

WHAT'S NEW?

Neuromodulation. Current Evidence and Future Implications

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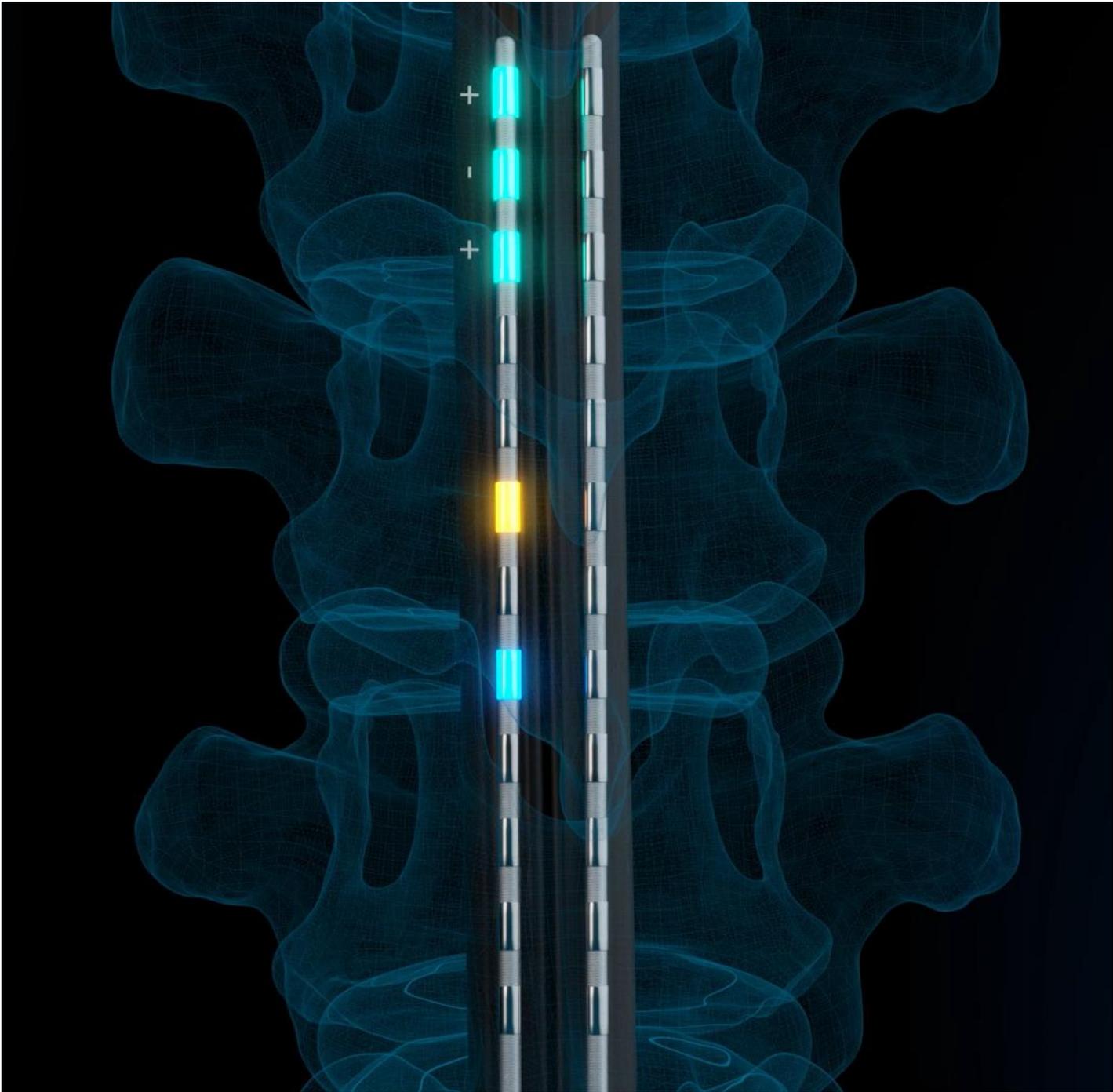
DISCLOSURES

- Consultant
 - Saluda Medical
 - Stratus Medical
 - Abbott
- Research Support
 - SPR Therapeutics
 - Mainstay Medical

PERTINENT DISCLOSURES

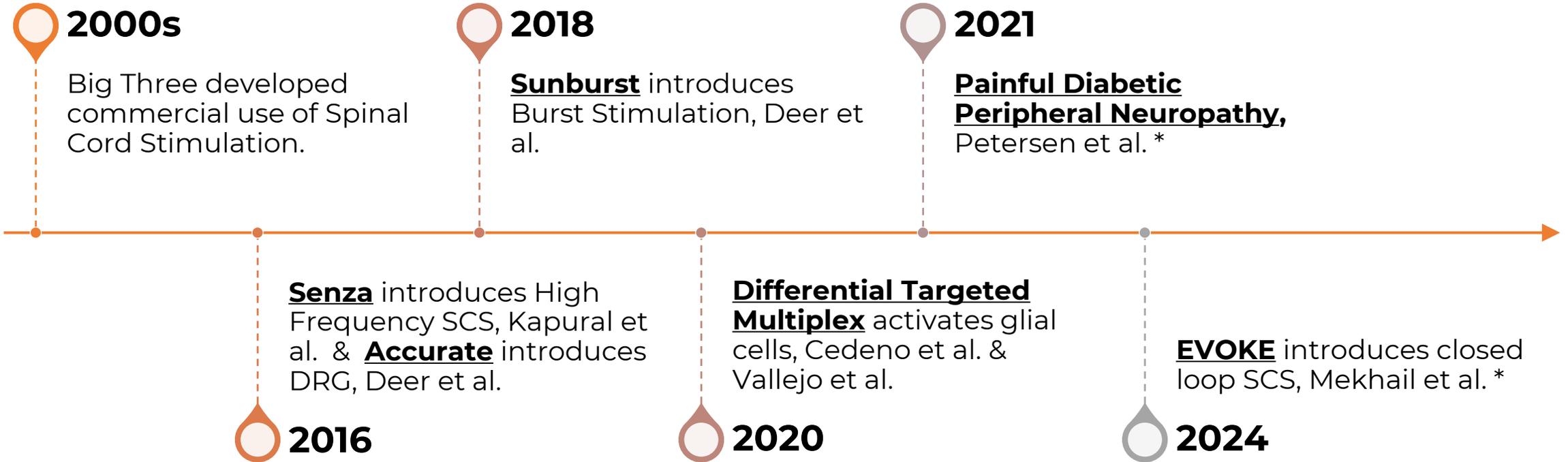
- I have been performing Neuromodulation for 11 years.
- I am a Board Member of North American Neuromodulation Society
- On the curve of new technology adoption, I'm an innovator.
- I am an author on the two largest prospective SCS trials in history (funded by Nevro and Saluda)
- I am currently site P.I. for two I.D.E studies for new devices in the Neuromodulation space.
- Many of these authors are my friends.
- I love this stuff!

NEUROMODULATION WORKS.



**WE DISAGREE ON HOW, WHAT, &
WHY.**

TIMELINE – GROUNDBREAKING RESEARCH





Where Are



We Now?

- 
- A scenic landscape featuring a river in the foreground, a dense forest of evergreen trees in the middle ground, and large, rugged mountains in the background. The sky is a mix of soft orange and light blue, suggesting a sunset or sunrise. The overall tone is serene and natural.
- SEVEN dorsal column stimulation companies
 - NOVEL stimulation paradigms currently being investigated
 - TWO approved closed loop stimulation strategies
 - OTHER strategies to improve stimulation feedback being explored.
- HEADWINDS from recent literature and payors

HARA 2022

JAMA®

QUESTION Among patients with chronic radicular pain after lumbar spine surgery, does spinal cord burst stimulation affect back pain-related disability?

CONCLUSION Among patients with chronic radicular pain after lumbar spine surgery, spinal cord burst stimulation, compared with placebo stimulation, resulted in no significant difference in back pain-related disability.

POPULATION

27 Women
23 Men



Adults with chronic radiculopathy after surgery for degenerative lumbar spine disorders

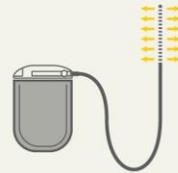
Mean age: 52 years

LOCATIONS

1
University hospital in Norway



INTERVENTION



50 Patients randomized
47 Patients analyzed
180 Crossover treatment allocations

91

Burst stimulation allocations

Closely spaced, high-frequency stimuli delivered to the spinal cord lasting for 3 months

89

Placebo stimulation allocations

Placebo stimulation lasting for 3 months

PRIMARY OUTCOMES

Change from baseline in self-reported Oswestry Disability Index

FINDINGS

Change in Oswestry Disability Index score (range, 0 [no disability] to 100 [maximum disability])

Mean baseline score: 44.7 points

Burst stimulation Change: **-10.6 points**

Placebo stimulation Change: **-9.3 points**

The difference was not significant:
Mean between-group difference, **-1.3 points**
(95% CI, -3.9 to 1.3 points); $P = .32$

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Hara S, Andresen H, Solheim O, et al. Effect of spinal cord burst stimulation vs placebo stimulation on disability in patients with chronic radicular pain after lumbar spine surgery: a randomized clinical trial. *JAMA*. Published October 18, 2022. doi:10.1001/jama.2022.18231



Trial with Tonic Stimulation.



All patients from Norwegian single center and programmed by research nurse



Patients randomized every 3 months to either “burst” or placebo for 12 months.



Patients only reprogrammed if they ask for reprogramming



Hard to control for sham v. active device. (Could there be bias in the evaluators/patients, i.e. I'm in the sham period, no reason to go back to hospital and get reprogrammed, this shouldn't work)

Table 2. Effect of Spinal Cord Burst Stimulation on Primary and Secondary Outcomes

	Mean score (95% CI)			Between-group difference	P value
	At baseline	Spinal cord burst stimulation	Placebo stimulation		
No. of stimulation periods		91	89		
Primary outcome					
Oswestry Disability Index, points ^a	44.7 (41.4 to 47.9)	34.0 (30.0 to 38.1)	35.4 (31.3 to 39.4)		
Change from baseline		-10.6 (-14.1 to -7.2)	-9.3 (-12.7 to -5.9)	-1.3 (-3.9 to 1.3)	.32
Secondary outcomes					
Numerical Rating Scale ^b					
Leg pain	7.3 (6.8 to 7.7)	5.9 (5.3 to 6.4)	6.1 (5.6 to 6.6)	-0.2 (-0.7 to 0.2)	.32
Back pain	6.8 (6.4 to 7.3)	5.7 (5.2 to 6.2)	6.1 (5.6 to 6.6)	-0.4 (-0.8 to 0.04)	.07
5-Dimension EuroQol index ^c	0.21 (0.13 to 0.28)	0.48 (0.39 to 0.56)	0.44 (0.35 to 0.53)	0.04 (-0.03 to 0.11)	.32
Physical activity level ^d					
No. of steps per day	6775 (5651 to 7899)	7561 (6411 to 8710)	7155 (6006 to 8305)	405 (-422 to 1233)	.34
Time spent standing or walking, h/d	3.8 (3.3 to 4.3)	4.0 (3.5 to 4.4)	4.0 (3.6 to 4.4)	-0.02 (-0.4 to 0.3)	.89

^a Scores range from 0 points (no disability) to 100 points (maximum disability). The minimal clinically important difference (MCID) was 10 points. A typical patient with moderate back pain and disability would have a score between 20 and 40. Scores greater than 40 indicate severe disability.

^b Scores range from 0 (no pain) to 10 (worst pain imaginable). The MCID was 1.0 points.

^c A score of 0 indicates death and a score of 1 indicates a perfect health state. The MCID was 0.03. Scores between 0.2 and 0.5 represented a severe to moderate reduction in overall health-related quality of life.

^d Measured using a body-worn accelerometer (ActivPAL, PAL Technologies, Ltd).

HUGYEN 2024

Table 1. Overview of Study Design Across Included Studies

Source	Study phase	Blinding	Intervention	Comparator	Study population	Sample size	Duration of follow-up
Kumar et al, ¹⁹ 2007	NA	Open label	SCS + CMM	CMM alone	Patients with neuropathic pain (FBSS)	100	24 mo
Petersen et al, ²⁰ 2021	NA	Open label	10 kHz SCS + CMM	CMM	Patients with neuropathic pain (PDN)	216	52 mo
de Vos et al, ²¹ 2014	NA	Open label	SCS + CMP	CMP	Patients with neuropathic pain (PDN)	60	6 mo
Rigoard et al, ²² 2019	4	Open label	SCS + OMM	OMM alone	Patients with FBSS diagnosis, mixed population	218	24 mo
Slangen et al, ²³ 2014	NA	Open label	SCS + BMT	BMT	Patients with neuropathic pain (moderate to severe PDPN)	36	6 mo
Kapural et al, ²⁴ 2022	NA	Open label	10 kHz SCS + CMM	CMM	Patients with neuropathic pain (NSRBP)	159	12 mo
De Andres et al, ²⁵ 2017	NA	Double-blind	High-frequency (10 kHz) SCS	Conventional SCS	Patients with neuropathic pain (FBSS)	55	12 mo
Bolash et al, ²⁶ 2019	NA	Open label	High-frequency (10 kHz) SCS	Low-frequency SCS	Patients with neuropathic pain (FBSS)	99	6 mo
Al-Kaisy et al, ²⁷ 2021	NA	Open label	SCS 10 kHz + CMM	CMM alone	Patients with possible neuropathic pain (NSRBP)	58	12 mo
Mekhail et al, ²⁸ 2020	NA	Double-blind	Closed-loop SCS (ECAP-controlled)	Open-loop SCS (manual stimulation)	Patients with chronic, intractable pain of the back and legs	134	3 y
Kapural et al, ²⁹ 2015	NA	Open label	High-frequency (10 kHz) SCS	Low-frequency therapy SCS	Chronic, intractable pain of the trunk or extremities	198	24 mo
Fishman et al, ³⁰ 2021	NA	Open label	Differential target multiplexed SCS	Traditional SCS	Chronic LBP and leg pain	128	12 mo
Leong et al, ³¹ 2021	NA	Open label	Burst stimulation SCS	Tonic stimulation SCS	Chronic intractable pain in the extremities and trunk	100	24 wk

Abbreviations: BMT, best medical treatment; CMM, conventional medical management; CMP, conventional medical practice; FBSS, failed back surgery syndrome; kHz, kilohertz; LBP, low back pain; NA, not available; NSRBP, non-surgical refractory back pain; OMM,

optimal medical management; PDN, painful diabetic neuropathy; PDPN, painful diabetic peripheral neuropathy; SCS, spinal cord stimulation.

Table 2. Matrix of Bayesian NMA Results^a

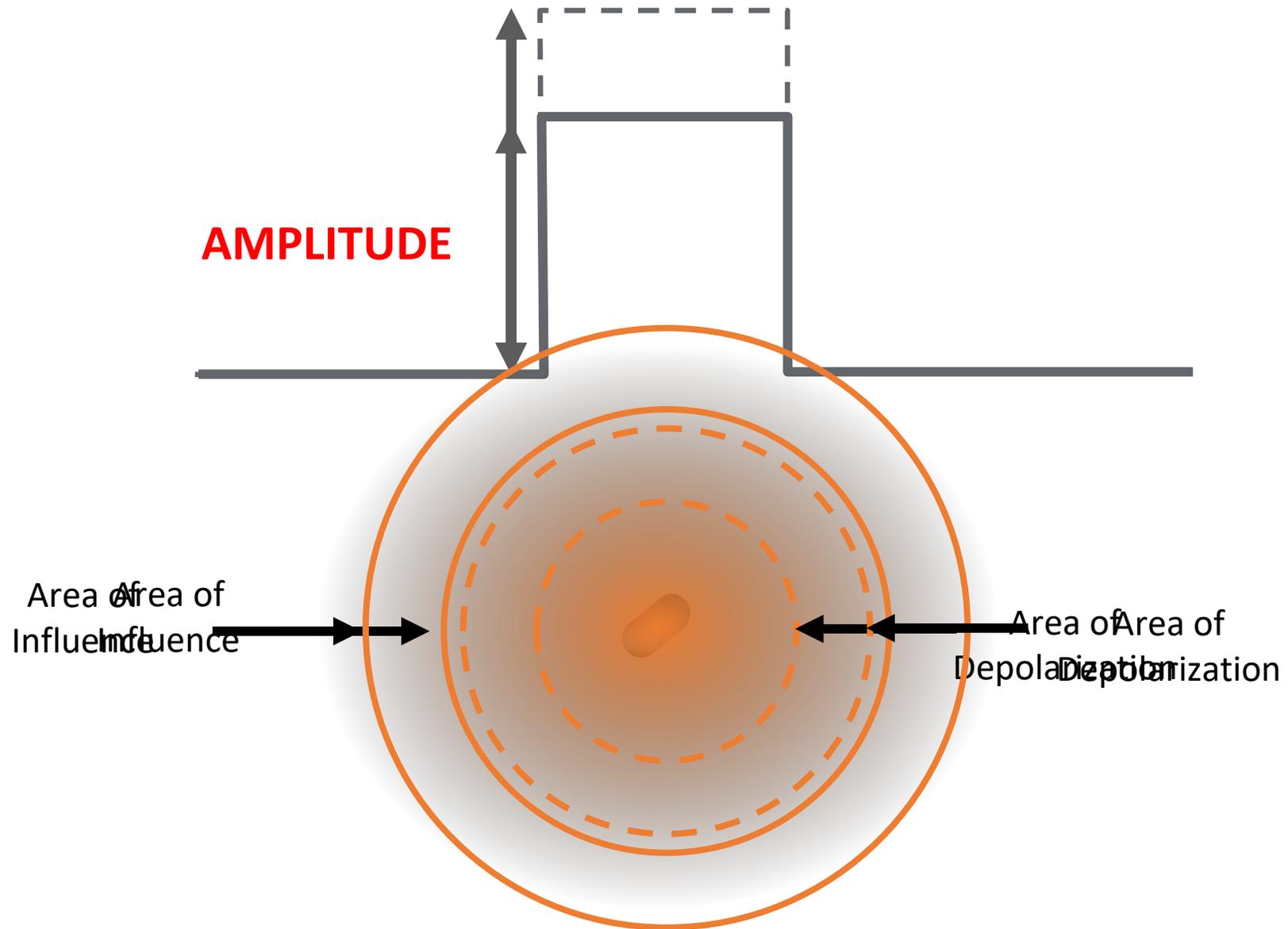
Measure	Estimate vs CMM
Proportion of patients achieving $\geq 50\%$ pain reduction in back^b	
Conventional SCS, OR (95% CrI)	3.00 (1.49 to 6.72) ^c
Novel SCS, OR (95% CrI)	8.76 (3.84 to 22.31) ^c
DIC	14.07
Studies in the network, No.	5
Total sample size, No.	683
Proportion of patients achieving $\geq 50\%$ pain reduction in leg^d	
Conventional SCS, OR (95% CrI)	6.93 (0.67 to 49.35) ^e
Novel SCS, OR (95% CrI)	10.13 (0.45 to 129.31) ^e
DIC	26.15
Studies in the network, No.	7
Total sample size, No.	831

HOW DOES STIMULATON WORK?

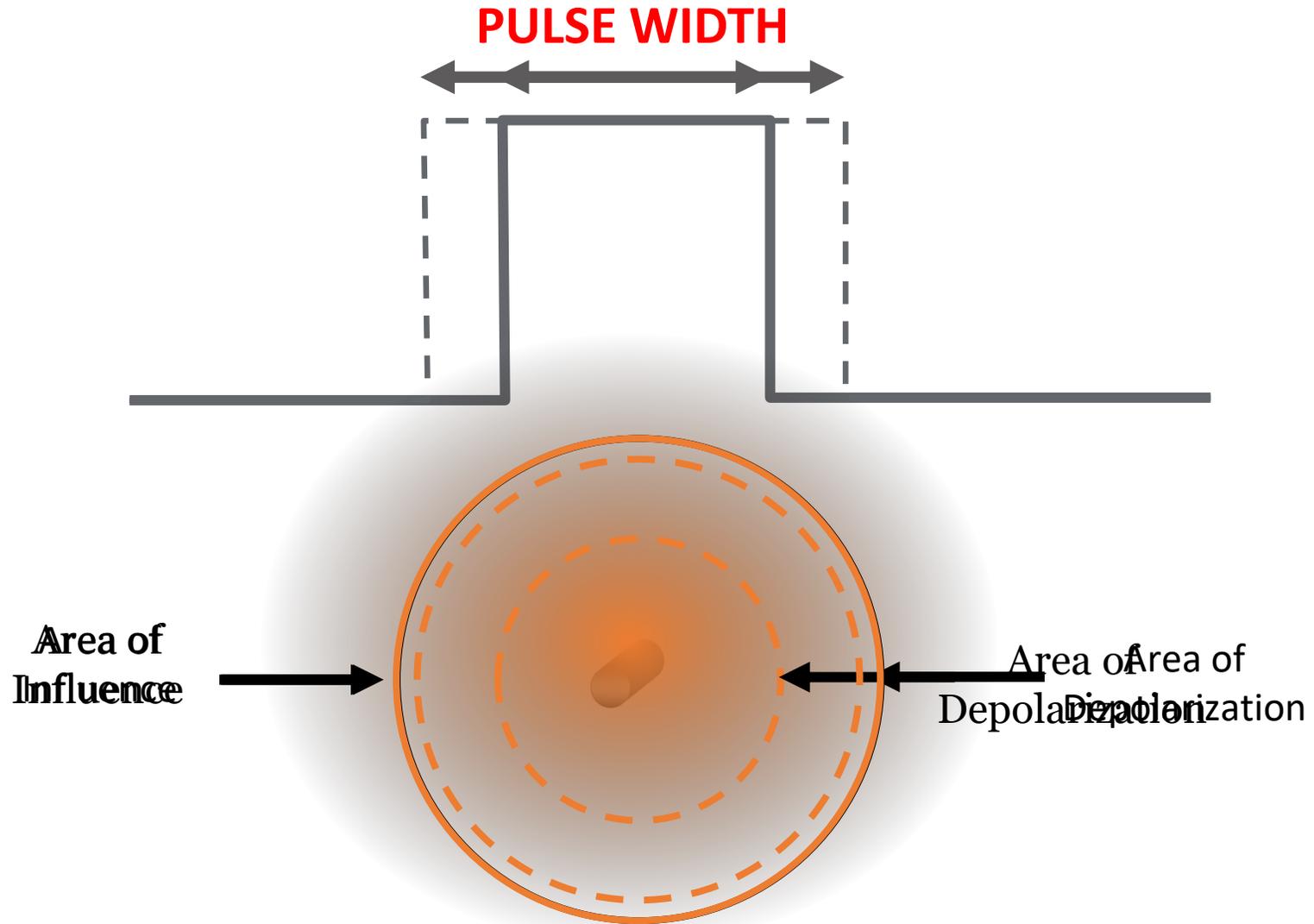




AMPLITUDE

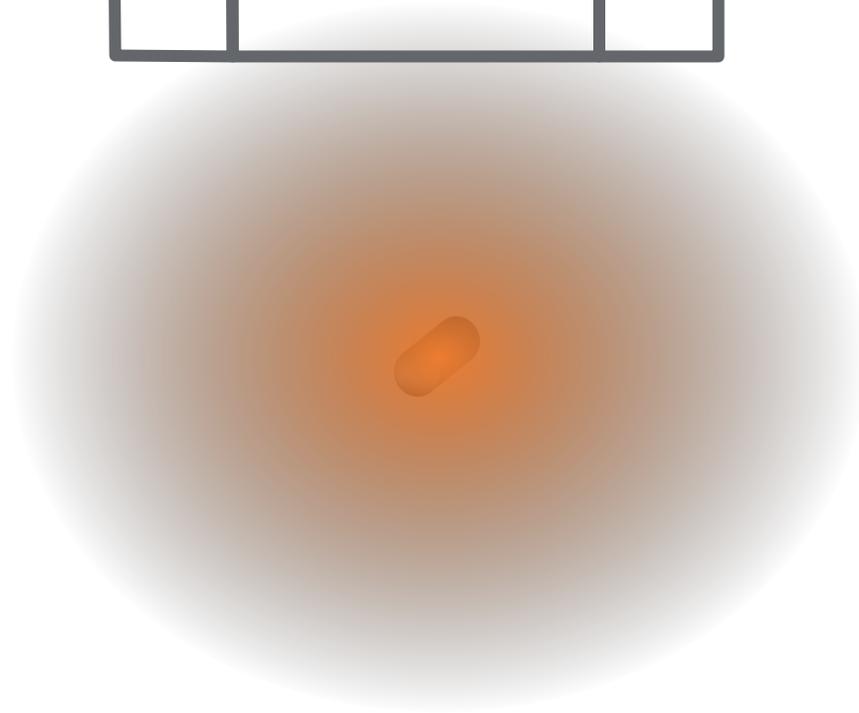
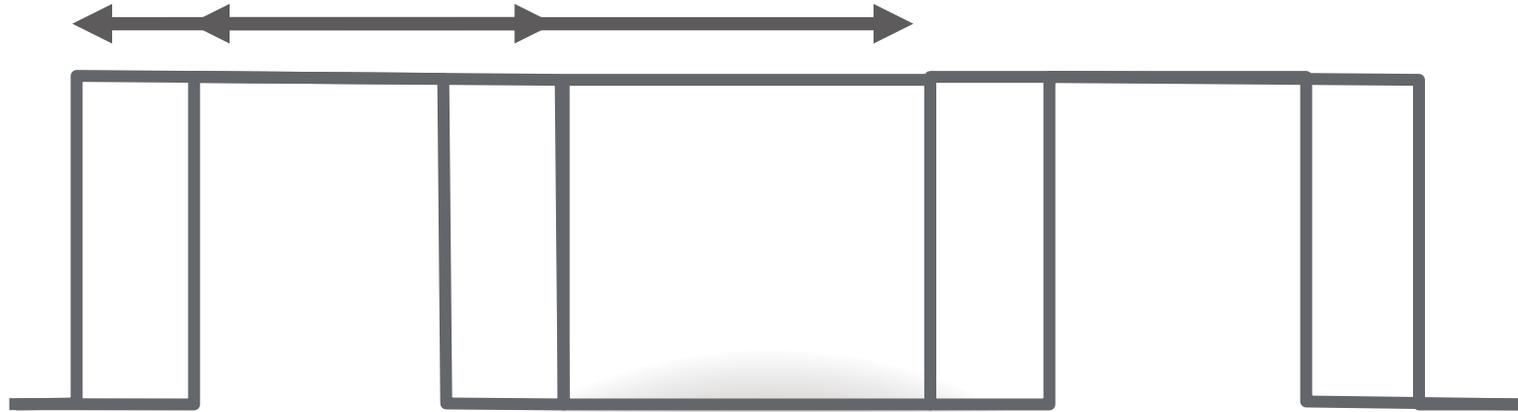


PULSE WIDTH



FREQUENCY

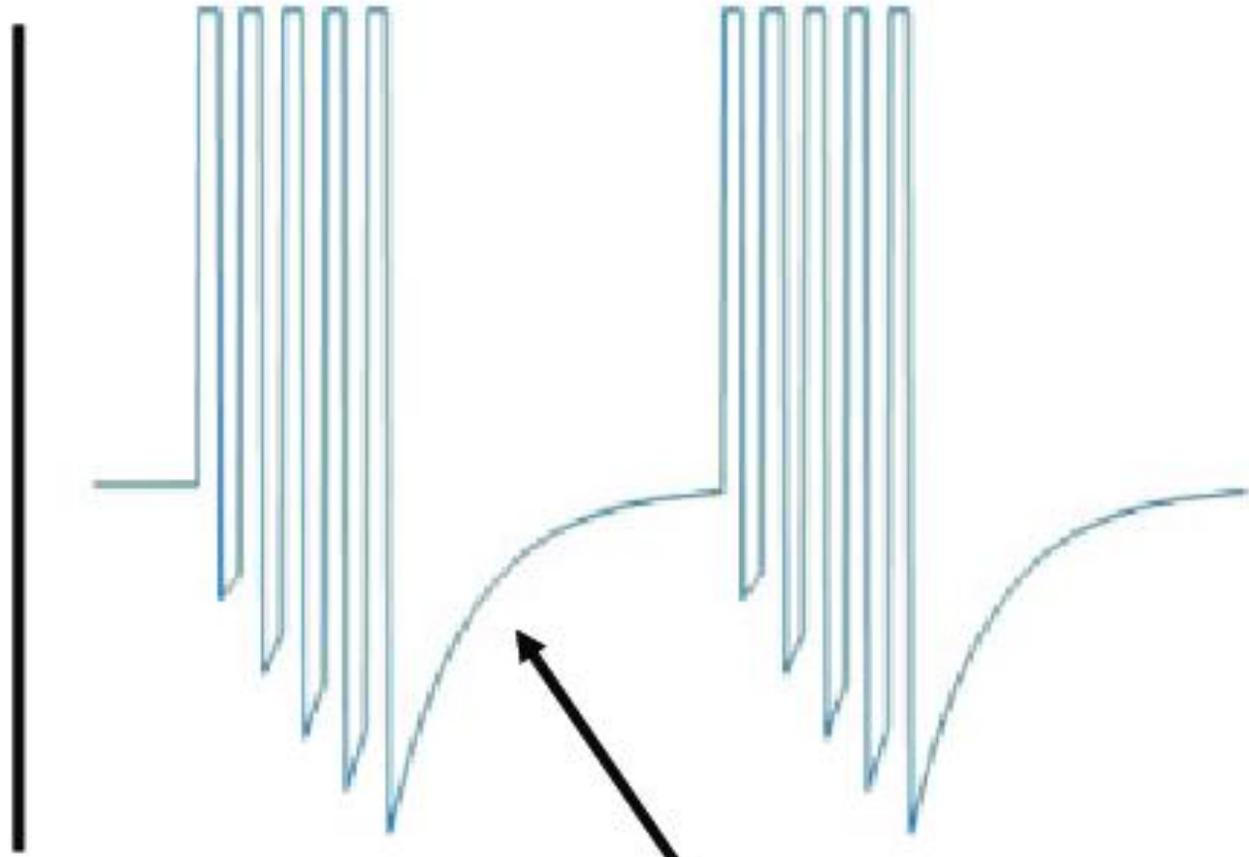
FREQUENCY



CURRENT STIMULATION PARADIGMS

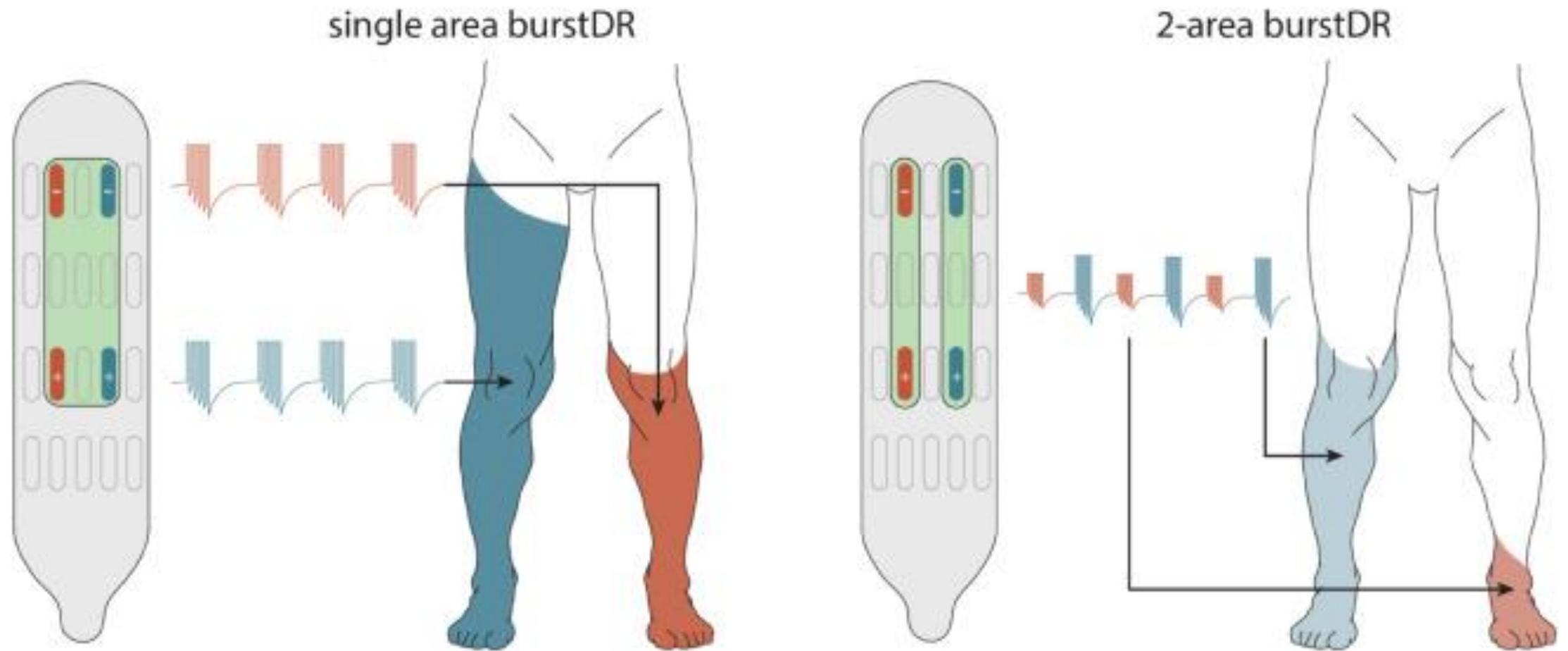
BURST-DR

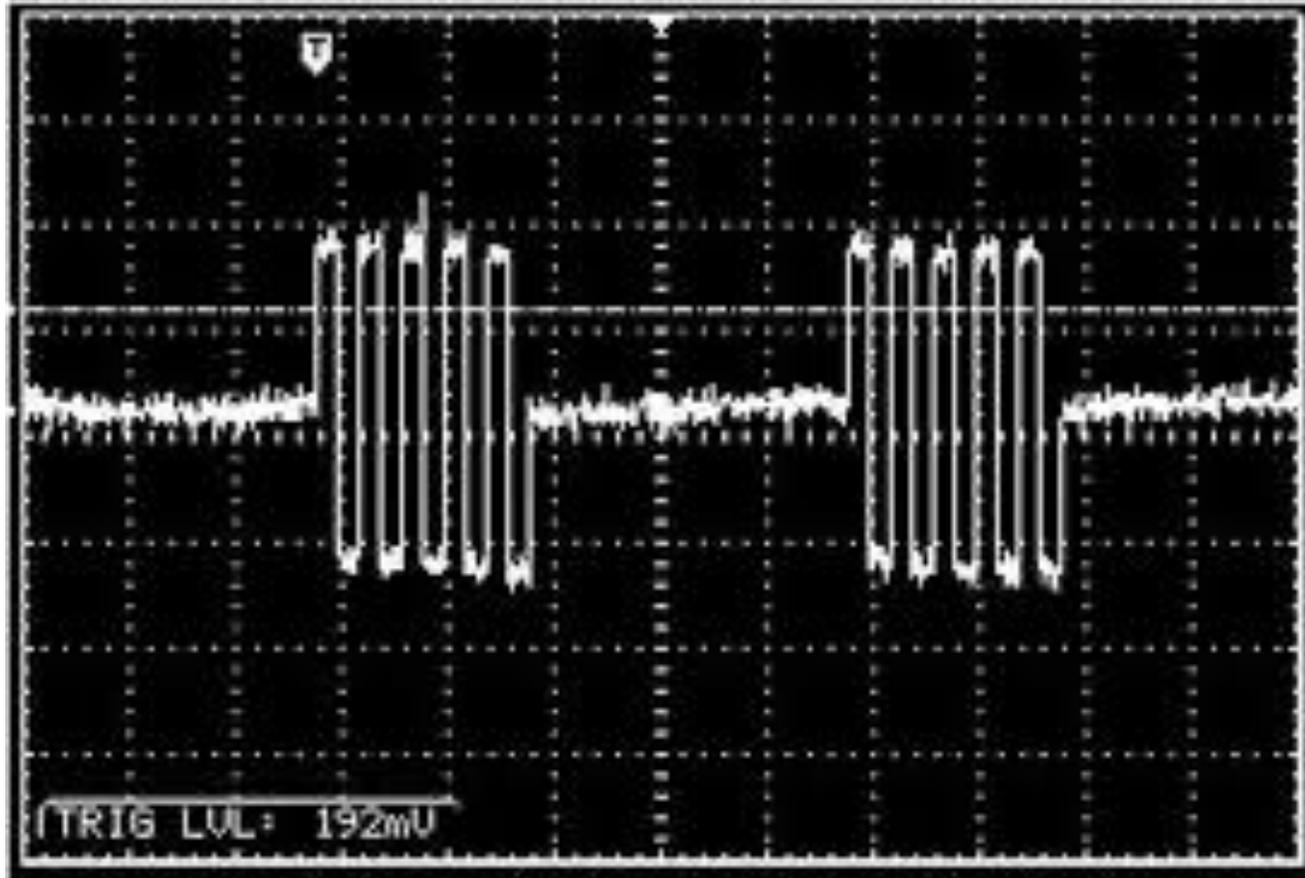
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FALOWSKI ET AL.



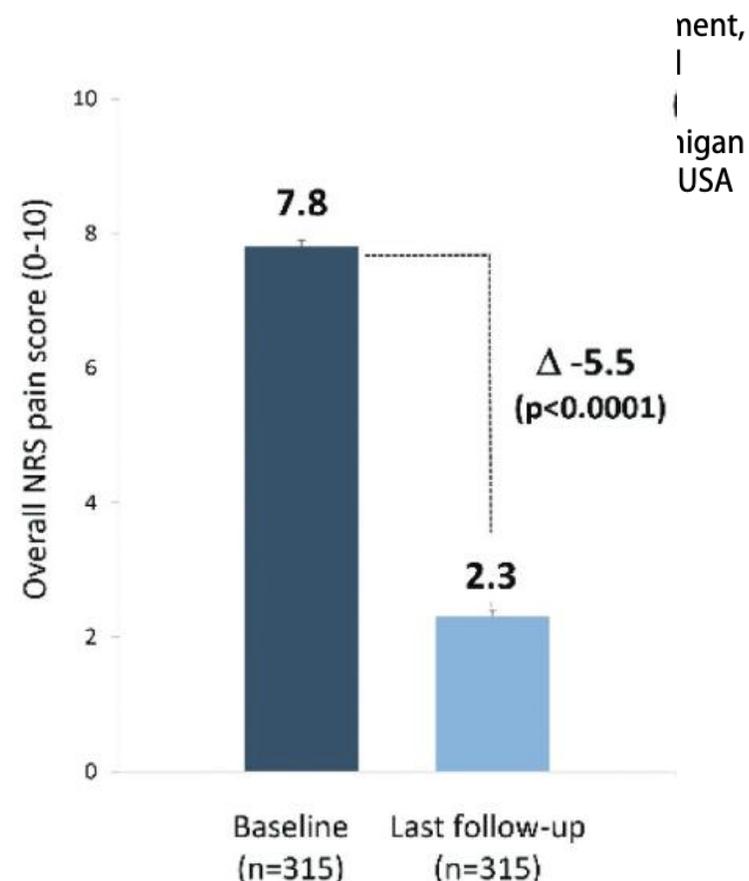
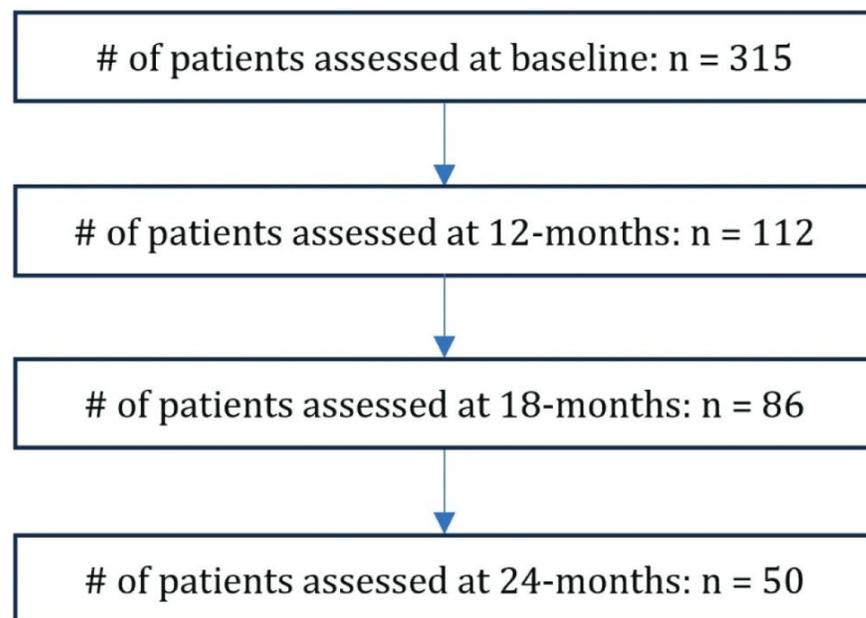


**FAST ACTING SUB-
PERCEPTION THERAPY**

Two-year outcomes using fast-acting sub-perception therapy for spinal cord stimulation: results of a real-world multicenter study in the United States

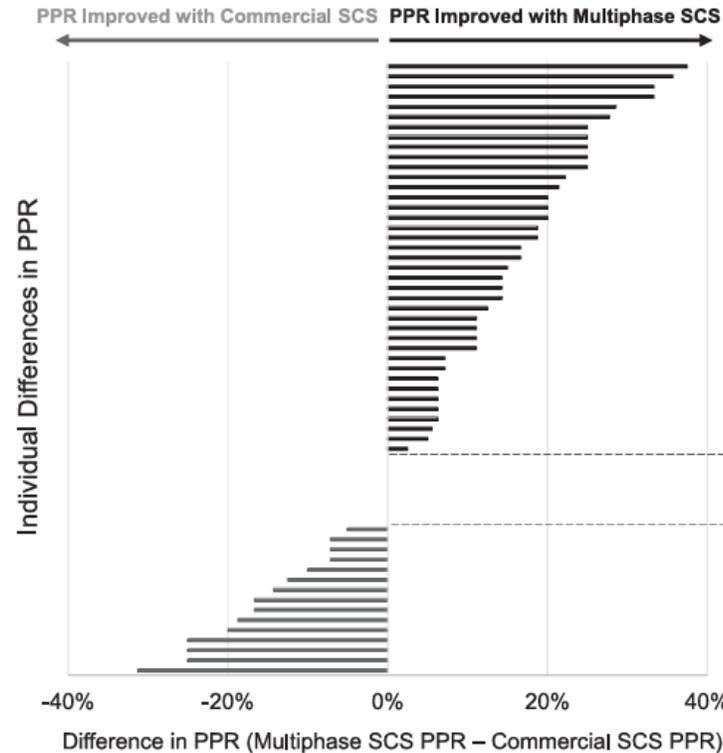
Clark Metzger^a, Blake Hammond^a, Richard Ferro^b, James North^c, Stephen Pyles^d, Andy Kranenburg^e, Edward Washabaugh^f and Edward Goldberg^g

^aOrthopedic Surgery Department, HCA Florida West Orthopedic Specialists, Pensacola, Florida, USA; ^bMultidisciplinary Pain Management Services, Okemos, Michigan, USA; ^cInterventional Pain Research, LLC, Winston-Salem, North Carolina, USA; ^dInterventional Pain Management Department, Winston-Salem, North Carolina, USA; ^eOrthopedic Surgery Department, Southern Oregon Orthopedics, Medford, Oregon, USA; ^fPain Specialists, Ann Arbor, Michigan, USA; ^gMedical Director, Clinical Department, Boston, Massachusetts, USA



Multiphase Spinal Cord Stimulation in Participants With Chronic Back or Leg Pain: Results of the BENEFIT-02 Randomized Clinical Trial

Leonardo Kapural, MD, PhD¹ ; Denis G. Patterson, DO²; Sean Li, MD³; John Hatheway, MD⁴; Corey Hunter, MD⁵; Steven Rosen, MD⁶; Michael Fishman, MD⁷; Mayank Gupta, MD⁸; Dawood Sayed, MD⁹; Anne Christopher, MD¹⁰; Abram Burgher, MD¹¹; Tory McJunkin, MD¹²; Edgar L. Ross, MD¹³; David Provenzano, MD¹⁴; Kasra Amirdelfan, MD¹⁵



39/61 (63.9%) participants reported greater pain relief with multiphase SCS

7/61 (11.5%) participants reported no difference between multiphase and commercial SCS

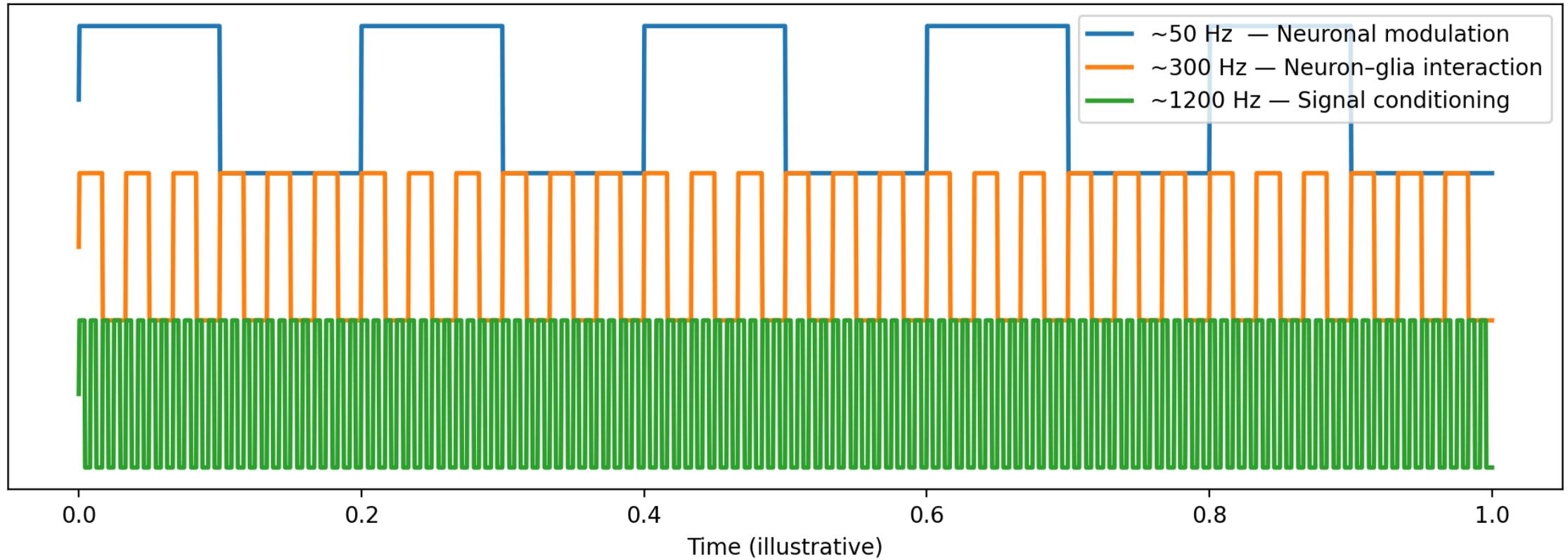
15/61 (24.6%) participants reported greater pain relief with commercial SCS



DIFFERENTIAL TARGET MULTIPLEXED

- **Three** concurrent frequencies (50Hz, 300Hz, and 1200Hz) to differentially target neurons and neuron-glia signaling

DTM: Multiplexed Frequency Architecture (Illustrative)



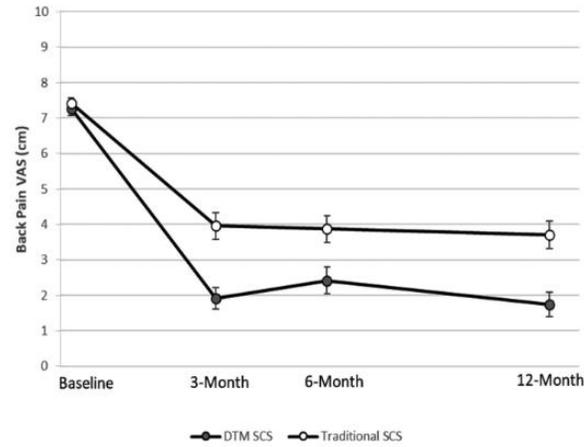


FIGURE 4 Mean visual analog scale (VAS) scores for longitudinal back pain with standard errors. Values correspond to the analysis with the ITT population with evaluable data at each time point. DTM, Differential Target Multiplexed; ITT, intention to treat; SCS, spinal cord stimulation

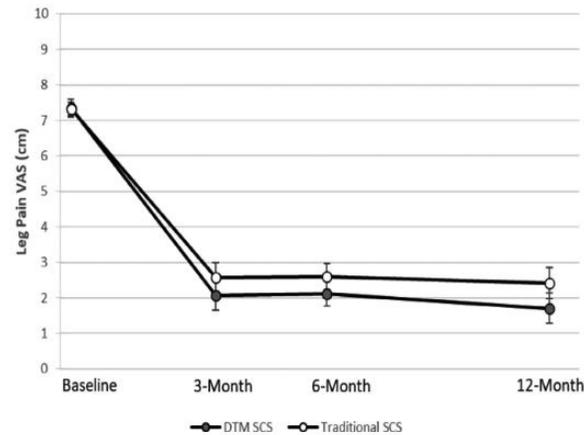


FIGURE 5 Mean visual analog scale (VAS) scores for longitudinal leg pain with standard errors. Values correspond to the analysis with the ITT population with evaluable data at each time point. DTM, Differential Target Multiplexed; ITT, intention to treat; SCS, spinal cord stimulation

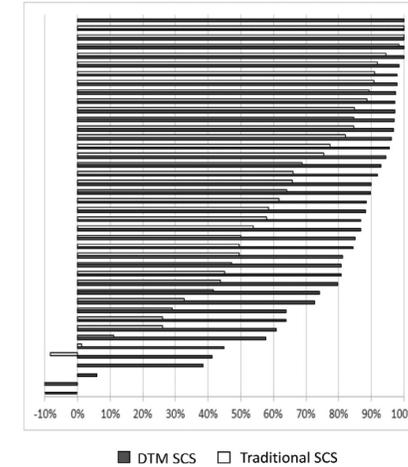


FIGURE 3 Back pain relief for individual subjects at the 12-month visit. Sixty-nine percent of the test subjects (DTM SCS) achieved profound response to back pain. Thirty-five percent of the control subjects (traditional SCS) achieved profound response to back pain. Profound response is defined as 80% or greater (dashed line) low back pain relief. Analysis included the ITT population with evaluable data at the 12-month visit. DTM, Differential Target Multiplexed; ITT, intention to treat; SCS, spinal cord stimulation

RESEARCH ARTICLE

Twelve-Month results from multicenter, open-label, randomized controlled clinical trial comparing differential target multiplexed spinal cord stimulation and traditional spinal cord stimulation in subjects with chronic intractable back pain and leg pain

Michael Fishman MD, MBA¹ | Harold Cordner MD² | Rafael Justiz MD³ | David Provenzano MD⁴ | Christopher Merrell MD⁵ | Binit Shah MD⁶ | Julian Naranjo MD⁷ | Philip Kim MD¹ | Aaron Calodney MD⁸ | Jonathan Carlson MD⁹ | Richard Bundschu MD¹⁰ | Mahendra Sanapati MD¹¹ | Vipul Mangal MD¹² | Ricardo Vallejo MD, PhD¹³

Low-energy differential target multiplexed SCS derivative reduces pain and chronic back pain in European randomized controlled trial evaluating differential target multiplexed spinal cord stimulation and conventional medical management in subjects with persistent back pain ineligible for spine surgery: 24-month results

Jeffery Peacock
Kasra Amirdelfi
Prabhdeep Grew
MD¹¹ | Binit
Jan Willem Kall
Calysta Rice BA

Jan W. Kallewaard^{1,2} | Bart Billet³ | Raf Van Paesschen⁴ | Iris Smet⁵ |
Agustin Mendiola⁶ | Isaac Peña⁷ | Pablo López⁸ | Javier Carceller⁸ |
Carlos Tornero⁹ | Xander Zuidema^{10,11} | Jan Vesper¹² | Jens Lehmborg¹³ |
Wim Laloo¹⁴ | David L. Cedeño¹⁴ | Ricardo Vallejo¹⁴

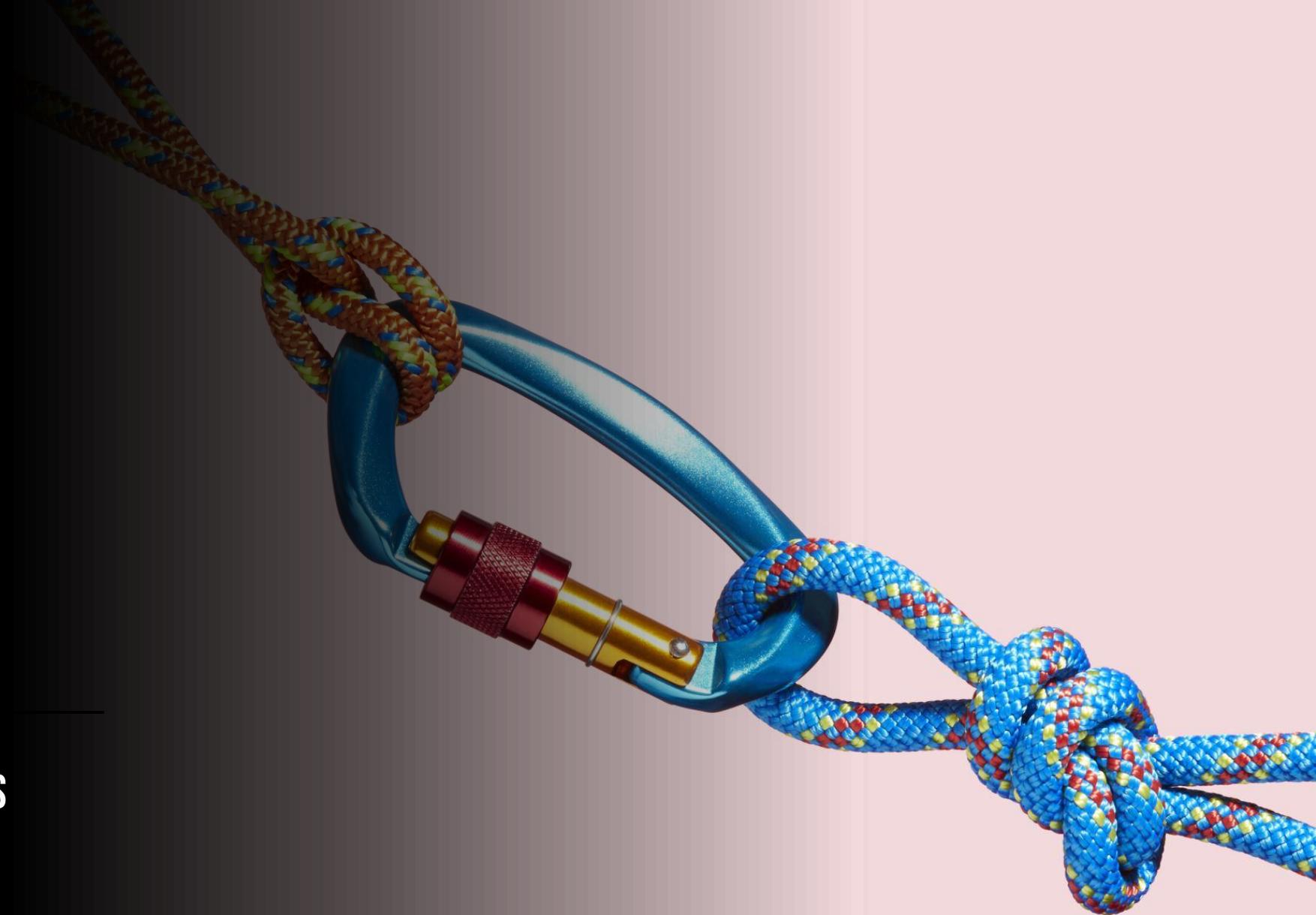
Gennady Gekht, MD⁷; Andrew Will, MD⁷; Philip Kim, MD⁷;
Richard Bundschu, MD⁸; Justin Sirianni, MD⁸; Amr El-Naggar, MD¹⁰;
Mayank Gupta, MD¹¹; Wesley Park, MPH¹²; David L. Cedeño, PhD¹²;
Ricardo Vallejo, MD, PhD¹²

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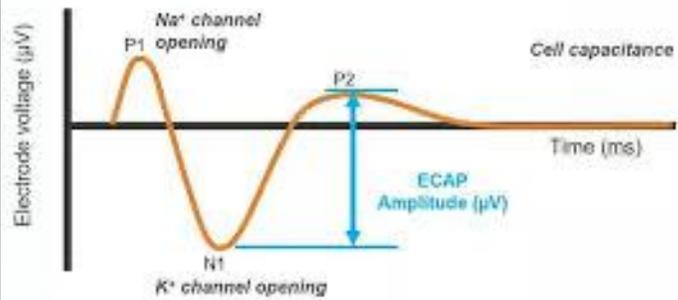


CLOSED LOOP STIMULATION

DYNAMIC VOLTAGE BASED ON ECAPS

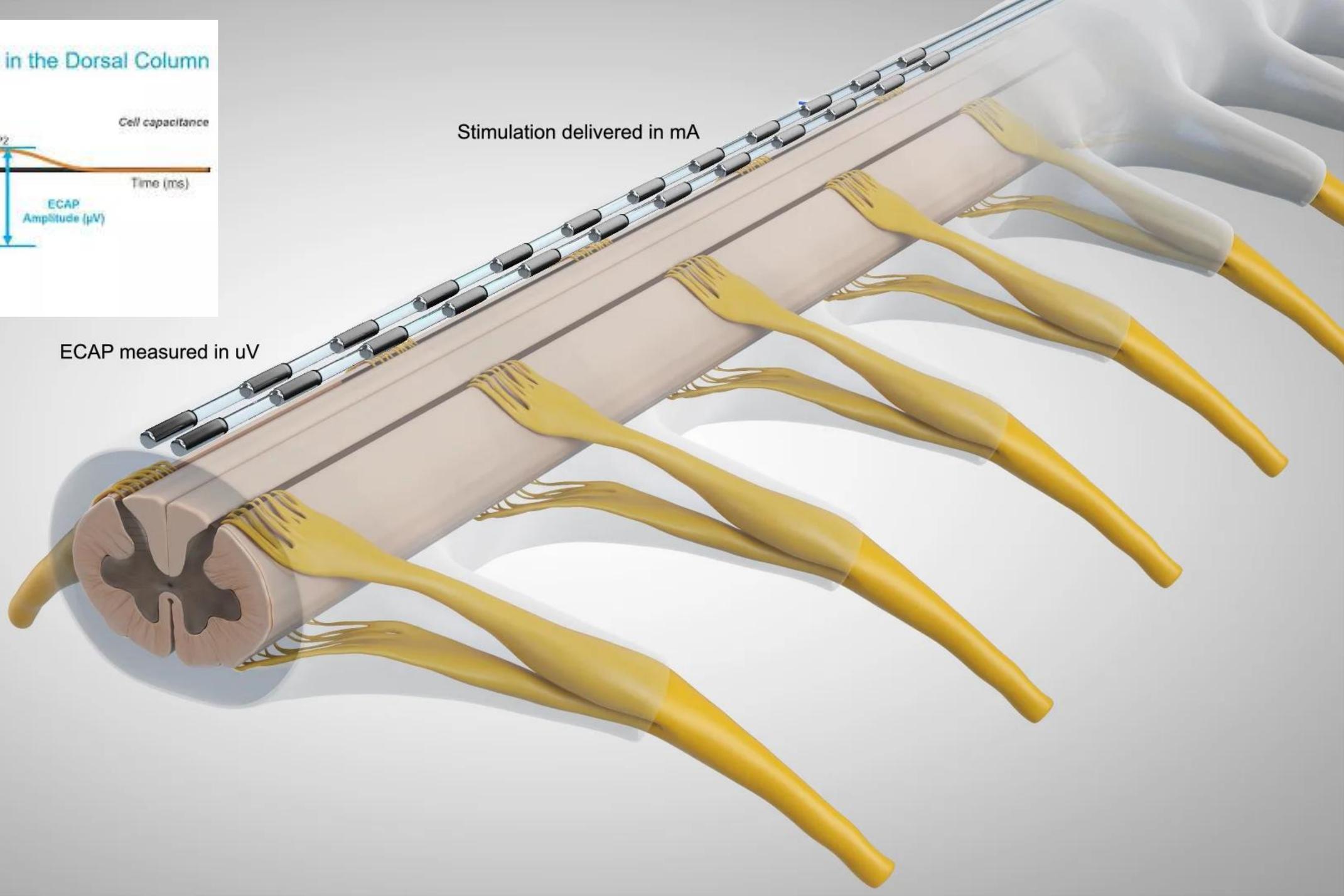


Measuring the ECAP in the Dorsal Column



Stimulation delivered in mA

ECAP measured in μV



EVOKE AND ECAP STUDY

Original research



OPEN ACCESS

ECAP-controlled closed-loop versus open-loop SCS for the treatment of chronic pain: 36-month results of the EVOKE blinded randomized clinical trial

Nagy A Mekhail ¹, Robert M Levy,² Timothy R Deer ³, Leonardo Kapural,⁴ Sean Li,⁵ Kasra Amirdelfan,⁶ Jason E Pope,⁷ Corey W Hunter,⁸ Steven M Rosen,⁹ Shrif J Costandi ¹, Steven M Falowski,¹⁰ Abram H Burgher,¹¹ Christopher A Gilmore,¹² Farooq A Qureshi,¹³ Peter S Staats,⁵ James Scowcroft,¹⁴ Tory McJunkin,¹⁵ Jonathan Carlson,¹⁶ Christopher K Kim,³ Michael I Yang,¹⁷ Thomas Stauss,¹⁸ Erika A Petersen,¹⁹ Jonathan M Hagedorn ²⁰, Richard Rauck,¹² Jan W Kallewaard,^{21,22} Ganesan Baranidharan,²³ Rod S Taylor,²⁴ Lawrence Poree,²⁵ Dan Brounstein,²⁶ Rui V Duarte ^{26,27}, Gerrit E Gmel,²⁶ Robert Gorman,²⁶ Ian Gould,²⁶ Erin Hanson,²⁶ Dean M Karantonis,²⁶ Abeer Khurram,²⁶ Angela Leitner,²⁶ Dave Mugan,²⁶ Milan Obradovic,²⁶ Zhonghua Ouyang,²⁶ John Parker,²⁶ Peter Single,²⁶ Nicole Soliday,²⁶ The EVOKE Study Group

Original research



OPEN ACCESS

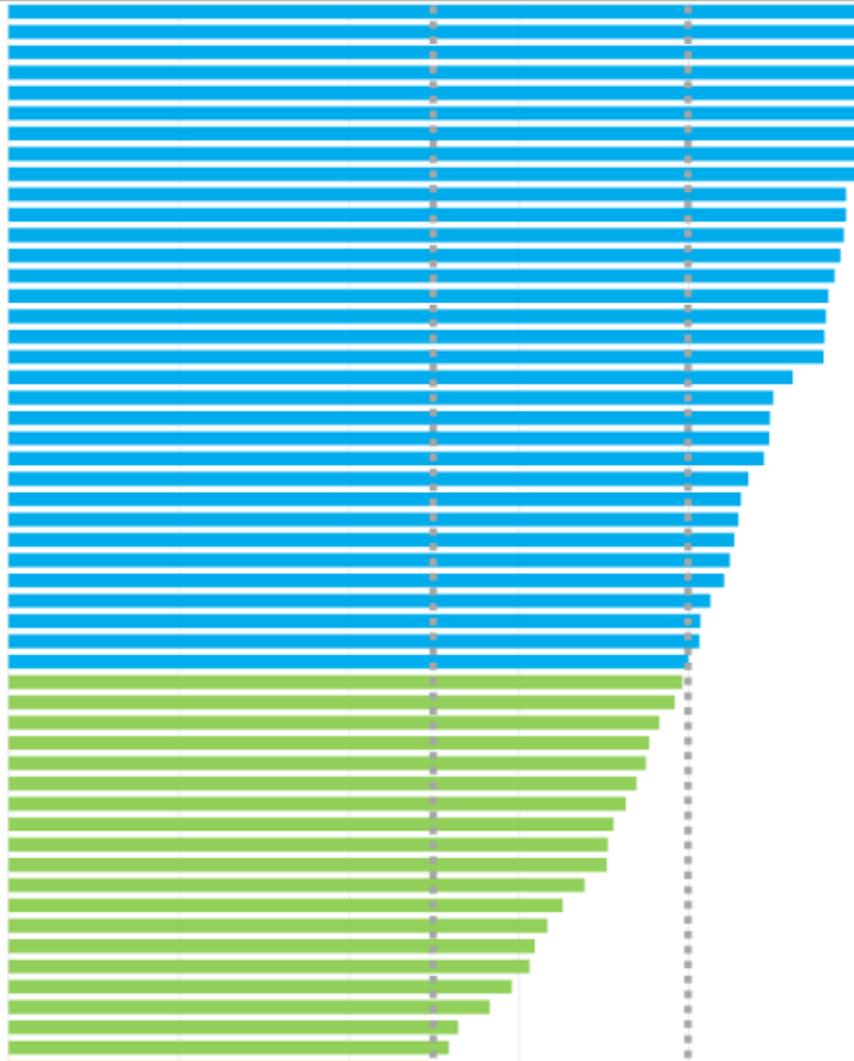
Clinical utility of ECAP dosing in a real-world population delivered via EVOKE therapy: the ECAP study

Jason E Pope,¹ Gregory L Smith ², Johnathan A Goree ², Nagy A Mekhail ³, Robert M Levy,⁴ Timothy R Deer ⁵, Chau M Vu,¹ Jarna Shah,² Shrif J Costandi ³, Steven M Rosen,⁶ Todd A Bromberg,⁶ Atish Patel,⁶ Dawood Sayed,⁷ Christopher M Lam ⁷, Usman Latif,⁷ Shivanand P Lad,⁸ Jessica B Jameson,⁹ Aaron K Calodney,¹⁰ Steven M Falowski,¹¹ Jack Smith,¹¹ Salim M Hayek ¹², Maged Guirguis,¹³ Ronald B Boeding,¹⁴ Jonathan M Hagedorn ¹⁵, Michael Sprintz,¹⁶ Ajay Antony,¹⁷ Denis Patterson,¹⁸ Robert D Heros,¹⁹ Andras Laufer,²⁰ Julie G Pilitsis,²¹ Nathan Miller,²² David Rosenfeld,²³ Jordan L Tate,²⁴ Ahmed M Raslan,²⁵ Jan Willem Kallewaard ^{26,27}, Angela Leitner,²⁸ Erin Hanson,²⁸ Nicole Soliday,²⁸ Rui V Duarte ^{28,29,30}, Erika A Petersen³¹

Individual patients

CL-SCS (n=67)

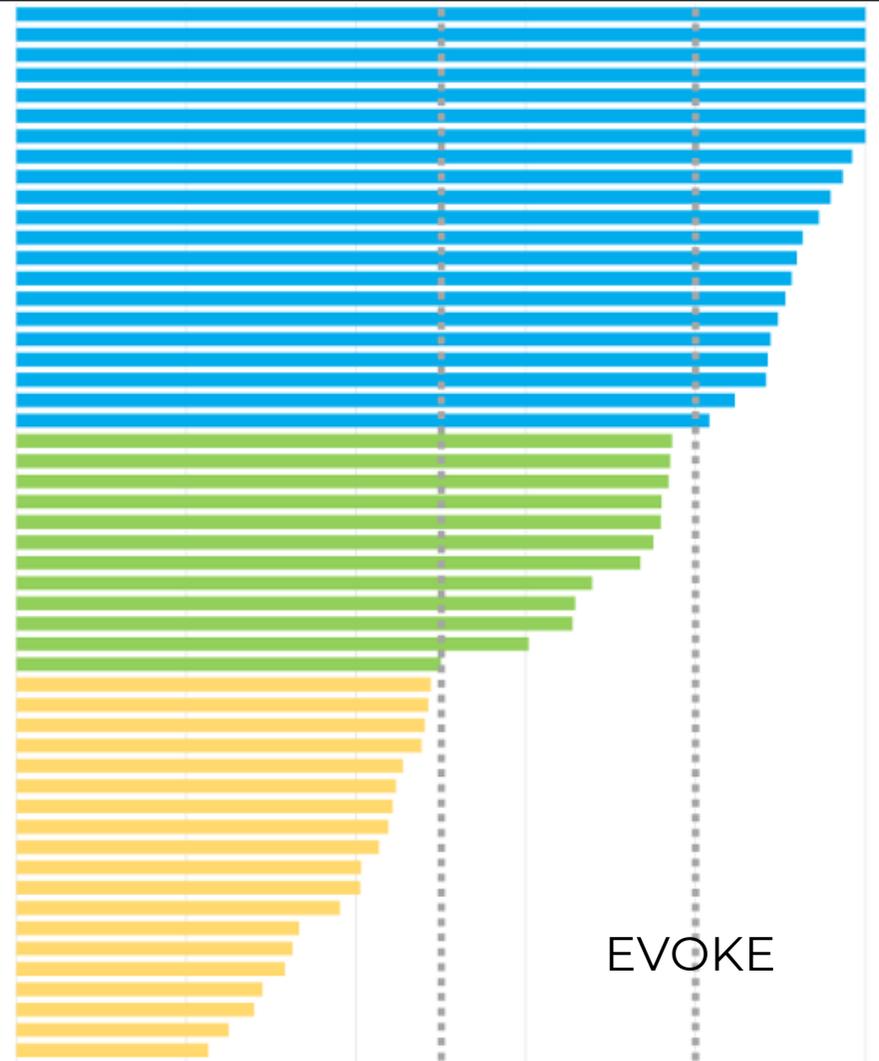
- >0 to <50% improvement (22.4%)
- High responders ($\geq 80\%$ improvement) (49.3%)
- Responders ($\geq 50\%$ improvement) (77.6%)



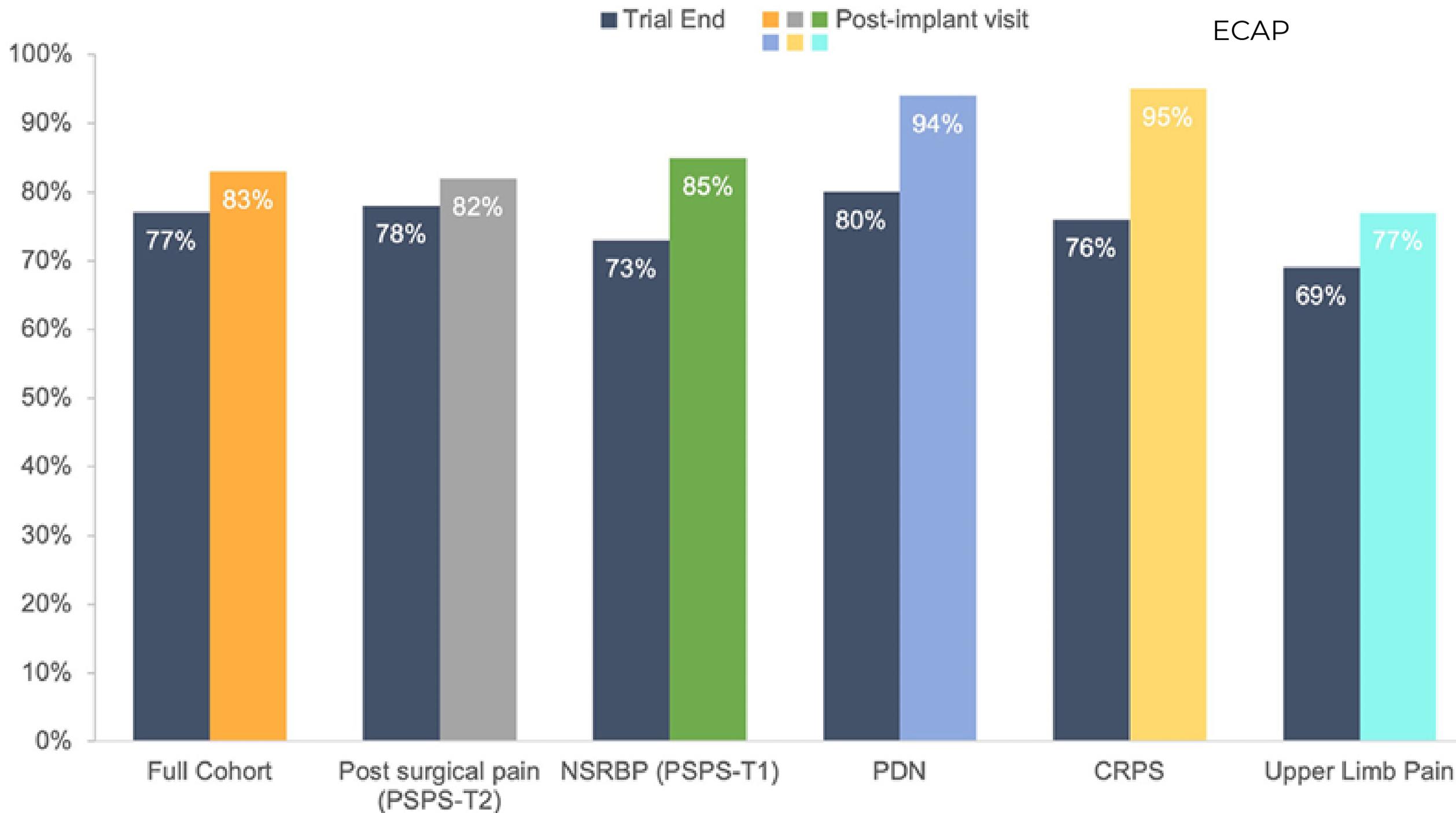
Individual patients

OL-SCS (n=67)

- >0 to <50% improvement (40.3%)
- High responders ($\geq 80\%$ improvement) (31.3%)
- No improvement (10.4%)
- Responders ($\geq 50\%$ improvement) (49.3%)



EVOKE



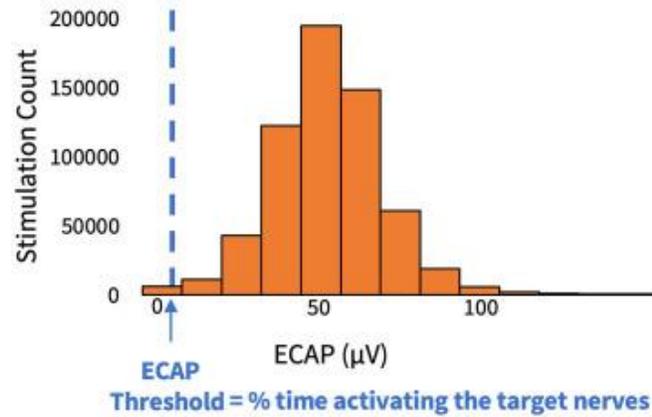
PREDICTIVE & ANATOMIC



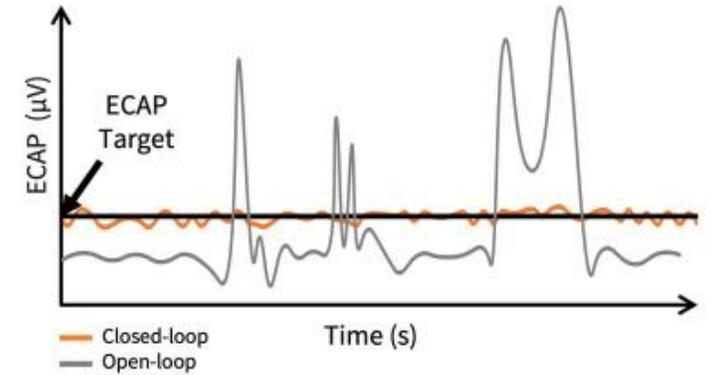
Maximal Analgesic Effect Attained by the Use of Objective Neurophysiological Measurements With Closed-Loop Spinal Cord Stimulation

Robert M. Levy, MD, PhD¹; Nagy A. Mekhail, MD, PhD²; Leonardo Kapural, MD, PhD³; Christopher A. Gilmore, MD³; Erika A. Petersen, MD⁴; Johnathan H. Goree, MD⁵; Jason E. Pope, MD⁶; Shrif J. Costandi, MD²; Jan Willem Kallewaard, PhD^{7,8}; Simon Thomson, MBBS⁹; Christopher Gilligan, MD¹⁰; Tariq AlFarra, DO¹¹; Mustafa Y. Broachwala, DO¹²; Harman Chopra, MD¹²; Corey W. Hunter, MD¹³; Steven M. Rosen, MD¹⁴; Kasra Amirdelfan, MD¹⁵; Steven M. Falowski, MD¹⁶; Sean Li, MD¹⁷; James Scowcroft, MD¹⁸; Shivanand P. Lad, MD, PhD¹⁹; Dawood Sayed, MD²⁰; Ajay Antony, MD²¹; Timothy R. Deer, MD²²; Salim M. Hayek, MD, PhD²³; Maged N. Guirguis, MD²⁴; Ronald B. Boeding, MD²⁵; Aaron K. Calodney, MD²⁶; Brian Bruel, MD²⁷; Patrick Buchanan, MD²⁸; Nicole Soliday, MPH²⁹; Rui V. Duarte, PhD^{29,30} ; Angela Leitner, MS²⁹; Peter S. Staats, MD¹⁷

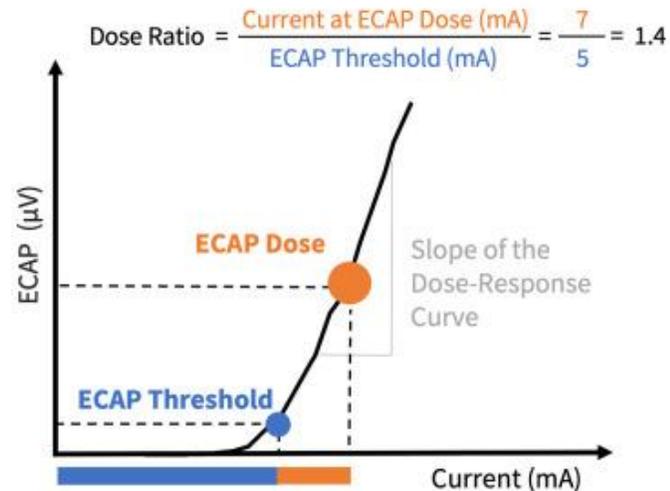
A Percent Time Above ECAP Threshold



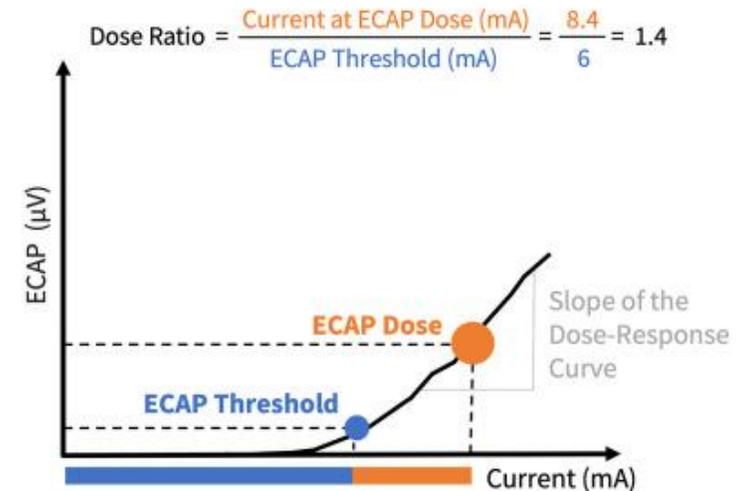
B Dose Accuracy



C1 Dose Ratio – Patient 1



C2 Dose Ratio – Patient 2



Clinical utility of ECAP dosing in a real-world population delivered via EVOKE therapy: the ECAP study

Jason E Pope,¹ Gregory L Smith,² Johnathan A Goree,² Nagy A Mekhail,³ Robert M Levy,⁴ Timothy R Deer,⁵ Chau M Vu,¹ Jarna Shah,⁶ Shirif J Costandi,³ Steven M Rosen,⁶ Todd A Bromberg,⁶ Atish Patel,⁶ Dawood Sayed,⁷ Christopher M Lam,⁸ Usman Latif,⁷ Shivanand P Lad,⁹ Jessica B Jameson,⁹ Aaron K Calodney,¹⁰ Steven M Falowski,¹¹ Jack Smith,¹¹ Salim M Hayek,¹² Maged Guirguis,¹³ Ronald B Boeding,¹⁴ Jonathan M Hagedorn,¹⁵ Michael Sprintz,¹⁶ Ajay Antony,¹⁷ Denis Patterson,¹⁸ Robert D Heros,¹⁹ Andras Laufer,²⁰ Julie G Piliitsis,²¹ Nathan Miller,²² David Rosenfeld,²³ Jordan L Tate,²⁴ Ahmed M Raslan,²⁵ Jan Willem Kallewaard,^{26,27} Angela Leitner,²⁸ Erin Hanson,²⁸ Nicole Soliday,²⁸ Rui V Duarte,^{28,29,30} Erika A Petersen³¹

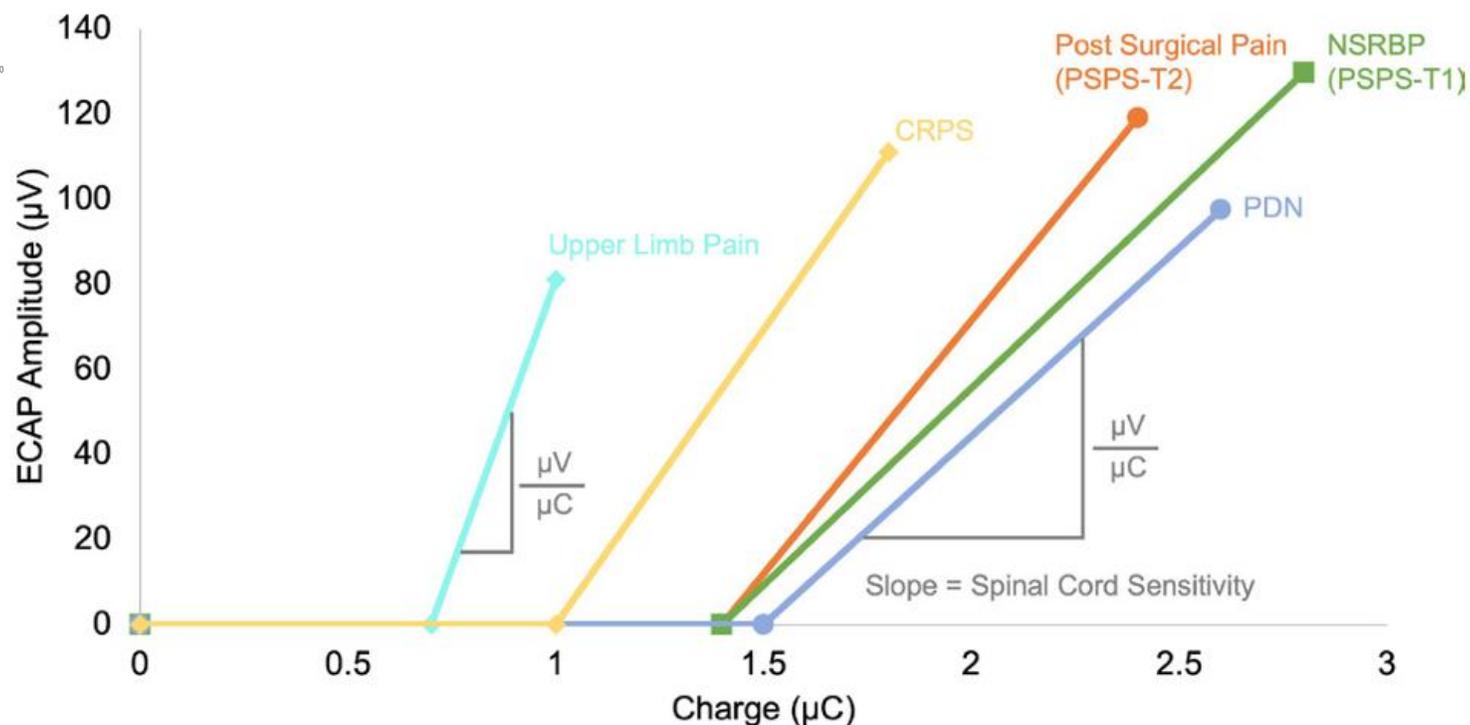
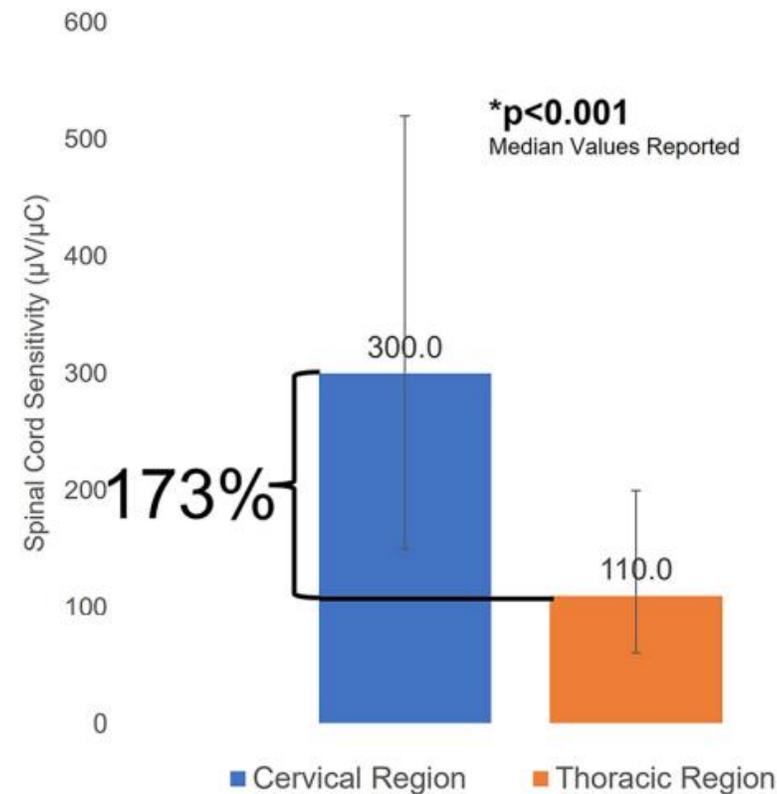
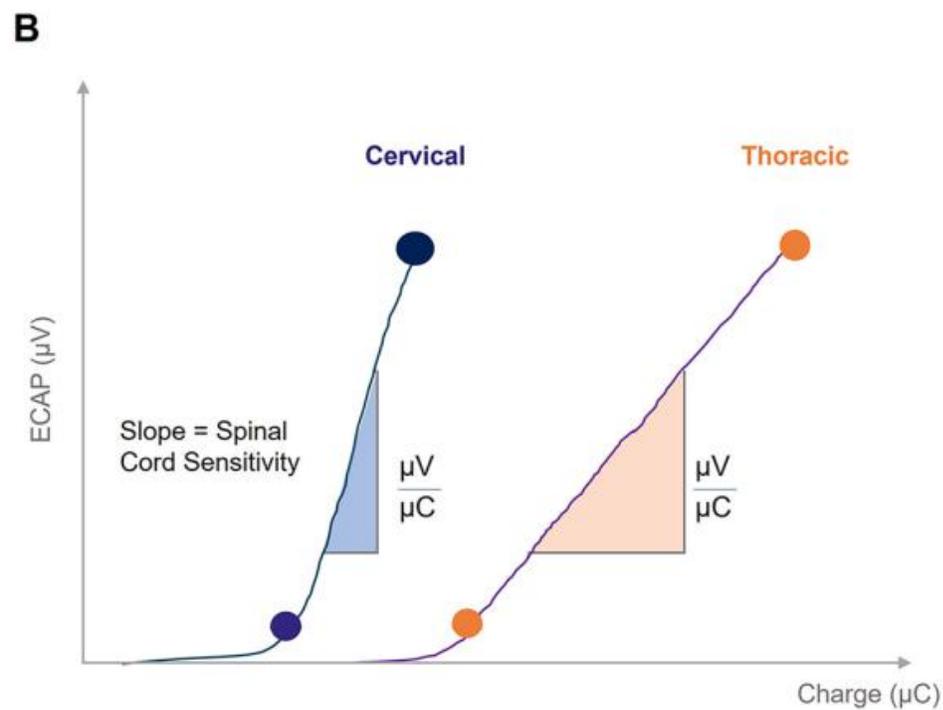


Figure 4 Sensitivity of the spinal cord to stimulation (dose sensitivity) for the different subgroups evaluated. CRPS, complex regional pain syndrome; ECAP, evoked-compound action potential; NSRBP, non-surgical refractory back pain; PDN, painful diabetic neuropathy; PSPS-T1, persistent spinal pain syndrome type 1; PSPS-T2, persistent spinal pain syndrome type 2.

First Objective Evidence Characterizing Differences in Cervical and Thoracic Spinal Cord Neurophysiology Using ECAP-Controlled Closed-Loop Technology

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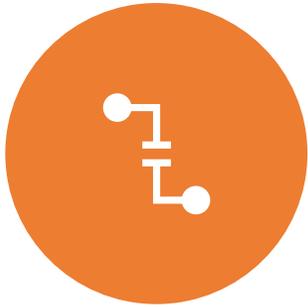
ONE SIZE
DOESN'T FIT ALL





WHAT'S COMING?

FUTURE STUDIES



INTERMITTENT CLOSED
LOOP STIMULATION WITH
DTM?



ARTIFICIAL INTELLIGENCE,
CLOSED LOOP, AND
PREDICTIVE MODELS



REMOTE MONITORING



ULTRA LOW FREQUENCY
NEUROMODULATION.

Spinal neuromodulation using ultra low frequency waveform inhibits sensory signaling to the thalamus and preferentially reduces aberrant firing of thalamic neurons in a model of neuropathic pain

Martyn G. Jones^{1,2*}, Liam A. Matthews^{3,4}, Scott Lempka^{3,4,5},
Nishant Verma⁶, James P. Harris⁶ ⁶ and Stephen B. McMahon^{1†}

WHAT WILL THE NEXT 5 YEARS LOOK LIKE?

- Closed Loop Stimulation
- Predictive Stimulation
- Artificial Intelligence
- Patient Based Paradigms
- Potential Ability to Selectively Modulate Sensory Nerves



THANK YOU.

Johnathan H Goree MD

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