Neuromodulazione periferica

Massimiliano Valeriani[1,2]

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Applications:

- Pain

  TENS, peripheral nerve stimulation (usually invasive)

- Dystonia

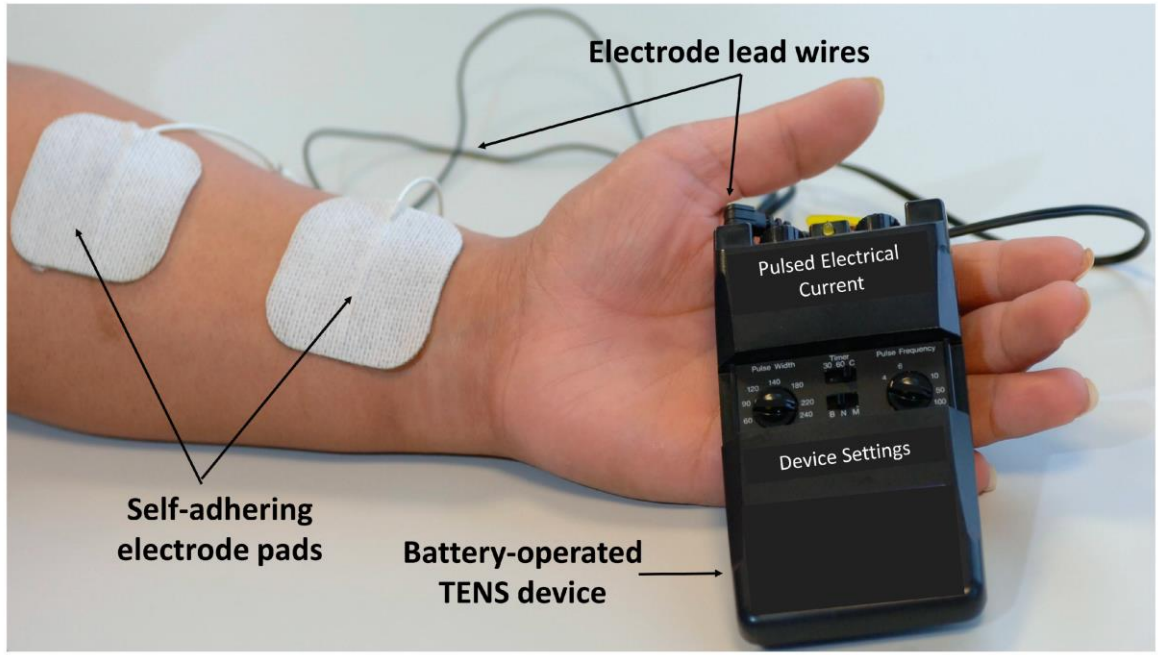
- Spasticity

- Neuro-urological dysfunction

- Stipsis (gut inflammation)

Transcutaneous Electrical Nerve Stimulation (TENS)

-Frequency of stimulation: usually around 100 Hz (also LF TENS)
-Stimulated area: proximal to painful region



Johnson, *Medicina* 2021

TENS reduces the amplitude of the brain responses evoked by the nociceptive input (laser evoked potentials – LEPs)

Clinical Neurophysiology 124 (2013) 1861–1867

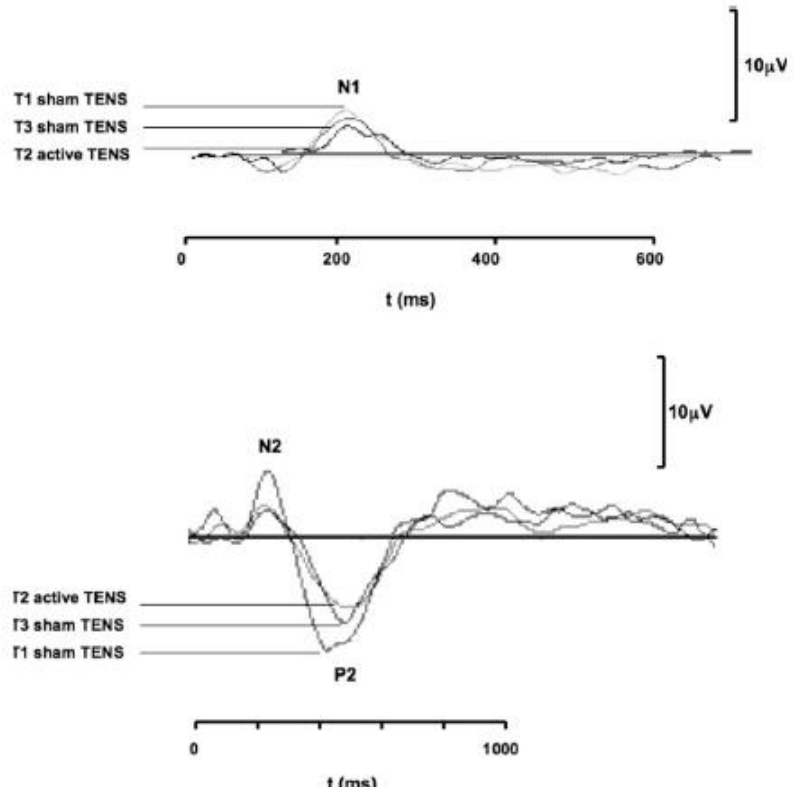
Contents lists available at SciVerse ScienceDirect

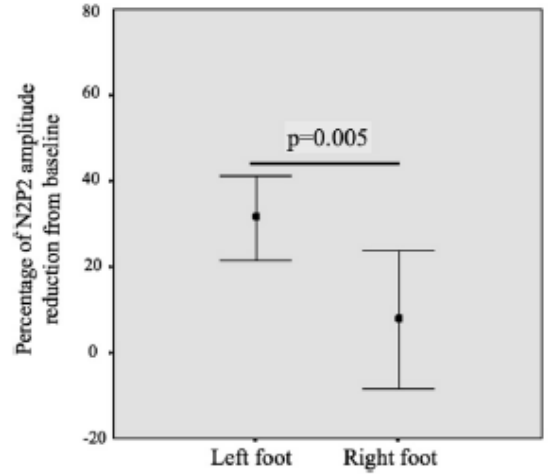
Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Modulation of laser-evoked potentials and pain perception by transcutaneous electrical nerve stimulation (TENS): A placebo-controlled study in healthy volunteers

François Vassal [a,b,*], C. Créac'h [b,c], Ph. Convers [b,c], B. Laurent [b,c], L. Garcia-Larrea [b], R. Peyron [b,c]





Current Pain and Headache Reports (2020) 24:14
https://doi.org/10.1007/s11916-020-0846-1

OTHER PAIN (AD KAYE AND N VADIVELU, SECTION EDITORS)

Transcutaneous Electrical Nerve Stimulation in Relieving Neuropathic Pain: Basic Mechanisms and Clinical Applications

Tahmineh Mokhtari[1,2] · Qiaoyue Ren[1,2] · Nuo Li[3] · Faguang Wang[4] · Yanzhi Bi[1,2] · Li Hu[1,2,5]

Table 1 Analgesic effects of TENS on peripheral and central neuropathic pain

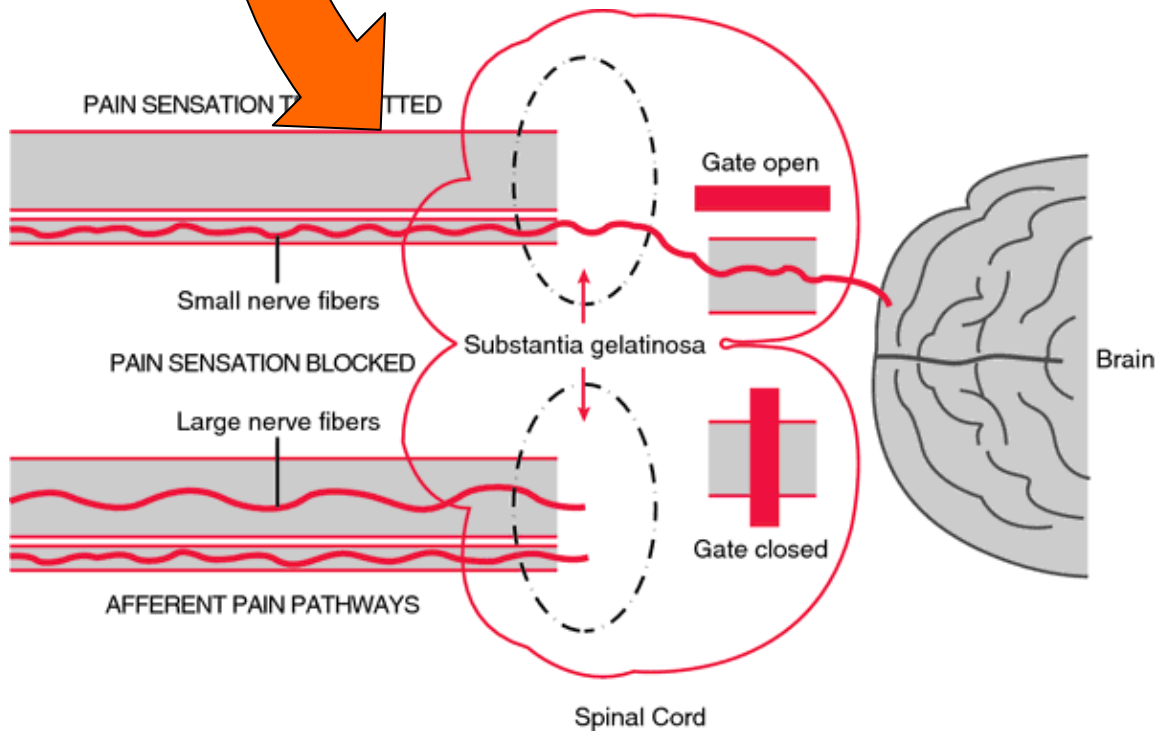
Authors (year)	Research type	Type of neuropathic pain	Number of participants	Type of TENS	Electrode placements	Stimulus parameters	Intervention duration	Main results
Kumar et al. (1998) [73]	A single-blind placebo–controlled randomized study	PNP-DPNP	$n = 23$ patients who failed to respond to amitriptyline or who only had partial relief Groups: Sham and amitriptyline ($n = 9$) TENS and amitriptyline ($n = 14$)	–	Four self-adhesive electrodes: 1) 3 in. above the patella and 3 in. medially, over the vastus medialis oblique 2) 3 in. above patella and 3 in. laterally, over the lower portion of vastus lateralis 3) on the neck of fibula 4) on the gastrocnemius muscle about 3 in. below the center of popliteal fossa	4 ms ≤ 35 mA 25–35 V 2-70 Hz	12 weeks	Symptomatic improvement occurred in 12 (85%) patients Five (36%) of the patients became asymptomatic Effective for patients who failed amitriptyline treatment Pain scores declined from 3.2 ± 0.2 to 1.4 ± 0.4. 66 ± 10% overall reduction in pain
Somers and Somers (1999) [72]	A case report	PNP-DPNP	A 73-year-old woman	HF	1.3 cm (1/2 in) lateral to the left/right posterior superior iliac spine on the back	200–400 ms 44–60 mA 80 Hz	20 min/time occasionally for 1 to 2 h during the day and more often at night 17 days	Following 20 min of TENS on the first day, a 38% reduction in intensity of pain After 17 days, the subject reported no pain following 20 min of TENS and she could sleep through the night
Dubinsky and Miyasaki (2010) [78]	A systematic review	PNP-DPNP	–	LF HF Sham	–	–	–	Modest reduction in pain severity for TENS compared to sham TENS A larger proportion felt benefit with high-frequency external muscle stimulation compared to TENS
Pieber et al. (2010) [77]	A systematic review	PNP-DPNP	–	–	–	–	–	Beneficial effects with prolonged use over an average period of 1.7 years
Jin et al. (2010) [23]	A meta-analysis of RCTs	PNP-DPNP	$n = 78$	LF Sham Other Frequenci-es	–	–	12 weeks	Significant reductions in mean pain score in four to 6 weeks follow-up (16.6%). Improvement in overall neuropathic symptoms in 12 weeks follow-up (70%)
Gossrau et al. (2011) [22]	A single-blind placebo–controlled randomized study	PNP-DPNP	$n = 41$ Groups: TENS ($n = 22$) Placebo ($n = 19$)	LF	Proximal dorsum pedis and the top of the caput fibulae on both legs	30–40 μA 2 Hz	30 min/time 3 times/week 4 weeks	No adverse effects No significant differences in the pain reduction between TENS and sham group No benefit for the patients' general life condition No side effects during and after the therapy
Naderi Nabi et al. (2015) [76]	A single-blind, randomized clinical trial	PNP-DPNP	$n = 60$ Groups: TENS ($n = 30$) PRF ($n = 30$)	HF	Two electrodes: 1) on the upper shin 2) above the ankle	0.2 ms 2 to 3 times sensory threshold 50 Amp 80 Hz	20 min/session 10 sessions every other day	Decreased pain severity (NRS) from 6.10 at baseline to 3.96, 5.23, and 5.90 at the first week, 1 month, and 3 months visits after treatment, respectively Long-term effects remained controversial

Authors (year)	Research type	Type of neuropathic pain	Number of participants	Type of TENS	Electrode placements	Stimulus parameters	Intervention duration	Main results
							day on the continuous setting that automatically alternates between 1-h treatment and 1-h rest periods (i.e., between 2 and 6 h of stimulation)	
Lee et al. (2019) [111]	A double-blind placebo–controlled randomized pilot study	PNP-cancer pain with radiation	$n = 40$ patients with head and neck cancer with 4 to 6 weeks radiation Groups: Active ($n = 12$) Placebo ($n = 12$) No TENS ($n = 16$)	HF	Four round adhesive electrodes: 1) bilaterally on the TMJ (one third of distance from the ear and nose) 2) bilaterally upper neck area (2 cm from the spine, i.e., cervical 1 and 2)	100 μs 125 Hz	30 min/time once/week over 3 weeks	Active TENS reduced VAS (from 3.2 to 1.9) and MPQ (from 6.8 to 3.7) scores in patients
Kolsek (2012) [90]	A retrospective observational study	PNP-herpes zoster	$n = 102$ patients Groups: TENS ($n = 29$) Antiviral drug ($n = 28$) Antiviral drug with TENS ($n = 24$) No therapy ($n = 21$)	HF	Two patches: 1) paravertebral region 2) the other side along the nerve	1–5 mA 20–40 Hz	30 min/time 5 times/week 2 or 3 weeks	The incidence of PHN was zero in herpes zoster patients treated with TENS
Stepanović et al. (2015) [92]	A multicenter prospective, randomized intervention study	PNP-herpes zoster	$n = 222$ patients with a new onset of HZ Groups: Control ($n = 38$) TENS ($n = 36$) Antiviral agents ($n = 71$) TENS and Antiviral agents ($n = 77$)	HF	Two electrodes: 1) Near the root of affected nerve 2) In the course of that nerve	0.02 ms 3–30 mA 20–40 Hz	30 min/time 10–15 days	The odds for subacute herpetic neuralgia are the lowest in acute herpes zoster patients treated with TENS
Warke et al. (2006) [99]	A randomized, placebo-controlled clinical trial	CNP-MS	$n = 90$ Groups: LF-TENS ($n = 30$) HF-TENS ($n = 30$) Placebo ($n = 30$)	LF HF	Lumbar spine (3 cm distance on either side of the spinous processes)	LF: 200 μs 4 Hz HF: 200 μs 110 Hz	45 min/time 2 times/day 6 weeks	Both methods (LF and HF) reduced pain in 50% of patients Mean weekly VAS score differences were − 16.59 mm for LF-TENS and − 20.60 mm for HF-TENS
Miller et al. (2007) [98]	A single-blind clinical trial	CNP-MS	$n = 32$ Groups: TENS (60 min/day, $n = 16$) TENS (8 h/day, $n = 16$)	HF	Either end of the quadriceps muscle	0.125 ms 100 Hz	60 min/day or 8 h/day daily 2 weeks	TENS does not appear effective in reducing spasticity Significant reduction in muscle spasm (from 4.1 to − 2.7) and pain (from 3.9 to − 2.2) in 8 h group Longer application (8 h) might be useful in treating MS patients with pain and muscle spasm
Cuypers et al. (2010) [112]	A clinical trial	CNP-MS	$n = 56$ **Groups:** $n = 26$ MS patients ($n = 15$ intervention, $n = 11$ control)	HF	Median nerve region of the dominant hand	250 μs 100 Hz	1 h/day 3 weeks	Long-lasting improvements in tactile sensitivity achieved by repetitive stimulation of sensory afferents in MS patients but not in healthy subjects Increased sensitivity was not only restricted to the median nerve area

Authors (year)	Research type	Type of neuropathic pain	Number of participants	Type of TENS	Electrode placements	Stimulus parameters	Intervention duration	Main results
			$n = 30$ healthy subjects ($n = 15$ intervention, $n = 15$ control)					but also expanded to the ulnar nerve area
Norrbrink (2009) [101]	A clinical trial	CNP-SCI	$n = 24$ Groups: LF-TENS ($n = 12$) HF-TENS ($n = 12$)	LF HF	Paraspinal site	LF: 180 μs 2 Hz HF: 180 μs 80 Hz	30–40 min/time 3 times/day 2 weeks	Favorable effects for 29% of the patients with HF and 38% of the patients with LF stimulation on a 5-point global pain-relief scale Median values of pain were 4 at baseline and 3.8 after the last HF session Median values of pain were 4 at baseline and 3.9 after the last LF session
Celik et al. (2013) [102]	A prospective, randomized and controlled study	CNP-SCI	$n = 33$ Groups: TENS ($n = 17$) Sham ($n = 16$)	LF	Two channels with four electrodes: 1) 2 electrodes: proximal parts of the region with pain 2) 2 electrodes: distal parts of the region with pain	200 μs 50 mA 4 Hz	30 min/time daily 10 days	Significant reduction of VAS score from 5.79 to 3.88 on the twelfth day in LF-TENS group
Bi et al. (2015) [113]	An RCT	CNP-SCI	$n = 52$ Groups: TENS ($n = 26$) Sham ($n = 26$)	LF	Region with pain	< 200 μs 50 mA 2 Hz	20 min/time 3 times/week 12 weeks	Significant decrease in the pain intensity scores after TENS intervention
Ozkul et al. (2015) [103]	A randomized controlled cross-over trial	CNP-SCI	$n = 24$ Groups: TENS first, then visual illusion ($n = 12$) Visual illusion first, then TENS ($n = 12$)	HF	Both sides of the spinal region	180 μs 0–100 mA 80 Hz	15 min/day 5 days/week 2 weeks	Pain intensity decreased immediately after both applications Significant decrease in most (VAS, from 8.92 to 8.41) and less (VAS, from 2.62 to 2) pain intensity after TENS application for 2 weeks, but not after 2 weeks for visual illusion Significant decrease in negative effect of pain on mood, relationships with others, and sleep after TENS application Both therapies can be used as a supportive or an alternative method separately or together
Price and Pandyan (2001) [108]	A systematic review	CNP-CPSP (shoulder pain)	$n = 170$ ES including TENS, functional ES or other	–	–	–	–	No significant change in pain incidence or change in pain intensity after ES treatment compared with control Significant treatment effect in favor of ES for improvement in pain-free range of passive lateral rotation of humerus ES reduced the severity of glenohumeral subluxation, but no

Gate control theory

Melzack and Wall, 1965



The simultaneous activation of non nociceptive and nociceptive fibres dampens the nerve conduction along the last ones at presynaptical level

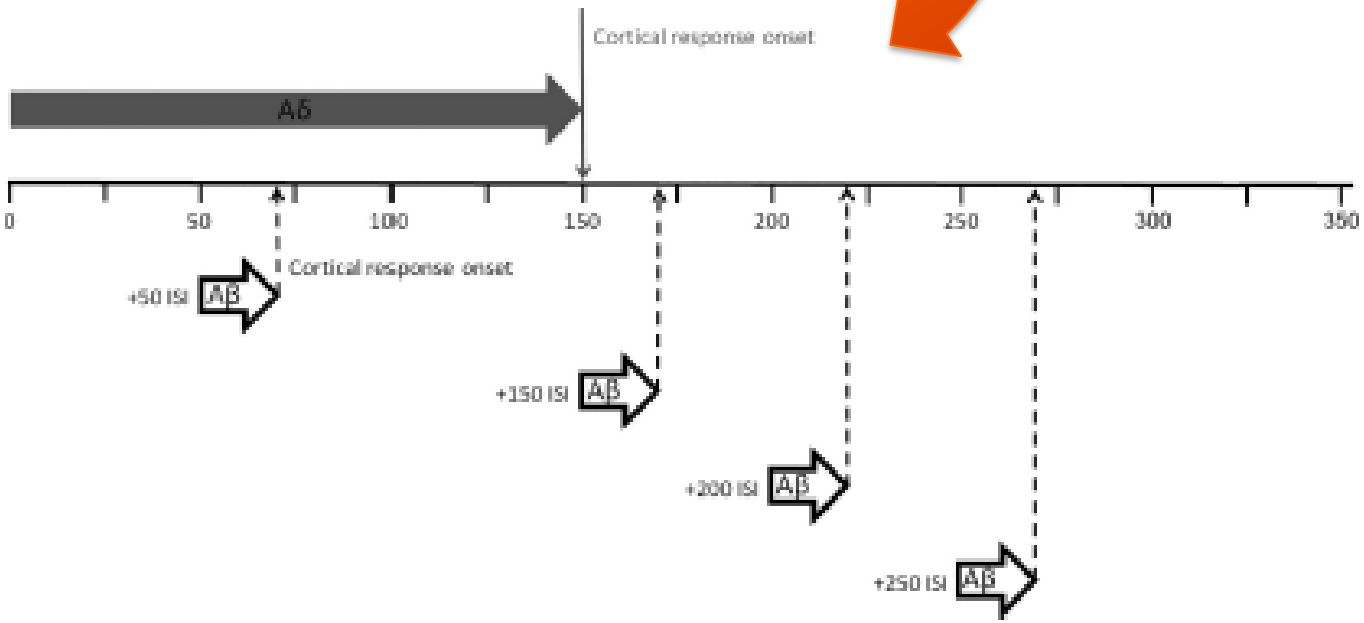
European Journal of Neuroscience, Vol. 42, pp. 2407–2414, 2015 doi:10.1111/ejn.13035

NEUROSYSTEMS

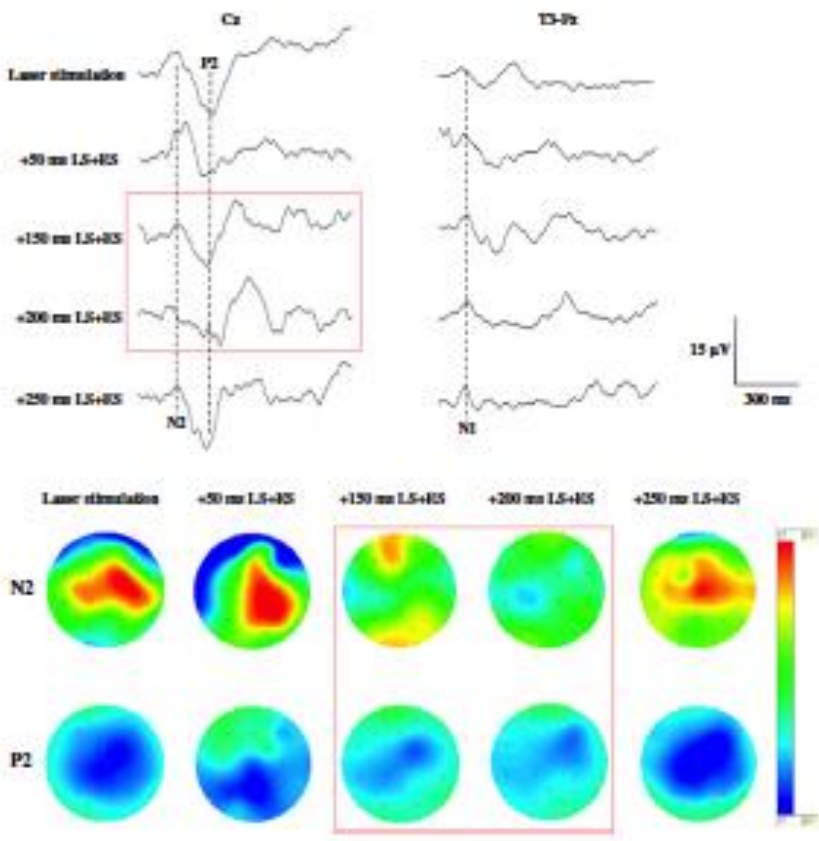
Cortical inhibition of laser pain and laser-evoked potentials by non-nociceptive somatosensory input

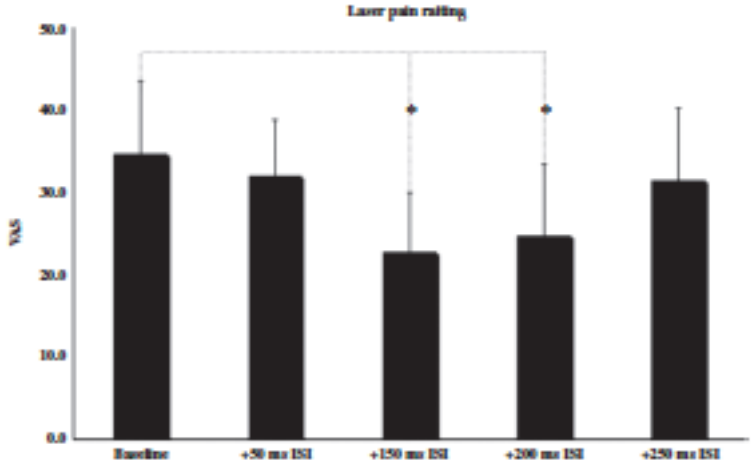
Elisa Testani,[1] Domenica Le Pera,[2] Claudio Del Percio,[3] Roberto Millucci,[4] Alfredo Brancucci,[5] Costanza Pazzaglia,[6] Liala De Armas,[2] Claudio Babiloni,[3,7] Paolo Maria Rossini[1] and Massimiliano Valeriani[1,8]

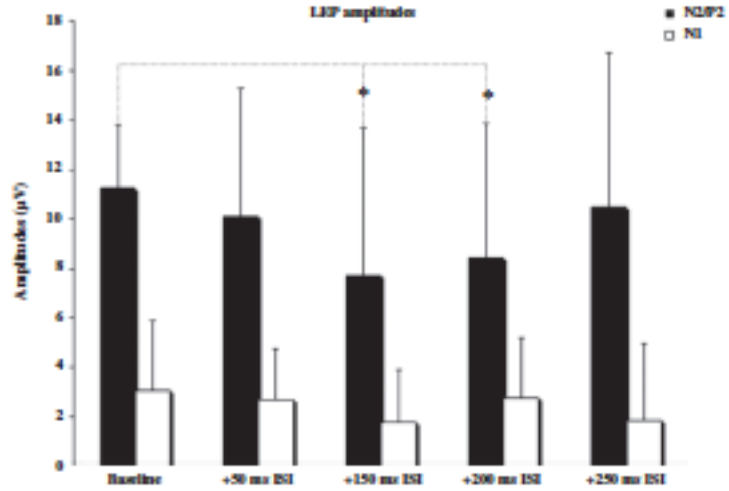
We tested the effect of a single non-nociceptive electrical stimulus on the nociceptive input with a 1:1 ratio



In this condition, non-painful electrical stimuli inhibit LEPs at supra-spinal level

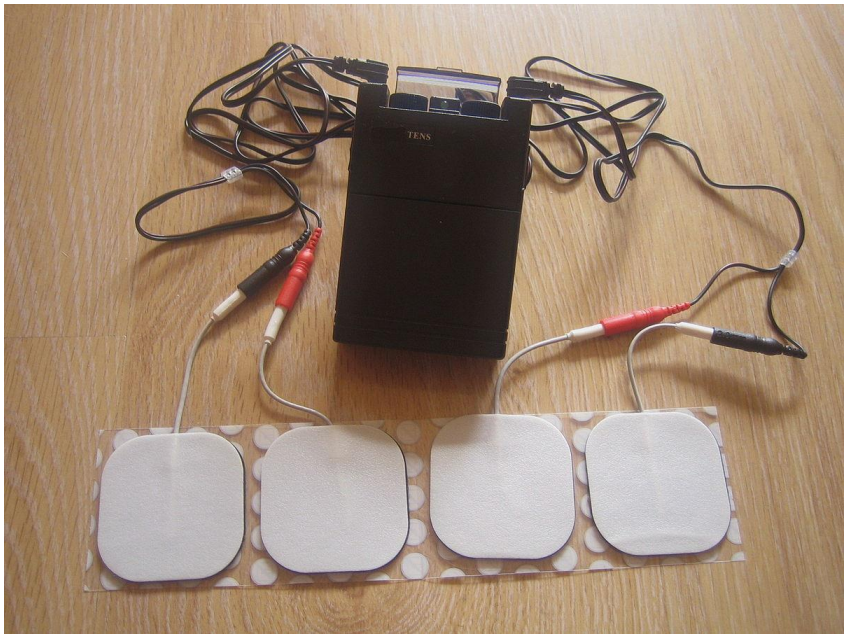






But…

… this is not an ecological condition, since both in daily life and clinical context it is higher frequency non-painfuli stimuli to reduce the pain perception



Clinical Neurophysiology 129 (2018) 920–925

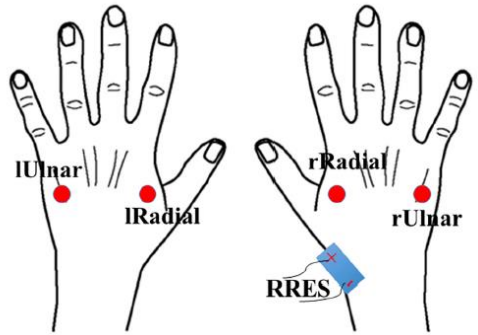
Contents lists available at ScienceDirect

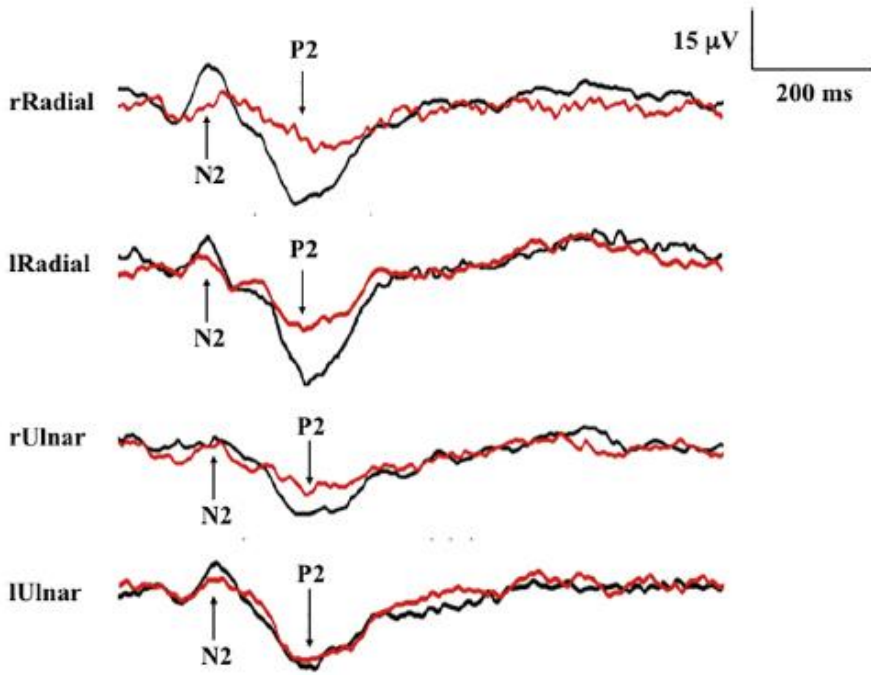
Clinical Neurophysiology

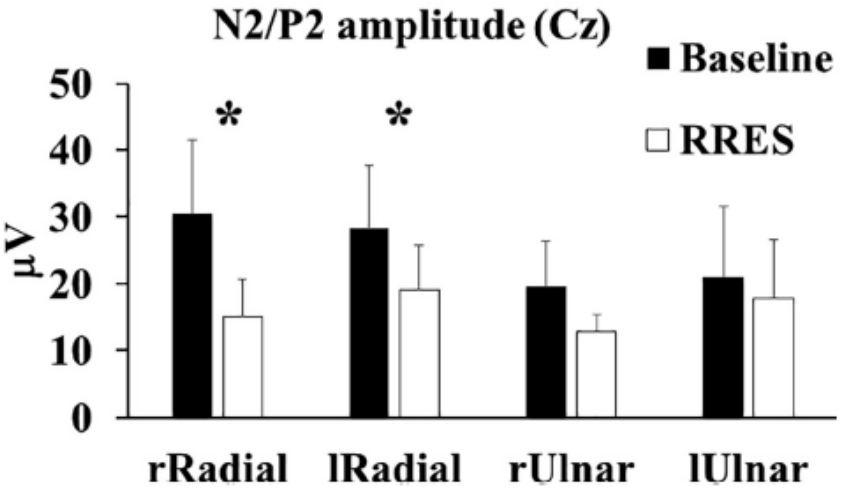
journal homepage: www.elsevier.com/locate/clinph

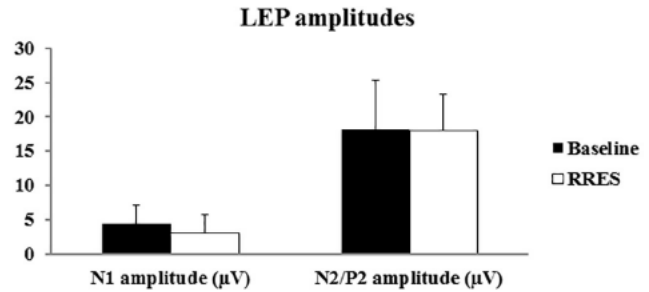
Laser evoked potential amplitude and laser-pain rating reduction during high-frequency non-noxious somatosensory stimulation

Massimiliano Valeriani [a,b,*], Costanza Pazzaglia [c], Vincenzo Rizzo [d], Angelo Quartarone [e,f], Catello Vollono [g]









Left foot stim.

Conclusions

1) Non-nociceptive stimuli inhibit the LEP amplitude

2) The pattern of inhibition suggests a spinal mechanism

3) Rostro-caudal and transversal propriospinal interneurons (Fitzgerald, 1982, 1983) can account for these findings

External trigeminal nerve stimulation (eTNS) - Cefaly® stimulator

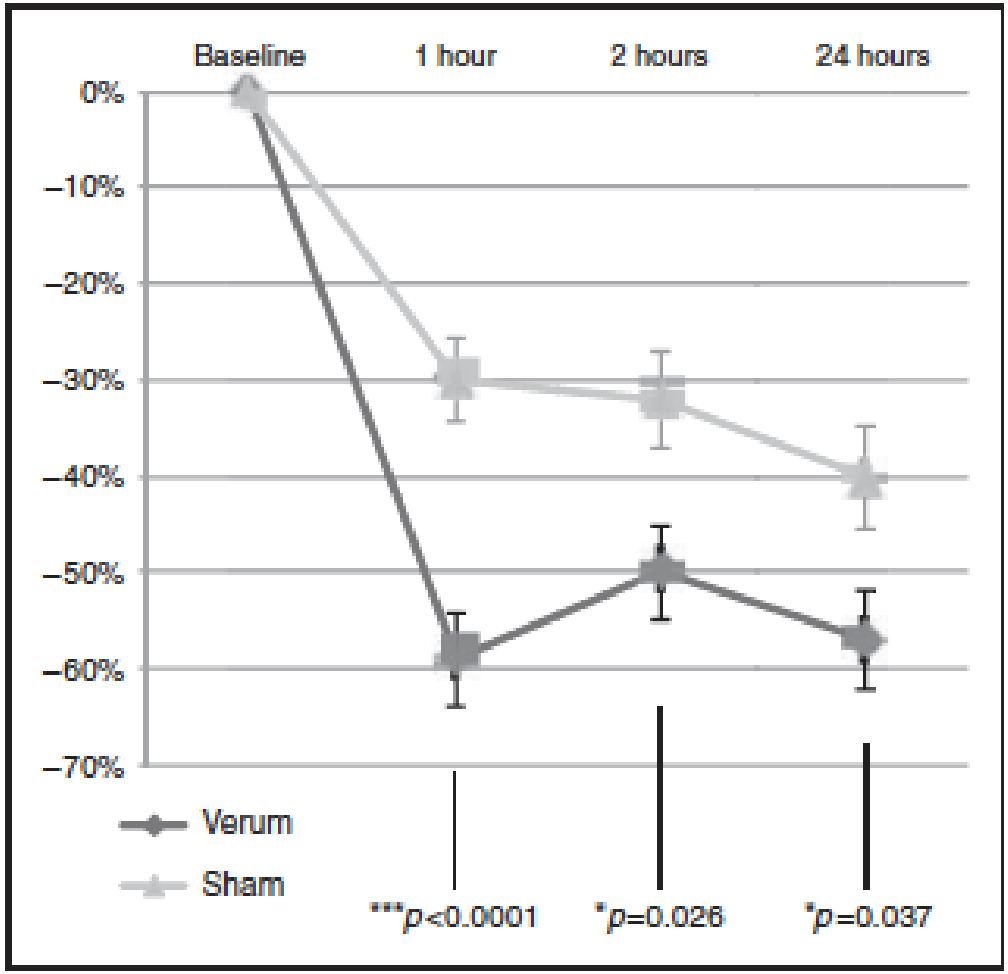
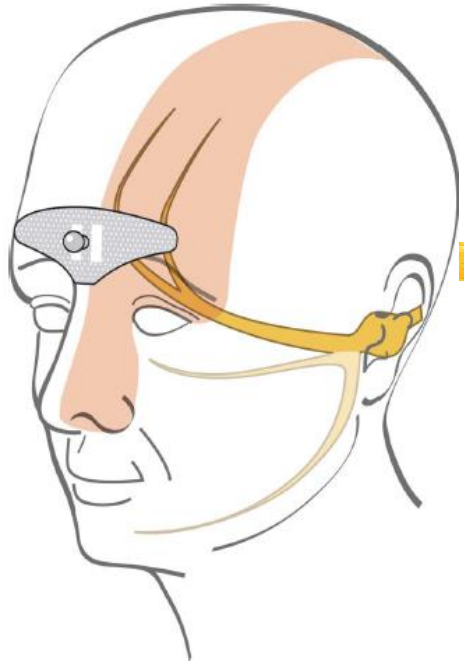


Figure 5. Relative change in mean VAS scores at 1 hour, 2 hours, and 24 hours after treatment, compared to baseline.



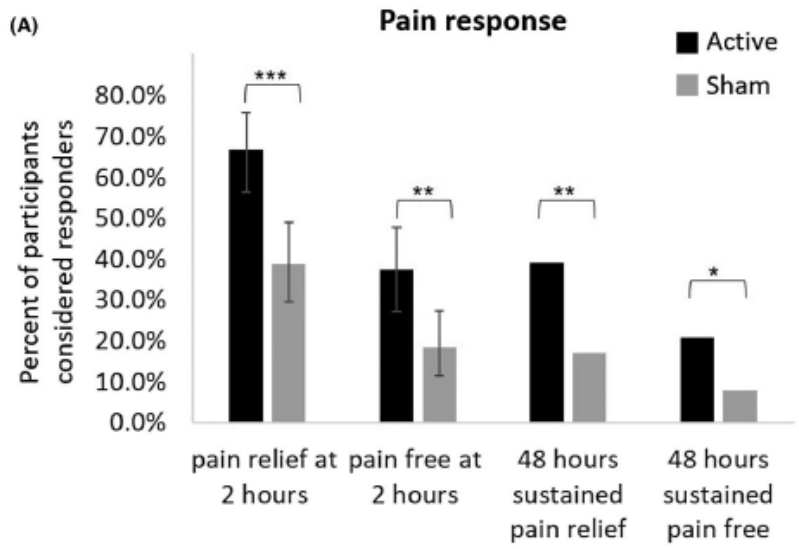
106 patients

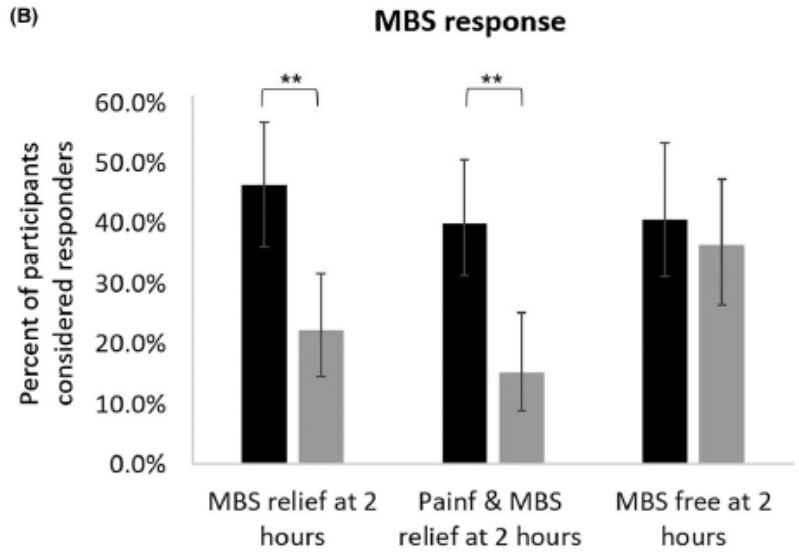
- biphasic rectangular impulses
- pulse width 250 µs
- frequency 100 Hz
- maximum intensity 16 mA
- Duration 60 min

Chou et al., *Cephalalgia* 2018

Remote electrical neuromodulation (REN) - Nerivio® stimulator

- biphasic rectangular impulses
- pulse width 400 μs
- frequency 100-120 Hz
- maximum intensity 40 mA
- duration 45 minutes





Yarnitski et al., *Headache* 2019

Pain Ther (2021) 10:985–1002
https://doi.org/10.1007/s40122-021-00306-4

REVIEW

Peripheral Nerve Stimulation for Chronic Pain: A Systematic Review of Effectiveness and Safety

Standiford Helm · Nikita Shirsat · Aaron Calodney · Alaa Abd-Elsayed · David Kloth · Amol Soin · Shalini Shah · Andrea Trescot

Key Summary Points

Chronic pain arising from peripheral nerve disorders is becoming more fully appreciated as a source of chronic pain.

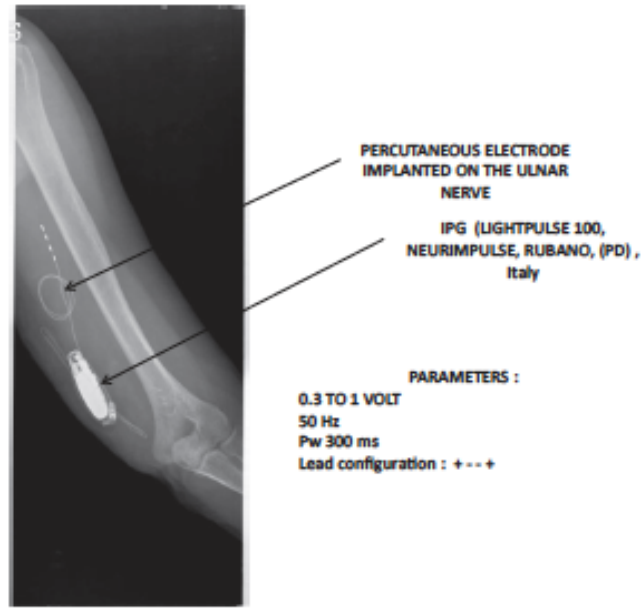
Peripheral nerve stimulation has benefited from technological advances which allow its wider application.

There is a need for a systematic review, with inclusion of the underlying methodology supporting that review, of the high-quality literature supporting the use of peripheral nerve stimulation.

Five randomized controlled trials and four observational studies of high or moderate quality support the use of peripheral nerve stimulation.

The best evidence is for neuropathic pain.

- Peripheral nerve lesions
- CRIPS
- Chronic pelvic pain
- Post-stroke shoulder pain
- Phantom limb pain



Reverberi et al., 2013

Current Pain and Headache Reports (2022) 26:267–278
https://doi.org/10.1007/s11916-022-01025-x

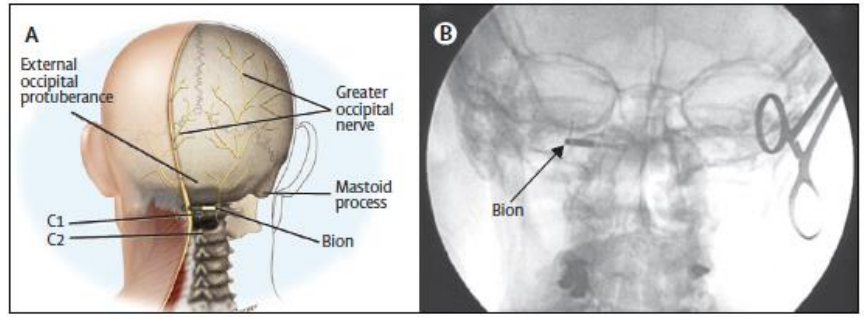
CHRONIC DAILY HEADACHE (SJ WANG AND SP CHEN, SECTION EDITORS)

Percutaneous occipital nerve stimulation

Neuromodulation for Chronic Daily Headache

Gianluca Coppola[1] · Delphine Magis[2] · Francesco Casillo[1] · Gabriele Sebastianelli[1] · Chiara Abagnale[1] · Ettore Cioffi[1] · Davide Di Lenola[1] · Cherubino Di Lorenzo[1] · Mariano Serrao[1]

Authors	Number of patients	Follow-up (months)	Patients with ≥ 50% improvement
Magis et al. [47, 103, 107]	15	36.8	11
Burns et al. [108, 109]	14	17.5	5
De Quintana et al. [110]	4	6	4
Mueller et al. [114]	10	12	9
Mueller et al. [104]	24	20	21
Fontaine et al. [111]	13	14.6	10
Strand et al. [112]	3	12	2
Leone et al. [113]	35	72	20
Miller et al. [106]	51	39.17	27
Leplus et al. [105]	93	43.8	64
TOTAL	262	39.1	173 (66%)



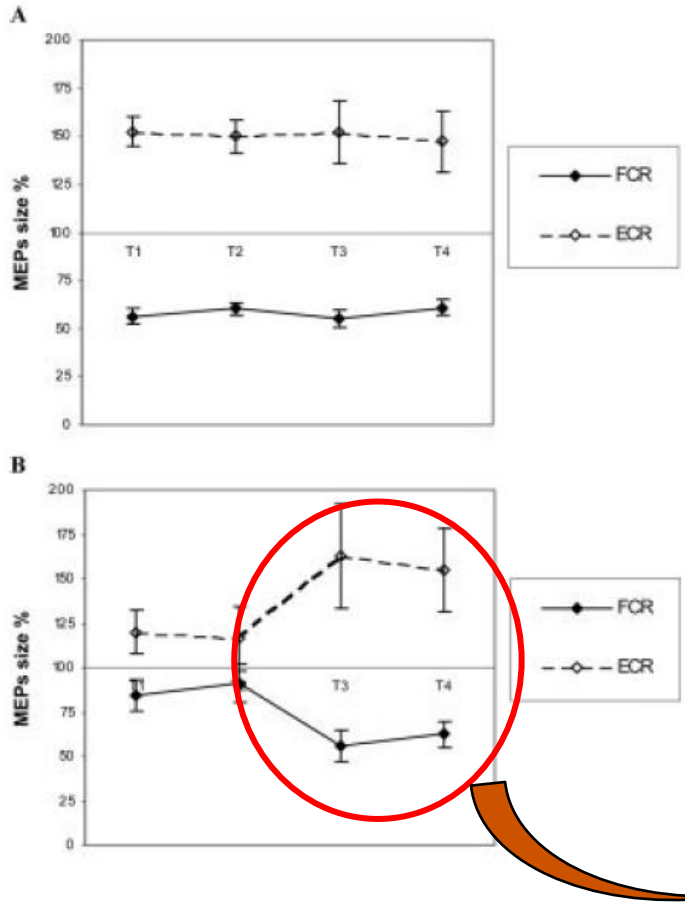
Burns et al., *Lancet* 2008

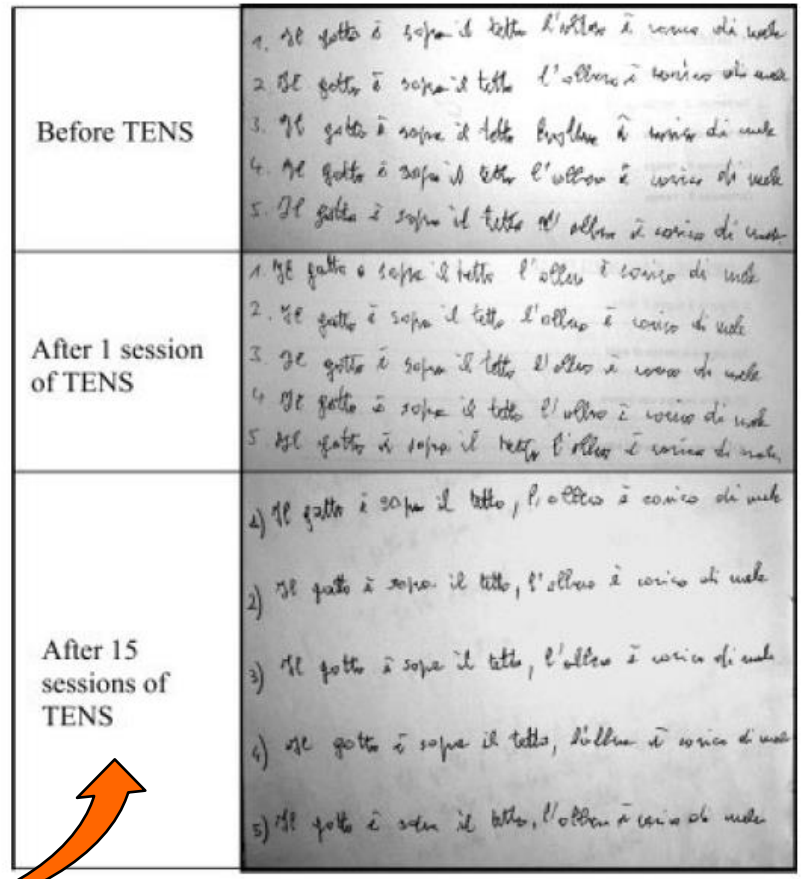
Movement Disorders
Vol. 21, No. 11, 2006, pp. 1908–1913

TENS on FCR muscle provides inhibition of FCR motoneurons and inhibitory neurons projecting on ECR motoneurons

Effects of Transcutaneous Electrical Nerve Stimulation on Motor Cortex Excitability in Writer's Cramp: Neurophysiological and Clinical Correlations

Michele Tinazzi, MD,[1,2*] Stefano Zarattini, MD,[1] Massimiliano Valeriani, MD,[3] Clementina Stanzani, MD,[1] Giuseppe Moretto, MD,[2] Nicola Smania, MD,[1] Antonio Fiaschi, MD,[1] and Giovanni Abbruzzese, MD[4]





IBRO Neuroscience Reports 11 (2021) 194–199

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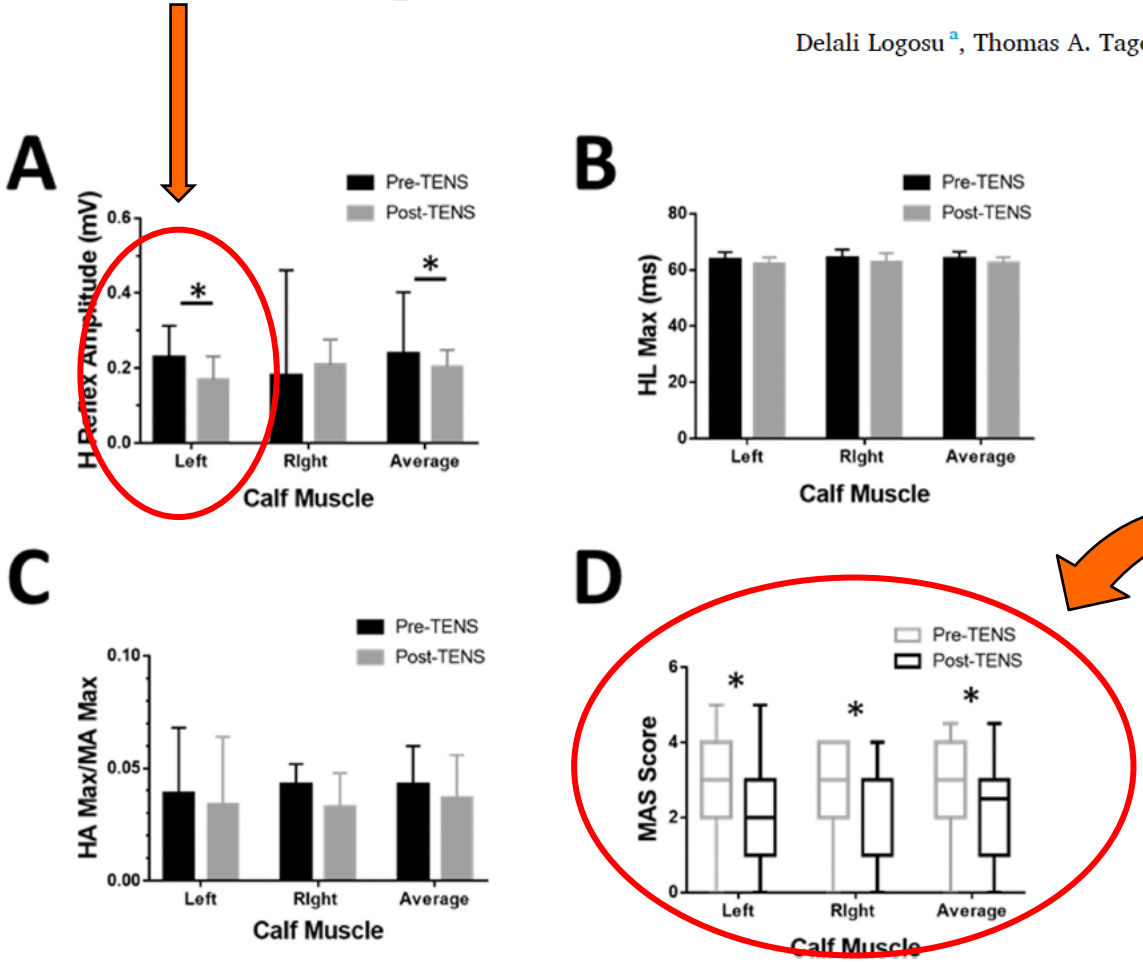
IBRO Neuroscience Reports

journal homepage: www.sciencedirect.com/journal/IBRO-Neuroscience-Reports

Transcutaneous electrical nerve stimulation in the management of calf muscle spasticity in cerebral palsy: A pilot study

Delali Logosu [a], Thomas A. Tagoe [a,*], Patrick Adjei [b,c]

Reduced H-reflex amplitude



Improvement of clinical measure

medicina

MDPI

Review

Neuromodulation of the Posterior Tibial Nerve for the Control of Urinary Incontinence

Álvaro Astasio-Picado * and María García-Cano

- Posterior tibial nerve stimulation (PTNS) is effective in urinary incontinence, especially in overactive bladder (OAB)
- PTNS is extremely safety
- Session frequency is uncertain (maybe 1.3 session per month)

Knowles et al., *Lancet* 2015

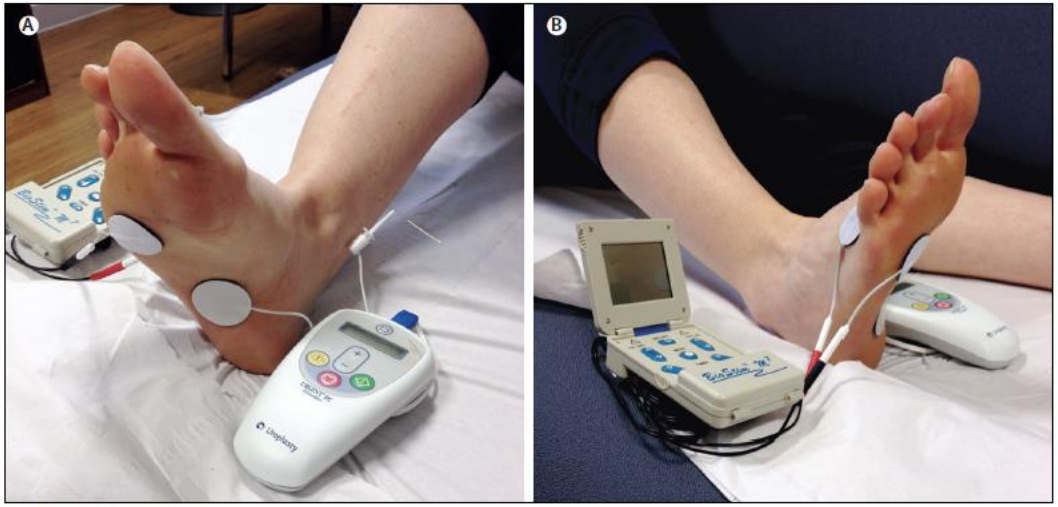
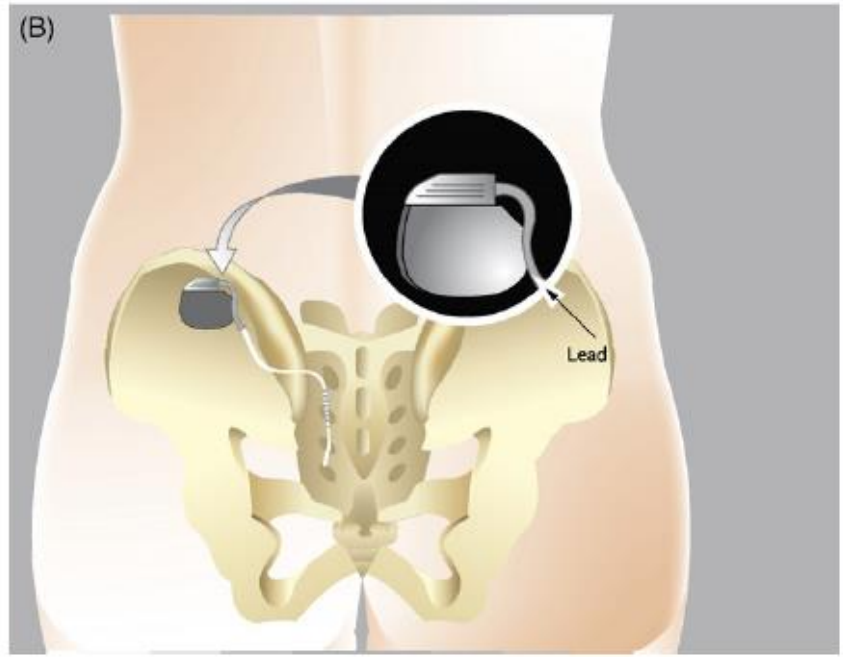


Figure 1: **Set-up for procedures**
(A) Percutaneous tibial nerve stimulation needle and calcaneal electrode. (B) Transcutaneous electrical nerve stimulation surface electrode placements.

Sacral neuromodulation (S3 root):

- **Overactive bladder**
- **Pelvic floor disorders**
- **Non-obstructive urinary retention**
- **Fecal incontinence**



Spinelli and Sivert, *Eur Urol* 2008

Take home messages:

- Peripheral neuromodulation (PN) can be useful in different neurological and non-neurological conditions
- Mechanisms of action are scarcely known
- PN may be non-invasive, but also invasive
- PN is generally safe, thus it may be added to pharmacological treatments
- There is a general methodological heterogeneity that makes metanalysis of results difficult