SAPIENZA
UNIVERSITÀ DI ROMA
Dipartimento di Neurologia e Psichiatria
Unità di Malattie Neuromuscolari

Diagnostica del dolore neuropatico

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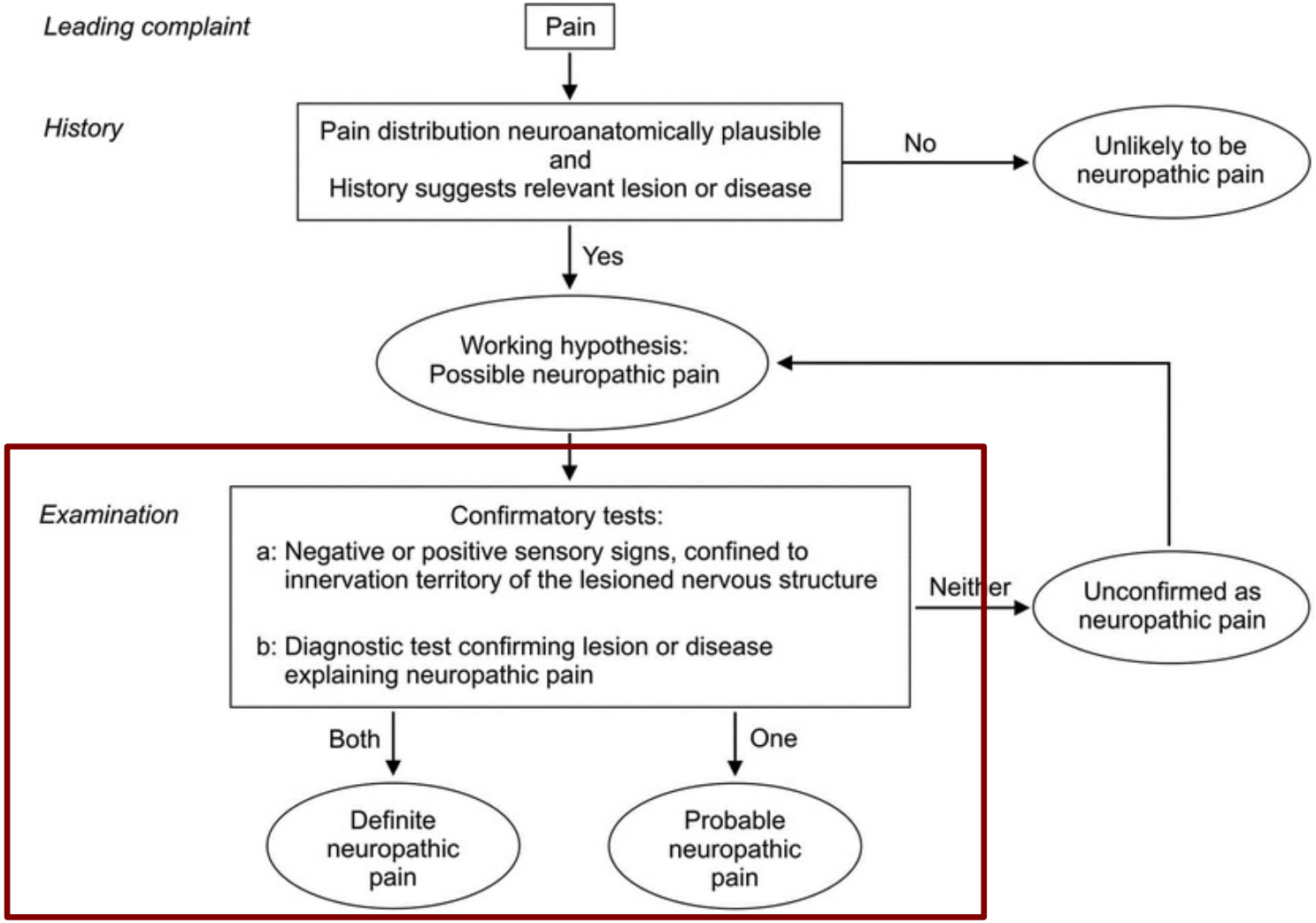
IMI-PainCare

SNC®

Grading system



(Treede et al., Neurology 2008)

Screening tools

DN4 Questionnaire PATIENT INTERVIEW
Question 1. Does the pain have any of the following characteristics?
1. Burning
2. Painful sensation of cold
3. Electric shocks
Question 2. Is the pain associated with any of the following symptoms in the same area?
4. Tingling
5. Pins and needles
6. Numbness
7. Itching
PATIENT EXAMINATION
Question 3. Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?
8. Hypoaesthesia to touch
9. Hypoaesthesia to prick
Question 4. In the painful area, can the pain be caused or increased by:
10. Brushing
YES = 1 point
NO = 0 points
Patient's score: _____/10 If the patient's score is ≥4, the test is positive. (sensitivity 82.9%; specificity 89.9%)

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painDETECT PAIN QUESTIONNAIRE

Date: _____ Patient: Last name: _____ First name: _____

How would you assess your pain **now**, at this moment?
0 1 2 3 4 5 6 7 8 9 10
none max.

How strong was the **strongest** pain during the past 4 weeks?
0 1 2 3 4 5 6 7 8 9 10
none max.

How strong was the pain during the past 4 weeks **on average**?
0 1 2 3 4 5 6 7 8 9 10
none max.

Mark the picture that best describes the course of your pain:
- Persistent pain with slight fluctuations ☐
- Persistent pain with pain attacks ☐
- Pain attacks without pain between them ☐
- Pain attacks with pain between them ☐

Please mark your **main area of pain**

Does your pain radiate to other regions of your body? yes ☐ no ☐
If yes, please draw the direction in which the pain radiates.

Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is light touching (clothing, a blanket) in this area painful?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have sudden pain attacks in the area of your pain, like electric shocks?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is cold or heat (bath water) in this area occasionally painful?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you suffer from a sensation of numbness in the areas that you marked?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Does slight pressure in this area, e.g., with a finger, trigger pain?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

(To be filled out by the physician)

never	hardly noticed	slightly	moderately	strongly	very strongly
x 0 = 0	x 1 =	x 2 =	x 3 =	x 4 =	x 5 =

Total score ____ out of 35

Development/Reference: R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle / Curr Med Res Opin, Vol.22, No. 10 (2006) ©2006 Pfizer Pharma GmbH
painDETECT questionnaire, ©2005 Pfizer Pharma GmbH, used with permission.

Fig. 2. DN4 questionnaire.

Neurological examination

Clinical examination shows negative (loss of function) and positive (hyperalgesia and/or allodynia) sensory signs

In patients with neuropathic pain, abnormal sensory findings should be neuroanatomically compatible with a definite lesion site but this apparently clear-cut point may be troublesome in the clinical setting, because of the possible extraterritorial spread of pain.

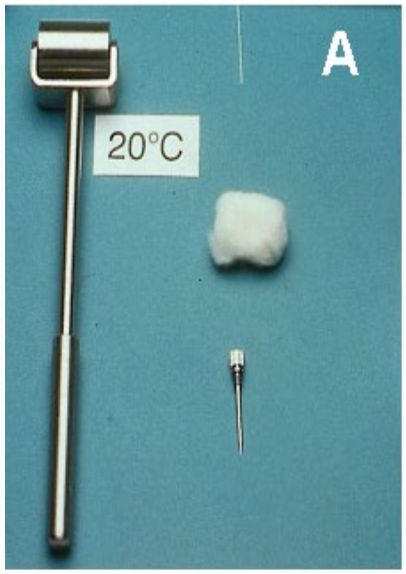
Sensory disturbances should be recorded in detail, preferably on body sensory maps

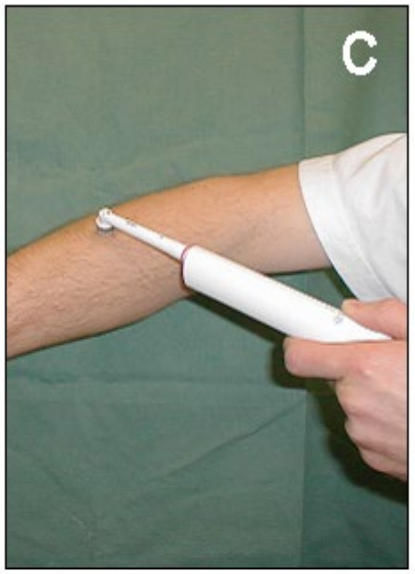
Simple instruments can be used to examine sensation: A cotton-tipped stick, a safety pin and a diapason.

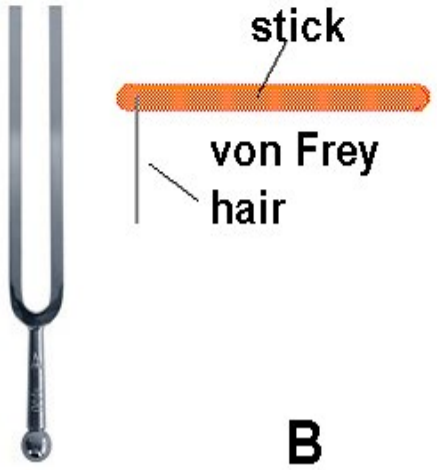
A comparison with the examination of the same site on the unaffected side of the body, or the nearest area not affected by disorders of sensation, facilitates the detection of the presence of negative sensory alterations (hypoesthesia, hypoalgesia) and positive sensory symptoms. Positive sensory symptoms consist of allodynia (pain due to a stimulus that does not normally provoke pain), hyperalgesia (increased pain from a stimulus that normally provokes pain), and dysesthesia (an unpleasant abnormal sensation, whether spontaneous or evoked).

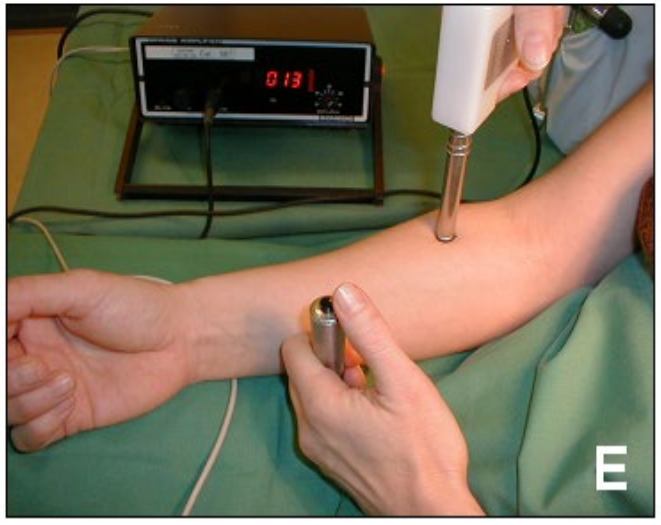
Quantitative sensory testing

Thermal detection thresholds for the perception of cold, warm and paradoxical heat sensations,
Thermal pain thresholds for cold and hot stimuli,
Mechanical detection thresholds for touch and vibration,
Mechanical pain sensitivity including thresholds for pinprick and blunt pressure, stimulus/response-functions for pinprick sensitivity and dynamic mechanical allodynia, and pain summation to repetitive pinprick stimuli (wind-up like pain).

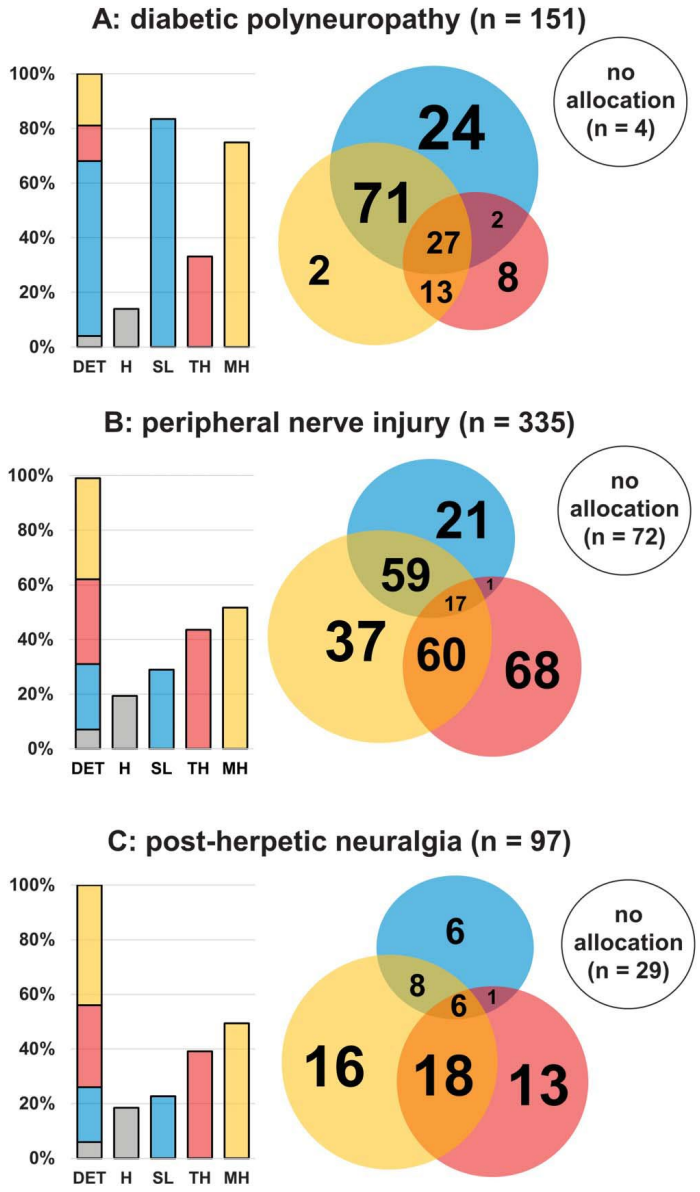








Sensory profile allocation



$$F(1):\frac{\sum_{i=1}^{13} p_{i_{n,m}}}{13} \quad \text{with} \quad p_{i_{n,m}} = \exp\left(-\left(\frac{(x_{i_n} - \mu_{i_m})^2}{\sqrt{2\sigma_{i_m}^2}}\right)\right)$$

Table 1

Mean QST z-values (μ) and SDs (σ, in brackets) for each of the 13 QST parameters separately for each of the 3 phenotypes.

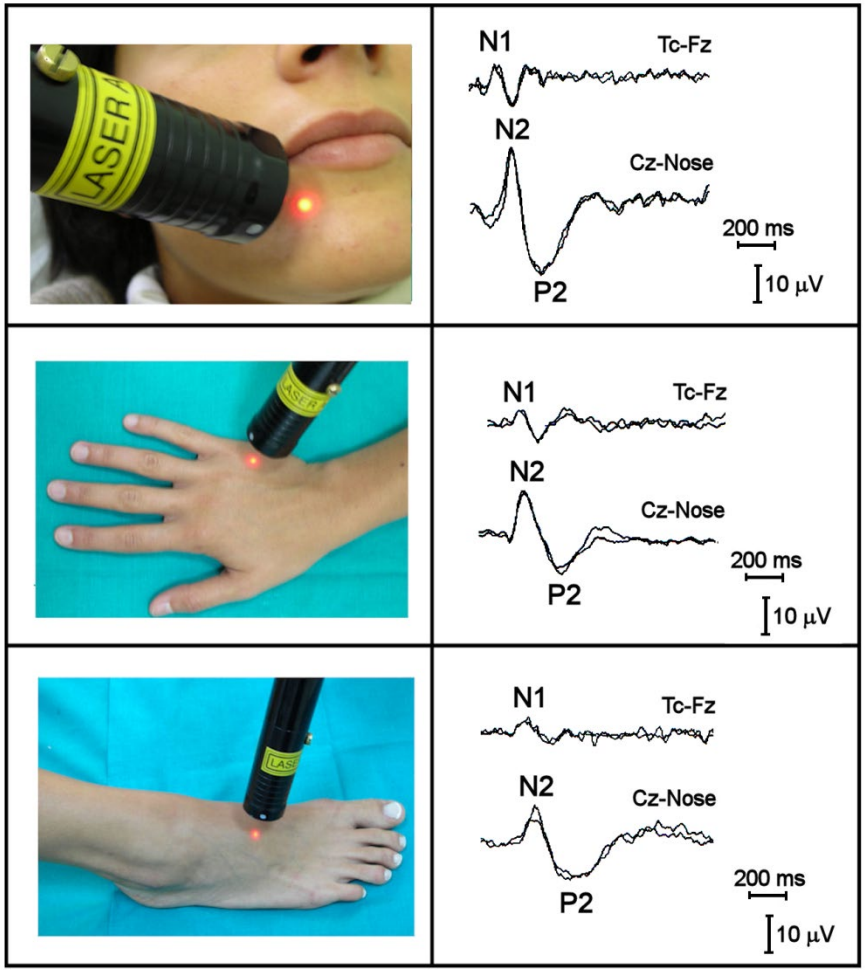
	CDT	WDT	TSL	CPT	HPT	PPT	MPT	MPS	WUR	MDT	VDT	DMA	PHS
Sensory loss, μ (σ)	−2.42 (1.16)	−1.96 (0.96)	−2.23 (0.92)	−0.56 (0.81)	−1.20 (0.87)	−0.53 (1.56)	−1.60 (1.23)	−1.14 (0.81)	0.13 (1.04)	−3.08 (4.94)	−2.88 (2.70)	0.24 (0.69)	0.72 (0.96)
Thermal hyperalgesia, μ (σ)	−0.47 (1.04)	−0.25 (0.97)	−0.45 (0.93)	0.59 (1.09)	0.78 (1.45)	0.34 (1.56)	0.42 (1.56)	0.49 (1.35)	−0.01 (1.03)	−0.91 (2.46)	−1.02 (1.84)	1.67 (1.21)	0.63 (0.93)
Mechanical hyperalgesia, μ (σ)	−2.03 (1.17)	−2.01 (1.14)	−2.10 (0.93)	−0.15 (1.01)	−0.67 (1.07)	1.09 (2.02)	0.86 (1.55)	1.31 (1.41)	0.21 (1.18)	−1.73 (2.48)	−1.18 (2.02)	0.54 (1.04)	0.44 (0.83)
Healthy subjects, μ (σ)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)

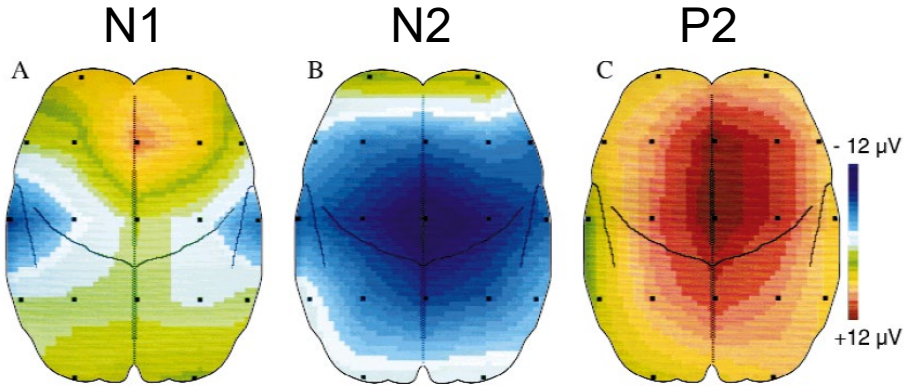
T-values for healthy subjects follow the definition of z-values: mean = 0 and SD = 1. PHS is coded as pseudo-normally distributed with 0 = absence and 2 = presence, DMA is coded pseudo-normally distributed with 0 = absence, 2 = 0 to 1 (on a 0-100 Numerical Rating Scale), and 3 = 1 to 100. CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PHS, paradoxical heat sensation; PPT, deep pain sensitivity to blunt pressure; QST, quantitative sensory testing; TSL, temperature sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.]

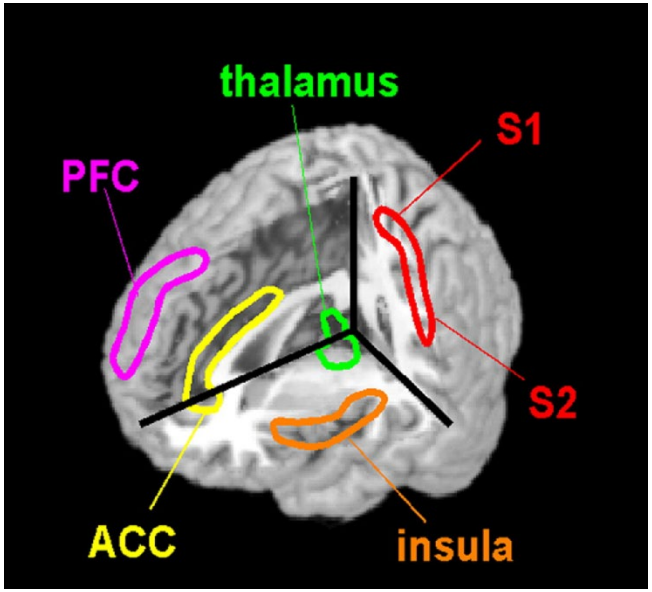
Vollert et al. Pain 2017

Tecniche per lo studio delle fibre di piccolo calibro

Aδ-Laser evoked potentials







Moisset and Bouhassira, Neuroimage 2007

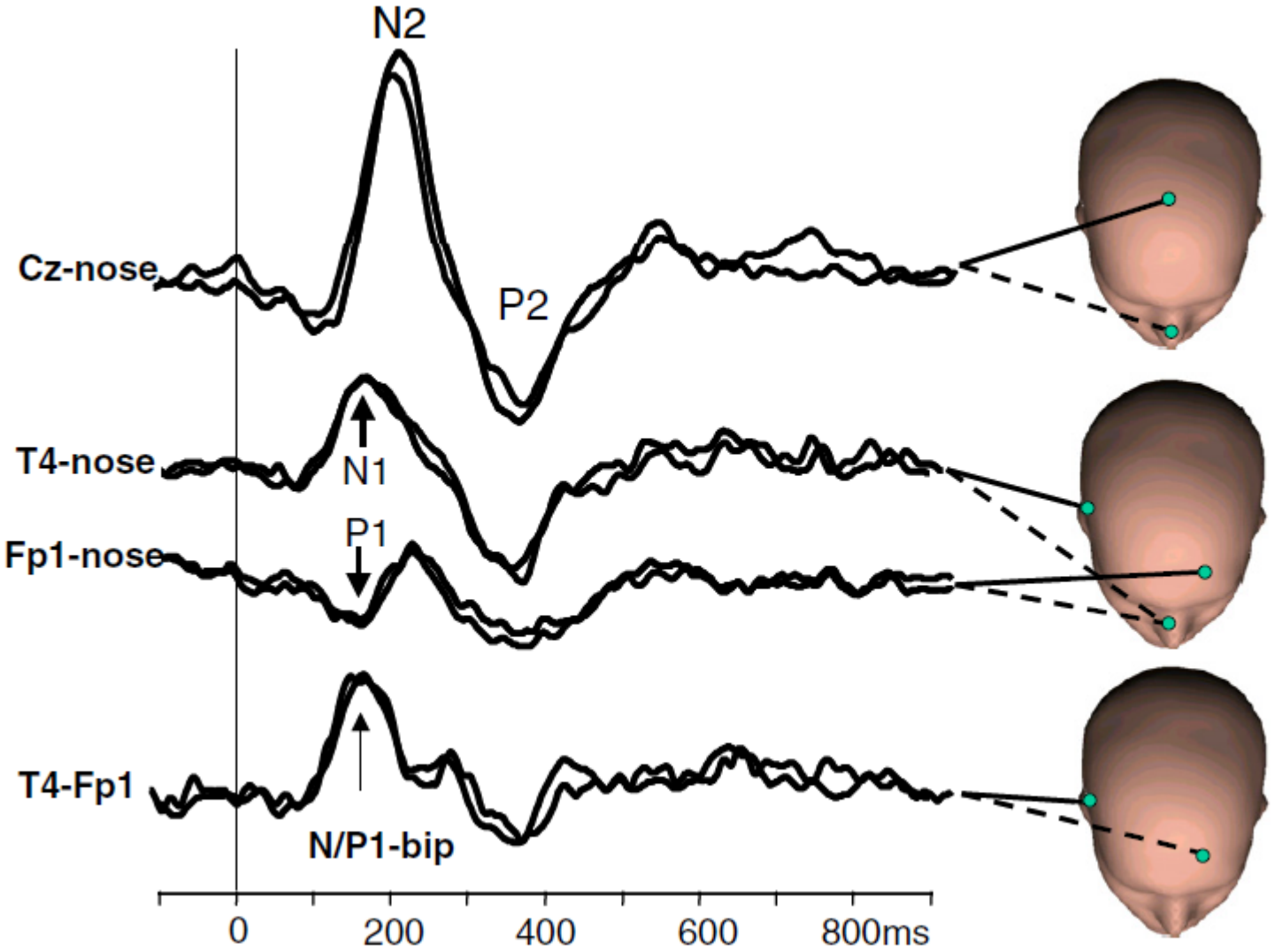
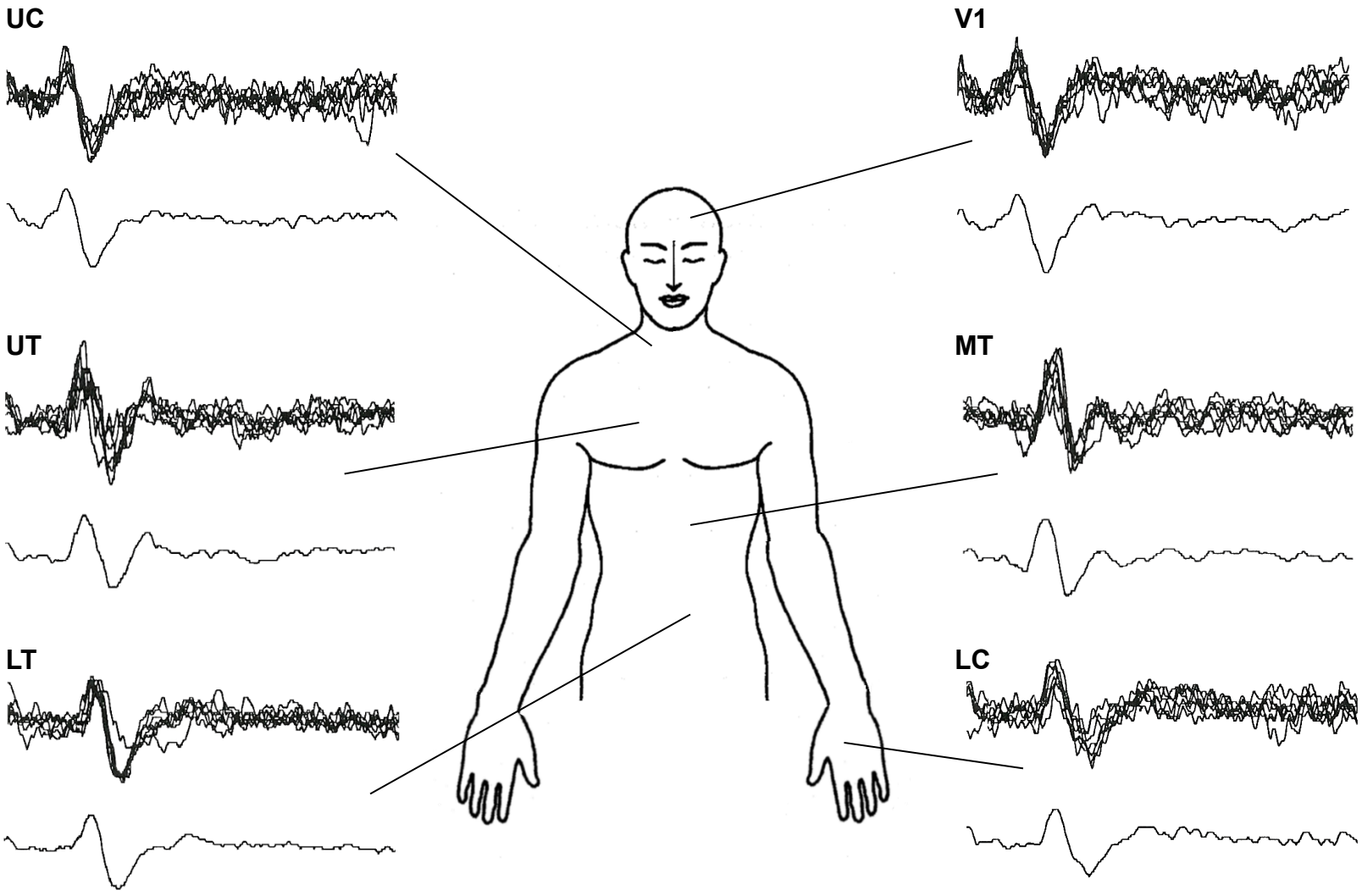


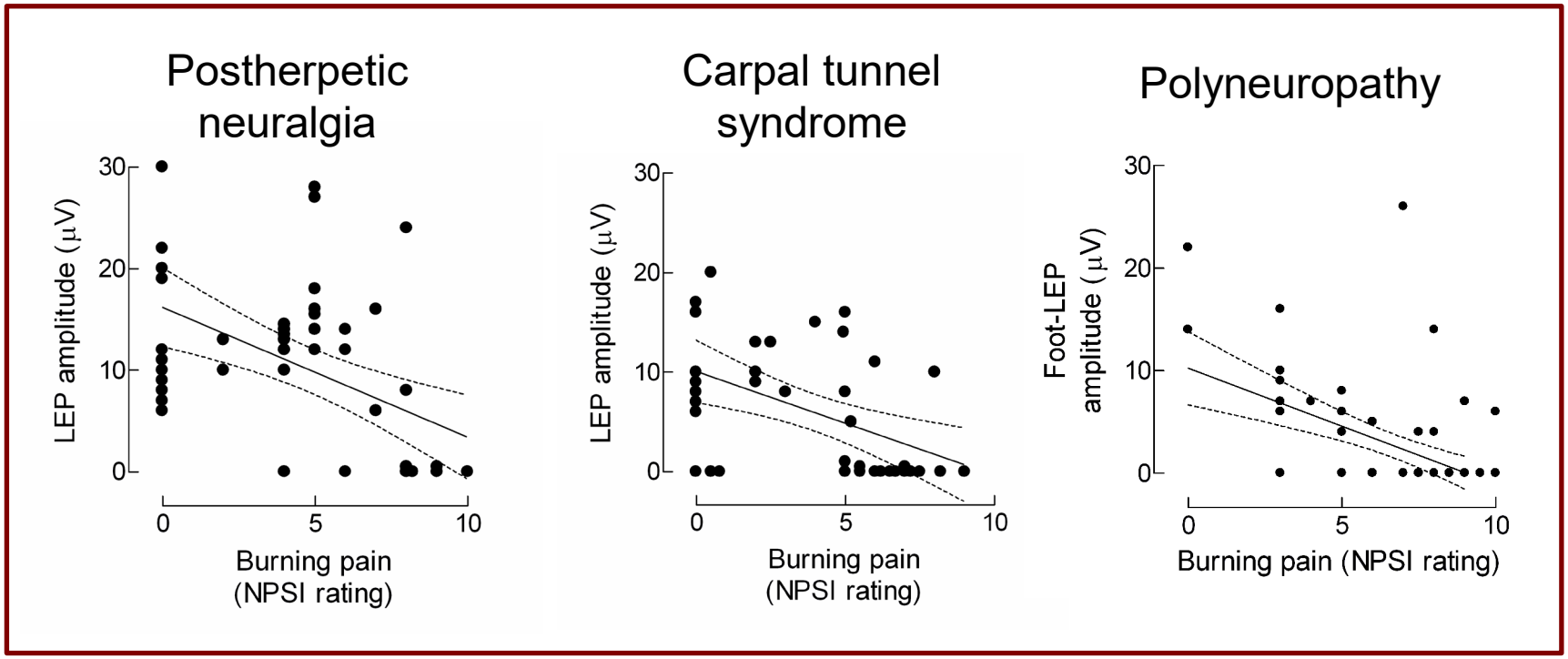
Fig. 3. Laser-evoked potentials (LEPs) after stimulation of the left hand (C6) with a Nd:YAP laser (k = 1.34 lm). The vertex complex (N2–P2, upper traces) is best recorded over the midline, with a nose reference. An earlier negative wave (opercular N1) generated in the suprasylvian operculum can be recorded over the temporal region (top of the middle traces); this component inverts polarity across the midline and is recorded as a positive wave (opercular P1) from frontal or frontopolar electrodes ipsilateral to the stimulus (bottom of the middle traces). Taking advantage of such phase reversal, a bipolar montage linking the contralateral temporal to the ipsilateral frontopolar electrodes allows to maximise the amplitude of the opercular N1/P1 response (bottom traces).

Dermatomal Aδ-LEPs



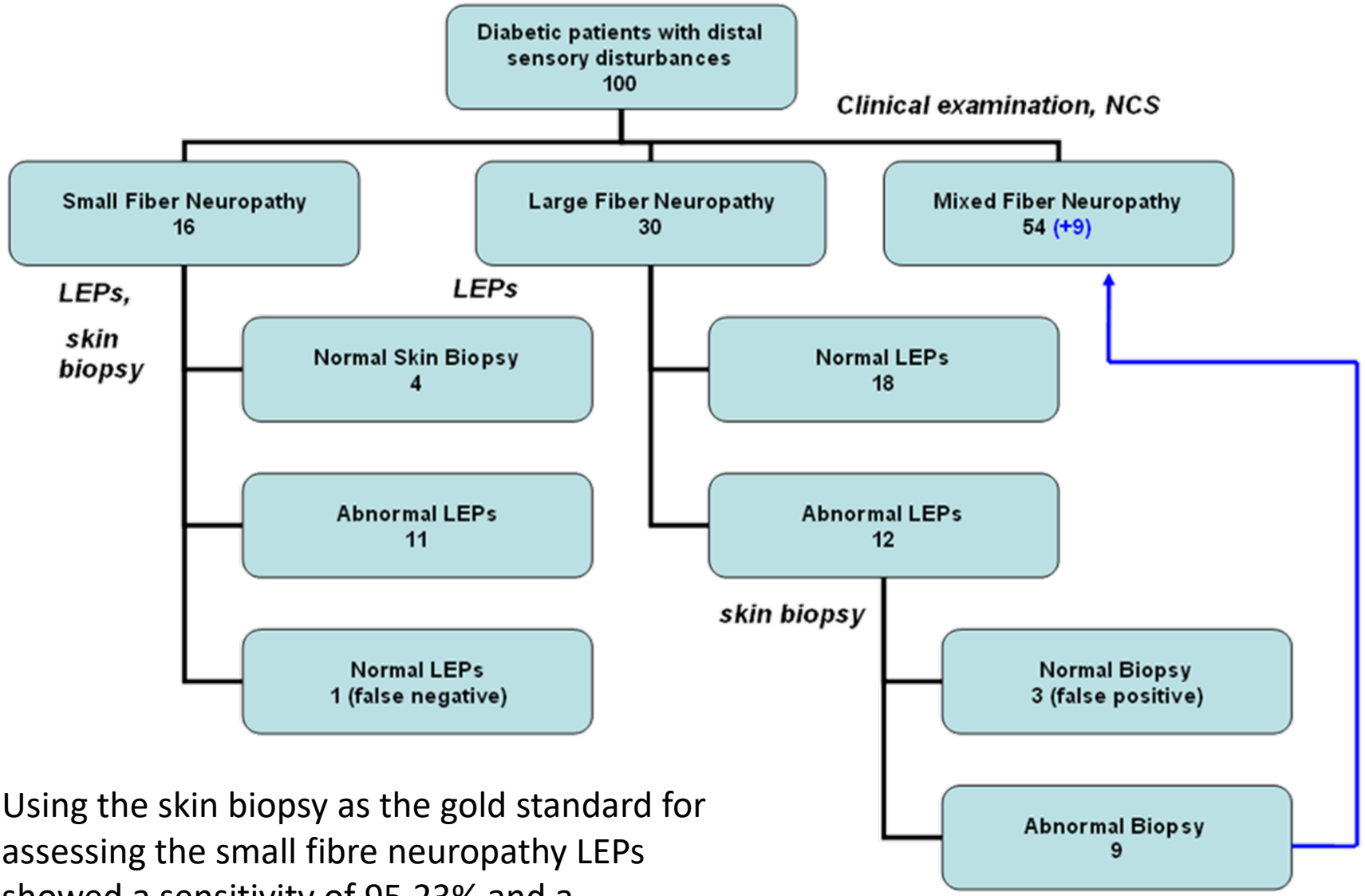
Truini et al., CLINPH 2003

Correlations between ongoing burning pain and LEPs



Truini et al, Pain 2008; 2009; 2010

Clinical usefulness



Using the skin biopsy as the gold standard for assessing the small fibre neuropathy LEPs showed a sensitivity of 95.23% and a specificity of 85.71%.

Laser evoked potentials

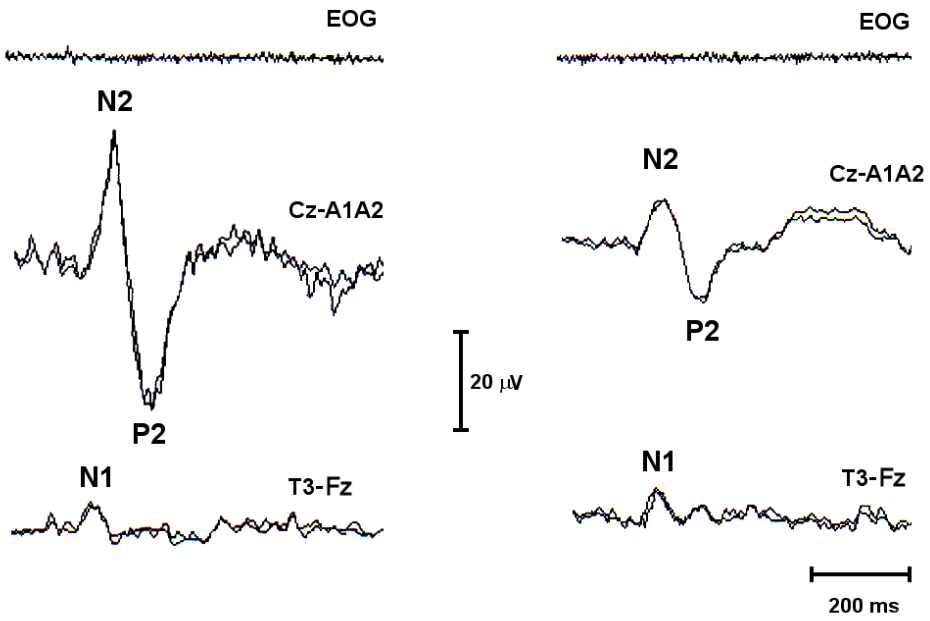
C-LEPs

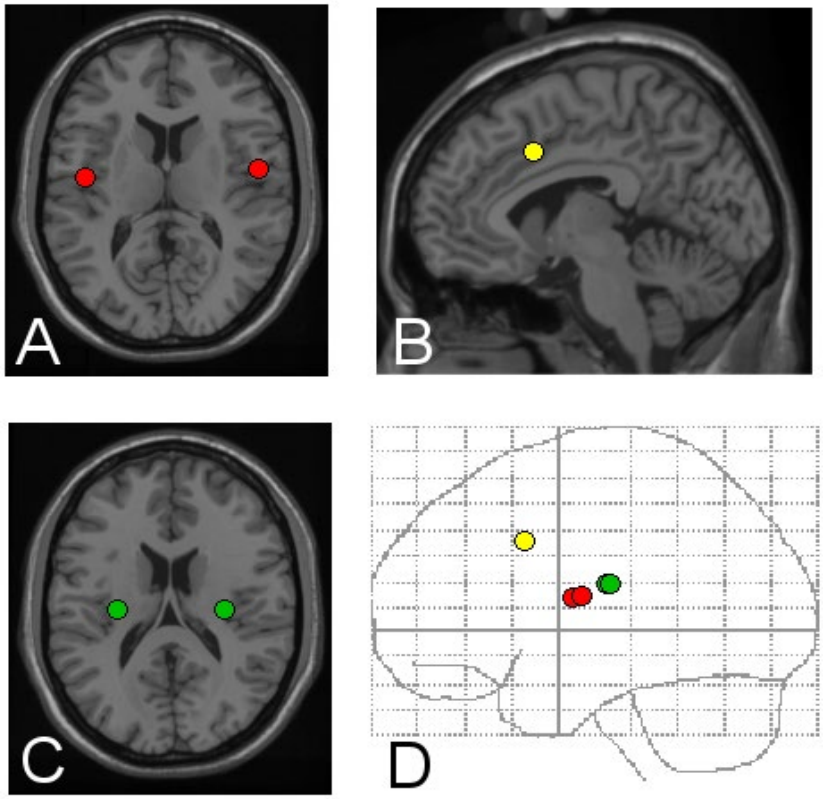
Standard laser stimuli evoking double sensation

Aδ-LEPs

Low intensity laser stimuli evoking thermal sensation

C-LEPs





Cruccu et al, Brain 2003

Micropatterned interdigitated electrode

A new surface micropatterned interdigitated electrode for selective stimulation of the nociceptive fibres has been recently designed (Leandri, Marinelli, Siri, & Pellegrino, **2018**).

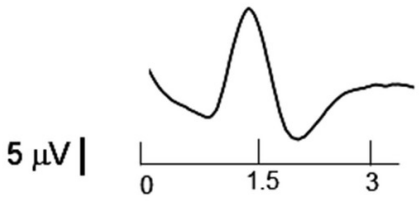
Its nociceptive specificity depends on the peculiar interdigitated conformation (IDE) of this electrode, made of conductive rails arranged in a comb-like micropattern, situated only 150 μm apart (150IDE) and alternately connected to the opposite poles of the stimulator.

The short distance between anode and cathode generates an electric field confined within 100 μm of depth in the skin, thus selectively activating intraepidermal free nerve endings (Leandri et al., **2018**).

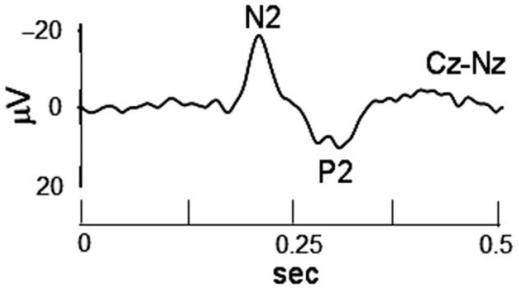
Is nociceptive specific?

Pre-lidocaine block

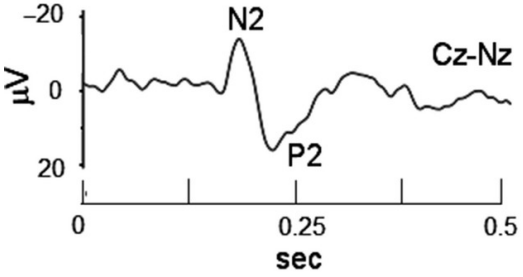
Radial SNAP



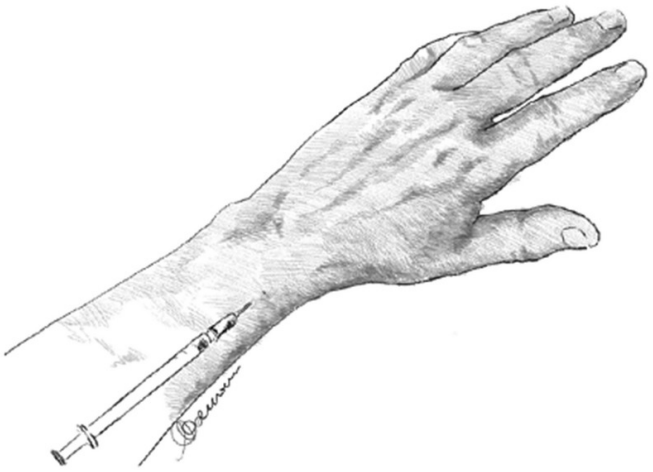
Laser-evoked Potentials



150IDE-evoked potentials

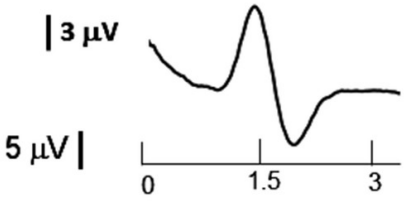


Lidocaine block

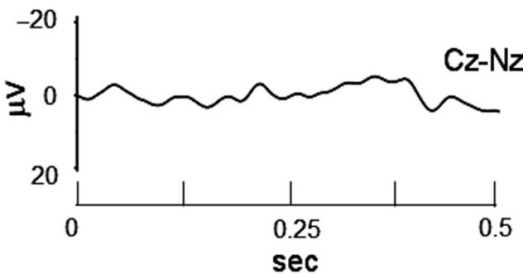


Post-lidocaine block

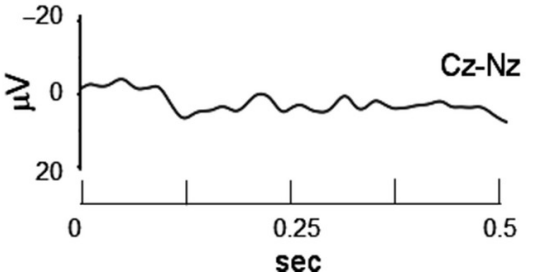
Radial SNAP



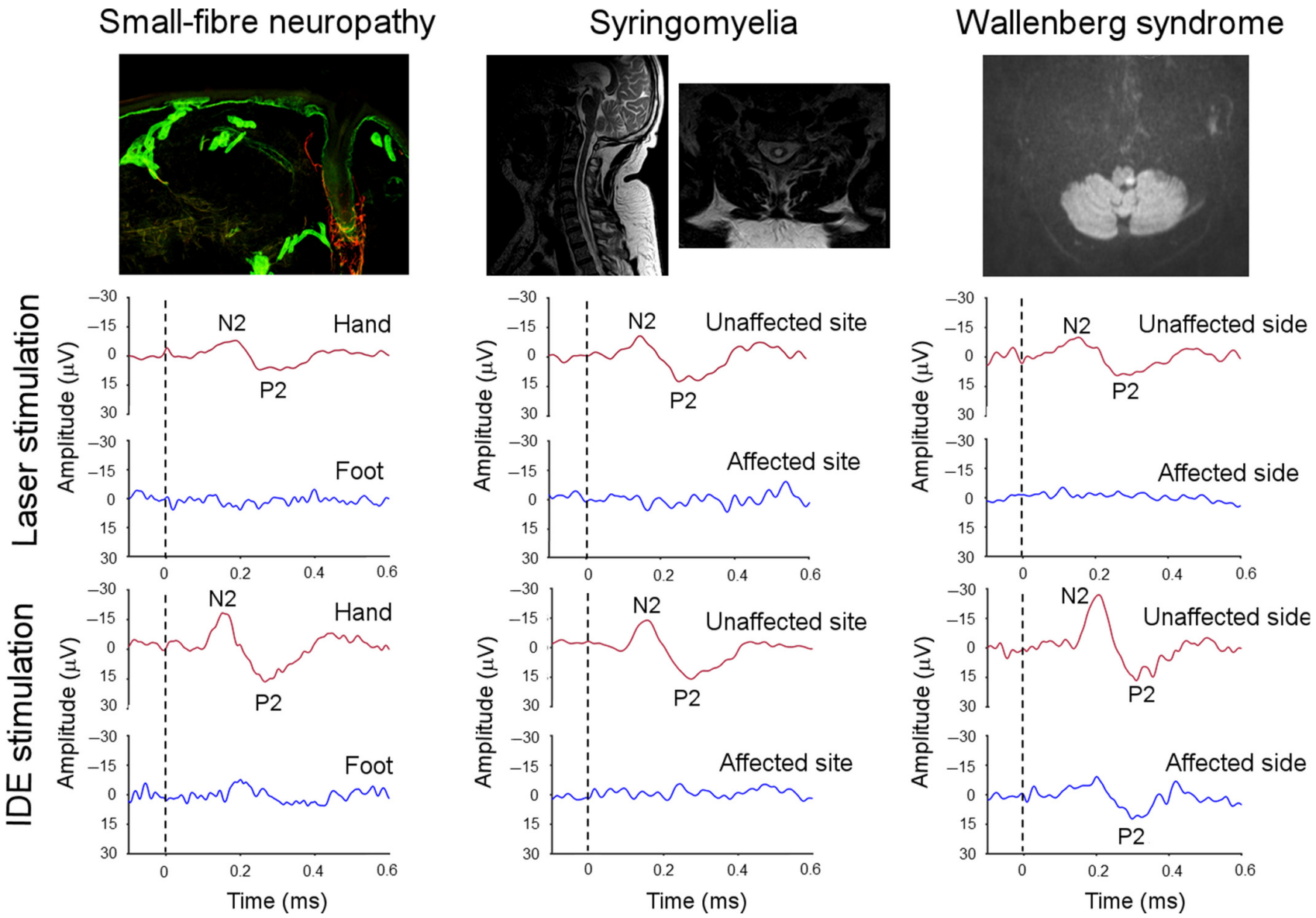
Laser-evoked Potentials



150IDE-evoked potentials



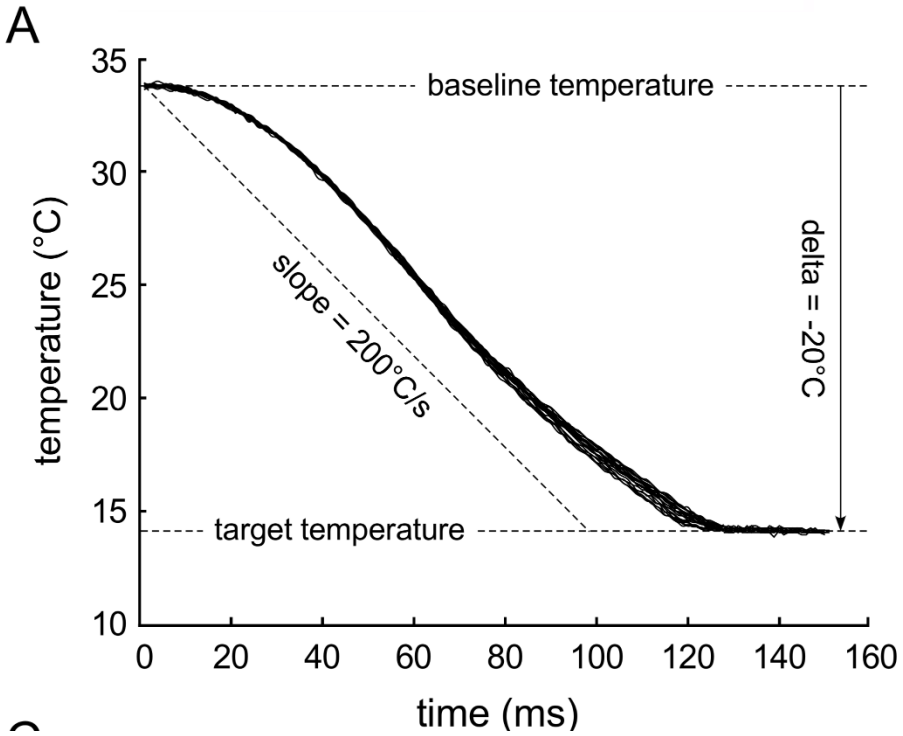
Clinical Usefulness

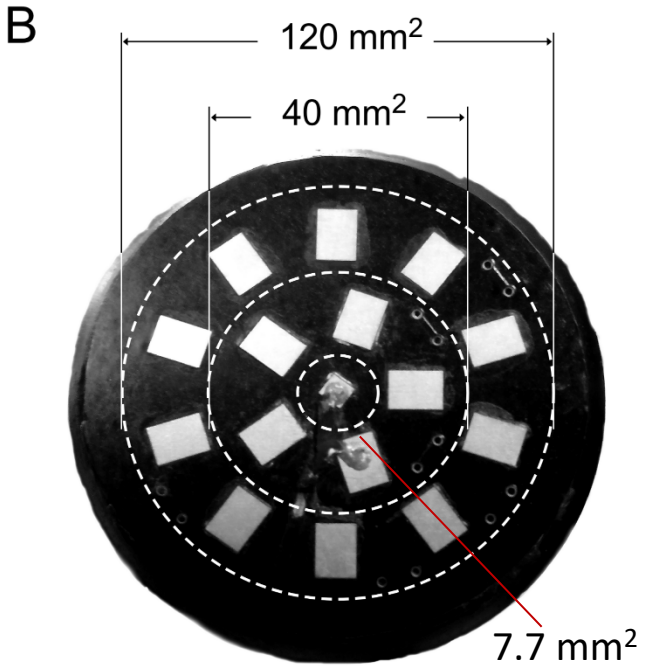


Di Stefano et al. EJP 2019

Cold Evoked Potentials

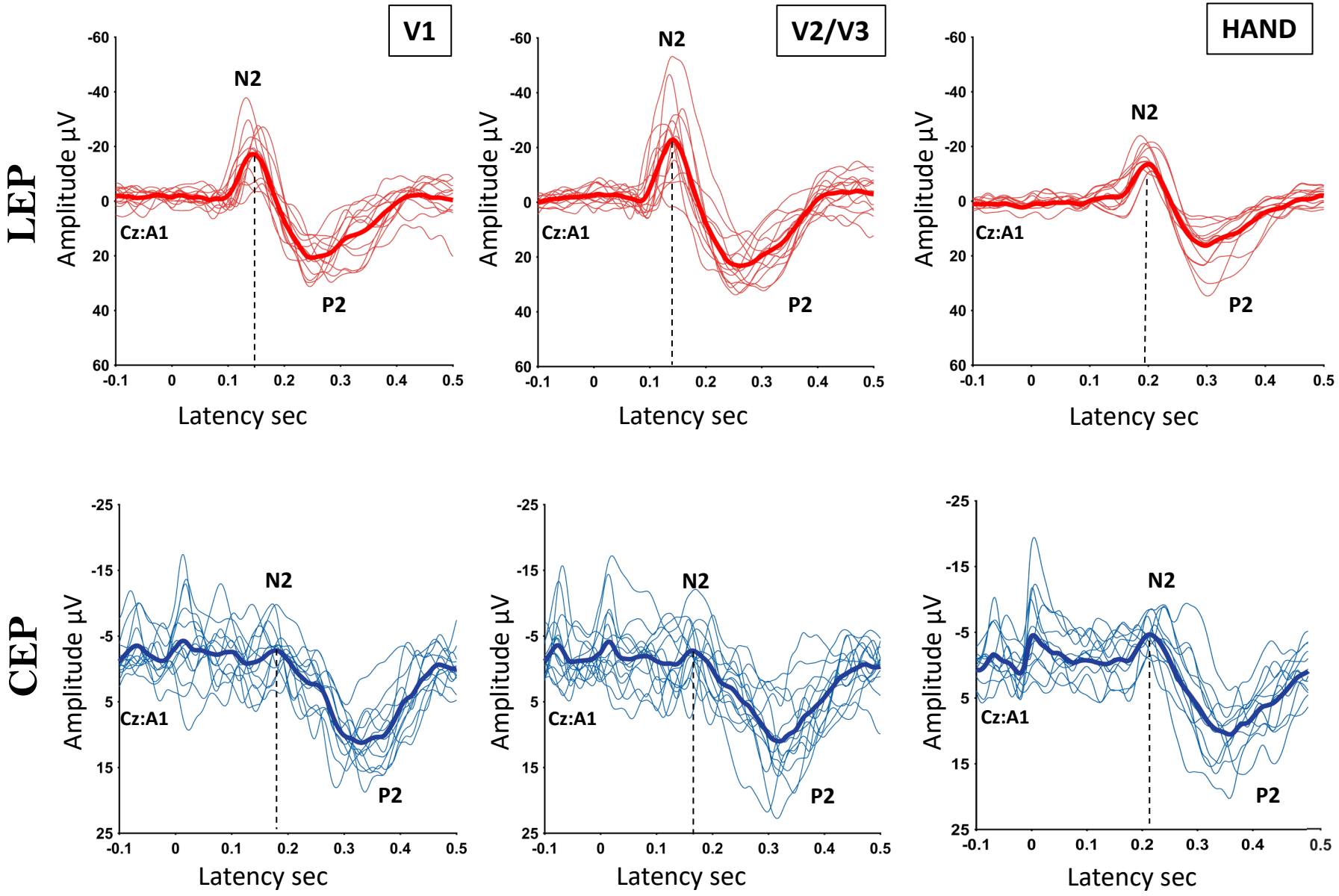
- Source: Micro-Peltier elements
- Power density: 20 W/cm²
- Stimulus: 10°C
- Area: 1 cm²
- Duration: 500 ms
- ISI: 10 s





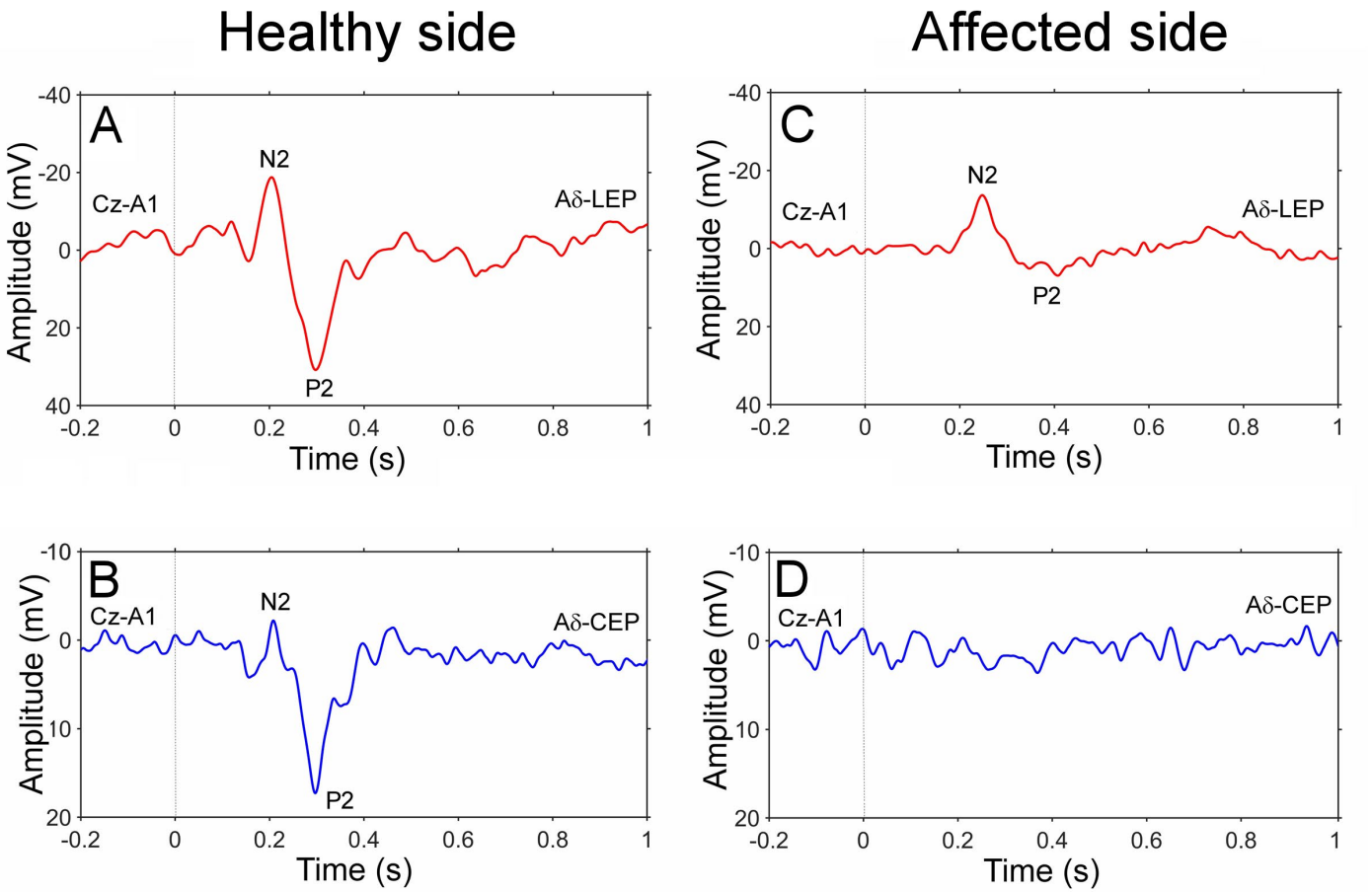
De Keyser et al. Clinph 2018

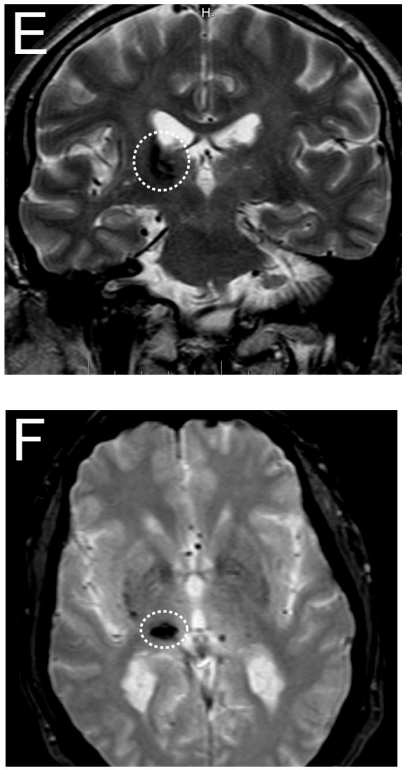
Cold Evoked Potentials



Leone et al. Pain 2019

Pt 2: CPSP

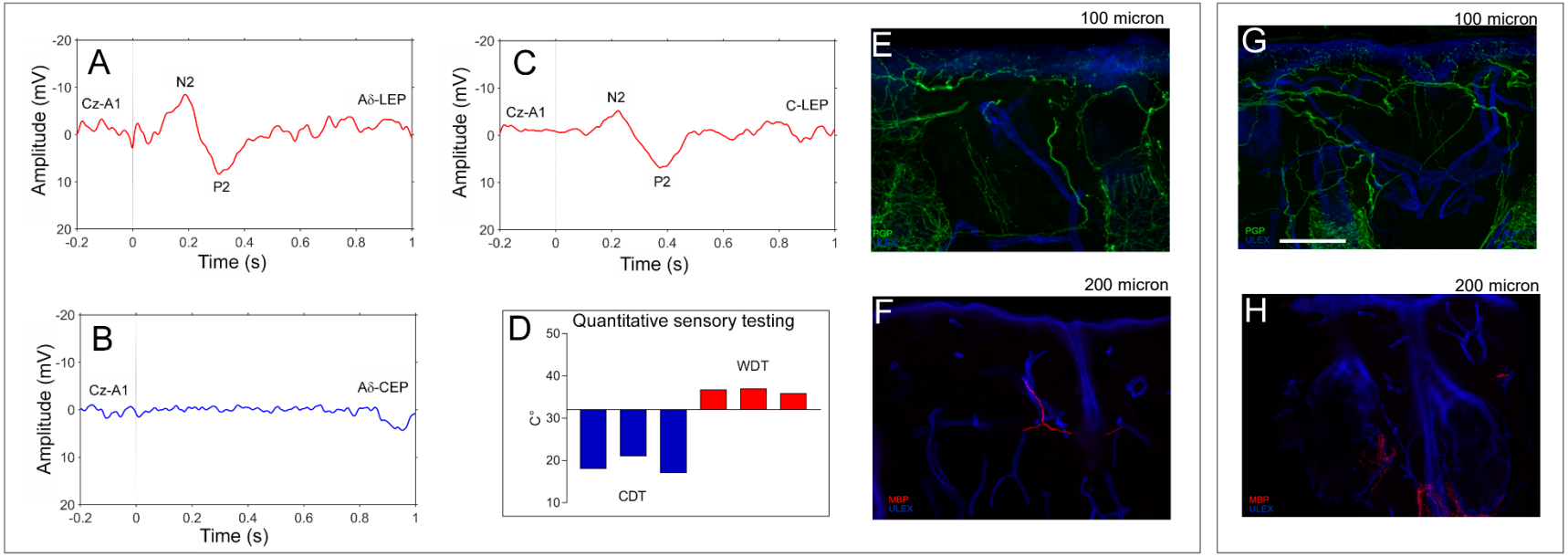




Leone et al., Pain 2019

The imbalance between cold afferent pathways and thermal-pain pathways is probably responsible from central post-stroke pain due to thalamic lesions. (Craig, 1998)

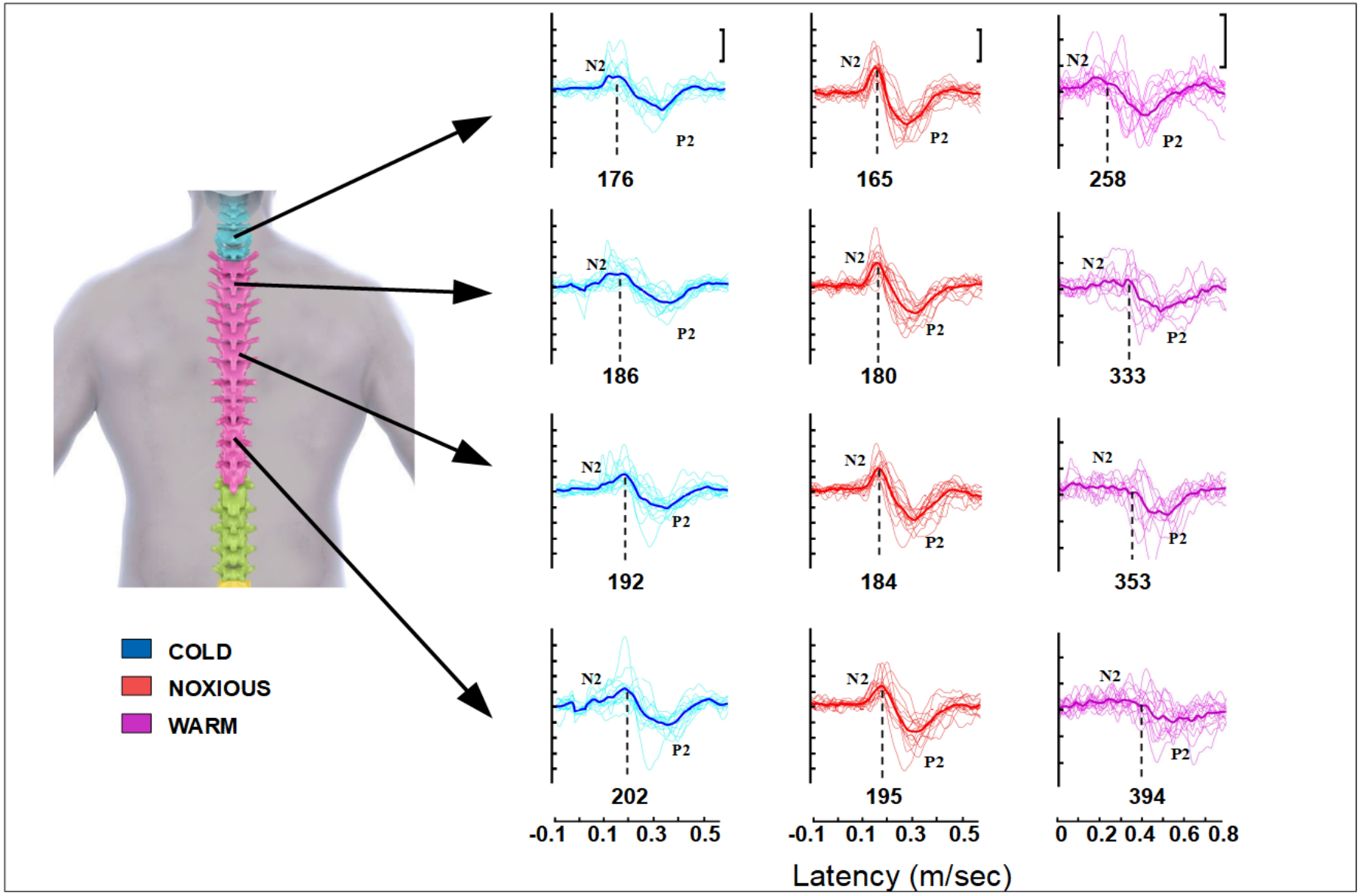
Pt 1: Trigeminal idiopathic sensory neuropathy



Leone et al., Pain 2019

The largest the diameter of myelinated fibre the more severe the axonal loss

Conduction velocity of the cold spinal pathway



Biomarker per lo valutazione della sensitizzazione centrale

Secondary Hyperalgesia

Central sensitization is defined as 'Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input'(IASP terminology; Arendt Nielsen 2018).

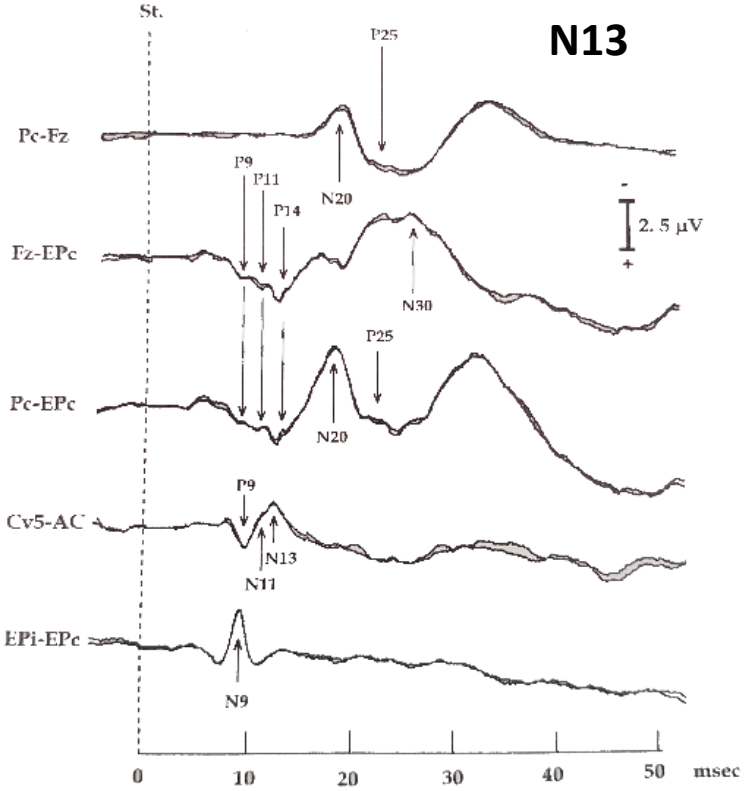
The phenomenon of secondary hyperalgesia is currently the only example where both input and output of spinal neurons have been documented in the same model and, hence, the IASP definition of central sensitization is fulfilled (Treede 2016).

In response to a tissue injury a primary hyperalgesia area, due to the peripheral sensitization of nociceptive fibres occur. Inputs to a given stimulus into the spinal cord consequently increase, thus leading to central sensitization manifesting with a zone of secondary hyperalgesia, defined as the undamaged area, surrounding the injury site, with an increased sensitivity to mechanical pinprick stimulation (Raja et al., 1984; LaMotte et al., 1991; Dahl et al., 1993).

Despite the large number of pain conditions underlying central sensitization, an objective measure for quantifying central sensitization within the dorsal horn of the human spinal cord is lacking so far.

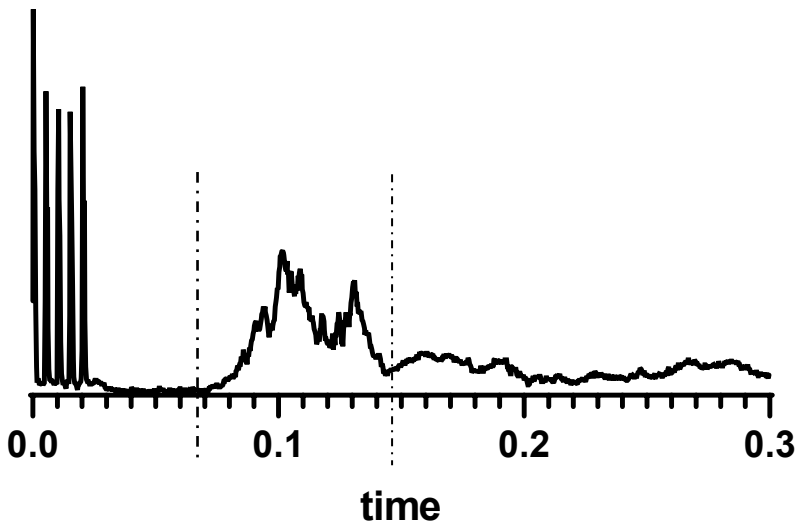
Candidate biomarkers

N13

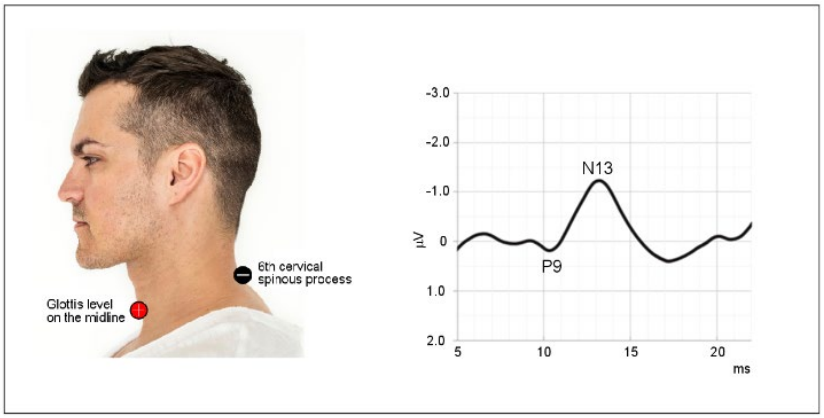


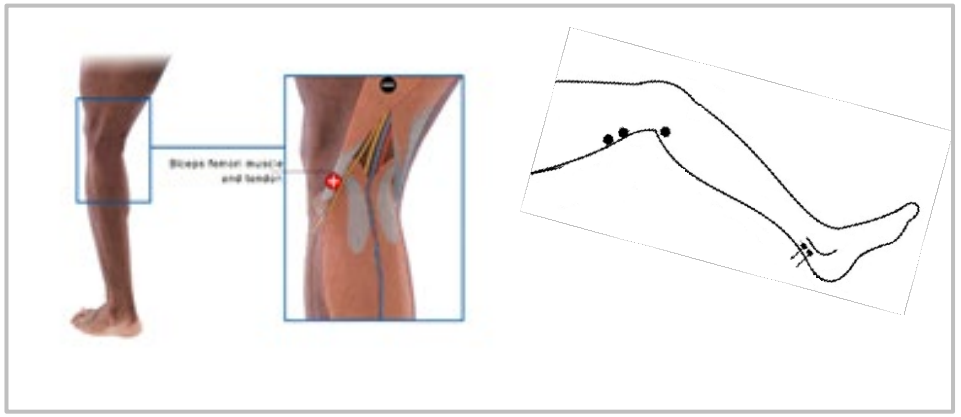
Mauguière et al. 1999

RIII



Leone et al.





Candidate biomarkers

N13

- reflects the response of dorsal horn neurons to non-noxious inputs.
- reaches its maximal amplitude close to the entry zone of the 5th — 7th cervical roots
- has a fixed latency from Cv7-Cv2 spinous processes
- reverses its polarity when recorded at the anterior aspect of the neck or of the cord itself
- remains unaffected in patients with cervical cord lesions above Cv4 level
- does not reflect the activity of pure nociceptive spinal cells
- the neurons generating N13 are close to, or intermingled with, pure nociceptors and wide dynamic range cells in the dorsal horn grey matter

RIII

- a pure nociceptive reflex, mediated by A-delta fibres, whose anatomical substrate is entirely located at spinal level
- has largely served as an ‘‘objective’’ measure of experimental pain in humans to investigate several aspects of pain processing at spinal and supraspinal level
- EFNS guidelines recommended the RIII reflex as the most reliable nociceptive reflex for assessing treatment efficacy, given the large body of evidence of reflex inhibition by drugs acting on the nociceptive system
- its use in the clinical evaluation of neuropathic pain is still limited
- Reflex threshold consistently reduced during central sensitization
- Uncertainty about reflex size

Questions

N13

WDR generator?

- Is the N13 modulated by excitability changes of dorsal horn neurons during central sensitization?
- Is this modulation prevented by pregabalin?
- Is the N13 modulated by an heterotopic noxious conditioning stimulation?

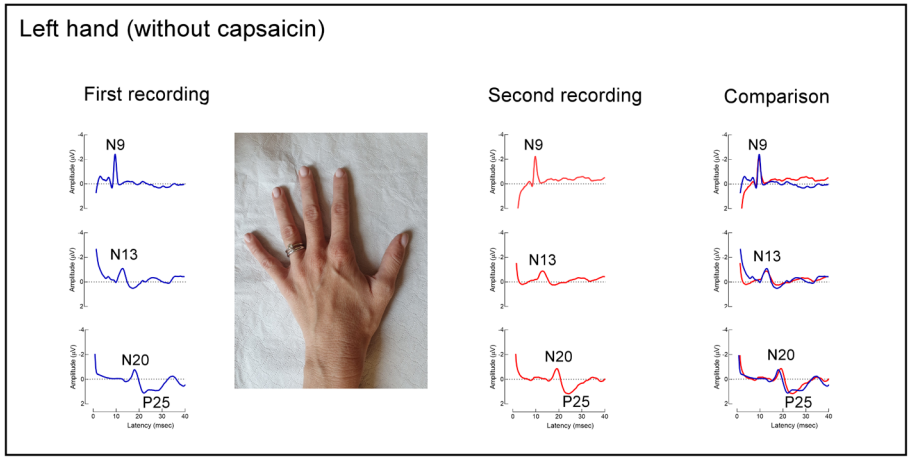
RIII

Which outcome?

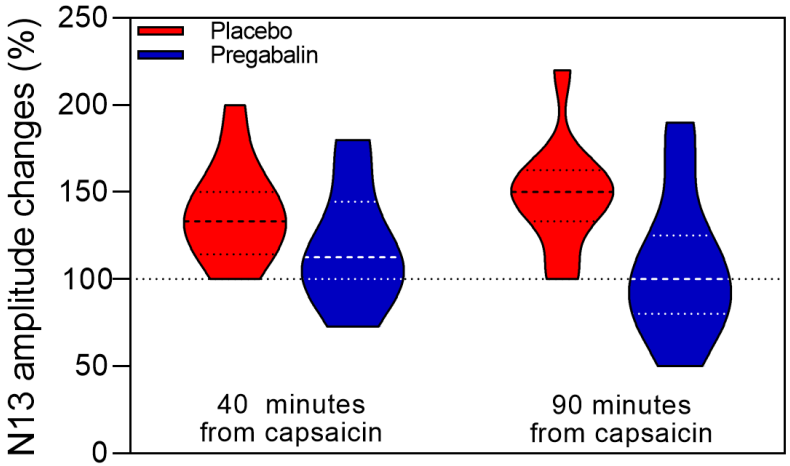
- Is the RIII modulated by excitability changes of dorsal horn neurons during central sensitization?
- Is this modulation different for different experimental models of secondary 2HA?
- Is the endogenous pain modulation system activated by capsaicine/HFS?

N13 modulation by capsaicine with and without pregabalyn

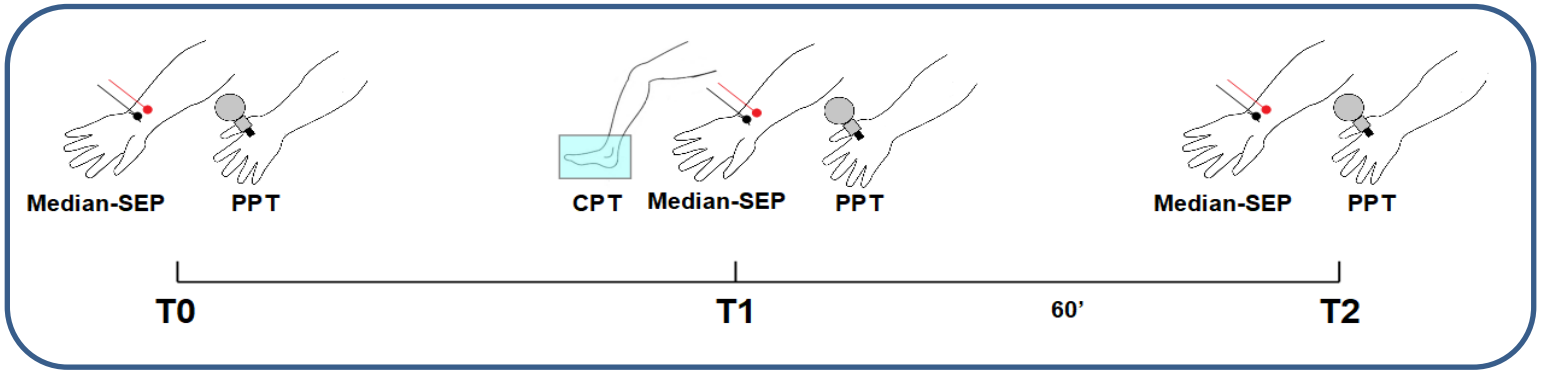
First experiment



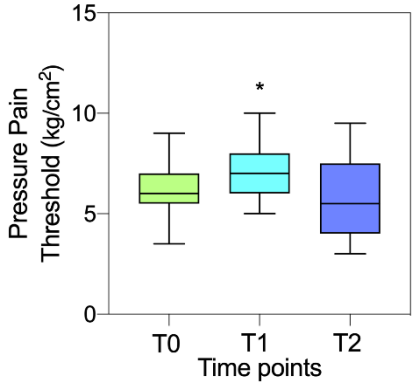
Second Experiment



N13 modulation by Heterotopic noxious conditioning stimulation



A



B

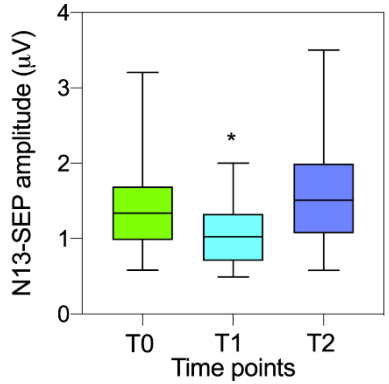
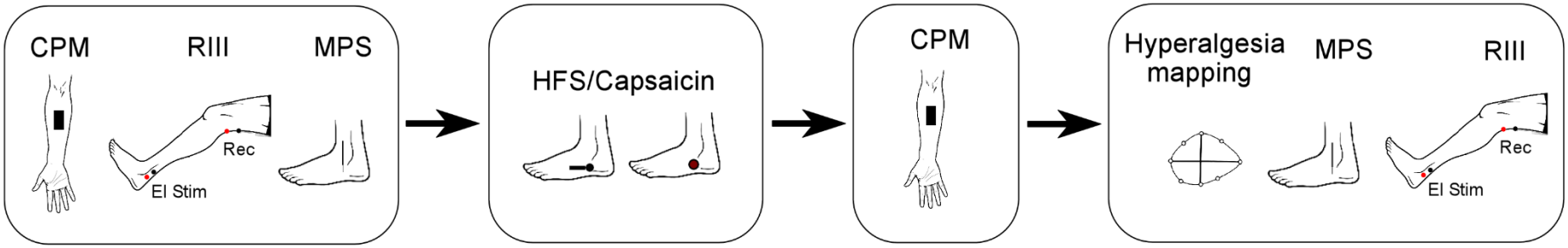


Table 1. Somatosensory evoked potentials variables

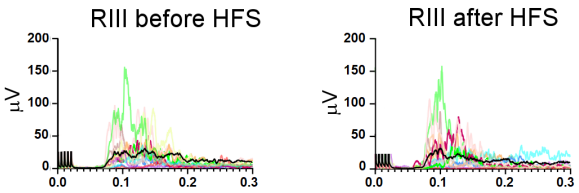
SEPs	T0	T1	p*	T2	p**
N9 latency (ms)	9.72±0.92	9.83±0.86	0.37	9.88±0.83	0.15
N9 amplitude (µV)	3.54±3.11	3.32±1.55	0.95	3.01±1.31	0.79
N13 latency (ms)	12.79±1.1	12.36±1.19	0.18	12.62±1.21	0.68
N13 amplitude (µV)	**1.39±0.68**	**1.04±0.43**	**0.04**	1.62±0.78	0.07
N20 latency (ms)	19.1±1.15	19.27±1.72	0.83	19±1.32	0.82
P25 latency (ms)	21.81±1.65	21.9±2.07	0.96	21.56±1.59	0.48
N20-P25 amplitude (µV)	3.76±1.74	4.29±3	0.80	3.7±2.37	0.92
PPT (kPa)	610.68±135.82	699.83±143.94	**0.04**	573.24±197.17	0.59

Data are expressed as Mean ± SD
T0: baseline; T1: during the cold pressor test; T2: after 60 minutes the cold pressor test
*by Dunnett's multiple comparisons test (T0-T1)
**by Dunnett's multiple comparisons test (T0-T2)
PPT: pressure pain threshold

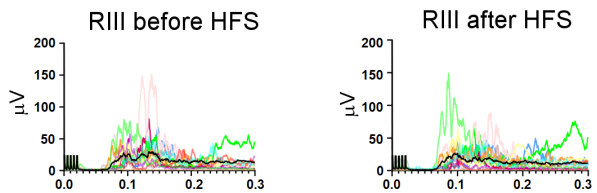
RIII modulation by capsaicine and HFS



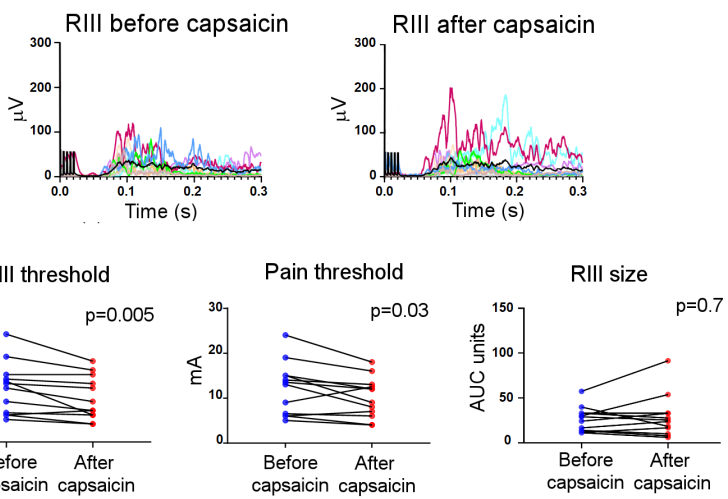
Active site



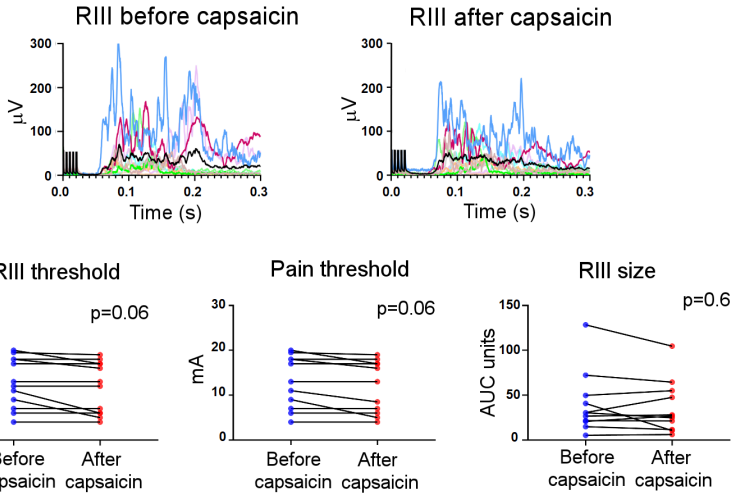
Control site



Active site



Control site



Answers

N13

WDR generator?

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- Is this modulation prevented by pregabalin? 
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RIII

Which outcome?

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- Is the endogenous pain modulation system activated by capsaicine/HFS? 

Conclusions

- The N13 reflect spinal excitability of the dorsal horn during central sensitization

- The N13 modulation by capsaicine is prevented by pregabalin

- The N13 is modulated by heterotopic noxious conditioning stimulation, suggesting WDR as a possible generator

- The RIII reflex size is not modulated by spinal excitability induced either by capsaicine or HFS

- The lack of modulation on the reflex size should not be attributed to the activation of the endogenous pain control system

Grazie per l’attenzione!