Innovation in SCS

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Disclaimer

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- Associate Editor “Pain Practice”
- Associate Editor, “Pain Physician”
- Chief Editor “Techniques in Regional Anesthesia and Pain Management”
- Editorial Board, “Journal of Opioid Management”
- Editorial Board “Clinical Journal of Pain”
DISCLOSURES

• Provisional patent application with USPTO (USSN 62/135,999) for a novel neuromodulation system.
• Basic Science Research Agreements with Boston Scientific Neuromodulation and Nevro Corporation.
• Clinical trials with Nevro Corporation, Medtronic Spinal and Biologics, and St. Jude Medical.
**Brief History, Spinal Cord Stimulation**

- 1965: Gate Control Theory
- 1967: First Case Report of SCS Implant
- 1968: First commercial SCS: Medtronic
- 1981: First fully implantable SCS: Medtronic
- 1996: Advance Neuromodulation Systems enters the market
- 2004: A third company enters the market: Advance Bionics - First rechargeable SCS - Acquired by Boston Scientific ($740 M)
- 2005: ANS is acquired by St Jude Medical ($1.3B)
- 2014: St. Jude Medical acquires Spinal Modulation ($300M)
- 2015 Nevro (HF10) obtains FDA approval
SCS Market Evolution and Share

Market share previous to Nevro’s introduction of HF10
Current paradigm is focused on Neuronal Stimulation

- SCS **MAY** suppress enhanced responsiveness of Wide Dynamic Range Neurons (WDR)

- WDR neurons **play** a major role on the development of Chronic Neuropathic Pain

- Many of the mechanisms of action are still **unknown** [X].

Spinal Cord Stimulation: Exploration of the Physiological Basis of a Widely Used Therapy
Linderoth, Bengt., Anesthesiology. 2010.

NE = norepinephrine; STT = spinothalamic tract.
Neurostimulation

Electrical field **PULSE** to neuron $\Rightarrow \Delta$ transmembrane potential

**Cathodic** stimulation is more effective

The Electric Field = current density

$I = 1/d_{CSF}$

Diameter = $1/ I \ Th$

Current density depends on

**DELIVERED CURRENT**

(key determinant of stimulation)
Activating Neurons with Single Pulses

- **Definition:**
  - **Stimulation Threshold:**
    - At a given PW, enough mA pulse current to activate neuron = generate an action potential

- Single pulse can depolarize neuron *if* meets mA & PW requirements

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**Fig. 2.** Response of the SENN model to rectangular monophasic current of 100 μs duration. Solid lines show membrane response at node nearest electrode for three levels of current. $I_T$ denotes threshold current.

*Reilly et al 1985*
Low Fc Stimuli

"unit" a

"unit" b
Change in Paradigm?

Traditional SCS

- Paresthesia coverage of pain is considered a necessary (though not sufficient) requirement for efficacy

- Low back coverage is known to be particularly challenging to achieve and maintain
  - Deeper penetration via midline placement

**Traditional SCS Thinking:** More paresthesia = more pain relief
Amplitude vs. Pulse Width

Strength-duration curve for large and small nerve fibers

At shorter PW: larger differences in thresholds between large and small fibers

At longer PW: smaller differences in thresholds between large and small fibers

Rheobase
Chronaxie
At longer PW: smaller differences in thresholds between large and small fibers.
High Frequency Effects on Neurons

Membrane Integration

- Effect of high frequency:
  - Multiple pulses delivered at high frequencies can activate neurons using less mA

- Neural Membrane Integration
  - Pulses delivered ‘fast enough’ are accumulated by the neural membrane, ultimately depolarizing the neuron to create an AP

1 ‘pulse’: 0.98mA

Reilly et al 1985
High Frequency Effects on Neurons

Membrane Integration

- Effect of high frequency:
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Reilly et al 1985
High Frequency Effects on Neurons

Membrane Integration

- Effect of high frequency:
  - Multiple pulses delivered at high frequencies can activate neurons using less mA

- Neural Membrane Integration
  - Pulses delivered ‘fast enough’ are accumulated by the neural membrane, ultimately depolarizing the neuron to create an AP

Reilly et al 1985
• Burst waveform is a quick succession or “pattern” of five 1ms pulses, separated by 1ms
  – This is where the “500Hz” comes from
  – Frequency is ‘how often you deliver a pulse’
  – In the burst waveform, you get:
    • 1 pulse every 2ms → “500Hz”
Burst is not 10 Khz

- The burst pattern is delivered at a 40Hz rate
- This is very similar to traditional/tonic SCS

Traditional
f=40Hz, PW=1ms

Burst
f=40Hz, PW=1ms x 5

1ms pulse repeated at a 40Hz repetition rate
5x 1ms pulse repeated at a 40Hz repetition rate
Burst May Drive Synapses ‘Harder’

- Preclinical studies showed that burst had:
  - Lower motor thresholds than traditional/tonic
  - In agreement with clinical data
  - Burst threshold is about 50% of tonic threshold

<table>
<thead>
<tr>
<th>Table 1. Motor Threshold of Animals.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCS</td>
</tr>
<tr>
<td>Burst</td>
</tr>
<tr>
<td>Tonic</td>
</tr>
</tbody>
</table>

*Compared with burst SCS, p < 0.05.
SCS, spinal cord stimulation; VMR, visceromotor reflexes.

- Thus, on average, burst is programmed ‘just’ subthreshold to paresthesia
- **Necessary for patients to tolerate it...?**

DeRidder et al, *Neurosurgery* 2010
Tang et al, *Neuromodulation* 2013
Single center, Prospective, Observational
12 pts: 7 LBP, 4 UE pain, 1 PNP

Pts were programmed for tonic and Burst

Mean f/u=20 months
Improvement in VAS and McGill at +/- 12 months

17% of pts felt paresthesias = THEY DID NOT LIKE IT
DBRC trial
1 week per treatment group
15 pts
Pts programmed for paresthesias

No significant difference vs. tonic for back and limb pain

Only difference observed:
*generalized pain*
EEG show activation of the DLPFC and dACC

“Burst stimulation… patients experienced a frontal lobectomies”

Affective/emotional portion of pain
“How do I feel about being pinched?”

sensory/discriminative portion of pain
“Where/How hard I being pinched?”
48 pts with >6 months of tonic SCS
24 FBSS, 12 PDN, 12 poor responders
14 days Burst
Pt preference:
Overall: 54% prefer burst
PDN: 43% prefer burst
FBSS: 29% prefer burst
PR: No preference
SUNBURST

• 0.5 mm difference
High Frequency Effects on Neurons: Desynchronization

- **Low Frequency:**
  - All neurons follow in “lock-step” with stimulus
  - Non-varying

- **High Frequency:**
  - Each neuron fires at its own rate, pattern
  - Average rate for each neuron different from neighboring neurons

Adapted from Rubinstein et al 1999
Higher frequencies may have even lower thresholds

“Trade rate for mA”

Fig. 9. Threshold current as a function of the duration of sinusoidal stimulation. Stimulus duration was stepped in half-cycle increments out to 4 cycles, and in full-cycle increments beyond that point.

Reilly et al 1985
High Frequency Effects on Neurons: Desynchronization

Overall nerve population response to high frequency:

- Mean neuron firing rate ~ 100s of Hz
- Individual neuron firing rate variable

Believed to be more ‘natural’ neuron pattern (“pseudospontaneous”)

Litvak et al 2003
At longer PW: smaller differences in thresholds between large and small fibers.
SENZA-RCT Key Patient Eligibility Criteria

Inclusion (all required)

- Chronic intractable pain of the trunk and/or limbs, refractory to conservative therapy for ≥3 months
- Average **back pain intensity of** ≥5 out of 10 cm on the VAS
- Average **leg pain intensity of** ≥5 out of 10 cm on the VAS
- **Severely disabled or crippled** as defined by an Oswestry Disability Index score of 41-80 out of 100
- Appropriate candidate for the required surgical procedures

Exclusion (none allowed)

- Active disruptive psychological or psychiatric disorder
- Mechanical spine instability
- Prior experience with SCS
- Involvement in an injury claim under current litigation or a pending or approved workers compensation claim
- Medical condition or pain in other area that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study endpoints
SENZA-RCT

Subject

Flowchart

241 Participants Assessed for Eligibility

198 Randomized

43 Excluded
• 43 Screen Failures

101 Assigned to HF10 therapy
• 97 trialed with SCS system
  ▫ 90 successful SCS trial
  ▫ 7 unsuccessful SCS trial
• 4 not trialed
  ▫ 2 medical contraindication
  ▫ 1 withdrew consent
  ▫ 1 lost to follow-up

90 implanted participants included in the 3 mo primary and 12 mo secondary analyses

97 Assigned to traditional SCS
• 92 trialed with SCS system
  ▫ 81 successful SCS trial
  ▫ 11 unsuccessful SCS trial
• 5 not trialed
  ▫ 4 withdrew consent
  ▫ 1 medical contraindication

81 implanted participants included in the 3 mo primary and 12 mo secondary analyses
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Test (HF10 Therapy)</th>
<th>Control (Traditional SCS)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>57 (62.0%)</td>
<td>51 (58.6%)</td>
<td>0.760</td>
</tr>
<tr>
<td>Male</td>
<td>35 (38.0%)</td>
<td>36 (41.4%)</td>
<td></td>
</tr>
<tr>
<td>Age (years) at Enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>54.6 ± 12.4</td>
<td>55.2 ± 13.4</td>
<td>0.717</td>
</tr>
<tr>
<td>Range</td>
<td>32.8 to 82.2</td>
<td>19.2 to 82.3</td>
<td></td>
</tr>
<tr>
<td>Years Since Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>13.0 ± 10.4</td>
<td>14.2 ± 12.2</td>
<td>0.659</td>
</tr>
<tr>
<td>Range</td>
<td>1.0 to 52.0</td>
<td>1.0 to 62.0</td>
<td></td>
</tr>
<tr>
<td>Previous Back Surgery – n (%)</td>
<td>80 (87.0%)</td>
<td>75 (86.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Baseline Use of Opioids – n (%)</td>
<td>83 (90.2%)</td>
<td>75 (86.2%)</td>
<td>0.488</td>
</tr>
</tbody>
</table>
## SENZA-RCT Most Frequent Study-Related AEs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test (HF10)</th>
<th>Control (Traditional)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of AEs</td>
<td>Subjects with AEs (N=101)</td>
</tr>
<tr>
<td>Uncomfortable Paresthesias</td>
<td>0</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Implant Site Pain</td>
<td>12</td>
<td>10 (9.9%)</td>
</tr>
<tr>
<td>Lead Migration</td>
<td>3</td>
<td>3 (3.0%)</td>
</tr>
</tbody>
</table>
SENZA-RCT Analysis Populations

- **Intention-to-Treat (ITT):** All randomized subjects
- **Per Protocol (PP):** All subjects with a primary endpoint assessment
- **Permanent Implant Subset (PS):** Only subjects who received a permanent implant
SENZA-RCT Primary Endpoint by Analysis Population

Non-Inferiority p-value: <0.001
Superiority p-value: <0.001 (post-hoc analysis)

Test (HF10) | Control (Traditional SCS)
---|---
PS | PP | ITT
80.9% | 75.0% | 75.7%
42.5% | 37.9% | 37.7%
89 | 92 | 101
80 | 87 | 97

Met Primary Endpoint

<table>
<thead>
<tr>
<th>PS</th>
<th>PP</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (HF10)</td>
<td>Control (Traditional SCS)</td>
<td></td>
</tr>
</tbody>
</table>
SENZA-RCT Back Pain

10% non-inferiority p-value:  <0.001
Superiority p-value:  <0.001 (post-hoc analysis)
SENZA-RCT Leg Pain

Leg Pain (VAS score) vs. Assessment (months)
- Test (HF10)
- Control (Traditional SCS)

Leg Pain Relief change in VAS score vs. Assessment (months)
- Test (HF10) 69.5%
- Control (Traditional SCS) 48.0%

Analysis of permanent implant population

10% non-inferiority p-value: <0.001
Superiority p-value: <0.001 (post-hoc analysis)
SENZA-RCT Responder Rates

Analysis of permanent implant population

Superiority p-value: <0.001 (post-hoc analysis) at all endpoints
At 12 months, **62.9% of HF10 subjects** had minimal or moderate disability compared with **45.7% of traditional SCS subjects** (p=0.03)
Comparison to Published, Prospective Results

### Back Pain

<table>
<thead>
<tr>
<th></th>
<th>Responder Rate</th>
<th>% VAS Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional SCS</td>
<td>Not Reported</td>
<td>18%</td>
</tr>
<tr>
<td>(Kumar 2006, 2007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traditional SCS</td>
<td>51%</td>
<td>45%</td>
</tr>
<tr>
<td>(control arm in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SENZA-RCT)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Leg Pain

<table>
<thead>
<tr>
<th></th>
<th>Responder Rate</th>
<th>% VAS Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional SCS</td>
<td>38%</td>
<td>42%</td>
</tr>
<tr>
<td>(Kumar 2006, 2007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traditional SCS</td>
<td>51%</td>
<td>48%</td>
</tr>
<tr>
<td>(control arm in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SENZA-RCT)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HF10 demonstrated superiority**

*Based on post-hoc superiority analyses.*
Just a Thought, Where is the lead?

Assuming that SCS functions

What am I stimulating?
Initial Nociception
Chronic Pain: Tripartite Synapse
Synthesis of neuronal Glutamate and GABA is mediated by glial cells.

**Glutamate Synthesis**

- Neuron: Glutamine is transported into the neuron where it is converted to glutamate by glutamine synthetase.
- Glial cell: Glutamine is transported into the glial cell where it is converted to glutamate by glutamine synthetase and then to glutamine by glutaminase.
- Mitochondria: Glutamate is transported into the mitochondria where it enters the Krebs cycle.

**GABA Synthesis**

- Neuron: Glutamate is transported into the neuron where it is decarboxylated to GABA by glutamate decarboxylase.
- Glial cell: GABA is transported into the glial cell where it is used to synthesize GABA by the GABA synthetase.
- Mitochondria: GABA is transported into the mitochondria where it is oxidized to succinate semialdehyde.

Can you Stimulate Glial Cells?

Fig. 2. Values of membrane potential of neurones (A) and glial cells (B). Abscissa: MP, mV; ordinate: number of cells, n.
Effects of Electrical Impulses on Glial Cells

Roibak, Neuroscience 1981
Bimodal Modulation: Neuron-Glial Interactions

- Glial cells and neurons communicate via release of glutamate and glutamine mediated by Ca\(^{2+}\) regulation in the synapse
- Internal Ca\(^{2+}\) increases in response to electrical stimulus.
- Glial Ca\(^{2+}\) dynamics modulate neuron signaling
- Ca\(^{2+}\) waves allow for intra-glial communication

Before stim

At end of stim (2 s of 50 Hz, 200 µA)

28 s after stim

Porter and McCarthy, 1996, J Neurosci
Which Causes the Glu release:
1. Neurons?
2. Astrocytes?

HFS = 100 Hz, 100 µs PW, 0.3 mA

Tawfik VL, Neurosurgery, 2010
Glutamate release from astrocytes depends on electrical parameters (frequency, intensity, pulse width and phase). Agnesi et al., 2011, J. Neural Eng.

**Biphasic Stimulation**

- **A** Current Pulse Waveform
- **B** Voltage Measured Across Electrode Contacts
- **C** Glutamate Oxidation Current
- **D** Unbalance Dependence

**HFS** = 100 Hz, 100 µs PW, 0.2 mA

OX-42

SNI
6 hours
90% MT

GFAP

MCP1

Relative lead location

- Lead with 4 contacts
- Dura Mater
- Arachnoid
- Pia Mater
Summary of SCS Pilot Study
IL-6 and GFAP expression, related?

<table>
<thead>
<tr>
<th>DM</th>
<th>IL-6</th>
<th>IL-6</th>
<th>GFAP</th>
<th>corr. GFAP 0.6mA</th>
<th>corr. GFAP 1.6mA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>5.60E+02</td>
<td>1.03E+03</td>
<td>1.15E+02</td>
<td>1.23E+03</td>
<td>1.15E+03</td>
</tr>
<tr>
<td>0.6</td>
<td>2.48E+03</td>
<td>2.27E+03</td>
<td>2.13E+02</td>
<td>2.27E+03</td>
<td>2.12E+03</td>
</tr>
<tr>
<td>1.2</td>
<td>1.10E+03</td>
<td>1.59E+03</td>
<td>1.18E+02</td>
<td>1.26E+03</td>
<td>1.18E+03</td>
</tr>
<tr>
<td>1.5</td>
<td>4.16E+02</td>
<td>6.79E+02</td>
<td>6.26E+01</td>
<td>6.67E+02</td>
<td>6.24E+02</td>
</tr>
<tr>
<td>1.6</td>
<td>1.92E+02</td>
<td>6.52E+02</td>
<td>6.53E+01</td>
<td>6.96E+02</td>
<td>6.52E+02</td>
</tr>
</tbody>
</table>

**IL-6 vs. 'Corrected GFAP'**

- **IL-6 DM**
- **IL-6 SC**
- corr. GFAP 0.6mA
- corr. GFAP 1.6mA
An animal model has been developed for continuous SCS in which animals that have been injured to develop neuropathic pain behavior were allowed to carry on with regular daily activities while being stimulated over 72 hours. Three corresponding sham groups (no SNI) were included. Mechanical and cold-thermal allodynia were evaluated using von Frey filaments and acetone drops, respectively. Continuous SCS attenuates mechanical allodynia in animals with neuropathic pain behavior. Mechanical withdrawal threshold increases significantly in SNI animals after 24 and 72 hours stimulation vs. SNI no stimulation ($p = 0.007$ and $p < 0.001$, respectively). SCS for 24 and 72 hours provides significant increase in mechanical withdrawal thresholds relative to values before stimulation ($p = 0.001$ and $p < 0.001$ respectively). SCS did not seem to attenuate cold-thermal allodynia.
Identifying Genes of interest

- Full genome microarray
- ~21,000 genes identified
PROVIDES a network
makes use of interaction patterns between genes

Analysis in the context of connectivity module (pathway) based analysis

Relate modules to external information
Array Information, Clinical Data, Gene Information: gene ontology
Identifies biologically interesting modules

Find the key drivers in interesting modules
Carry out experimental validation, therapeutics, biomarkers

Adapted from S. Horvath: Extended Overview of Weighted Gene Co-Expression Network Analysis (WGCNA)
Microarray Data for DRG (~21,000 genes)

WGCNA

Module Assignment (9 modules, 4275 genes)

Module 1 (1047 genes)
Module 2 (1009 genes)

Module 8 (53 genes)
Module 9 (39 genes)

GO Analysis

Pathways Identified

KME vs. p-value correlation

Genes of Interest (80)
Microarray Data for SC (~21,000 genes)

WGCNA

Module Assignment (29 modules, 7800 genes)

Module 1 (1790 genes)
Module 2 (1365 genes)

... ... ...

Module 28 (36 genes)
Module 29 (33 genes)

GO Analysis

Pathways Identified

KME vs. p-value correlation

Genes of Interest (53)
## Genomics of the SCS on SNI

### Related to Glial Activation Processes

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Regulation level</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Binding Protein (cabp1)</td>
<td>↓ 1.45-fold</td>
<td>Regulates calcium-dependent activity of inositol 1,4,5-triphosphate (ITP) receptors. This receptors are involved in the <strong>signaling between astrocytes via calcium waves</strong>, which play a key role in the intercellular communication that propagates astrocyte activation.</td>
</tr>
<tr>
<td>Toll-like receptor 2 (tlr2)</td>
<td>↑ 2.41-fold</td>
<td>Expressed by activated glial cells. Associated to cascades that may lead to the <strong>secretion of anti-inflammatory cytokines</strong>, such as IL-10.</td>
</tr>
<tr>
<td>Chemokine cxcl16 (cxcl16)</td>
<td>↑ 2.18-fold</td>
<td>Drives the interplay between glial cells and neurons as a result of stimulus. Expressed by glial cells as a <strong>neuroprotective agent</strong>.</td>
</tr>
</tbody>
</table>
## Modulation of Glial-Neuron Interaction:

### Genomics of the SCS on SNI model

<table>
<thead>
<tr>
<th>Process</th>
<th>Gene (regulation)</th>
<th>Process</th>
<th>Gene (regulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation and Immune Response</td>
<td>Lymphocyte antigen 86 (ly86, 2.86)</td>
<td>Ion channel regulation</td>
<td>Glutamate receptor, ionotrophic, N-methyl D-aspartate 2A (grin2a, 1.48 ↓)</td>
</tr>
<tr>
<td></td>
<td>Cluster of differentiation 68 (cd68, 2.78 ↑)</td>
<td></td>
<td>Mitochondrial calcium uptake family (micu3, 1.38 ↓)</td>
</tr>
<tr>
<td></td>
<td>Interleukin 1β (il1b, 3.78 ↑)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TIMP metallopeptidase inhibitor 1 (timp1, 3.00 ↑)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell growth</td>
<td>Potassium Voltage-Gated Channel, Shaker-Related Subfamily (kcna1, -1.39 ↓)</td>
<td>Binding and metabolic pathways</td>
<td>Amphiphysin (amph, 1.39 ↓)</td>
</tr>
<tr>
<td></td>
<td>Immunoglobulin Superfamily (igsf1, 2.20 ↓)</td>
<td></td>
<td>GABA A receptor, Gamma 1 (gabrg1, 1.52 ↓)</td>
</tr>
<tr>
<td>ATP related, transmembrane/transporter activity</td>
<td></td>
<td></td>
<td>GABA A Receptor, Alpha 2 (gabra2, 1.40 ↓)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glutamate receptor, ionotropic, AMPA 3 (gria3, 1.35 ↓)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cell regulation</td>
<td>Opioid Receptor, Mu 1 (oprm1, 1.28 ↓)</td>
</tr>
</tbody>
</table>
Identifying Proteins of interest

Tissue Dissection

Protein Extraction

BioRep 1

BioRep 2

TMT

126-128

126-128

129-131

129-131

Combine Labels

HPLC Fractions

LC - MS

Bioinformatics

OMSSA

TagQuant

Andy Tac
Proteomics of E-M stimulation - SNI animal model

Proteins (6,742 SC/ 5,903 DRG)

Phosphoproteins (7,494 SC/ 879 DRG)

Tissues

LC/MS/MS

Relevant Phosphoproteins: 152 SC/ 40 DRG

Statistical Analysis (FDR-p value, fold-change discrimination), Cluster Analysis
Modulation of Glial-Neuron Interaction: 
Proteomics E-M stim on SNI model

- Notable proteins:
  - phosphorylated metabotropic Glutamate receptors (MGLUR3, MGLUR5 and MGLUR7) are down regulated in the SC.
  - Phosphorylated glutamate transporter (VGLUT2) is upregulated in the SC.
  - Chronic pain is associated to persistent synaptic plasticity at glutamatergic synapses in the CNS.
  - This is critically dependent on post-translational modification of GLURs by phosphorylation.
  - Thus electromagnetic fields modulate these critical proteins.

Liu & Salter, 2010, Eur J Neurosci
Summary

• Not a clear understanding about the mechanism of pain relief.

• Pain relief without paresthesia: Bye bye Gate Control Theory

• High frequency stimulation is a novel technique with strong evidence for sustained pain relief

• Clinical use of high frequency neuromodulation is emerging
• Thank you