Localizing and Characterizing Neural Plasticity in Spinal Cord Injury

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Restorative Neurology in Spinal Cord Injury
What is the problem?

This spinal cord can walk. How?

This one cannot. Why not?

How do we get from Anatomy to Behavior? Physiology!
Wiring Diagram of Sensory and Supraspinal Inputs to Spinal Central Pattern Generator (CPG) Circuits involved in Stepping after Incomplete Spinal Cord Injury

So what is the circuitry for locomotor recovery after spinal cord injury? Plasticity in afferents or interneurons? Can the spinal cord recover the ability to walk with fewer supraspinal inputs? Where might we generate neural plasticity to get locomotor recovery after spinal cord injury?

Plasticity in remaining supraspinal projections? Can the brain recover the ability to tell the spinal cord to walk with fewer connections? Plasticity in afferents or interneurons? Can the spinal cord recover the ability to walk with fewer supraspinal inputs?

SSN = supraspinal neuron; In = interneuron; Mn = motoneuron; DRG = dorsal root ganglion; aPSN = ascending propriospinal neuron; dPSN = descending propriospinal neuron; CPG = central pattern generator
Locomotor Training of SCI Patients
Training Parameters

Dosing of Training
  3 - 5 times per week, 30 - 60 minutes per day,
  6 weeks - 3 months - 6 months duration

Training Variables
  Body weight support
  Treadmill/over ground gait speed
  Hip & knee angles, range of movement
  Choice of biofeedback
  Medications
  Criteria to change variables

Concepts usually agreed upon: loading is important,
physiological walking speeds are good, maintaining good
gait kinematics is a goal
Robotic Training of Spinal Cord Injury Patients

Rationale for Robotic Training  
(Clinical Application)

Standardization of stepping
Longer training sessions
Variable assistance
Biofeedback to patients
Who will benefit (and how much) from locomotor training in SCI?

Final over ground walking speed (cm/s) = 21.48
+ (voluntary bowel & bladder voiding x 18.78)
  + (spasticity affecting stance x 14.30)
  + (initial walking speed x 0.87)
− (square root time from injury onset x 6.06)

(Voluntary voiding of B & B: yes=1, no=0; Spasticity affecting stance: yes=0, no=1)

(Winchester et al ‘09)
Functional Recovery with Locomotor Training

After 2 wks BWSTT
Changes in Supraspinal Activation Patterns following Robotic Locomotor Therapy in Subjects with Motor Incomplete Spinal Cord Injury

Study Patient characteristics:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Level of injury</th>
<th>ASIA class</th>
<th>Time since injury</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>C5</td>
<td>C</td>
<td>14 weeks</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>C6</td>
<td>D</td>
<td>6 months</td>
<td>Oral Baclofen</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>C5</td>
<td>C</td>
<td>1 year</td>
<td>IT Baclofen</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>C6</td>
<td>C</td>
<td>4 years</td>
<td>None</td>
</tr>
</tbody>
</table>

Change in Walking Index for Spinal Cord Injury II (WISCI II) and over ground gait speed for each patient.

The percentage of body weight supported and training treadmill speed at the beginning and end of BWSTT for each patient.

<table>
<thead>
<tr>
<th>Patient</th>
<th>WISCI II</th>
<th>Gait Speed cm/sec</th>
<th>Body Weight Supported (% body weight)</th>
<th>Treadmill Speed (kmph)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>19</td>
<td>*</td>
<td>80.6</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>15</td>
<td>23.8</td>
<td>62.0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>6</td>
<td>*</td>
<td>10.5</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* unable to ambulate at time of testing
Supraspinal Neural Plasticity following Locomotor Training

(A) Patient 1 with an incomplete C5 SCI who achieved independent ambulation with a single tip cane

(B) Patient 2 with an incomplete C6 SCI who achieved independent ambulation with a single tip cane and left AFO

(C) Patient 3 with an incomplete C5 SCI who achieved limited ability to ambulate over ground with a forearm walker, right AFO and physical assistance

(D) Patient 4 with an incomplete C6 SCI who did not achieve any ability to walk over ground

(Winchester et al '05)
Infra-Injury Spinal Neural Plasticity following Locomotor Training

Soleus H-Reflex recordings in the Lokomat

(Querry et al. ‘08)
Summary of H-Reflex Responses under Different Conditions

Bar chart showing H/M ratio for different conditions: prone, standing, mid-stance slow, mid-stance fast, mid-swing slow, mid-swing fast, motor incomplete, and controls. The chart indicates varying H/M ratios across these conditions.
On average, mid-stance H-Reflex responses in motor incomplete SCI subjects did not change following 3 months of robotic training.

### Mid-stance H-Reflex parameters, mean +/- SD

<table>
<thead>
<tr>
<th></th>
<th>Motor Incomplete Pre-BWSTT (n=8, 2/8 walking)</th>
<th>Motor Incomplete Post-BWSTT (n=8, 7/8 walking)</th>
<th>Controls (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/M prone</td>
<td>0.70 +/- 0.27</td>
<td>0.71 +/- 0.29</td>
<td>0.40 +/- 0.22</td>
</tr>
<tr>
<td>H/M stand</td>
<td>0.68 +/- 0.26</td>
<td>0.64 +/- 0.16</td>
<td>0.39 +/- 0.17</td>
</tr>
<tr>
<td>H/M 1.8 km/hr</td>
<td>0.41 +/- 0.22</td>
<td>0.42 +/- 0.20</td>
<td>0.31 +/- 0.09</td>
</tr>
<tr>
<td>H/M 2.5 km/hr</td>
<td>0.44 +/- 0.25</td>
<td>0.44 +/- 0.21</td>
<td>0.28 +/- 0.07</td>
</tr>
<tr>
<td>Over-ground gait speed cm/s</td>
<td>7.8 +/- 17.4</td>
<td>24.4 +/- 26.2</td>
<td>130 – 135</td>
</tr>
</tbody>
</table>
While average mid-stance H-Reflex responses in motor incomplete SCI do not change following 3 months of robotic training, there is a relationship between final gait speed achieved and change in mid-stance H/M ratios post vs. pre-training.
Next Studies to Measure Neural Plasticity in Locomotor Recovery (VA 1IO1RX000417-01A1)

Determine if H-reflexes “worsen” then “improve” as gait speed recovers in all patients, just with different duration of training

OR

Determine that some patients have reflex worsening and slow recovered gait while others have reflex improvement and faster recovered gait with training

Use posterior root motor reflexes (PRMRs) to monitor multiple muscle groups over time
Comparison of Posterior Root Motor Reflexes (PRMRs) evoked by Single Epidural Spinal Cord Stimulations (eSCS) and by Single Transcutaneous Spinal Cord Stimulations (tSCS) (Minassian et al. ’07)
Posterior root muscle reflexes (PRMRs) and classical soleus H-reflexes during standing and at mid-stance/mid-swing during stepping in the Lokomat.
Conclusions so far and Hypothesis

Locomotor training can improve functional recovery of gait in incomplete spinal cord injury.

Locomotor training is correlated with both supraspinal and infra-injury spinal cord neural circuit plasticity but not necessarily in simple ways.

It should be possible to augment this neural plasticity with a variety of therapeutic interventions (new physical therapies, pharmacology, and/or electrical stimulation) to realize faster or greater functional recovery in patients who currently benefit from locomotor training and possibly in patients who currently do not benefit from locomotor training.
Effects of increased stimulation rates

2 Hz

16 Hz

21 Hz
PRM reflexes to stimulation with different frequencies – alternative pathways

Constant stimulation site and strength, effect of different frequencies

PRM reflexes to stimulation with different frequencies – alternative pathways

2 Hz stimulation

22 Hz stimulation

Proposed trans-synaptically activated structures of spinal gray matter

monosynaptic response  polysynaptic response

EMG recording
Locomotor-like activity induced by tonic eSCS

Stimulation parameters:
30 Hz, 9 V

EMG bursts consist of series of individual PRM reflexes

Single stimuli
2 Hz; 1.5 x Th(Q)
simple PRM reflexes

Repetitive stimulation
22 Hz; 1.5 x Th(Q)
reciprocity between
single PRM reflexes

Repetitive stimulation
33 Hz; 1.7 x Th(Q)
reciprocity between
series of PRM reflexes
(bursts)
Locomotor Movements in **Complete** SCI induced by **Tonic** Epidural Spinal Cord Stimulation (eSCS) (10V, 25Hz)

Assumption and Hypothesis

Tonic transcutaneous spinal cord stimulation can modify the central state of excitability of lumbar spinal cord locomotor neural circuits similarly to epidural spinal cord stimulation.

Tonic transcutaneous spinal cord stimulation and step-related proprioceptive feedback can interact so as to facilitate locomotor output in spinal cord injured individuals.

Tonic transcutaneous spinal cord stimulation, when combined over time with locomotor training, might augment neural plasticity and locomotor recovery in spinal cord injured individuals.
Tonic tSCS, at sub-motor threshold stimulation strengths, can increase rhythmic motor output when combined with phasic afferent input during weight supported treadmill stepping in complete SCI.

50% BWS, 25 V, 30 Hz
Tonic tSCS, at supra-motor threshold stimulation strengths, can increase rhythmic motor output in standing and that can override phasic afferent input from treadmill stepping in complete SCI.

50% BWS, 35 V, 24 Hz
Tonic tSCS, at sub-motor threshold stimulation strengths, can increase locomotor motor output in treadmill stepping in incomplete SCI and improve leg kinematics.
Robotic Stepping of Spinal Cord Injury Patients

Rationale for Robotic Stepping  
(Research Applications)

Standardization of stepping  
Experiment condition setting  
Real time measurement of data  
Triggering of external devices  
Ongoing software development

The Lokomat as Research Tool
Effect of Loading, Gait Speed and tSCS on EMG Patterns and Joint Forces during Lokomat Stepping in Motor Incomplete SCI
Conclusions and Future Directions

Like epidural stimulation, transcutaneous spinal cord stimulation can alone, or in combination with phasic afferent input, generate, or augment, locomotor output in motor complete spinal cord injury.

In motor incomplete spinal cord injury, transcutaneous spinal cord stimulation can combine with residual descending supraspinal commands and phasic afferent input to augment locomotor output and improve muscle activity patterns, joint forces, and gait kinematics and can ameliorate abnormal motor patterns like clonus.

We anticipate that an integrated use of transcutaneous spinal cord stimulation and locomotor training might promote faster or greater recovery of locomotion in spinal cord injured individuals, including in those individuals who currently do not benefit from locomotor training alone.
Effect of tSCS frequency on EMG patterns, Extensor Clonus and Joint Forces during Stepping in Motor Incomplete SCI
Interactions of Gait Speed and tSCS Frequency
Sub-motor threshold tSCS at 50 Hz for 30 minutes can decrease Spasticity in Motor Incomplete SCI
Sub-motor threshold tSCS at 50 Hz for 30 minutes can decrease Spasticity in Motor Incomplete SCI

Assessment before SCS

Assessment after SCS
Sub-motor threshold tSCS at 50 Hz for 30 minutes can decrease Spasticity in Motor Incomplete SCI.
Collaborators

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