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

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

"Self-Esteem" area

(Spurzheim, 1825; KSJ4)

“Neuroprostheses” = “BCIs”, “BMIs”

Nerves are dumb

(The axon doesn’t think—it only ax.” -G. Bishop)

FINAL COMMON PATHWAY

Motor: CNS → muscle
Sensory: CNS ← body

Recycle Bin
“Language”

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.”
What does the customer want?

“I told Doc he can do whatever he wants to my arm, but he ain’t messing with my head.”

Motor and Sensory Neuroprostheses

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

Motor System: A huge area of investigation

Somato-Sensory: A huge area of investigation
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

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

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

- 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

- Stimulate efferents
- Record afferents

Neuroprosthetic Limb

- Record efferents
- Stimulate afferents

Both: Can we record from and stimulate nerve fibers?
Neuroprosthetic Interventions for SCI

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

Peripheral Nervous System
- Sensors
- Muscles

Peripheral Nerves

Sensory Neuroprosthesis

Spinal Cord

Injury

Motor Neuroprosthesis

Cerebral Cortex

S1

M1

**
“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**

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

- 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

Michael Weisskopf
“Amputee Alley,” Ward 57, Walter Reed
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

Tip Mean Impedance

Time after Implant

Impedance (KΩ)

Preimplant  Day 0  Day 4  Week 1  Week 2  Month 1  Month 2  Month 3  Month 4

N = 5  N = 4  N = 3
3a. Successful Long-Term *Recordings* (2.5 Mo)
3a: Long-Term Recordings

- Typical
  - “Noise”: \( \sim \pm 10 \text{ uV, 0 to peak (3 x SD)} \)
- Spike threshold settings: \( \sim -20 \text{ uV, } 6 \times \text{ RMS} \)
- Underestimate; sensory only
- More channels (motor) active in awake animals

Anesthetized, Sensory Units Recorded

- Time after Implant

- Days:
  - Day 0
  - Day 4
  - Week 1
  - Week 2
  - Month 1
  - Month 2
  - Month 3
  - Month 4

- Sample sizes:
  - N = 5
  - N = 4
  - N = 3
3b: EMG-Free Recordings in Behaving Animal

**Without** 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

Time after Implant

Selectivity Index

Proportion Responding

Day 0  Day 4  Week 1  Week 2  Month 1  Month 2  Month 3  Month 4
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

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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 $\rightarrow$ better USEAs (Solzbacher et al.)
  • General
    • Improved insulation $\rightarrow$ ↓ 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 $\rightarrow$ ↑ osseointegration
    • (Alternatively, locking head screws may help)
  • Ti-surface treatment and form factor $\rightarrow$ ↑ tissue adhesion, ↓ infection

More a magic “machine gun” than a single “magic bullet”
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 Response
- Recruitment Curve
- Pulse Train Response
- Multi Electrode Interaction
- Electrode Pair Overlap

15 µs

-1.14 V

1000 ms
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

**Stimulus-Response Feedback Loop**

**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

![Image of Closed-Loop FES Platform with control module, custom stimulator, and data acquisition unit.](image)
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

Synchronous vs. Interleaved Stimulation

July-01-2009

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

- 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

Hindlimb EMGs

S1 Cortex

MG, LG, Sol, TA
<table>
<thead>
<tr>
<th>EMG Without Sensory Responses (cat; SCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graphs showing EMG activity for different muscles and time frames." /></td>
</tr>
</tbody>
</table>
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 Ledbetter¹, C Ethier², ER Oby², NM Sachs², SD Hiatt¹, AM Wilder¹, JH Ko², JM Souza², LE Miller², and GA Clark¹

¹Univ. of Utah, ²Feinberg School of Medicine, Northwestern University
First-Ever (and Only-Ever): USEAs in Arm Nerves of Non-Human Primates

3 Arrays, Near Plexus

✓ Stimulation
  – Efferent fibers (record EMG & movements)
  – Afferent fibers (record S1 Cx EPs)

✓ Recording
  – Unit discharges to sensory stimulation & imposed movements

3 Arrays, Near Elbow (with containment systems)

Ulnar ➔
Proximal ➔
Median ➔
Radial ➔
Rostral ➔

Crook of elbow

With Lee Miller et al.
Selective Finger and Wrist Movements

Finger (FDP)

Wrist (FCR)
6 Hand Movements Evoked by USEA Median N. Stimulation

- 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

- 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

- 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

50 µV
1 s
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

- Clock
- ADC
- Telemetry
- Etc.

100 Amps & Spike Detectors

Reid Harrison et al.

100-channel bare die

16-channel QFP

Integrated Neural Interface Project
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

- Record and “decode” nerve activity
- Use that “decode” to control virtual prosthetic arm

Wired USEA + 16-ch QFP (or Integrated System)
Real-Time Wireless Control of Virtual Prosthetic Limb: Random Movements, Chronic Wired USEA

Movie: INIData_v090626_145054_R.wmv (click on blue background, not picture)
INIS1 (Wireless Stimulation)

- INIS1 chip
- 10x10 array of stimulators with configuration registers (400 μm pitch)
- Voltage rectifier
- Master controller
- Clock and command recovery
- Bias generators
Wireless Stimulator Circuit Evokes Selective, Systematic Motor Responses

Muscle CAPs (raw data)

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

Quantification

![Graph showing EMG magnitude vs. pulse amplitude for different muscles]
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
Acknowledgements

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– Cat physiology (UoU)
  – Richard Normann, Noah Ledbetter, David Warren, Brett Dowden, Mitch Frankel, Andrew Wilder

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  – Reid Harrison

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– DOD N66001-12-C-4042 (RPI; GAC)
Thank you