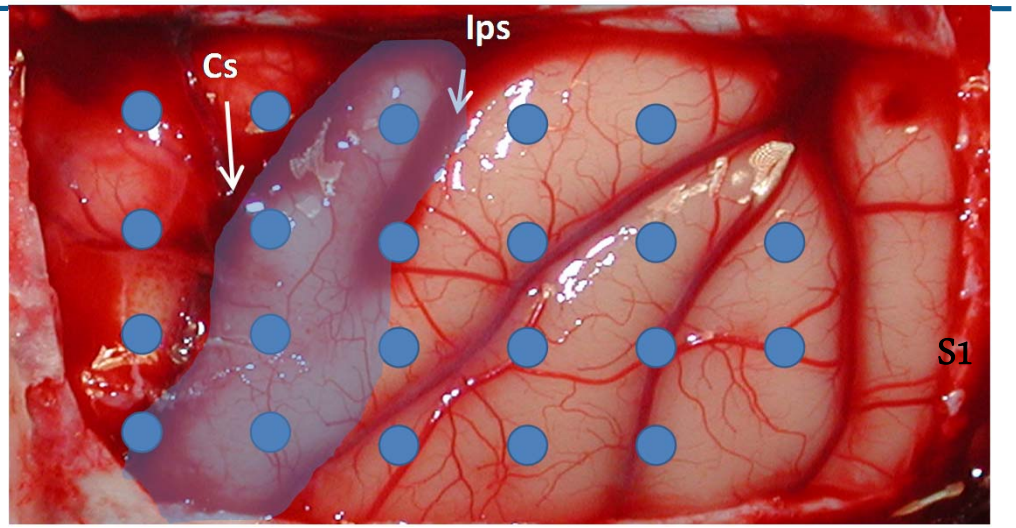


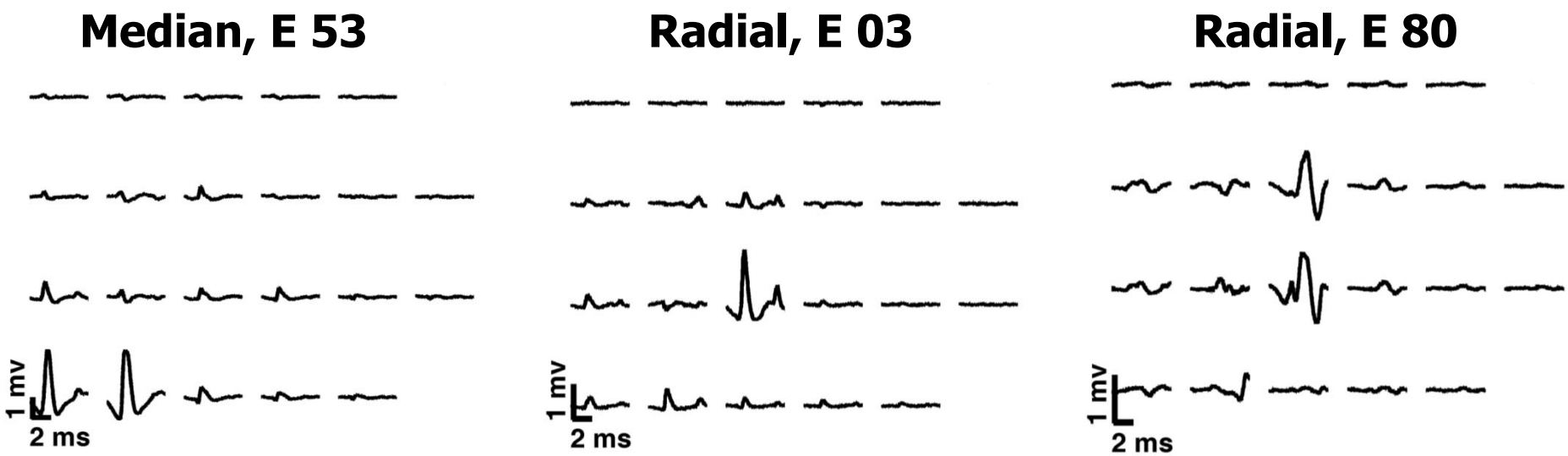
Finger Extension



Somatosensory Cx EPs





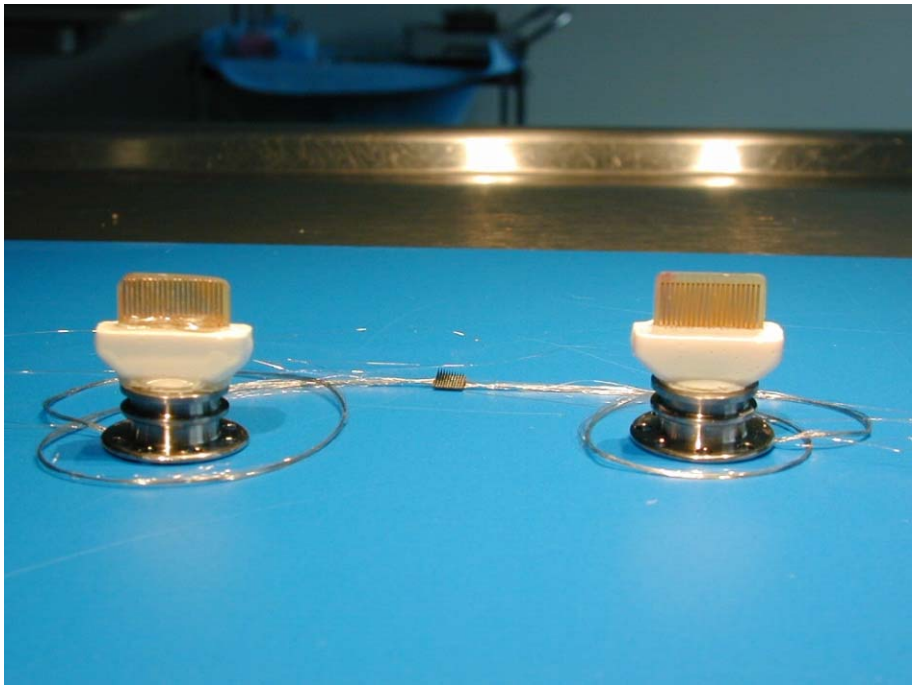


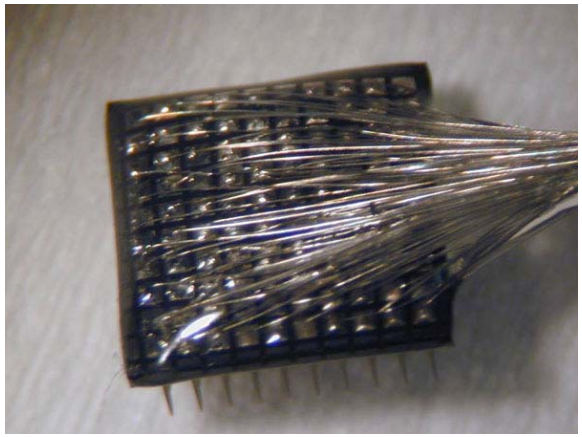
- ✓ Short-latency, localized EPs evoked by stimulation of afferents
- ✓ Focal point varies with electrode (and muscle activated)

Wireless Recording & Stimulation

With Reid Harrison (chip design),
Florian Solzbacher (systems integration),
et al.

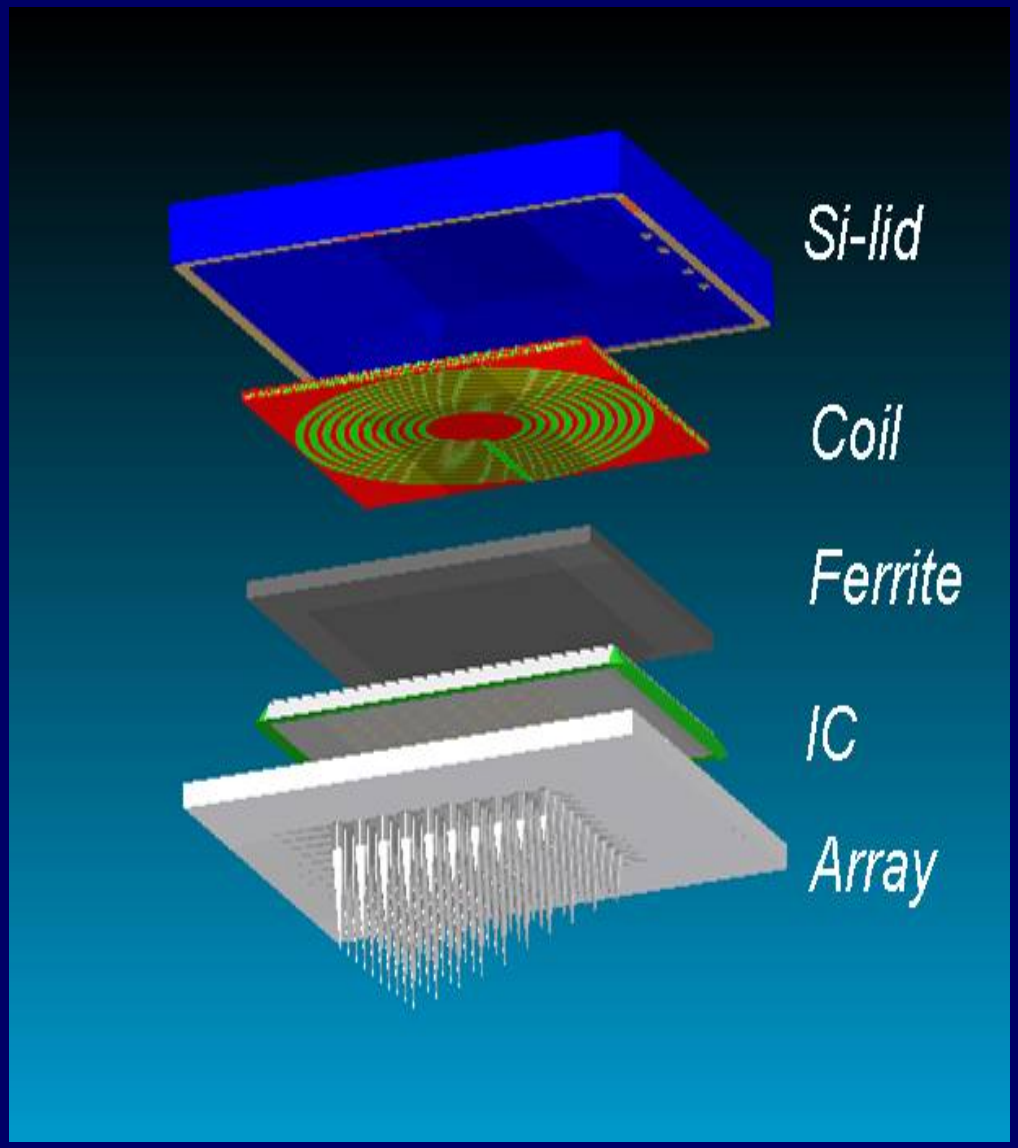
Problem: Wires and Connectors!





- Infection risk, from break in skin
- Tethering forces
- Electrically noisy
- Wire breakage

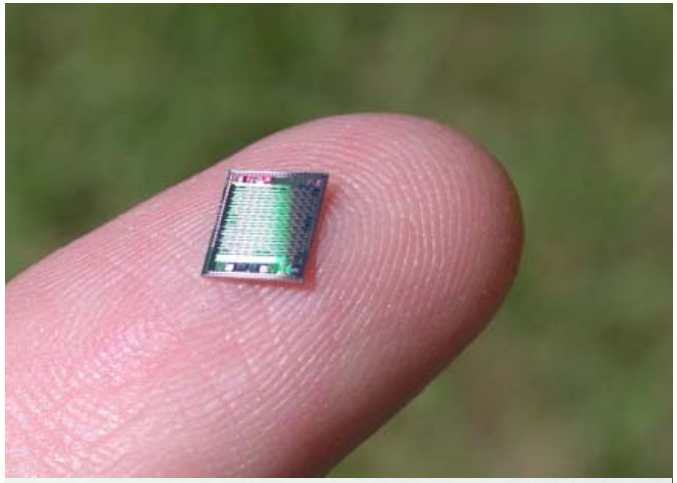
Integrated Wireless Recording Array

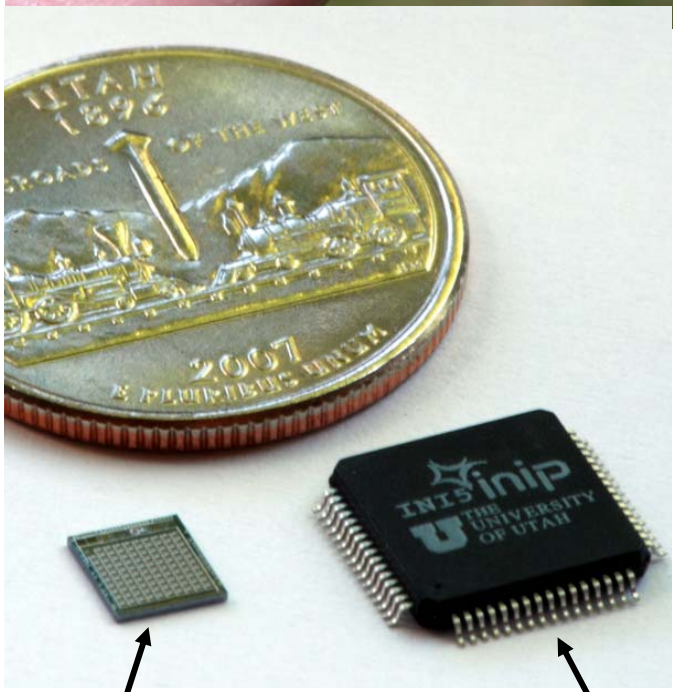


- ✓ Packaging & encapsulation
- ✓ Power & command coil
- ✓ Integrated circuit & SMDs
  - 100 amplifiers or stimulators
  - DSP
  - Telemetry
- ✓ Array electrodes

With Reid Harrison (chip design)
and F. Solzbacher & IZM (integration & encapsulation)

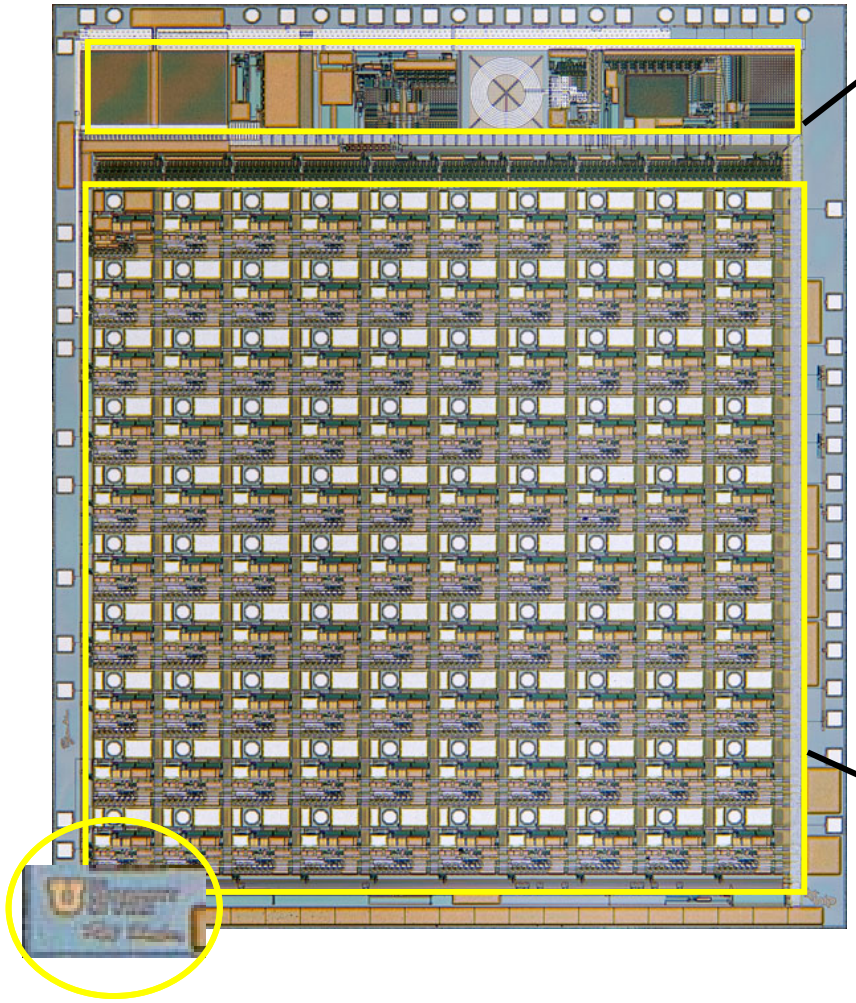
100-Channel Wireless Recording Integrated Circuit





100-channel bare die

16-channel QFP



– Clock
– ADC
– Telemetry
– Etc.

100 Amps & Spike Detectors

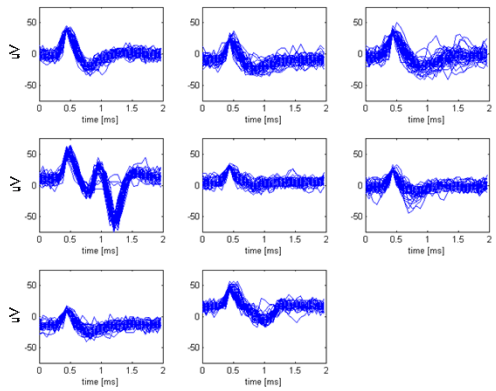
Reid Harrison et al.

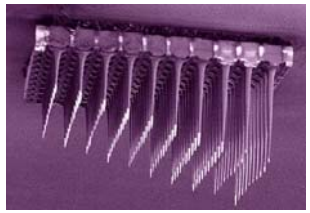
FAQs

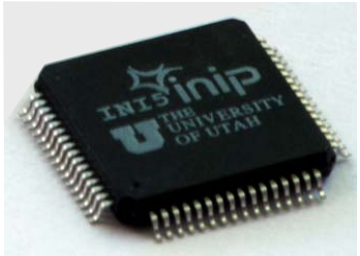
- ✓ Can we wirelessly record nerve fiber discharges?
- ✓ Can we decode these discharges to infer limb position?

- ✓ Yes
- ✓ Yes

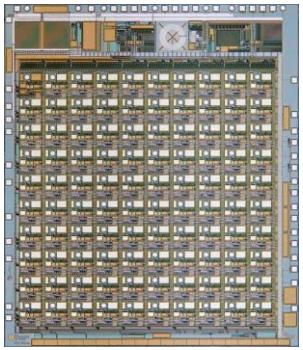
Real-Time Wireless Control of Virtual Prosthetic Arm via Nerve Discharges





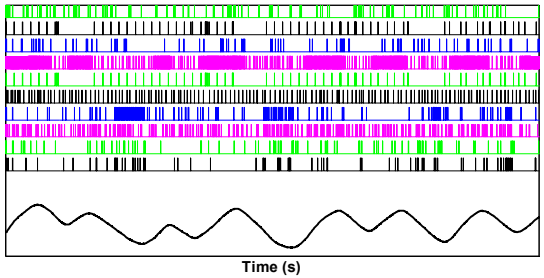


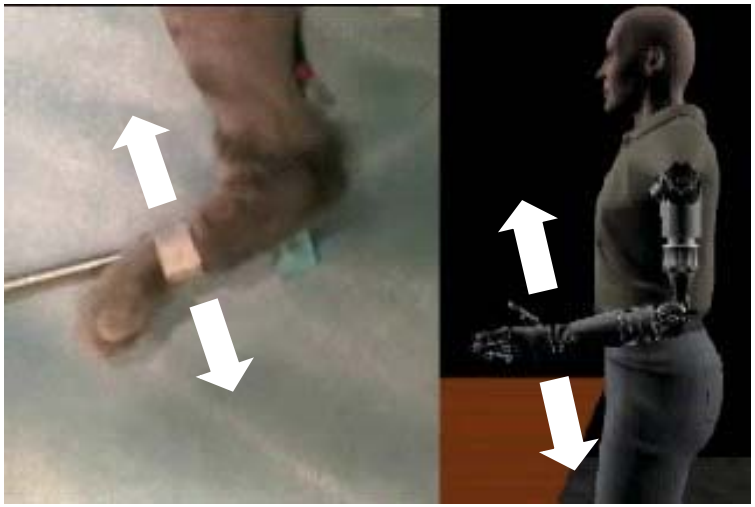
Or

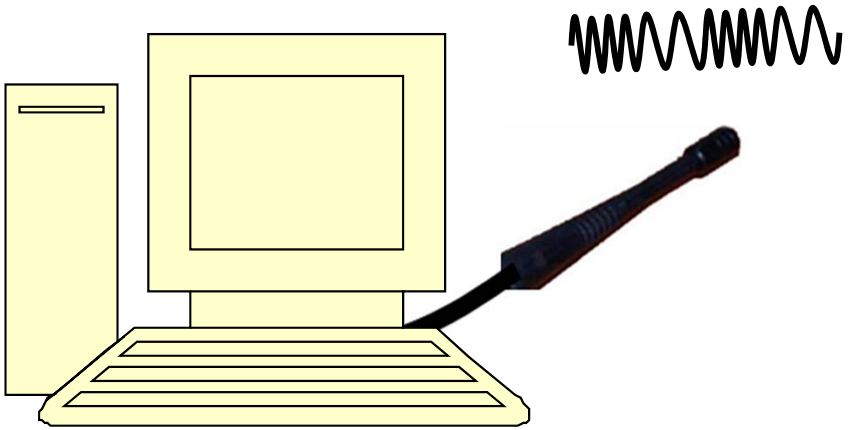


Wired USEA + 16-ch QFP

(or Integrated System)

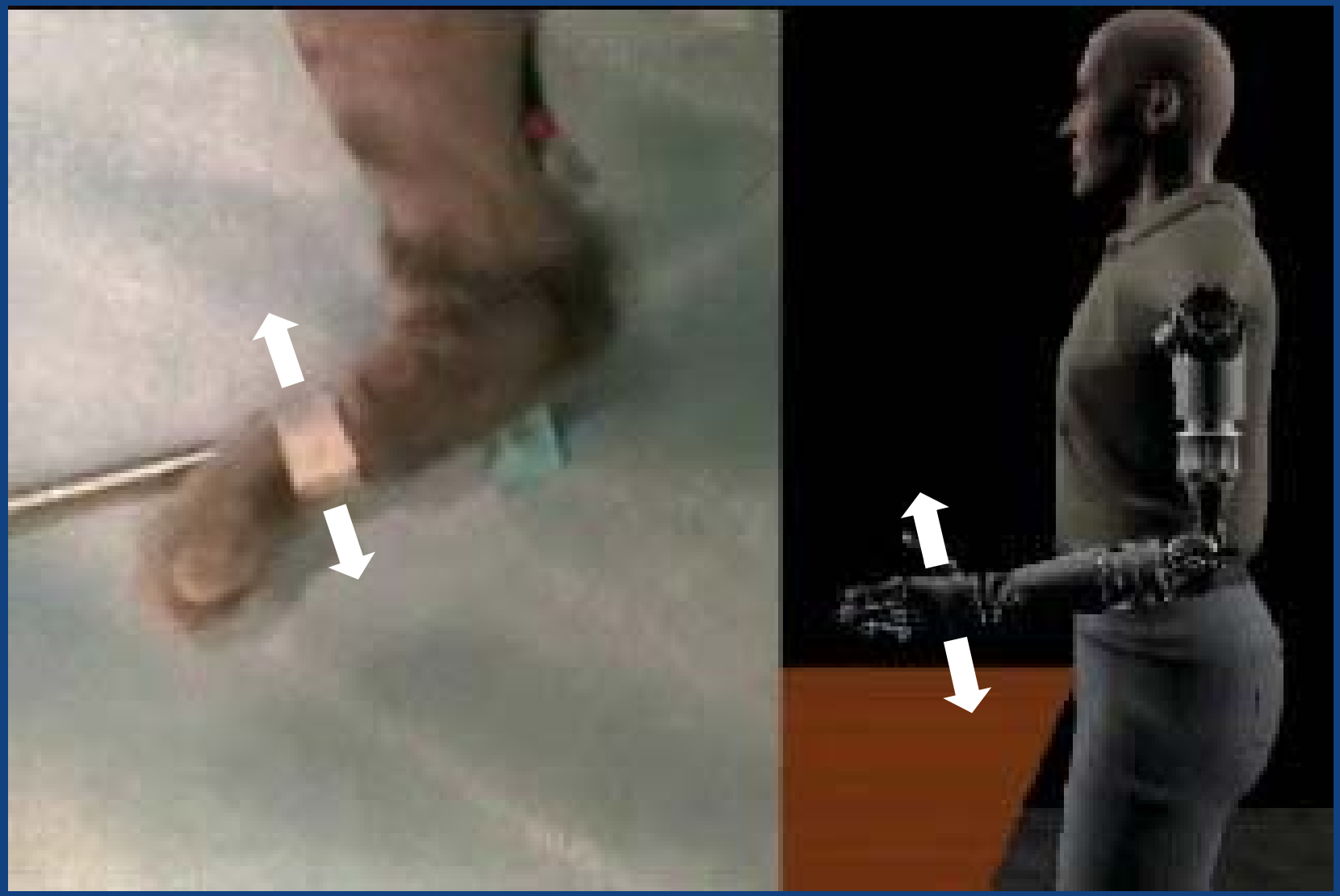






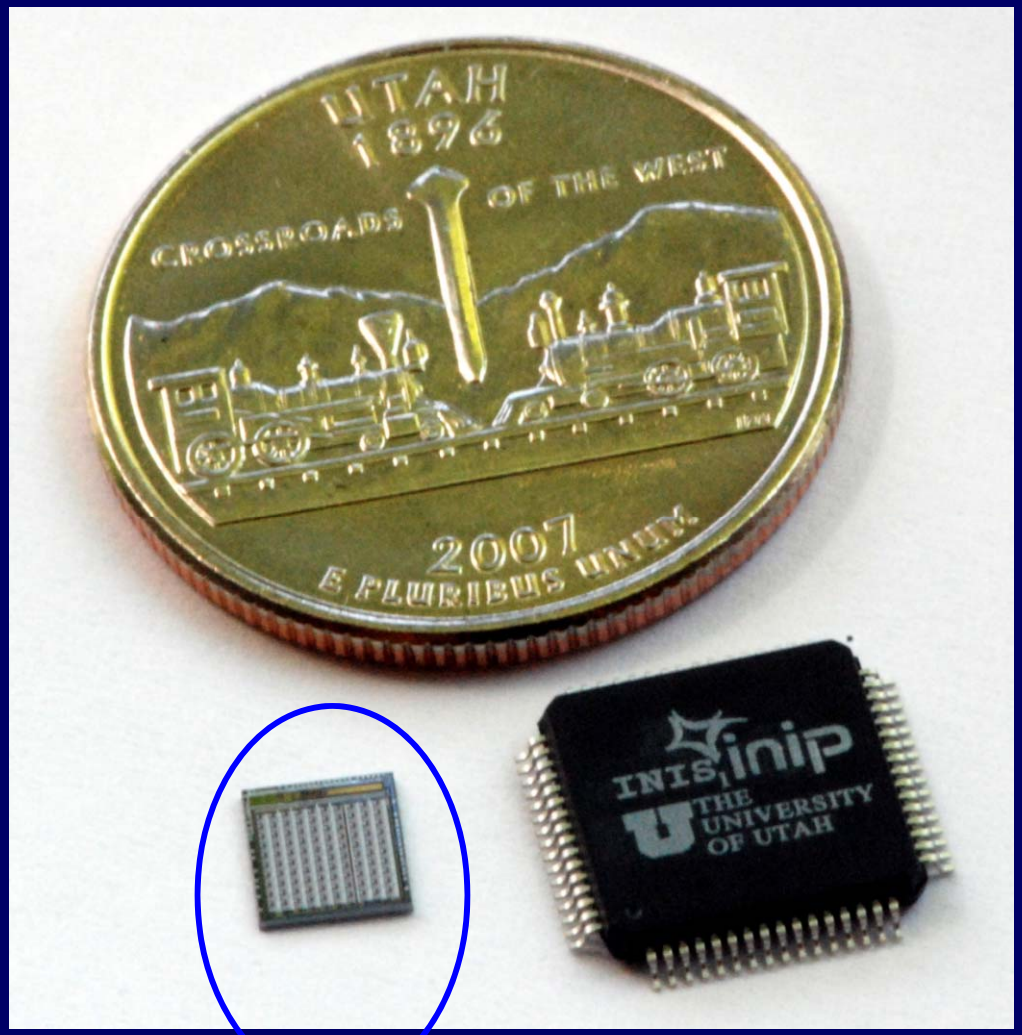
- ✓ **Record and "decode" nerve activity**
- ✓ **Use that "decode" to control virtual prosthetic arm**

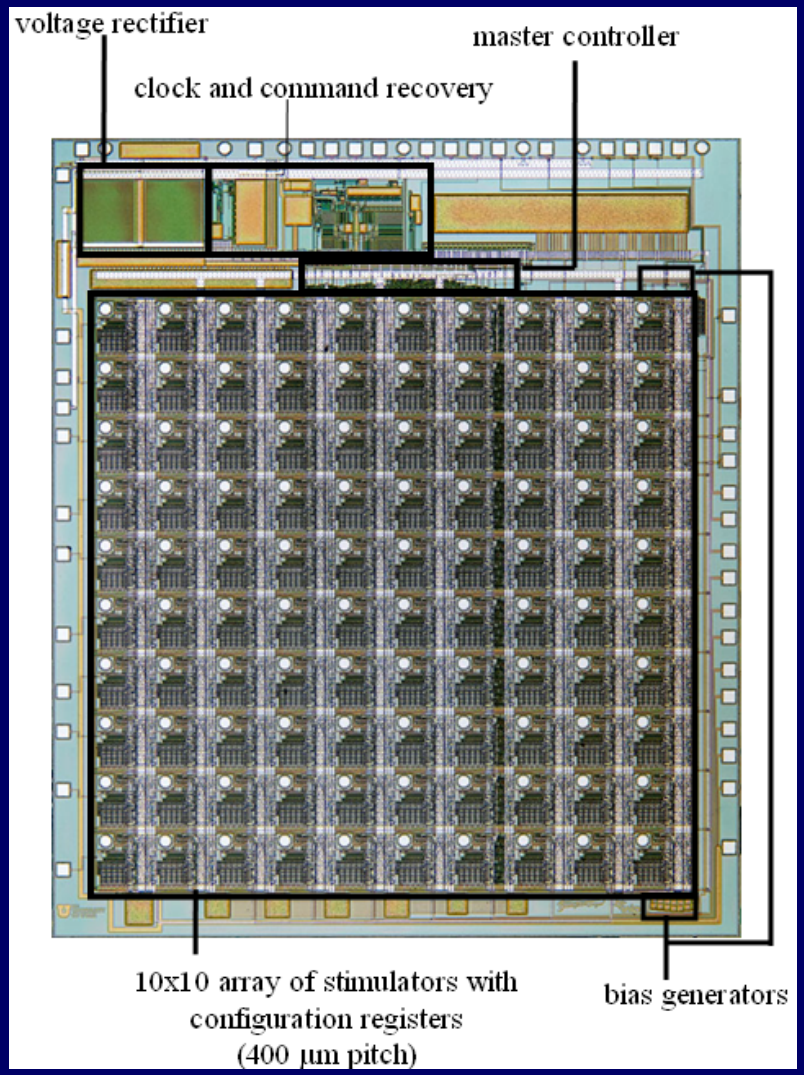
Real-Time Wireless Control of Virtual Prosthetic Limb: Random Movements, Chronic Wired USEA



Movie: INIData_v090626_145054_R.wmv (click on blue backgroud, not picture)

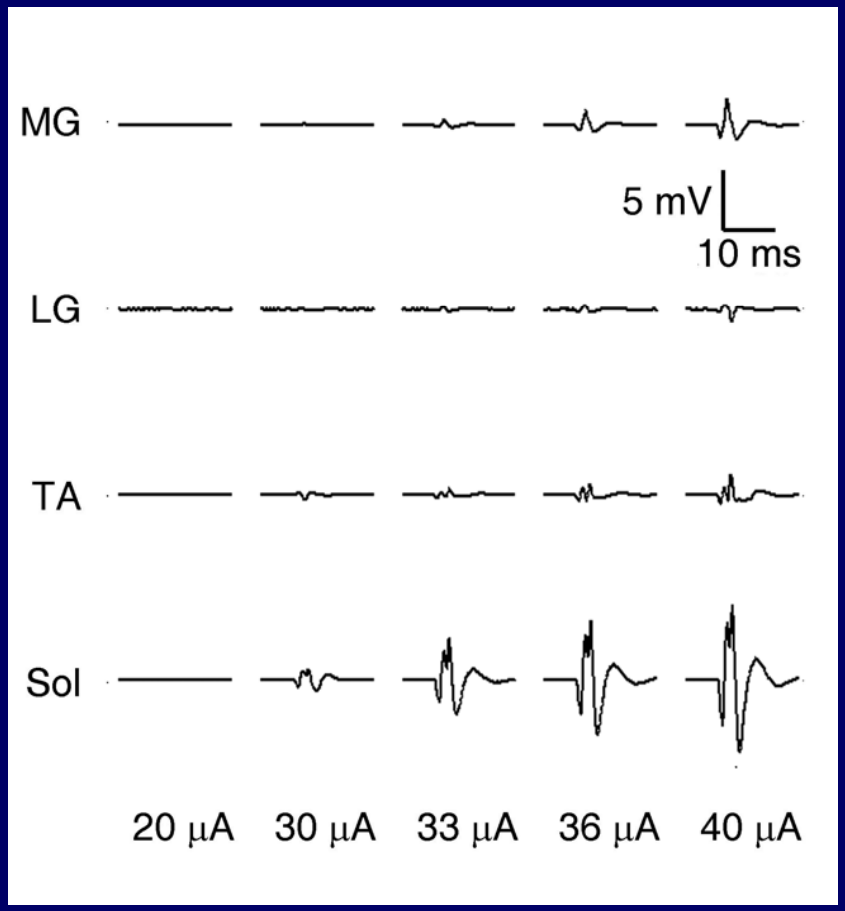
INIS1 (Wireless *Stimulation*)



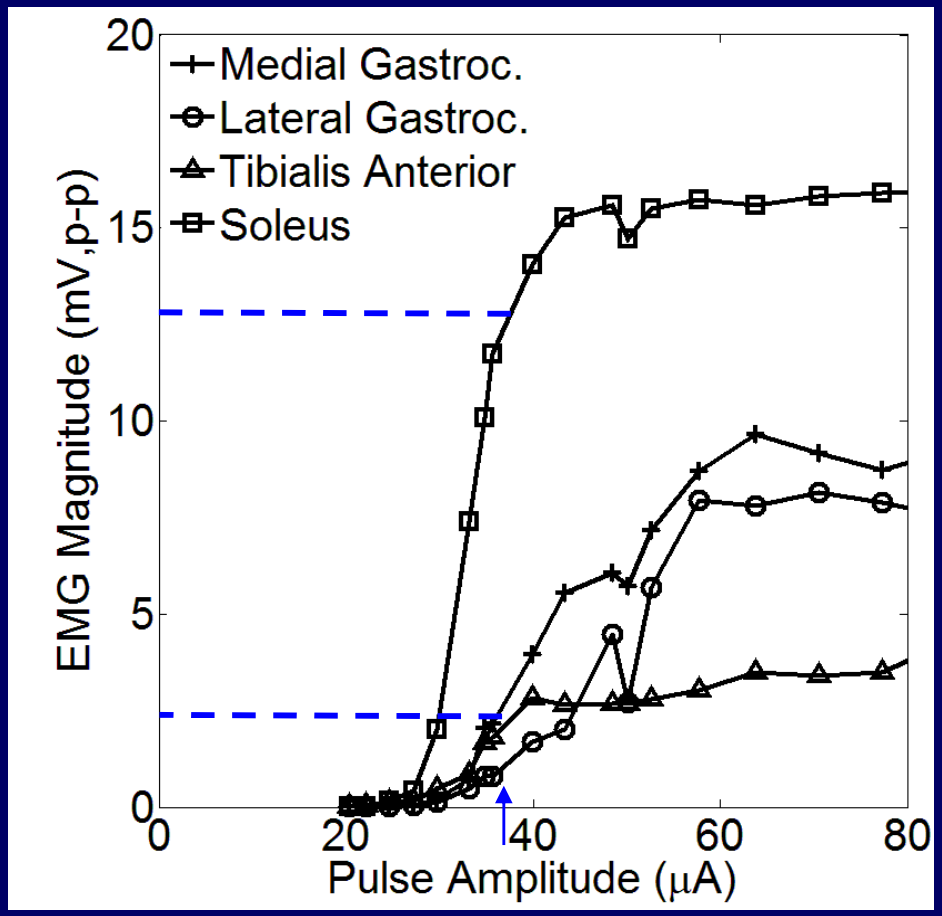


Wireless Stimulator Circuit Evokes Selective, Systematic Motor Responses

Muscle CAPs (raw data)



Quantification



- ✓ Selective: Activates Sol >> MG or LG (3 calf muscles), or TA (antagonist)
- ✓ Systematic: smooth I/O curves obtained with pulse-width modulation

Conclusions

- ✓ **Initial progress is encouraging**
  - Neural interfaces have demonstrated important progress toward restoring sensorimotor function and other neural functions

- ✓ **Remaining Challenges**
  - Further improvements
  - Clinical implementation
  - A growing field, still in its infancy
  - It's going to take a lot of brain power….
  - And (of course!) a lot of nerve

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