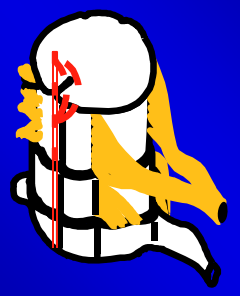

The history of research on the mechanisms, efficacy, and safety of spinal cord stimulation

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President
Neuromodulation Foundation, Inc.

Professor of Neurosurgery, Anesthesiology and
Critical Care Medicine (ret.)
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Disclosures

Richard B. North, MD

Support to nonprofit Neuromodulation Foundation, Inc. (unpaid officer), 2007 – present

Research support to Johns Hopkins University and Sinai Hospital (former employers, 1974-2013)

- Abbott
- Boston Scientific
- Medtronic
- Nevro
- Nuvectra

Consulting/royalty/equity

- Algostim/Nuvectra
- Stimwave (spouse)

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Former Chief of Neurosurgical Service
Massachusetts General Hospital
Professor of Surgery, Emeritus
Harvard Medical School

and

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Chief of Neurosurgical Service
Massachusetts General Hospital
Professor of Surgery
Harvard Medical School

PAIN AND THE NEUROSURGEON

A Forty-Year Experience

BASED ON A SERIES OF OVER 1700 PATIENTS AND ON THE AUTHOR'S STUDY OF THE WORLD LITERATURE AIDED BY THEIR OWN EXPERIENCE, THIS VOLUME IS AN EVALUATION OF NEUROSURGICAL PROCEDURES FOR THE RELIEF OF OTHERWISE INTRACTABLE PAIN.

CHARLES C THOMAS • PUBLISHER
Springfield • Illinois

With Assistance in the Psychiatric Section of Chapter XVII from

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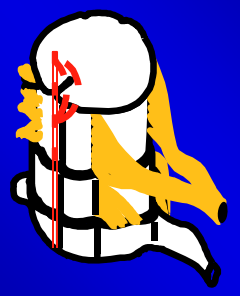
White & Sweet, 1969



The history of research on the mechanisms, efficacy, and safety of spinal cord stimulation

Mechanisms and rationale

(onlinelibrary.wiley.com) DOI: 10.1111/j.1525-1403.2012.00484.x

FROM THE EDITOR-IN-CHIEF

The Need for Mechanism-Based Medicine in Neuromodulation

"How are we to know how to alter stimulation parameters, other than by trial and error, to optimize outcomes if we do not know where and how they act on neural tissues?"

Neuromodulation 2012; 15: 273–279

Merging evidence-based and mechanism-based medicine

The example elucidates several points. First, the questions of an intervention's effectiveness and its mechanism are closely linked: an intervention is always based on an idea or a model of how the symptoms of a disease present, and how an intervention might exert its effect. This model and its empirical basis might, however, become obscured over time. Second, an intervention can be effective, even though it is based on an erroneous assumption about its mechanism of action. Third, the effectiveness of an intervention can be assessed, without inquiring into its mechanism. Although such a study might produce important information, it does not improve knowledge of the underlying pathophysiological processes. Not having such knowledge might hinder development of novel and potentially more efficacious interventions in the long term. Fourth, efficacy and mechanistic issues can be addressed in one study, but the underlying model needs to be made explicit and additional data obtained to test it.

*Gert Jan van der Wilt, Gerhard A Zielhuis
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THE LANCET
Volume 372, Issue 9638, 16–22 August 2008, Pages 519-520

ORIGINAL CONTRIBUTION

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

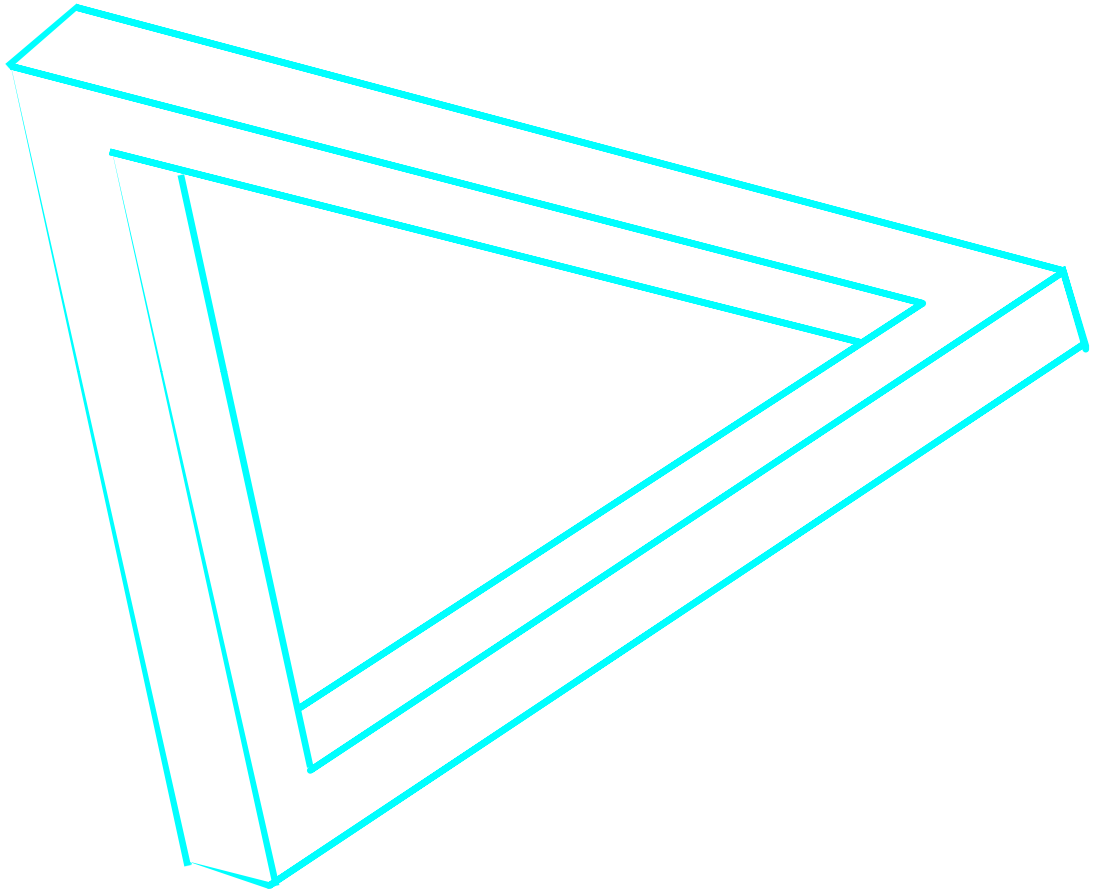
John P. A. Ioannidis, MD

Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these,

- 7 (16%) were contradicted by subsequent studies,
- 7 others (16%) had found effects that were stronger than those of subsequent studies,
- 20 (44%) were replicated, and
- 11 (24%) remained largely unchallenged.

JAMA. 2005;294:218-228.

Mechanisms



Methods

Results

“Gate theory"

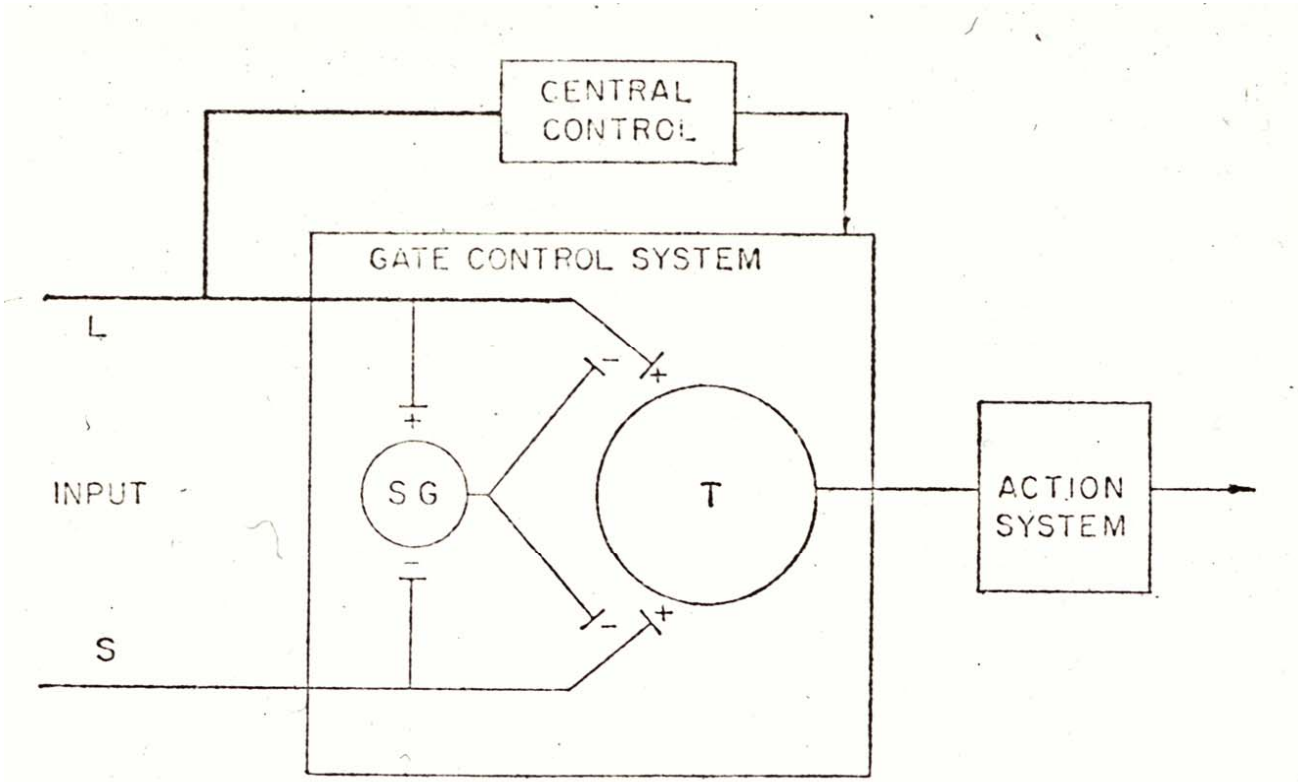


Fig. 4. Schematic diagram of the gate control theory of pain mechanisms: *L*, the large-diameter fibers; *S*, the small-diameter fibers. The fibers project to the substantia gelatinosa (*SG*) and first central transmission (*T*) cells. The inhibitory effect exerted by *SG* on the afferent fiber terminals is increased by activity in *L* fibers and decreased by activity in *S* fibers. The central control trigger is represented by a line running from the large-fiber system to the central control mechanisms; these mechanisms, in turn, project back to the gate control system. The T cells project to the entry cells of the action system. +, Excitation; —, inhibition (see text).

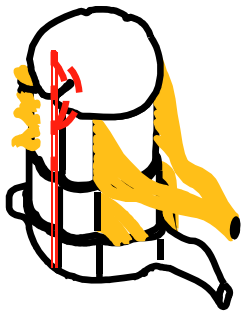
Melzack & Wall, Science 150:971-9,1965

“Gate theory"

"Gate" in dorsal horn governs central transmission of neural activity signaling pain

Opened by excess of small over large fiber activity in the peripheral nervous system.

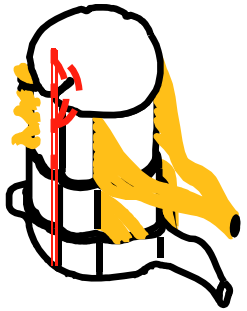
Closed by excess of large fiber activity



Selectivity of Electrical Stimulation

Large fibers have relatively low threshold for recruitment by externally applied electrical stimulation pulses

At the proper stimulation amplitude, they may be activated selectively, closing the "gate."



Temporary Abolition of Pain in Man

Abstract. *In eight patients with intense chronic cutaneous pain, sensory nerves or roots supplying the painful area were stimu millisecond puls second were ap was raised unti tingling in the a lation, pressure areas failed to tients, who had ripheral nerves, their pain for n after stimulation for 2 minutes.*

PATRICK D. WALL
Department of Biology and
Research Laboratory of Electronics,
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WILLIAM H. SWEET
Department of Neurosurgery,
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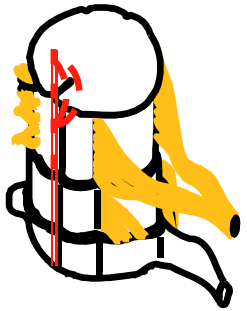
Wall & Sweet 1967

Peripheral Nerve Stimulation

Mixed sensory and motor fibers

Similar thresholds for large diameter sensory afferents and motor efferents [Law]

Uncomfortable motor effects at amplitudes near sensory threshold

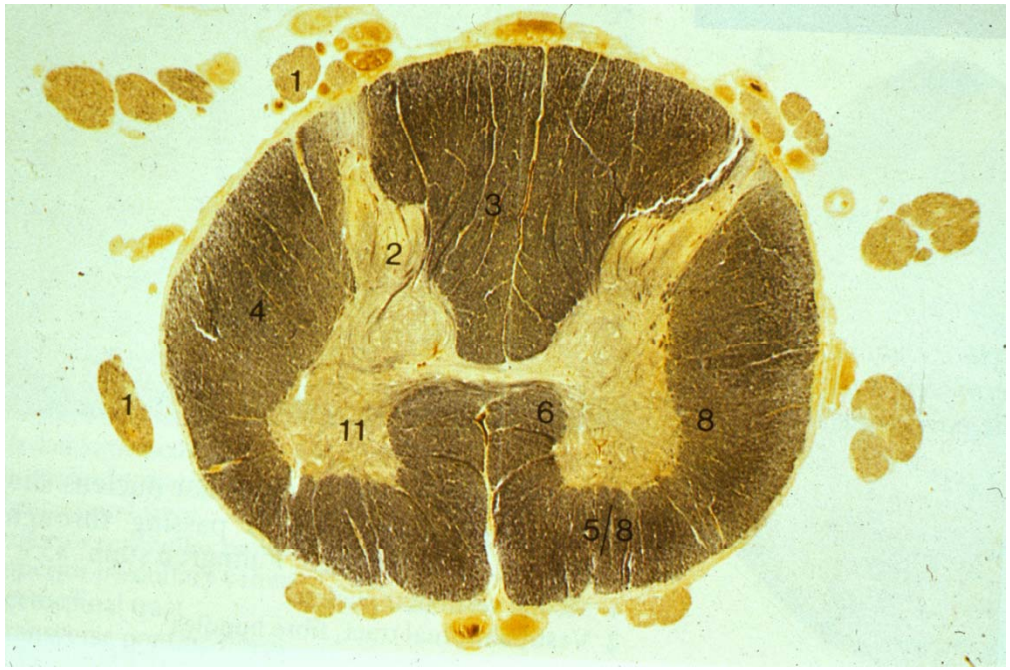


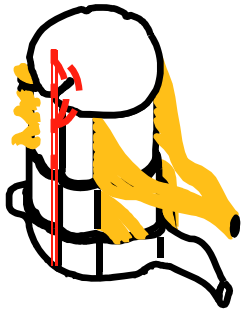
Dorsal Column Stimulation

Primary afferents, conveniently segregated from motor fibers

Antidromic activation

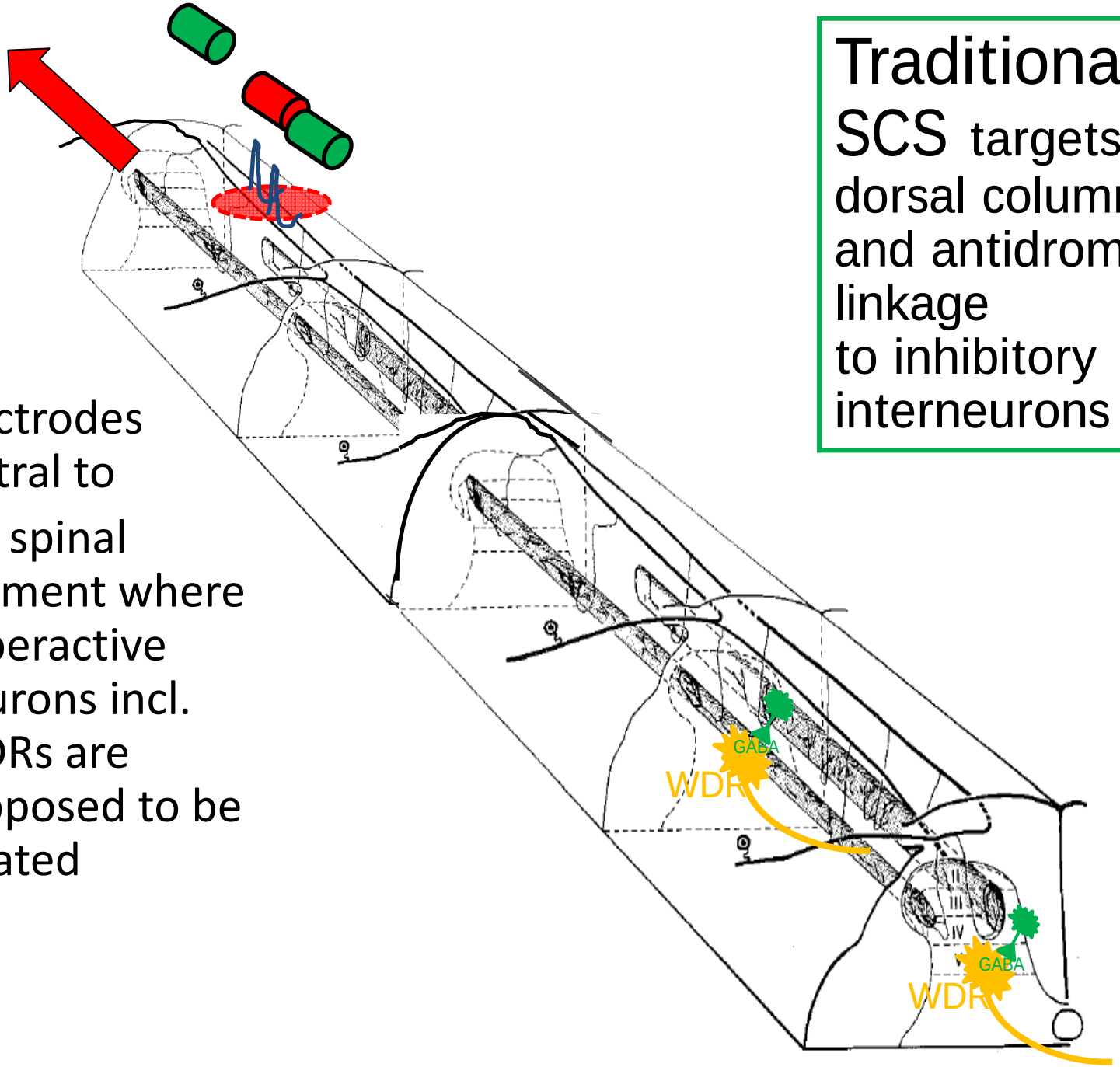
Collateral processes to dorsal horn provide access to "gate"





Traditional SCS targets dorsal columns and antidromic linkage to inhibitory interneurons

- Electrodes rostral to the spinal segment where hyperactive neurons incl. WDRs are supposed to be located



Courtesy of Bengt Linderoth Adapted from Brown 1981; and further from Bradley K. (personal comm Nov 2015)

50th anniversary!

electrical inhibition of pain: *experimental evaluation*

C. NORMAN SHEALY,* M.D.
NORMAN TASLITZ, Ph.D.
J. THOMAS MORTIMER, M.E.
DONALD P. BECKER, M.D.
Cleveland, Ohio†

RECENT neurophysiologic studies have raised the possibility of electrical inhibition of pain. Electronarcosis has been widely investigated[1-5] but no previous attempts are known of application of inhibiting currents to the spinal cord. Wall[6] demonstrated that activity in large peripheral sensory nerve fibers carrying nonpainful impulses inhibits in the spinal cord subsequent activity from the smallest fibers considered essential to pain conduction. Melzack and Wall[7] suggested using this knowledge to suppress pain. Mechanical surface activation of the nonpainful large fibers, such as rubbing or vibration, however, is not practical for prolonged use. Furthermore, it is probable that such stimuli must be applied to a wide area to block pain effectively from even a small focus.

Unfortunately, most "intractable" pain arises from diffusely involved structures. Thus it seems reasonable to concentrate on stimulation of the dorsal columns, where large fibers are compactly arranged, or of the anterolateral spinal cord where small fibers predominate.

Using the tegmental and medullary r
cording sites first described by Collins ar
Randt[3,4] (fig. 1) one finds a prolonged a
ter discharge (PSAD) upon electrical te
anic stimulation of a peripheral nerve abo
delta threshold. This response lasts fro
500 msec. to many seconds. It has prev
ously been demonstrated that most of th
after discharge is elicited by stimulation
C fibers, although a small early compone
comes from delta.[3,4]

When the whole nerve stimulus respon
is compared with isolated C stimulus r
sponse, however, the isolated C response
found to be of greater amplitude than th
response to whole nerve stimulation.[3] Ele
trical stimulation of skin through two sul
cutaneous needles at current intensity su
ficient to elicit pain in man (greater tha
40 volts) also elicits prolonged small fib
after discharge in cats. Similarly, PSA
can be evoked by pinching a paw with a h
mostat, by heat sufficient to produce tissu
damage, and by subcutaneous injection
noxious substances. Nonpainful mechanic
stimuli such as hair movement, deep rubbi

*A preliminary report of Dr. Shealy's first successful clinical application of this technic will appear
the July-August 1967 issue of *Anesthesia and Analgesia—Current Researches*.—Ed.

†Division of Neurosurgery and Department of Anatomy, Western Reserve University School of Medic
and University Hospitals, Cleveland, Ohio. Dr. Shealy's present address: Gundersen Clinic, Ltd.,
Grosse, Wisconsin.

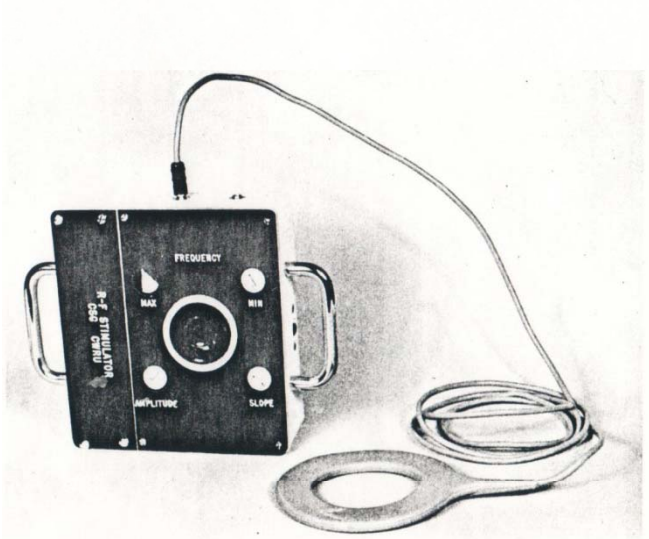


Figure D14. Variable frequency transmitter-stimulator used on patient R. W.

Shealy March 24, 1967

Mortimer 1968 PhD thesis

Brain (1976), **99**, 123–158

THE GATE-CONTROL THEORY OF PAIN

A CRITICAL REVIEW

by P. W. NATHAN[1]

(*From The National Hospital for Nervous Diseases, Queen Square, London WC1N 3BG*)

J. psychiat. Res., 1971, Vol. 8, pp. 273–287. Pergamon Press. Printed in Great Britain.

IS PAIN A SPECIFIC SENSATION?

EDWARD R. PERL*

Department of Physiology, University of Utah College of Medicine, Salt Lake City, Utah

PAIN became classified as a sensory quality relatively late in the evolution of ideas on sensation and consciousness. Prior to the Nineteenth Century most authorities had followed Aristotle's view in setting pain opposite to pleasure and assigning it to the realm of emotion. Under impetus of the analyses that followed BELL'S (1811)[1] and MAGENDIE'S (1822)[2] separation of peripheral sensory and motor pathways in the spinal roots, concepts of nervous organization and function clarified. In company with the increasing dominance of experimentally dictated views of the nervous system, pain came to be more commonly thought of in terms of a sensory phenomenon; however, the specificity of neural mechanisms leading to it has been continually doubted.

As a first step in deciding whether or not pain has the characteristics associated with a specific sensation, it is necessary to set down attributes that might be accepted for this category. Some possible semantic problems may be avoided by starting from an unambiguous model. Vision begins with the excitation of structures in the eye, a particular and unique sense organ. Under ordinary conditions the receptive tissue of the eye has a responsiveness limited to a clearly definable set of environmental events. The receptive elements of the retina, in turn, excite a chain of nerve cells that transmit signals related to incoming light to regions of the forebrain. Consequently, a neural sequence from the receptive structure to neurons of the thalamus and cortex are dedicated to the relaying and analysis of information contained in the light reaching the eyes of the organism. Generalizing from this example, a specific sensation has a kind of receptive apparatus (receptor) that is particularly responsive to a limited class of events. Activity generated by specialized receptors then engages a series of neurons forming a projecting system (to higher centers) devoted to the signals initiated by the effective stimuli. Current opinion would agree that the 'special senses' (vision, hearing, smell and taste) are associated with mechanisms fitting this generalization. On the other hand, the situation for somatic sensibility, particularly pain, is less clear.

As the Twentieth Century began, the physiologists and their allies in this cause, the clinical neurologists, apparently had won the argument with the philosophically-oriented over the nature of pain, and it was widely accepted as a sensory experience rather than the emotional reaction opposite to pleasure. At that time there were two viewpoints on the

BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 88, Number 6, June 2002

Editorial I

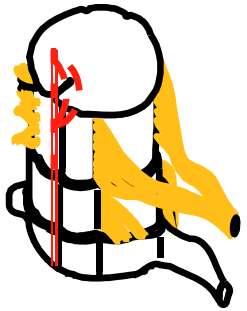
Gate Control Theory of pain stands the test of time

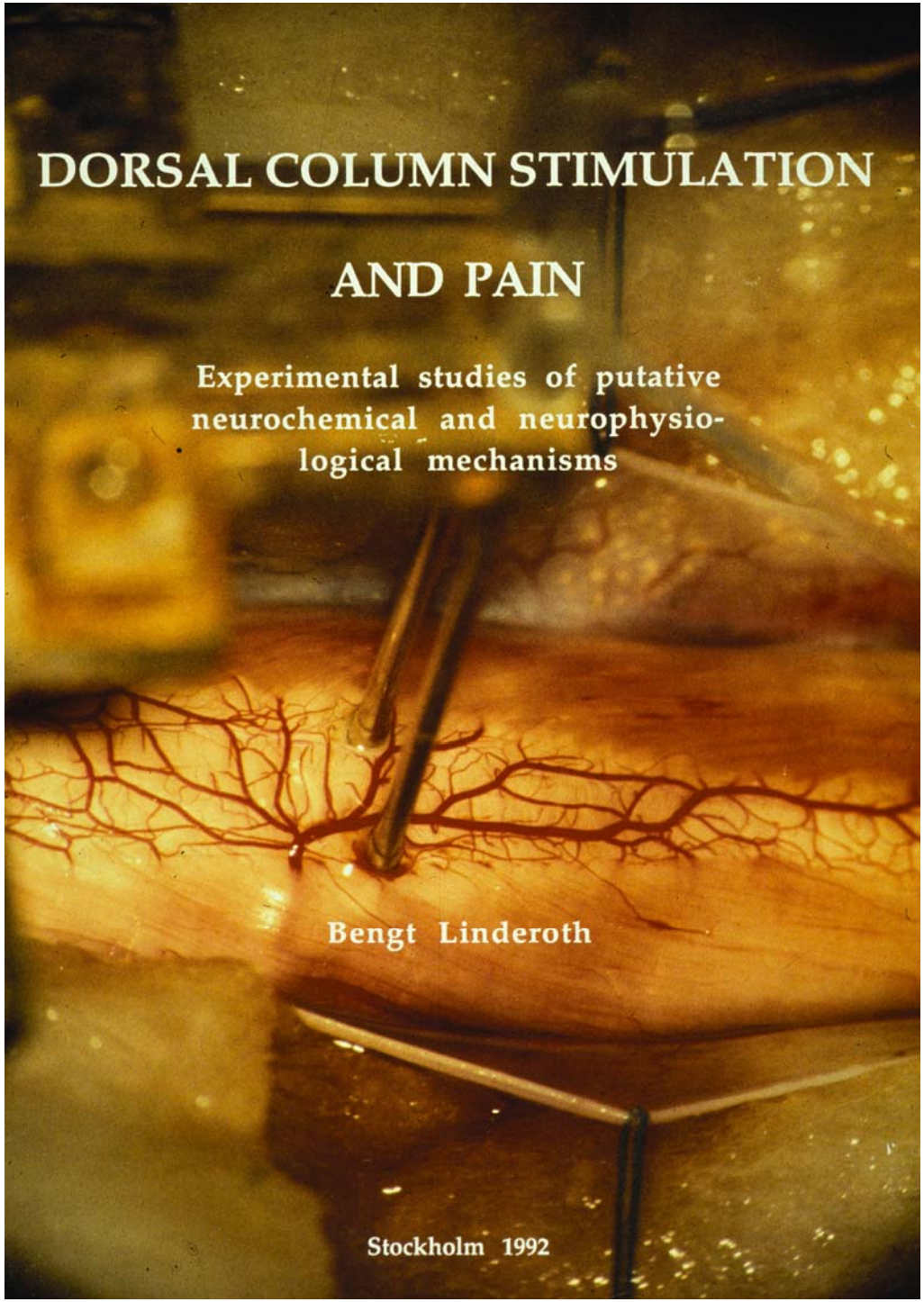
A. H. Dickenson
Department of Pharmacology
University College
London
WC1E 6BT
UK

"Dorsal Column" Stimulation

Topographically accurate
Physiologically confirmed
but
Physiologically simplistic, as other structures are affected; therefore

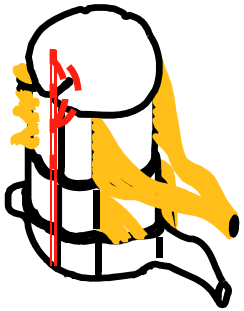
"Spinal cord stimulation" preferred



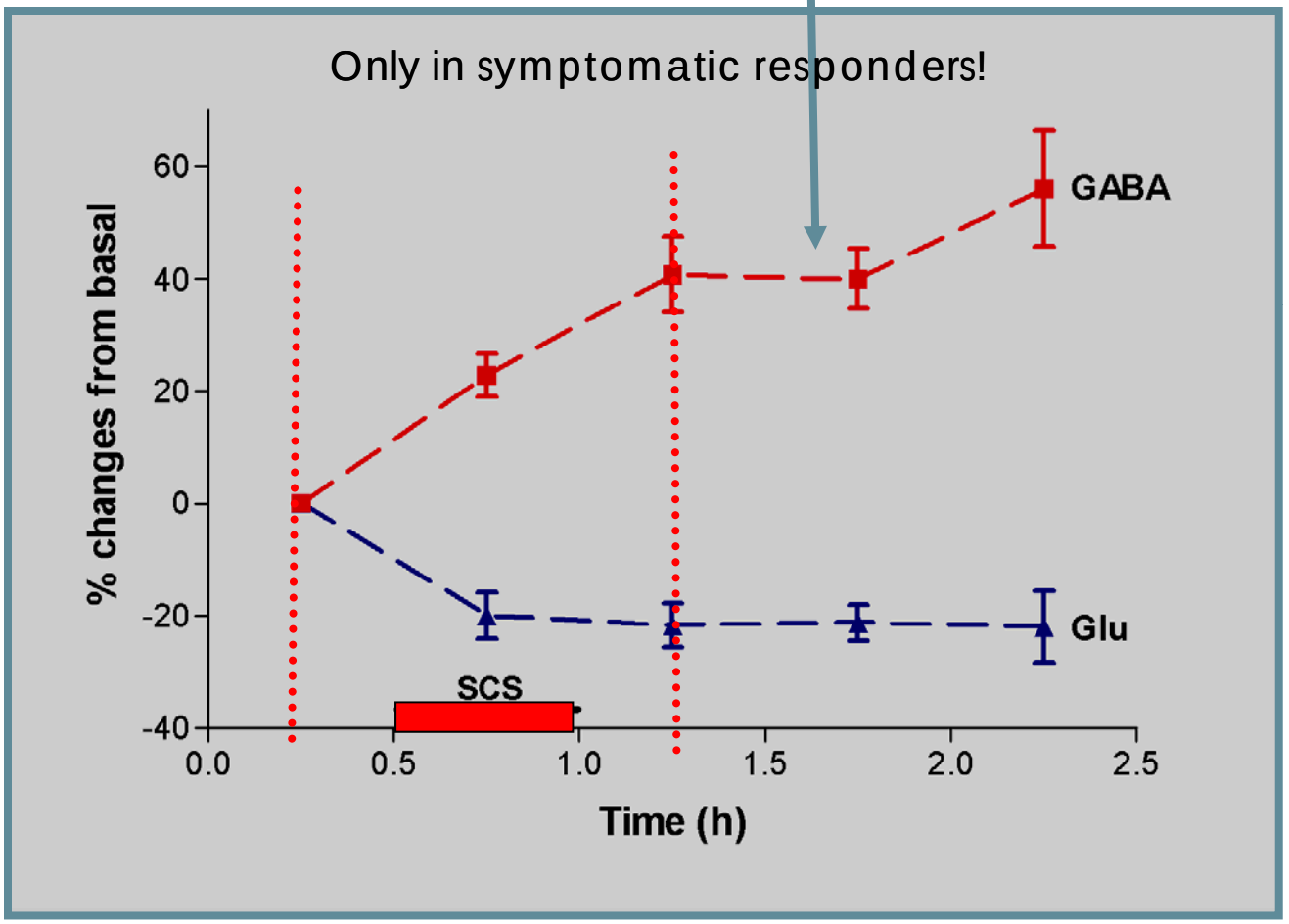

DORSAL COLUMN STIMULATION
AND PAIN
Experimental studies of putative neurochemical and neurophysiological mechanisms
Bengt Linderoth
Stockholm 1992

Animal models

Scaling electrodes and stimulation parameters problematic
Chronic pain model problematic
Neuropathic pain (sciatic n. ligature)
    Hyperactive flexion withdrawal reflex attenuated by SCS [Meyerson][Simpson]



EFFECTS OF SCS



If the GABA-B receptor is blocked, the reduction of GLU is abolished

Courtesy of Bengt Linderoth

From Cui et al 1996;1997; Stiller et al 1996

Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pain 12 (2008) 132–136
www.EuropeanJournalPain.com

Clinical Note

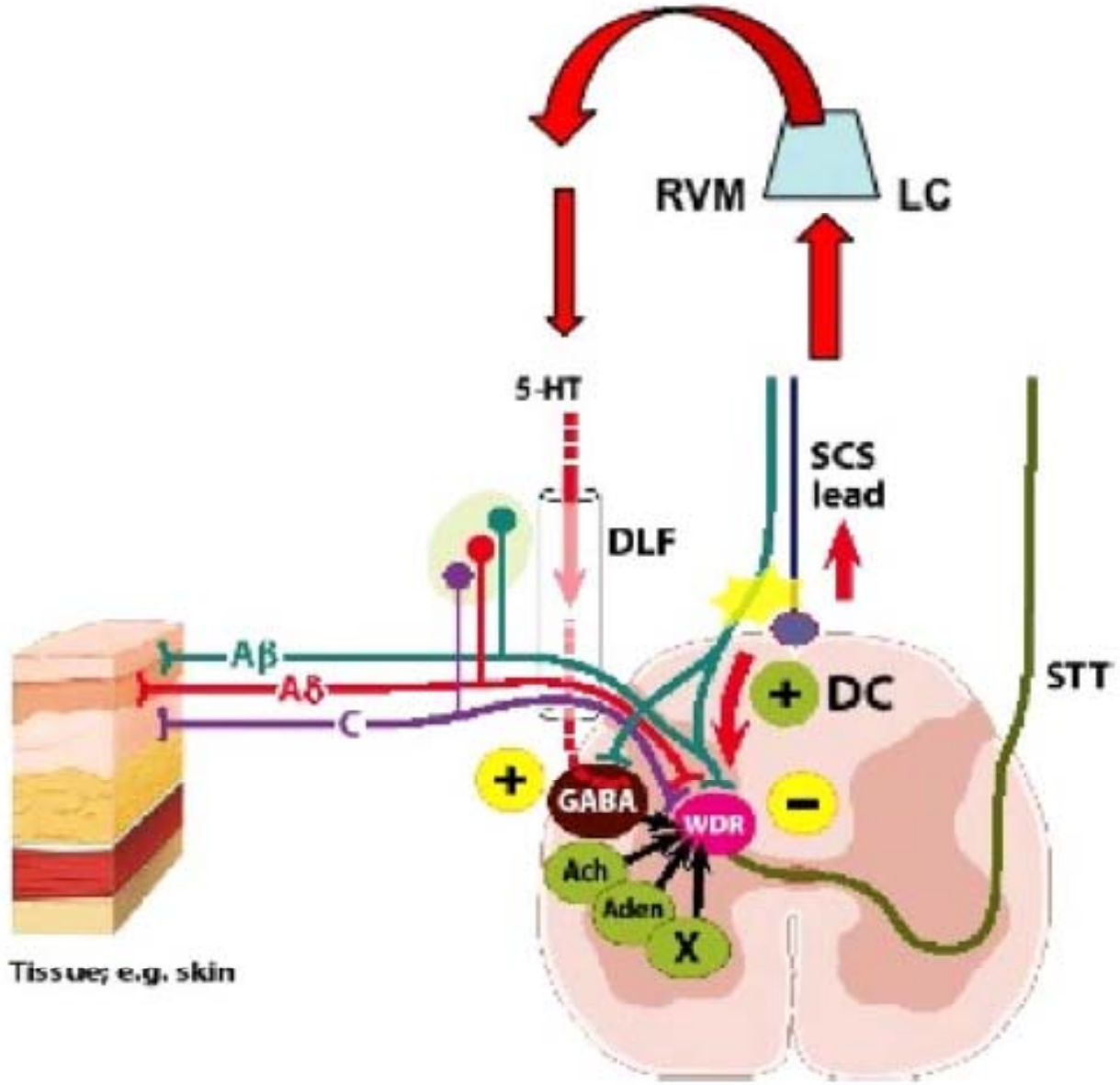
Baclofen-enhanced spinal cord stimulation and intrathecal baclofen alone for neuropathic pain: Long-term outcome of a pilot study

Göran Lind *, Gastón Schechtmann, Jaleh Winter, Björn A. Meyerson, Bengt Linderoth

Department of Neurosurgery, Karolinska University Hospital, SE-171 76 Stockholm, Sweden

Received 31 August 2006; received in revised form 8 March 2007; accepted 10 March 2007
Available online 1 May 2007

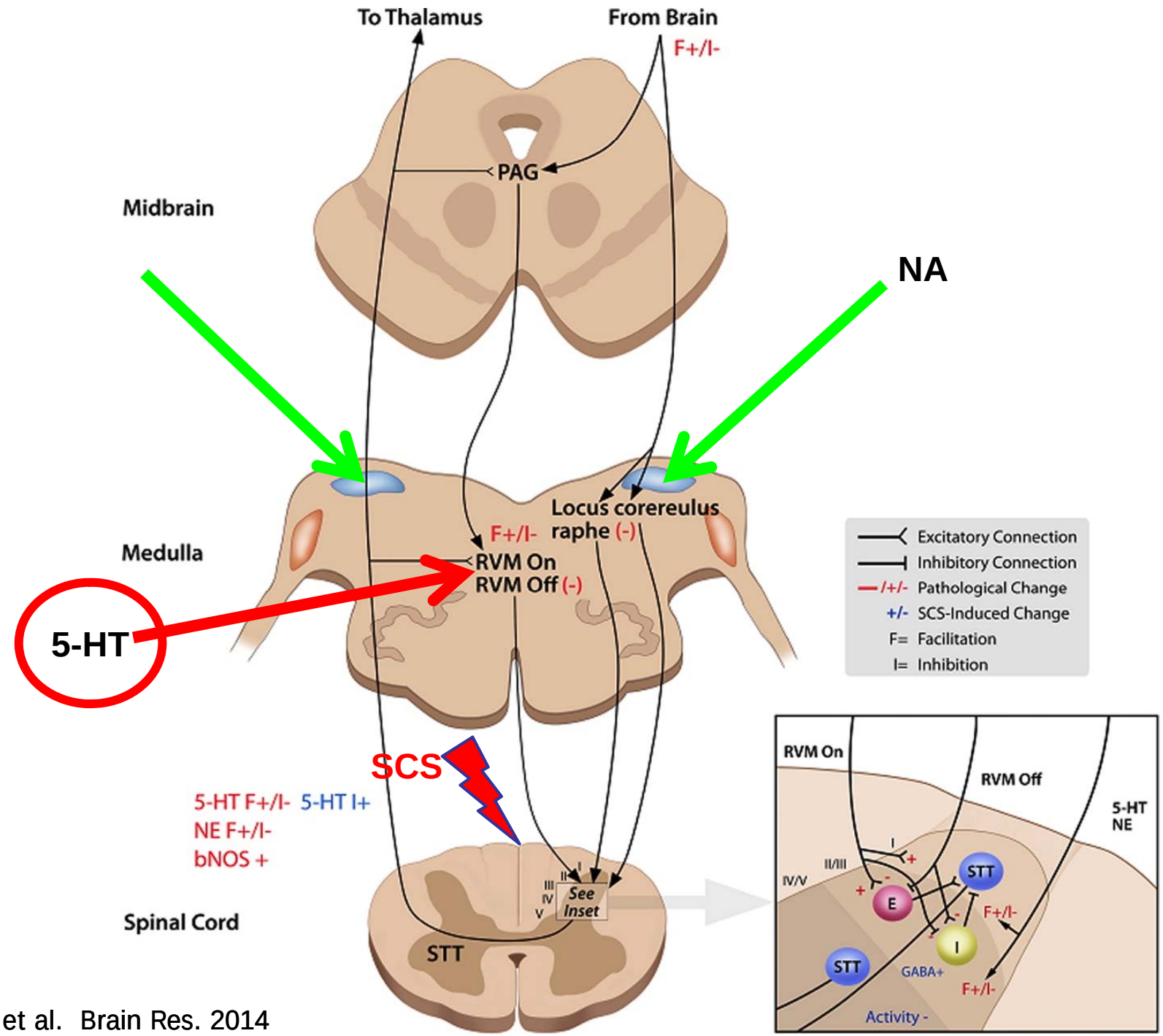
"A deficient SCS effect in neuropathic pain may be considerably improved by intrathecal baclofen"
Average followup 67 months
n = 7



(adapted from Linderoth and Meyerson, Anesthesiology 2010 (38)).

Rostral orthodromic

Segmental and antidromic



From Zhang TC. et al. Brain Res. 2014

DOI: 10.3171/2012.7.SPINE11642

Spinal cord stimulation paresthesia and activity of primary afferents

Case report

Richard B. North, M.D.,[1,2] Karen Streelman, M.S.H.S., P.A.-C.,[1] Lance Rowland, B.S., C.N.I.M.,[1] and P. Jay Foreman, M.D., Ph.D.[1]

[1]Sandra and Malcolm Berman Brain & Spine Institute, and [2]Johns Hopkins University School of Medicine, Baltimore, Maryland

A patient with failed back surgery syndrome reported paresthesia in his hands and arms during a spinal cord stimulation (SCS) screening trial with a low thoracic electrode. The patient's severe thoracic stenosis necessitated general anesthesia for simultaneous decompressive laminectomy and SCS implantation for chronic use. Use of general anesthesia gave the authors the opportunity to characterize the patient's unusual distribution of paresthesia. During SCS implantation, they recorded SCS-evoked antidromic potentials at physiologically relevant amplitudes in the legs to guide electrode placement and in the arms as controls. Stimulation of the dorsal columns at T-8 evoked potentials in the legs (common peroneal nerves) and at similar thresholds, consistent with the sensation of paresthesia in the arms, in the right ulnar nerve. The authors' electrophysiological observations support observations by neuroanatomical specialists that primary afferents can descend several (in this case, at least 8) vertebral segments in the spinal cord before synapsing or ascending. This report thus confirms a physiological basis for unusual paresthesia distribution associated with thoracic SCS.
(http://thejns.org/doi/abs/10.3171/2012.7.SPINE11642)

Properties of afferent nerve impulses originating from a neuroma

Patrick D. Wall

Department of Anatomy, University College, London WC1E 6BT
Department of Zoology, Hebrew University, Jerusalem

Michael Gutnick

Department of Zoology, Hebrew University, Jerusalem, Israel

Damaged nerves attempt to regenerate. The nerve membrane changes its properties, becomes spontaneously active and may be the source of pain. These impulse generators have unusual properties. They become silent after high frequency activity. This silence may partially explain the effect of counterstimulation as a pain therapy.

Nature Vol. 248 April 26 1974

What is "Stimulation"?

Depolarization, action potential propagation
- Primarily cathodal effect

Hyperpolarization
- Primarily anodal effect
- "Anodal break" causing depolarization
  - At high amplitudes and longer pulse widths (over 400 microseconds)

Brain Research, 98 (1975) 417–440

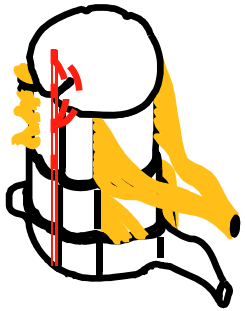
Review Article

WHICH ELEMENTS ARE EXCITED IN ELECTRICAL STIMULATION OF MAMMALIAN CENTRAL NERVOUS SYSTEM: A REVIEW

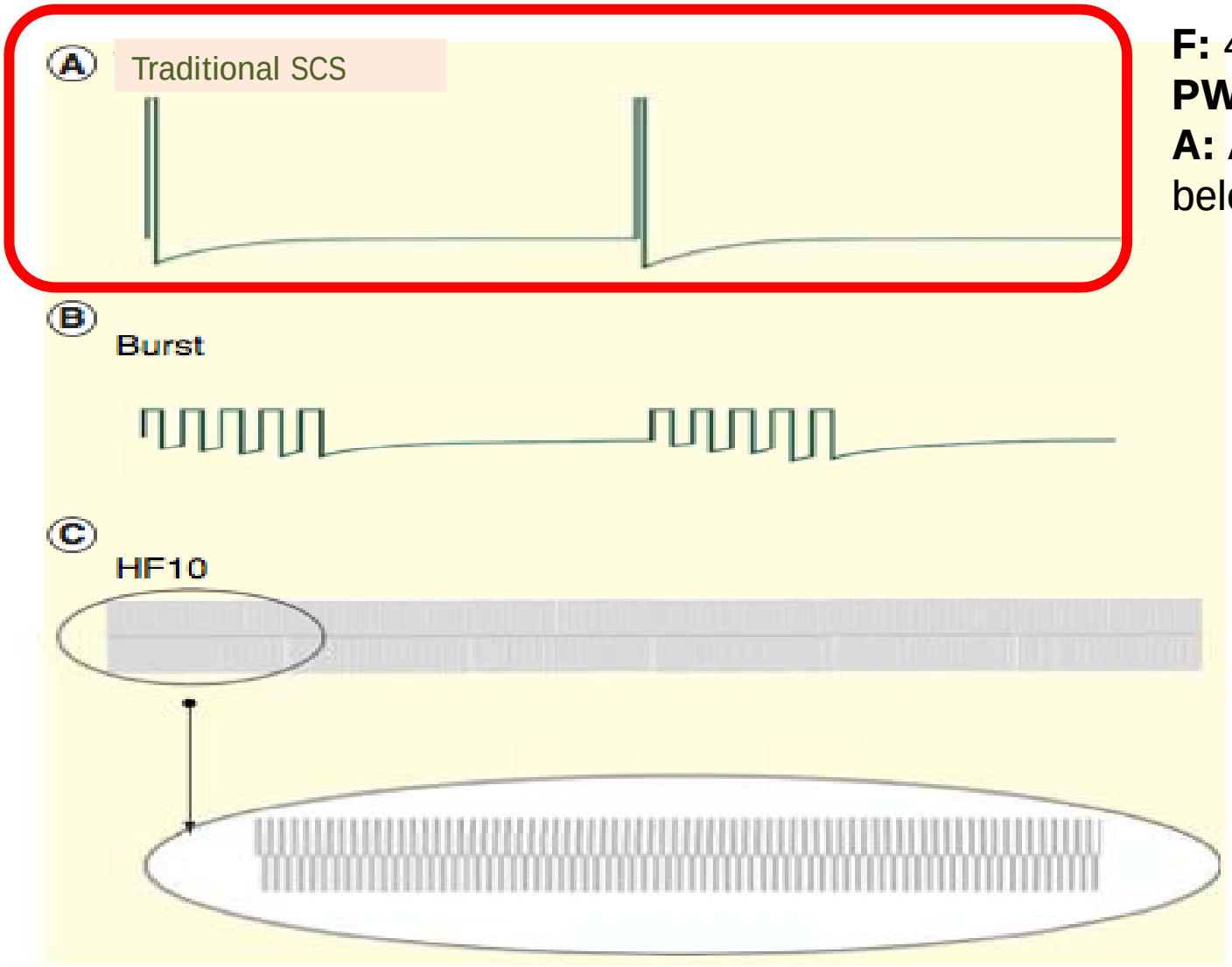
JAMES B. RANCK, Jr.*

Department of Physiology, University of Michigan, Ann Arbor, Mich. 48104 (U.S.A.)

(Accepted May 23rd, 1975)



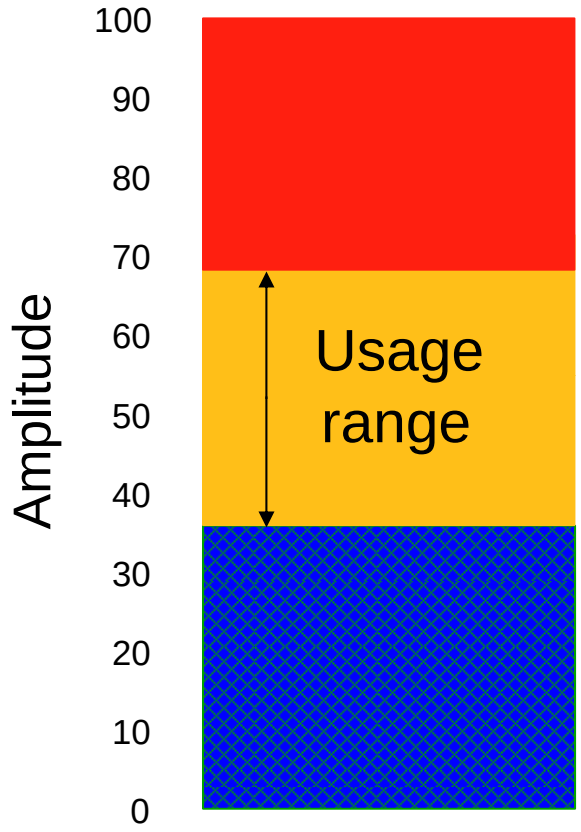
Traditional (tonic, paresthesia based) SCS



F: 40-80 Hz
PW: 200-450 microsec
A: Above perceptual, below motor threshold

From Pope, Falowski & Deer 2015

Paresthesia-based stimulation: Dosing



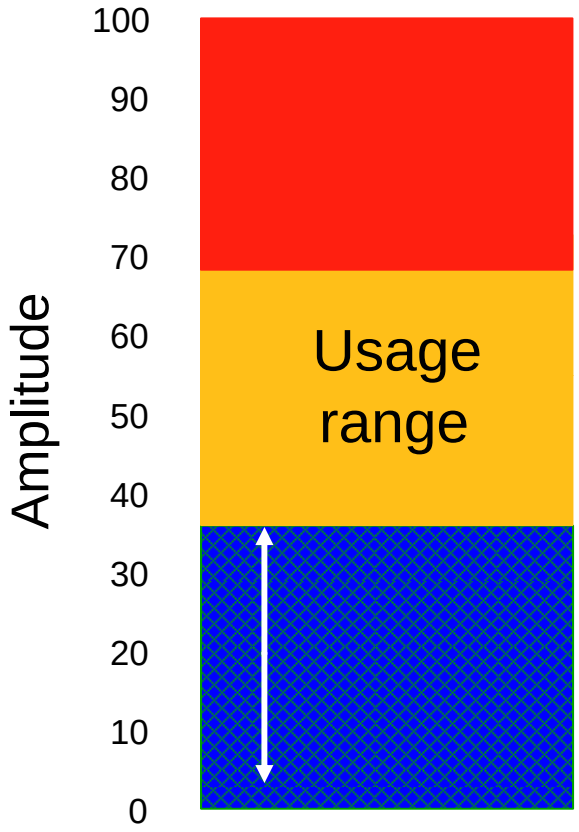
Discomfort (or motor) threshold

Perceptual (paresthesia) threshold

Pulse parameters (amplitude, width, rate) scaled to usable or tolerable range eliciting paresthesia

[Law 1982]

Paresthesia-free stimulation

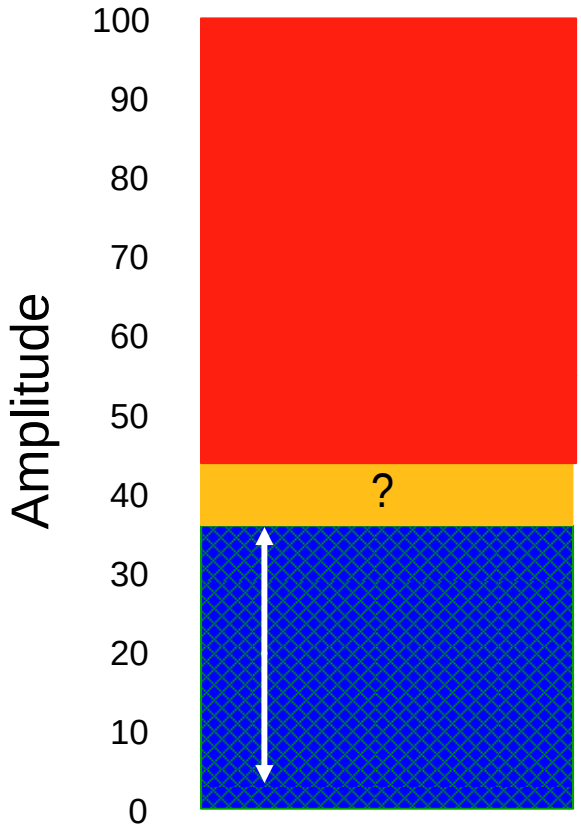


Discomfort (or motor) threshold

Perceptual (paresthesia) threshold

Paresthesia no longer a surrogate for pain relief; neither necessary nor sufficient

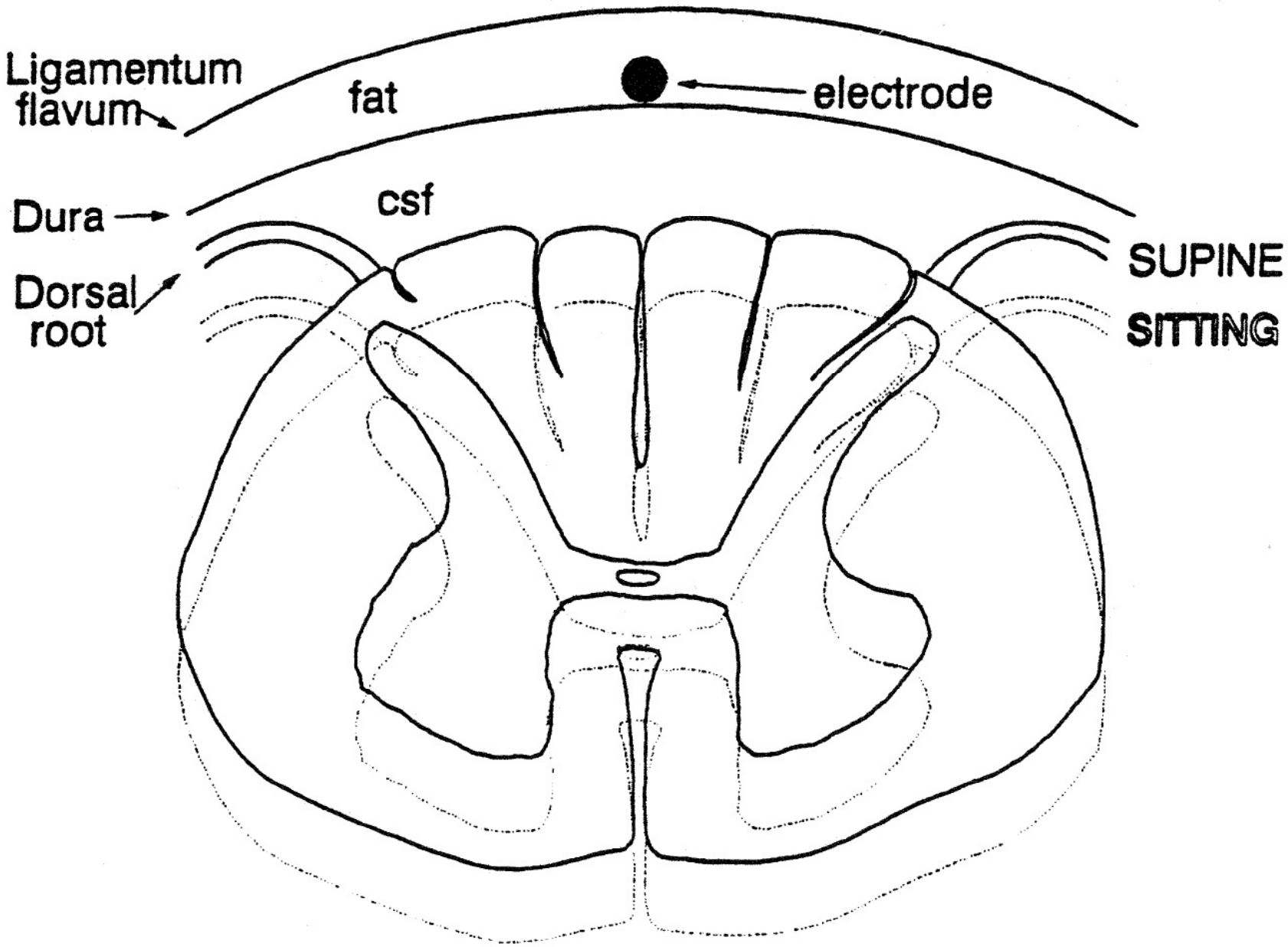
Paresthesia-free stimulation



Discomfort (or motor) threshold

Perceptual (paresthesia) threshold

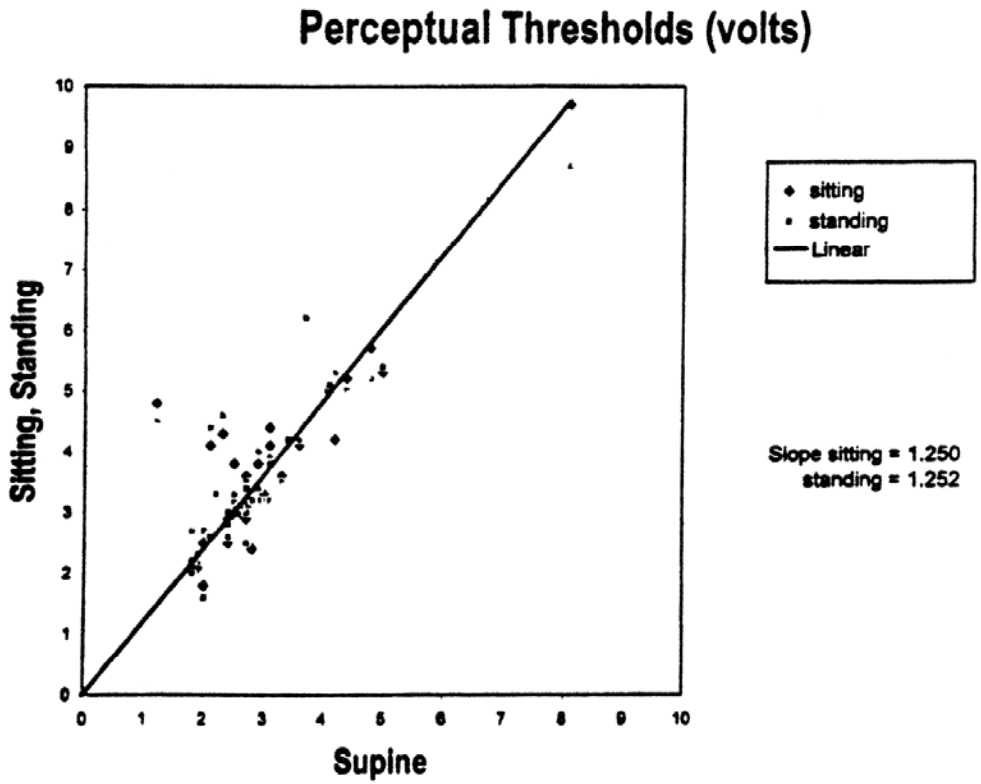
New “usage range” or “therapeutic window”


Ligamentum flavum
fat
electrode
Dura
csf
Dorsal root
SUPINE
SITTING

Postural Changes in Spinal Cord Stimulation Perceptual Thresholds

John C. Olin, PA ▪ David H. Kidd, MS ▪ Richard B. North, MD

Department of Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA



Neuromodulation, Volume 1, Number 4, 1998 171-175

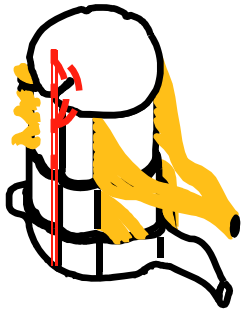
Computer Modeling of SCS

Distribution of electrical fields and current densities in the spinal cord

Finite element methods - tissue volumes (e.g. CSF, white matter) considered as multiple, small geometric figures [Coburn, Holsheimer, Rustioni, Sin, Strujik]

Variable electrical conductivity of different tissues

- Cerebrospinal fluid has the highest conductivity
- Anisotropy (e.g., white matter has greater conductivity longitudinally than transversely)



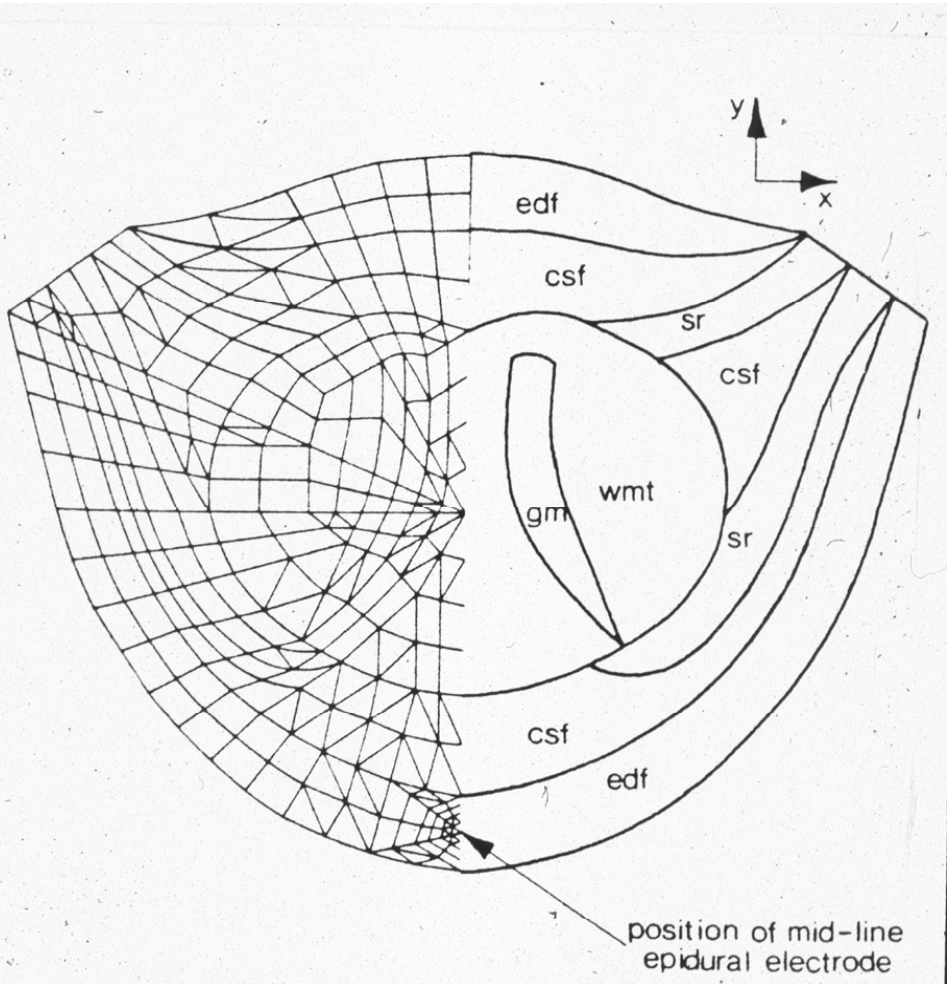
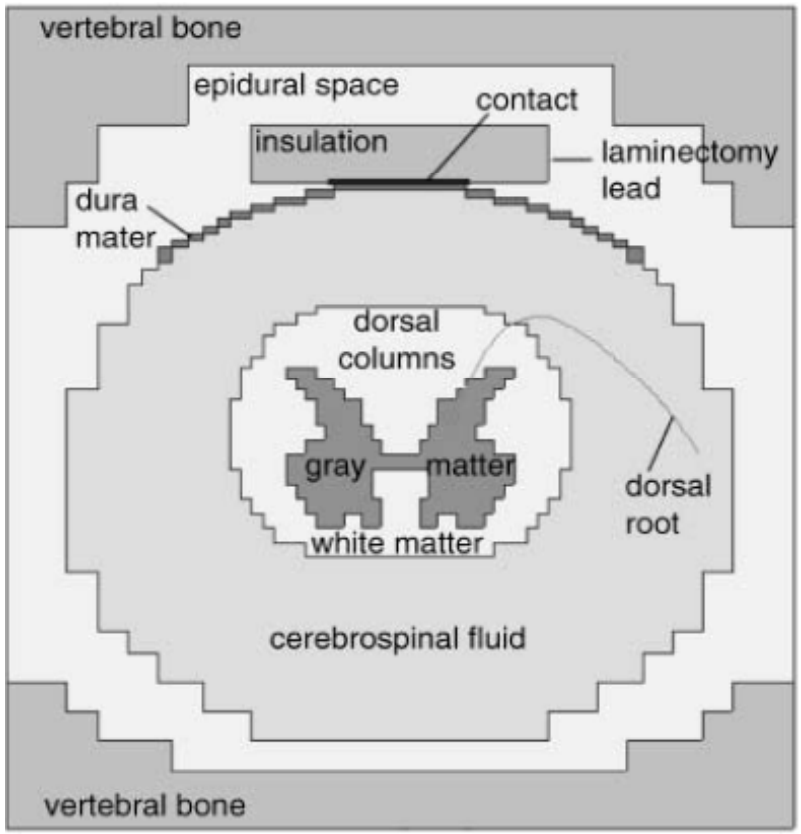
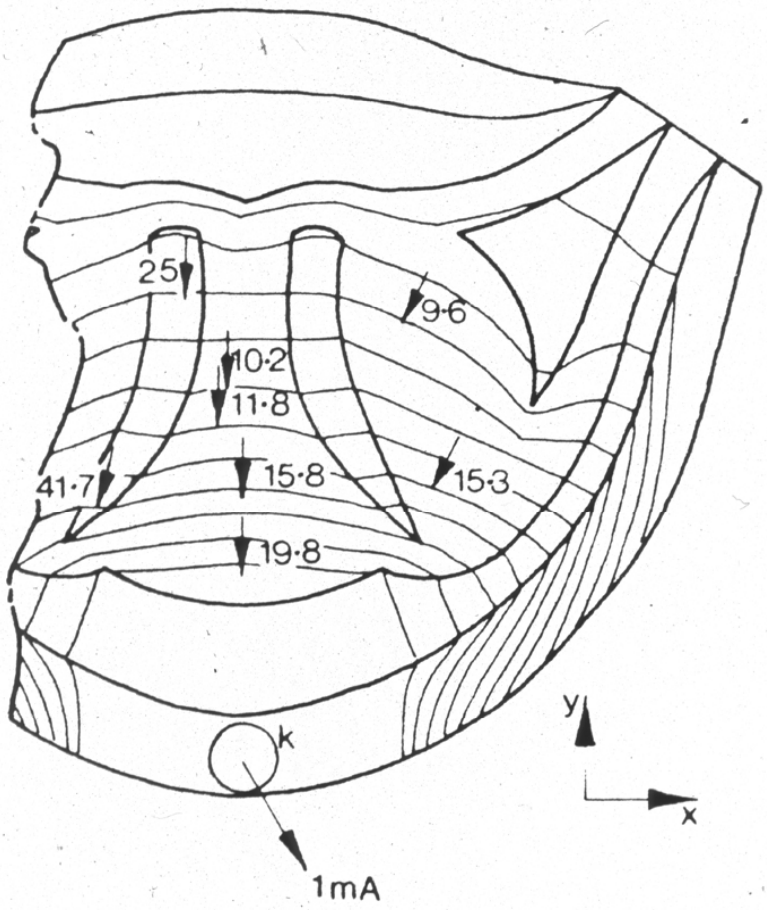


Fig. 3 *Finite-element mesh of transverse section through the spinal canal. Abbreviations are given in Table 1. Approximate scale, 4*





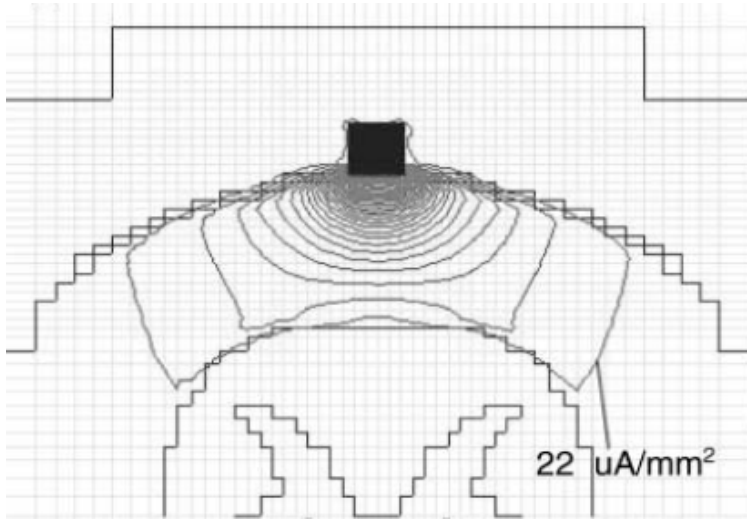


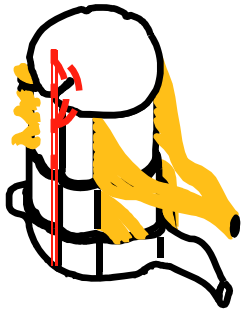
Fig. 15 *Isopotentials and current density vectors, μA mm⁻², within a transverse section of upper-thoracic spinal canal. Mid-line EDS-M cathodic current 1 mA as Fig. 13. Contours, excluding k, spacing 0·1 V, min. (inner) −11·6 V. Contour k −15·2 V. Approx. scale 4·4*

Modeling Predictions

Recruitment threshold varies as depth of dorsal cerebrospinal fluid space

Minimizing lateral recruitment (dorsal roots, lateral dorsal columns)

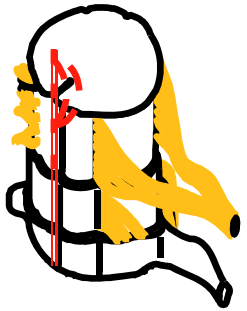
- Optimal longitudinal contact spacing (to maximize selectivity for deep, medial fibers) is approximately 1.4 times CSF depth, or 6-8 mm.
- Longitudinal cathode position is more important than arrangement of anodes in a linear array



Modeling Predictions (cont.)

To minimize lateral recruitment (dorsal roots, lateral dorsal columns):

- Dual (side by side) linear arrays are inferior
  - (lacking midline cathode position(s))
- Triple (side by side) linear arrays are superior
  - Retain midline cathode position(s).
  - Add lateral anodes, shielding roots and lateral dorsal columns
  - “Transverse tripole” [Holsheimer]



SPINE Volume 30, Number 12, pp 1412–1418

Spinal Cord Stimulation for Axial Low Back Pain

A Prospective, Controlled Trial Comparing Dual With Single Percutaneous Electrodes

Richard B. North, MD,* David H. Kidd, MA,* John Olin, PA,* Jeffrey M. Sieracki, MS,* Farrokh Farrokhi, MD,* Loredana Petrucci, MS,* and Protagoras N. Cutchis, MD†

"We observed disadvantages for dual electrodes in treating axial low back pain."

Meet Am Soc Stereotact Funct Neurosurg, Snowbird, Utah, 1999
Stereotact Funct Neurosurg 1999;73:126–130

Stereotactic and Functional Neurosurgery

Efficacy of Transverse Tripolar Stimulation for Relief of Chronic Low Back Pain

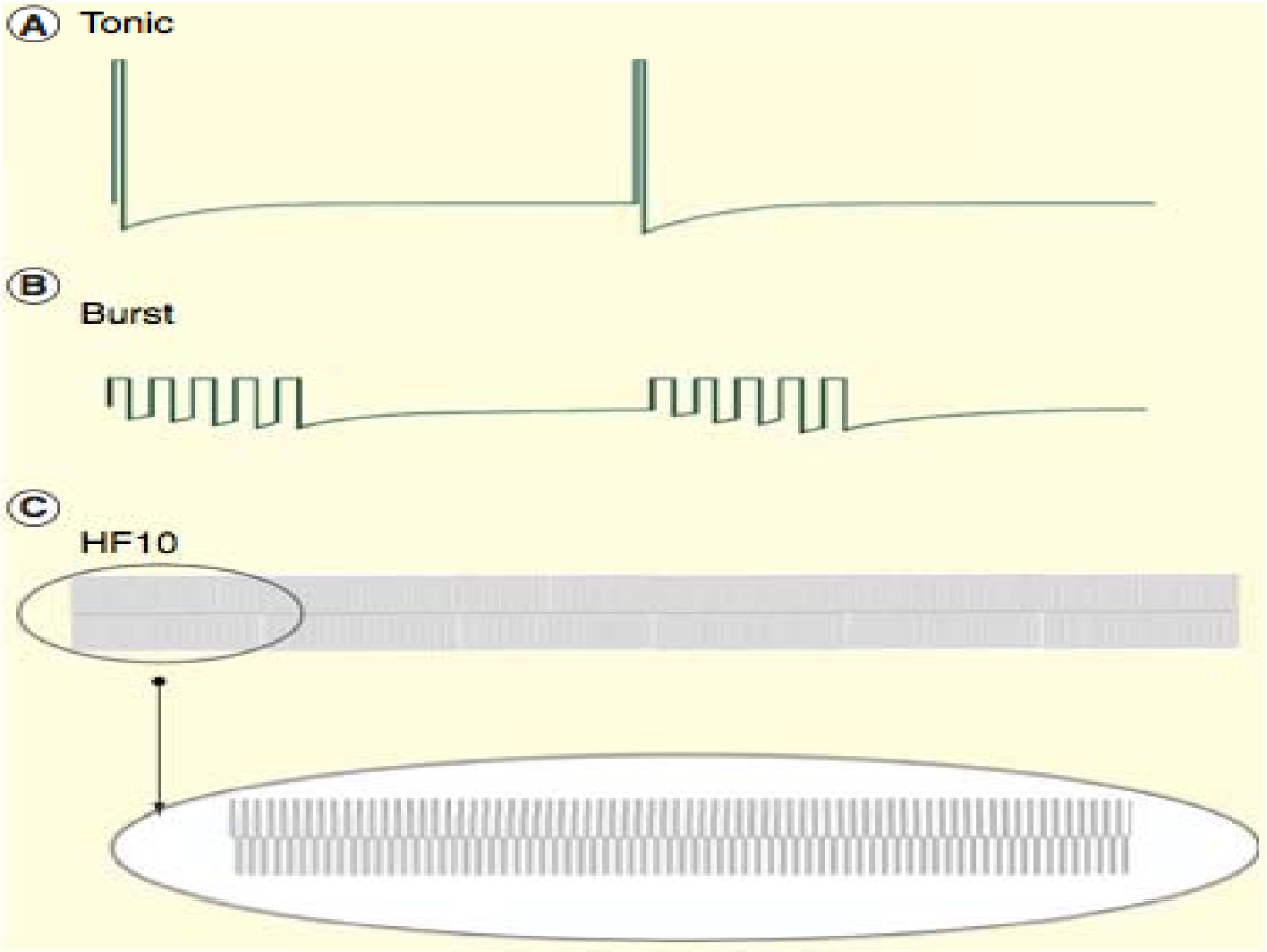
Results of a Single Center

Konstantin V. Slavin Kim J. Burchiel Valerie C. Anderson
Beverly Cooke

Department of Neurological Surgery, Oregon Health Sciences University, Portland, Oreg., USA

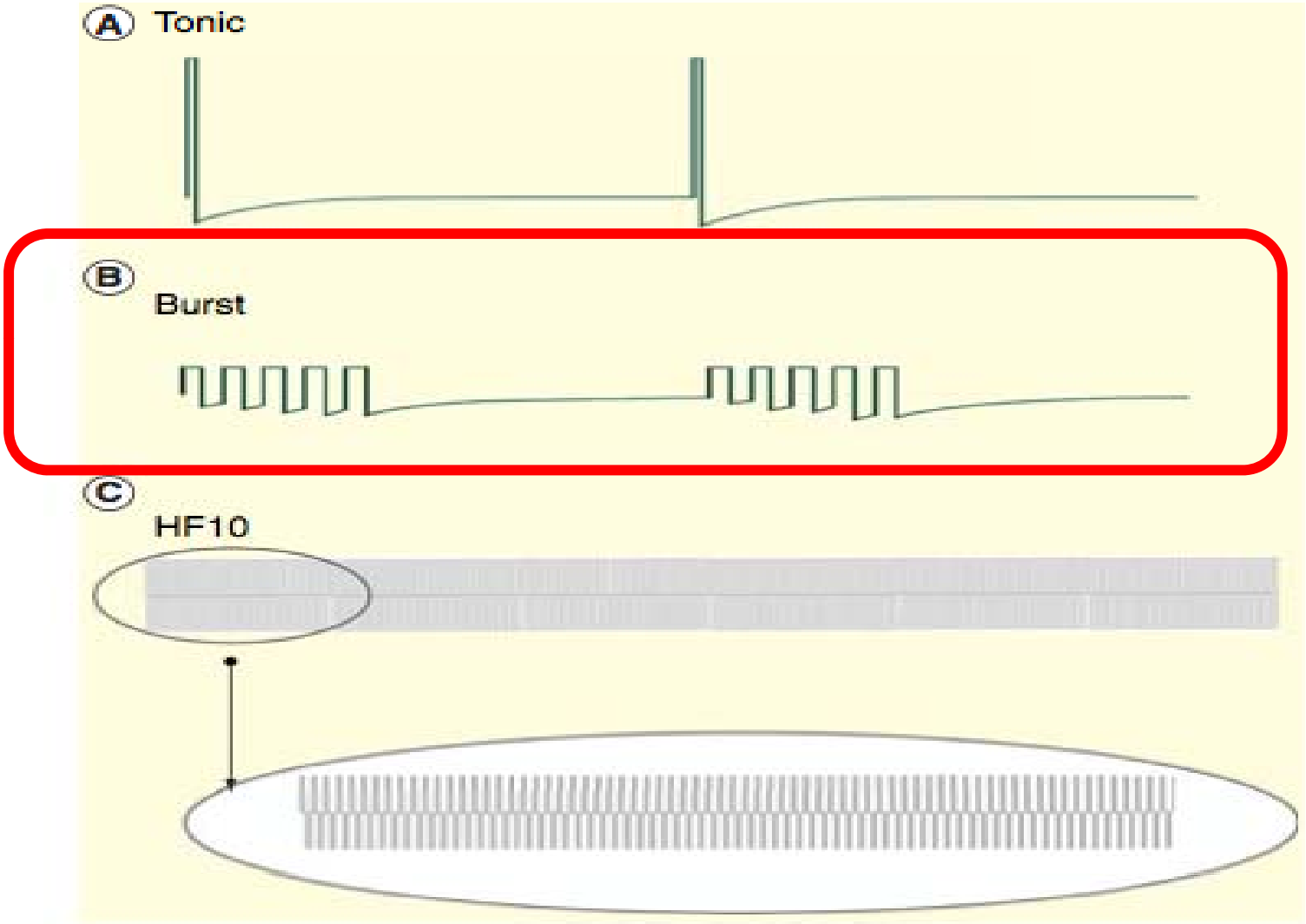
“We conclude that chronic low back pain is not particularly responsive to the transverse stimulation provided by the TTS system.”

SCS waveforms 2010 ff



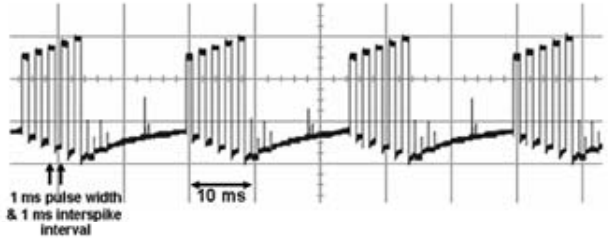
From Pope, Falowski & Deer 2015

SCS waveforms 2010 ff

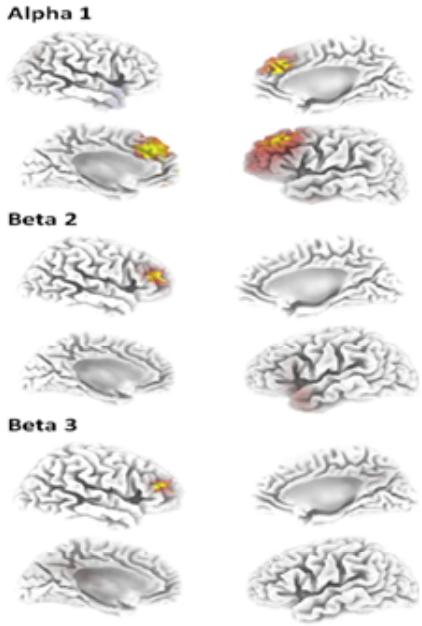


From Pope, Falowski & Deer 2015

- Bursts (intermittent tonic stimulation) resemble normal neural activity



- "Source localized EEG" has demonstrated that burst SCS activates the dorsal anterior cingulate and the dorsolateral prefrontal cortex (regions involved in emotions) more than does tonic SCS.



- Burst SCS might modulate attention to pain.

De Ridder 2010, 2013, 2015

Received: June 1, 2015 Revised: September 5, 2015 Accepted: September 24, 2015

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12368

Burst and Tonic Spinal Cord Stimulation: Different and Common Brain Mechanisms

Dirk De Ridder, MD, PhD*; Sven Vanneste, PhD†

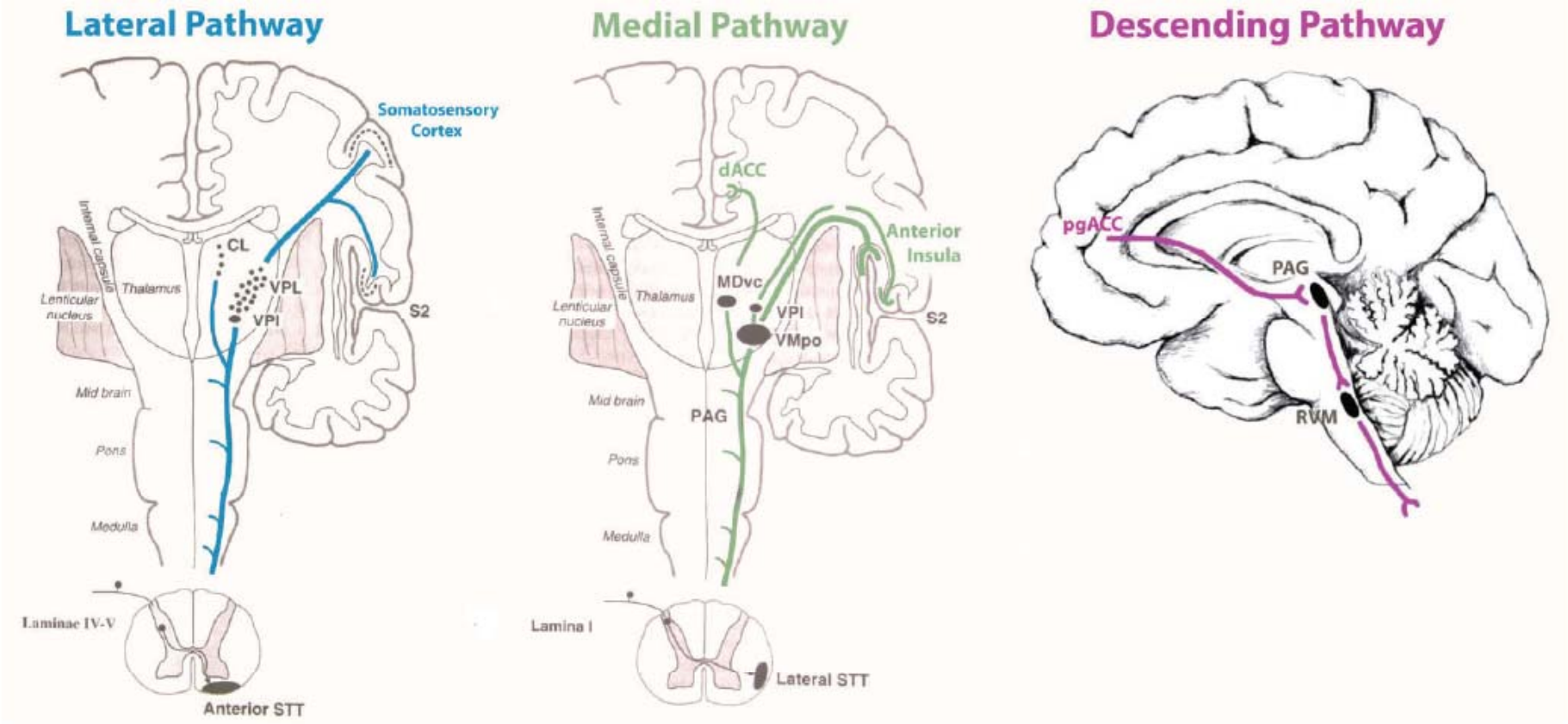
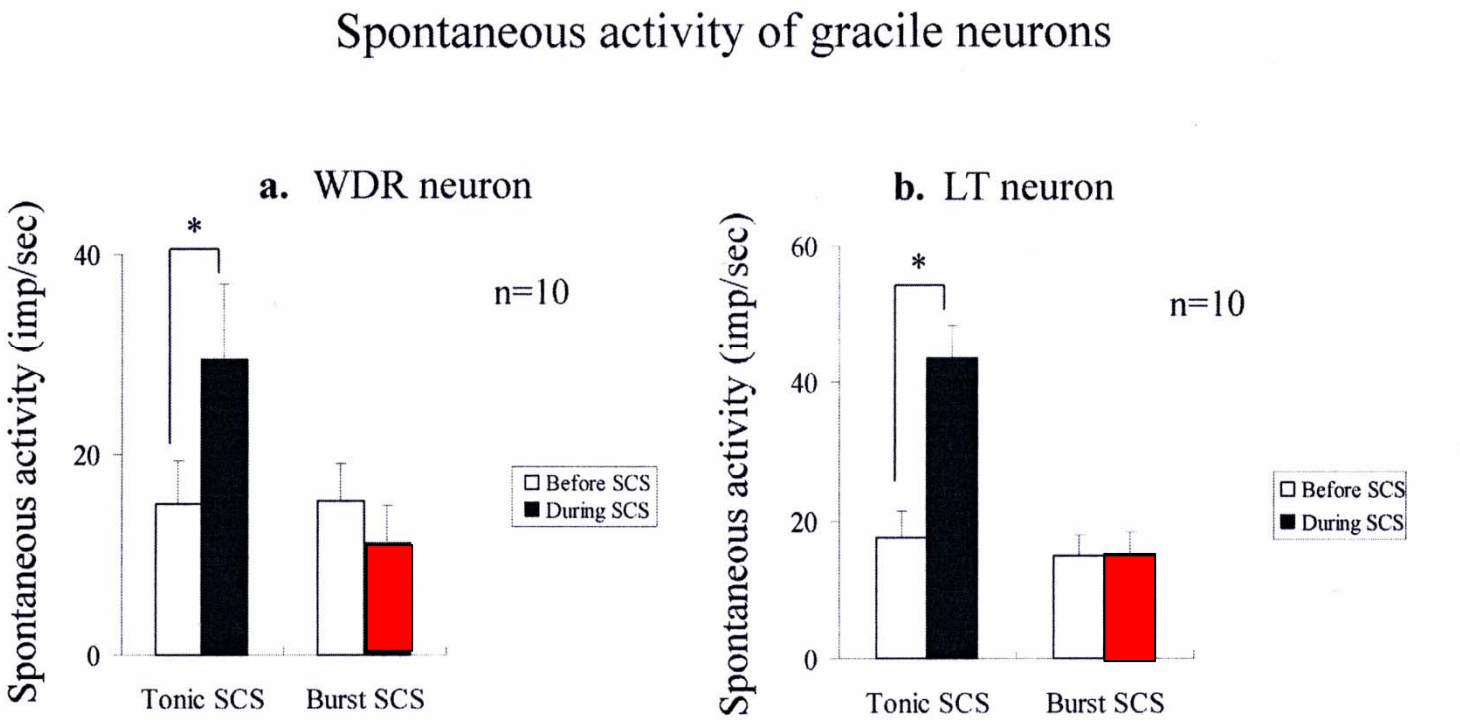


Figure 1. Ascending and descending pain pathways. Two ascending pain-supporting pathways have been described, and one pain-inhibitory descending pathway. The lateral ascending pathway processes the discriminatory components of pain, whereas the medial pathway processes the motivational, affective, attentional components of pain. The pain inhibitory pathway suppresses ongoing pain (figure modified and extended from Squire (12)).

Live animal experiments

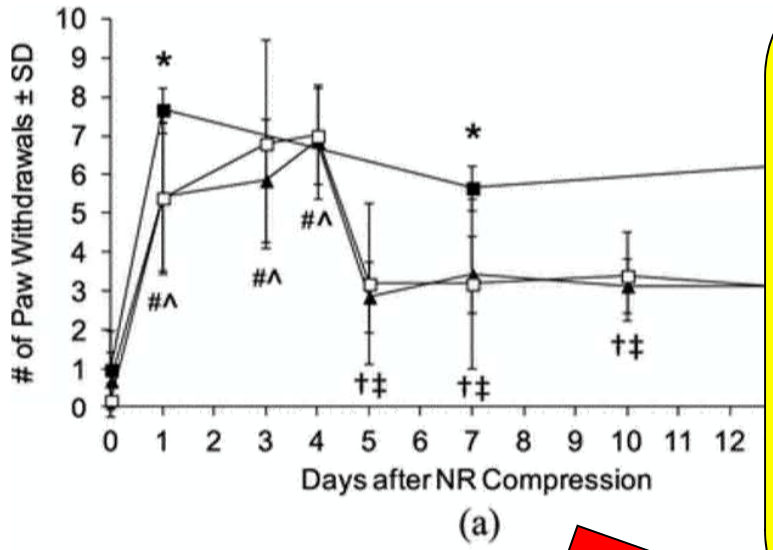
Burst effect **NOT** dependent on **DC** activation or block

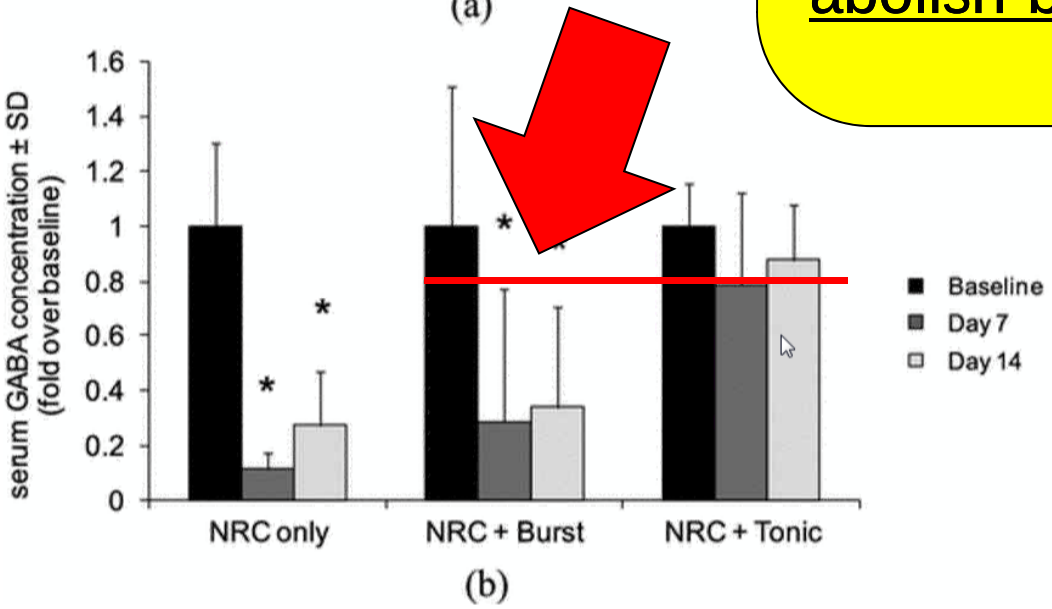


Tang R. et al 2014

ALLODYNIA AND SERUM GABA CONCENTRATIONS DURING BURST AND TONIC SCS

Live animal experiments





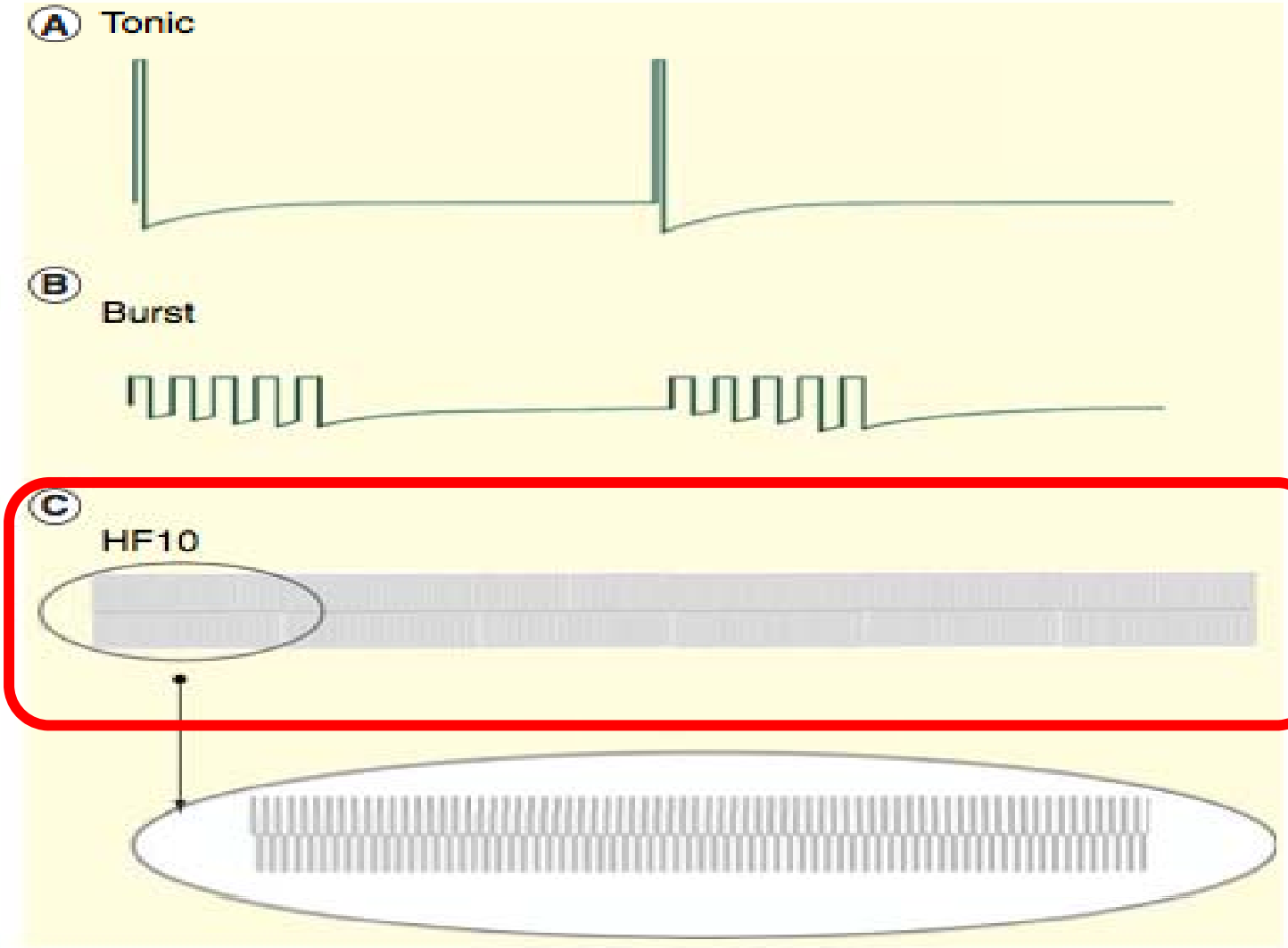
Burst effect **NOT dependant on GABA** receptor activation. Other exp showed that block of the $GABA_B$ receptor did not abolish burst effect

Bipolar stimulation was applied continuously beginning after behavioral assessment on day 4. Burst SCS was applied with 5 pulses per burst at 500 Hz with a pulse width of 1 ms, a burst frequency of 40 Hz, and amplitude of 80% MT. Tonic SCS was applied at 50 Hz with a pulsewidth of 0.25 ms and amplitude of 80% MT.

Courtesy of Bengt Linderoth

Crosby et al.., IEEE Transactions on Biomedical Engineering 2015; 62: 1604-1613

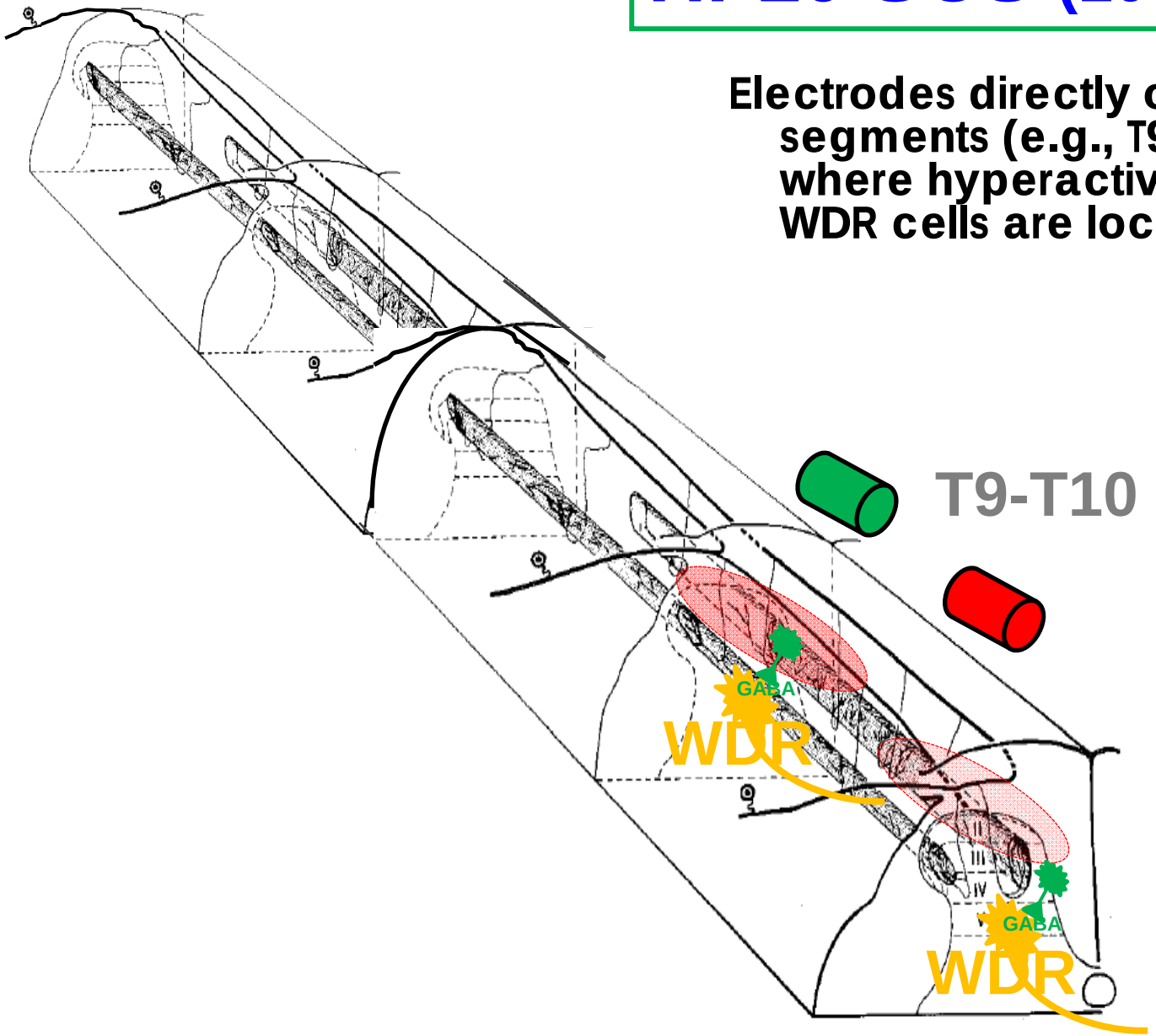
SCS waveforms 2010 ff



From Pope, Falowski & Deer 2015

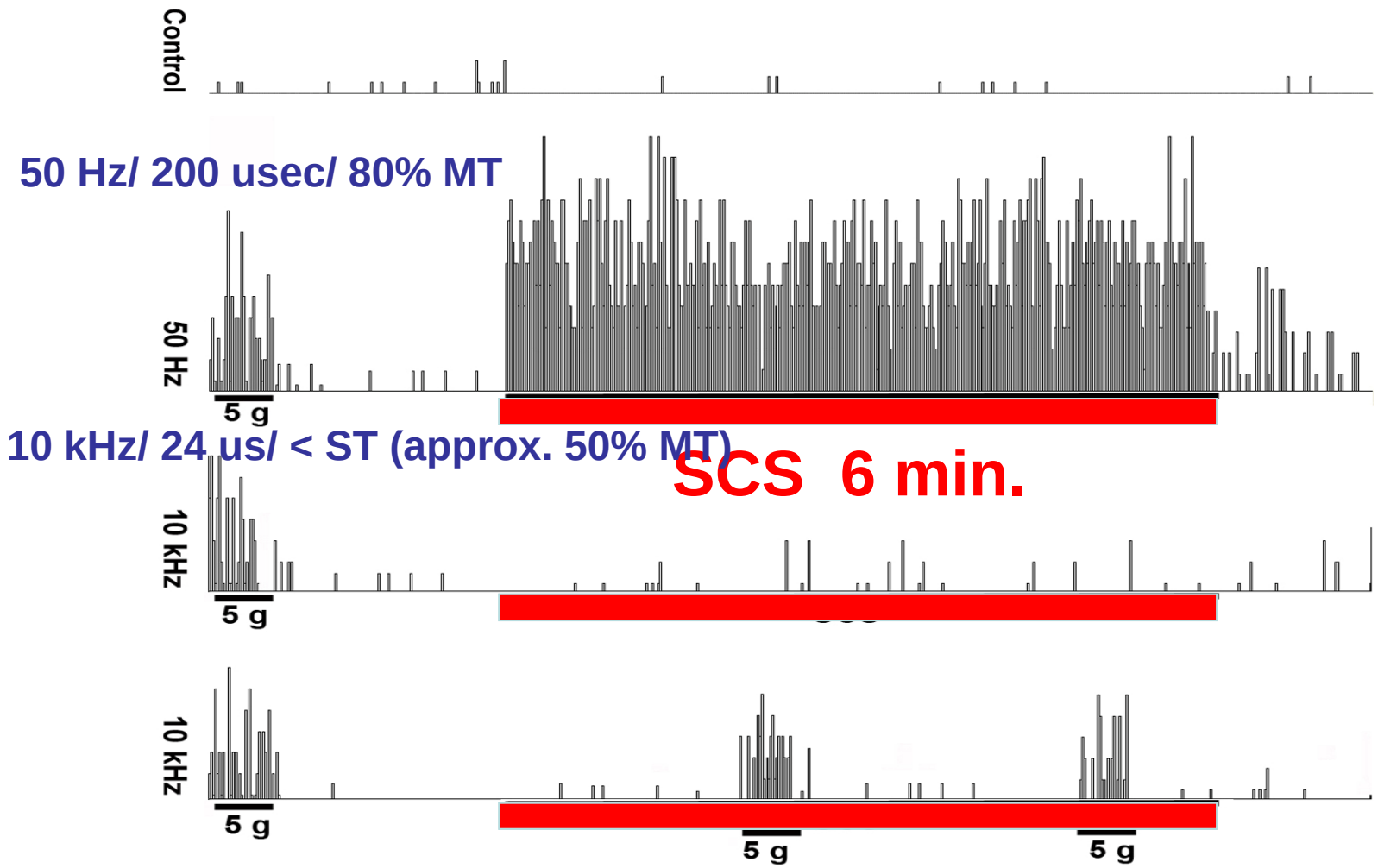
HF10 SCS (10 kHz)

Electrodes directly over segments (e.g., T9-T10) where hyperactive / WDR cells are located



Courtesy of Bengt Linderoth Adapted from Brown 1981; and further from Bradley K. (personal comm Nov 2015)

No block or activation of DC neurons by HF10 SCS



Example recording from a group of 6 rats; HF SCS:
No total block of sensory input (v Frey)

Song et al. Neuromodulation 2014.

Courtesy of Bengt Linderoth

Karolinska Institutet

Data from J. Hopkins Univ. Group

30 min. SCS (applied to DCs T10-T12

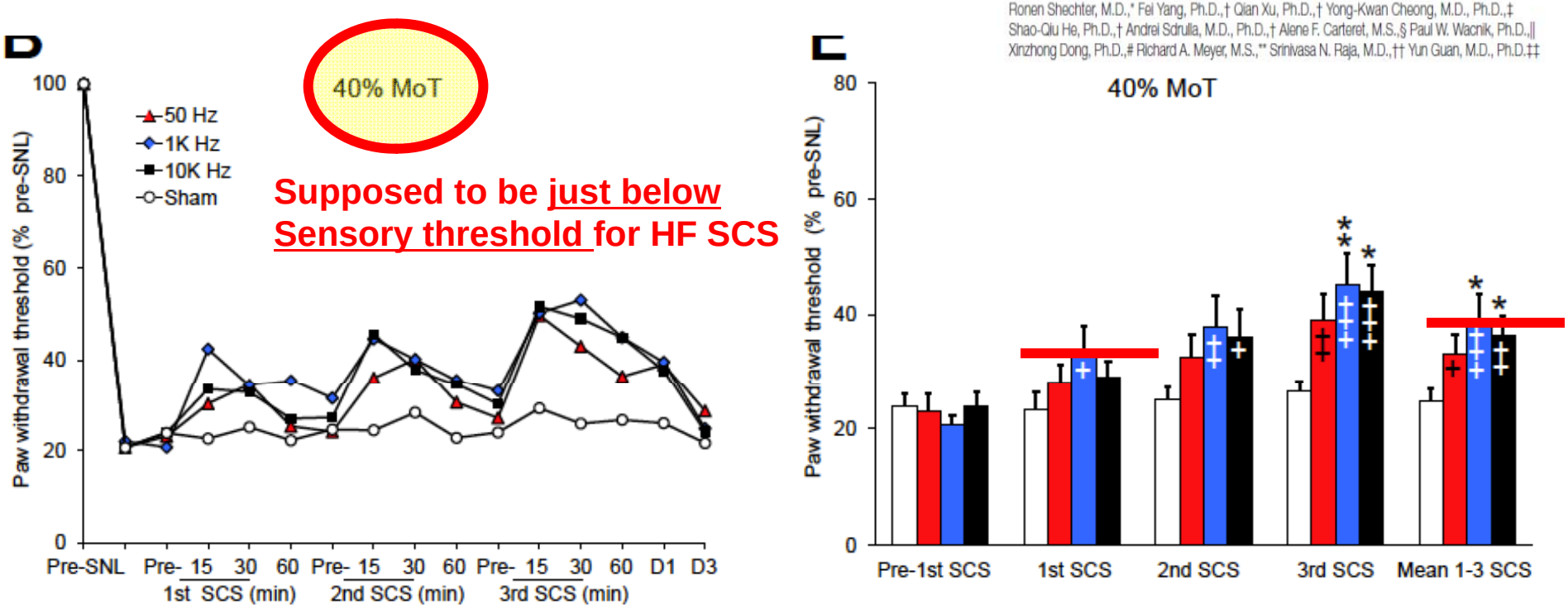
(biphasic; 24 μsec) on 3 consequtive days

PAIN MEDICINE

Live animal experiments

Conventional and Kilohertz-frequency Spinal Cord Stimulation Produces Intensity- and Frequency-dependent Inhibition of Mechanical Hypersensitivity in a Rat Model of Neuropathic Pain

Ronen Shechter, M.D.,* Fei Yang, Ph.D.,† Qian Xu, Ph.D.,† Yong-Kwan Cheong, M.D., Ph.D.,‡ Shao-Qiu He, Ph.D.,† Andrei Sdrulla, M.D., Ph.D.,† Alene F. Carteret, M.S.,§ Paul W. Wacnik, Ph.D.,‖ Xinzhong Dong, Ph.D.,# Richard A. Meyer, M.S.,** Srinivasa N. Raja, M.D.,†† Yun Guan, M.D., Ph.D.‡‡



Supposed to be just below Sensory threshold for HF SCS

They also used 20% MT: no sign differences at all

Stimulation at 80% MT: Larger differences for all freq., best for 1000 Hz

- BUT NOT clinically relevant for HF SCS

Courtesy of Bengt Linderoth

Shechter et al 2013

HF Sensory Threshold Determination:

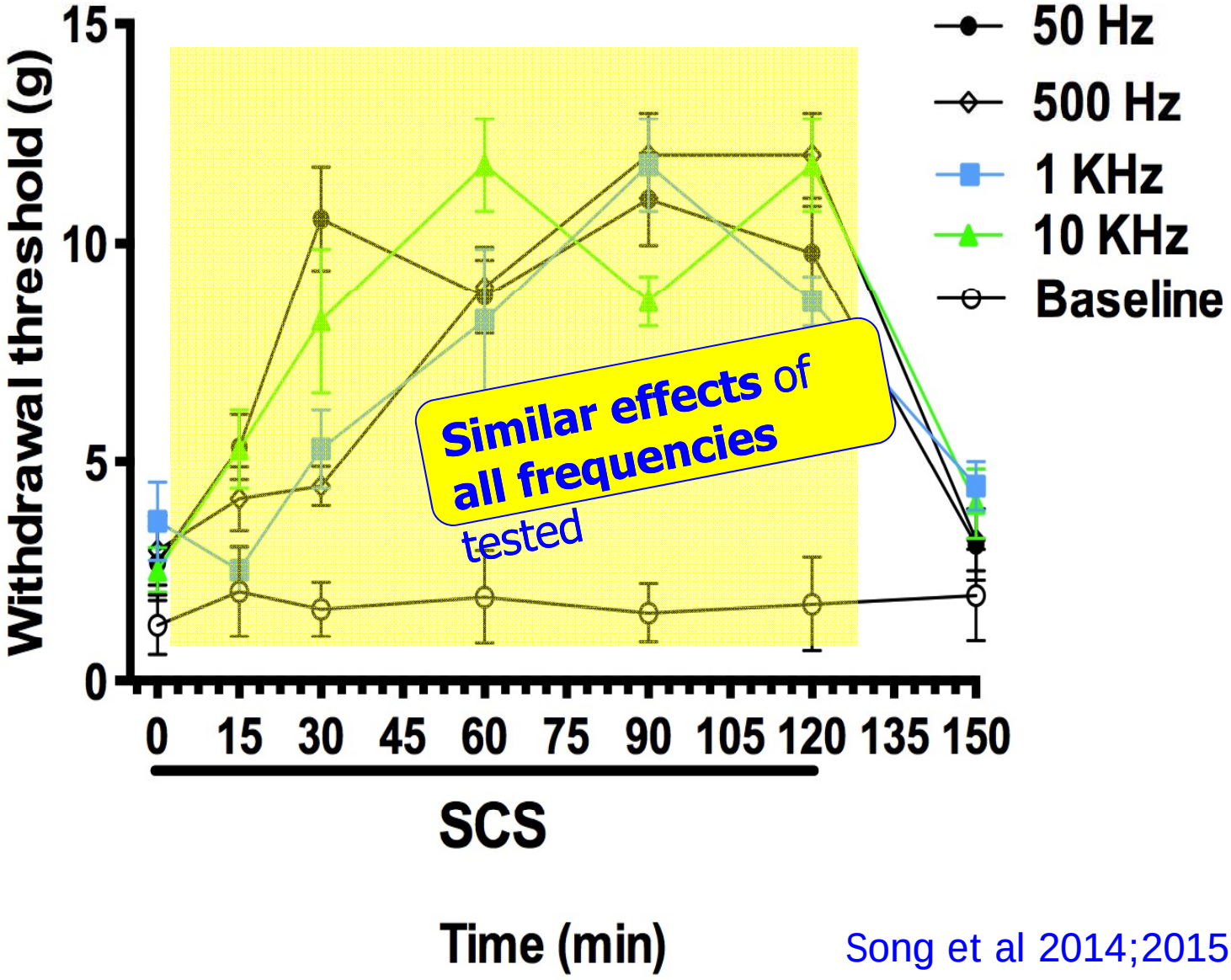
Karolinska Institutet

Behav

Exploration/

0

Amplitude



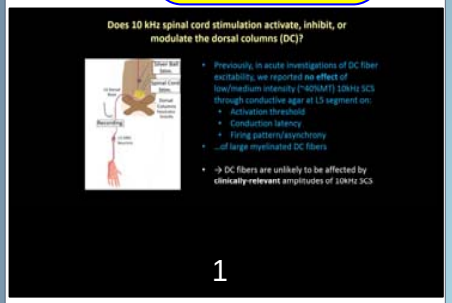
Chose

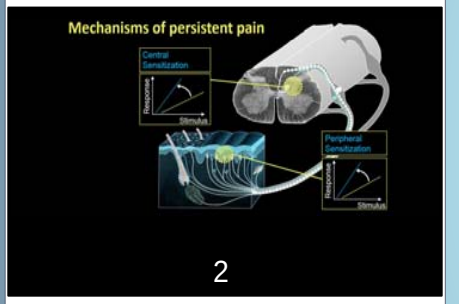
Song et al 2014;2015

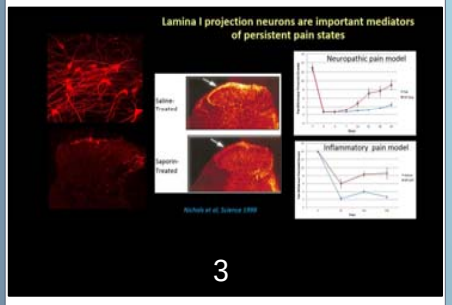
Effect of Different Frequencies of Spinal Cord Stimulation on Pain-Model Rodent Superficial Dorsal Horn Neuronal Excitability

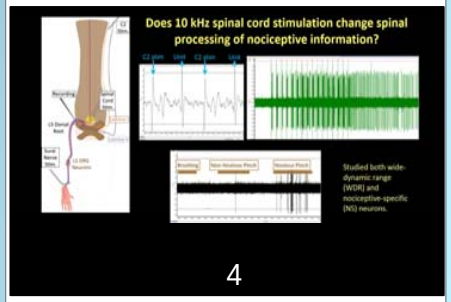
NANS 2018

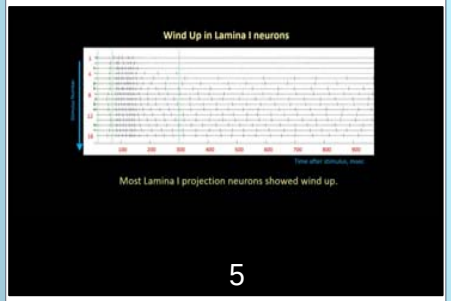
Professor Stephen McMahon PhD
King's College London
London Pain Consortium

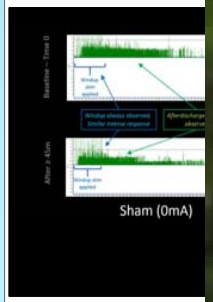


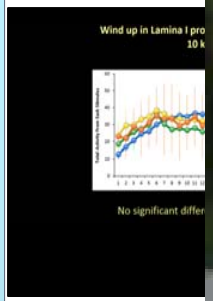


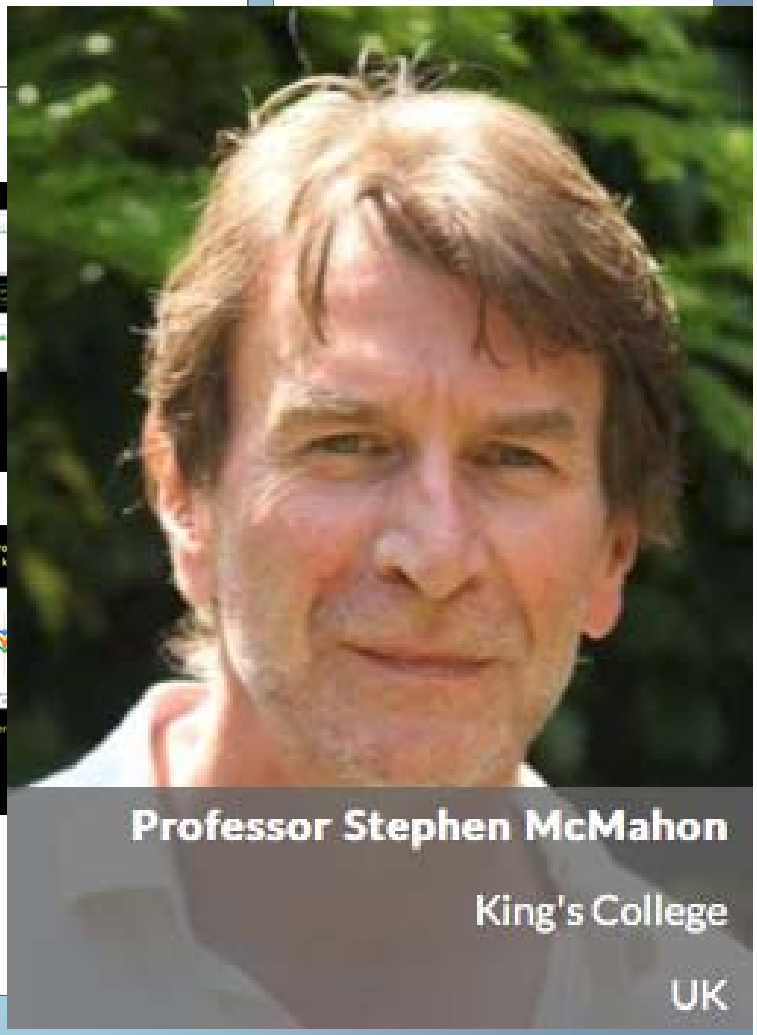










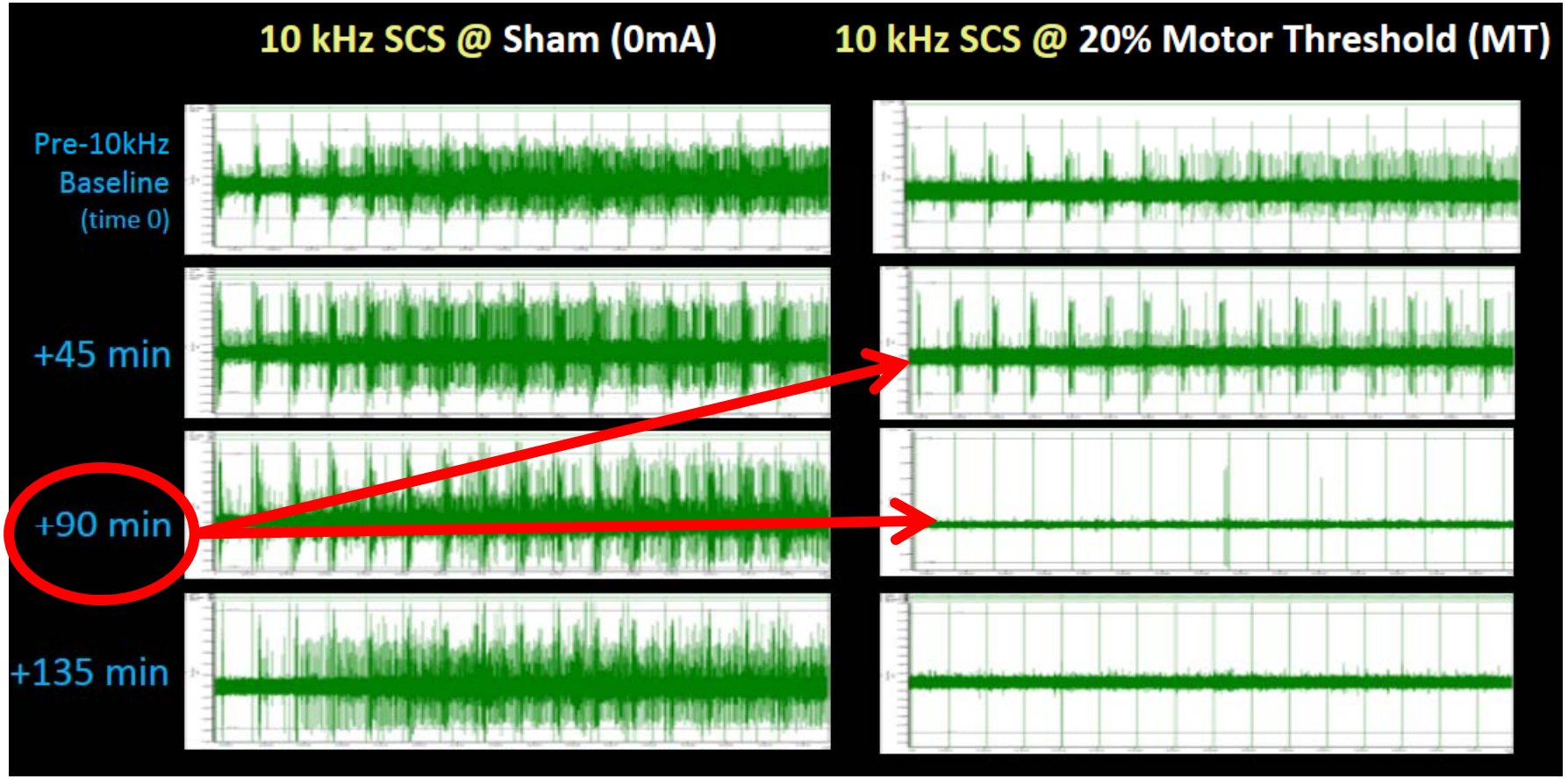


21ST ANNUAL MEETING
EXPANDING OUR MINDS

Live animal experiments

Electrophysiological investigation of the effects of 10 kHz spinal cord stimulation on the excitability of superficial dorsal horn neurons in experimental pain models

S. McMahon et al, King's College London (Unpubl 2016-2017 -2018)



Courtesy of Bengt Linderoth

Electrophysiological investigation of the effects of 10 kHz spinal cord stimulation on the excitability of superficial dorsal horn neurons in experimental pain models

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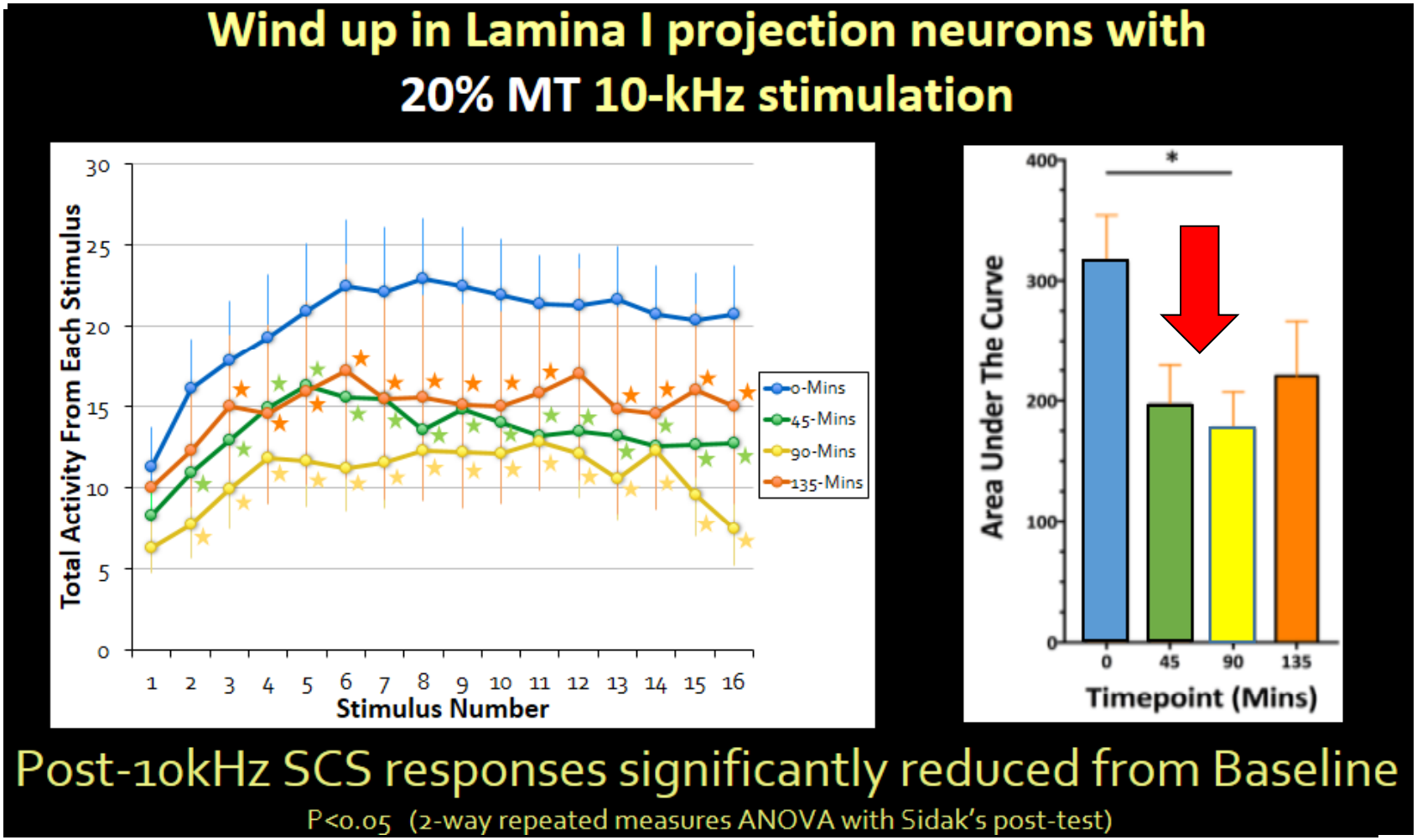
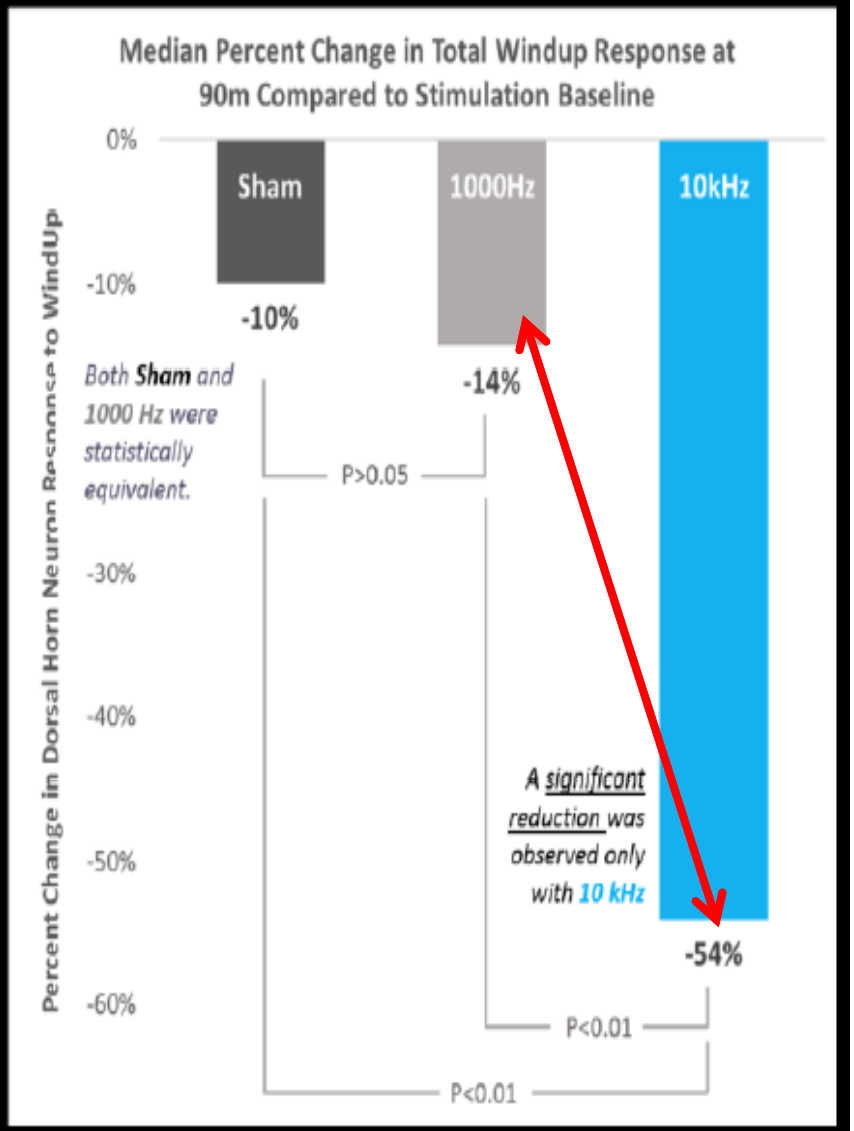


Wind up in Lamina I projection neurons

Effect of Frequency

- Wind up after 90m of:
  - **Sham** @ 0mA
  - **1kHz** @ 20% MT
  - **10kHz** @ 20% MT
- **Only 10kHz SCS** responses significantly reduced from Baseline



From S. McMahon et al.: Poster at NANS, Las Vegas Jan. 2018

Neuromodulation: Technology at the Neural Interface

Received: January 13, 2017 Revised: March 28, 2017 Accepted: March 30, 2017

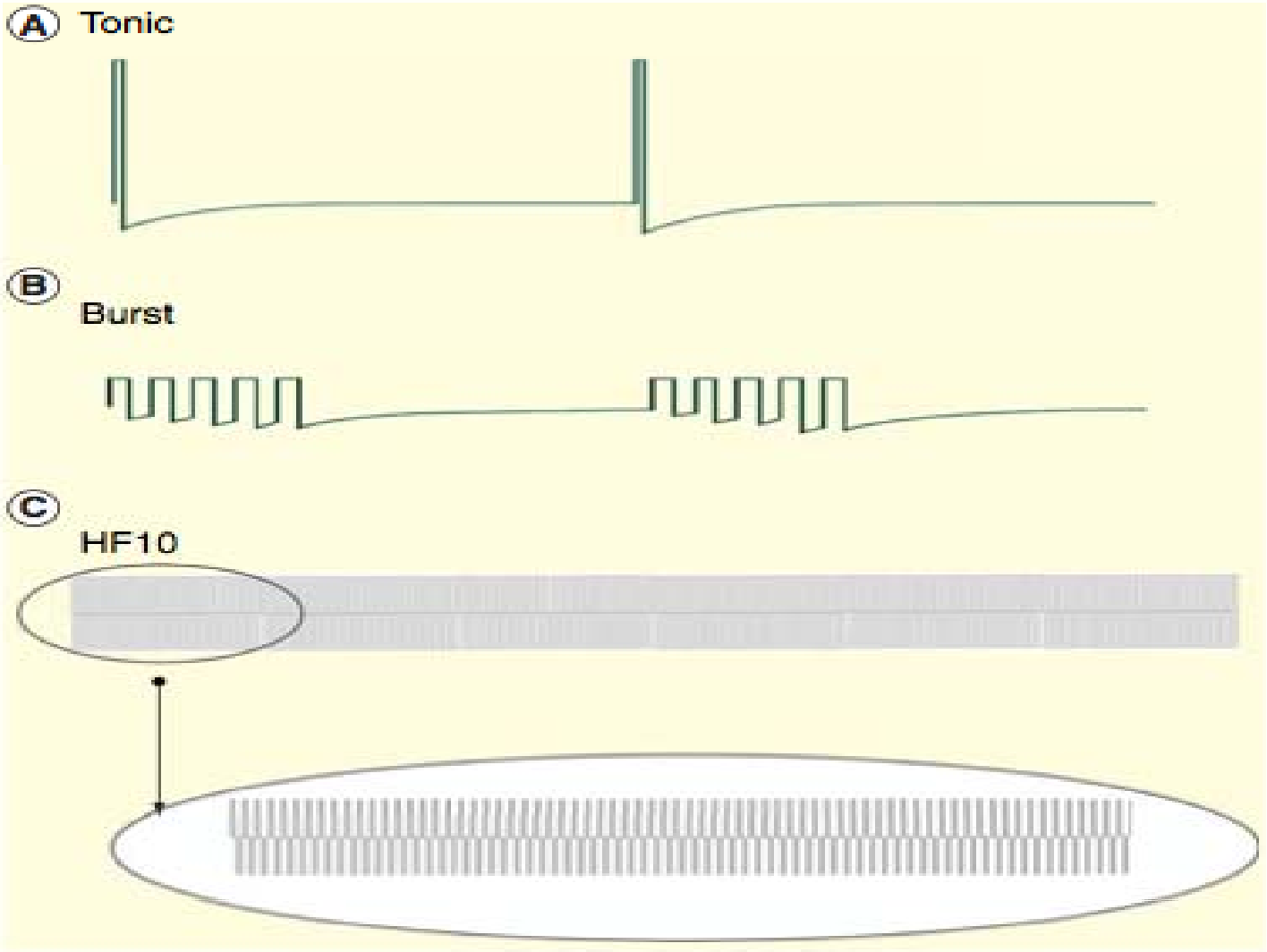
(onlinelibrary.wiley.com) DOI: 10.1111/ner.12614

Are 10 kHz Stimulation and Burst Stimulation Fundamentally the Same?

Dirk De Ridder, MD, PhD*; Sanjaya Perera, MD*; Sven Vanneste, PhD†

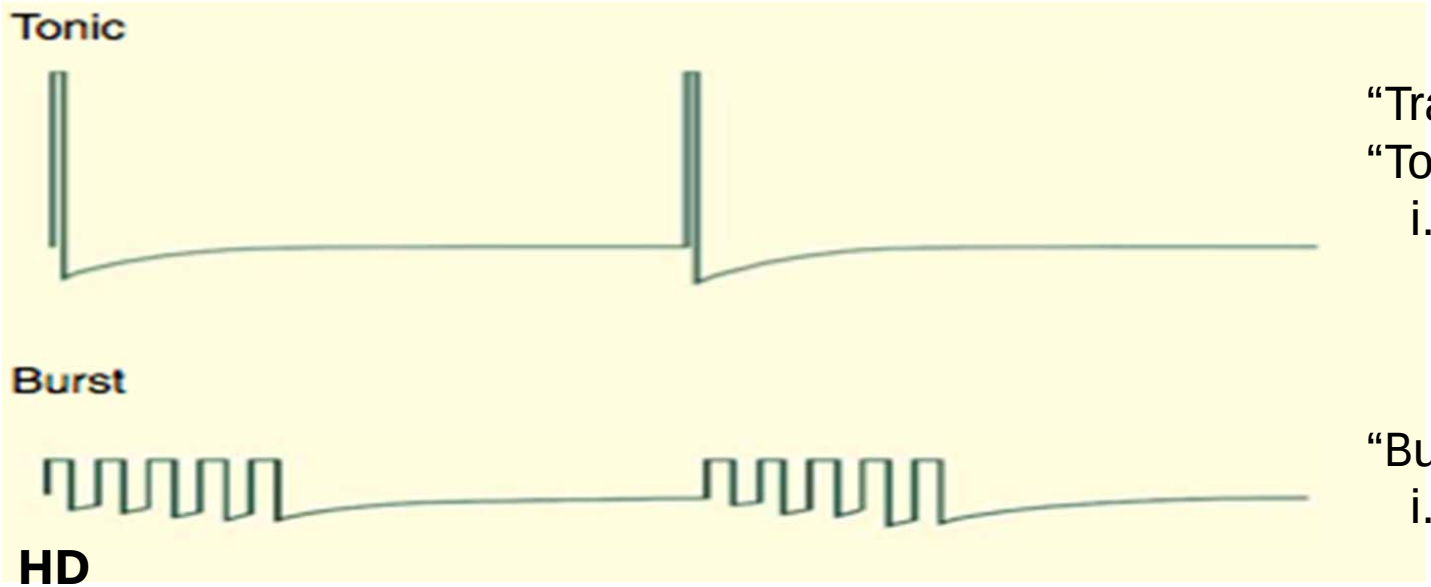
"By performing EEGs or PET or fMRI studies a conjunction analysis can demonstrate whether both stimulation designs modulate the dACC, that is, the medial pain pathway, and a subtraction analysis can demonstrate where they differ, analogous to what has been done for burst versus classical tonic stimulation."

SCS waveforms 2010 ff



From Pope, Falowski & Deer 2015

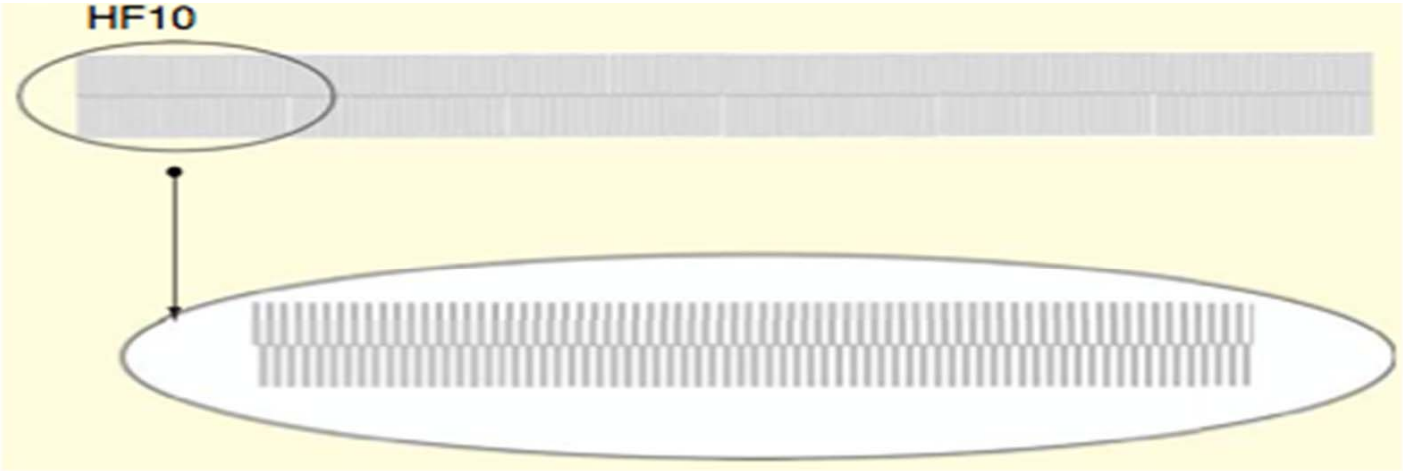
SCS waveforms 2016 ff



"Traditional"
"Tonic"
i.e., continuous

"Burst"
i.e., continual

"High density"
(still "tonic")



"High frequency"
(still "tonic")

Modified from
Pope 2015

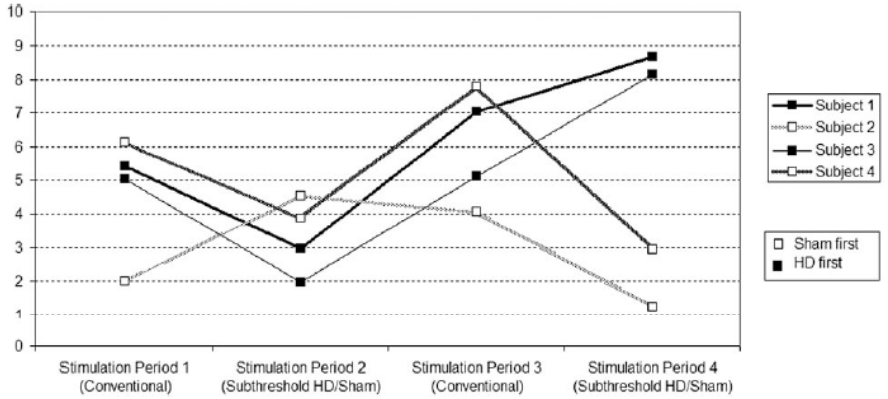
Neuromodulation: Technology at the Neural Interface

Received: July 13, 2015 Revised: August 26, 2015 Accepted: September 1, 2015

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12357

Paresthesia-Free High-Density Spinal Cord Stimulation for Postlaminectomy Syndrome in a Prescreened Population: A Prospective Case Series

Jennifer Sweet, MD; Anish Badjatiya, BS; Daniel Tan, PhD; Jonathan Miller, MD



n = 4

"VAS was 2.29 ± 0.41 during subthreshold HD stimulation and 6.31 ± 1.22 during sham stimulation, which was a significant difference ($p < 0.05$ . . .)

Received: April 15, 2016 Revised: August 1, 2016 Accepted: August 23, 2016

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12529

Altering Conventional to High Density Spinal Cord Stimulation: An Energy Dose-Response Relationship in Neuropathic Pain Therapy

Frank Wille, MD*†; Jennifer S. Breel, MPA*†; Eric W.P. Bakker, PhD‡; Markus W. Hollmann, MD, PhD†

Objectives: To examine whether converting from conventional Spinal Cord Stimulation (SCS) to High Density (HD) SCS reduces neuropathic pain over a period of 12 months in patients with failed SCS therapy.

Methods: Retrospective, open label, single center, consecutive case series of 30 neuropathic pain patients (Failed Back Surgery Syndrome [FBSS], Complex Regional Pain Syndrome [CRPS], and polyneuropathy [NP]). Patients with an initial adequate response to conventional SCS, but in whom pain increased over time, were included (Numeric Rating Scales [NRS] >6). These patients were stimulated with HD-SCS parameters and followed-up for 12 months. We report pain intensity, measured with NRS, before SCS implantation, 1 and 3 months after starting SCS with conventional stimulation, and after 1, 6, and 12 months of HD SCS.

Results: Pain reduction with conventional stimulation was initially adequate (NRS mean 8.6 to 5.3 at three months postimplant) but increased over time to a mean NRS of 7.7 at the time of reprogramming. NRS scores decreased significantly to 4.3 ($p = 0.015$) after reprogramming from conventional SCS (30 Hz, 300 μsec, 3.0 V) to HD SCS (409 Hz, range 130–1000 Hz, 409 μsec, 2.4V) in the patients still using HD-SCS at 12 months. In the nonresponders (patients who stopped HD-SCS for any reason), 76% had a diagnosis of FBSS. Almost half of the patients aborting HD-SCS preferred to feel paresthesias despite better pain relief. There was a significant difference between nonresponders and responders regarding the amount of electrical energy delivered to the spinal cord.

Conclusion: Neuropathic pain suppression is significantly enhanced after converting from failed conventional SCS to HD SCS in patients with FBSS, CRPS, and NP over a measured period of 12 months. There appears to be a dose-related response between the amount of energy delivered to the spinal cord and clinical effect.

Received: April 15, 2016 Revised: August 1, 2016 Accepted: August 23, 2016

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12529

Altering Conventional to High Density Spinal Cord Stimulation: An Energy Dose-Response Relationship in Neuropathic Pain Therapy

Frank Wille
Markus W.

Objectives: To
D) SCS reduces neuropathic pa

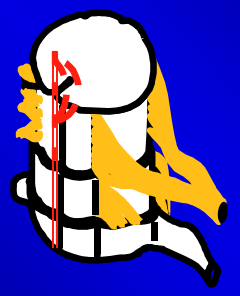
Methods: Retr
d Back Surgery Syndrome [FBS
quate response to conventiona
e patients were stimulated wit
RS, before SCS implantation, 1
SCS.

Results: Pain r
ns postimplant) but increased c
4.3 ($p = 0.015$) after reprogram
ec, 2.4V) in the patients still usi
had a diagnosis of FBSS. Almost
as a significant difference betw
l cord.

Conclusion: N
S to HD SCS in patients with F
onse between the amount of


STEREO
COUNTRY JOE & THE FISH
VANGUARD
180 gram
VINYL
Electric Music for the Mind and Body

1967



The history of research on the mechanisms, efficacy, and safety of spinal cord stimulation

Potential overlap with:

Rod Taylor

John Markman

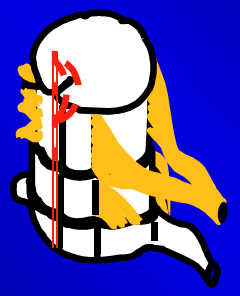
Ali Rezai

Salim Hayek

Simon Thomson

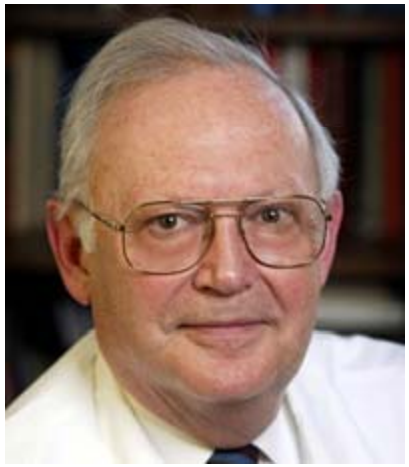
Brian Kopell

Sam Eldabe



The history of research on the mechanisms, efficacy, and safety of spinal cord stimulation

Johns Hopkins Department of Neurosurgery



Donlin M. Long, MD, PhD
Professor and Chairman
1973 ff

Early enthusiasm

"Thus far there appear to be no major pain syndromes which of themselves are not, at least in part, amenable to temporary or perhaps permanent control by electrical stimulation methods."

Seminar on the Electrical Stimulation of the Human Nervous System for the Control of Pain 1975

Advances in Pain Research and Therapy, *Vol. 5*, edited by John J. Bonica et al.
Raven Press, New York © 1983.

Ten-Year Follow-up of Dorsal Column Stimulation

*D. L. Erickson and **D. M. Long

*Department of Neurosurgery, University of Minnesota, Minneapolis, Minnesota 55455; and **Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, Maryland 21205

"Followup was carried out by different personnel who were entirely new to the patients . . . only 15% of the original 60 were considered successes."

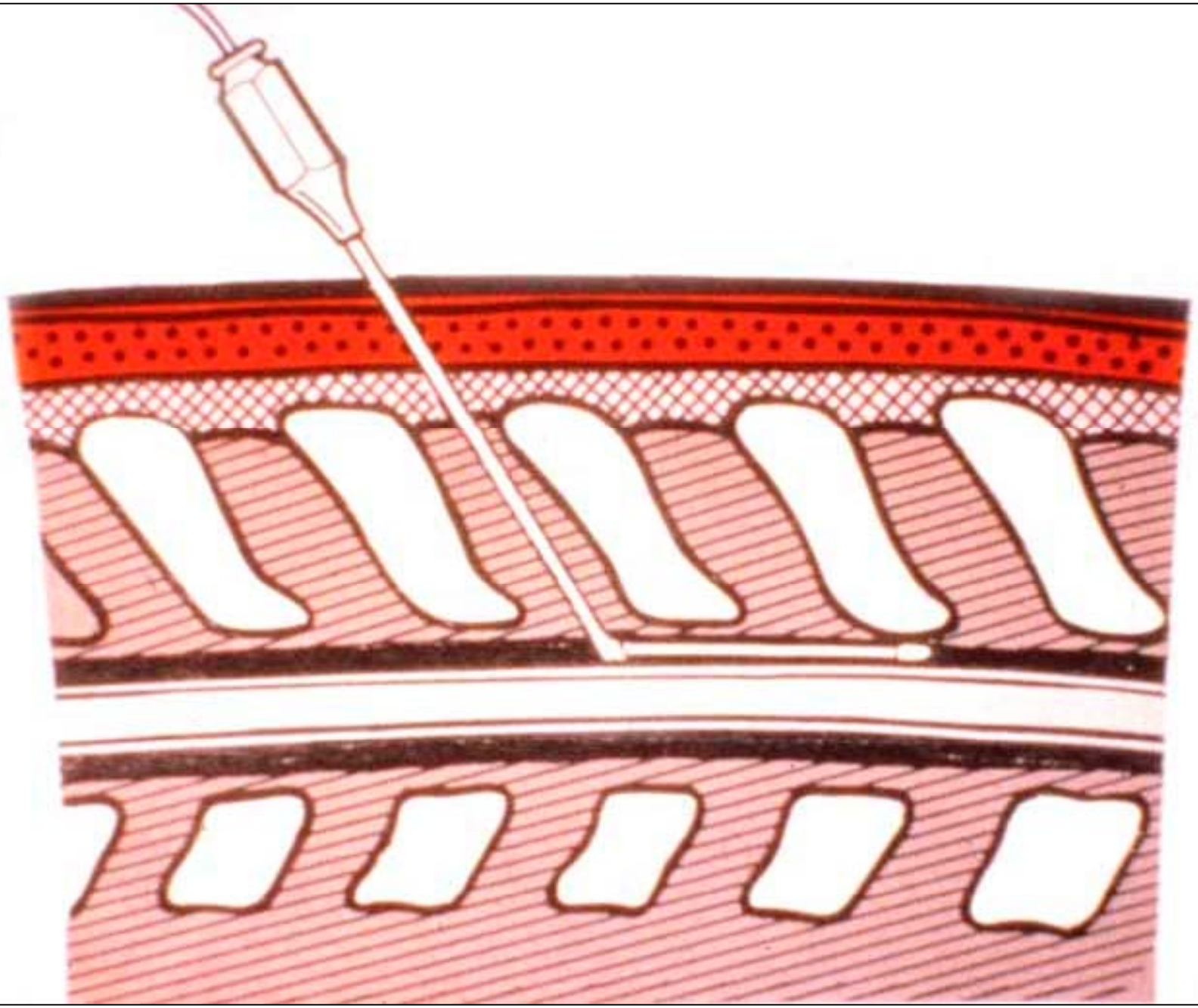
"We believe that unsophisticated methods of evaluating pain patients led to the early enthusiastic reports."

Percutaneous trial of stimulation for patient selection for implantable stimulating devices

Donald L. Erickson, M.D.

Department of Neurosurgery, University of Minnesota Hospitals, Minneapolis, Minnesota

✔ The author describes a flexible electrode which can be inserted percutaneously for a period of several days in candidates for an implantable electrical stimulating device for pain relief. This allows the patient a trial of stimulation which closely mimics that of the intended implantable system. If this trial does not give adequate pain relief in a variety of situations, the patient is not considered to be a suitable candidate for an implantable device. The trial of stimulation in no way obviates the need for careful scrutiny of the social and psychological factors accompanying chronic pain problems.



APL/JHU
CP 052
MARCH 1977

Biomedical Engineering

A CLINICAL STUDY OF SPINAL EPIDURAL STIMULATION FOR THE TREATMENT OF INTRACTABLE PAIN

R. B. NORTH (Applied Physics Laboratory)
T. A. FISCHELL (Cornell University)
R. E. FISCHELL (Applied Physics Laboratory)
D. M. LONG (Johns Hopkins Hospital)

"Third party followup"

This work was supported by the National Aeronautics and Space Administration, under Contract IPD 55719A, as part of the Technology Utilization Program, established to apply NASA technology in the public domain.

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Operating under Contract N00017-72-C-4401 with the Department of the Navy

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LAUREL, MARYLAND

Table 5

Efficacy of Epidural Stimulation for Pain Relief:
Summary by Diagnosis

Diagnosis	Number of Patients	Average Duration of Use (months)	Percent Pain Relief			Would Do Again for Same Relief			Comparison with Relief by Other Methods		
			0-40	40-70	70-100	No	Neutral	Yes	Less Effective	Same	More Effective
Chronic Low Back Syndrome	24	6.0	6	6	12	3	1	20	2	4	18
Cervical Syndrome	1	9.5	-	-	1	-	-	1	-	-	1
Terminal Cancer	2	5.7	1	-	1	1	-	1	-	-	2
Phantom Limb	1	7.2	-	-	1	-	-	1	-	-	1
Amputation Neuroma	1	1.0	-	-	1	-	-	1	-	-	1
Thoracic Outlet Syndrome	1	9.0	-	1	-	-	-	1	-	-	-
Muscular Dystrophy	1	5.5	-	-	1	-	-	1	-	n/a	-
Total	31	6.0	7	7	17	4	1	26	3	4	23

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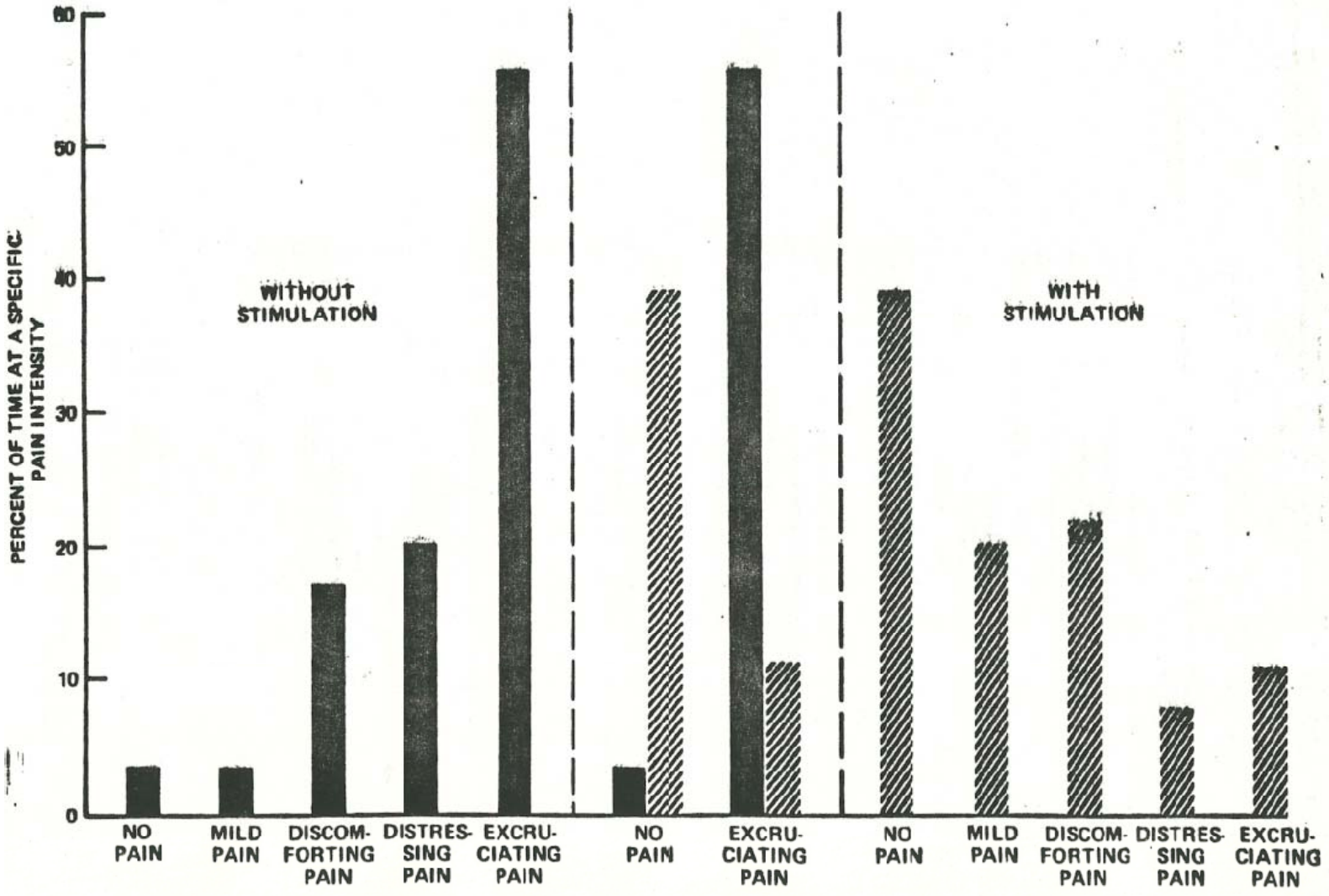

Fig. 6 Effect of Epidural Stimulation on Patients' Pain Experience

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Table 6

Time Lags of Analgesic Effect

Time Period	Latency*	Persistence**
0-1 min	8 Patients	3 Patients
1-30 min	18 Patients	11 Patients
30-120 min	4 Patients	7 Patients
2-12 h	0 Patients	8 Patients
Over 12 h	0 Patients	1 Patient
No Impression	1 Patient	1 Patient

*Time elapsed after stimulation begins until relief is felt

**Time elapsed after stimulation ends until relief ceases

Table 8

Drug Usage Eliminated as a Result of Epidural Stimulation

Drug Classification	Trade Name	Generic Name	No. of Patients	Daily Dosage (mg)			Duration of Use (years)		
				Min	Med	Max	Min	Med	Max
Narcotic Analgesic	Percodan	Oxycodone + APC	15	4	12	24	0.5	2	9
	Demerol	Meperidine	7	50	300	1200	1	3	12
	Codeine	Codeine	4	60	240	240	3	4	7
	Morphine	Morphine	1	*	*	*	3	3	3
	Dilaudid	Hydromorphone	1	*	*	*	*	*	*
Nonnarcotic Analgesic	Darvon	Propoxyphene	5	65	195	500	2	2	4
	Talwin	Pentazocine	4	*	150	150	2	2	5
	Parafon Forte	Chloroxazone + Acetaminophen	1	*	*	*	3	3	3
	Empirin	APC	1	*	*	*	*	*	*
	Percogesic	Acetaminophen + Phenyltoloxamine	1	*	*	*	2	2	2
Tranquilizer	Valium	Diazepam	7	5	20	60	1	4	10
	Miltown	Meprobamate	1	1600	1600	1600	3	3	3
	Prolixin	Fluphenazine	1	*	*	*	*	*	*
Sedative	Dalmane	Flurazepam	3	30	30	30	*	0.3	*
	Fiorinal	Butalbital + APC	1	1	*	*	*	*	*
	Nembutal	Pentobarbital	1	100	100	100	10	10	10
	Doriden	Glutethimide	1	50	50	50	*	*	*
	Placidyl	Ethchlorvynol	1	700	700	700	3	3	3
Antidepressant	Elavil	Amitriptyline	4	75	75	75	*	0.3	2

*Not known by patient.

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Table 7

Grading Scale for Ability to Perform Various Activities

0 - Able to do easily and normally
1 - Able to do with slight difficulty because of pain
2 - Able to do with difficulty because of pain
3 - Able to do only with extreme difficulty because of pain
4 - Unable to do at all because of pain
X - Impossible because of non-pain factors

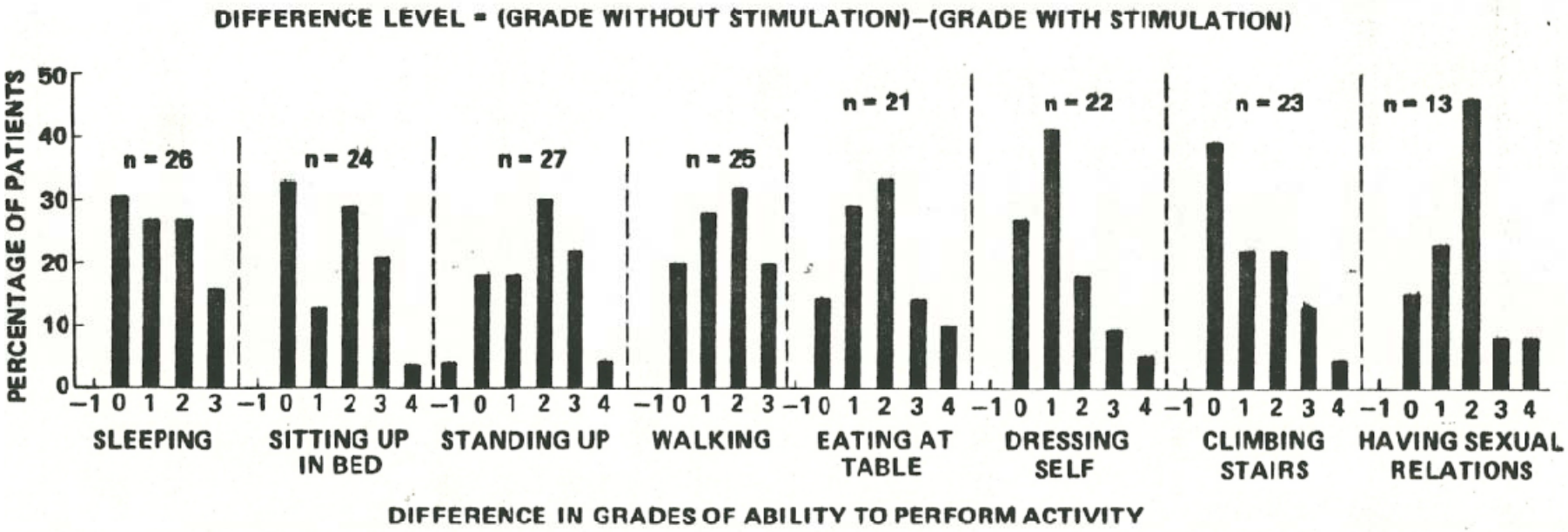
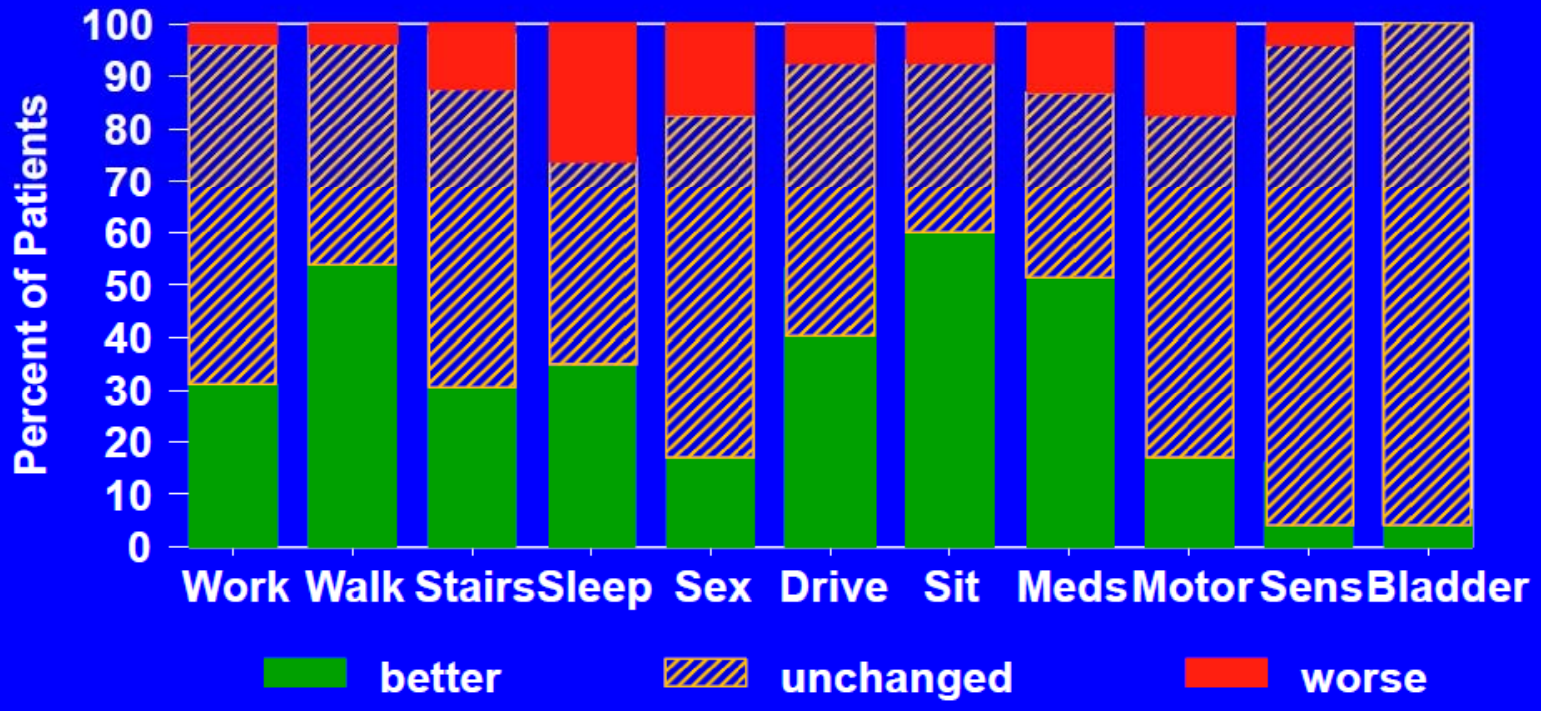


Fig. 7 Effect of Epidural Stimulation on Patients' Ability to Perform Various Activities

Results

Spinal Cord Stimulation

3-year followup



Chronic Stimulation *via* Percutaneously Inserted Epidural Electrodes

Richard B. North, Timothy A. Fischell, and Donlin M. Long

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SYMPOSIUM: NEUROAUGMENTIVE DEVICES *Neurosurgery, Vol. 1, No. 2*

September/October 1977

TABLE 1

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Diagnosis	No. of Patients	Average Duration of Use (Mo)	% Pain Relief			Would Do Again for Same Relief			Comparison with Relief by Other Methods		
			0–40	40–70	70–100	No	Neutral	Yes	Less effective	Same	More effective
Chronic low back syndrome	24	6.0	6	6	12	3	1	20	2	4	18
Cervical syndrome	1	9.5			1			1			1
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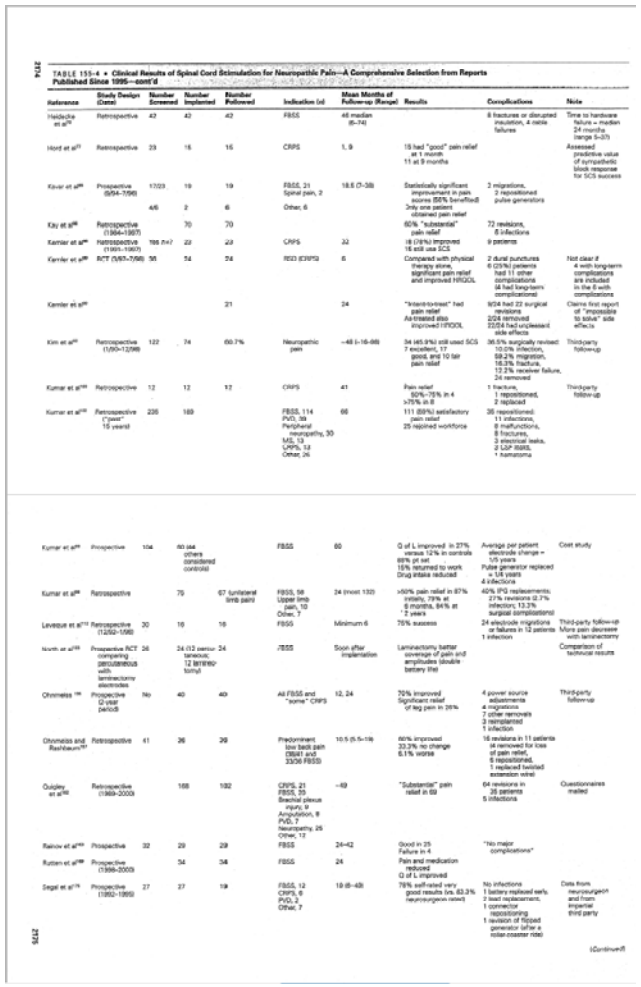
Phantom limb	1	7.2			1			1			1
Amputation neuroma	1	1.0			1			1			1
Thoracic outlet syndrome	1	9.0		1				1	1		
Muscular dystrophy	1	5.5			1			1		N/A	
Total	31	6.0	7	7	17	4	1	26	3	4	23

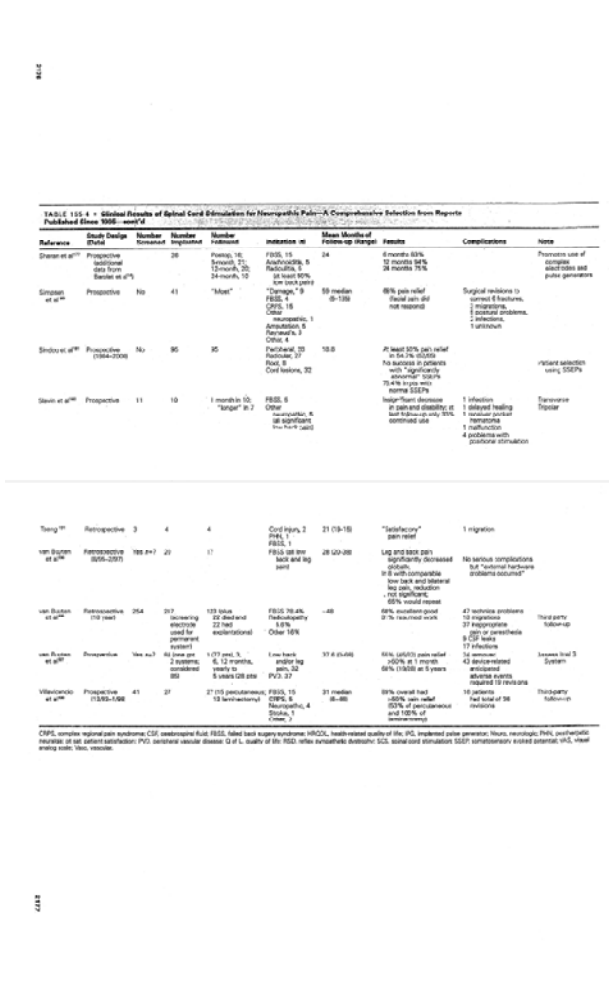
TABLE I

A review of the literature on spinal cord stimulation reveals a variety of indications for the procedure, temporary electrode screening protocols, follow-up methods and intervals, and criteria for success; comparisons are difficult.

Author, year	No. screened	No. implanted	No. FBSS	Other diagnoses	Follow-up mean	Follow-up range	Third party follow-up	Exc/good results	Exc/good FBSS results
Broseta 82		11		Causalgia, amputations		3–20 mos.			
Burton 75	0	75	55		1 yr.		y (mfr)	58.7%	
Burton 77		198	186					43%	
Clark 75		13	6					54%	67%
De La Porte 83	94	36	36		36 mos.	3–96 mos.		60%	
De Vera 90	124	110	18	PVD, RSD, spasticity, Ca				75%	
Devulder 90		45						78%	
Erickson 83	10	70				up to 10 yrs.	y (60)	15–20%	
Hoppenstein 75		27	12					58%	64%
Hunt 75		13	5			9 mos.–4 yrs.		15–31%	20–60%
Kälin 90			77					88%	88%
Koeze 87	0	26	5	PVD	28 mos.		y	46–62%	
Krainick 85	126	91	5	Amputations					
Kumar 86		60	54			6–60 mos.		62%	
Law 83		81						36–80%	
Law 87		46	46		25 mos.				
Leclercq 81		20	20			1– > 24 mos.		50%	50%
Leclercq 84	50	36							
Long 75		69	54			12–35 mos.	y	18%	
Long 81		31	24			4–7 yrs.	y	73% @ 3 yrs.	
McCarron 87		22				3–24 mos.		68%	
Meglio 89	109	64	19	PVD 40, SCI 15, PHN 10, Ca 11			n	59% PVD; 100% PHN	23%
Mittal 87	31	26	21					46%	
Nielson 75	221	130	79	Ca, postcordotomy		1– > 35 mos.	y	49%	46%
North 77		31	24	Ca 2	6 mos.		y	55–77%	50–75%
North 84		20	20		8 yrs.		y	35%	35%
Pineda 75		76	56						43%
Racz 89	0	26	18			12–42.7 mos.	n	65%	
Richardson 79	36	22	12	Ca		1–3 yrs.		56%	
Robb 90	65	79	22	"Peripheral" 22, "deaff" 21		6 mos.–5 yrs.		72%	69%
Shatin 86		116				0.9–13.3 mos.	y (mfr)	74% @ 6 mos.	
Shealy 75	0	80				7 mos.–?	n	25%	15–45%
Shelden 75		27	3	Ca 17					67%
Siegfried 82	191	89	75		−4 yrs.	1–8 yrs.		37%	
Sweet 74	100	98	33						
Urban 78	20	7	9					86%	
Winkelmüller 81	94	71	56	Amputation, SCI		4 mos.–7 yrs.			69%

Diagnoses: Ca = cancer; deaff = deafferentation; FBSS = failed back surgery syndrome; PHN = postherpetic neuralgia; RSD = reflex sympathetic dystrophy; SCI = spinal cord injury.
Third party follow-up: mfr = device manufacturer.





North R, Linderoth B in Schmidek & Sweet Operative Neurosurgical Techniques 5th edition, 2006

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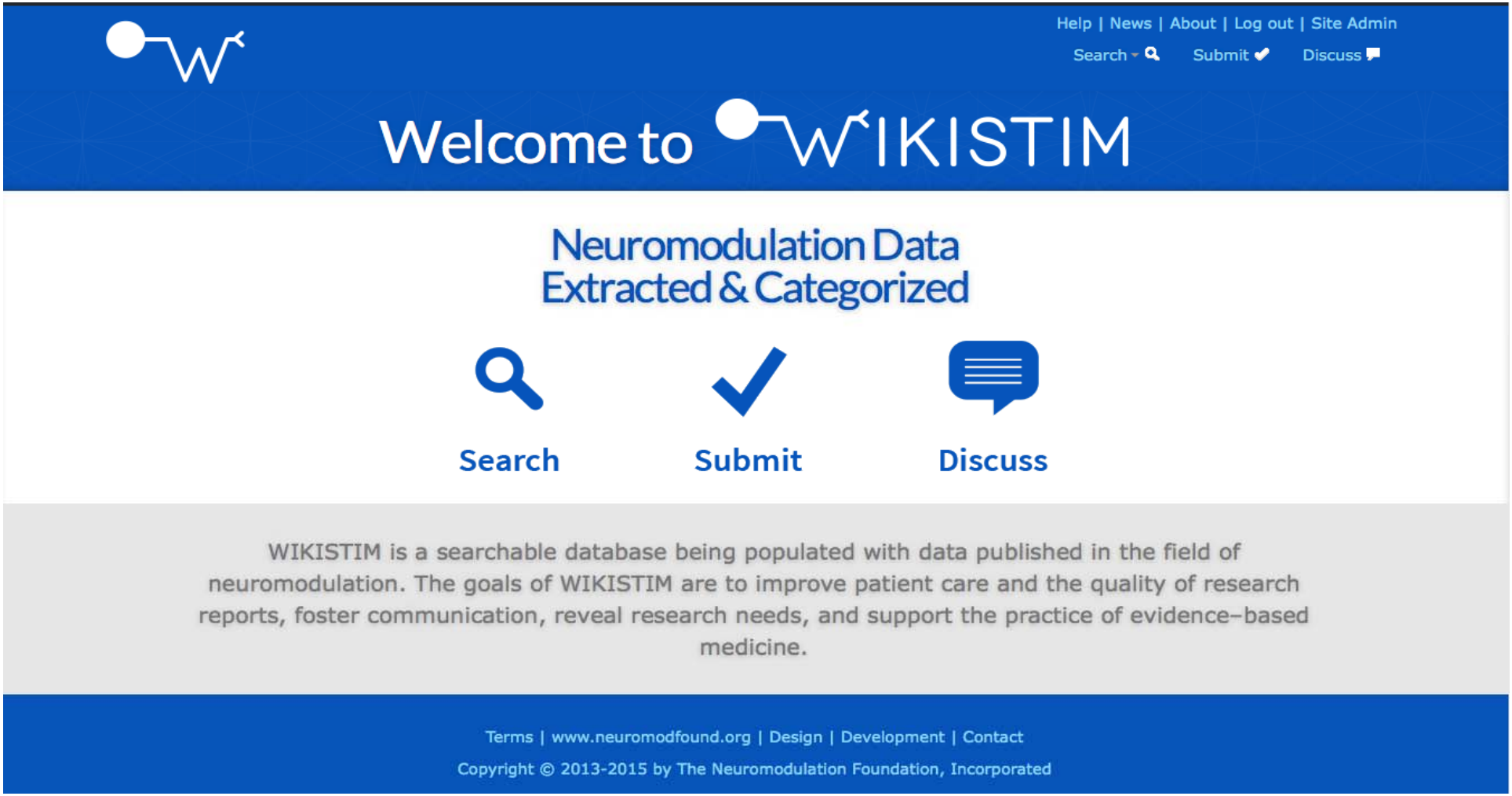

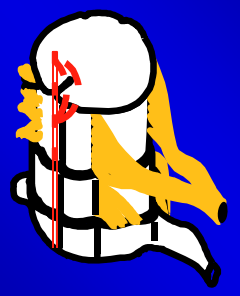

The history of research on the mechanisms, efficacy, and **safety** of spinal cord stimulation

Chronic Stimulation *via* Percutaneously Inserted Epidural Electrodes

Richard B. North, Timothy A. Fischell, and Donlin M. Long

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SYMPOSIUM: NEUROAUGMENTIVE DEVICES

Neurosurgery, Vol. 1, No. 2

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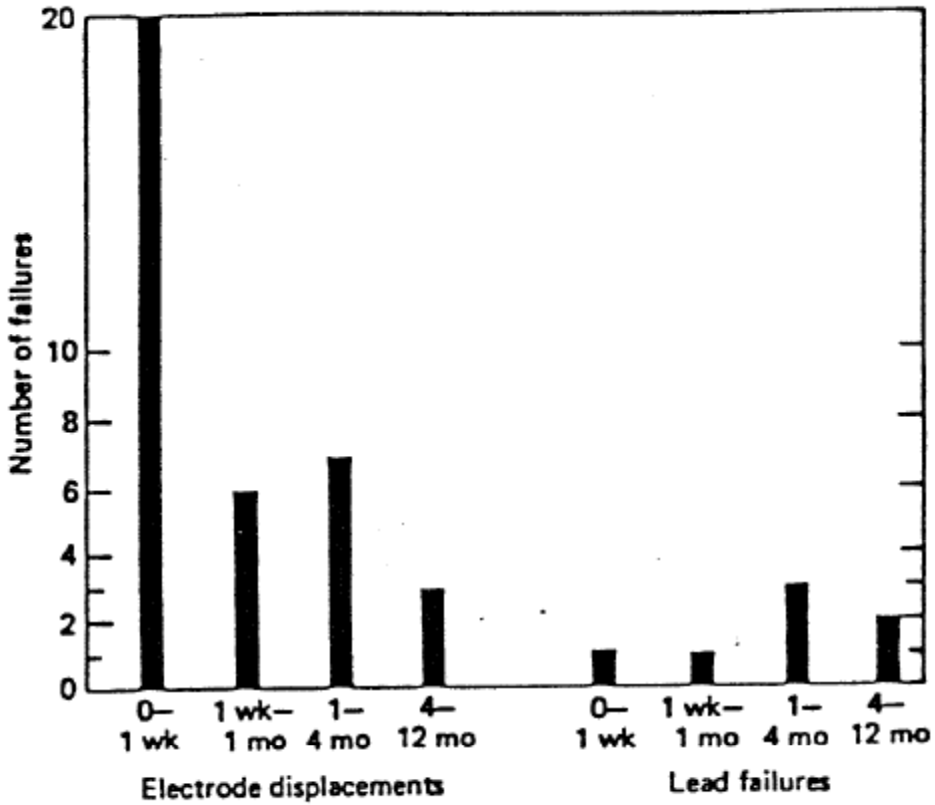

FIG. 3. Reliability: time to failure by mode.

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12206

The Appropriate Use of Neurostimulation: Avoidance and Treatment of Complications of Neurostimulation Therapies for the Treatment of Chronic Pain

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Incidence and Avoidance of Neurologic Complications with Paddle Type Spinal Cord Stimulation Leads

Robert Levy, MD, PhD*, Jaimie Henderson, MD†, Konstantin Slavin, MD‡, Brian A. Simpson, MD§, Giancarlo Barolat, MD¶, Jane Shipley, BA, Richard North, MD††**

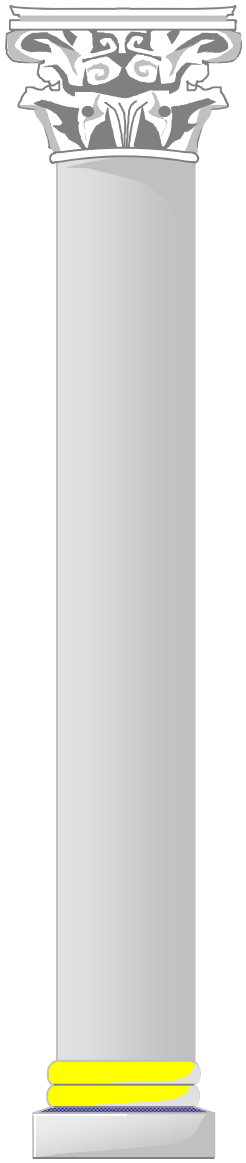
Introduction: While reference is frequently made to the risk of spinal cord or nerve root injury with the surgical implantation of paddle type spinal cord stimulation (SCS) electrodes, data are lacking on the frequency, causes, and prevention of these complications.

Methods: To determine the incidence and frequency of neurologic complications, we performed 1) a comprehensive analysis of the literature to determine the incidence of complications that have caused or could lead to neurologic injury; 2) an analysis of the US Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) data base; and 3) an investigation of manufacturers' data on surgically implanted paddle electrodes. We then convened an expert panel of neurosurgeons experienced in the surgical implantation of paddle electrodes to provide recommendations to minimize the risk of neurologic injury.

Results: The scientific literature describes the breadth of neurologic complications that can result from SCS electrode implantation but does not provide interpretable data with respect to the incidence and frequency of these complications. The MAUDE data base is not constructed to be sensitive or specific enough to provide these critical data. Primary data show a risk of neurologic injury from implantation of paddle electrodes below 0.6%.

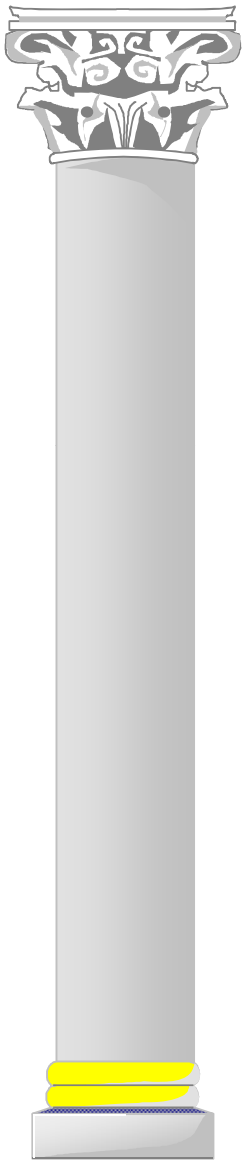
Discussion: Preoperative, intraoperative, and postoperative measures to further minimize this risk are described.

Conclusions: This investigation, the first comprehensive evaluation of the incidence and frequency of neurologic injury as a result of SCS paddle electrode implantation, suggests that neurologic injury is a rare, but serious, complication of SCS. The incidence of these complications should be decreased by the adoption of approaches that improve procedural safety and by careful patient follow-up and complication management. Physicians should be aware of these approaches and take every precaution to reduce the risk of neurologic injury. Physicians also should report any adverse event leading to injury or death and work together to improve access to these data.



For what a man
had rather were true
he more readily believes.

-Sir Francis Bacon
1561-1626



A Numbers Needed to Treat (NNT) Analysis of the Pivotal SUNBURST Study

Richard North[A]; Tim Deer[B]; Konstantin Slavin[C]; Peter Staats[D];
Chananit Hutson[E]; Kristina Davis[E]

[A] Johns Hopkins University School of Medicine, Baltimore, MD;
[B] Center for Pain Relief, Charleston, WV; [C] University of Illinois, Chicago, IL; [D] Premier Pain Centers, Shrewsbury, NJ; [E] Abbott

INTRODUCTION

New spinal cord stimulation (SCS) devices have expanded options, including multiple stimulation modes (burst and tonic). With initiatives to reduce opioid use for chronic pain patients, the context of SCS efficacy compared to pharmacological therapies is important. Number Needed to Treat/Harm (NNT/H) analyses provide relative prevalence of benefit and harms for comparison to pharmaceutical therapies.

Number Needed to Treat (NNT) – a marker for the rate of benefit - is defined as the number of subjects that need to be treated with a given therapy for one subject to achieve benefit. An NNT of 1 is a perfect score whereby all subjects achieved benefit; lower values are more favorable for a therapy. Conversely, Number Needed to Harm (NNH) is defined as the number of subjects that need to be treated with a given therapy for one subject to have a specified adverse outcome; higher values are more favorable.

METHODS

SUNBURST Study

SUNBURST, a randomized, crossover study, implanted subjects with a spinal cord stimulation (SCS) device (Prodigy™, Abbott) capable of delivering both burst (BurstDR™, Abbott) and tonic stimulation. Subjects completed a 7-day visual analog scale (VAS) diary for overall daily pain (Overall VAS) prior to each visit. Percentage change in mean overall VAS was calculated for the ITT population (N = 100) at 24 weeks, after subjects used tonic for 12 weeks and burst for 12 weeks. Percentage change in VAS was computed for available data at 1 year (N=80). After 24 weeks, subjects were free to select programs at-will. Subjects completed the Oswestry Disability Index (ODI) at baseline and 24 weeks and completed a Patient Global Impression of Change (PGIC) scale at 24 weeks. The majority of subjects (93% or 74/80) were using burst or a combination of burst and tonic programs at the 1-year visit.

Primary results of the study were previously published. [1]

Table 1 shows the baseline demographics of the SUNBURST subjects.

Table 1. SUNBURST Subject Demographics and Pain History (N=100)

Age [Mean (SD)]	59.1 (13.5)
Male [N(%)]	43 (43%)
Time Since Onset of Pain [Mean(SD)]	12.9 (10.1)
Using or had Used Oral Medications [N(%)]	97 (97%)
Primary Diagnosis [N(%)]	
Arachnoiditis	1 (1%)
CRPS I/CRPS II	2 (2%)
Degenerative spine disease	3 (3%)
Failed back surgery syndrome (FBSS)	42 (42%)
Neuritis/neuropathy/neuralgia	2 (2%)
Postoperative chronic pain	3 (3%)
Radiculopathies	38 (38%)
Chronic pain (non-postoperative)	9 (9%)

METHODS

Comparative Data from Pharmaceutical Pain Treatments

To provide context to the NNT and NNH values calculated for SUNBURST, comparative values were extracted from published meta-analyses of pharmaceutical therapies.[2,3] In both reviews, NNTs were based upon 50% reduction in pain and NNHs were based upon number of subjects who exited a study due to an adverse event.

Comparative NNT values extracted from published meta-analyses were calculated from studies with the following:

- Treatment duration of 3 to 24 weeks
- Placebo-controlled RCTs
- Subjects with neuropathic pain; radiculopathy is noted as underrepresented

Statistical Methods (SUNBURST)

For SUNBURST, NNT was calculated for the device overall, irrespective of the specific therapy mode delivered to the patient. As such, NNTs were calculated, using within-subject methods [4],as the inverse of the proportion of subjects meeting pre-specified benchmarks. Per IMMPACT guidelines [5], the following benchmarks were used in calculating NNT values:

- Clinically meaningful reduction in mean overall VAS (30% reduction)
- Clinically substantial reduction in mean overall VAS (50% reduction)
- Clinically perceptible improvement in function (10 pt improvement in ODI)
- Patient reported moderately better, much better, or great deal better on the PGIC (5 or better rating)

To be consistent with the NNH benchmarks in the comparative systematic reviews, SUNBURST NNH was calculated using the number of subjects who exited the study due to an adverse event or intolerable side effect through 24 weeks.

For all NNT and NNH values calculated using SUNBURST data, 95% Confidence Intervals for each were calculated using the Bender method [4]. Statistical comparisons of SUNBURST data to pharmacological meta-data were not appropriate due to potential differences in patient populations and none were performed.

The Likelihood of being harmed or helped (LHH), a marker of the relative risk/benefit, was calculated as NNH/NNT [7].

RESULTS

Table 2. NNTs for the SCS Device Overall (Change from Baseline)

Clinical Benchmark	NNT (95% CI)
24 Weeks	
30% Reduction in VAS	1.4 (1.3, 1.7)
50% Reduction in VAS	2.0 (1.7, 2.5)
ODI (10 pt improvement)	1.4 (1.3, 1.7)
PGIC (5 or better rating)	1.2 (1.1, 1.3)
1 Year	
30% Reduction in VAS	1.7 (1.4, 2.0)
50% Reduction in VAS	2.7 (2.1, 3.5)

RESULTS

NNT Values for the SCS device and Pharmaceutical Pain Management Therapies

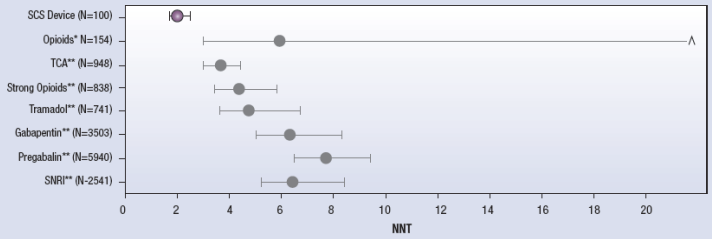


FIGURE 1. Numbers Needed to Treat for Benefit (NNT) was defined as the number of subjects needed to treat for one subject to obtain 50% reduction in pain intensity. Multi-mode SCS device (SUNBURST) NNT value was calculated using pain relief at 24 weeks. All pharmacological NNT values were published in systematic reviews and included studies with a treatment duration between 3 and 24 weeks. Bars represent 95% confidence intervals. ^ Error bar truncated for scale (upper bound = 50) *Cochrane Review of 5 RCTs for the treatment of neuropathic pain, including morphine, methadone, oxycodone, levorphanol and dihydrocodeine.[2] **Systematic review and metanalysis of 229 RCTs examining treatments for neuropathic pain.[3] TCA: tricyclic antidepressants; strong opioids: morphine or oxycodone or similar; SNRI: serotonin-norepinephrine reuptake inhibitor

NNH Values for the SCS device and Pharmaceutical Pain Management Therapies

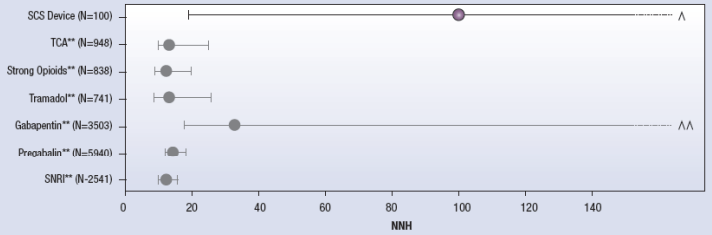


FIGURE 2. Numbers Needed to Harm (NNH) was defined as the number of subjects to be treated for one subject to exit the study due to an adverse event or intolerable side effect. Multi-mode SCS device (SUNBURST) NNH was calculated using subjects withdrawn through 24 weeks of the study. All pharmacological NNH values in published systematic reviews were based upon treatment duration between 3 and 24 weeks. Bars represent 95% confidence intervals. ^ Error bar truncated for scale (upper bound = 565) ^^ (upper bound = 230) *Cochrane Review of 5 RCTs for the treatment of neuropathic pain, including morphine, methadone, oxycodone, levorphanol and dihydrocodeine.[2] **Systematic review and metanalysis of 229 RCTs examining treatments for neuropathic pain.[3] TCA: tricyclic antidepressants; strong opioids: morphine or oxycodone or similar; SNRI: serotonin-norepinephrine reuptake inhibitor

Benefit/Risk Profile (LHH) for the SCS device and published pain management medications

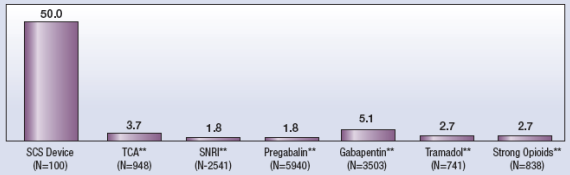


FIGURE 3. Likelihood of being harmed or helped (LHH) is an estimate of benefit/risk profile. LHH > 10 is considered very favorable [7]. **Systematic review and metanalysis of 229 RCTs examining treatments for neuropathic pain[3]. TCA: tricyclic antidepressants; strong opioids: morphine or oxycodone or similar; SNRI: serotonin-norepinephrine reuptake inhibitor

RESULTS

- For the SCS device, NNTs ranged from 1.2 to 2.0 at 24 weeks (Table 2).
- At 1 year post-implant, NNT values were similar.
- NNH values indicated 1 of every 100 subjects would exit the study due to an adverse event.
- The multi-modal SCS device had lower NNT and higher NNH values than a variety of common pain management medications (Figures 1 & 2).
- The overall risk/benefit profile (LHH) of the SCS device was more favorable than those calculated for the pharmacological therapies (Figure 3).

DISCUSSION

At 24 weeks, NNT values were similar across a variety of benchmarks (pain reduction, functioning, patient global impression). Moreover, NNT was lower than reported for a variety of pain management medications, indicating that the SCS device resulted in a 50% pain reduction more often than occurred with pharmacological therapies. Furthermore, NNH values were higher than those reported for oral medications. The LHH value is one indicator for the risk/benefit profile for the SCS device and results were favorable as compared to the other therapies included in this analysis.

The favorable profile of the SCS device is especially notable in this population of subjects with an average of 12 years of pain history for which almost all subjects had used or were using pharmacological pain management therapies upon entry in the study.

Interpretation of the comparisons to the pharmacological literature is limited by the fact that all the reviewed studies used a placebo comparator and had variable follow-up periods. Additionally, surgically implanted SCS devices require a bigger financial and emotional investment in the therapy, and the patient populations were unlikely to be directly comparable. In addition, differences in patient populations may limit the ability to make strong conclusions from this analysis; additional work with meta-analytic methods will provide a more accurate comparison of the device to other pain management therapies.

CONCLUSIONS

- Examination of NNT and NNH values, developed and used primarily for pharmaceuticals, confirms that the multi-modal SCS device provides an effective and safe therapy, which may have a better treatment profile than pain medications.
- The more favorable benefit/risk profile (high LHH value) is especially notable in this population of subjects who failed to achieve adequate pain control with pharmacological therapies.

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1. Deer TR, Slavin KV, Amirdelfan K, Kroth RB, Burton AW, et al. Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform. Neuromodulation, 2017, online ahead of print, DOI: 10.1111/ner.12698
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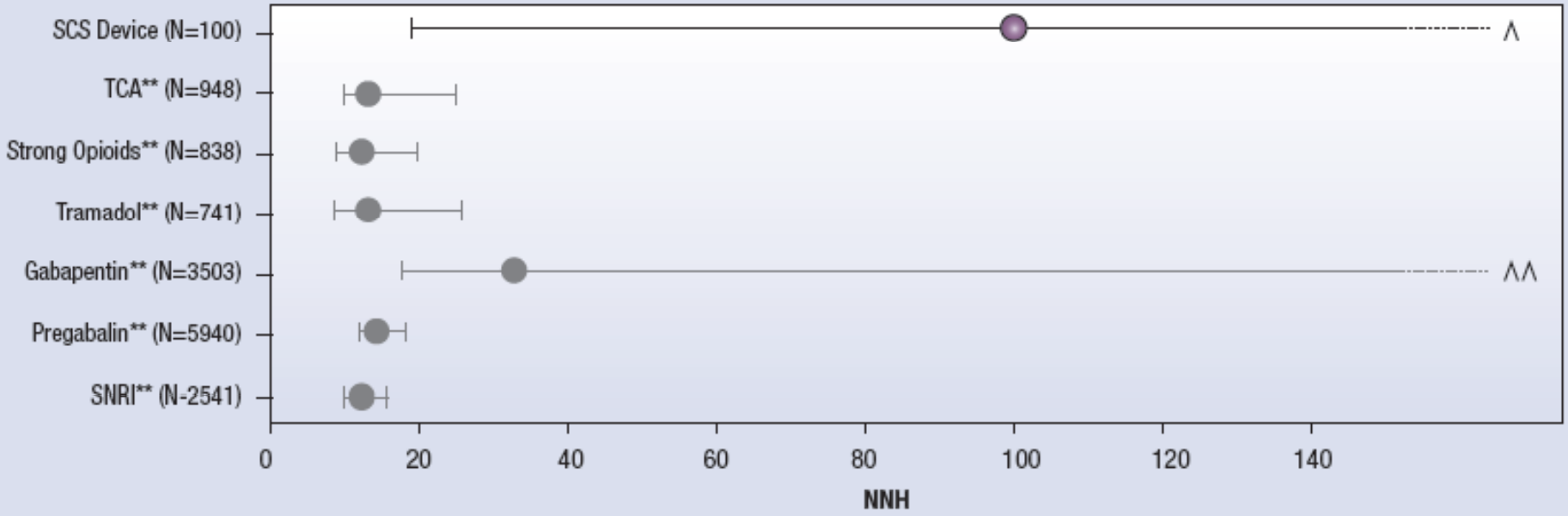

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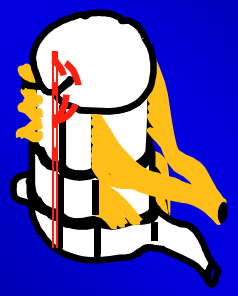
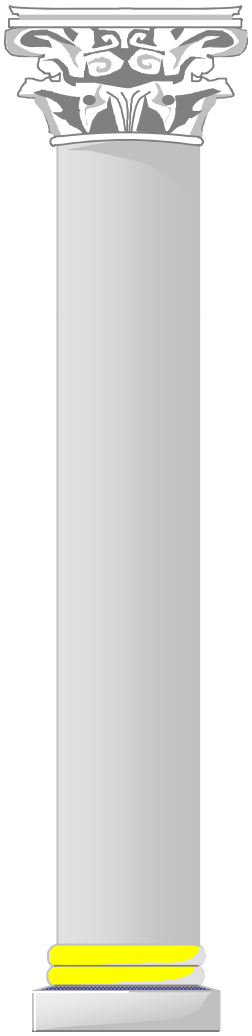


Conclusions

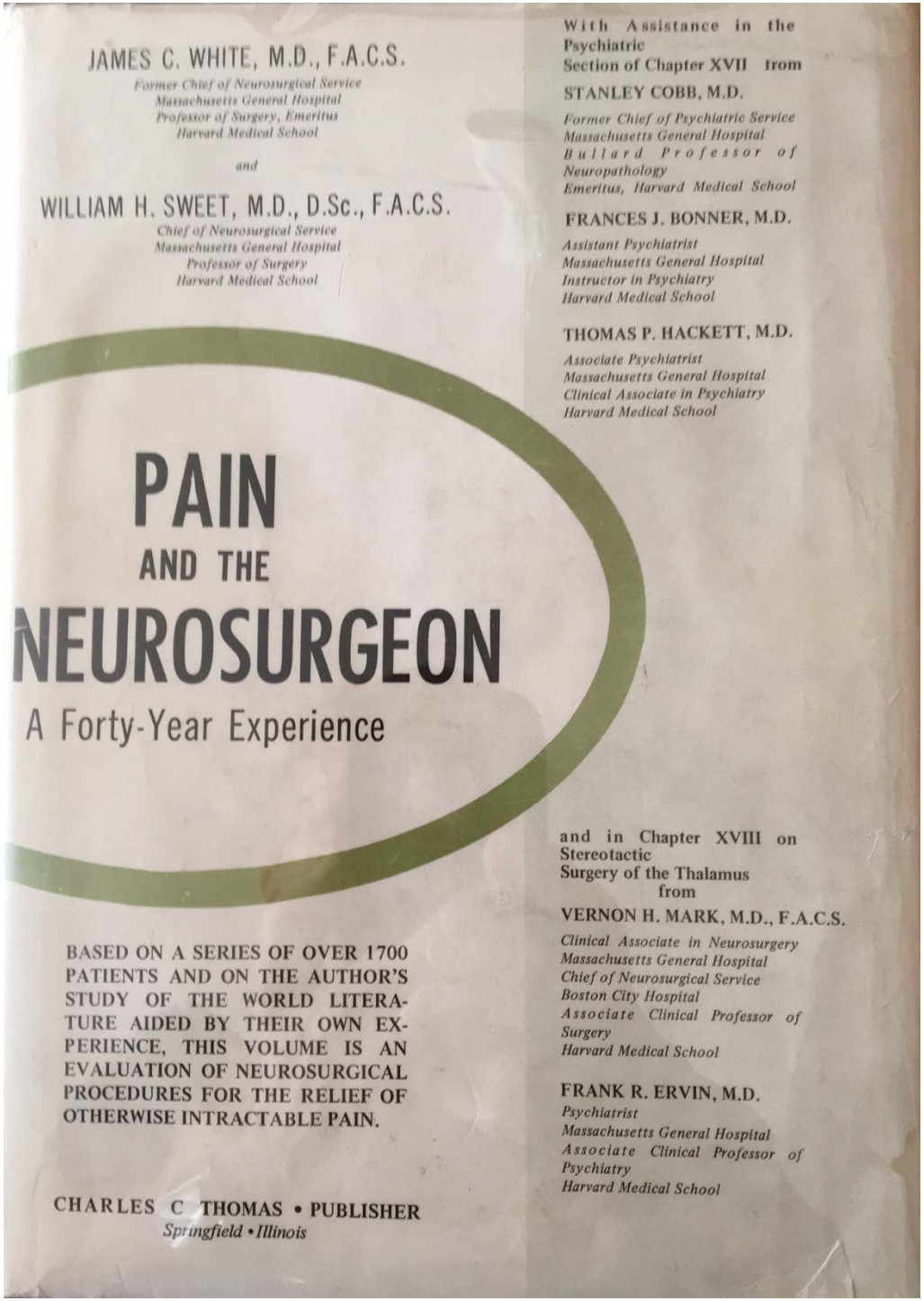
The history of research on the mechanisms, efficacy, and **safety** of spinal cord stimulation

Mechanisms-based Medicine



"An efficiently working reflex [gives] a correct answer, so to say, to an improper or wrong question."

Sir Charles Sherrington
1932 Nobel laureate



White & Sweet, 1969

TABLE 9.1

Neurosurgical Procedures for Pain Management[a]

Anatomic	Augmentative	Ablative
Decompression	Electrical stimulation	Open
Stabilization	Transcutaneous	Neurotomy
Reconstruction	Implanted devices	Sympathectomy
	Peripheral nerve	Ganglionectomy
	Spinal cord	Rhizotomy
	Intracerebral	DREZotomy
	Chemical infusion systems	Cordotomy
	Spinal epidural	Myelotomy
	Spinal subarachnoid	Tractotomy
	Intraventricular	Percutaneous radiofrequency
		Neurotomy (*e.g.* facet)
		Rhizotomy (*e.g.* trigeminal)
		Cordotomy
		Cingulumotomy
		Percutaneous chemical
		Lytic subarachnoid block
		Celiac alcohol block
		Stereotaxic hypophysectomy

[a] Neurosurgical procedures for the relief of pain may be divided into three categories: 1) anatomic procedures are directed at the structural cause, 2) augmentative procedures modulate pain transmission by electrical or chemical means, and 3) ablative procedures block pain transmission by destroying pain pathways.

North RB: Neurosurgical procedures for chronic pain: General neurosurgical practice. *Clinical Neurosurgery 40:182-196, 1992.*

LIFEBRIDGE HEALTH

The Sandra and Malcolm Berman Brain & Spine Institute

Functional Neurosurgery Versus Reconstructive Spine Surgery for Failed Back Surgery Syndrome: An Evidence-Based Approach

Richard B. North, MD, Baltimore, Maryland

Introduction

Repeated lumbosacral spine surgery for persistent or recurrent pain (FBSS) yields diminishing returns, as is well known (e.g., Fritsch 1996). Spinal cord stimulation (SCS), a reversible pain-relieving procedure performed by functional neurosurgeons and interventional pain specialists, compares favorably with repeated surgery by virtue of higher yield with lower morbidity and greater cost-effectiveness.

Methods

This review of the evidence comparing SCS with surgical and medical alternatives clarified future study design issues and objectives.

Results

A single-center RCT of SCS vs. reoperation for FBSS demonstrated significantly better clinical outcomes (North 2005) and greater cost effectiveness (North 2007a) for SCS in patients with prominent radicular pain. A multi-center RCT comparing SCS with conservative medical management reached similar conclusions (Kumar 2007). This is consistent with the nonrandomized studies that comprise the rest of the evidence base (North 2007b). A multi-center RCT of SCS vs. reoperation, which will incorporate the latest techniques and equipment for each, is underway (North 2010).

Discussion

SCS is a minimally invasive treatment for otherwise intractable neuropathic pain. SCS treatment success depends upon proper patient selection, equipment choice, and physician training. Studies of SCS must include protocols to protect patient safety, including careful patient selection criteria. SCS studies must also rely on appropriate outcome measures to determine treatment success. Additional outcomes can and should be collected, but pain relief should be the primary outcome. SCS studies must follow accepted standards regarding patient selection, sample size calculation, group comparability, standardized group treatment during data collection, reduction of bias, data analytical methods, and appropriate follow-up methods, including basing intervals on intervention dates (instead of study entry). Data reporting should include raw figures as well as percentages and information on all sub-group outcome.

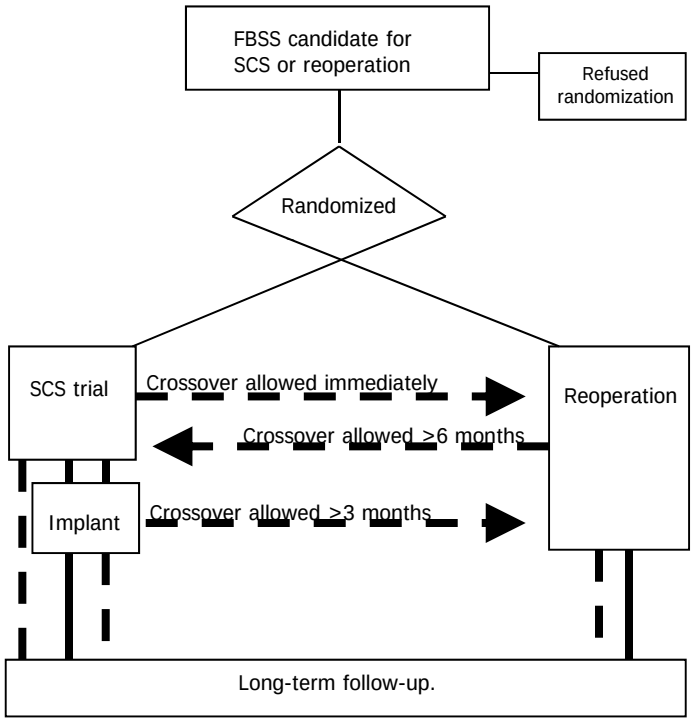


Figure 1. This RCT protocol allows crossover to occur once. Randomized treatment success is indicated by solid lines. Randomized treatment failure is indicated by dashed lines.

Conclusion

The evidence indicates that SCS, a functional procedure, is superior to reconstructive spine surgery in selected cases. A new multi-center RCT will provide additional up-to-date evidence.

Disclosure

Neither I nor a member of my immediate family has received anything of value* from or own stock (or stock options) in a commercial entity related directly or indirectly to the subject of this presentation. The FDA has cleared SCS for the use described in this presentation.

*In the past five years. Usual disclosure follows: Dr. North has no personal income from or equity interest in the medical device industry. His former employer (Johns Hopkins University) received funding from industry as does the non-profit Neuromodulation Foundation, of which he is an unpaid officer.

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A Numbers Needed to Treat (NNT) Analysis of the Pivotal SUNBURST Study

Richard North[A]; Tim Deer[B]; Konstantin Slavin[C]; Peter Staats[D];
Chananit Hutson[E]; Kristina Davis[E]

[A] Johns Hopkins University School of Medicine, Baltimore, MD;
[B] Center for Pain Relief, Charleston, WV; [C] University of Illinois, Chicago, IL; [D] Premier Pain Centers, Shrewsbury, NJ; [E] Abbott

INTRODUCTION

New spinal cord stimulation (SCS) devices have expanded options, including multiple stimulation modes (burst and tonic). With initiatives to reduce opioid use for chronic pain patients, the context of SCS efficacy compared to pharmacological therapies is important. Number Needed to Treat/Harm (NNT/H) analyses provide relative prevalence of benefit and harms for comparison to pharmaceutical therapies.

Number Needed to Treat (NNT) – a marker for the rate of benefit - is defined as the number of subjects that need to be treated with a given therapy for one subject to achieve benefit. An NNT of 1 is a perfect score whereby all subjects achieved benefit; lower values are more favorable for a therapy. Conversely, Number Needed to Harm (NNH) is defined as the number of subjects that need to be treated with a given therapy for one subject to have a specified adverse outcome; higher values are more favorable.

METHODS

SUNBURST Study

SUNBURST, a randomized, crossover study, implanted subjects with a spinal cord stimulation (SCS) device (Prodigy™, Abbott) capable of delivering both burst (BurstDR™, Abbott) and tonic stimulation. Subjects completed a 7-day visual analog scale (VAS) diary for overall daily pain (Overall VAS) prior to each visit. Percentage change in mean overall VAS was calculated for the ITT population (N = 100) at 24 weeks, after subjects used tonic for 12 weeks and burst for 12 weeks. Percentage change in VAS was computed for available data at 1 year (N=80). After 24 weeks, subjects were free to select programs at-will. Subjects completed the Oswestry Disability Index (ODI) at baseline and 24 weeks and completed a Patient Global Impression of Change (PGIC) scale at 24 weeks. The majority of subjects (93% or 74/80) were using burst or a combination of burst and tonic programs at the 1-year visit.

Primary results of the study were previously published. [1]

Table 1 shows the baseline demographics of the SUNBURST subjects.

Table 1. SUNBURST Subject Demographics and Pain History (N=100)

Age [Mean (SD)]	59.1 (13.5)
Male [N(%)]	43 (43%)
Time Since Onset of Pain [Mean(SD)]	12.9 (10.1)
Using or had Used Oral Medications [N(%)]	97 (97%)
Primary Diagnosis [N(%)]	
Arachnoiditis	1 (1%)
CRPS I/CRPS II	2 (2%)
Degenerative spine disease	3 (3%)
Failed back surgery syndrome (FBSS)	42 (42%)
Neuritis/neuropathy/neuralgia	2 (2%)
Postoperative chronic pain	3 (3%)
Radiculopathies	38 (38%)
Chronic pain (non-postoperative)	9 (9%)

METHODS

Comparative Data from Pharmaceutical Pain Treatments

To provide context to the NNT and NNH values calculated for SUNBURST, comparative values were extracted from published meta-analyses of pharmaceutical therapies.[2,3] In both reviews, NNTs were based upon 50% reduction in pain and NNHs were based upon number of subjects who exited a study due to an adverse event.

Comparative NNT values extracted from published meta-analyses were calculated from studies with the following:

- Treatment duration of 3 to 24 weeks
- Placebo-controlled RCTs
- Subjects with neuropathic pain; radiculopathy is noted as underrepresented

Statistical Methods (SUNBURST)

For SUNBURST, NNT was calculated for the device overall, irrespective of the specific therapy mode delivered to the patient. As such, NNTs were calculated, using within-subject methods [4],as the inverse of the proportion of subjects meeting pre-specified benchmarks. Per IMMPACT guidelines [5], the following benchmarks were used in calculating NNT values:

- Clinically meaningful reduction in mean overall VAS (30% reduction)
- Clinically substantial reduction in mean overall VAS (50% reduction)
- Clinically perceptible improvement in function (10 pt improvement in ODI)
- Patient reported moderately better, much better, or great deal better on the PGIC (5 or better rating)

To be consistent with the NNH benchmarks in the comparative systematic reviews, SUNBURST NNH was calculated using the number of subjects who exited the study due to an adverse event or intolerable side effect through 24 weeks.

For all NNT and NNH values calculated using SUNBURST data, 95% Confidence Intervals for each were calculated using the Bender method [4]. Statistical comparisons of SUNBURST data to pharmacological meta-data were not appropriate due to potential differences in patient populations and none were performed.

The Likelihood of being harmed or helped (LHH), a marker of the relative risk/benefit, was calculated as NNH/NNT [7].

RESULTS

Table 2. NNTs for the SCS Device Overall (Change from Baseline)

Clinical Benchmark	NNT (95% CI)
24 Weeks	
30% Reduction in VAS	1.4 (1.3, 1.7)
50% Reduction in VAS	2.0 (1.7, 2.5)
ODI (10 pt improvement)	1.4 (1.3, 1.7)
PGIC (5 or better rating)	1.2 (1.1, 1.3)
1 Year	
30% Reduction in VAS	1.7 (1.4, 2.0)
50% Reduction in VAS	2.7 (2.1, 3.5)

RESULTS

NNT Values for the SCS device and Pharmaceutical Pain Management Therapies

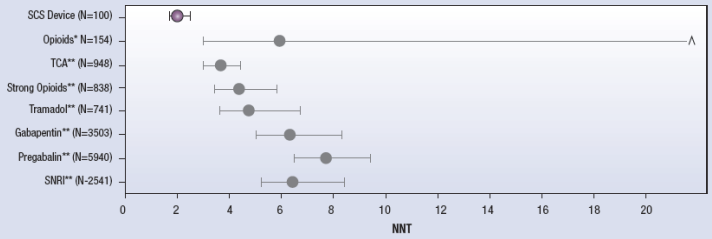

FIGURE 1. Numbers Needed to Treat for Benefit (NNT) was defined as the number of subjects needed to treat for one subject to obtain 50% reduction in pain intensity. Multi-mode SCS device (SUNBURST) NNT value was calculated using pain relief at 24 weeks. All pharmacological NNT values were published in systematic reviews and included studies with a treatment duration between 3 and 24 weeks. Bars represent 95% confidence intervals. ^ Error bar truncated for scale (upper bound = 50) *Cochrane Review of 5 RCTs for the treatment of neuropathic pain, including morphine, methadone, oxycodone, levorphanol and dihydrocodeine.[2] **Systematic review and metanalysis of 229 RCTs examining treatments for neuropathic pain.[3] TCA: tricyclic antidepressants; strong opioids: morphine or oxycodone or similar; SNRI: serotonin-norepinephrine reuptake inhibitor

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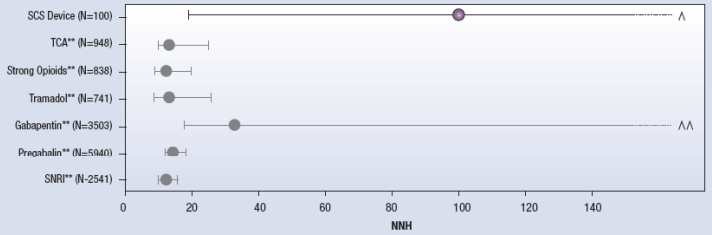

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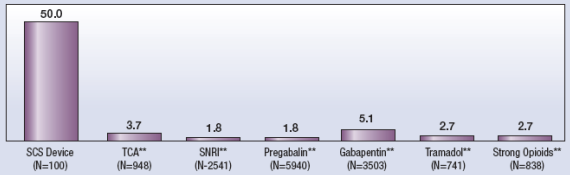

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