Sub-Perception SCS "neural dosing" parameter relationships

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Session Chair: Dr. Simon Thomson This sess Session Speakers: Dr. Simon Thomson Session Administrator (Zoom Co-Host): Dr. Simon Thomson

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Zoom Session Rules

-Chat is open to all for any ongoing discussion. Disrespectful attendees will be immediately removed.

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NYC Neuromodulation 2020 Online Conference A free, self-organized community meeting

Background: Paresthesia-based SCS

Benefits

- Effective pain relief ^{1,2,3}
- Low charge burden (~weekly charging)
- Fast-onset analgesia (up to several minutes)
 - → Rapid program optimization





Key Challenge: Paresthesia required for pain relief

1. Kumar K. *et al., Neurosurgery.* 2008 Oct;63(4): 762-70

2. North R. et al., Neurosurgery. 2005;56(1): 98-106.

3. Veizi E. *et al., Pain Med.* 2017 Aug 1;18(8): 1534-1548.

Background: Sub-perception SCS

2006: Early research on sub-perception SCS (Yearwood et al., CNS)

A Prospective Comparison of Spinal Cord Stimulation (SCS) Using Dorsal Column Stimulation

(DCS), Intraspinal Nerve Root Stimulation (INRS), and Varying Pulse Width in the Treatment of

Chronic Low Back Pain

Thomas Yearwood, MD, PHD; Allison Foster, PhD

Comprehensive Pain & Rehabilitation, Daphne, AL; Advanced Bionics, a Boston Scientific company

During the temporary trial period, study activities were

intended to identify optimal settings for each individual subject. Pairs of electrodes were attached to a 16-channe individually current-controlled external trial stimulator for

for two days: subthreshold INRS, subthreshold DCS, and suprathreshold DCS. Questionnaires assessing pain levels

disability, overall health, and quality of life were completed

after each 2-day test

control of stimulation. Subjects tested three programs, each

as assessing pain k



Patient satisfaction and effective pain control are critical Patient sensebutive and concerning pair Contract and concern elements of any pair management modality. Spinal cord stimulation (SCS), also known as dorsal column stimulation (DCS) of the lumbar spinal cord has demonstrated efficacy in the treatment of chronic low back pair (1). There is some evidence that low-intensity stimulation of intraspinal nerve erve root stimulation: INRS) may also be

Here, we describe the preliminary findings of an active prospective clinical trial comparing patient preference I subtreeshold INRS with that of subtreeshold DCS and suprathreshold DCS. We also describe a substudy investigating the pain relief and sensations associated with variety of pulse widths during stimulation: previous work indicates that a majority of patients may prefer pulse widths in excess of 500 µsec (3).

This is a prospective randomized This is a prospective, randomized clinical trial. Three subjects with failed back surgery syndrome were implanted with four 8-electrode percutaneous leads (Advanced Bionics, Valencia, CA; Figure 1).

Figure 1 (right, above): Photo of components of the Precision™ spinal cord stimulation sys

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Two leads were place in the epidural space for DCS, while two leads were retrogradely plac against intraspinal nerv roots at L1-2 for INRS (Figure 2, right). All leads were externalized distally and attached to an external trial stimulato

SENZA RCT @ 10 kHz (Kapural *et al.*, 2015)

Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain

The SENZA-RCT Randomized Controlled Trial

Leonardo Kapural, M.D., Ph.D., Cong Yu, M.D., Matthew W. Doust, M.D., Bradford E. Gliner, M.S., Bicardo Vallaio, M.D., Ph.D., B. Todd Sitzman, M.D., M.P.H., Kasra Amitolefan, M.D., Donna M. Morgan, M.D., Lora L. Brown, M.D., Thomas L. Yearwood, M.D., Ph.D., Fichard Bundschu, M.D., Alen W. Burton, M.D., Thomas Yang, M.D., Ramsin Beryamin, M.D. Abram H. Burgher, M.D.

PROCO RCT @ 1 kHz - 10 kHz (Thomson et al., 2018)

1 H

AH AH

10442



Higher Frequency SCS Can Provide Effective Sub-perception Pain Relief

Subject 01-001 Subject \$1-052 Figure 3 (above): Pain relief with each of three programs was ited over two days by study subjects (data is unavailable for subject 01-003). Suprathreshold DCS was reported to to brookly. Suprammeshold LCS was reported to te the highest percentage of pain relief, and was red by all three subjects.

2. Yearwood TL, Tackett S, Bridges B. Intradiscal pressure tolerance before and after grav ramus communicans blockad in primary discogenic pain. (Poster; AAPM annual meeting. San Diego, 2006.) Gould B, Bradley K. Pulse width programming in spinal cord stimulators. (Poster: AAPM annual meeting, San Diego, 2005.)

All subjects participated in an extended programming session in

general, that longer pulse widths felt smoother. Subjects SCS systems were programmed with a total of five programs, in four programs, the subjects selected pulse widths equal to or greater

which various pulse widths were tested. Subjects stated, in

Pulse Witths Chosen for Pa

than 450 usec (Figure 4, below).

*BIONICS

The PROCO Randomised Controlled Trial:

Effects of <u>Pulse Rate On Clinical Outcomes</u> in Kilohertz Frequency Spinal Cord Stimulation A Multicentre, Double-blind, Crossover Study

> Dr. Simon Thomson, MBBS Chief Investigator Basildon and Thurrock University Hospitals NHSFT - Sponsor

Moein Tavakkoli Zadeh, MD¹, Sarah Love-Jones, MBBS², Nik Patel, MD², Jianwen Wendy Gu, PhD³, Amarpreet Bains, PhD³, Que Doan, BSc³, Michael Moffitt, PhD³

1: University College London Hospitals, London, UK

- 2: Southmead Hospital, Bristol, UK
- 3: Boston Scientific Neuromodulation, Valencia, USA

All R&D departments at participating hospitals and the Multicentre Research Ethics Committee (MREC) approved this study Thomson SJ. et al. Neuromodulation. 2018 Jan;21(1):67-76

Study design: Multicentre, double-blind, randomised, crossover



- Lead placement: Spanning T9 to T10 vertebral region
- Paraesthesia-based trial
- Over the course of the study, patients experience high rate stimulation for 8–9 months

1: Stubbs et al. 2000 2: Whybrow 2006 3: Hampton & Middleton 2011

Randomized Crossover Increases Statistical Power



Advantages

- Each blinded patient experiences all 4 frequencies
- Patients act as their own control
- The crossover design of the PROCO RCT has the equivalent statistical power of a parallel design study with over 100 patients.

Importance of electronic real-time diary

- Compliance with paper diaries is only 11%¹
- Many studies just collect VAS or NRS at clinic visit → 1 data point per patient per evaluation period



 Memory of pain intensity is unreliable²
 Real-time E-diary prompted each patient for 180 pain scores over the rate randomisation phase

Larger sample size \rightarrow More accurate results^{3,4}

CamNtech Ltd. Validated^{5,6,7} e-diary

> 1: Stone et al. 2013 2: Broderick et al. 2008 3: McCollough et al. 1963 4:Walpole et al. 2002 5: Stubbs et al. 2000 6: Whybrow 2006 7: Hampton & Middleton 2011

Sweet spot search protocol

- Search done at 10 kHz
- The T9-10 interspace was always tested but was not the most commonly identified sweet spot
- For scientific purposes, the study afforded the opportunity to exhaustively test stimulation locations along both leads
- Multiple bipoles tested to identify best stimulation location
- Best stimulation location used for all frequencies in the randomisation period
 - Only 10 kHz responders continued in the study
 - Potential bias in favour of 10 kHz

Rate randomisation protocol

- Rates used: 1 kHz, 4 kHz, 7 kHz, 10 kHz
- Randomised Rate sequencing
- Each rate experienced for 4 weeks (last 5 days was data-collection period)
- Pulse width & amplitude optimised at each frequency for each patient
- Washout period between frequencies

Patient flowchart



PROCO RCT

NRS Results

Rule of Neural Dosing

To maintain pain relief, as frequency is DECREASED from 10 kHz to 1 kHz...



(1) Pulse Width must be INCREASED

(2) Charge Delivery is DECREASED





Thomson SJ. et al. INS European Chapter 2018

Thomson SJ. et al. Neuromodulation. 2018 Jan;21(1):67-76

Discussion: Neural dosing

- Achieving pain relief requires delivering the right waveform to the right target
 - Optimal target varied by patient
 - Optimal stimulation at each frequency required titration of pulse width and amplitude to deliver appropriate neural dose
 - Frequency cannot be looked at in isolation
 - Different frequencies required different pulse width and amplitude combinations



Future directions

- What is the best target? Beyond T8–T11?
- Is there a better field shape? Beyond bipole?
- What is the optimal neural dosing algorithm?
 - How low can we go in frequency/energy use while maintaining therapy?
 - What is the minimum effective neural dose?
 - Further analysis of PROCO RCT data in progress...stay tuned

Research into mechanisms and optimization paradigms is accelerating. The future is bright for our field and our patients!

Key PROCO Findings

Rule of Neural Dosing

arget Variability

To maintain pain relief, as frequency is DECREASED from 10 kHz to 1 (1) Pulse Width must be KHz... (2) Charge Delivery is DECREASED anywhere from T8-11







Thomson SJ. et al. *Neuromodulation*. 2018 Jan;21(1): 67-76

Modified from Thomson SJ. et al. Neuromodulation. 2018 Jan;21(1):67-76.

3 Key Challenges of Conventional High Frequency

(1) Lengthy "sweet spot" search Are tight 8mm bipoles the best approach to anatomical sub-p?



(2) Latency of analgesia (1-3 days) Lengthy program optimization (up to 2 weeks)



Tiede J., et al. *Neuromodulation* 2013; 16:370-375. Al-Kaisy A., et al. *Neuromodulation* 2015; 18: 18-23. Thomson S. et al. *Neuromodulation* 2018 Jan; 21(1):67-76. *Thomson S. *et al. Neuromodulation* 2018 Jan; 21(1):67-** 50 Hz, 300 µs, 5.5 mA

* 1kHz

0.08

** Conventional SCS

(3) High charge burden

x10 charge than Conventional

SCS

1.0

0.9

0.8

0.7

0.6 0.5 0.4 0.3 0.2

0.1

0.0

* 10kHz

Mean charge per second (mC/sec)

EXPLORATION OF HIGH AND LOW FREQUENCY OPTIONS FOR SUB-PERCEPTION PAIN RELIEF:

THE HALO STUDY

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SCS modalities scenario



PROCO RCT

NRS Results

Rule of Neural Dosing

To maintain pain relief, as frequency is DECREASED from 10 kHz to 1 kHz...



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Thomson SJ. et al. INS European Chapter 2018

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HALO Study

Motivation

- Does the Rule of Neural Dosing hold for frequencies below 1,000 Hz?
- How low can we go? Is there a clinical difference in sub-p pain relief from 1,000 Hz to 10 Hz?
- Can we improve sweet-spot search and targeting in sub-perception SCS with a novel field shape designed to preferentially engage the dorsal horn?

Study Design

- Multicenter, Observational, Real-World, Consecutive, Case-Series (n = 30)
- Program optimization with progressive frequency reduction [1000, 600, 400, 200, 100, 50 and 10 Hz]
- Data collection by site personnel (Retrospective): Pain Scores (NRS/Diary), Satisfaction, Program preference

Programming

Implant

- Dual 16-contact perc leads
- T8-T10 vertebral span
- SCS System: 32 contacts with multiple independent current control capable of calibrated field shape and multiple waveforms



Sweet-spot search

Broad field

Faster search

- 1000 Hz stimulation
- Broad field covers multiple

T10

"sweet-spot"



- Frequency reduction in sub-p: [1000, 600, 400, 200, 100, 50, 10] Hz
- Pulse width and amplitude adjustment



Results





Conclusions

- The Rule of Neural Dosing holds for frequencies below 1,000 Hz
 - Effective sub-perception pain relief is achieved for all frequencies (10 Hz-10 KHz) by staying within the neural dosing window
 - Charge-per-second can be drastically reduced, thus enabling patient charging burden to be largely reduced
 - Some known waveforms (e.g. 10 kHz) are just a single point within the neural dosing curve

In contradiction with constant duty cycle hypotheses

Results: Neural Dosing Curves



SCS modalities scenario

Sub-perception SCS

BurstDR

Neural Dosing	Neural dosing curves define the relationship between: waveform parameters & effective sub-p pain relief (10 Hz-10 KHz)	
HF (10 KHz)	X Frequencies below 10 kHz \rightarrow Less/ineffective pain relief?	
High Density	X Must maintain duty cycle constant (20-25%) [Yang, 2019]?	

One Fixed burst pattern X (5 x 1000 μs @ 500 Hz) is best?

> • Thomson, 2018 Paz, 2019

🛧 Kapural, 2015

1000

900

800

700

10

Yang, 2019

Pulse width (µs)

mean

st. dev.

50

100

Al-Kaisy, 2017 Deer, 2017 Vesper, 2019

200

400 600 1k

Frequency (Hz)

4k 7k 10k

Neural Dosing in context of literature

Sub-perception SCS

	<u> </u>
Neural	k
Dosing	

HF (10 KHz)

High Density

BurstDR

Kapural, 2015

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• Thomson, 2018

• Paz, 2019

Neural dosing curves define the relationship between: waveform parameters & effective sub-p pain relief (10 Hz-10 KHz)

Frequencies < 10 kHz provide effective sub-p pain relief

- No need to maintain constant density when reducing frequency
- Many waveform patterns can provide effective sub-p pain relief

Al-Kaisy, 2017 🖈 Deer, 2017 Yang, 2019 🛕 Vesper, 2019





NRAC Team 2019; BTUH and La Paz Clinical & Research Teams





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