MEDICAL UNIVERSITY OF VIENNA

The Science Behind the Origins and Recent Developments of Transcutaneous Spinal Cord Stimulation

Karen Minassian

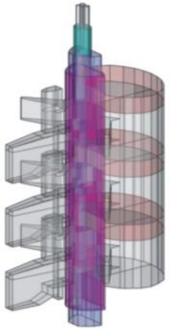
Center for Medical Physics and Biomedical Engineering
Medical University of Vienna, Austria

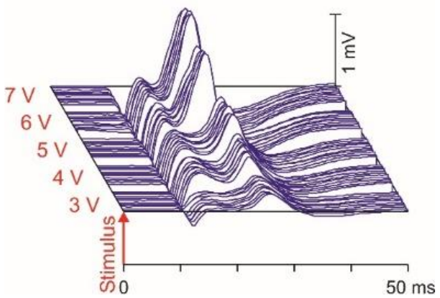
Human Motor Control and Neuromodulation Group

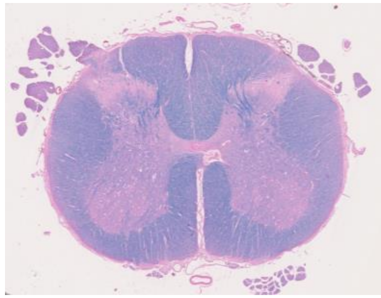
Ursula Hofstötter & Karen Minassian

Center for Medical Physics and Biomedical Engineering
Medical University of Vienna, Austria

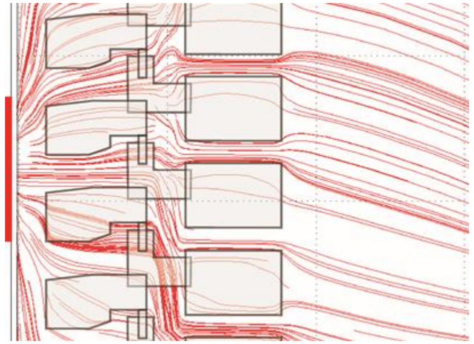
Understanding human spinal motor control



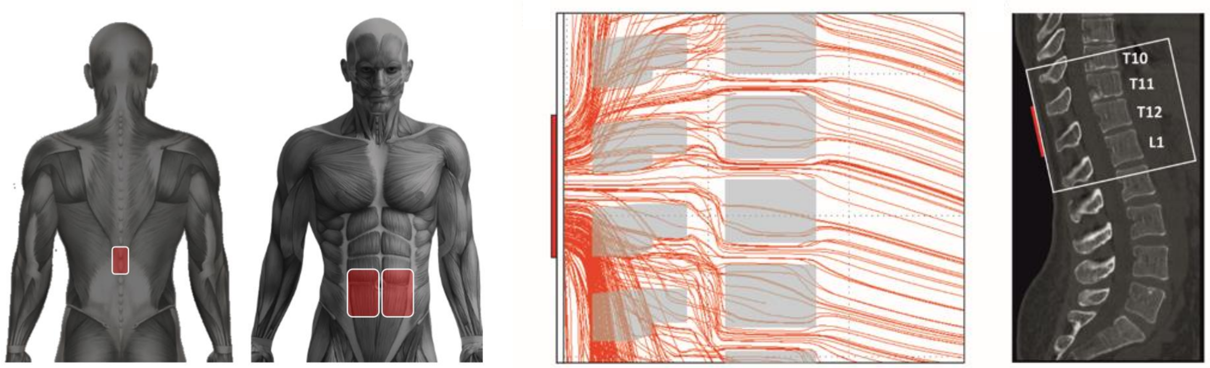




Developing innovative neuromodulation strategies

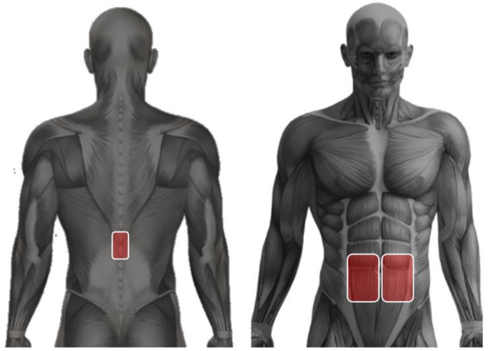


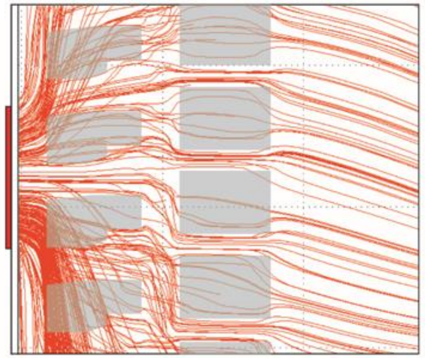
Transcutaneous SCS - Introduction



- Non-invasive neuromodulation method
- To augment functional activity of spinal circuits
- Based on stimulating surface electrodes

Transcutaneous SCS - Introduction





Applications

- Lower limb function
  - Improve spasticity
  - Facilitate volitional movements and locomotion
- Upper limb function
- Autonomic functions

Methods

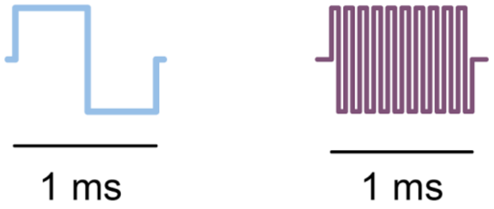
⇨ Lumbar tSCS

⇨ Cervical tSCS

⇨ Thoracic tSCS

Stimulation technology

Conventional vs. ‘Russian’ stim.



Transcutaneous SCS - Introduction

nature medicine

Article

https://doi.org/10.1038/s41591-024-02940-9

Non-invasive spinal cord electrical stimulation for arm and hand function in chronic tetraplegia: a safety and efficacy trial

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Chet Moritz[1,26], Edelle C. Field-Fote[2,26], Candace Tefertiller[3,26], Ilse van Nes[4], Randy Trumbower[5,6], Sukhvinder Kalsi-Ryan[7], Mariel Purcell[8], Thomas W. J. Janssen[9,10], Andrei Krassioukov[11], Leslie R. Morse[12], Kristin D. Zhao[13], James Guest[14,15], Ralph J. Marino[16], Lynda M. Murray[17,18], Jill M. Wecht[18], Markus Rieger[19], Jared Pradarelli[19], Amanda Turner[19], Jessica D'Amico[19,20,21], Jordan W. Squair[22,23,24,25] & Gregoire Courtine[22,23,24,25]

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Spinal motor evoked responses elicited by transcutaneous spinal cord stimulation in chronic stroke: Correlation between spinal cord excitability, demographic characteristics, and functional outcomes

Nicole C. Veit, Chen Yang, Shreya Aalla, Ameen Kishta, Kelly McKenzie, Elliot J. Roth, Arun Jayaraman

Journals & Magazines > IEEE Transactions on Biomedic... > Early Access

Transcutaneous Spinal Stimulation and Short-burst Interval Treadmill Training in Children with Cerebral Palsy: A Pilot Study

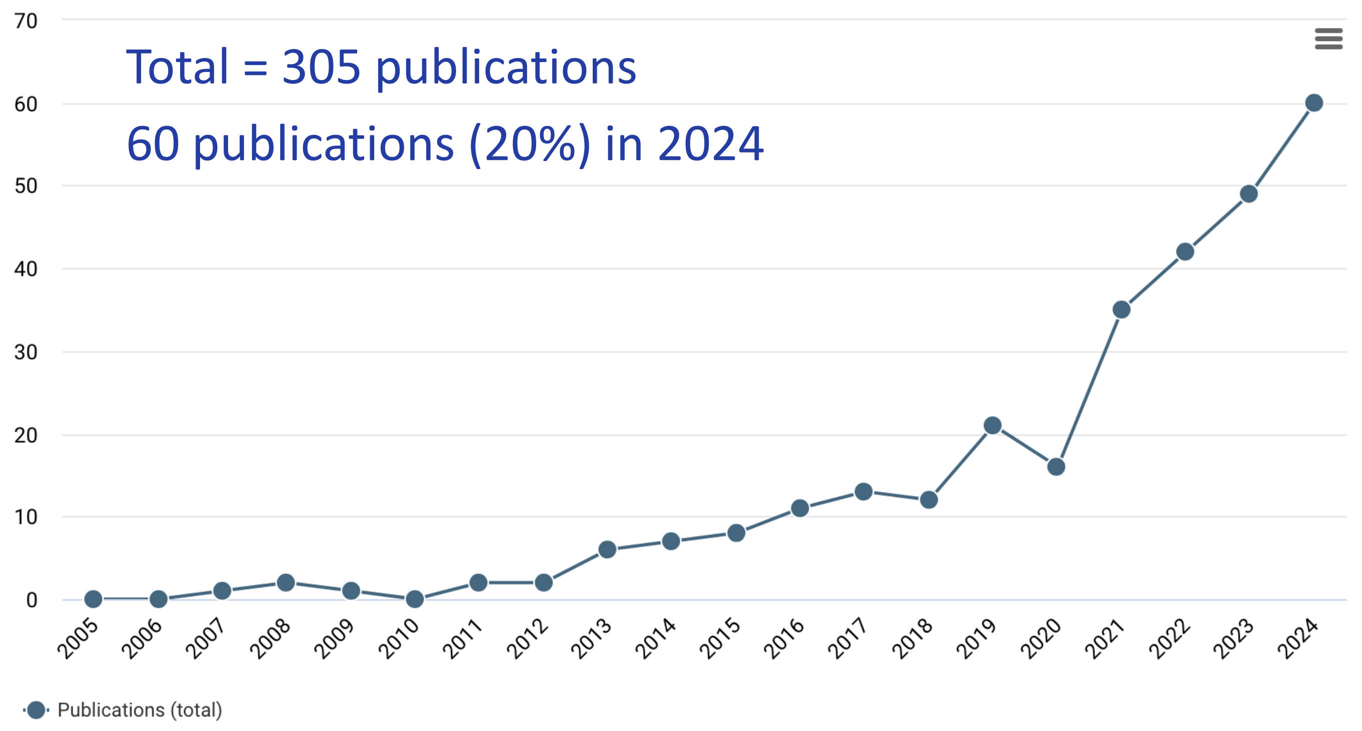
Publisher: IEEE | Cite This | PDF

Siddhi R. Shrivastav ; Charlotte R. DeVol ; Victoria M. Landrum ; Kristie F. Bjornson ; Desiree Roge ; Katherine M. Steele | All Authors

brain sciences | MDPI

Article

Transcutaneous Spinal Cord Stimulation Enhances Walking Performance and Reduces Spasticity in Individuals with Multiple Sclerosis



Publications with "transcutaneous spinal cord stimulation" OR "posterior root-muscle" OR "transcutaneous electrical spinal cord stimulation" on title or abstract since 2005

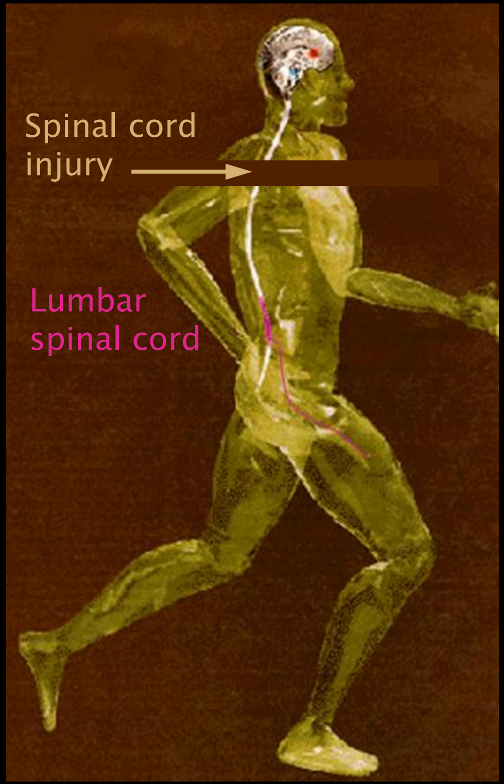
Ismael Seáñez, Washington University

Objectives

- Science-based development of transcutaneous lumbar SCS
- Defining characteristics of transcutaneous SCS
- Methodological developments of transcutaneous SCS
- Current scientific challenges

Origins – investigating mechanisms of epidural SCS

Individuals with spinal cord injury



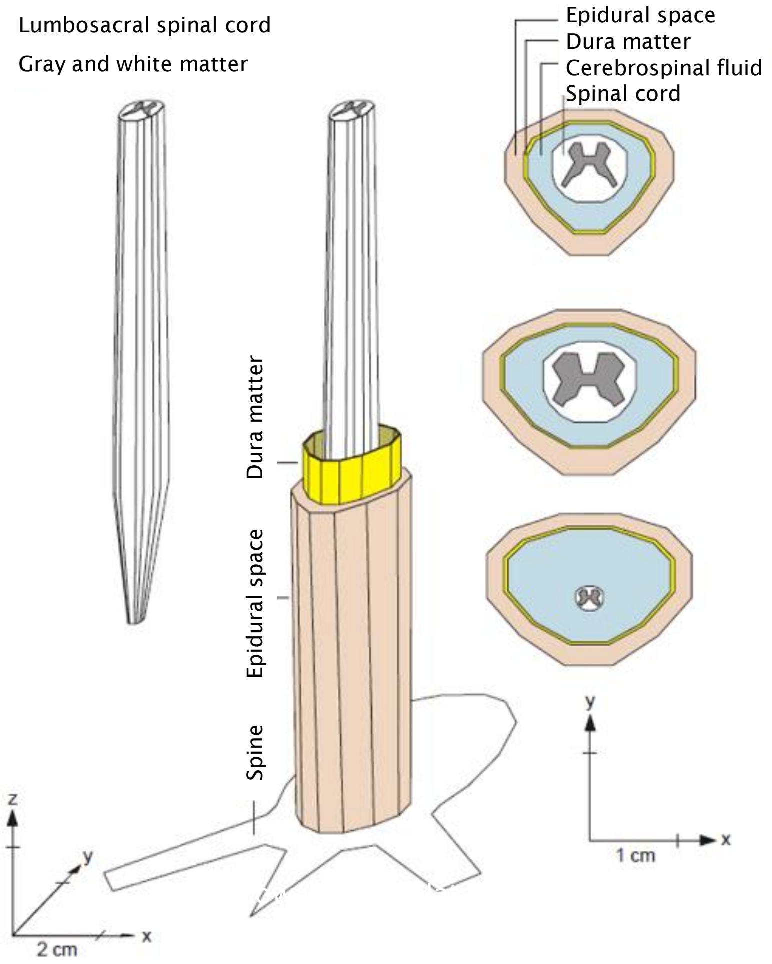
Epidural electrical stimulation of the *lumbar* spinal cord

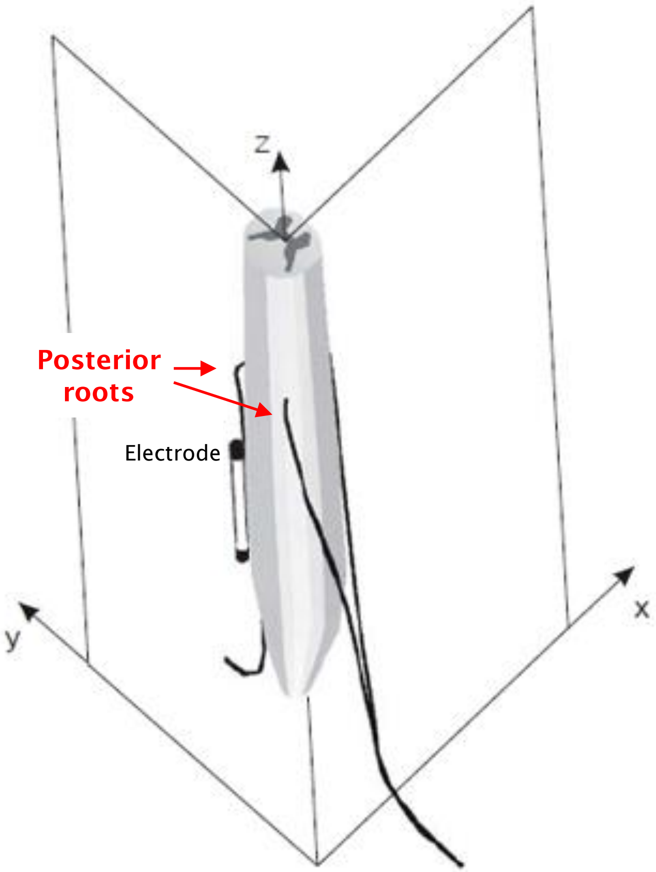
Involuntary coordinated rhythmic movements in paralyzed legs

Dimitrijevic et al. **Evidence for a spinal central pattern generator in humans**. Ann N Y Acad Sci. **1998**;860:360-76.

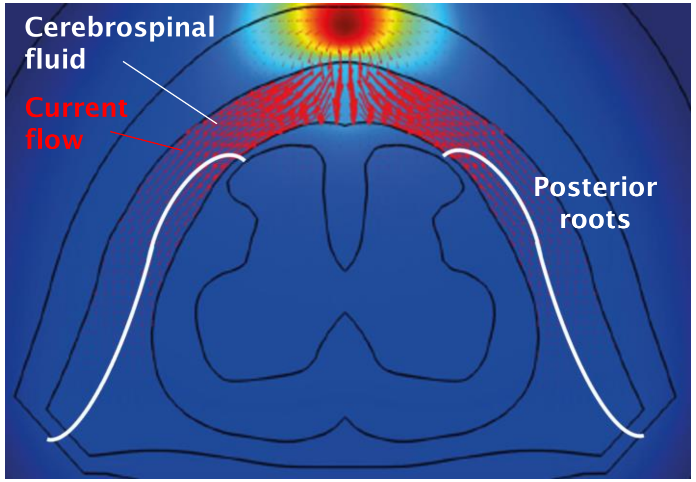
Computer models propose posterior root stimulation

Rattay F, Minassian K, Dimitrijevic MR. Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 2. **quantitative analysis by computer modeling**. Spinal Cord. **2000**;38:473-89.

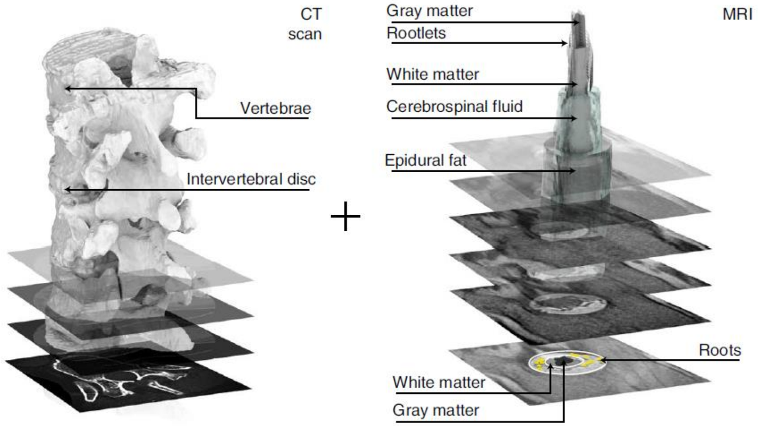




Capogrosso et al. J Neurosci. **2013**;33:19326-40.

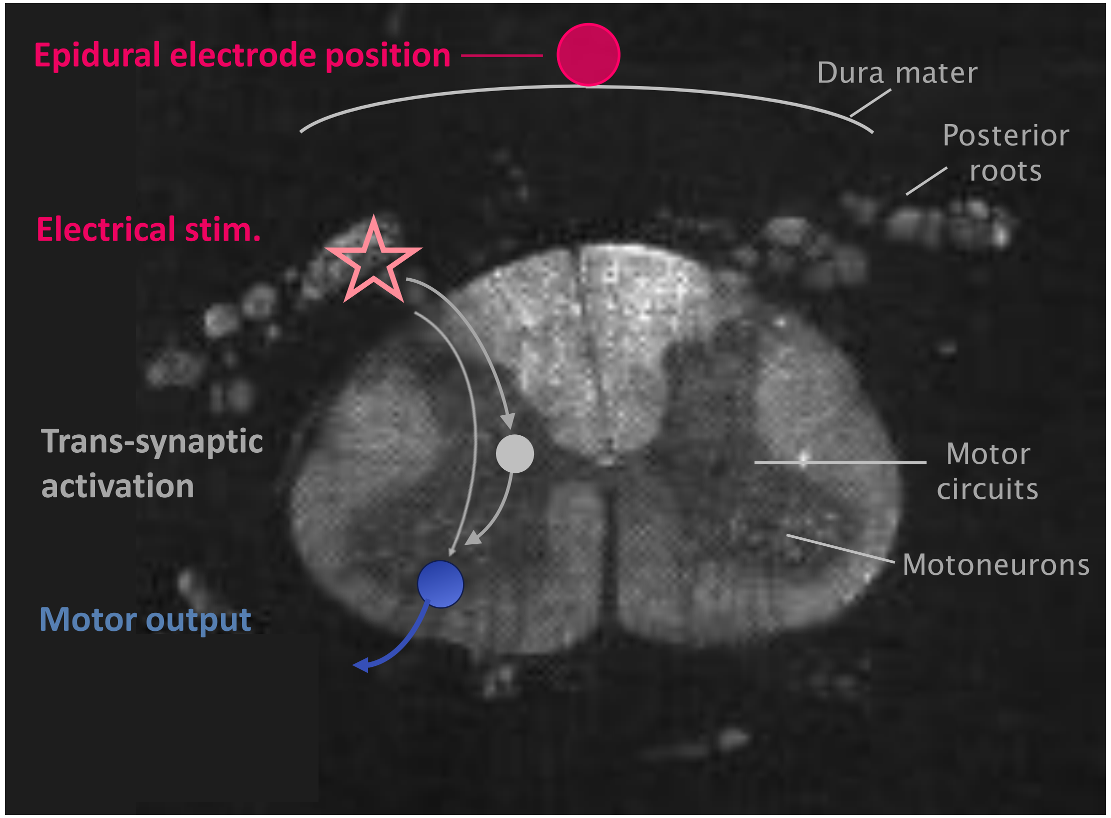


“Electricity follows the path of least resistance”

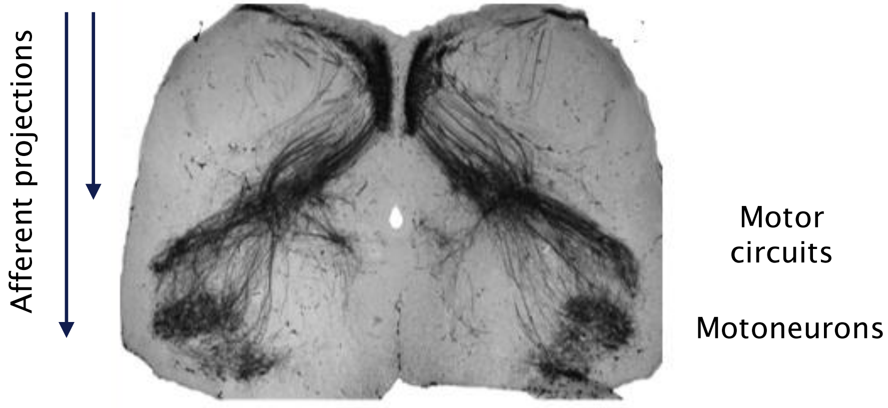


Rowald et al. Nat Med. **2022**;28(2):260-271.

Trans-synaptic recruitment of spinal circuits



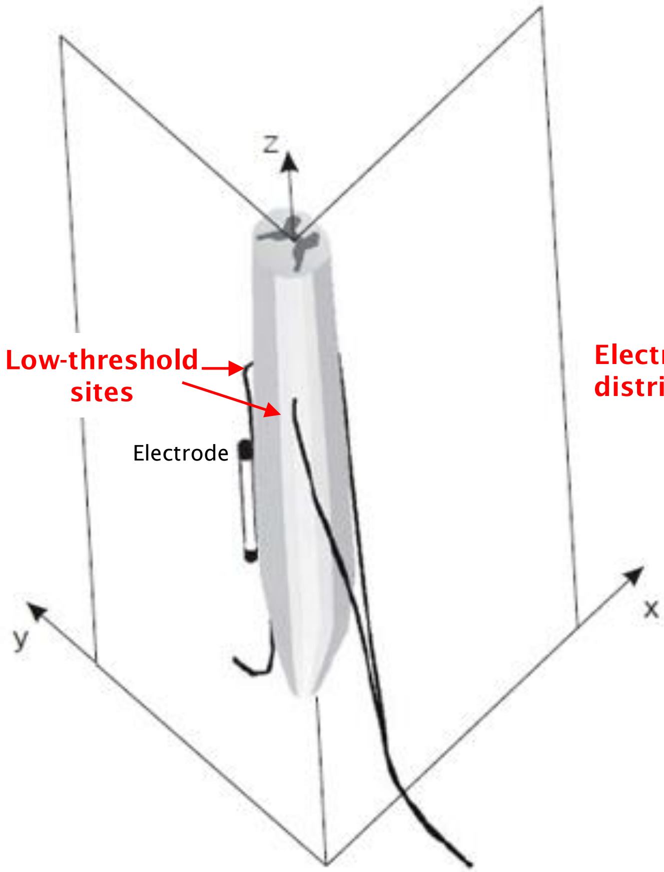
Rich connectivity of proprioceptive fibers with spinal interneurons and motoneurons



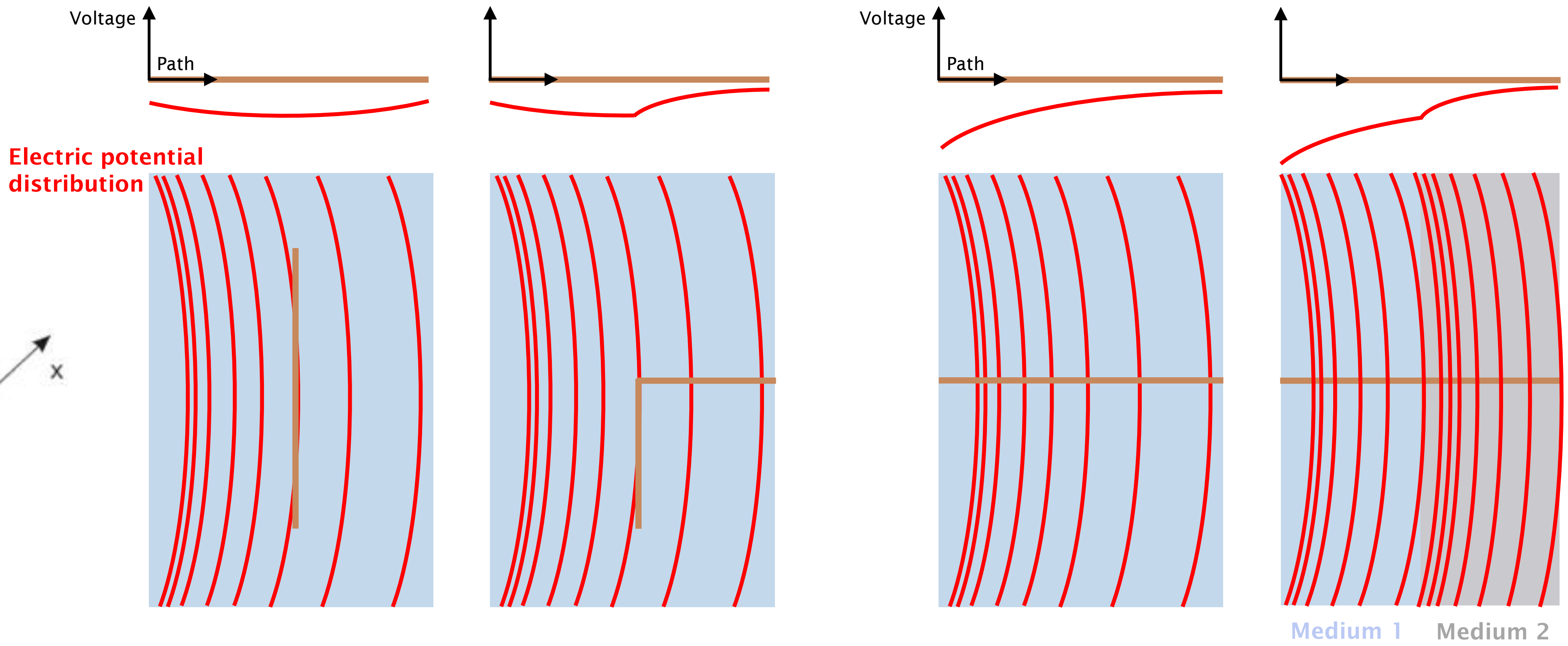
Histological staining of proprioceptive afferent fibers

Computer models propose stimulation 'hot spots'

Rattay F, Minassian K, Dimitrijevic MR. Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 2. **quantitative analysis by computer modeling**. Spinal Cord. **2000**;38:473-89.

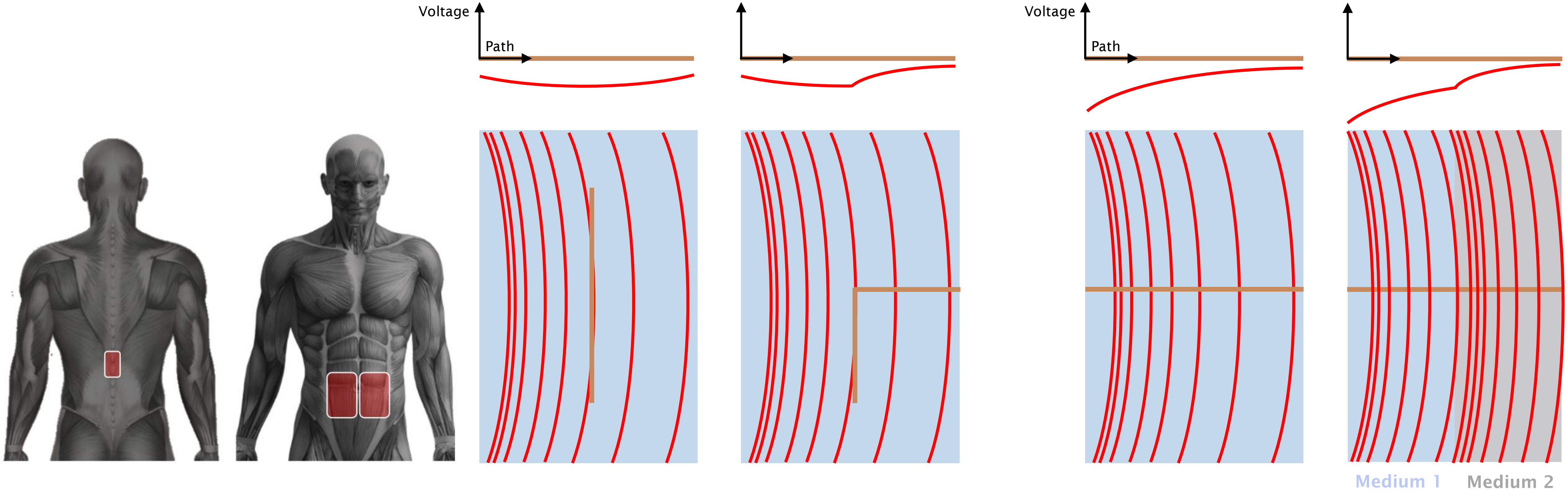


- **Low-threshold sites ('hot spots') are created by abrupt changes of electric potential distribution along a nerve fiber**
  … by local peaks of the second order spatial difference of the electric potential along the nerve fiber

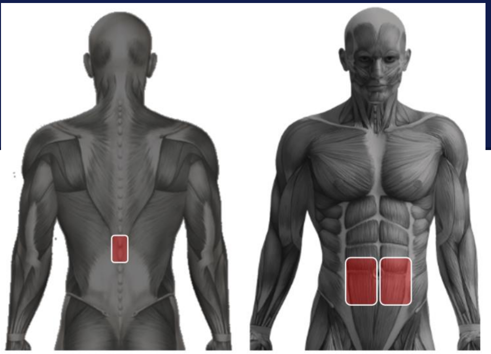


Computer models propose stimulation 'hot spots'

These mechanisms are dictated by the ***underlying anatomy and tissue conductivity***
→ posterior root afferents could potentially be targeted even by diffuse, non-focused electric fields

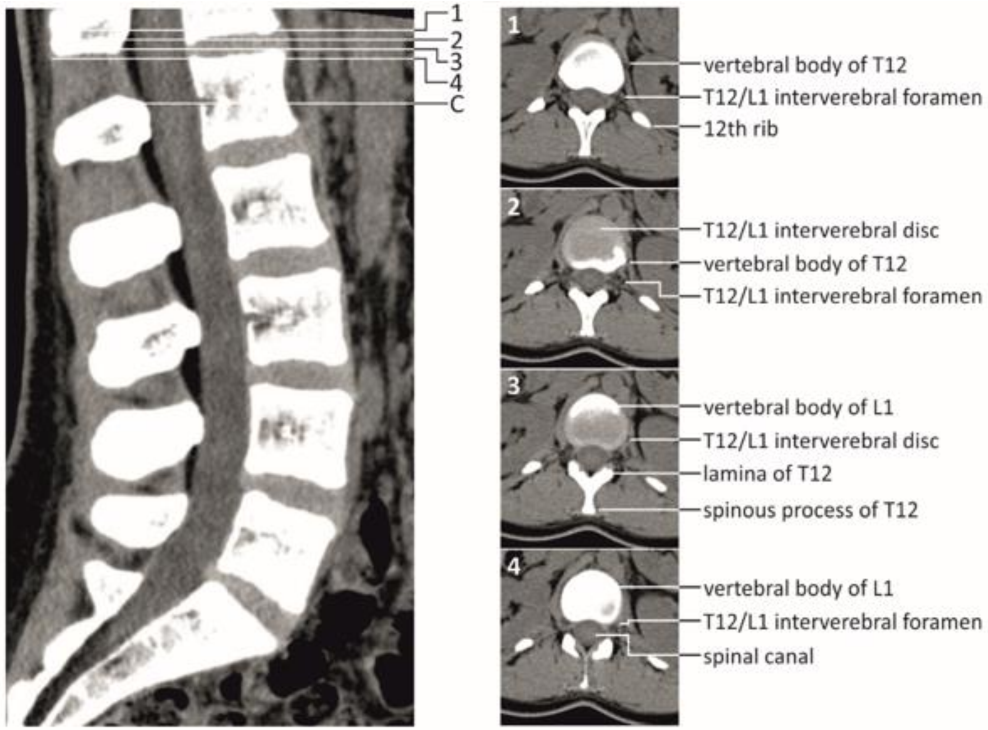


Development of transcutaneous SCS

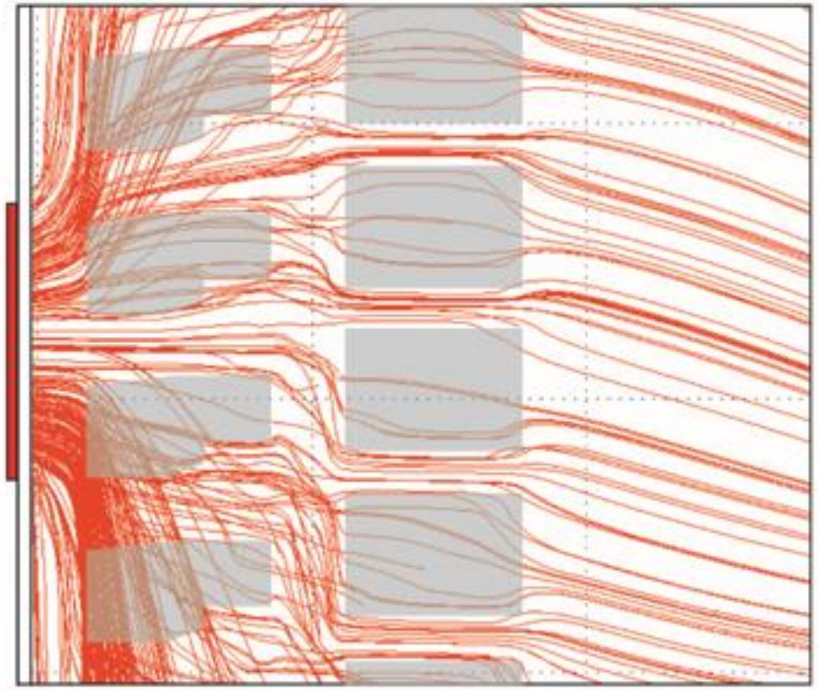


But the vertebral bones have a low electrical conductivity … ?

Sagittal / axial CT scans of the spine



Computer simulation of the current flow in the sagittal plane



bones

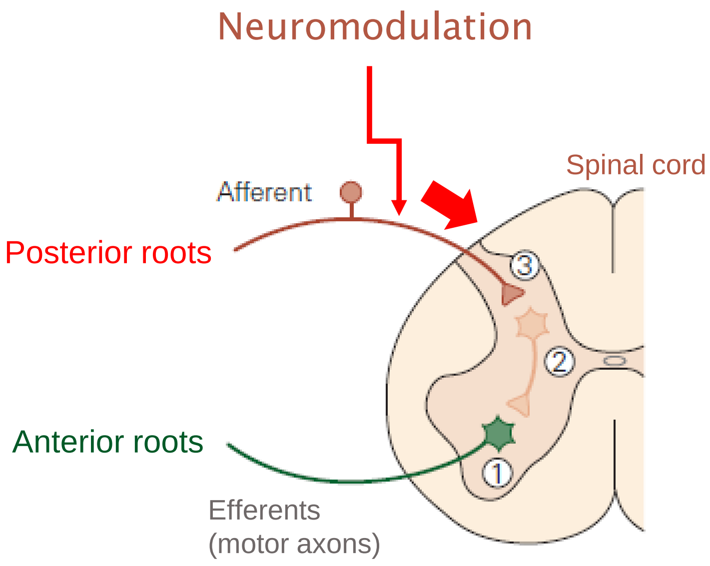
Ladenbauer et al. IEEE Trans Neural Syst Rehabil Eng. 2010;18:637-45.
Binder et al. J Clin Med. 2021;10:5543.

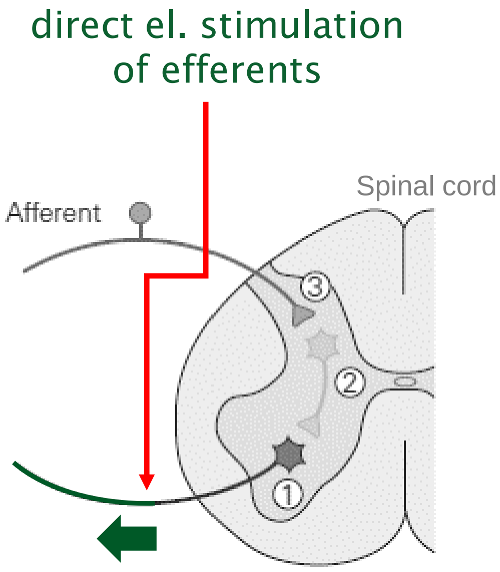
Development of transcutaneous SCS – The pulse duration

Holsheimer, J.
Neuromodulation 2003; 6: 270–3

Basic characteristics of neuromodulation include:

" … the activity of specific neural networks is affected by ongoing *electrical stimulation* of part of its afferents, …"



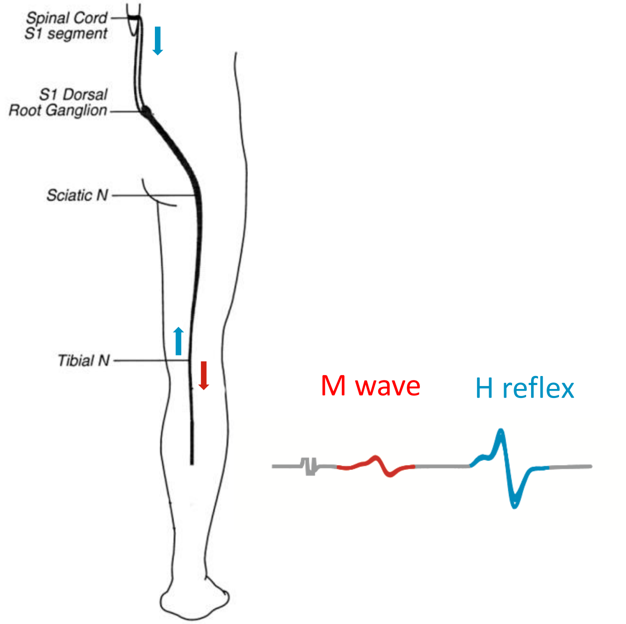


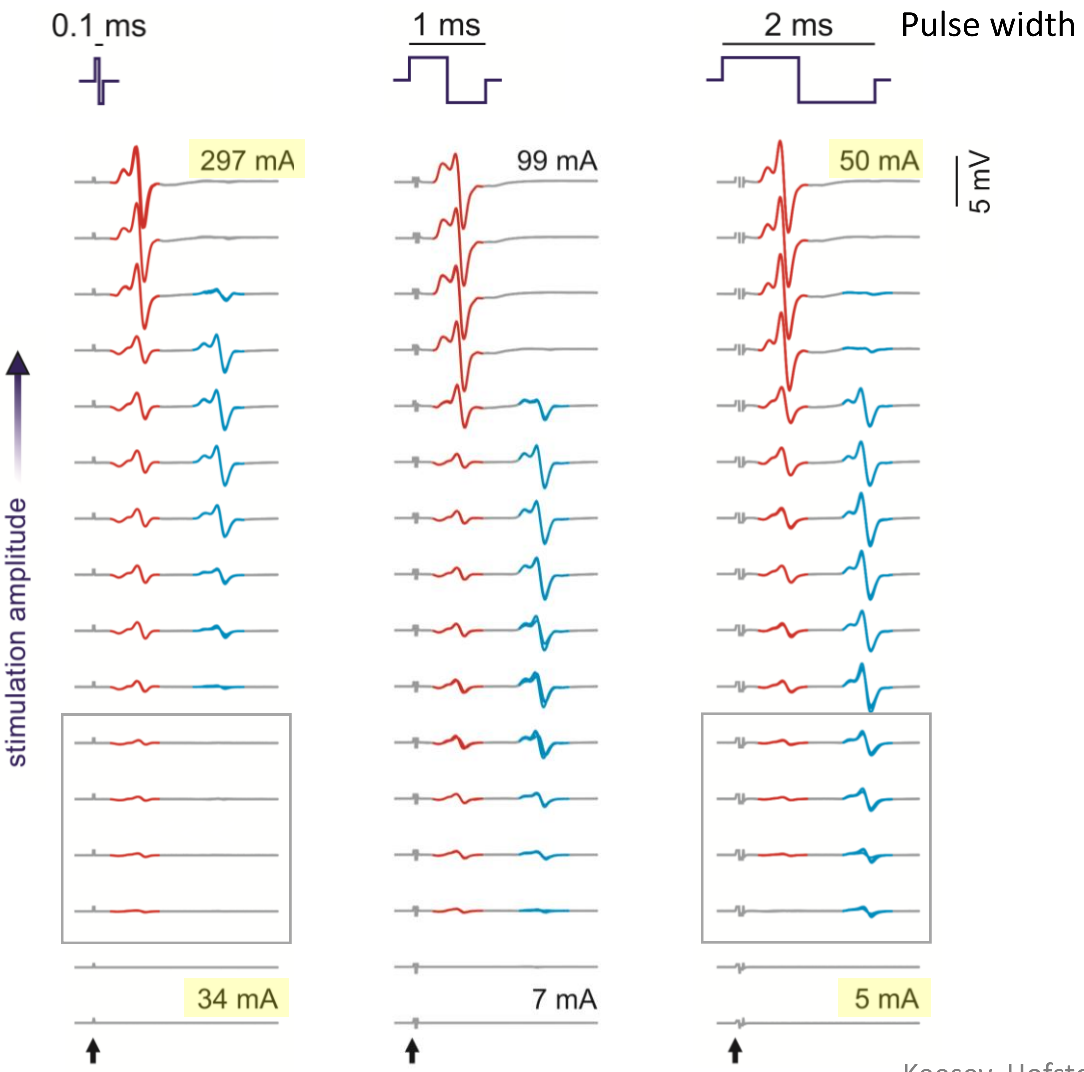
Development of transcutaneous SCS – The pulse duration

Long pulse-durations produce a bias towards afferent stimulation

H reflexes, stimulation of the mixed tibial nerve at the knee

- M wave: direct motor response elicited by stimulation of motor efferent fibers
- H reflex: reflex response elicited by stimulation of proprioceptive afferent fibers





Keesey, Hofstoetter, et al., | bioRxiv | 2024

Transcutaneous SCS

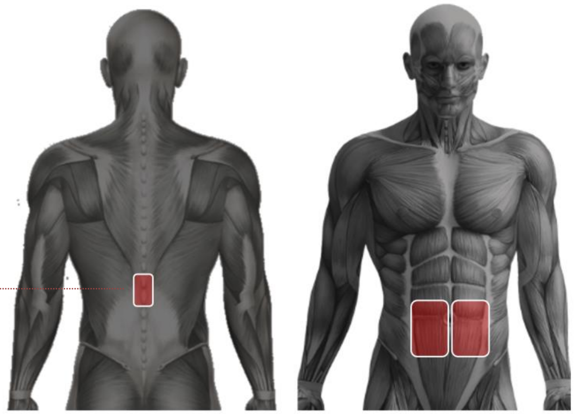
Science-based development of transcutaneous SCS:

- Current penetration into the spinal canal via soft tissues
- Anatomically determined low-threshold sites ("hot spots") at spinal cord entrance of posterior roots
- Long-duration pulses (≥1 ms) to further prioritize the recruitment of proprioceptive afferents

Minassian K, Persy I, Rattay F, Dimitrijevic MR, Hofer C, Kern H. Posterior root-muscle reflexes elicited by **transcutaneous stimulation of the human lumbosacral cord**. Muscle Nerve. **2007** Mar;35(3):327-36.

Transcutaneous stimulation with <30 V elicited simultaneous, bilateral reflexes in quadriceps, hamstrings, tibialis anterior, and triceps surae — indicative of posterior root activation.

T11/T12
vertebral level



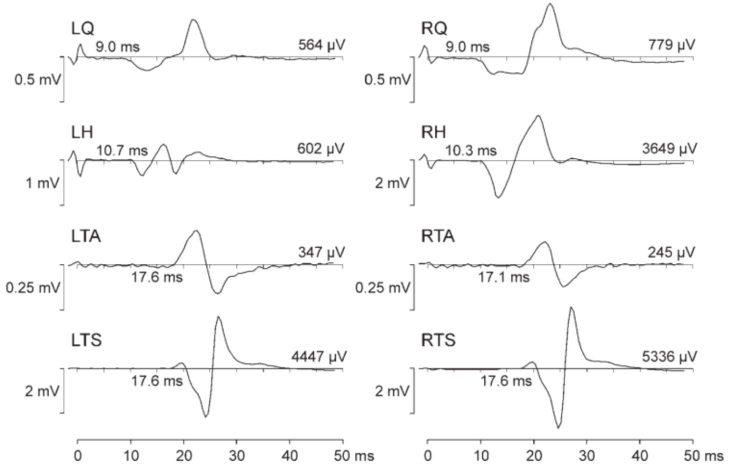


FIGURE 1. PRM reflexes simultaneously recorded from the left (L) and right (R) quadriceps (Q), hamstrings (H), tibialis anterior (TA), and triceps surae (TS). Stimulation site: T11–T12 interspinous space; stimulus intensity: 30 V (subject 6). Inserted values are onset latencies and peak-to-peak amplitudes of the EMG responses.

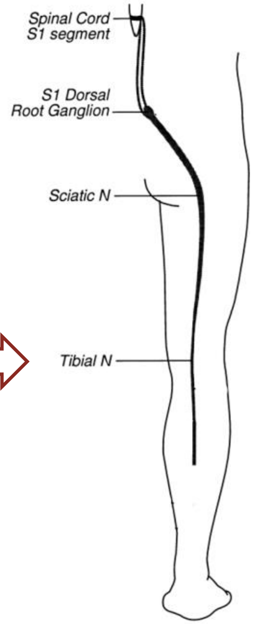
PRM reflexes ('posterior root-to-muscle reflexes') in L2 to S1 innervated muscles

Q, quadriceps
H, hamstrings
TA, tibialis anterior
TS, triceps surae

Transcutaneous SCS and the PRM reflex

tSCS

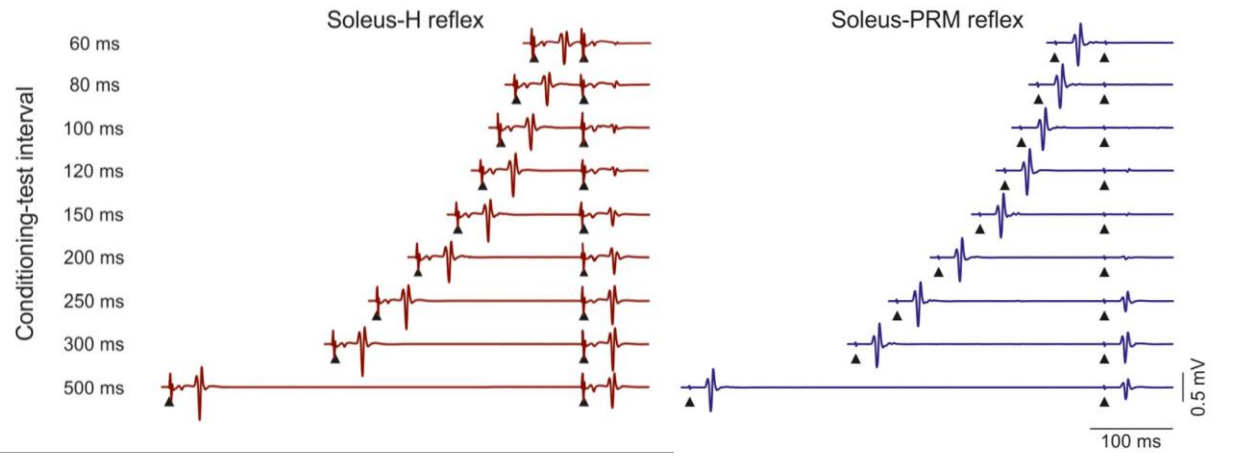
periph. n. stim

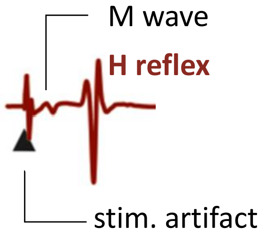


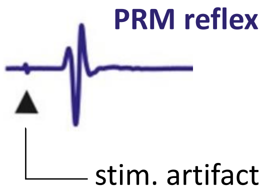
PRM reflex

H reflex

Post-activation depression demonstrated by paired pulses



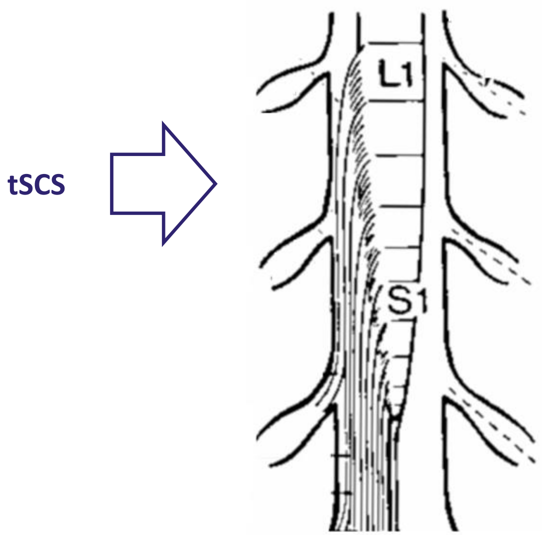




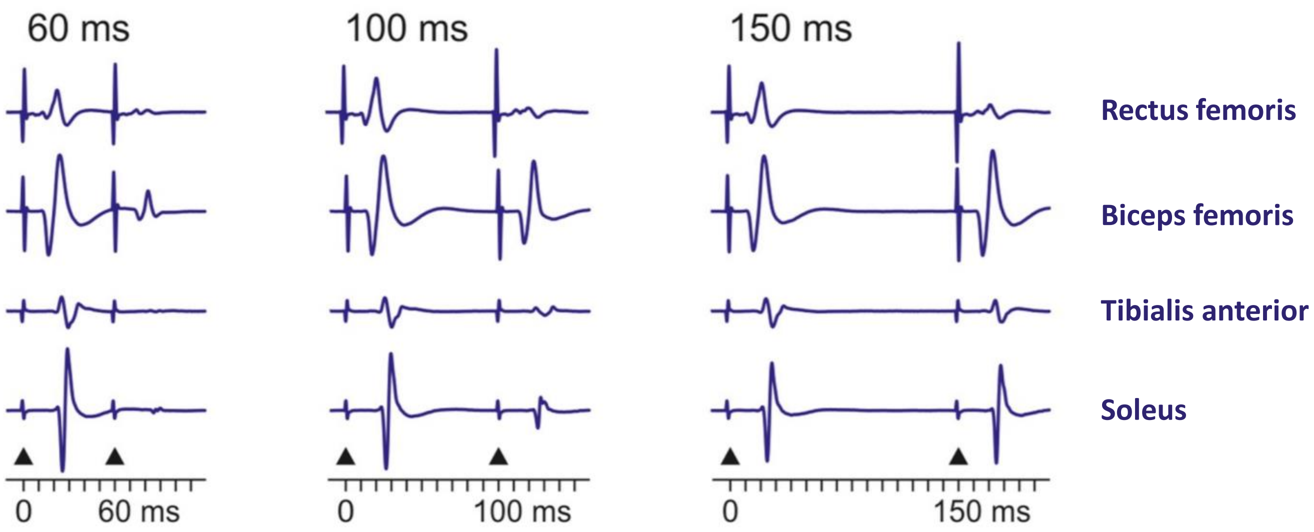
Hofstoetter US, Freundl B, Binder H, Minassian K. PLoS One. 2019;14(12):e0227057.

Transcutaneous SCS and the PRM reflex

Post-activation depression of PRM reflexes demonstrated by paired pulses



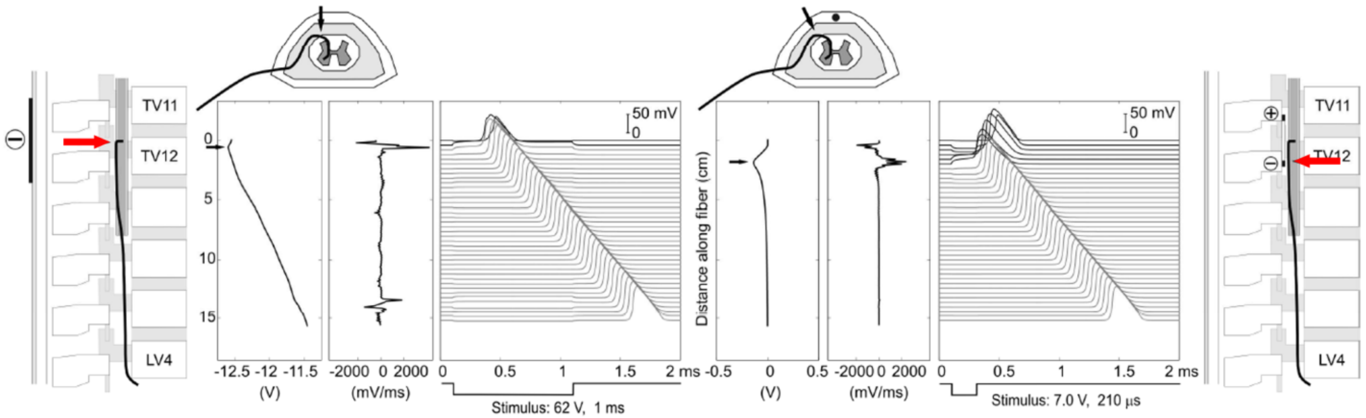
Spinal cord and roots



Hofstoetter US, Freundl B, Binder H, Minassian K. PLoS One. 2019;14(12):e0227057.

tSCS and Epidural SCS: Overlapping neural activation pathways

Ladenbauer, Minassian et al.
IEEE Trans Neural Syst Rehabil Eng.
2010;18:637-45.

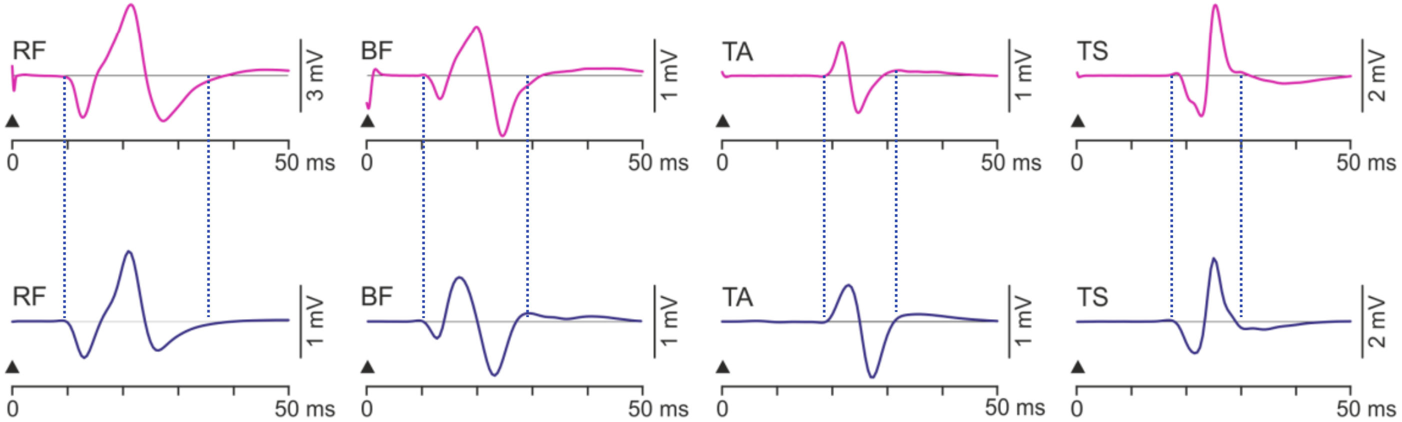


Hofstoetter US, Freundl B, Binder H, Minassian K. **Common neural structures activated by epidural and transcutaneous** lumbar spinal cord stimulation: Elicitation of posterior root-muscle reflexes. PLoS One. 2018 Jan 30;13(1):e0192013. doi: 10.1371/journal.pone.0192013. PMID: 29381748; PMCID: PMC5790266.

Transcutaneous and epidural SCS elicit near-identical PRM reflexes — indicative of similar stimulation of proprioceptive afferents in posterior roots.

- Transcutaneous SCS

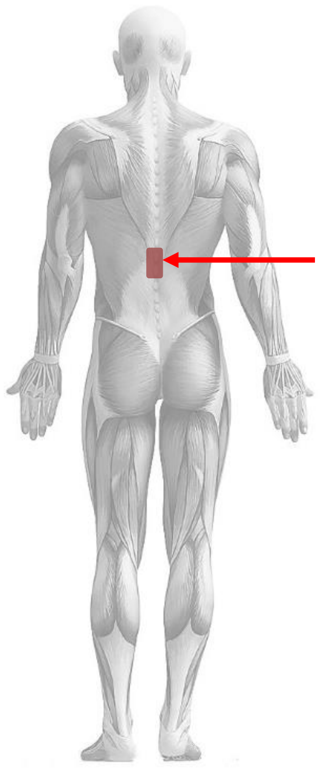
- Epidural SCS



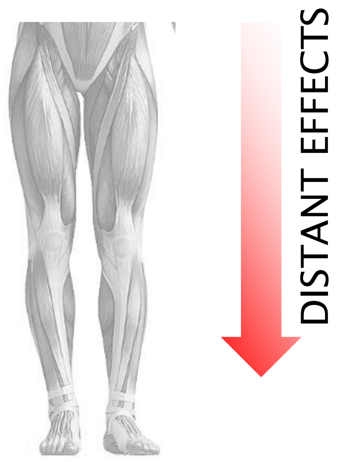
What is transcutaneous SCS?

… How do I define it?

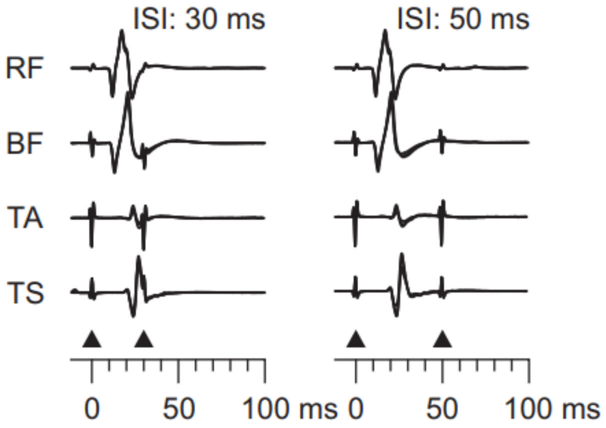
Physiological markers of afferent spinal cord/root stimulation define transcutaneous SCS



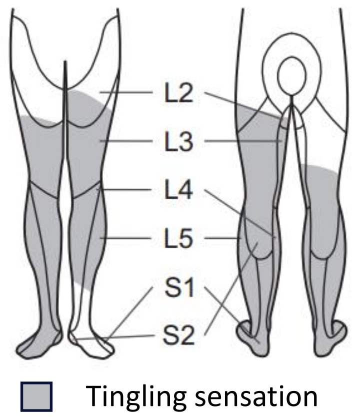
Electrode over low-thoracic dermatomes but over *lumbar* spinal cord segments



Elicitation of PRM reflexes in lower-limb myotomes, confirmed by double stimuli



Elicitation of paraesthesias in lower-limb dermatomes by 50-Hz stimulation



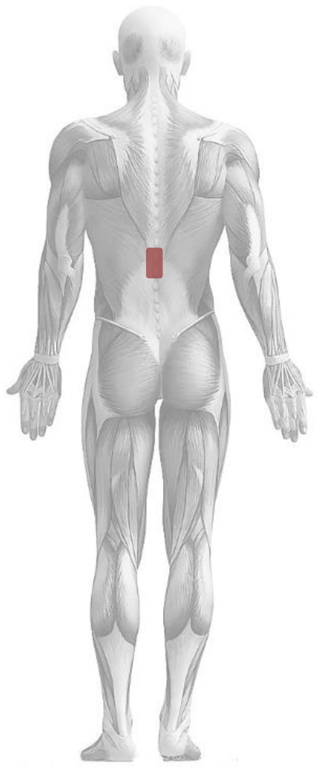
Transcutaneous SCS is associated with distant effects

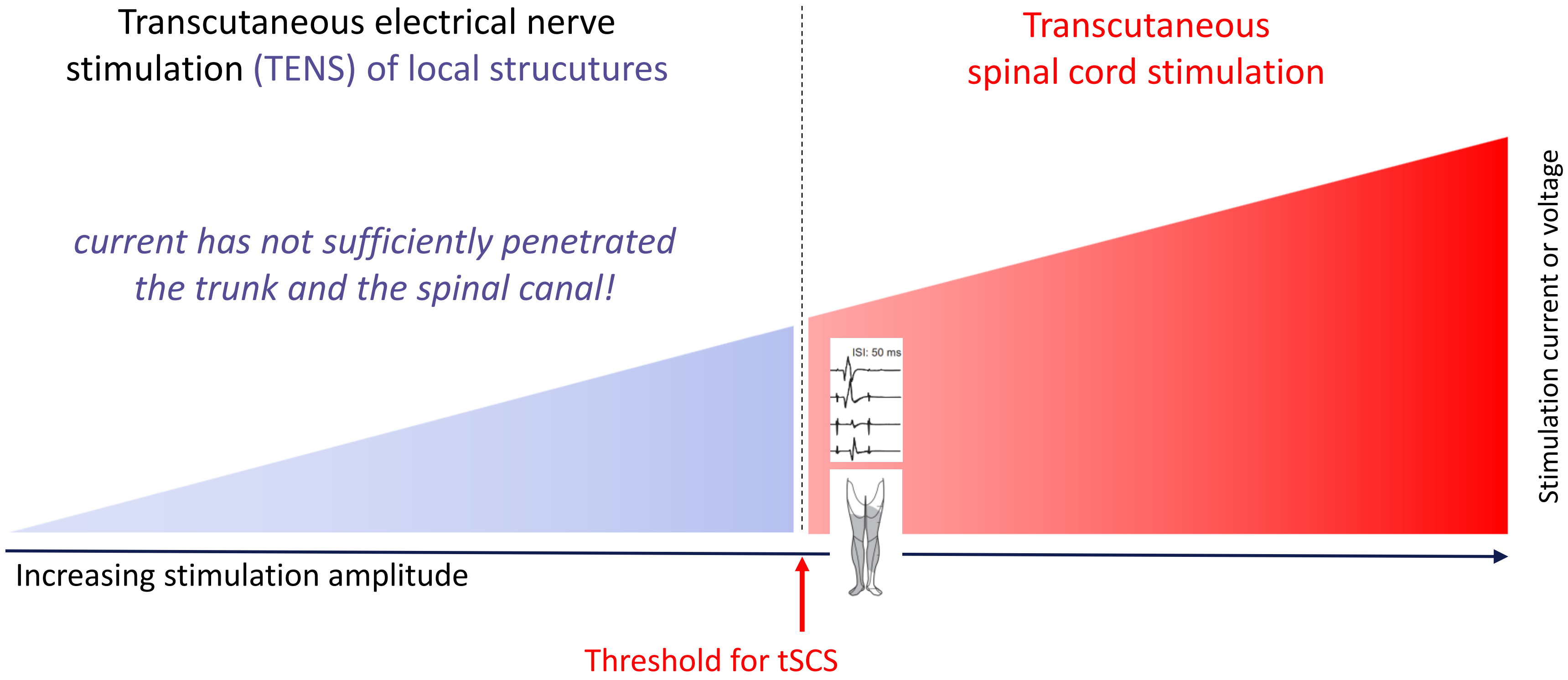
Hofstoetter et al. J Neurotrauma. 2020;37(3):481-493.

What is transcutaneous SCS?

… How do I define it?

Transcutaneous SCS is defined by a minimum stimulation amplitude





Clinical investigations using tSCS should *always* report the applied stimulation amplitudes relative to individual PRM reflex or paresthesia thresholds

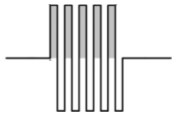
History of transcutaneous SCS – methodological developments

2007 — Paper on **transcutaneous lumbar SCS**, Minassian et al., Muscle&Nerve. 2007;35:327-36, Vienna group

2013 — First **patent** on transcutaneous lumbar SCS, WO2013/071309A1, Gerasimenko/Edgerton, UCLA

(10) International Publication Number
WO 2013/071309 A1

2015 — First papers proposing the use of ‘**Russian stimulation**’ in transcutaneous lumbar SCS ,
Gerasimenko et al., Ann Phys Rehabil Med. 2015;58:225-231
Gerasimenko et al. J. Neurophysiol. 2015;113:834–842
Gerasimenko/Edgerton, UCLA



kilohertz-frequency modulated pulses

2018 — First paper on transcutaneous **cervical** SCS, Gad et al., J Neurotrauma. 2018;35:2145-2158, Gerasimenko/Edgerton, UCLA

2024 — First **FDA approval** of a transcutaneous SCS System "ARC-EX", ONWARD Medical, Courtine group, Switzerland

Scientific challenges in current applications

Lessons learned from lumbar tSCS with conventional pulses *do not directly translate to* cervical stimulation and Russian currents

- Cervical stimulation

    In lumbar tSCS, mechanisms dictated by the underlying anatomy and tissue conductivity enable a relatively selective recruitment of posterior root afferents within the DREZ

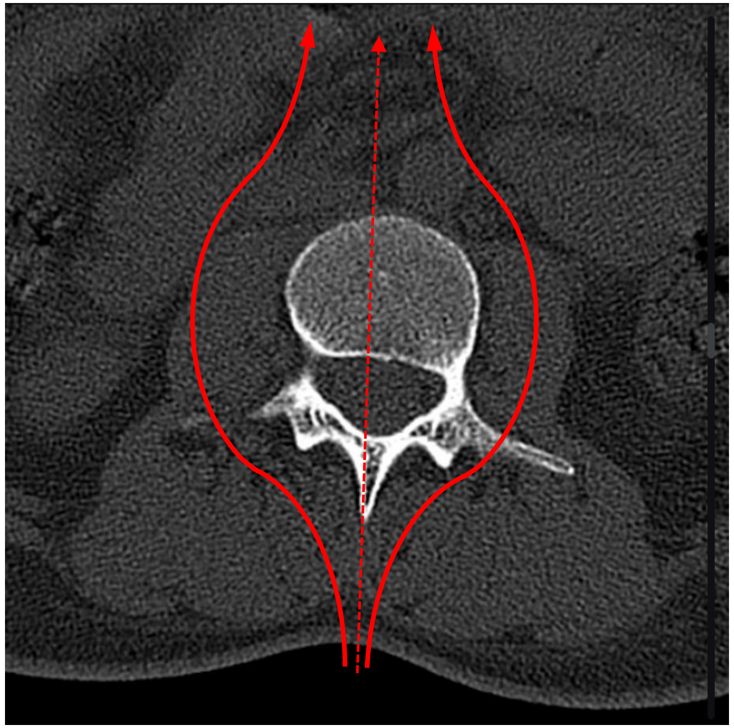
    Are these conditions in cervical tSCS comparable to lumbar tSCS?

Scientific challenges in current applications

Lessons learned from lumbar tSCS with conventional pulses *do not directly translate to* cervical stimulation

Normal lumbar spine CT

Normal cervical spine CT



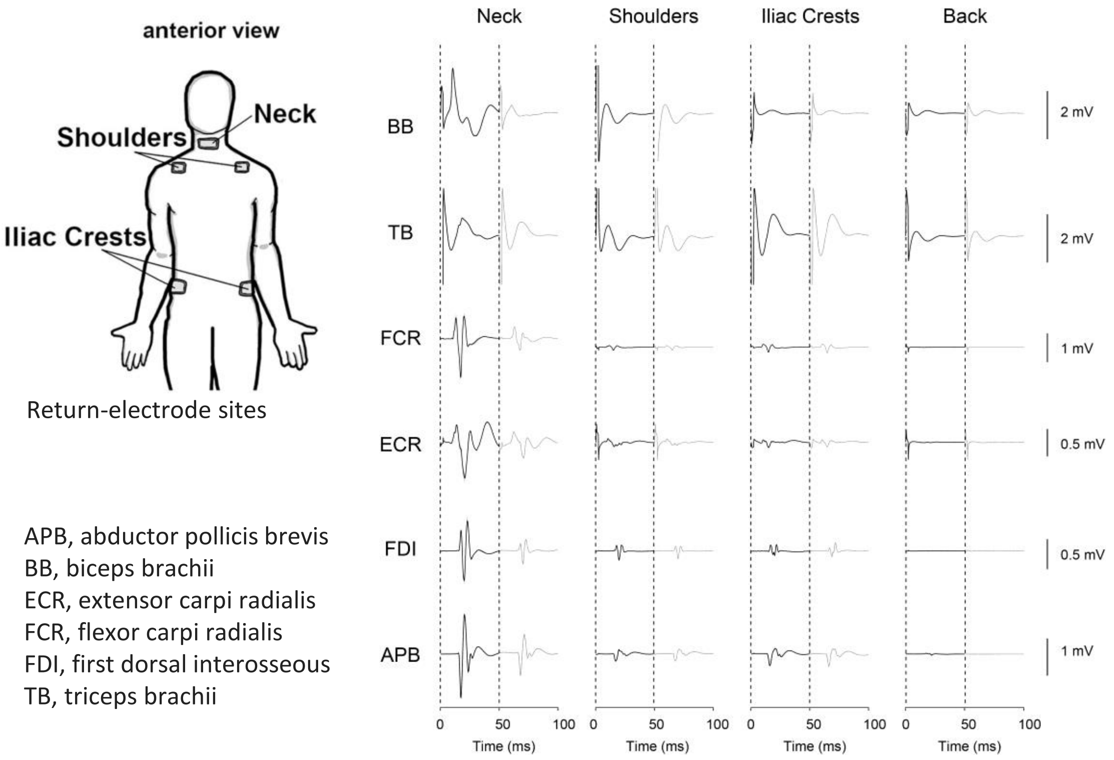
Only the portion of current that actually reaches the spinal canal will contribute to tSCS

Karen Minassian
Center for Medical Physics and Biomedical Engineering

Cervical stimulation

There is good – *but overlooked* – evidence, that cervical stimulation does not efficiently recruit spinal root or spinal cord afferents

- *Cervical evoked responses show absent or incomplete post-activation depression*



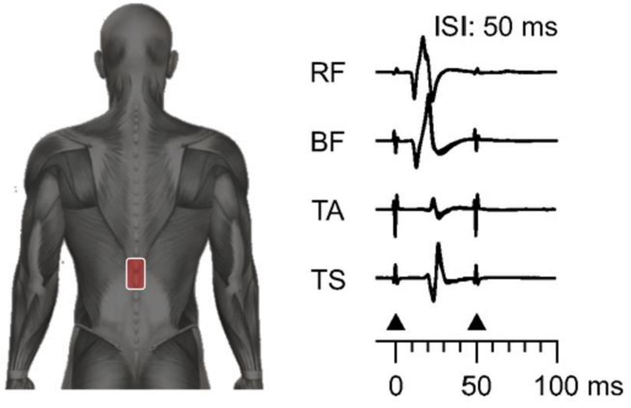
Return-electrode sites

APB, abductor pollicis brevis
BB, biceps brachii
ECR, extensor carpi radialis
FCR, flexor carpi radialis
FDI, first dorsal interosseous
TB, triceps brachii

-------*direct, M wave-like responses*--------

de Freitas et al. J Appl Physiol (1985). 2021;131:746-59. (Matja Milosevic)

Lumbar tSCS



RF, rectus femoris
BF, biceps femoris
TA, tibialis anterior
TS, triceps surae

Hofstoetter US. J Neurotrauma. 2020 Feb 1;37(3):481-493.

Cervical stimulation

There is good – *but overlooked* – evidence, that cervical stimulation does not efficiently recruit spinal root or cord afferents

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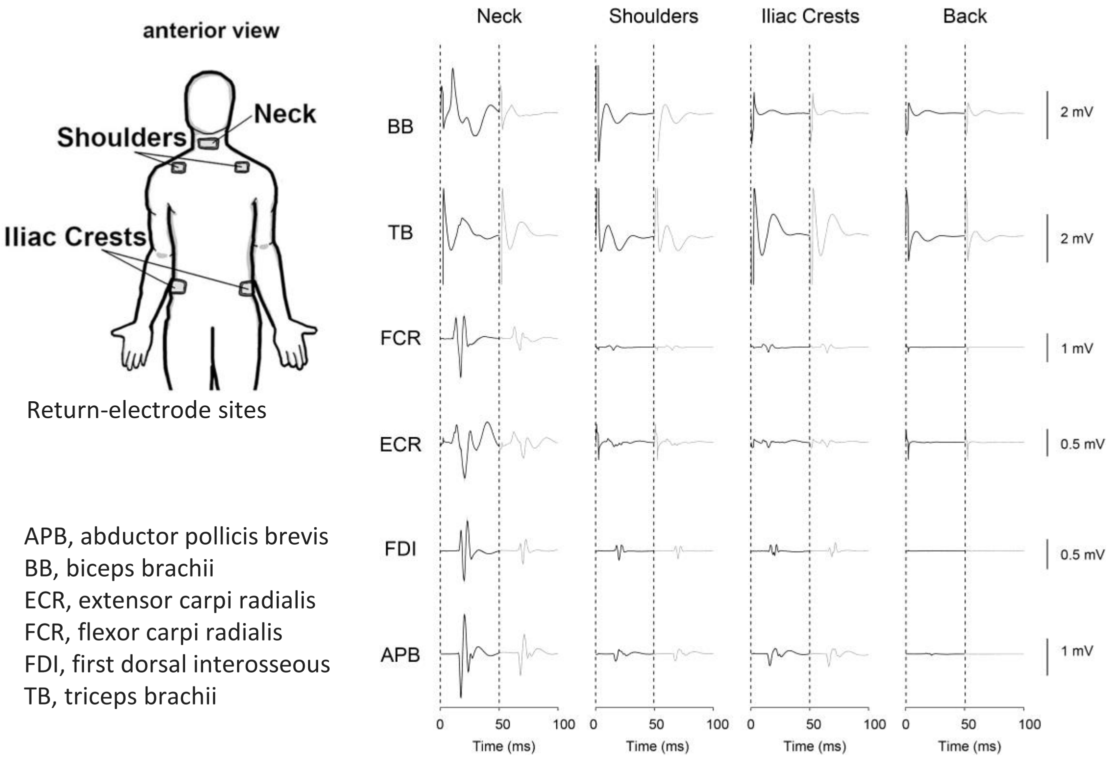

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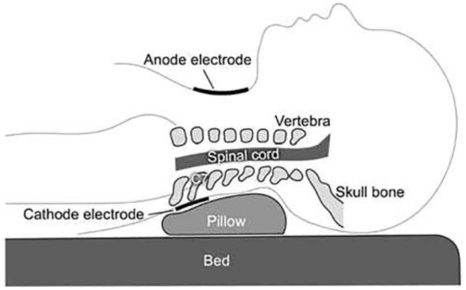
-------*direct, M wave-like responses*--------

de Freitas et al. J Appl Physiol (1985). 2021;131:746-59.



Milosevic et al. J Neurophysiol. 2019;121(5):1672-1679.

Wu et al. Clin Neurophysiol. 2020;131(2):451-460.

… our findings also demonstrate lack of complete abolishment of the second response … the evoked potentials may partially be due to direct activation of motor axons.

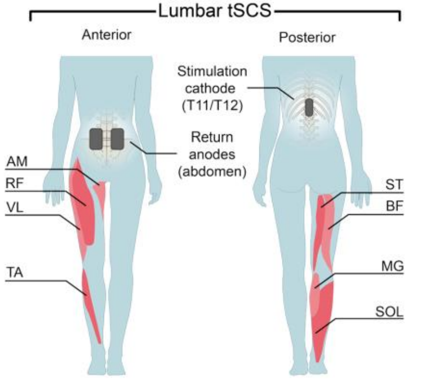
… stimuli bypass the spinal interneuronal circuitry and activate the motor axons to cause direct contraction of muscles, with limited therapeutic effects.

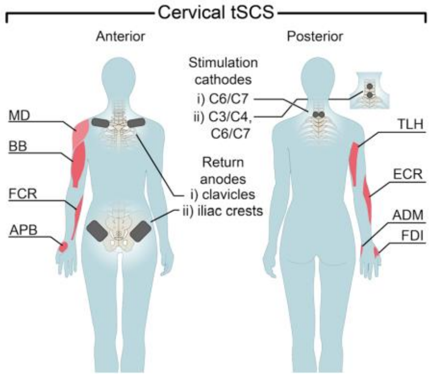
… caused mixed activation of afferent and efferent axons … at lower stimulus intensities, and predominantly efferent axon activation at higher stimulus intensities

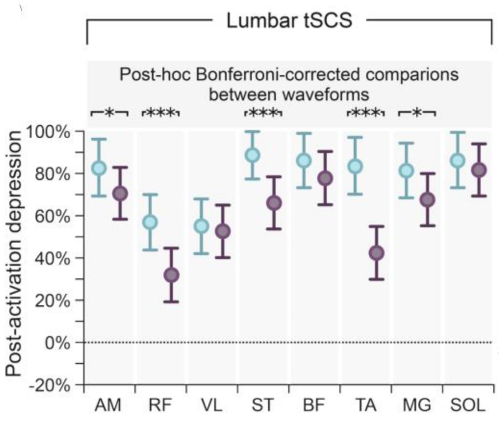
Cervical stimulation

There is good – *but overlooked* – evidence, that cervical stimulation does not efficiently recruit spinal root or cord afferents

- *Cervical evoked responses show absent or incomplete post-activation depression*

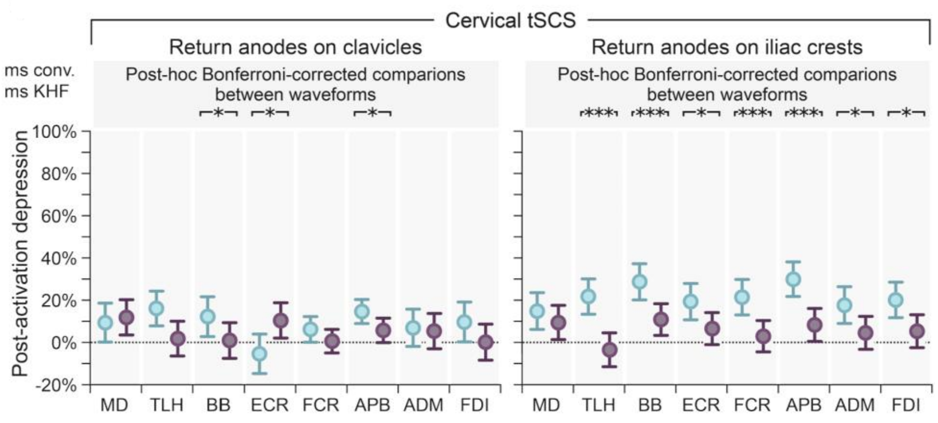






Reflex origin

No suppression



No suppression

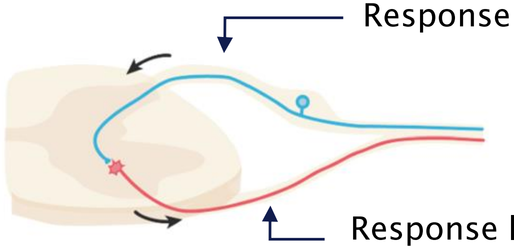
Keesey et al. Fundamental limitations of kilohertz-frequency carriers in afferent fiber recruitment with transcutaneous spinal cord stimulation. Nat Biomed Eng. *(accepted)*

Cervical stimulation

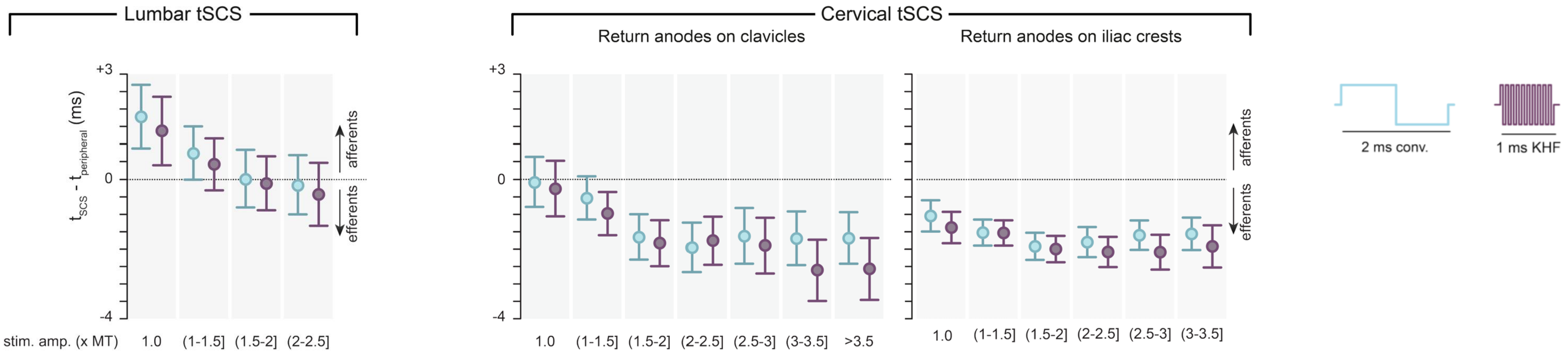
There is good – *but overlooked* – evidence, that cervical stimulation does not efficiently recruit spinal root or cord afferents

- *Cervical evoked responses have latencies shorter than the peripheral conduction time*

Response latency > peripheral conduction time → afferent stim.



Response latency < peripheral conduction time → efferent stim.



medial gastrocnemius

abductor pollicis brevis

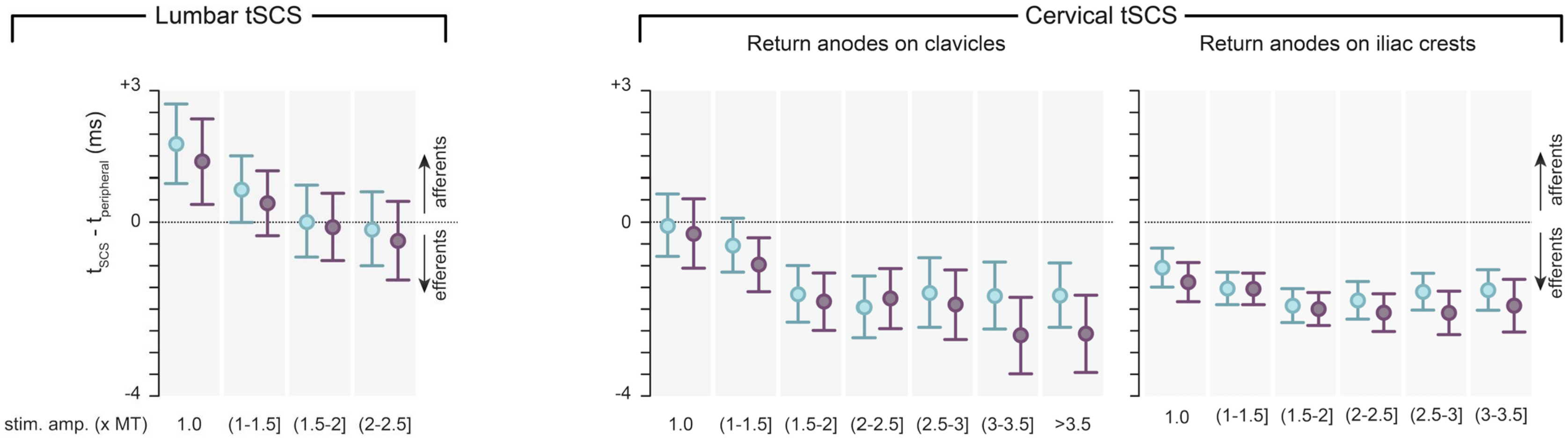
Keesey et al. Fundamental limitations of kilohertz-frequency carriers in afferent fiber recruitment with transcutaneous spinal cord stimulation. Nat Biomed Eng. *(accepted)*

Cervical stimulation

There is good – *but overlooked* – evidence, that cervical stimulation does not efficiently recruit spinal root or cord afferents

- *Cervical stimulation largely activates motor axons directly, likely outside the spine*

Cervical stimulation may still recruit some afferents, but does so inefficiently



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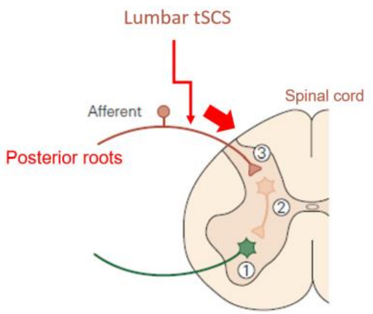
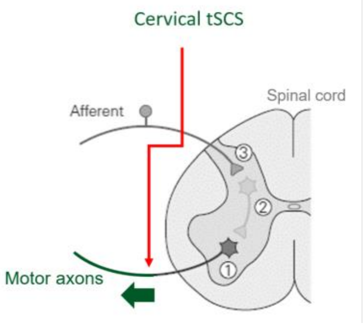




Cervical stimulation may still recruit some afferents, but does so inefficiently

In Summary:

If the basic idea of cervical tSCS is similar to epidural or transcutaneous lumbar SCS, i.e., to neuromodulate spinal circuits through 'electrical stimulation of part of its afferents', then it is inefficient

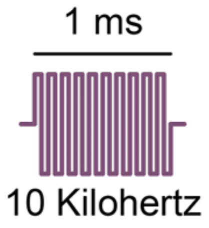
Scientific challenges in current applications

Lessons learned from lumbar tSCS with conventional pulses *do not directly translate to* cervical stimulation and Russian currents

- Russian stimulation

Gerasimenko et al., Ann Phys Rehabil Med. 2015;58:225-231

" … One of the innovative features is the use of a specific stimulation waveform that does not elicit pain even when used at energies required to transcutaneously reach the spinal networks …"



10 kilohertz-frequency modulated pulses of 1 ms duration

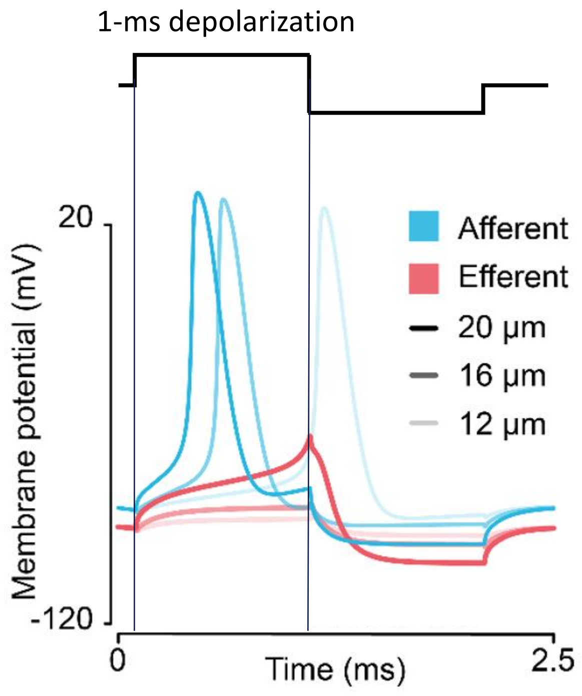
1-ms pulses with a 10 kilohertz-carrier

Series of increasing numbers of brief, biphasic pulses

Russian stimulation

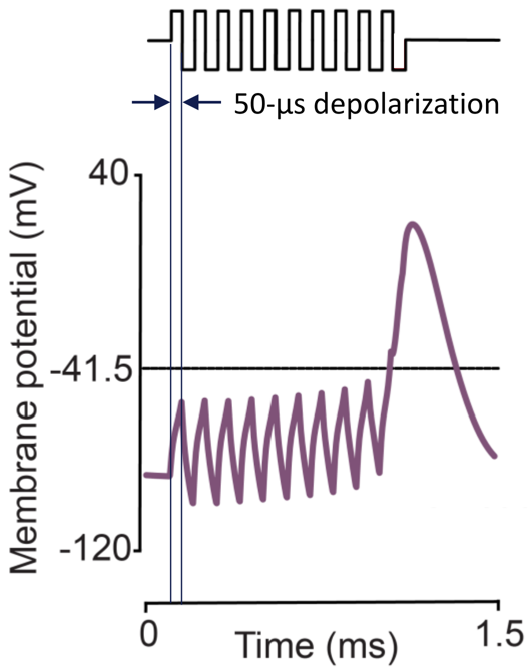
The use of 10-kilohertz modulated pulses to activate neuronal axons is counterintuitive

Conventional pulse



(Computer simulations)

10-kilohertz modulated pulses ('Russian stim')



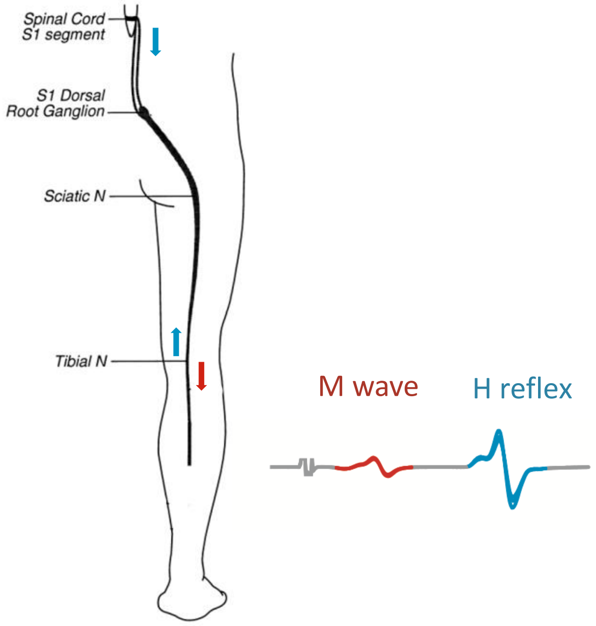
- Brief depolarizations interrupted by re- and even *hyper*polarization
- Brief depolarization phases are suboptimal for afferent stimulation

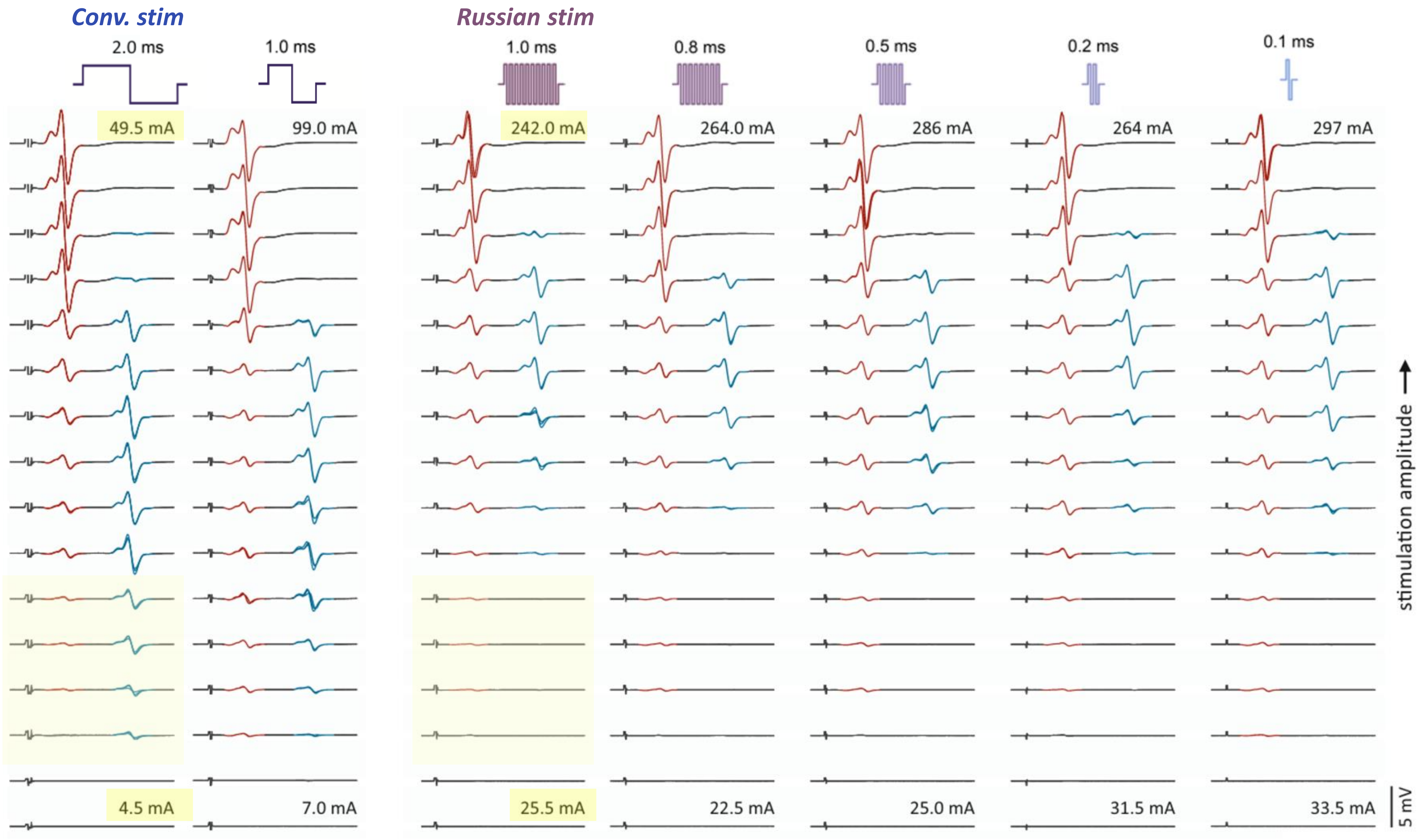
Keesey et al. Fundamental limitations of kilohertz-frequency carriers in afferent fiber recruitment with transcutaneous spinal cord stimulation. Nat Biomed Eng. *(accepted)*

Russian stimulation

M wave: direct motor response elicited by stimulation of motor efferent fibers

H reflex: reflex response elicited by stimulation of proprioceptive afferent fibers





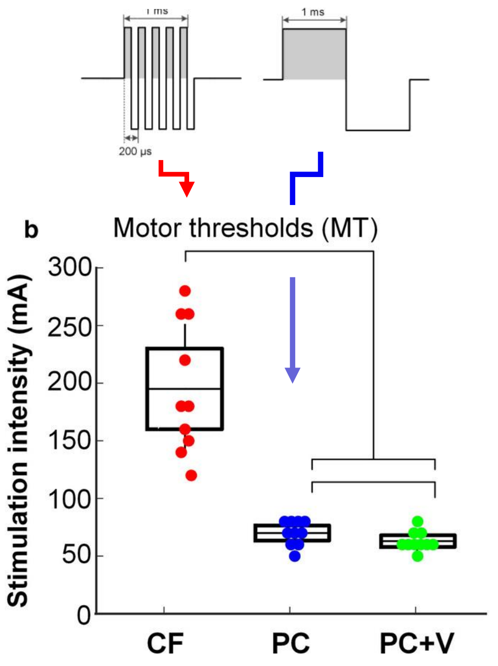
Keesey et al. Fundamental limitations of kilohertz-frequency carriers in afferent fiber recruitment with transcutaneous spinal cord stimulation. Nat Biomed Eng. *(accepted)*

Russian currents

tSCS using 10-kilohertz modulated pulses are inefficient at activating neural axons

Manson et al. Physiol Rep. 2020;8(5):e14397. (D. Sayenko)

Lumbar tSCS

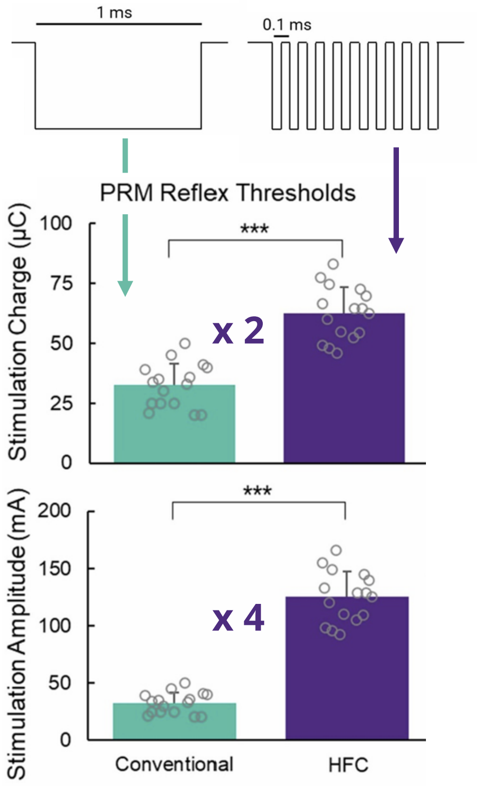


195 ± 56 mA

70 ± 10 mA

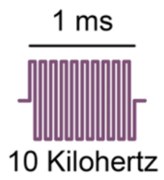
Dalrymple et al. J Neural Eng. 2023;20(1). (D. Weber)

Lumbar tSCS



Sayenko DG, Rath M, Ferguson AR, Burdick JW, Havton LA, Edgerton VR, Gerasimenko YP. J Neurotrauma. 2019;36(9):1435-1450.

1-msec pulses filled by a carrier frequency of 10 kHz



Ineffective (sham) stimulation

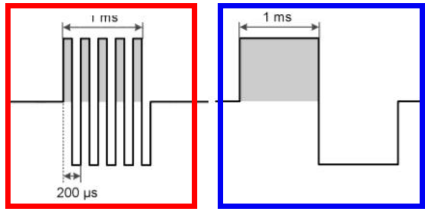
" … intentionally ineffective for standing sham stimulation was administered …., and intensities up to 200 mA …"

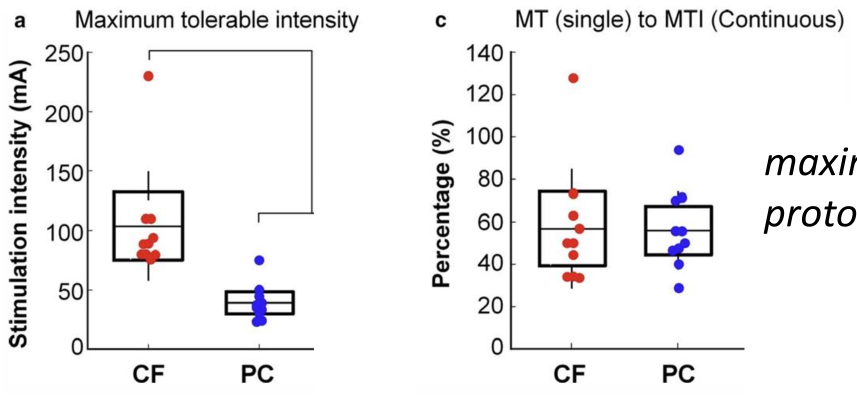
" … Even with a higher stimulation intensity, however, biphasic pulses filled by a 10 kHz carrier frequency did not induce detectible activity of motor pools projecting to the leg muscles …"

Russian currents – is it really 'painless'?

Manson GA, Calvert JS, Ling J, Tychhon B, Ali A, Sayenko DG.
The relationship between maximum tolerance and motor activation during transcutaneous spinal stimulation **is unaffected by the carrier frequency** or vibration. Physiol Rep. 2020;8(5):e14397.

Lumbar tSCS



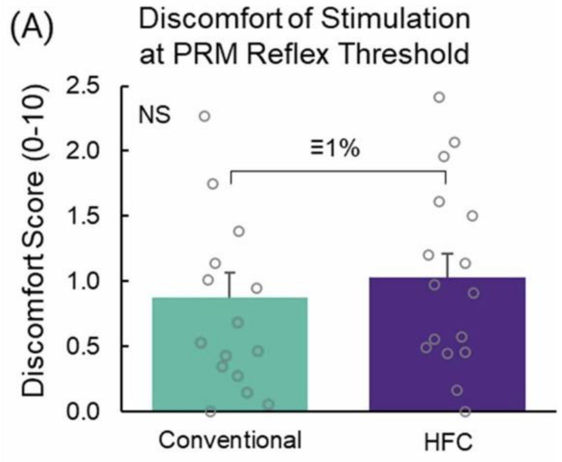


*maximum tolerable intensity in the continuous protocol **normalized to motor threshold***

" …. these results suggest that neither of the alternative paradigms has the advantage of reducing pain while inducing a similar motor response, as compared with a conventional, unmodulated pulse configuration …"

Russian currents – is it really 'painless'?

Dalrymple AN, Hooper CA, Kuriakose MG, Capogrosso M, Weber DJ.
Using a high-frequency carrier **does not improve comfort** of transcutaneous spinal cord stimulation.
J Neural Eng. 2023 Jan 18;20(1).



" … tSCS neuromodulation for motor recovery requires stimulation amplitudes near PRM reflex threshold … . At reflex thresholds, high-frequency carrier stimulation is not more comfortable than conventional stimulation, despite several claims of pain-free stimulation when a high-frequency carrier is used. …"

Luu BL, Trinh T, Finn HT, Aplin FP, Gandevia SC, Héroux ME, Butler JE. Pain tolerance and the thresholds of human sensory and motor axons to single and repetitive bursts of kilohertz-frequency stimulation. J Physiol. 2024;602(22):6281-6299.

Yang C, Veit NC, McKenzie KA, Aalla S, Kishta A, Embry K, Roth EJ, Lieber RL, Jayaraman A. The effects of stimulation waveform and carrier frequency on tolerance and motor thresholds elicited by transcutaneous spinal cord stimulation in stroke. Clin Neurophysiol Pract. 2025;10:150-158.

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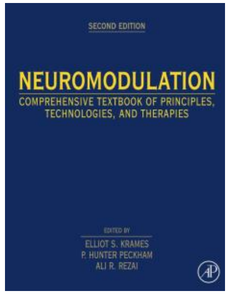
spinal research
curing paralysis together

“ … As sometimes happens in medicine, rapid advances in treatment precede scientific understanding of mechanism. …”



Chapter 17

karen.minassian@meduniwien.ac.at