Targeted Muscle Reinnervation: “Somewhere to go and something to do”

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No financial disclosures or conflicts of interest
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Specialties:
Neurology
Neurosurgery
Orthopedics
Otolaryngology
Physical medicine and rehabilitation
Plastic and Reconstructive Surgery
Pain Management
Special Thanks

- Gregory Dumanian, MD (Northwestern)
- Jason H. Ko, MD (Northwestern)
- Albert Chi, MD (OHSU)
What is Targeted Muscle Reinnervation (TMR)?

• A procedure that “re-routes” cut nerves into nearby muscles, allowing them to innervate and control the muscle

• Improves myoelectric *prosthesis* control
  – Currently upper extremity only

• Can treat and prevent *pain* in amputees
  – Upper and lower extremity
Major Limb Amputation

• 2 million amputees in US
• 185,000 per year
  – ~½ Trauma or Oncologic
  – ~½ Vascular, diabetes
• Projected: 3.6 million by 2050

Pain and amputation

- Residual limb pain - 30-70%\(^1,2\)
  - “Stump pain”

- Phantom limb pain
  - Variable reported prevalence: 10-85%\(^3\)

- Post-operative pain
  - In early months can have all three

- Fewer than 9% report living pain-free\(^4\)

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Myoelectric Prosthetics

Historically low rates of prosthetic use amongst upper extremity amputees (except bilateral and transradial)

Traditional myoelectric and body-controlled prostheses limited in control and functionality

Impetus for Targeted Muscle Reinnervation: improved control of myoelectric upper limb prostheses


Courtesy of Greg Dumanian, MD
Goals

1. Review current understanding of residual and phantom limb pain
2. Understand the concept of targeted muscle reinnervation and its uses
   a. Improved control of myoelectric prostheses
   b. Treat/prevent amputation related pain
Nerve Regeneration

Diagram showing the process of nerve regeneration:

A. Initial state
B. After 2 weeks
C. After 3 weeks
Residual Limb Pain

- Definition: Pain experienced in the remaining limb (stump pain)
  - Includes neuroma pain
  - But also:
    - Bony prominence, HO, infection, MSK pain
    - Interferes with prosthetic use

- Neuroma: disorganized nerve fibers intertwined with scar tissue
  - Results from uncoordinated nerve fiber regeneration
Phantom limb pain

- 10-80%. Likely under-reported in many older studies
- Often similar in character/location to pain felt before amputation (noxious stimuli)
- May fluctuate with position, pressure on extremity, emotional state, weather
- May be “driven” by neuroma, but distinct entity
- Psych factors not causative but may affect severity
- Long-term course unclear (high rate reported in long-term amputees)

Centralization of Pain

- **Peripheral**: “noise-like” input from neuroma increases cortical reorganization

- **Spine**: disinhibition/ectopia of DRG, reduction in GABAergic activity and downregulation of opioid receptors

- **Sympathetic**: up-regulation of nociceptors

- **Cortex/Thalamus**: Reorganization—invasion of deafferented zone by adjacent zones (ie mouth/hand)
<table>
<thead>
<tr>
<th>Commonly used treatments for phantom-limb pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacological</strong></td>
</tr>
<tr>
<td>Conventional analgesics</td>
</tr>
<tr>
<td>Opioids*</td>
</tr>
<tr>
<td>β-blockers</td>
</tr>
<tr>
<td>Neuroleptics</td>
</tr>
<tr>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>NMDA-receptor antagonists</td>
</tr>
<tr>
<td>Ketamine*</td>
</tr>
<tr>
<td>Memantine†</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Barbiturates</td>
</tr>
<tr>
<td>Muscle relaxants</td>
</tr>
<tr>
<td><strong>Surgical</strong></td>
</tr>
<tr>
<td>Stump revision</td>
</tr>
<tr>
<td>Neurectomy</td>
</tr>
<tr>
<td>Sympathectomy</td>
</tr>
<tr>
<td>Rhizotomy</td>
</tr>
<tr>
<td>Cordotomy</td>
</tr>
<tr>
<td>Tractotomy</td>
</tr>
<tr>
<td>Dorsal column stimulation</td>
</tr>
<tr>
<td>Deep brain stimulation</td>
</tr>
<tr>
<td><strong>Anaesthetic</strong></td>
</tr>
<tr>
<td>Nerve blocks</td>
</tr>
<tr>
<td>Epidural blockade</td>
</tr>
<tr>
<td>Sympathetic blockade</td>
</tr>
<tr>
<td>Local anaesthesia</td>
</tr>
<tr>
<td>Lidocaine*</td>
</tr>
<tr>
<td><strong>Psychological</strong></td>
</tr>
<tr>
<td>Electromyographic biofeedback</td>
</tr>
<tr>
<td>Temperature biofeedback</td>
</tr>
<tr>
<td>Cognitive-behavioural pain management</td>
</tr>
<tr>
<td>Sensory discrimination training*</td>
</tr>
<tr>
<td>Hypnosis</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Transcutaneous nerve stimulation (TENS)*</td>
</tr>
<tr>
<td>Acupuncture</td>
</tr>
<tr>
<td>Physiotherapy</td>
</tr>
<tr>
<td>Ultrasound</td>
</tr>
<tr>
<td>Manipulation</td>
</tr>
<tr>
<td>Prosthesis training</td>
</tr>
</tbody>
</table>
TARGETED REINNERVATION

1. NEURAL SIGNALS STILL EXIST

Courtesy of Jason Ko, MD
The brain still creates signals that go to the nerves.

Can we tap into these signals to control an artificial arm?

TARGETED REINNERVATION

Courtesy of Jason Ko, MD
CAN WE RECORD CONTROL SIGNALS FROM THE BRAIN??

Courtesy of Jason Ko, MD
CAN WE RECORD CONTROL SIGNALS FROM THE NERVES??

Courtesy of Jason Ko, MD
1. NEURAL SIGNALS STILL EXIST

2. AVAILABLE MUSCLE SITES

TARGETED MUSCLE REINNERVATION

Courtesy of
Jason Ko, MD
TARGETED MUSCLE REINNERVATION

1. NEURAL SIGNALS STILL EXIST
2. AVAILABLE MUSCLE SITES
3. INTUITIVE CONTROL

Courtesy of
Jason Ko, MD
TARGETED MUSCLE REINNERVATION (TMR)

COMBINES AVAILABLE TECHNOLOGY WITH MODIFICATION OF THE RESIDUAL ANATOMY

Courtesy of Jason Ko, MD
Broader concept: Nerve transfers

- A sea change for high nerve injuries
- A donor nerve is repaired into an injured nerve distal to the site of injury
- Axons regenerate into target muscle and can control it
- Must undergo motor re-education
- Up to 95% success rate for certain transfers
Nerve transfers

Double Fascicular Transfer for Elbow Flexion

Triceps Branch to Axillary Transfer
Targeted Muscle Reinnervation

Major nerve divided as part of amputation

Nerve transferred into a motor branch using microsurgical technique

Instead of forming neuroma, axons regenerate to motor endplates of muscle. The nerve can now control this muscle.
Improved Myoelectric Prosthesis Control Accomplished Using Multiple Nerve Transfers

John B. Hijjawi, M.D.
Todd A. Kuiken, M.D.
Robert D. Lipschutz, M.D.
Laura A. Miller
Kathy A. Stubblefield
Gregory A. Dumanian, M.D.

Chicago, Ill.

**Background:** The control of shoulder-level disarticulation prostheses is significantly more difficult than that of prostheses for more distal amputations. Amputees have significant difficulties coordinating the separate functions of prosthetic shoulder, elbow, wrist, and hand/hook components. The user must lock one joint at a particular position in space before subsequently moving a different joint.

**Methods:** A patient with bilateral humeral disarticulations after an electrical injury underwent a novel nerve transfer procedure designed to improve the control of a myoelectric prosthesis. The median, radial, ulnar, and musculocutaneous nerves were transferred to the nerves of segments of the pectoralis major and minor.

![Fig. 2. Intraoperative photograph of the left side of the chest after division of the pectoralis muscle into three segments, mobilization of the pectoralis minor muscle, and performance of nerve transfers (A, radial; B, median; C, musculocutaneous).](image)

![Fig. 5. The patient with his current prosthesis. His experimental prosthesis controlled with myoneurosomes is on the left. He has a more traditional body-powered prosthesis on the right.](image)
• 54-year-old electrical utility lineman

• May 2001: suffered 7200 volt burns

• Immediate bilateral shoulder disarticulation

First TMR Patient

Courtesy of Jason Ko, MD
Gregory Dumanian, MD
Feinberg School of Medicine
Northwestern University

Todd Kuiken, MD, PhD
Rehabilitation Institute of Chicago

*T Surgery performed January 2002

TMR Nerve Transfer Surgery
Myoneuromeosome – segment of muscle under control of a single nerve
• **Mobilize nerve stumps**
• Divide normal pectoralis major and minor innervation
• Create distinct segments of pectoralis muscle
• Coapt nerves & muscle segments
• Mobilize nerve stumps
• **Divide normal pectoralis major and minor innervation**
• Create distinct segments of pectoralis muscle
• Coapt nerves & muscle segments
- Mobilize nerve stumps
- Divide normal pectoralis major and minor innervation
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- Coapt nerves & muscle segments
- Mobilize nerve stumps
- Divide normal pectoralis major and minor innervation
- Create distinct segments of pectoralis muscle
- **Coapt nerves & muscle segments**
Targeted Muscle Reinnervation

Pre-Op: 1 myoneurosome

Post Op: 4 myoneurosome
Targeted Muscle Reinnervation

- “Elbow up”
  Musculocutaneous
- “Close hand”
  Median
- “Open hand”
  Median
  - Thumb abduction
- “Elbow down”
  Radial
- Ulnar nerve: no signal
Courtesy of Greg Dumanian, MD
and Jason Ko, MD
Wrist Supination

Thumb Abduction

Thumb Adduction

PATTERN RECOGNITION

Courtesy of Jason Ko, MD
Hand Close
Elbow Flexion
Elbow Extension
Hand Close
Hand Open

PATTERN RECOGNITION

Courtesy of
Jason Ko, MD
Original Prosthesis
(Used more than 20 months)

Nerve Transfer Prosthesis
(Used about 2 months)
Transhumeral Surgical Procedure

- Median nerve → Medial biceps
- Radial nerve → Lateral head triceps
- Ulnar → Brachialis (if long limb)
- Musculocutaneous nerve → Lateral biceps
- Proximal radial nerve → Long head triceps
Conventional Treatment
2 signals

TMR Post-Op
4 to 5 signals
Targeted Muscle Reinnervation
A Novel Approach to Postamputation Neuroma Pain

Jason M. Souza MD, Jennifer E. Cheesborough MD, Jason H. Ko MD, Mickey S. Cho MD, Todd A. Kuiken MD, PhD, Gregory A. Dumanian MD
## Neuroma Pain in Targeted Reinnervation Patients

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<tr>
<td>Northwestern University/Rehabilitation Institute of Chicago (NU/RIC)</td>
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<td></td>
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<tr>
<td>Shoulder Disarticulation</td>
<td>8</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Transhumeral</td>
<td>7</td>
<td>4</td>
<td>1</td>
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<td>San Antonio Military Medical Center (SAMMC)</td>
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<tr>
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<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Transhumeral</td>
<td>10</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Total (%)</td>
<td>26</td>
<td><strong>15 (58%)</strong></td>
<td><strong>1 (4%)</strong></td>
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Souza et al. CORR, 2014.
# Neuroma Pain in Targeted Reinnervation Patients

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Souza et al. CORR, 2014.
The Effects of Targeted Muscle Reinnervation on Neuromas in a Rabbit Rectus Abdominis Flap Model

Peter S. Kim, MD, Jason H. Ko, MD, Kristina K. O'Shaughnessy, MD, Todd A. Kuiken, MD, PhD, Eric A. Pohlmeier, PhD, Gregory A. Dumanian, MD

FIGURE 7: Myelinated fiber count in the median (n = 5 normal, 5 neuroma, 4 post-TMR), radial (n = 5 normal, 4 neuroma, 3 post-TMR), and ulnar (n = 4 normal, 4 neuroma, 3 post-TMR) nerves (*P = .05; **P = .02).

FIGURE 8: Myelinated fiber cross-sectional area in the medial (n = 5 normal, 5 neuroma, 5 post-TMR), radial (n = 5 normal, 4 neuroma, 3 post-TMR), and ulnar (n = 4 normal, 4 neuroma, and 3 post-TMR) nerves. Units are in square microns (*P = .002; **P = .007; ***P = .02).
TARGETED MUSCLE REINNERVATION (TMR)

- Neurotrophic factors
- Vascularized scaffold
- Denervated target
TARGETED MUSCLE REINNERVATION (TMR)

- Neurotrophic factors
- Vascularized scaffold
- Denervated target

Regenerating nerves have somewhere to go AND something to do...
Targeted Reinnervation in the Transfemoral Amputee: A Preliminary Study of Surgical Technique

Sonya P. Agnew, M.D.
Aimee E. Schultz, M.S.
Gregory A. Dumanian, M.D.
Todd A. Kuiken, M.D.

Background: Lower limb amputation is a common and growing problem in the United States. Current prosthetic technology is insufficient for transfemoral amputees to safely control their prostheses for demanding exercise such as stair climbing. Using a technique called targeted reinnervation, intuitive control of prosthetic devices has been achieved for upper limb amputees. To bring this technique to transfemoral amputees, we describe a series of patients who have undergone targeted reinnervation.

Targeted Muscle Reinnervation Technique in Below-Knee Amputation

J. Byers Bowen, M.D., M.S.
Daniel Ruter, B.S.
Corinne Wee, M.D.
Julie West, M.S., P.A.-C.
Ian L. Valerio, M.D., M.S.
M.B.A.
Columbus, Ohio

Summary: Approximately 25 percent of major limb amputees will develop chronic localized symptomatic neuromas and phantom limb pain in the residual limb. A method to treat and possibly prevent these pain symptoms is targeted reinnervation. Previous studies prove that targeted reinnervation successfully treats and, in some cases, resolves peripheral neuropathy and phantom limb pain in patients who have undergone previous amputation (i.e., secondary targeted reinnervation). This article seeks to share the authors' clinical experiences and surgical technique for targeted reinnervation.

Targeted Muscle Reinnervation for Transradial Amputation: Description of Operative Technique

Emily N. Morgan, MD,* Benjamin Kyle Potter, MD,† Jason M. Souza, MD,† Scott M. Tintle, MD,† and George P. Nanos, III, MD†

Table 1. Typical Nerve Transfers for Below-Knee Amputation

<table>
<thead>
<tr>
<th>Donor Nerve</th>
<th>Target Motor Nerve Branches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior tibial nerve</td>
<td>Medial or lateral gastrocnemius; tibialis posterior; medial or lateral soleus</td>
</tr>
<tr>
<td>Deep peroneal nerve</td>
<td>Tibialis anterior; peroneus longus; peroneus brevis; medial soleus</td>
</tr>
<tr>
<td>Superficial peroneal nerve</td>
<td>Peroneus longus; peroneus brevis</td>
</tr>
<tr>
<td>Saphenous nerve</td>
<td>Medial gastrocnemius; medial soleus; vastus medialis</td>
</tr>
<tr>
<td>Sural nerve</td>
<td>Tibialis posterior; soleus</td>
</tr>
</tbody>
</table>

Novel Use of Targeted Muscle Reinnervation in the Hand for Treatment of Recurrent Symptomatic Neuromas Following Digit Amputations

Timothy H.F. Daugherty MD, MS
Reuben A. Bueno, Jr., MD
Michael W. Neumeister, MD

Summary: Targeted muscle reinnervation (TMR) has been shown to decrease neuroma pain after major limb loss; however, it has not previously been described for the treatment of symptomatic neuromas in the hand after digit amputations.
Above Knee Amputation

Courtesy of Jason Ko, MD
<table>
<thead>
<tr>
<th>NERVE</th>
<th>PRIMARY TARGETED MUSCLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPHENOUS</td>
<td>Vastus medialis</td>
</tr>
<tr>
<td>PERONEAL COMPONENT OF SCIATIC</td>
<td>Biceps femoris</td>
</tr>
<tr>
<td>TIBIAL COMPONENT OF SCIATIC</td>
<td>Semitendinosis or Semimembranosis</td>
</tr>
<tr>
<td>POSTERIOR FEMORAL CUTANEOUS</td>
<td>Biceps femoris (distal motor branch)</td>
</tr>
</tbody>
</table>

Access via posterior midline incision

Courtesy of Jason Ko, MD
Above Knee Amputation (Primary)
## LOWER EXTREMITY -- AKA

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<th>NERVE</th>
<th>PRIMARY TARGETED MUSCLES</th>
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<td>POSTERIOR FEMORAL CUTANEOUS</td>
<td>Biceps femoris (distal motor branch)</td>
</tr>
</tbody>
</table>

Access via posterior midline incision

---

Courtesy of Jason Ko, MD
31yo Female, 3 years s/p AKA for trauma
- Phantom and neuroma pain
- Redundant soft tissue envelope, poor prosthetic socket fit
- Unable to use prosthesis
Below Knee Amputation

Courtesy of Jason Ko, MD
### LOWER EXTREMITY -- BKA

<table>
<thead>
<tr>
<th>NERVE</th>
<th>PRIMARY TARGETED MUSCLES</th>
<th>LOWER LEG COMPARTMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEEP PERONEAL</td>
<td>Tibialis anterior</td>
<td>Anterior (via anterolateral incision)</td>
</tr>
<tr>
<td>SUPERFICIAL PERONEAL</td>
<td>Extensor digitorum longus</td>
<td>Anterior (via anterolateral incision)</td>
</tr>
<tr>
<td>TIBIAL</td>
<td>Soleus</td>
<td>Superficial posterior (via posterior midline incision)</td>
</tr>
<tr>
<td>MEDIAL SURAL</td>
<td>Medial gastrocnemius</td>
<td>Superficial posterior (via posterior midline incision)</td>
</tr>
<tr>
<td>LATERAL SURAL</td>
<td>Lateral gastrocnemius</td>
<td>Superficial posterior (via posterior midline incision)</td>
</tr>
</tbody>
</table>

**Courtesy of Jason Ko, MD**
28 Amputees with chronic pain randomized and blinded to TMR vs “Standard Treatment”

Primary outcome: Pain (11 point numerical rating scale)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TMR (n = 18)</th>
<th>Standard Care (n = 15)</th>
<th>Mean (95% CI)</th>
<th>Difference of Change Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst phantom limb pain</td>
<td></td>
<td></td>
<td>4.1 (1.1, 7.1)</td>
<td></td>
</tr>
<tr>
<td>Worst residual limb pain</td>
<td></td>
<td></td>
<td>2.5 (0.4, 4.6)</td>
<td></td>
</tr>
</tbody>
</table>

- Nerve volume MRI: TMR 378cm² vs Standard 552cm²
- 72% of TMR patients had no phantom pain at one year (vs Standard 40%)
Targeted Muscle Reinnervation Treats Neuroma and Phantom Pain in Major Limb Amputees: A Randomized Clinical Trial

<table>
<thead>
<tr>
<th>Standard neurectomy &amp; muscle burying</th>
<th>AVERAGE PAIN OUTCOMES AT 1-YR</th>
<th>TMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phantom Limb Pain</td>
<td>-3.2/10, p=0.06</td>
</tr>
<tr>
<td></td>
<td>Residual Limb Pain</td>
<td>-2.9/10, p=0.15</td>
</tr>
</tbody>
</table>

- **Rule of 1/4ths**
  - 25% of established amputees experience SEVERE phantom limb pain
  - 25% MODERATE
  - 25% MILD
  - 25% NONE

- TMR decreases chronic phantom limb pain in established amputees


Northwestern Targeted Muscle Reinnervation Course, Chicago, IL 2019
• Prospective Cohort Study
• 51 Primary TMR (within 14 days of definitive amputation)
• Compared to 438 unselected limb amputees
Preemptive Treatment of Phantom and Residual Limb Pain with Targeted Muscle Reinnervation (TMR) at the Time of Amputation

<table>
<thead>
<tr>
<th>Major Limb Amputees</th>
<th>N=438</th>
<th>N=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Amputees</td>
<td>No Intervention</td>
<td>AVERAGE PAIN OUTCOMES</td>
</tr>
<tr>
<td>5/10</td>
<td>1/10</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Residual Limb Pain</td>
<td>4/10</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

- Reduces odds of more severe residual limb and phantom limb pain by 3.9 and 3.0-fold, respectively
- 45% of TMR patients vs 21% control have NO phantom limb pain; 49 vs 20% have NO residual limb pain
- TMR May be done after initial amputation within a couple of weeks

Upper limb cortical maps in amputees with targeted muscle and sensory reinnervation

Andrea Serino,1,2,3,※ Michel Akselrod,1,2,3,※ Roy Salomon,1,2,4 Roberto Martuzzi,1,2,5 Maria Laura Blefari,1,2 Elisa Canzoneri,1,2 Giulio Rognini,1,2 Wietske van der Zwaag,6,7 Maria Iakova,8 François Luthi,9 Amedeo Amoresano,9 Todd Kuiken10 and Olaf Blanke1,2,11

fMRI study of 3 TMR Patients

Motor and sensory cortical maps more similar to healthy control than to non-tmr amputee
Virtual Rehabilitation

Albert Chi, M.D. laboratory at OHSU
TMR for neuroma treatment in non-amputees
Albert Chi, MD
A Training Strategy for Learning Pattern Recognition Control for Myoelectric Prostheses

Michael A. Powell, BS, Nitish V. Thakor, PhD

• Virtual Interactive Environment Real-time control and feedback
  – Confusion Matrix Performance Feedback
  – Able to classify multiple grips and finger control
TMR Downsides

- Not 100% effective
- Increased operative time (1-3 hours)
- Microsurgical technique
- Expense and bulk of advanced myoelectric prostheses
- More complicated coordination (more teams involved)
- Additional incisions (increased complications)
- May complicate allotransplantation (alters anatomy)
The Future

• Primary TMR as standard of care for amputees
• Large multi-institutional RCT for pain
• Targeted Sensory Innervation – tactile prostheses
• Advanced lower limb myoelectrics
• Widespread implementation of osseointegration
• Institutional protocols
Summary

• TMR enables significant improvement in myoelectric prosthetic control
• Amputation related pain remains a difficult challenge
• TMR is a promising treatment for established amputation related pain
• TMR may be more effective at preventing the establishment of centralized pain axes
OHSU Nerve Center

www.ohsu.edu/nervecenter

Physician advice line: 800-245-6478

Fax patient referrals to
503-346-6854

Specialties:
Neurology
Neurosurgery
Orthopedics
Otolaryngology
Physical medicine and rehabilitation
Plastic and Reconstructive Surgery
Pain Management
Thank You
Lipira@ohsu.edu