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DORSAL ROOT GANGLION STIMULATION IN CRPS

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WHAT IS COMPLEX REGIONAL PAIN SYNDROME (CRPS)?

Historically also known as causalgia, reflex sympathetic dystrophy (RSD)*.

*"CRPS is a chronic pain condition characterized by continuing (spontaneous and/or evoked) **regional pain** that is seemingly **disproportionate in time or degree** to the usual course of pain after trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor edema, and/or trophic findings."*

International Association for the Study of Pain

*Please note that in 1994, a consensus group of pain medicine experts gathered by the International Association for the Study of Pain (IASP) reviewed diagnostic criteria and agreed to rename reflex sympathetic dystrophy (RSD) and causalgia, as complex regional pain syndrome (CRPS) types I and II, respectively.

CRPS WAS FIRST DESCRIBED OVER 150 YEARS AGO

- Dr. SW Mitchell, a neurologist, described this syndrome in injured civil war soldiers in 1872[1]
  - "… Causalgia, the most terrible of all tortures which a nerve wound may inflict."
  - "Its favorite site is the foot or hand*. . . Its intensity varies from the most trivial burning to a state of torture, which can hardly be credited, but reacts on the whole economy, until the general health is seriously affected."
- Today, controversy remains about many aspect of CRPS including:[2,3]
  - Progression of CRPS through various stages (vs. different subtypes of the disease)
  - Psychological aspects of the disorder
  - Peripheral vs. central causes/maintenance of symptoms – the disorder is viewed differently across the globe, underscoring the complexity of the disorder.

1. Mitchell SW. Injuries of the Nerves and Their Consequences. Philadelphia: JB Lippincott & Co.; 1872
2. Marinus J, et al. Lancet Neurology 2011
3. Janig W and Baron R. Lancet Neurology. 2003

*DRG stimulation therapy with the Axium™ Neurostimulator system is not indicated for areas outside of the lower limbs.

CRPS INCIDENCE RATE IS BETWEEN 5.46-26.2 PER 100,000 PERSON-YEARS AT RISK[1,2]

1. Sandroni P, et al. Pain 2003
2. De Mos, et al. Pain 2007

PATHOPHYSIOLOGY OF CRPS IS NOT FULLY UNDERSTOOD

Multifactorial process involving both peripheral and central mechanisms

- Possible mechanisms involved in CRPS
- Nerve injury
- Ischemic reperfusion injury or oxidative stress
- Central sensitization
- Peripheral sensitization
- Altered sympathetic nervous system function or sympatho-afferent coupling
- Inflammatory and immune related factors
- Brain changes
- Genetic factors
- Psychological factors and disuse

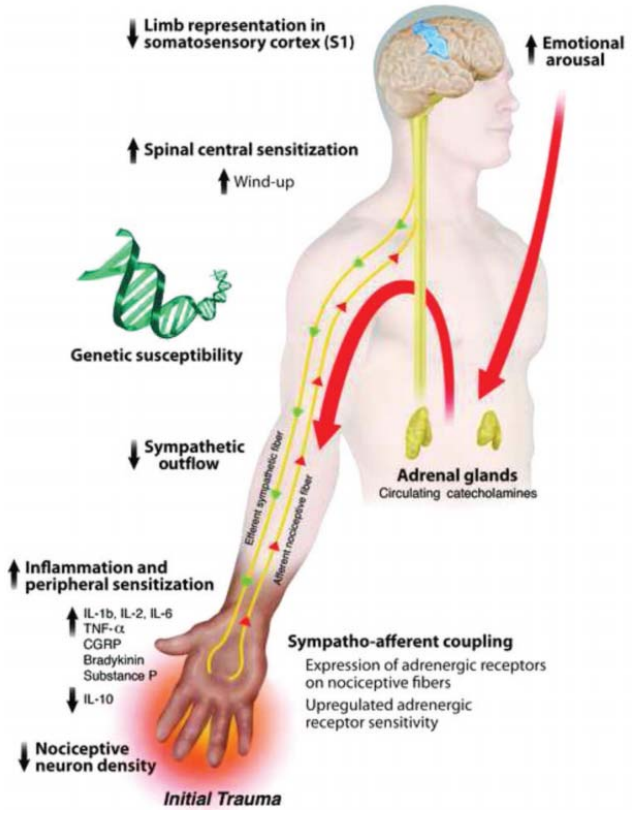


Image from: Bruehl S. Anesthesiology 2010.*

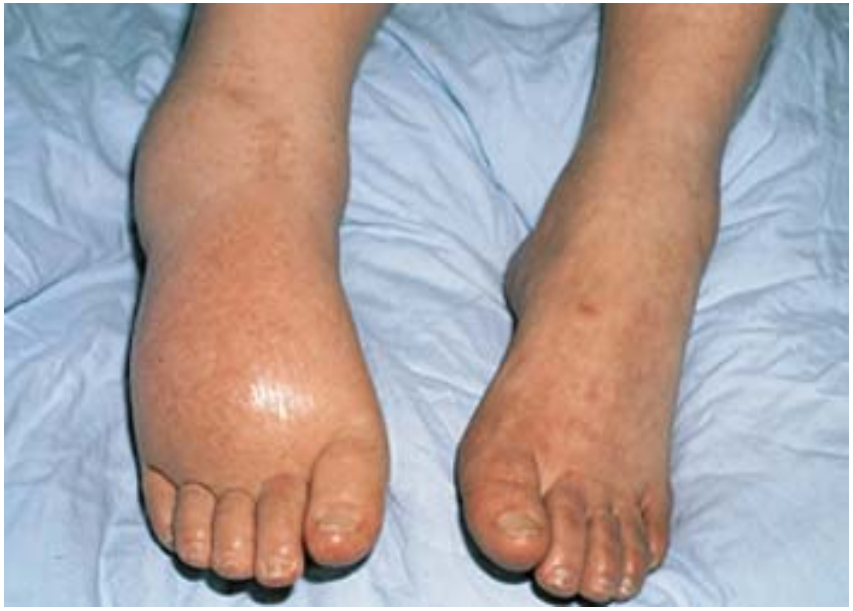
Bruehl S. BMJ 2015.

*DRG stimulation therapy with the Axium™ Neurostimulator system is not indicated for areas outside of the lower limbs.

CRPS: MOST COMMON SIGNS AND SYMPTOMS

Distinguished from other chronic pain conditions by the presence of signs indicating prominent autonomic and inflammatory changes in the region of pain.

- Limb displaying extreme hyperalgesia and allodynia (normally non-painful stimuli such as touch or cold are experienced as painful)
- Obvious changes to skin color, skin temperature, and sweating relative to the unaffected side
- Edema and altered patterns of hair, skin, or nail grown in the affected region
- Reduced strength
- Tremors
- Dystonia
- Altered body perception and proprioception may also be present (i.e. reduced limb positioning accuracy, delays in recognizing limb laterality, abnormal referred sensations, and tactile perception)



Bruehl S. BMJ. 2015

CLINICAL CHARACTERISTICS CHANGE OVER TIME

Acute phase – mixture of noxious sensations and sensory loss	Months – clinical features spread proximally	> 5 years
▪ Extremely painful limb ▪ Redness ▪ Warm (can quickly become cold) ▪ Swollen ▪ Allodynia ▪ Hyperalgesia ▪ Changes in sweating ▪ Changes in hair and nail growth ▪ Muscle weakness ▪ Mechanical and thermal hyperalgesia ▪ Reduction in voluntary motor control ▪ Hyperpathia ▪ Hypoesthesia, hypoalgesia, and hypothermesthesia	▪ Warm limb often becomes cold ▪ Dystonia, tremor, and myoclonus may develop ▪ Activity of the limb exacerbates signs and symptoms ▪ Clinical features may spread proximally (but not distally) and emerge on the opposite or ipsilateral limb	▪ Urological symptoms ▪ Syncope ▪ Mild cognitive defects

Marinus J, et al. Lancet Neurology 2011.

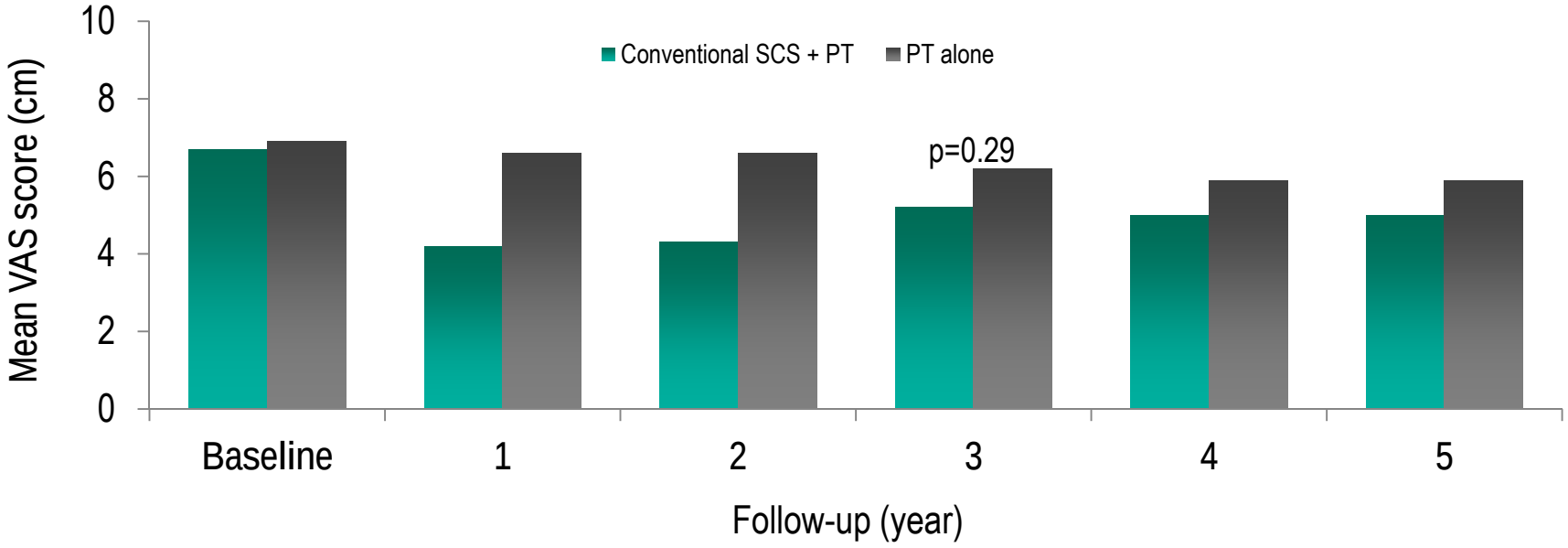
TREATMENT OF CRPS

Treatment usually consists of several objectives:

- Functional restoration of affected limb - often should be considered first before other treatments
- Sympathetic and/or motor blocks
- Cognitive behavioral techniques
- Psychotherapy
- Pharmacotherapy
- Occupational and physical therapy

FOR CRPS PATIENTS, PAIN RELIEVING EFFECTS OF CONVENTIONAL SCS DIMINISH OVER TIME

- Objective: Prospective RCT to determine whether treatment of CRPS with conventional SCS and PT is more effective than PT alone
  - 5 year analysis compared 31 patients with SCS device and 13 patients in control group
- After 3 years, pain-alleviating effect of conventional SCS in CRPS patients is no longer statistically significant



Kemler MA, et al. NEJM 2000, 2006.

THE DORSAL ROOT GANGLION: REVIEW OF ANATOMY

The DRG: A collection of bipolar cell bodies of neurons surrounded by glial cells and the axons of the DRG sensory cells that form the primary afferent sensory nerve

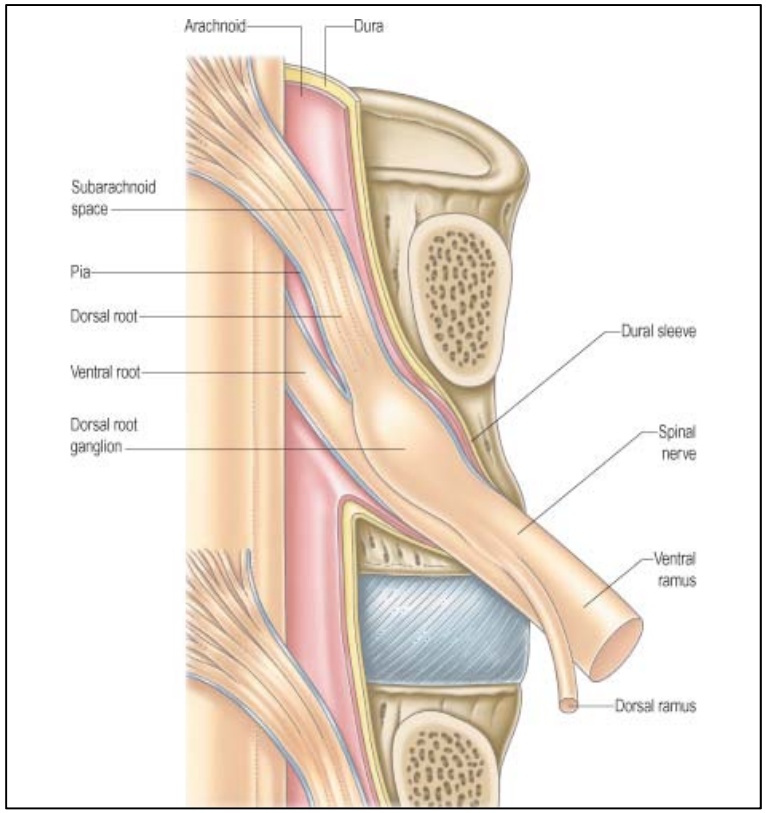


Image from: Gray's Anatomy (2005). Standring, S. (Ed.).

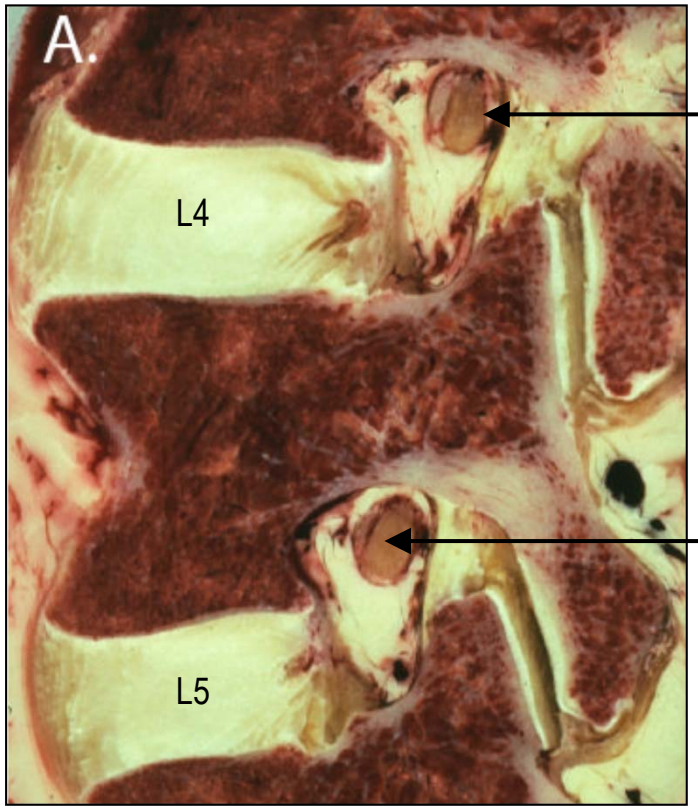
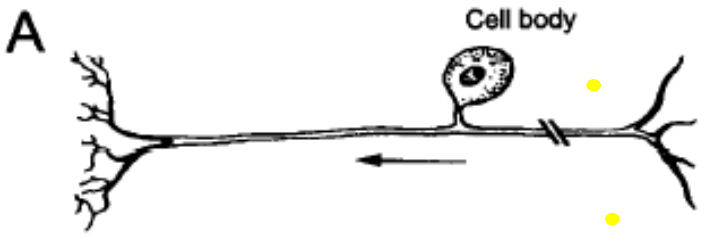


Image from: Hogan Q. Reg Anesth Pain Med. 2010.

THE PECULIAR PROPERTIES OF THE DORSAL ROOT GANGLION

- **Special structure**: DRG neurons have a peculiar pseudounipolar morphology – unique in the nervous system
- **Unique Function**: T-junctions act as the filter function for cell transduction and potential neuromodulation target
- **Highly Organized and Selective**: Small and large soma consistent with axonal specificity of sensory transduction therefore dictating electrophysiological selectivity
- **Specialized Membrane Characteristics**: Somata of many DRG neurons have the specialized membrane characteristics necessary for spike initiation, and some are even capable of repetitive firing
- **Minimal CSF**: Subdural structure with minimal surrounding CSF unlike the spinal cord



Devor, Pain Supplement 6. 1999.

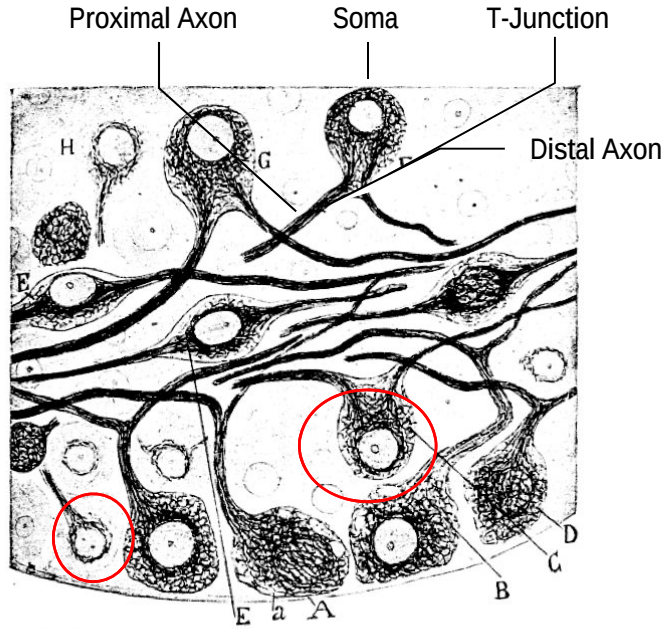


FIG. 235. Nerve cells of a sensory ganglion in process of evolution. *A* and *B*, monopolar corpuscles showing the reticulum of the neurofibrils; *E*, bipolar neurones.

Ramon y Cajal, et al. (Eds.) Histology. 1933.

THE DORSAL ROOT GANGLION: TARGET FOR NEUROMODULATION

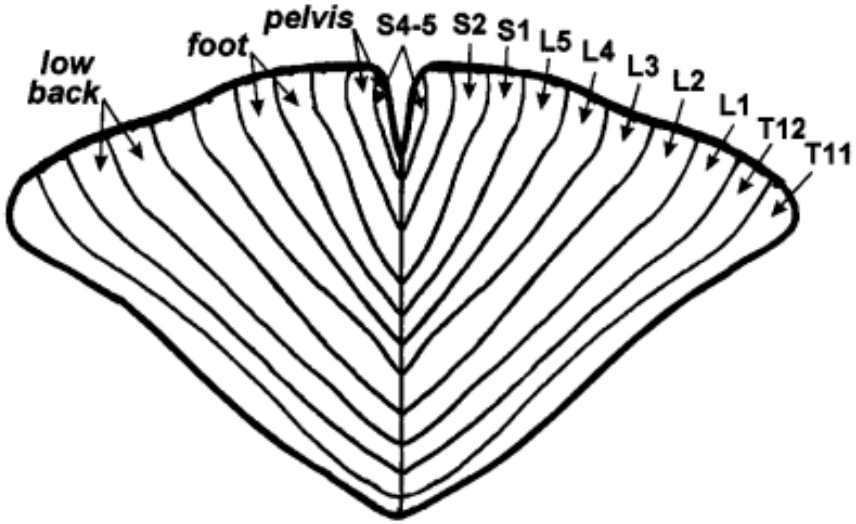
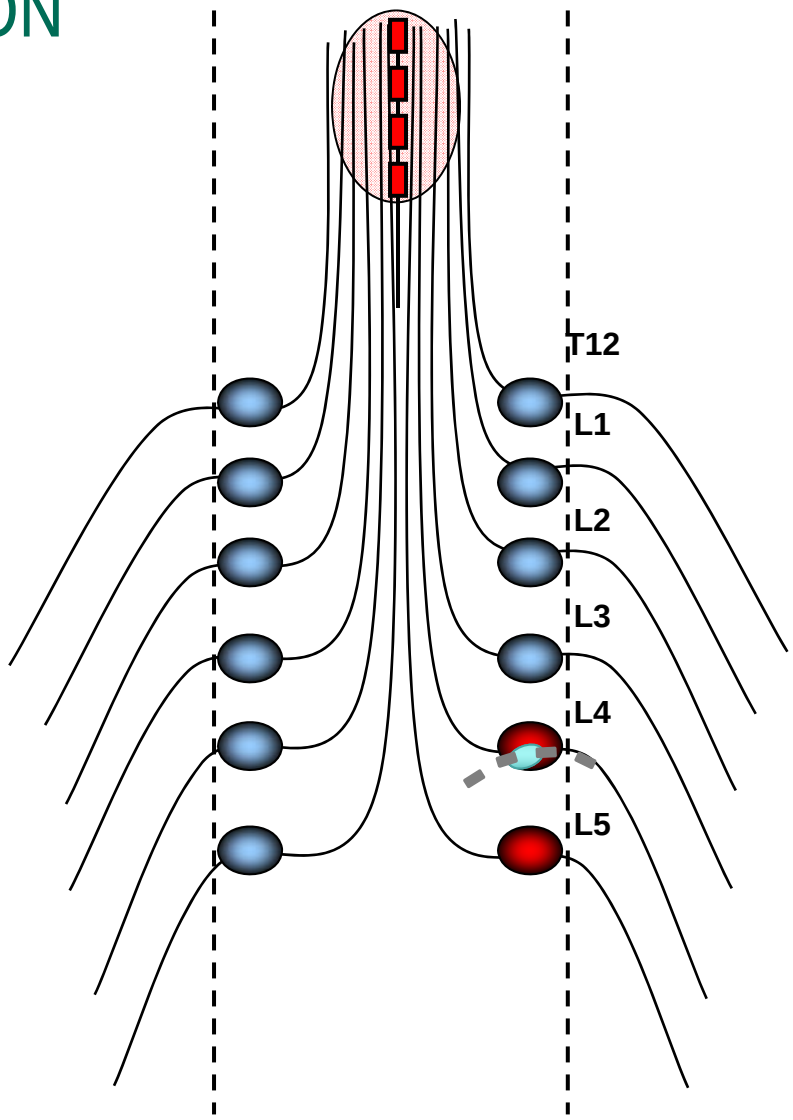


Image from: Feirabend HKP, et al. Brain. 2002.



WHY TARGET THE DRG?

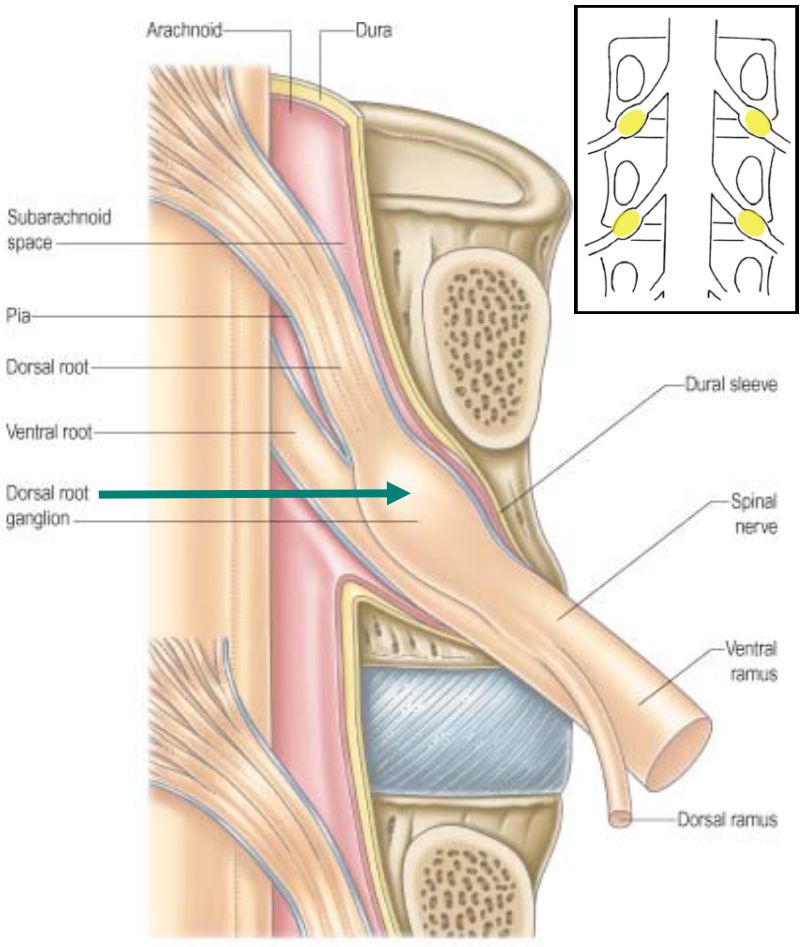
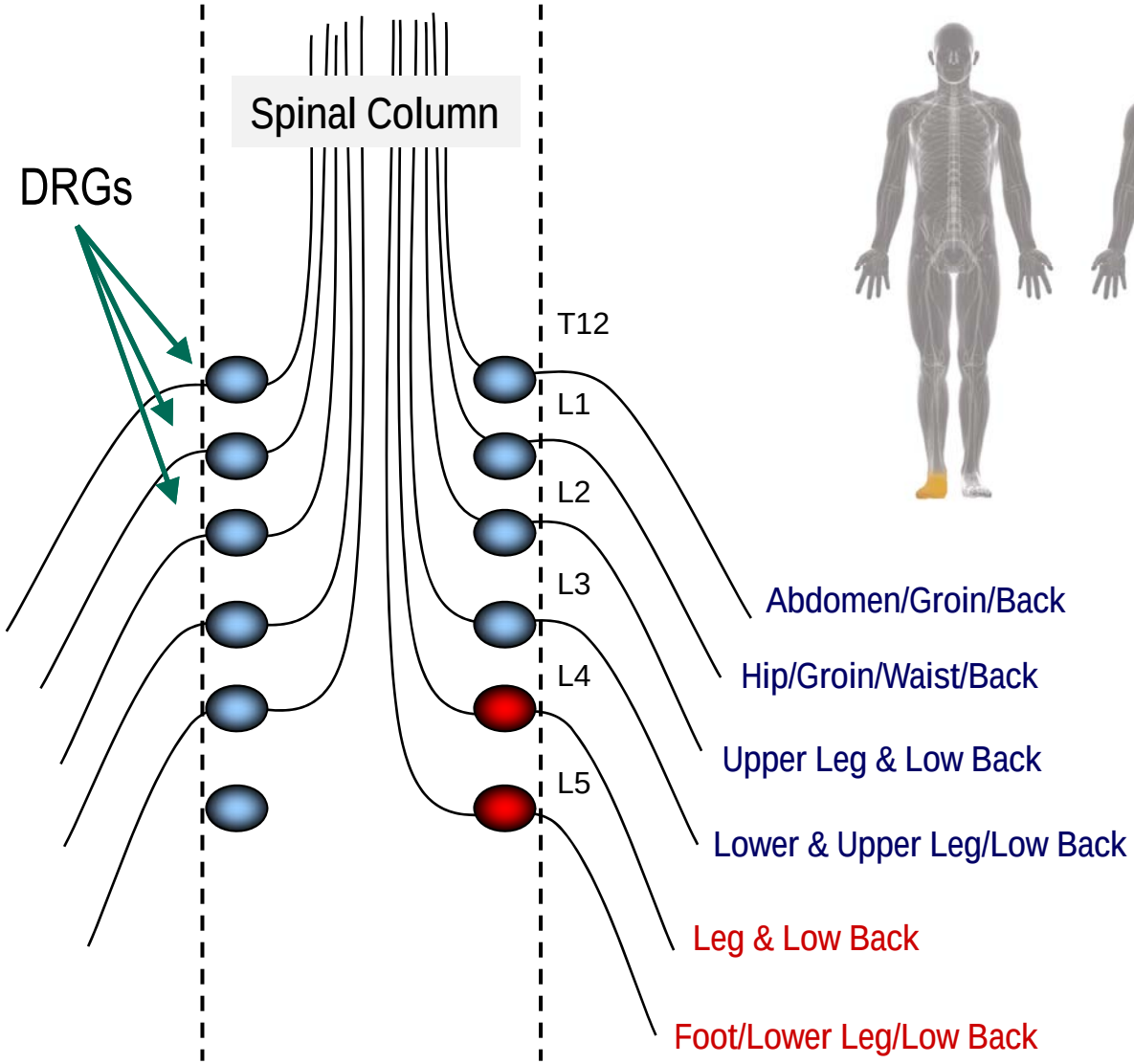
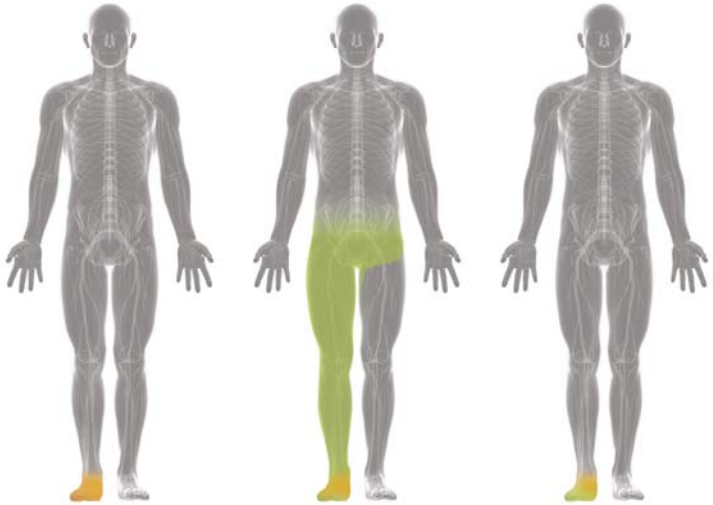


Image from: Gray's Anatomy (2005). Standring, S. (Ed.).

- **Known mechanisms & processes:** DRGs are known target for pain relief
- **Predictable & accessible location** in the epidural space within the neural foramen: easy target for neuromodulation by adapting current SCS needle techniques
- **Limited Cerebrospinal Fluid** (CSF) around the DRG allows the leads to be closer to the anatomical target & requires less energy to stimulate (compared to conventional SCS)
- **Separation of sensory & motor nerve fibers** prevents unintentional stimulation

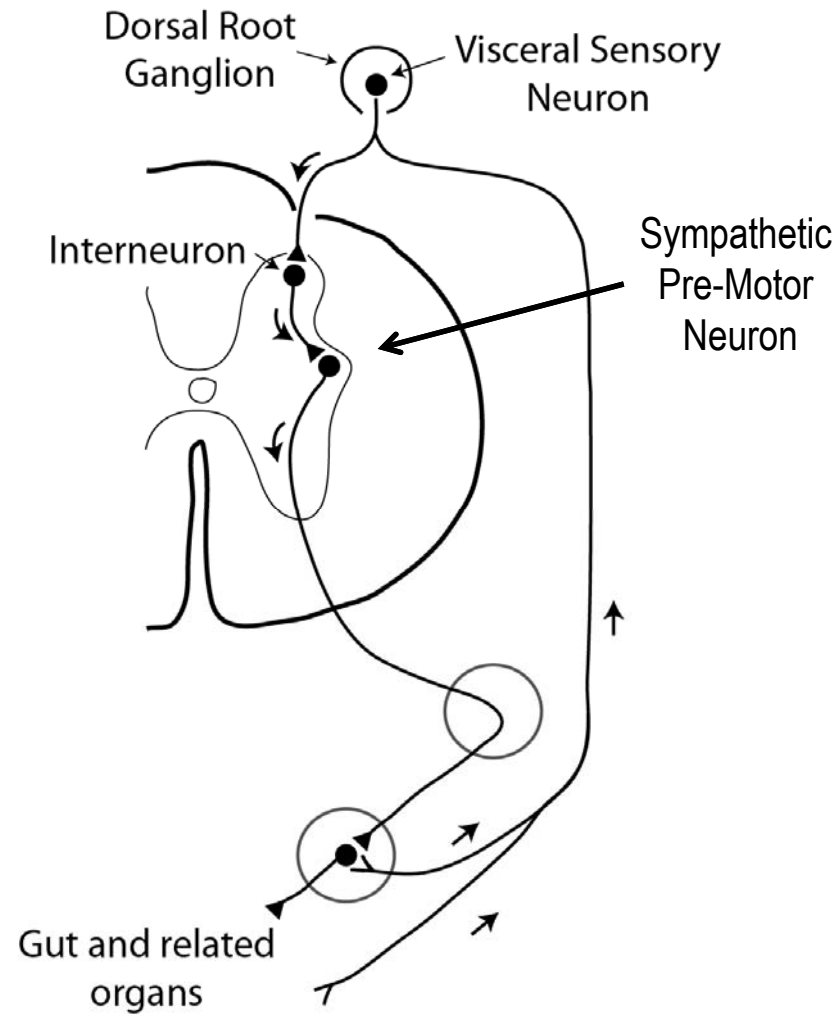
WHY TARGET THE DRG? (CONT'D)



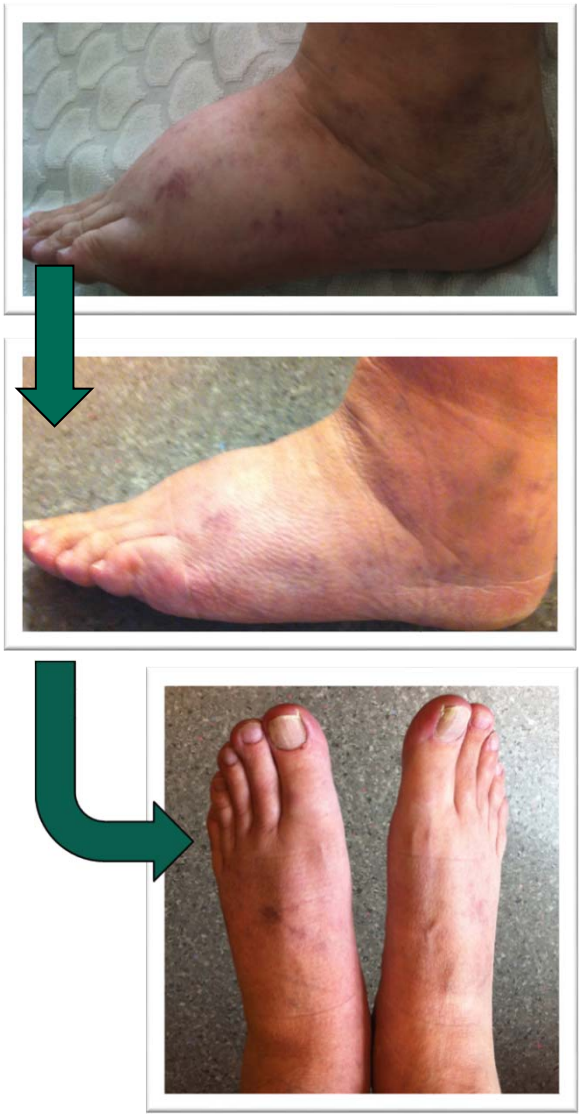


Well mapped & organized to corresponding anatomies – allowing for highly focused treatment of pain

DRG STIMULATION & SOMATOSYMPATHETIC REFLEXES



Adapted from: Loewy and Spyer, Central Regulation of Autonomic Function, 1990.



Baseline

1 month

CURRENT LIMITATIONS OF CONVENTIONAL SCS

Unstable Stimulation

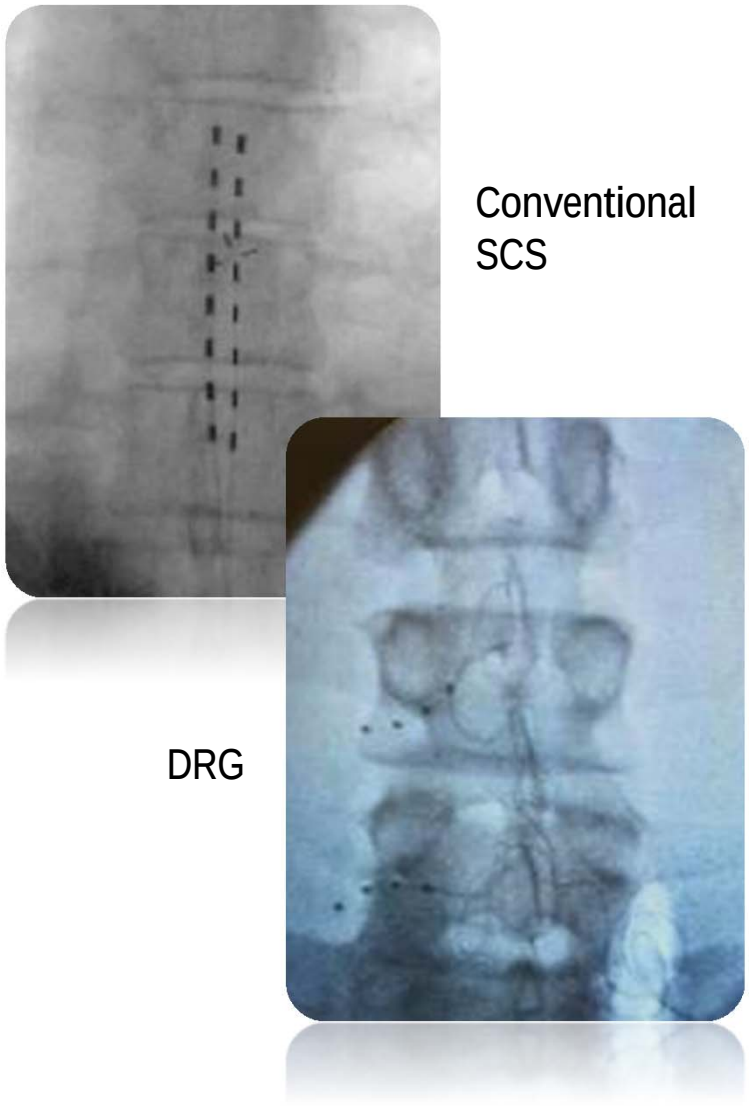
- Susceptible to body position due to variations in distance between stimulation lead & target
- Lead migrations rates (percutaneous) reported between 9-27%[1,2,3]

Unspecific Stimulation

- Broad Stimulation Coverage: targeting spinal cord sensory nerves
- Unspecific to anatomical location of pain/disease
- Energy is delivered to multiple types of nerves, not just pain- or disease-specific nerves

High Energy Usage

- Significant energy loss to surrounding anatomy (i.e. cerebral spinal fluid, CSF) before stimulation reaches target in spinal cord



Conventional SCS

DRG

1. Deer et al, Neuromodulation 2014.
2. Cameron T. J Neurosurg. 2004
3. Kim DD, et al. Pain Physician. 2011

DRG STIMULATION IS DESIGNED TO ADDRESS LIMITS OF CONVENTIONAL SCS

Unstable Stimulation

Limited Cerebrospinal Fluid (CSF) around the DRG allows the leads to be closer to the anatomical target: potentially producing less postural effects (compared to conventional SCS)[1,2]

Unspecific Stimulation

Separation of sensory & motor nerve fibers may prevent unintentional stimulation

Well mapped & organized to **corresponding anatomies** – allowing for highly focused treatment of pain

High Energy Usage

Limited Cerebrospinal Fluid (CSF) around the DRG allows the leads to be closer to the anatomical target: potentially less energy needed to stimulate sensory fibers (compared to conventional SCS)

1. Van Buyten, J. P., et al. Pain Practice 2015..
2. Liem, L., et al. Neuromodulation 2015.

CRPS CASE SERIES

ORIGINAL ARTICLE

Stimulation of Dorsal Root Ganglia for the Management of Complex Regional Pain Syndrome: A Prospective Case Series

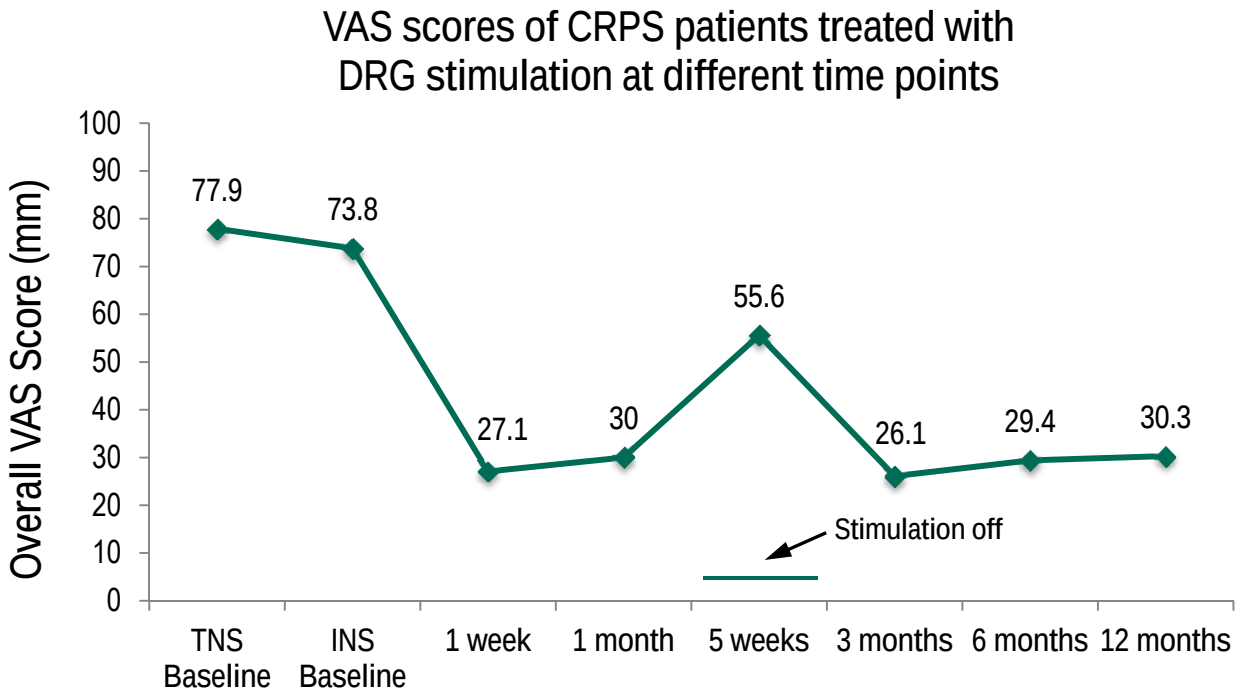
Jean-Pierre Van Buyten, MD*; Iris Smet, MD*; Liong Liem, MD†; Marc Russo, MD‡; Frank Huygen, MD, PhD§

*Multidisciplinary Pain Center, Algemeen Ziekenhuis Nikolaas, Sint-Niklaas, Belgium; †Sint Antonius Hospital, Nieuwegein, the Netherlands; ‡Hunter Pain Clinic, Broadmeadow, New South Wales, Australia; §Erasmus University, Rotterdam, the Netherlands

- Objective: To evaluate the effects of DRG stimulation in CRPS patients (n=11).
- Prospective case-series study; 72% (8/11) patients had successful trials and moved onto permanent implant
- Follow-ups occurred at 1 week, 1 month, 5 weeks (stimulation off), 2 months, 3 months, 6 months, and 12 months post-implant

Van Buyten JP, et al. Pain Practice 2015.

CRPS CASE SERIES

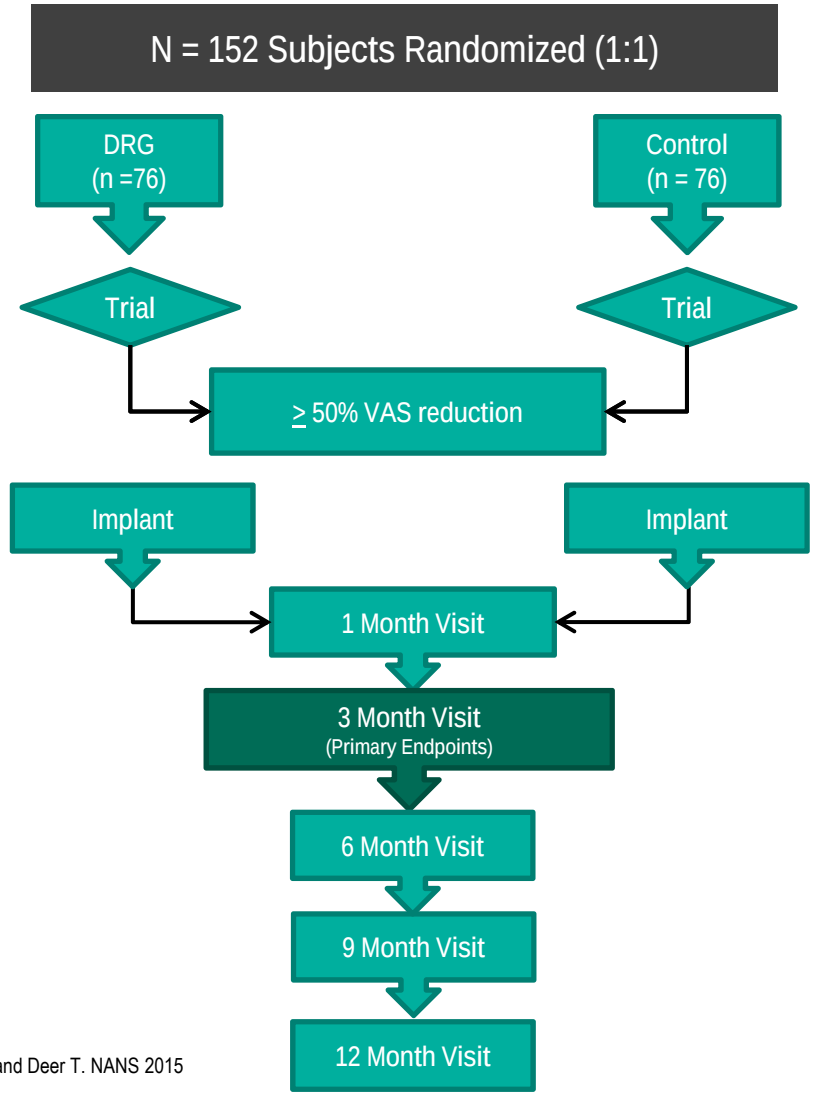


At 12 months subjects reported a 61.7% (±16.4%) decrease from baseline in pain ($P<0.05$)

- Similar results were reported for foot pain and leg pain at all time points. At 12 months, 85.7% (6/7) of patients with foot pain and 80.0% (4/5) of patients with leg pain had ≥ 50% pain relief
- Statistically significant improvements from baseline were observed in all secondary endpoints at 12 months (pain severity and pain interference, quality of life, and mood disturbance)
- Pain relief remained stable over time and across all body positions.

Van Buyten JP, et al. Pain Practice 2015.

ACCURATE STUDY: OBJECTIVE AND STUDY DESIGN



Levy R and Deer T. NANS 2015

- Objective: To assess the safety and efficacy of DRG stimulation compared to a commercially available SCS device
- 152 subjects enrolled
- Randomized 1:1 ratio
  - DRG vs.
  - Control (commercially available SCS device)
- 22 Investigational sites
- 3 month Primary Endpoint
- Subject population
  - Chronic, intractable pain of the lower limbs
  - Complex Regional Pain Syndrome (CRPS) or Peripheral Causalgia

ACCURATE STUDY: MAIN INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria

- Subject has chronic, intractable pain of the lower limb(s) for at least 6 months
- Subjects are diagnosed with complex regional pain syndrome (CRPS) and/or peripheral causalgia.
- Subjects have a minimum VAS >60 mm in the area of greatest pain in the lower limb(s).

Exclusion Criteria

- Subject has exhibited escalating or changing pain condition within the past 30 days as evidenced by Investigator examination
- Subject's pain medication(s) dosage(s) are not stable for at least 30 days
- Subject has previously failed spinal cord stimulation therapy

Levy R and Deer T. NANS 2015

ACCURATE STUDY: BASELINE DEMOGRAPHICS

	DRG (n=76)	Control (n=76)	p-value
	Mean (SD)	Mean (SD)	
Age (years)	52.4 (12.7)	52.5 (11.5)	0.936
Gender (n/N (%))			
Male	37/76 (48.7)	37/76 (48.7)	
Female	39/76 (51.3)	39/76 (51.3)	1.000
Duration of Lower Limb Pain (years)	7.5 (7.5)	6.8 (7.6)	0.557
Primary Diagnosis (n/N (%))			
Complex Regional Pain Syndrome	44/76 (57.9)	43/76 (56.6)	
Peripheral Causalgia	32/76 (42.1)	33/76 (43.4)	0.870

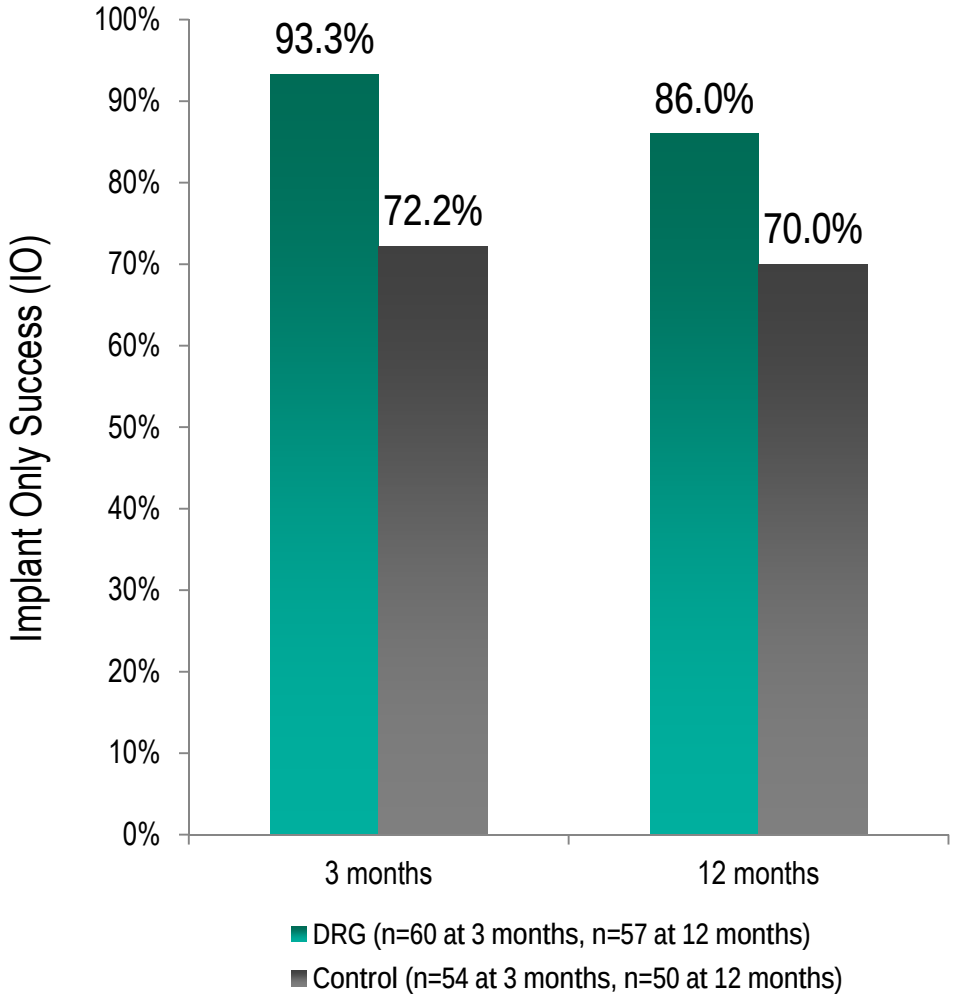
Levy R and Deer T. NANS 2015

ACCURATE STUDY: PRIMARY ENDPOINT

- A subject was considered a primary endpoint success if the subject met 3 criteria:
  - ≥ 50% pain relief in their primary area of pain at the end of the trial phase, and
  - ≥ 50% pain relief in their primary area of pain at the 3 month visit post implant, and
  - Freedom from stimulation-induced neurological deficit through 3 months

Levy R and Deer T. NANS 2015

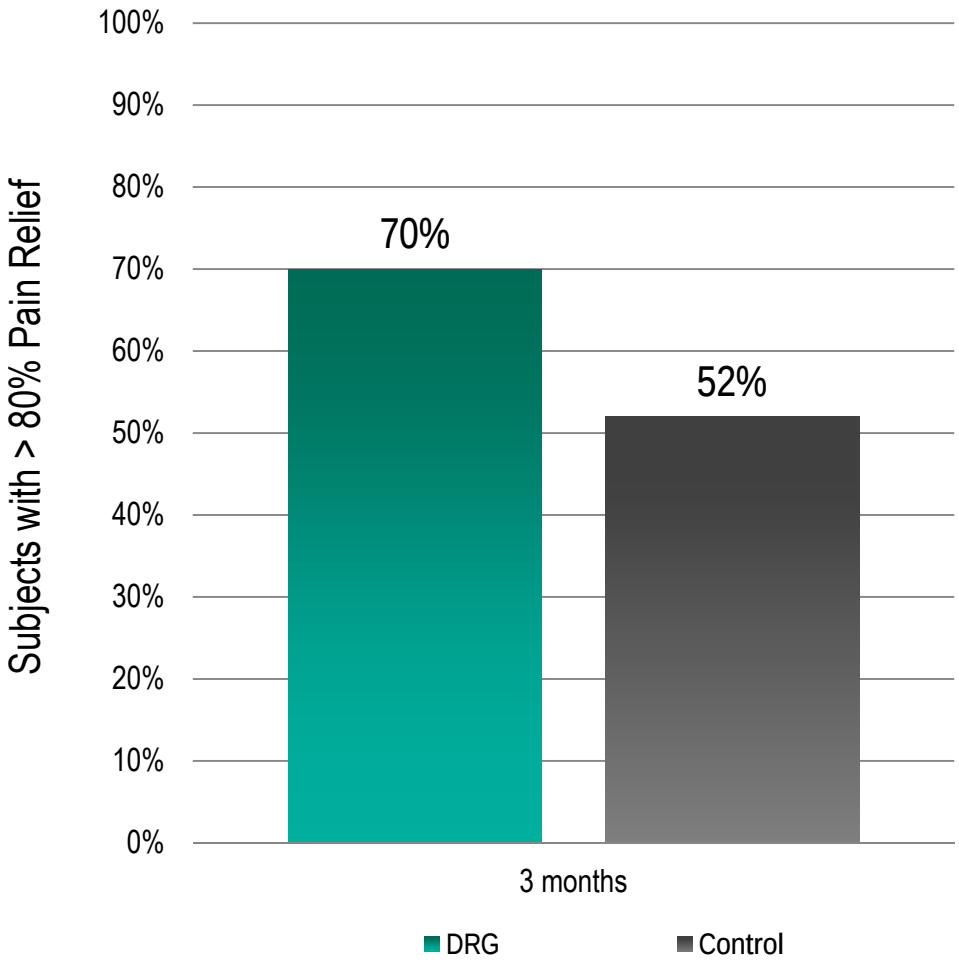
ACCURATE STUDY RESULTS: IMPLANT ONLY



Superiority Achieved	
P-value for non-inferiority at 3 months	<0.0001
P-value for superiority at 3 months	0.0011

Levy R and Deer T. NANS 2015

ACCURATE STUDY: HIGH RESPONDERS >80% VAS IMPROVEMENT POST-HOC ANALYSIS



- Percentage subjects obtaining at least 80% pain relief
- Implant Only responders at 3 months
- Trend towards significance at 3 months ($p<0.055$)

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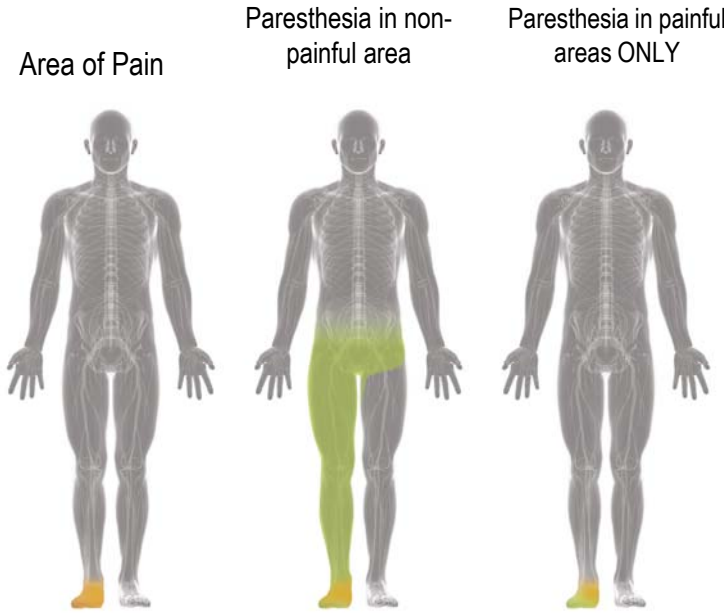
ACCURATE STUDY: THERAPY SPECIFICITY AT 12 MONTHS

Methodology:

- Patient reported area of pain
- Patient reported area of paresthesia
- Overlap of pain and paresthesia assessed



	DRG	Control
Subjects receiving targeted stimulation in the area of pain without extraneous paresthesia	94.5%	61.2%

Subjects in the DRG group experienced greater stimulation specificity than subjects in the control group.

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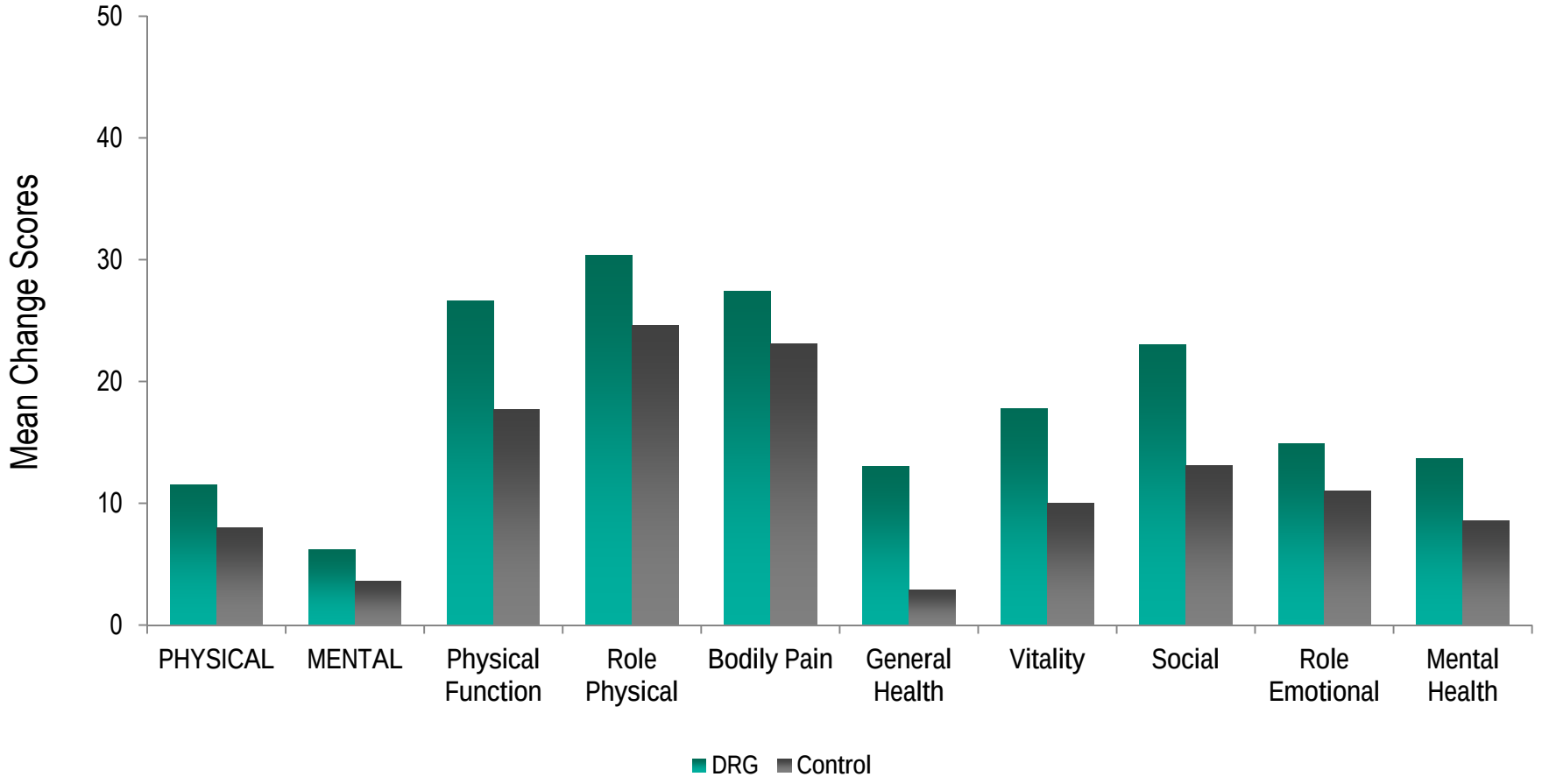
ACCURATE STUDY: CHANGE IN SF-36 BASELINE TO 12 MONTHS

HIGHER SCORES = IMPROVEMENTS IN SF-36



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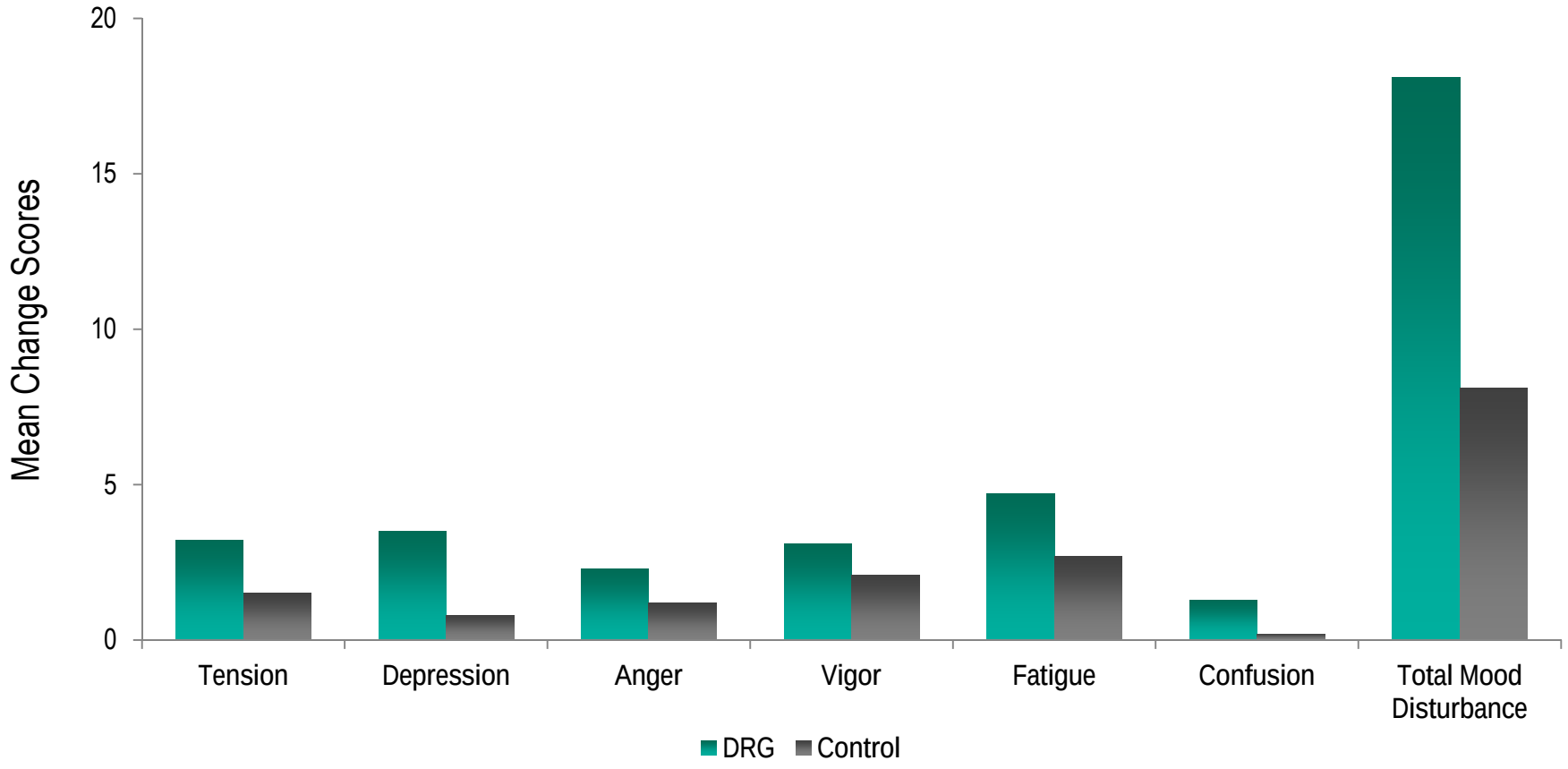
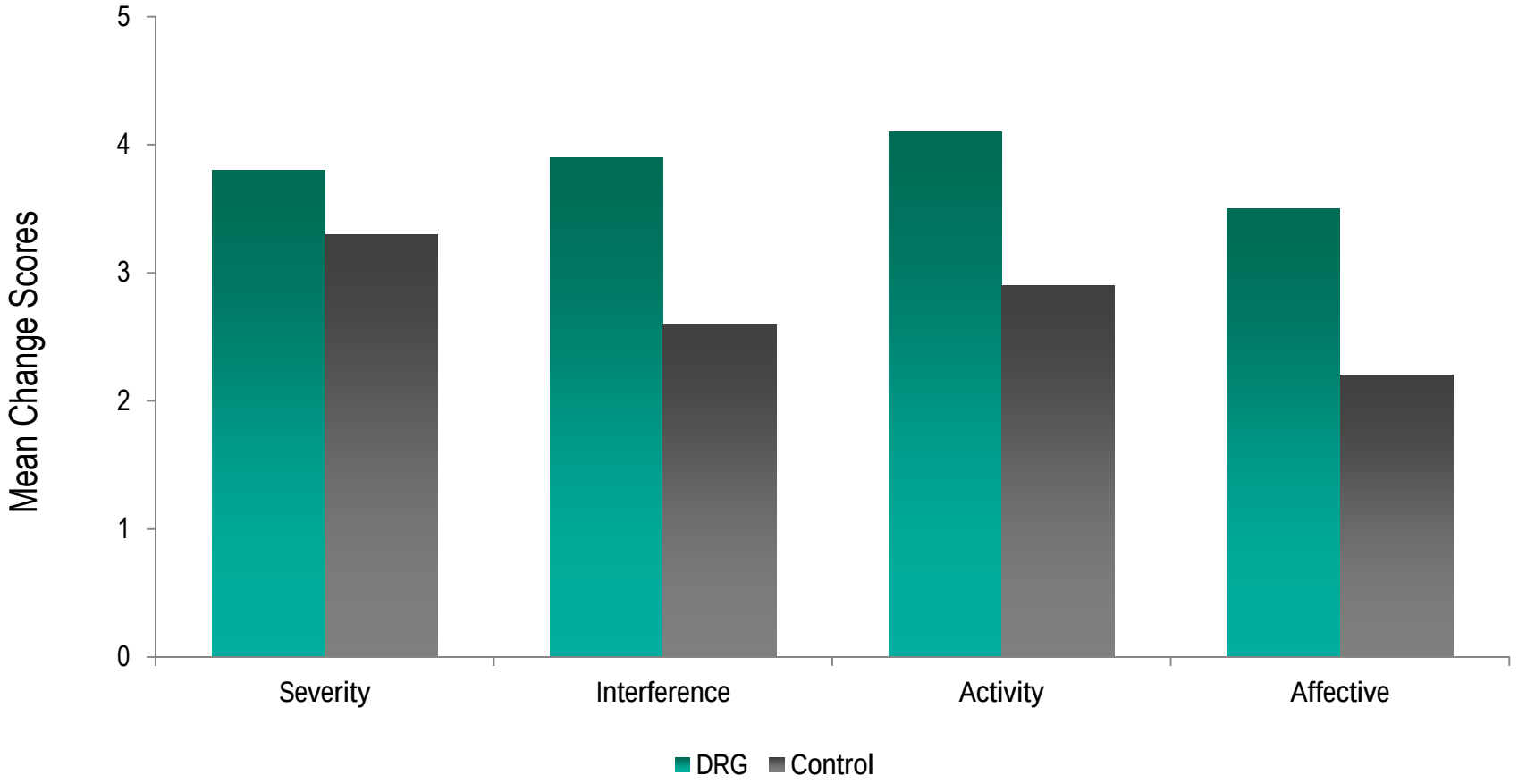
ACCURATE STUDY: CHANGE IN POMS BASELINE TO 12 MONTHS



Levy R and Deer T. NANS 2015

ACCURATE STUDY: CHANGE IN BRIEF PAIN INVENTORY BASELINE TO 12 MONTHS



Levy R and Deer T. NANS 2015

CONCLUSIONS

The 12-month outcome data have confirmed DRG stimulation provides long-term, sustained and superior pain relief over traditional SCS for patients with chronic lower limb pain due to Complex Regional Pain Syndrome (CRPS) and peripheral causalgia.

DRG Stimulation offered patients:

- **Sustained and superior pain relief:** After 12 months, significantly more DRG stimulation patients achieved pain relief and treatment success versus control SCS (74.2% vs. 53.0%)
- **Improved therapeutic targeting:** DRG stimulation patients reported better stimulation targeting in their area of pain without extraneous paresthesia (94.5% vs. 61.2%)
- **Enhanced quality of life and functionality:** DRG stimulation patients experienced improved quality of life measures, psychological disposition and physical/activity levels*
- **Reduced paresthesia:** At 12 months, more than a third of DRG stimulation patients experienced no paresthesia and had on average an 86% reduction in pain, suggesting that DRG stimulation may provide paresthesia-free analgesia.*

Levy R and Deer T. NANS 2015

* Groups were not statistically powered to show superiority over traditional tonic stimulation

THANK YOU!

- Brian J. Snyder, MD

  Director of Functional and Restorative Neurosurgery

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  NSPC

  516-255-9031