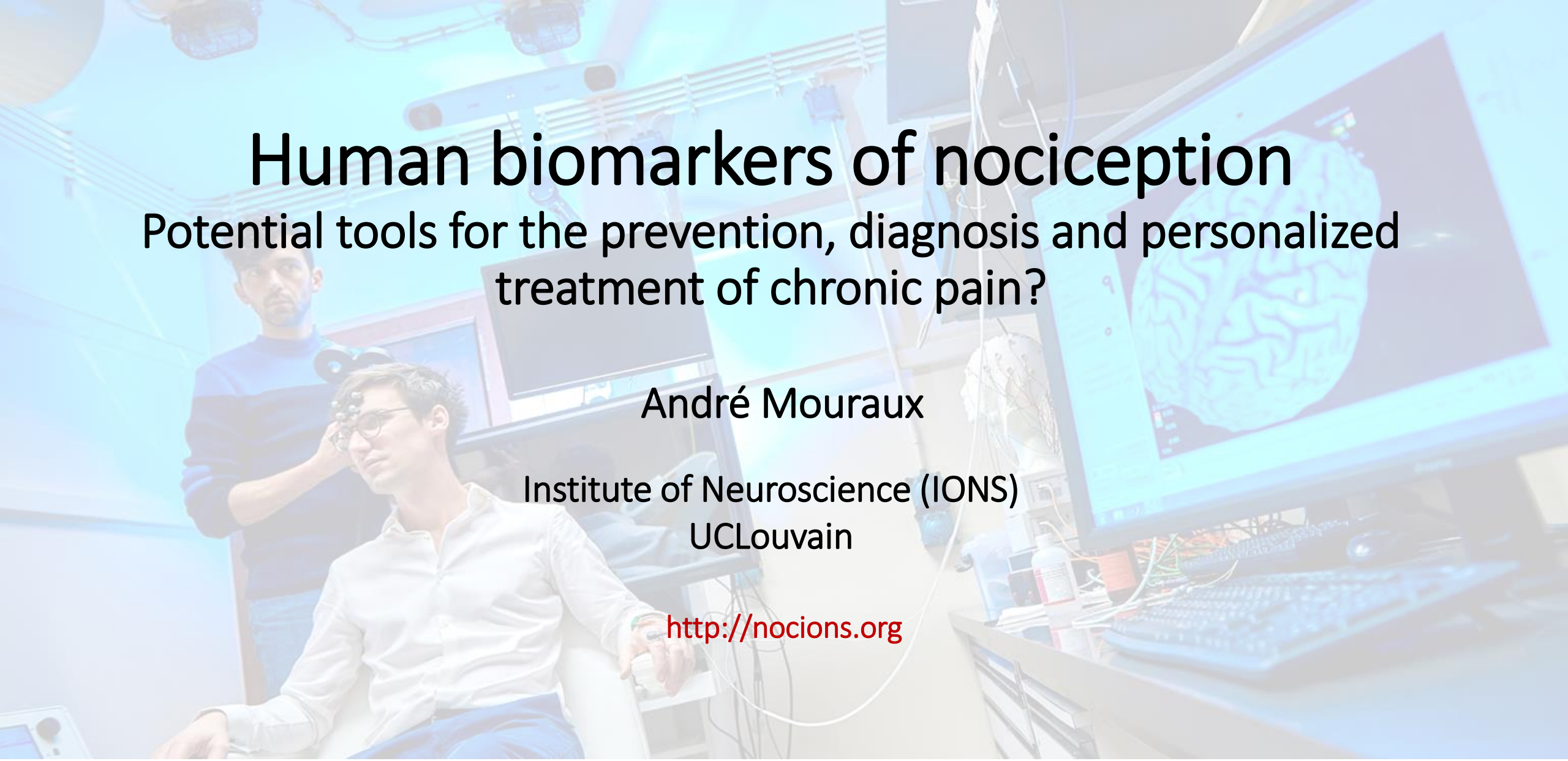


Human biomarkers of nociception

Potential tools for the prevention, diagnosis and personalized treatment of chronic pain?

André Mouraux

Institute of Neuroscience (IONS)
UCLouvain

http://nocions.org

UCLouvain

IoNS INSTITUTE OF NEUROSCIENCE

Human biomarkers of nociceptive processing and its modulation

Understanding nociception and pain

- Explore nociceptive processing in humans and its modulation

Tools for the pharmacological development of novel pain treatments

- Pharmacodynamic biomarkers to evaluate target engagement in early-stage clinical trials?
- (Surrogate) biomarkers of clinical efficacy?

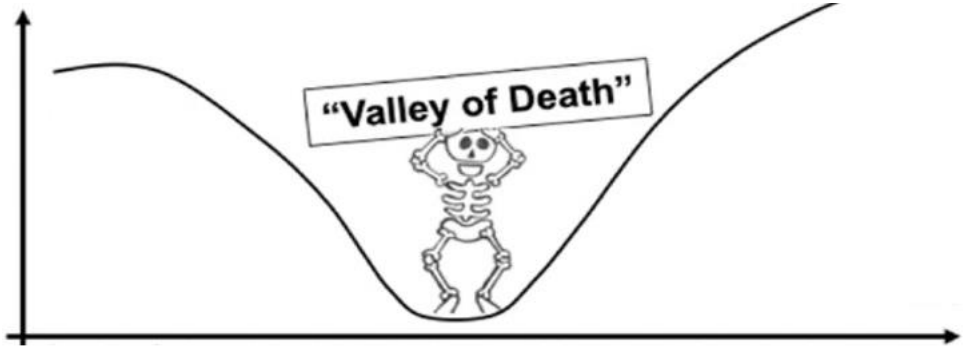
Clinical diagnosis and personalized medicine

- Neuropathic pain : *“pain caused by a lesion or disease of the somatosensory nervous system”*
- Mechanism-based diagnosis, patient selection and stratification, predicting response to treatment?

Preventing chronic pain

- Early diagnosis for potential preventive treatments?
- Biomarkers of the susceptibility to develop chronic pain?

Tools for the pharmacological development of novel pain treatments



Preclinical and animal studies	Phase 1 clinical trials in healthy humans	Phase 2/3 clinical trials in patients	Phase 4 trials, clinical outcomes	Population-level outcome research
T0	**T1**	**T2**	**T3**	**T4**

Tools for the pharmacological development of novel pain treatments

Pharmacodynamic biomarkers

Increasing use of **human pharmacodynamic biomarkers** signalling whether a pharmacologically efficacious dose is attained

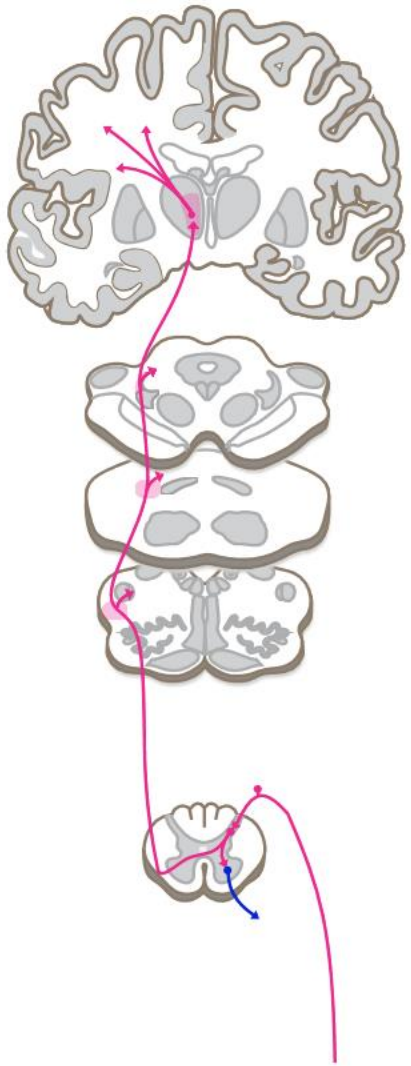
Preclinical and animal studies	Phase 1 clinical trials in healthy humans	Phase 2/3 clinical trials in patients	Phase 4 trials, clinical outcomes	Population-level outcome research
T0	**T1**	**T2**	**T3**	**T4**

- Understanding the physiology and pathophysiology (disease mechanisms)
- Identify new pharmacological targets, identify new compounds

Phase 1 clinical trials in humans to determine metabolism, pharmacologic actions and side effects with increasing dose, and obtain early evidence of effectiveness (target engagement, physiological process).

In healthy volunteer studies, use pharmacodynamic biomarkers of nociceptive processing must be coupled with **experimental models that engage and/or mimick the changes in nociceptive function associated with clinical pain**.

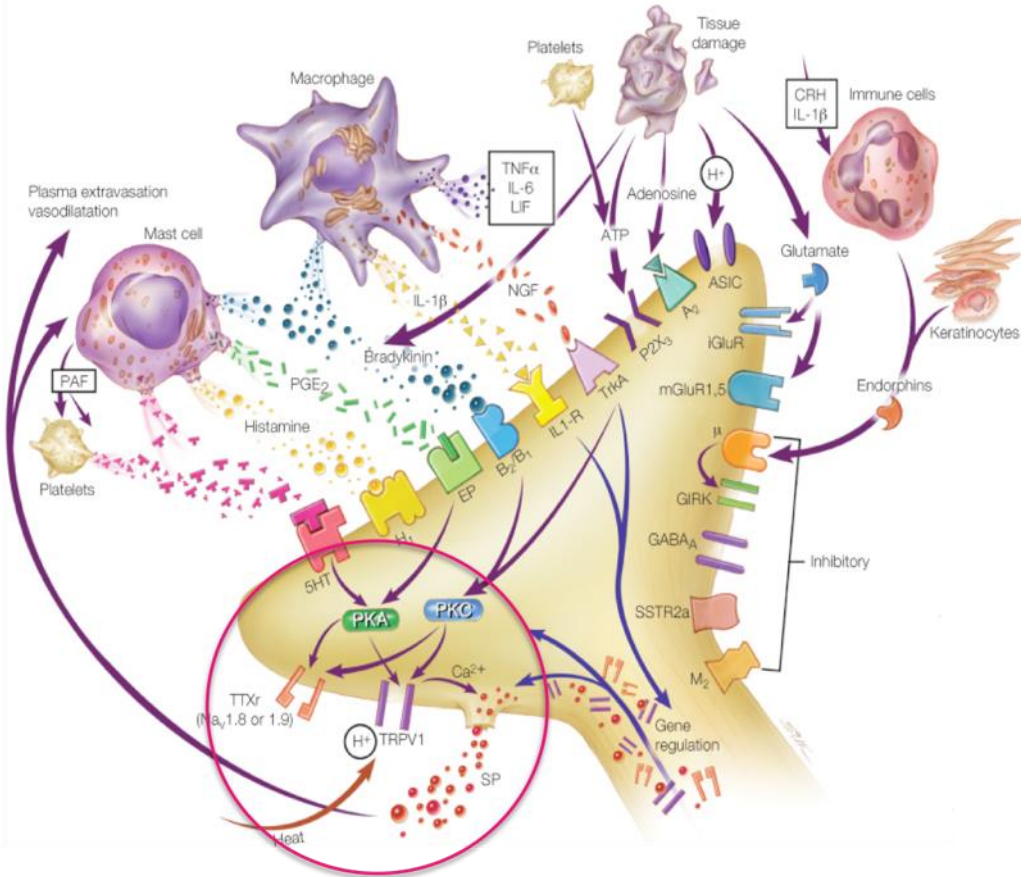
Models to probe nociceptive processing in clinically-relevant states



Nociceptive pain
Inflammatory pain
Nociplastic pain
Neuropathic pain

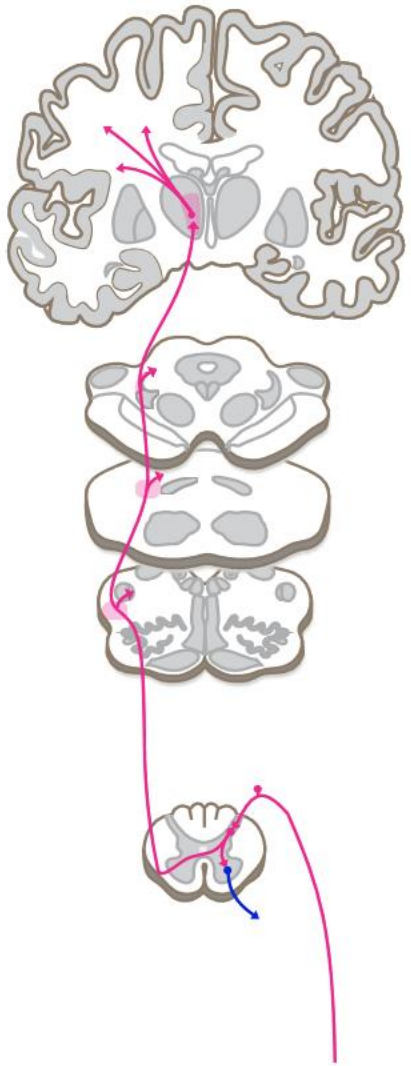
Tissue lesions and pathology produce inflammation and induce changes in the function/structure of peripheral nociceptors leading to **peripheral sensitization**

Experimental models of inflammatory pain

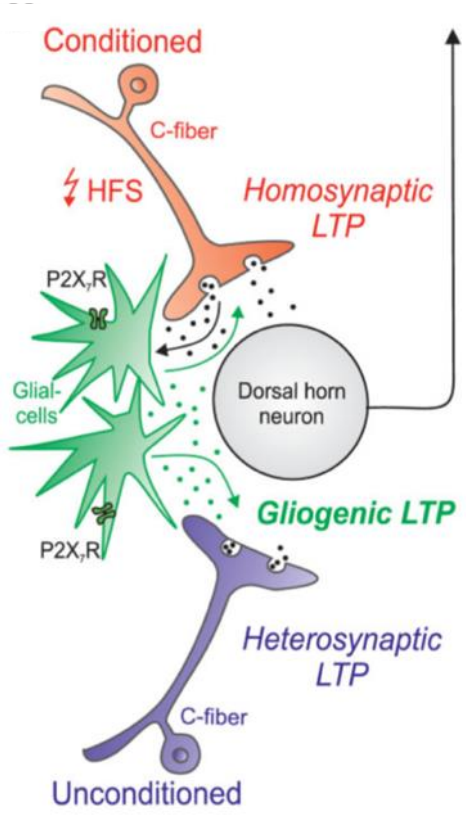


Meyer et al. in Textbook of Pain, 5th Ed (2006)

Tools to probe nociceptive processing in clinically-relevant states



Nociceptive pain
Inflammatory pain
Nociplastic pain
Neuropathic pain



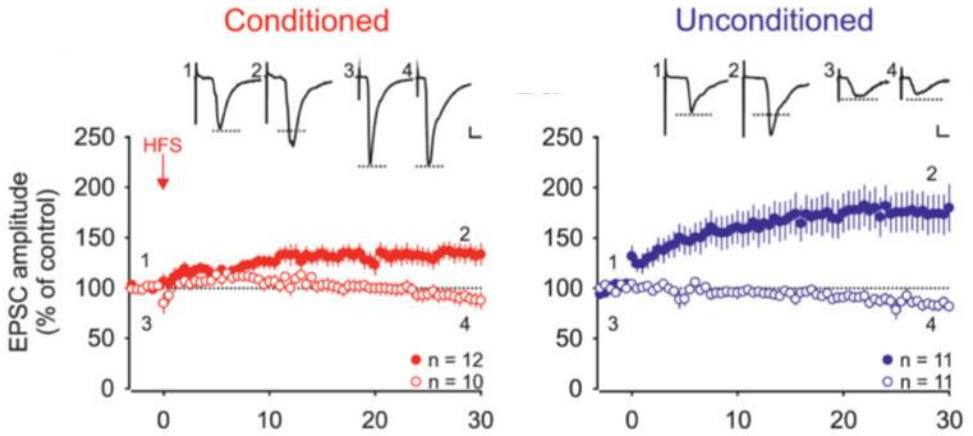
Khasabov et al. (J Neurosci 2002)
Kronschläger et al. (Science 2016)

Tissue lesions and pathology produce inflammation and induce changes in the function/structure of peripheral nociceptors leading to **peripheral sensitization**

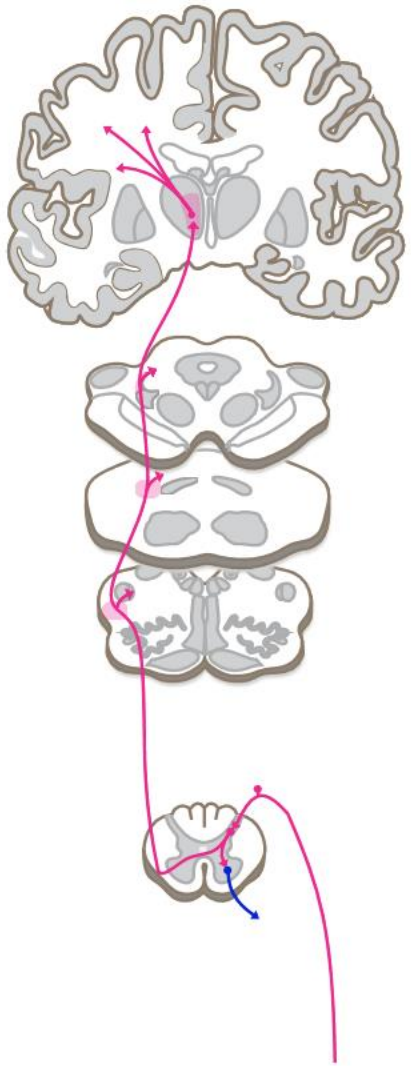
Experimental models of inflammatory pain

Sustained peripheral nociceptive input produces functional and structural changes in the CNS leading to **central sensitization**

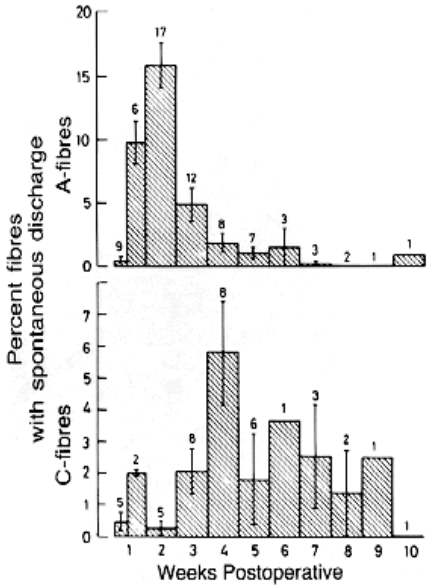
Experimental models of central sensitization



Tools to probe nociceptive processing in clinically-relevant states



Nociceptive pain
Inflammatory pain
Nociplastic pain
Neuropathic pain



Devor in Textbook of Pain, 5th Ed (2006)

Tissue lesions and pathology produce inflammation and induce changes in the function/structure of peripheral nociceptors leading to **peripheral sensitization**

Experimental models of inflammatory pain

Sustained peripheral nociceptive input produces functional and structural changes in the CNS leading to **central sensitization**

Experimental models of central sensitization

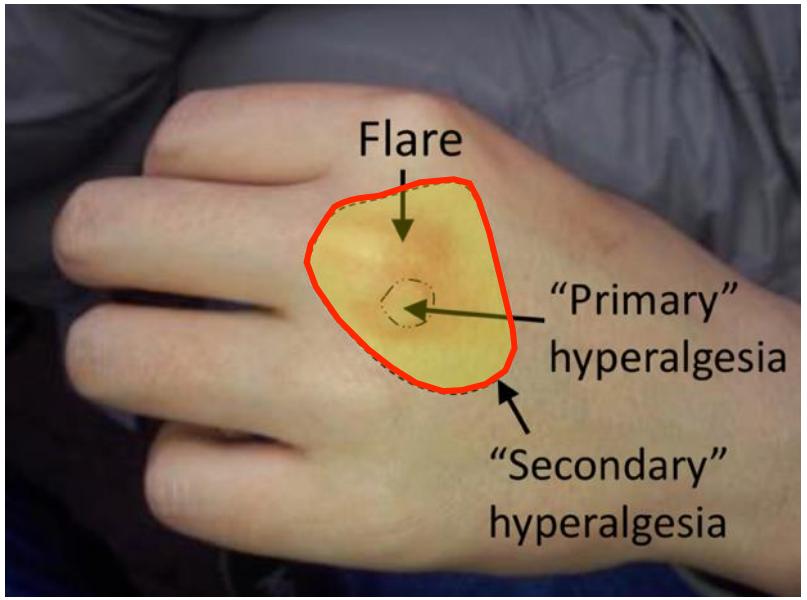
Neuropathic pain. Lesions or disease of the somatosensory nervous system induce functional/structural changes responsible for the positive signs of neuropathic pain (ectopic discharges, ephaptic connexions, …)

(Lack) of experimental models of neuropathic pain

Dysregulation of pain modulation?

Experimental induction of primary and secondary hyperalgesia

Hardy et al. (J Clin Invest, 1950)



— Increased pinprick sensitivity

Primary hyperalgesia

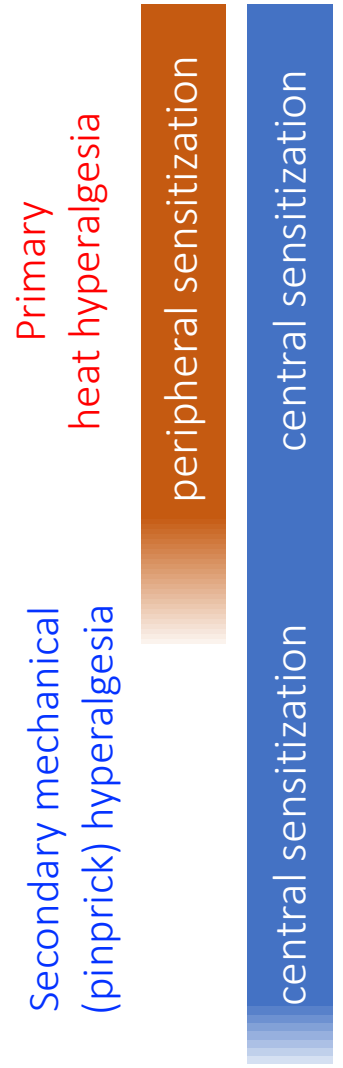
"Hyperalgesia associated with tissue damage and occurring at the site of tissue damage"

"is the result of local elaborations of agents which excite terminal pain endings"

Secondary hyperalgesia

"Hyperalgesia associated with tissue damage but occurring in undamaged tissue adjacent and at some distance from the site of injury

"is the result of a central excitatory state (...) in a network of internuncial neurons which intercalate the noxious impulses from visceral, deep somatic and cutaneous tissues"



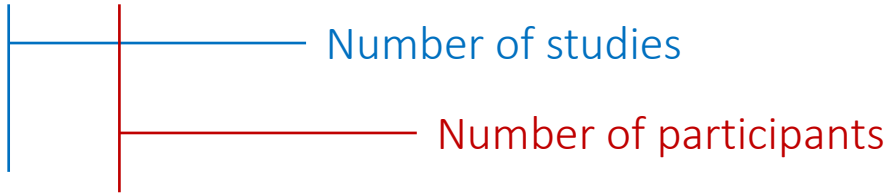
Human experimental models of nociception in a clinically-relevant state

Intradermal capsaicin		
Topical capsaicin (+heat)		
Topical menthol		
Topical CA		
Topical mustard oil	Chemical irritants	
Topical sodium lauryl sulfate		
Intradermal NGF		
Intradermal glutamate		
Intradermal acid solutions		
UVB		
Burn injury		
Cold freeze injury	Injury	
Mechanical incision injury		
Repetitive pinching		
Intracutaneous LFS	Electrical stimulation	
Transcutaneous HFS		

More than a dozen human experimental models inducing primary and/or secondary hyperalgesia due to peripheral and/or central sensitization have been described.

Human experimental models of nociception in a clinically-relevant state

Intradermal capsaicin	61	1,063
Topical capsaicin (+heat)	47	1,228
Topical menthol		
Topical CA		
Topical mustard oil		
Topical sodium lauryl sulfate		
Intradermal NGF		
Intradermal glutamate		
Intradermal acid solutions		
UVB	28	490
Burn injury	43	940
Cold freeze injury		
Mechanical incision injury		
Repetitive pinching		
Intracutaneous LFS	21	378
Transcutaneous HFS	15	281



More than a dozen human experimental models inducing primary and/or secondary hyperalgesia due to peripheral and/or central sensitization have been described.

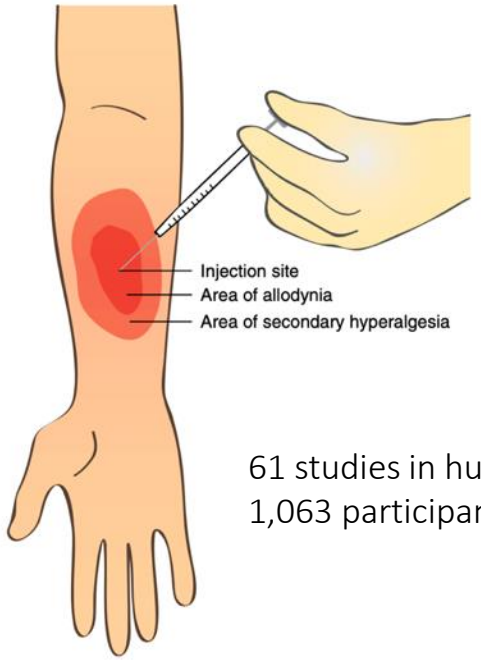
REVIEW ARTICLE
2021

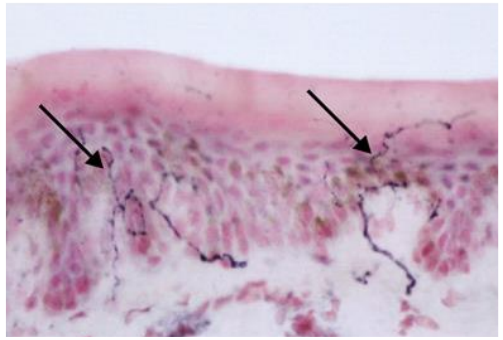
Human surrogate models of central sensitization: A critical review and practical guide

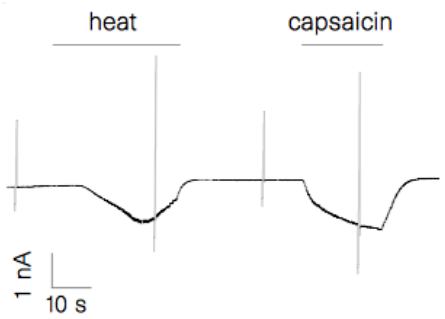
Charles Quesada[1,2] | Anna Kostenko[3] | Idy Ho[4] | Caterina Leone[5] | Zahra Nochi[6] | Alexandre Stouffs[7] | Matthias Wittayer[3] | Ombretta Caspani[3] | Nanna Brix Finnerup[6] | André Mouraux[7] | Gisèle Pickering[8] | Irene Tracey[4] | Andrea Truini[5] | Rolf-Detlef Treede[3] | Luis Garcia-Larrea[1,2]

Intradermal capsaicin

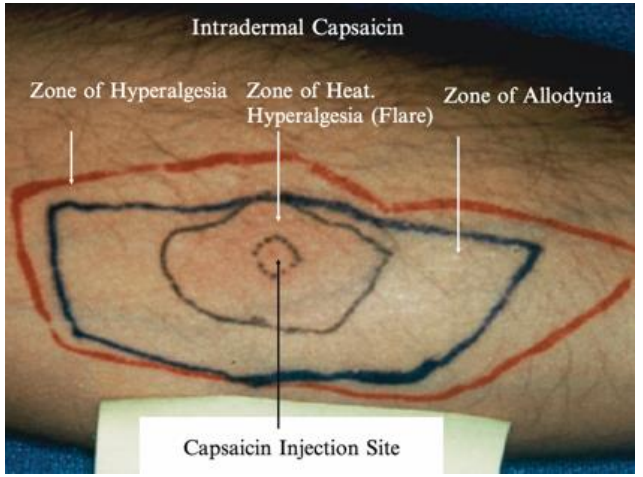
- **Intradermal capsaicin**
- **Topical capsaicin (+heat)**
- Topical menthol
- Topical CA
- Topical mustard oil
- Topical sodium lauryl sulfate
- Intradermal NGF
- Intradermal glutamate
- Intradermal acid solutions
- **UVB**
- Burn injury
- Cold freeze injury
- Mechanical incision injury
- Repetitive pinching
- **Intracutaneous LFS**
- **Transcutaneous HFS**







61 studies in humans
1,063 participants

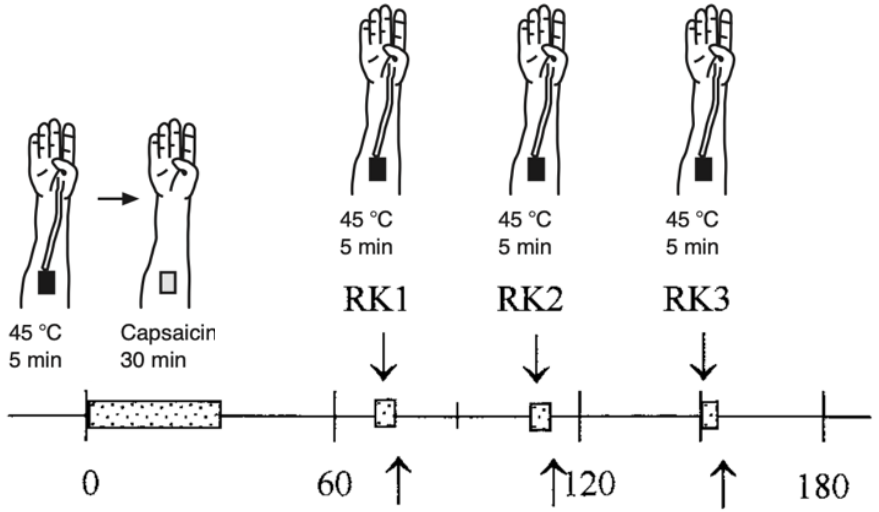


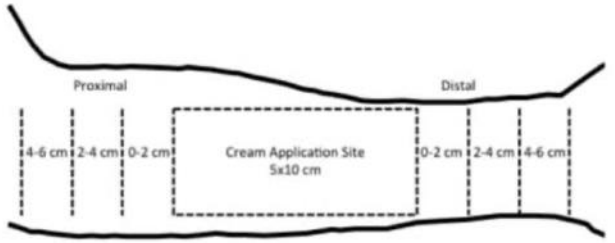
- Slightly invasive technique (injection).
- Difficulty to target injection to the dermis layer.
- Requires administration of a pharmacologically-active compound (capsaicin)
- Intense but short-lasting pain during and immediately after injection.
- Limited induction of peripheral sensitization and 1HA.
- Induces 2HA with a high rate of responders (93.3%) lasting 0.5-2 hours.
- No or minimal spontaneous ongoing pain during the testing period.

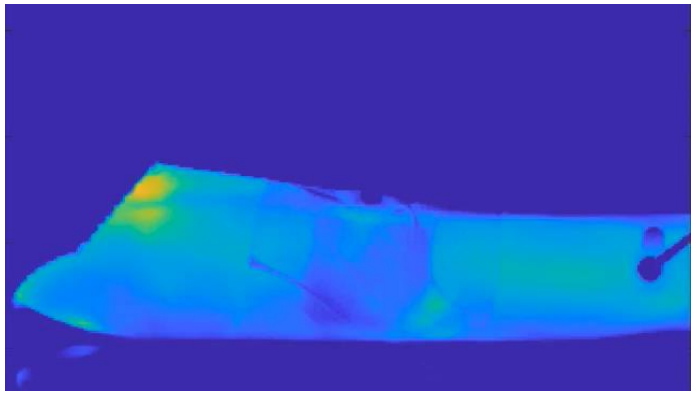
Topical capsaicin

- Intradermal capsaicin
- **Topical capsaicin (+heat)**
- Topical menthol
- Topical CA
- Topical mustard oil
- Topical sodium lauryl sulfate
- Intradermal NGF
- Intradermal glutamate
- Intradermal acid solutions
- **UVB**
- Burn injury
- Cold freeze injury
- Mechanical incision injury
- Repetitive pinching
- **Intracutaneous LFS**
- **Transcutaneous HFS**

47 studies in humans
1,228 participants







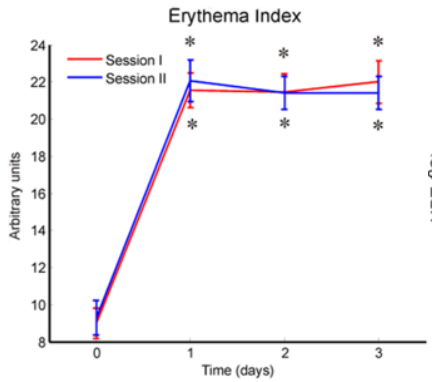
- Moderate pain at induction (compared to intradermal capsaicin).
- Requires (topical) administration of a pharmacologically-active compound (capsaicin)
- Topical capsaicin alone tends to produce inconsistent results. Variations in capsaicin skin penetration and/or skin temperature may be an important source of inter-individual and between-session variability
- Iterative applications of heat (heat kindling) can be used to sustain the capsaicin-induced 1HA and 2HA during several hours = preferred method.
- Some amount of spontaneous ongoing pain during the testing period.

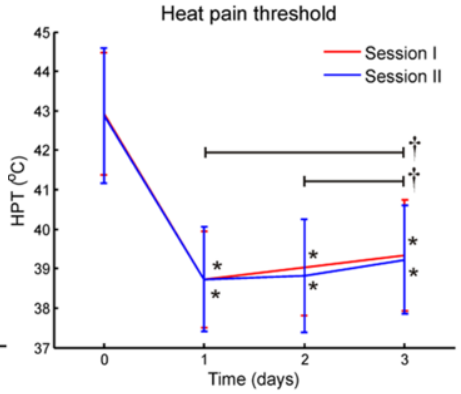
UVB-induced inflammation

- Intradermal capsaicin
- Topical capsaicin (+heat)
- Topical menthol
- Topical CA
- Topical mustard oil
- Topical sodium lauryl sulfate
- Intradermal NGF
- Intradermal glutamate
- Intradermal acid solutions
- **UVB**
- Burn injury
- Cold freeze injury
- Mechanical incision injury
- Repetitive pinching
- Intracutaneous LFS
- Transcutaneous HFS

28 studies in humans
490 participants

Dahl Morch et al. (Int J Physiol Pathophysiol Pharmacol, 2013)



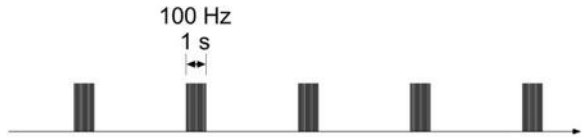


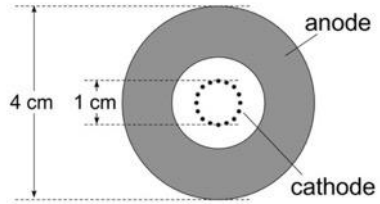
- Used extensively as a model mimicking inflammation-related hyperalgesia without ongoing pain.
- UVB dosage defined in each participant relative to “Minimal Erythema Dose” (MED), typically determined 1-7 days before the experiment.
- Erythema and 1HA develops systematically, approximately 6 hours after irradiation, reaching maximum intensity after 12-36 hours.
- Very inconsistent development of 2HA.
- Mechanism of UVB-induced inflammation and sensitization may be mediated primarily through keratinocyte TRPV4 activation in turn triggering inflammation and nociceptor sensitization.
- Skin hyperpigmentation in >50% participants, sometimes visible up to 3 years after exposure.

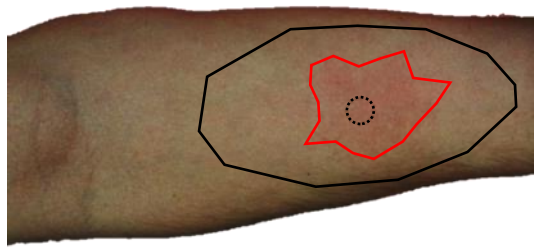
High-frequency electrical stimulation of the skin (HFS)

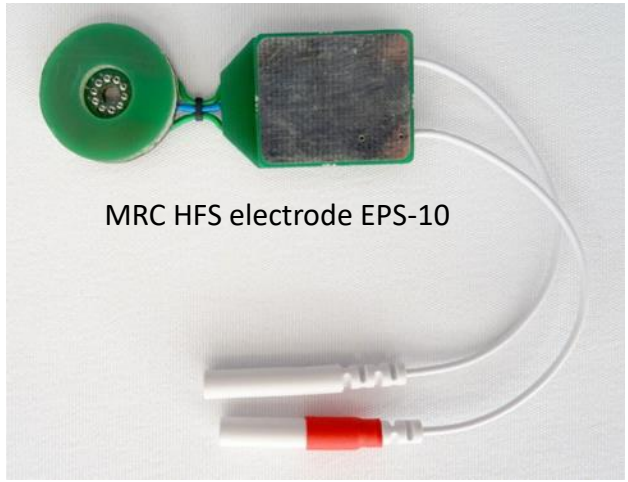
- Intradermal capsaicin
- Topical capsaicin (+heat)
- Topical menthol
- Topical CA
- Topical mustard oil
- Topical sodium lauryl sulfate
- Intradermal NGF
- Intradermal glutamate
- Intradermal acid solutions
- UVB
- Burn injury
- Cold freeze injury
- Mechanical incision injury
- Repetitive pinching
- Intracutaneous LFS
- Transcutaneous HFS

15 studies in humans
281 participants





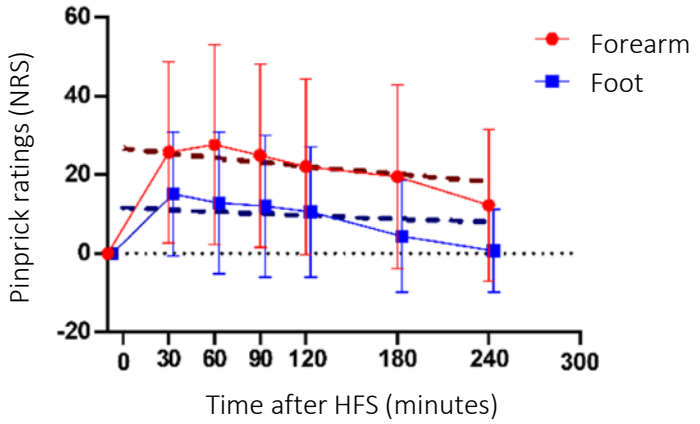


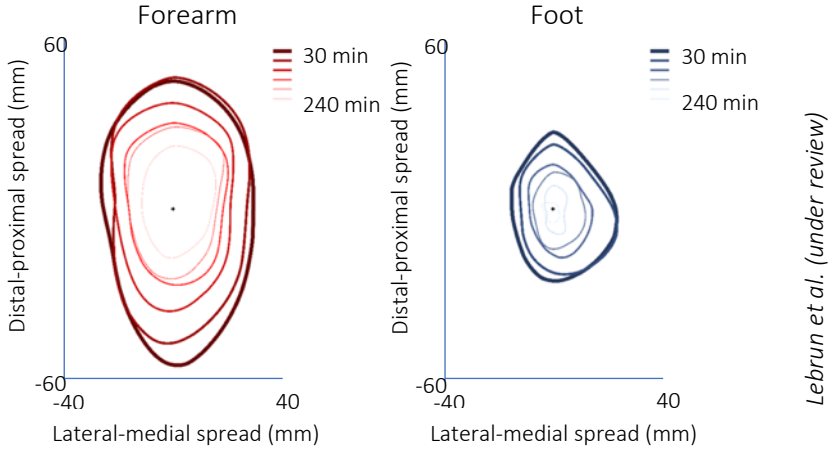


- Transcutaneous high-frequency electrical stimulation using a multi-pin surface electrode to induce central sensitization via the direct electrical activation of skin nociceptors.
- Non-invasive and very short lasting induction procedure, but intense unpleasant sensation during stimulation.
- Can be administered in very standardized and operator-independent fashion
- Does not require administration of a pharmacologically-active compound.

High-frequency electrical stimulation of the skin (HFS)

- Intradermal capsaicin
- **Topical capsaicin (+heat)**
- Topical menthol
- Topical CA
- Topical mustard oil
- Topical sodium lauryl sulfate
- Intradermal NGF
- Intradermal glutamate
- Intradermal acid solutions
- **UVB**
- Burn injury
- Cold freeze injury
- Mechanical incision injury
- Repetitive pinching
- **Intracutaneous LFS**
- **Transcutaneous HFS**



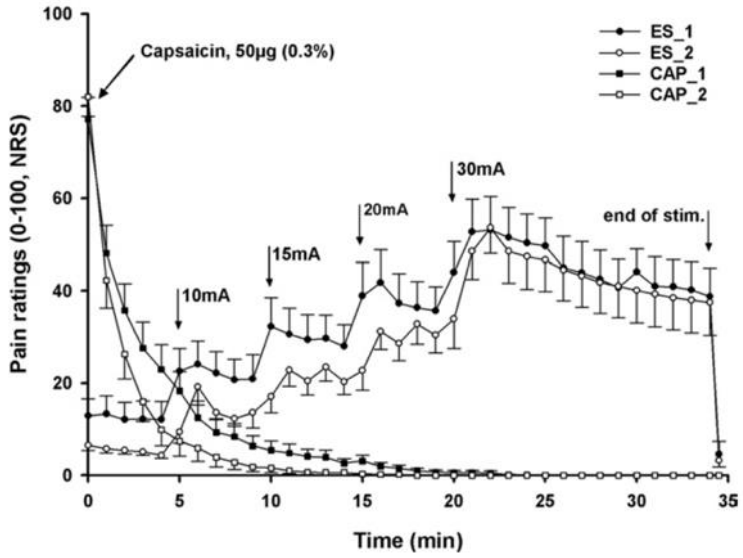


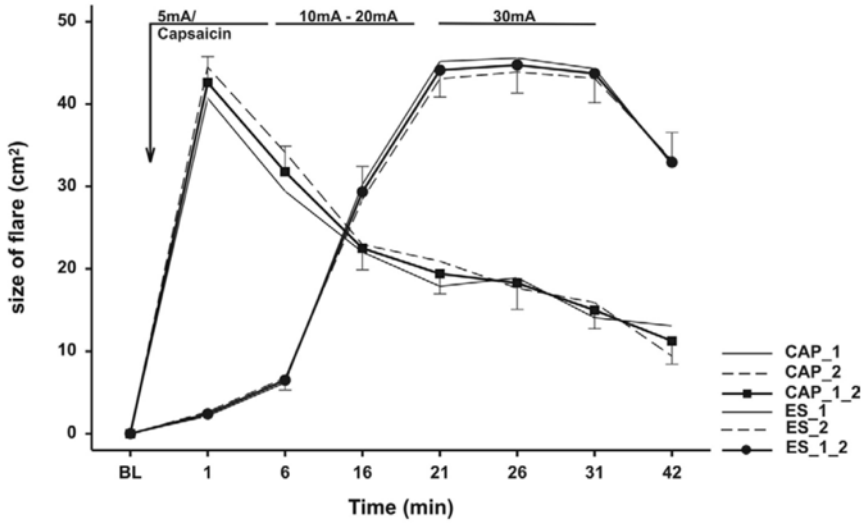
- Consistent induction of 2HA lasting several hours.
- Minimal and short-lived induction of peripheral sensitization and 1HA.
- No or minimal spontaneous ongoing sensations during testing.
- Can be applied at different body locations (some differences reported pending application site).

Intracutaneous low-frequency stimulation (LFS)

- Intradermal capsaicin
- Topical capsaicin (+heat)
- Topical menthol
- Topical CA
- Topical mustard oil
- Topical sodium lauryl sulfate
- Intradermal NGF
- Intradermal glutamate
- Intradermal acid solutions
- UVB
- Burn injury
- Cold freeze injury
- Mechanical incision injury
- Repetitive pinching
- Intracutaneous LFS
- Transcutaneous HFS

21 studies in humans
378 participants

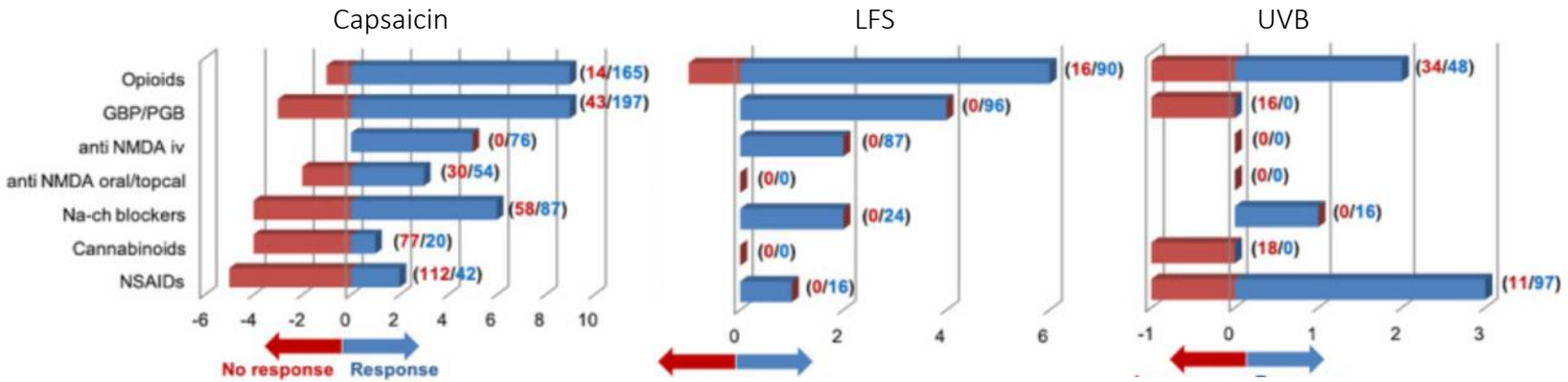




- Percutaneous low-frequency stimulation (LFS) as originally described by Koppert et al. (2001):
  - Thin stainless-steel needle inserted intracutaneously (anode).
  - Continuous 5 Hz electrical stimulation. Current gradually increased during the first 15 minutes targeting a pain rating of 5/10, and then kept constant for the remaining of the experiment.
- Slightly invasive technique, but easy to use and well-controlled stimulation.
- Moderate pain during induction.
- Consistent induction of 2HA which can be maintained for several hours.
- Limited amount of inflammation and 1HA (but some neurogenic inflammation)
- Continuous LFS may mimic to some extent the ectopic activity of peripheral neuropathic pain.

Human experimental models of nociception in a clinically-relevant state

Intradermal capsaicin	
Topical capsaicin (+heat)	
Topical menthol	
Topical CA	
Topical mustard oil	
Topical sodium lauryl sulfate	
Intradermal NGF	
Intradermal glutamate	
Intradermal acid solutions	
UVB	
Burn injury	
Cold freeze injury	
Mechanical incision injury	
Repetitive pinching	
Intracutaneous LFS	
Transcutaneous HFS	



Quesada et al. (Eur J Pain 2021)

Pharmacodynamic biomarkers of nociceptive processing

Pharmacodynamic biomarkers

T0	T1	T2	T3	T4
Preclinical and animal studies	Phase 1 clinical trials in healthy human volunteers	Phase 2/3 clinical trials in patients	Phase 4 trials, clinical outcomes research	Population-level outcome research

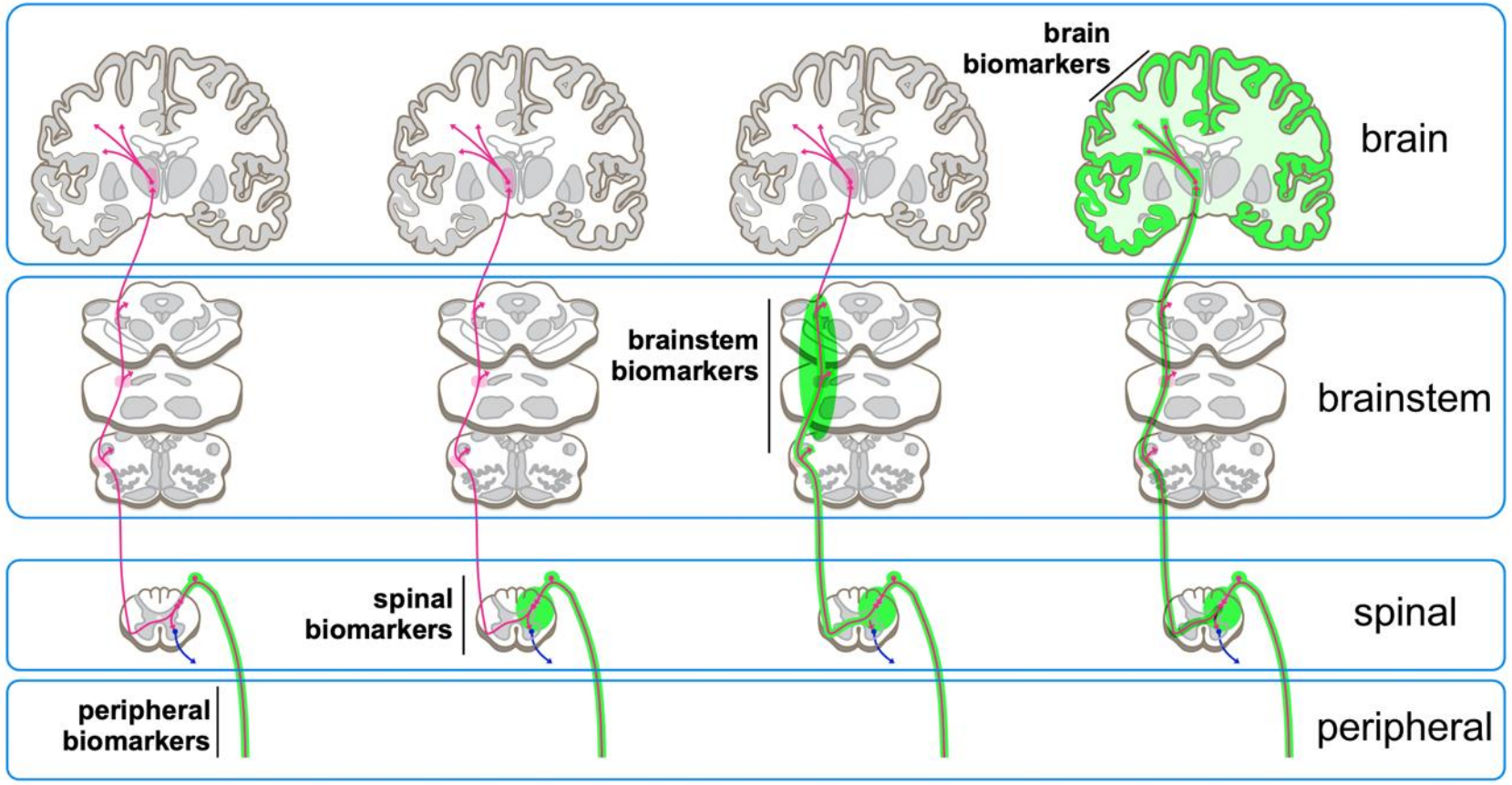
Pharmacodynamic biomarkers for drugs acting on these mechanisms must be coupled with experimental models of pain that engage and/or mimick these mechanisms.

Clinically-relevant experimental models

- Pain in the context of inflammation / peripheral sensitization
- Pain in the context of central sensitization
- Neuropathic pain

Pharmacodynamic biomarkers of nociceptive processing

An array of pharmacodynamic biomarkers sensitive to drug effects on nociception can be derived from non-invasive or minimally-invasive measures of peripheral and central nervous system activity.

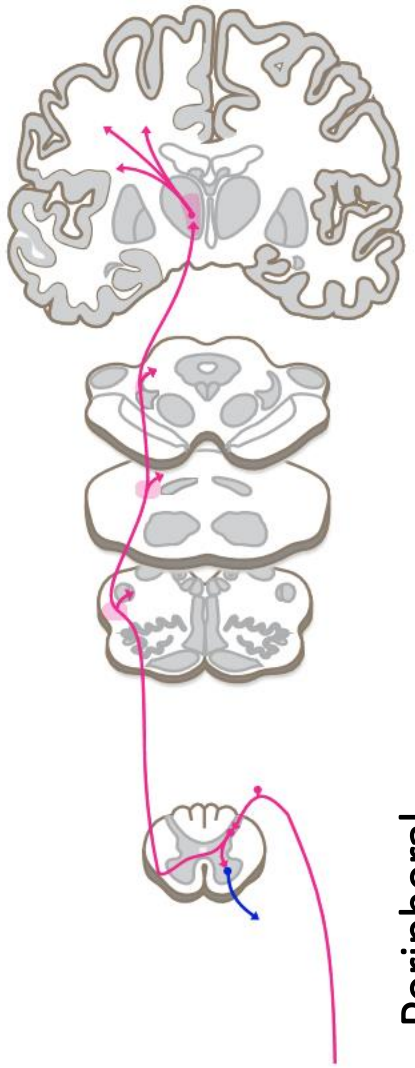


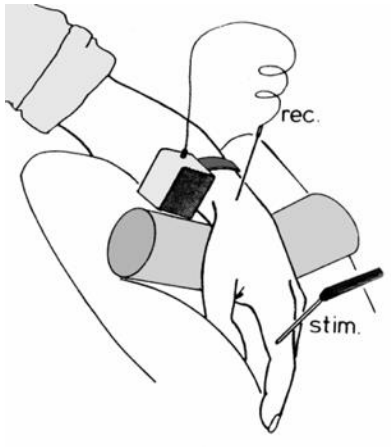
Mouraux et al. (Trials 2021)
Nochi et al. (Trials 2022)
Leone et al. (Trials 2022)

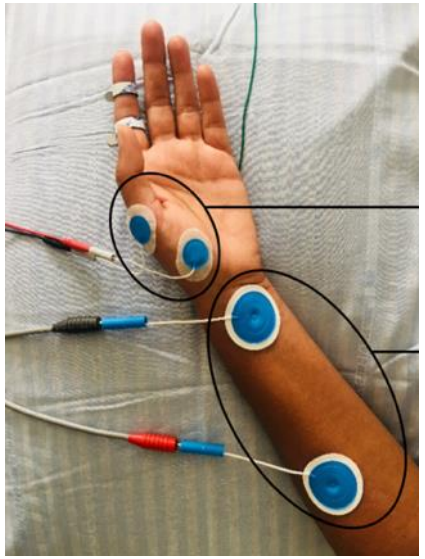
IMI-PainCare

http://imi-paincare.eu

Peripheral biomarkers of nociceptive processing



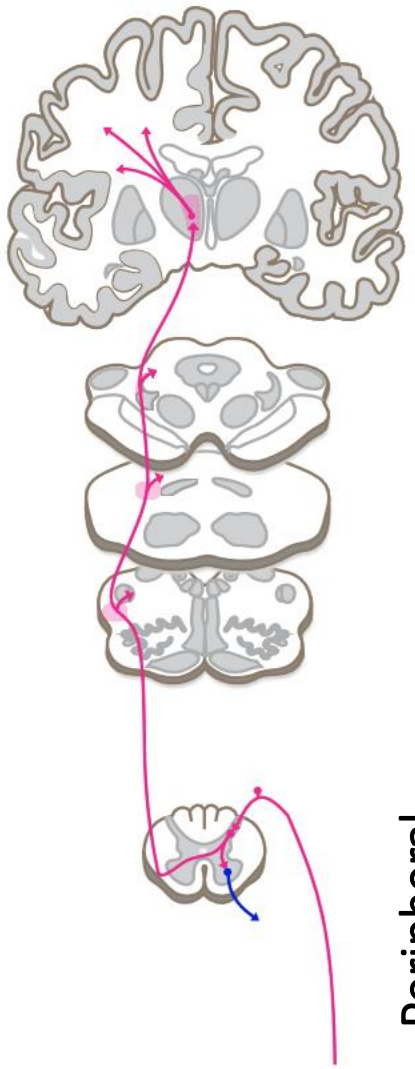




Peripheral biomarkers

- Microneurography
- Nerve excitability testing (NET) and perceptual threshold tracking (PTT)
- …

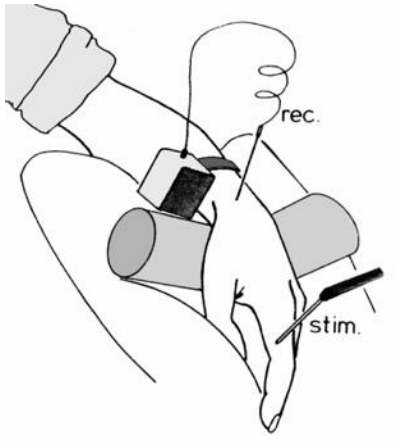
Peripheral biomarkers of nociceptive processing

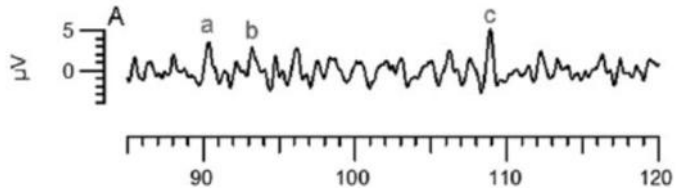


Peripheral biomarkers

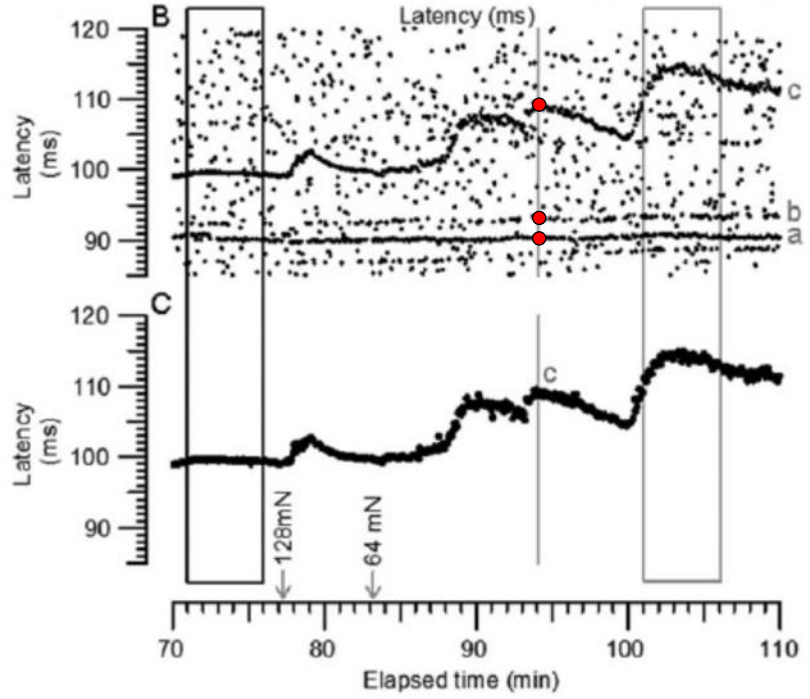
Microneurography

Spontaneous activity-dependent slowing as a marker of abnormal spontaneous discharges in C-fiber nociceptors

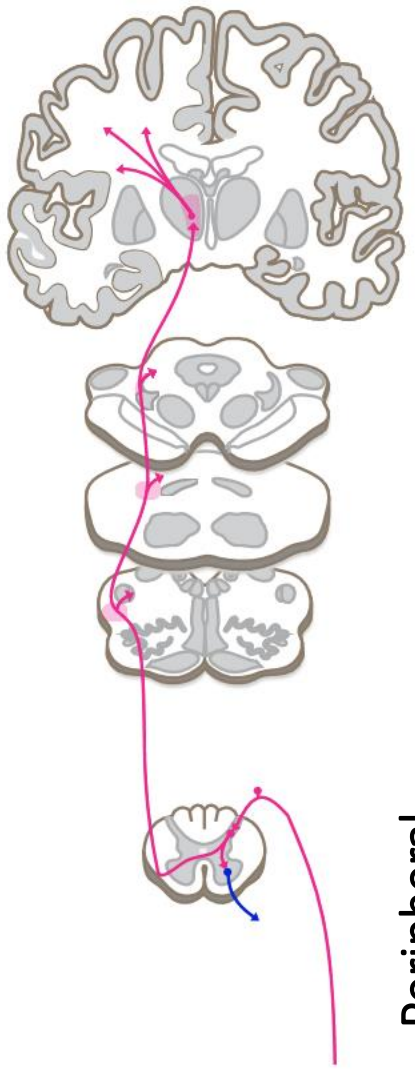




Serra et al. (Ann Neurol, 2018)



Peripheral biomarkers of nociceptive processing

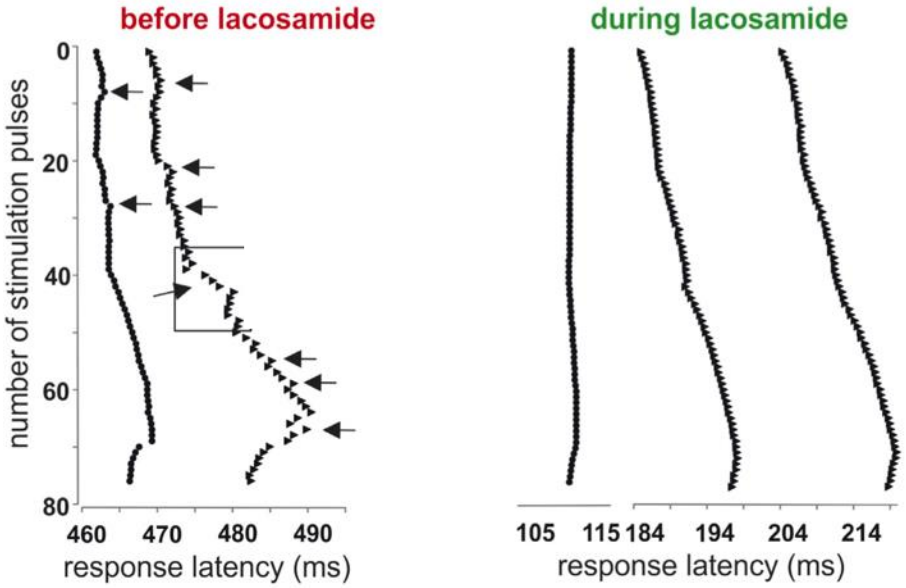


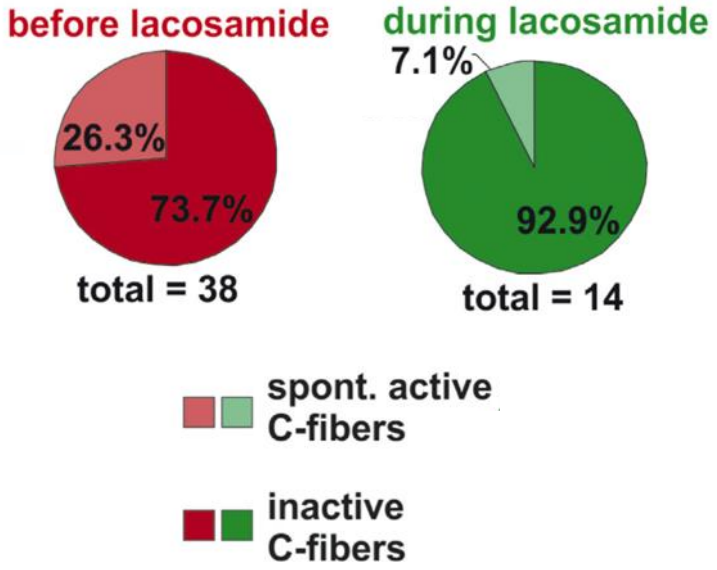
Peripheral biomarkers

Microneurography

Spontaneous activity-dependent slowing as a marker of abnormal spontaneous discharges in C-fiber nociceptors

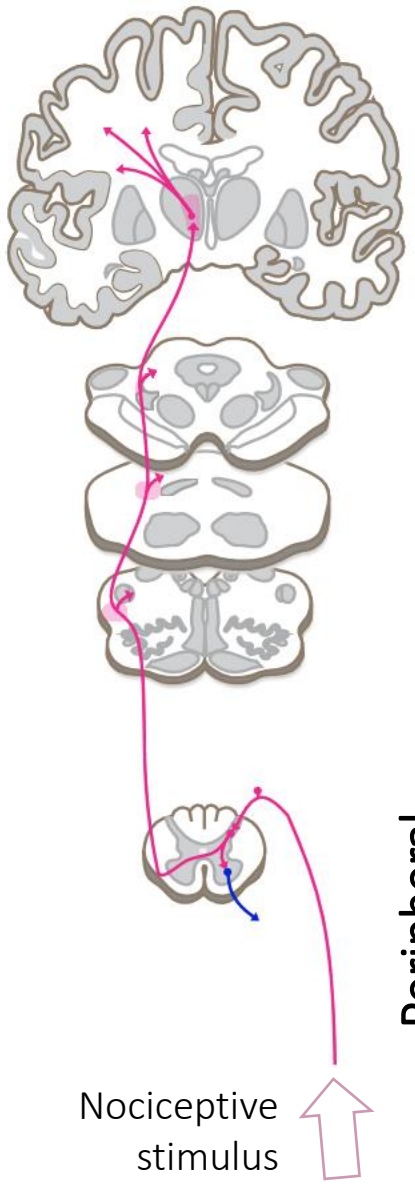
Therapy-refractory Caucasian patient suffering from SFN for over ten years
Microneurography before and during treatment with lacosamide



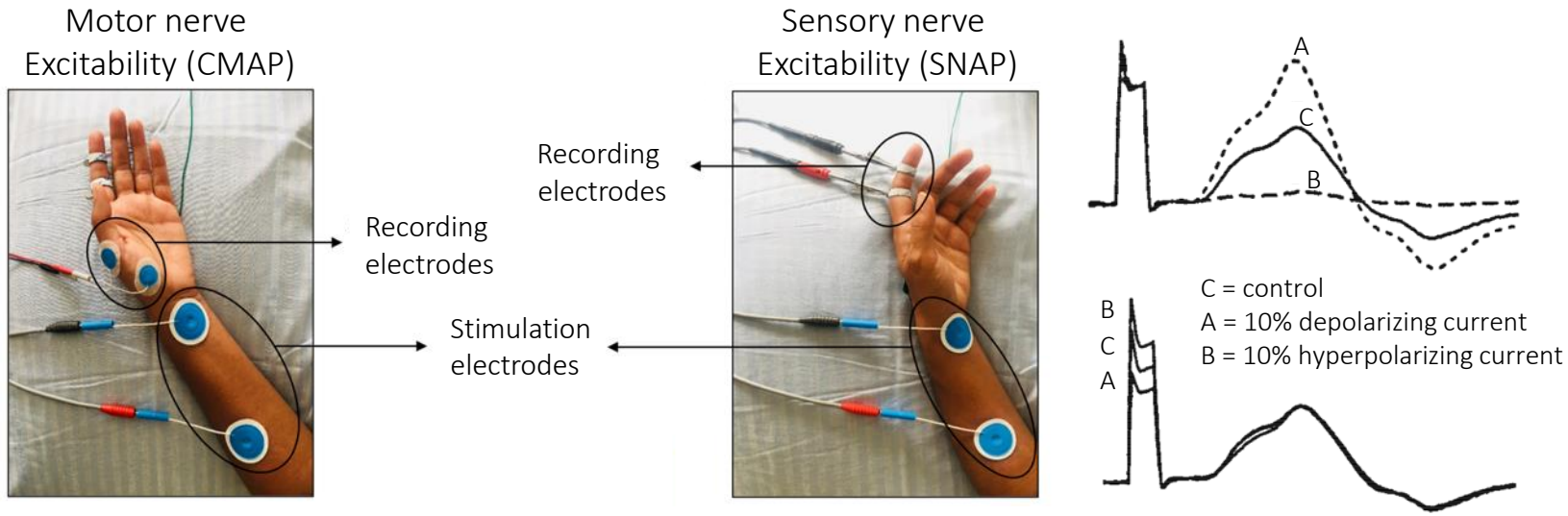


Namer et al. EBioMedicine (2018)

Peripheral biomarkers of nociceptive processing



Nerve excitability testing (NET)



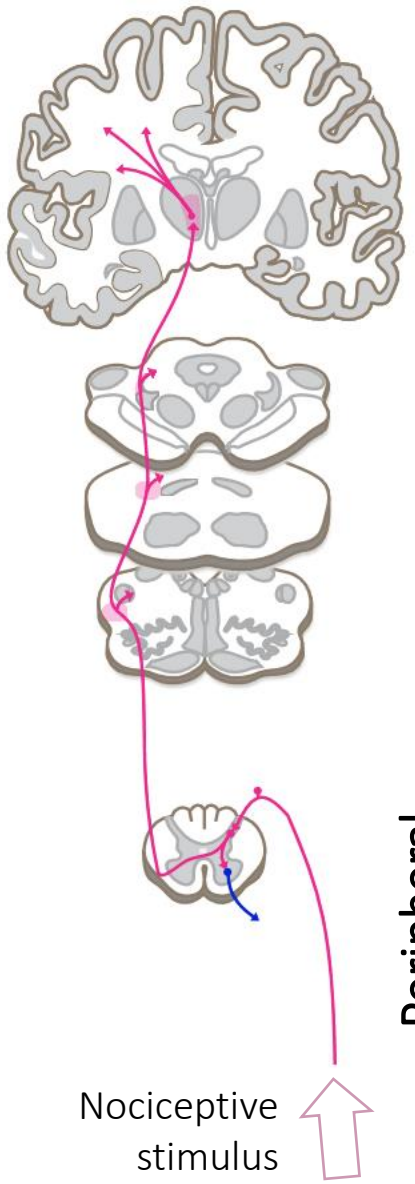
Bostock et al. (Muscle & Nerve, 1998)

Threshold tracking

Automatic adjustment of stimulation intensity to reach a target response amplitude.
Assess differences in threshold as a function of stimulation parameters.
Assess drug-induced effects on the estimated thresholds

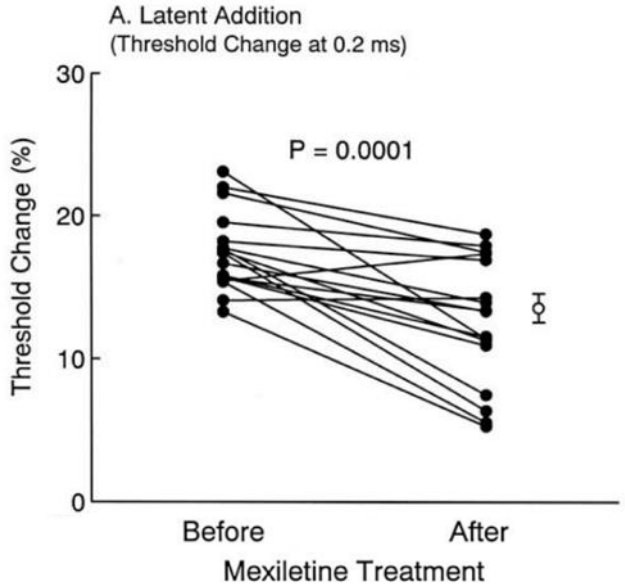
By varying the parameters of the test pulse or combining the test pulse with a conditioning stimulus, several measures can be derived that are sensitive to membrane potential and to nodal/internodal changes in membrane potential caused by activation of ion channels and electrogenic ion pumps.

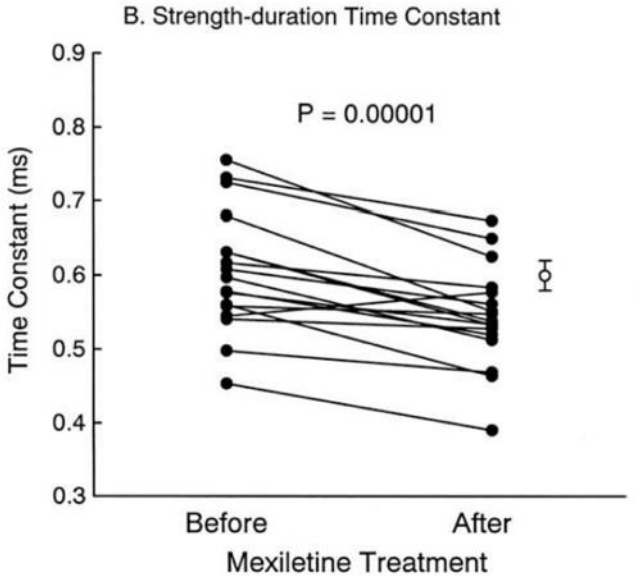
Peripheral biomarkers of nociceptive processing



Nerve excitability testing (NET)

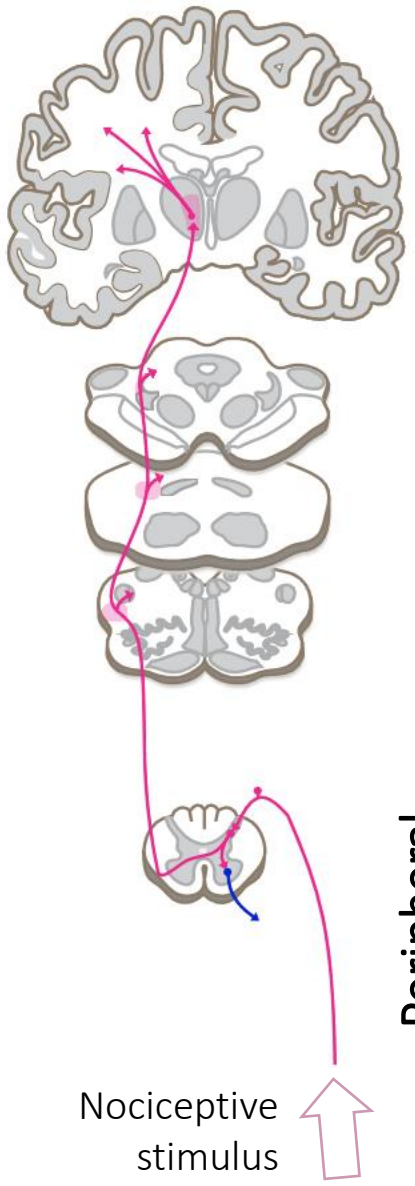
Mexiletine treatment in a group of patients with neuropathic pain





Isose et al. (Clin Neurophysiol, 2010)

Peripheral biomarkers of nociceptive processing

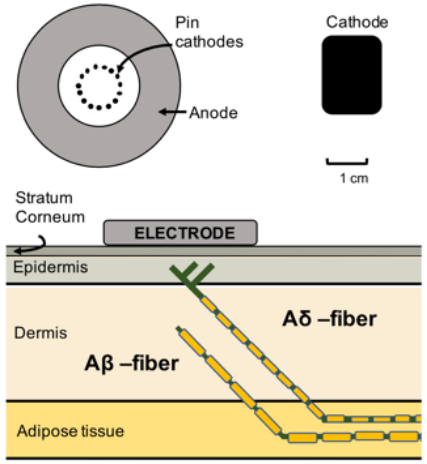


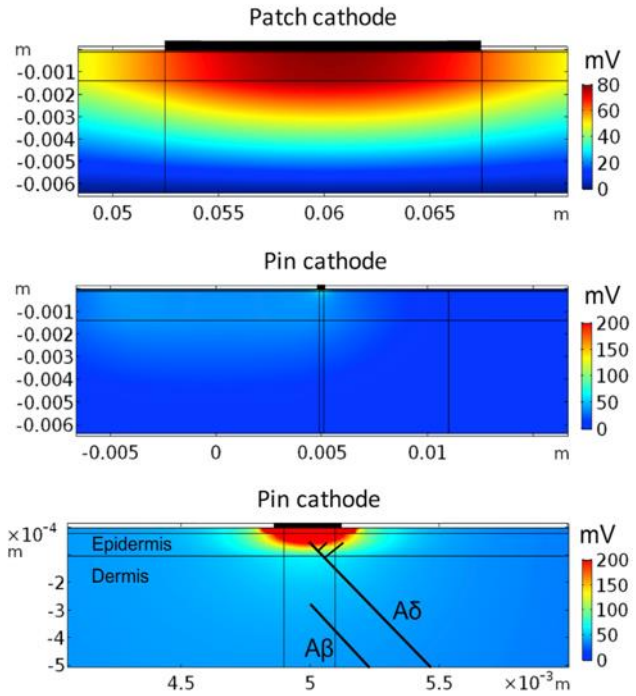
Peripheral biomarkers

Nerve excitability testing (NET)

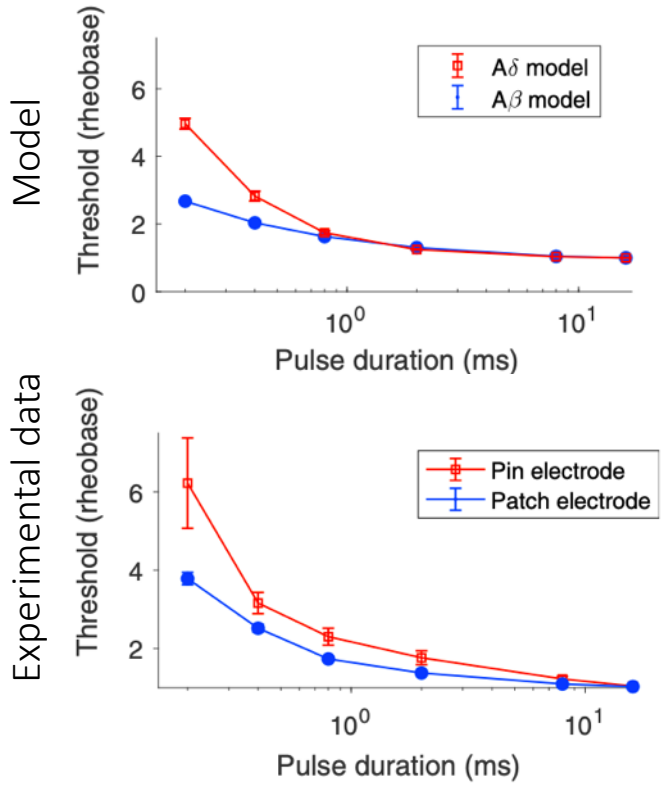
Conventional NET only assess excitability of non-nociceptive large-diameter fibers.

Focal pin electrode designed to **preferentially activate epidermal nociceptive afferents**.
Adjustment of intensity to reach a **target percentage of detected stimuli (perception)**.



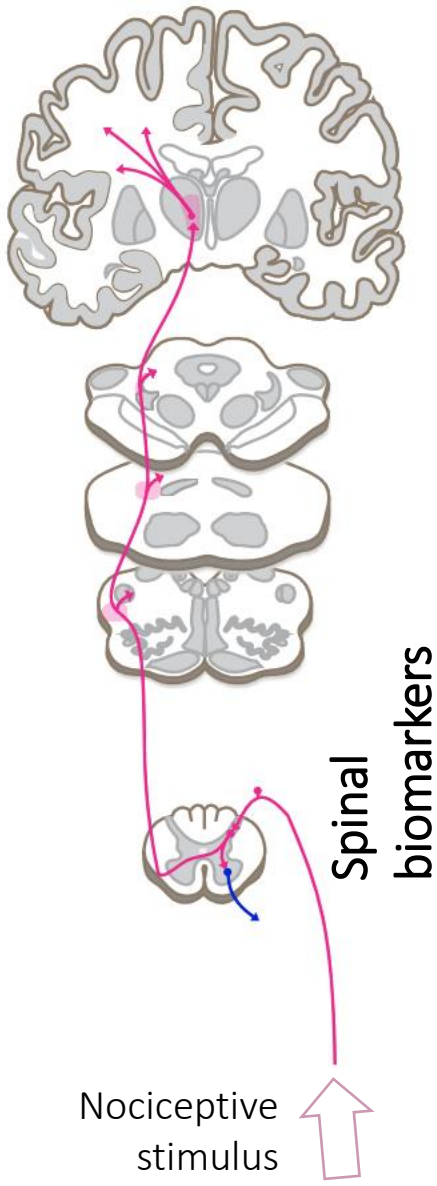


Strength-duration curve



Tigerholm et al. (BioPhysical Journal, 2019)

Spinal biomarkers of nociceptive processing



Spinal biomarkers

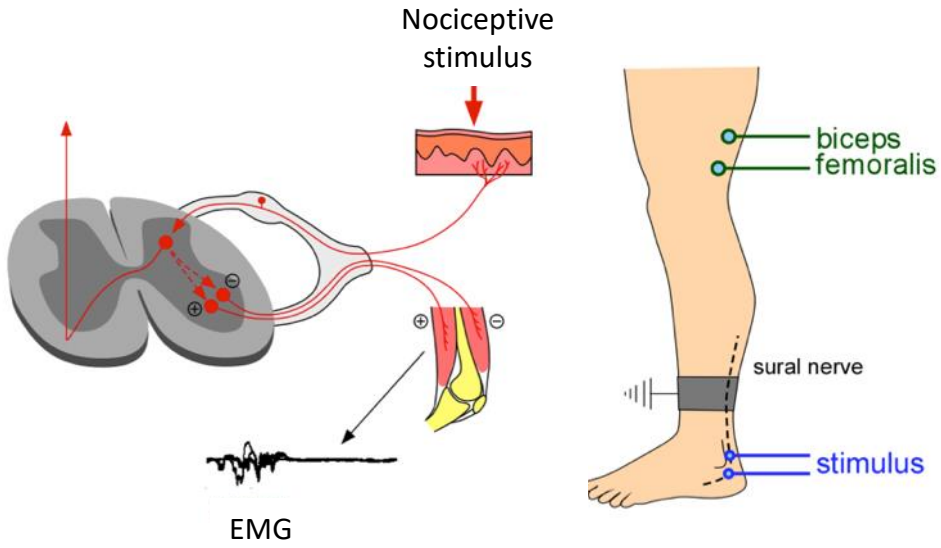
Nociceptive withdrawal reflex (NWR)

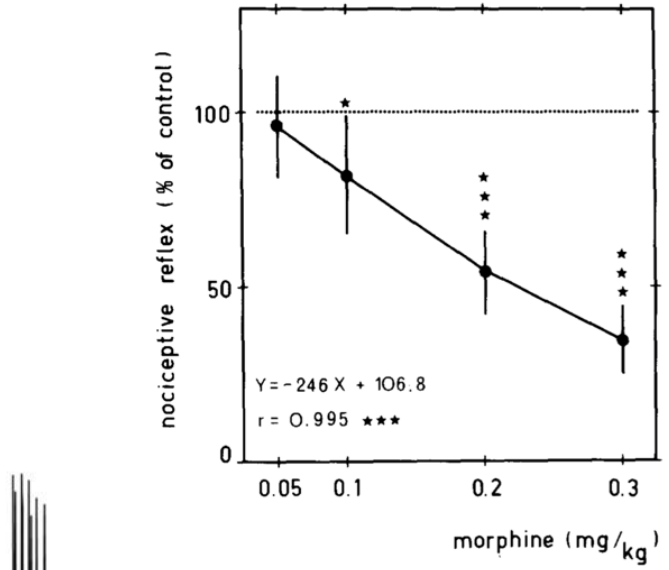
Electrical stimulation of the sural nerve

EMG response recorded from biceps femoralis.

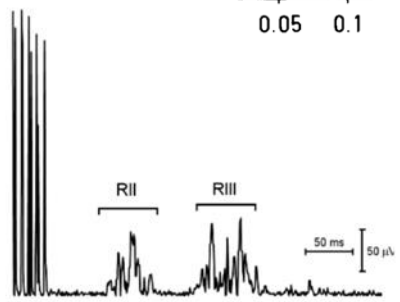
Pure nociceptive reflex mediated by dorsal horn circuitry

Modulated at spinal level and via descending modulatory influences



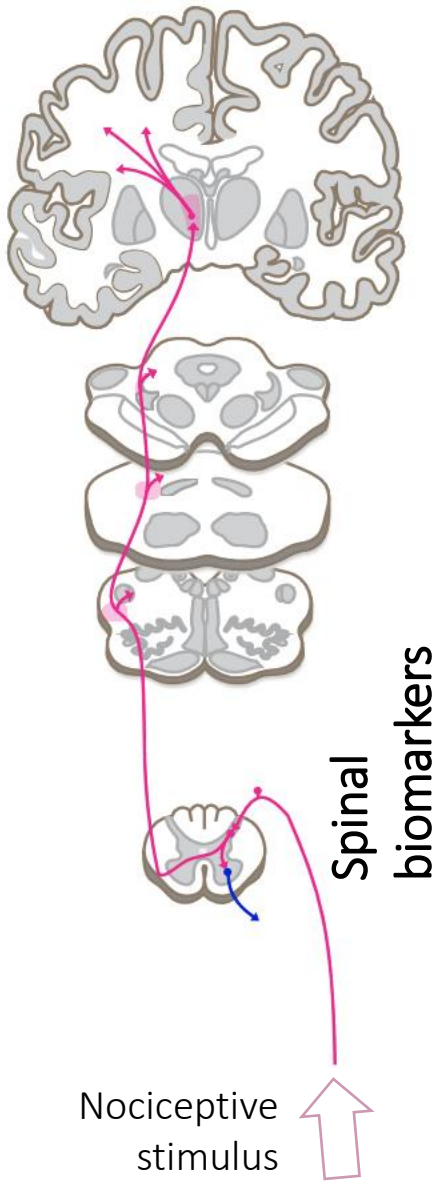


Willer (Brain Res, 1985)



Willer et al. (Brain Res 1977)

Spinal biomarkers of nociceptive processing



Nociceptive withdrawal reflex (NWR)

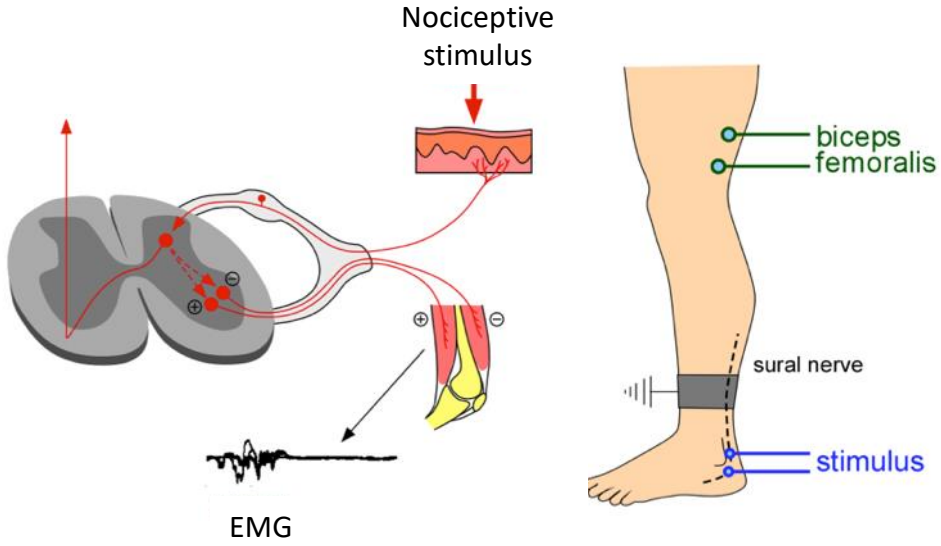
Electrical stimulation of the sural nerve

EMG response recorded from biceps femoralis.

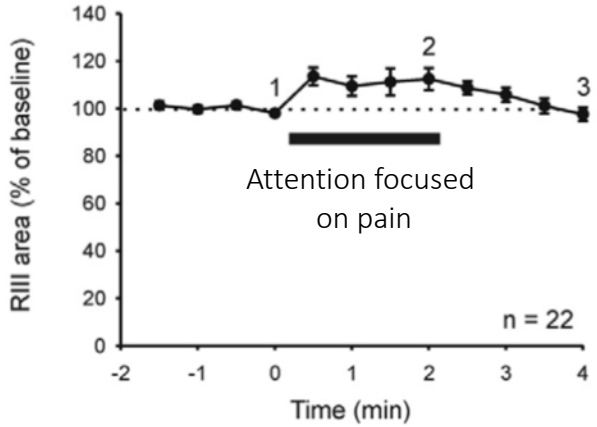
Pure nociceptive reflex mediated by dorsal horn circuitry

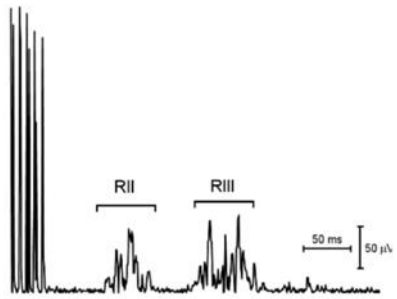
Modulated at spinal level and via descending modulatory influences

Spinal biomarkers



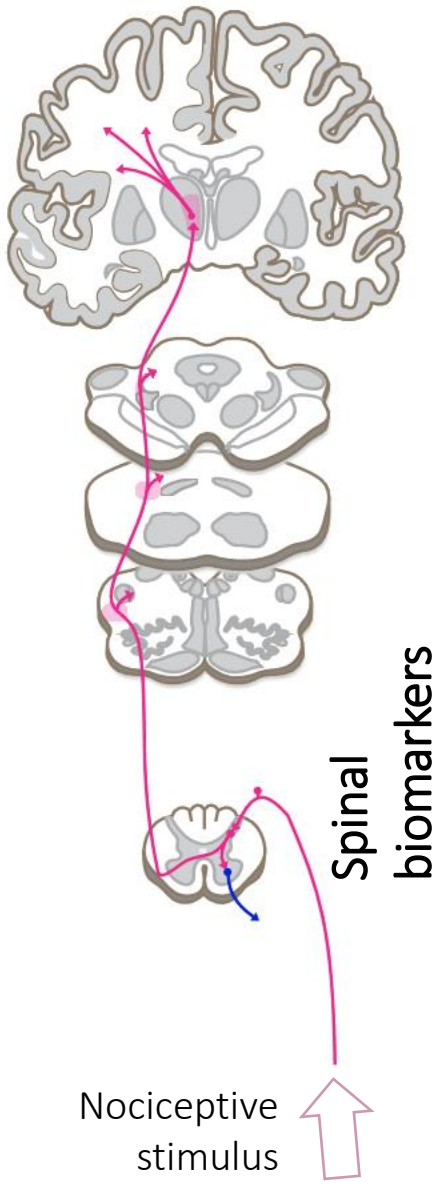
Ruscheweyh et al. (Pain 2013)





Willer et al. (Brain Res 1977)

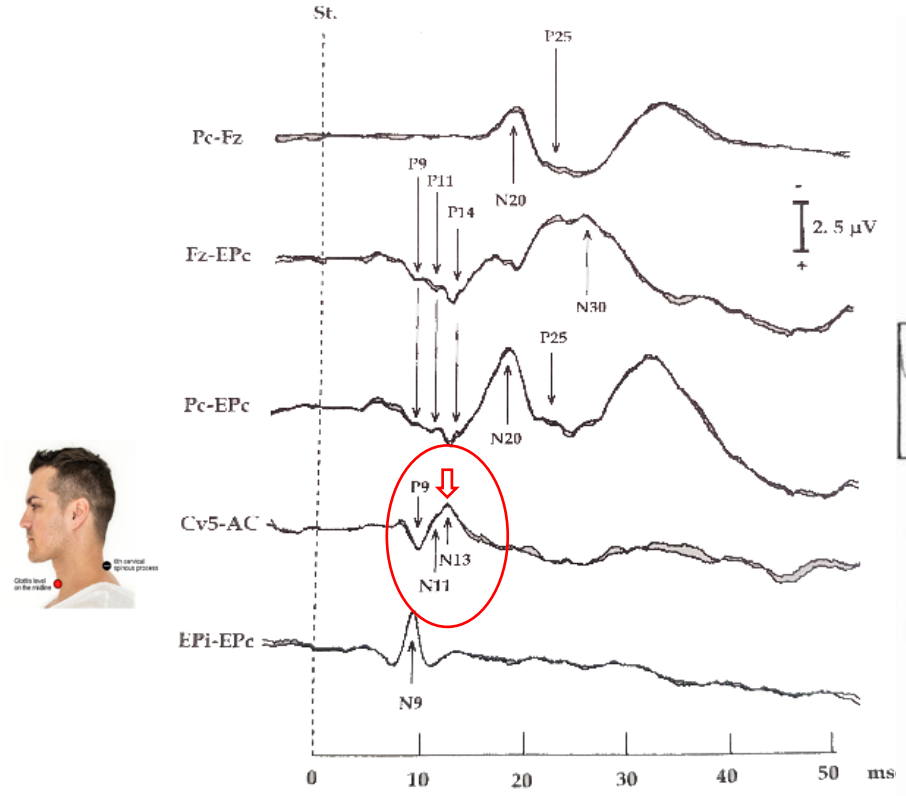
Spinal biomarkers of nociceptive processing



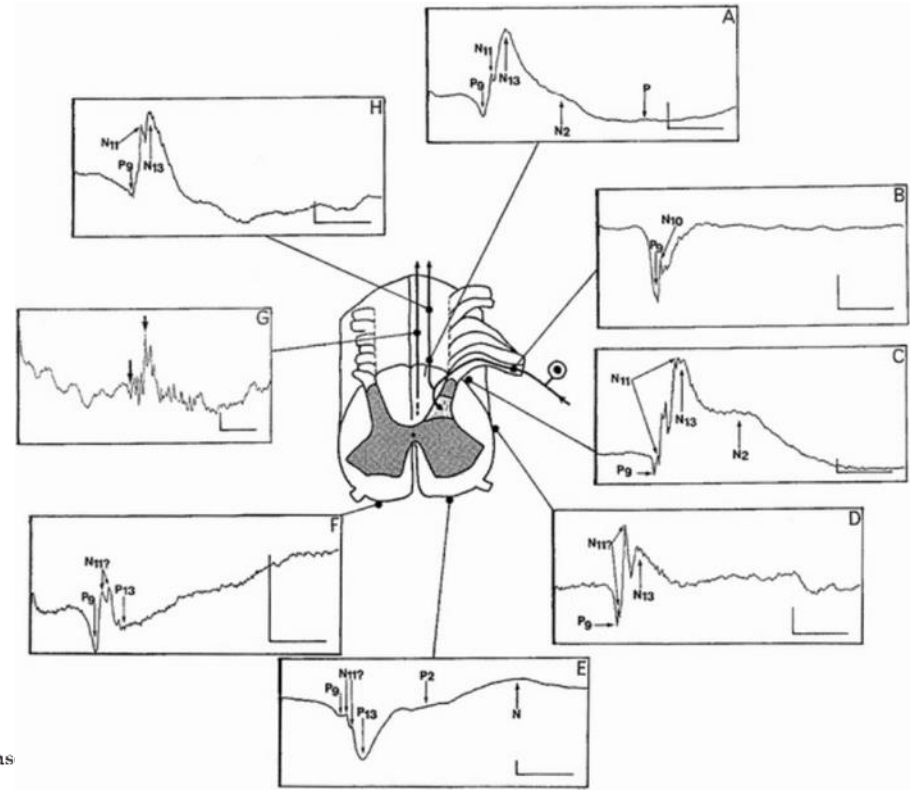
N13 cervical component of upper-limb somatosensory-evoked potentials

Electrical stimulation of the median or ulnar nerve at the level of the wrist

N13 SEP reflects the response of dorsal horn neurons to non-noxious inputs.

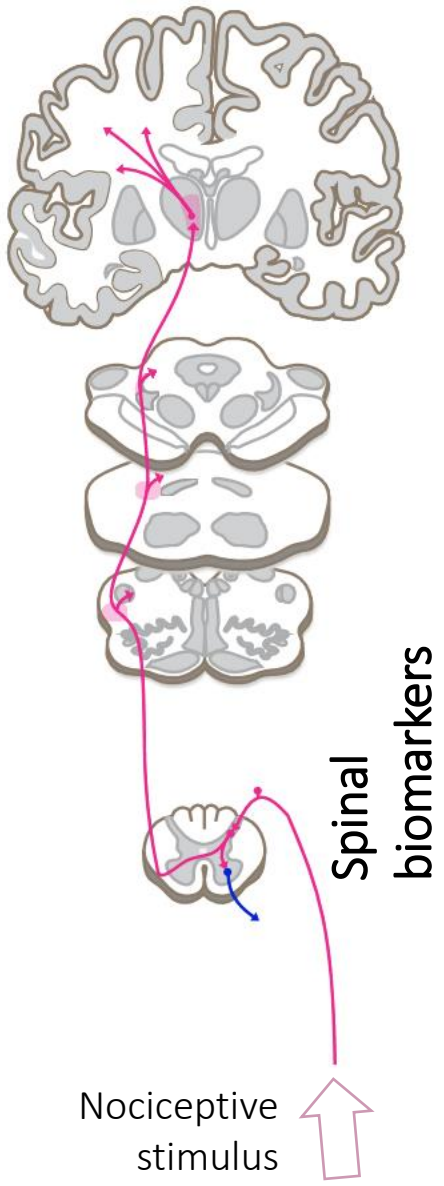


Mauguière et al.
(Electroencephalogr Clin Neurophysiol Suppl, 1999)



Mauguière
(J Clin Neurophysiol, 2000)

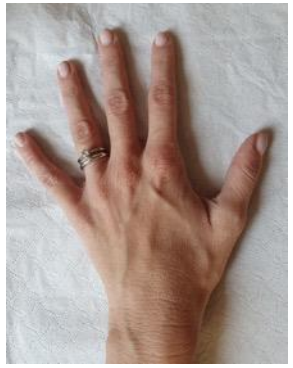
Spinal biomarkers of nociceptive processing

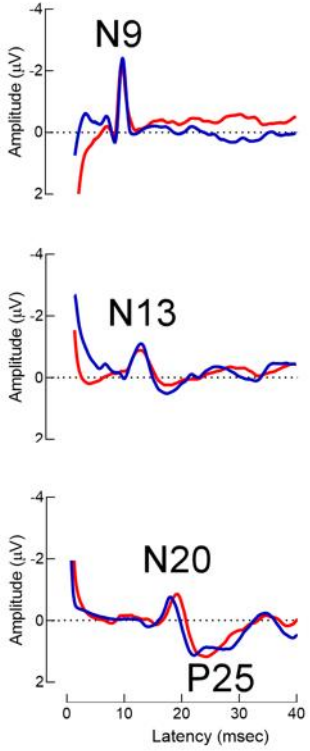


N13 cervical component of upper-limb somatosensory-evoked potentials

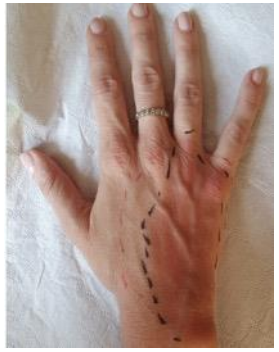
N13 SEP may be sensitive to changes in dorsal horn excitability and might be used as a biomarker of central sensitization in human studies.

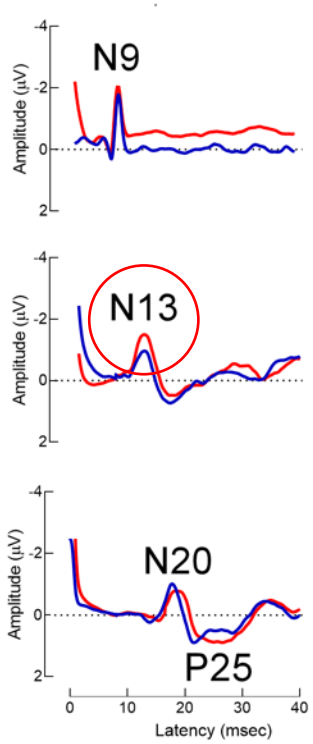
Control hand (without capsaicin)

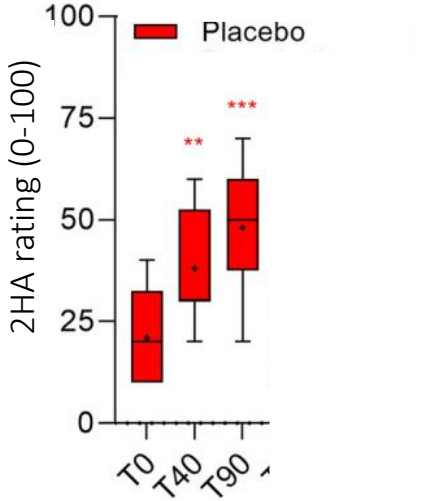


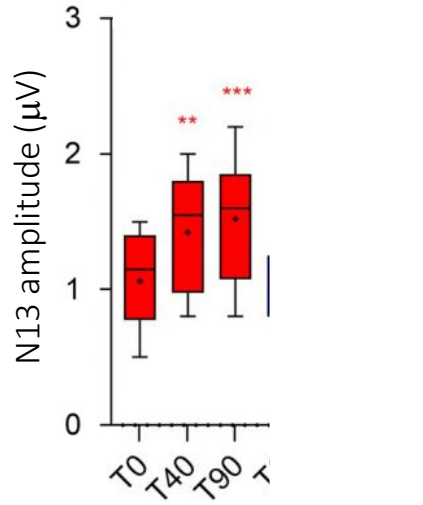


Sensitized hand (topical capsaicin)



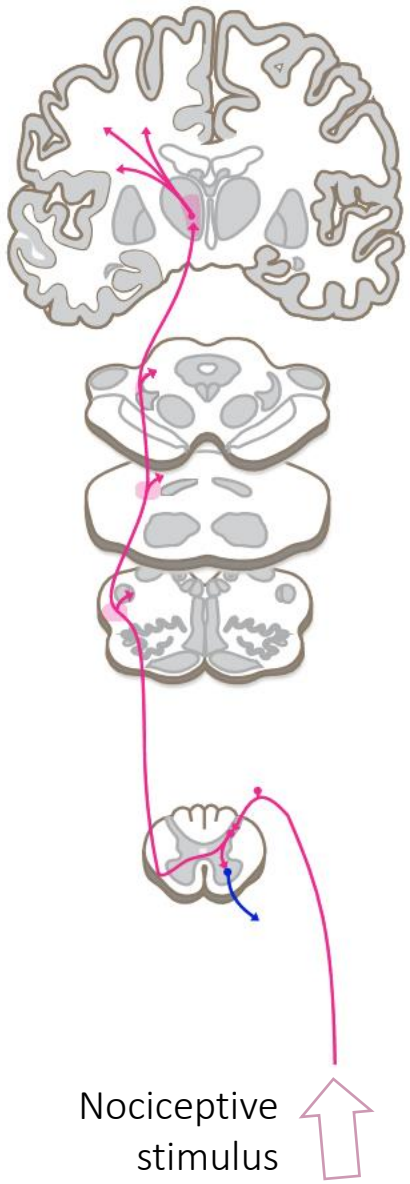






Di Lionardo et al.
(Scientific Reports, 2021)

Brain biomarkers of nociceptive processing



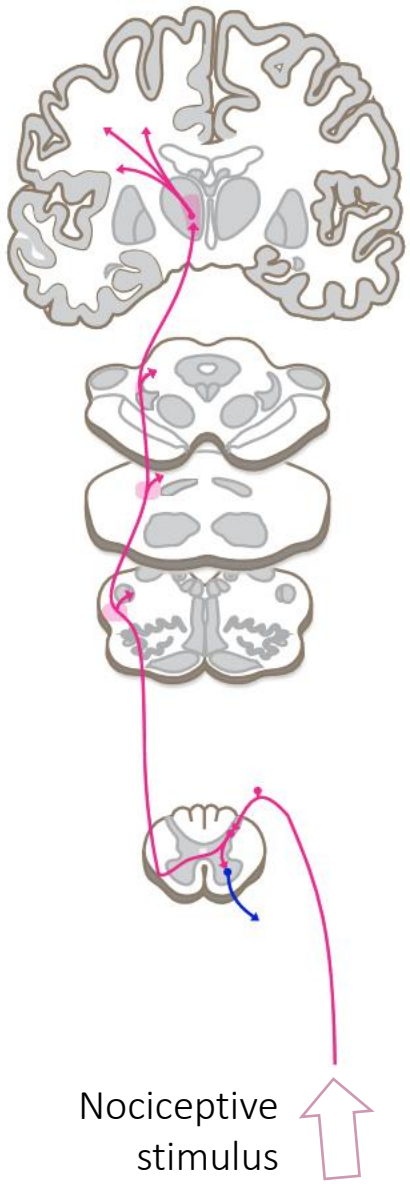
Spontaneous brain activity

- EEG
- Functional MRI
- …

Stimulus-evoked brain activity

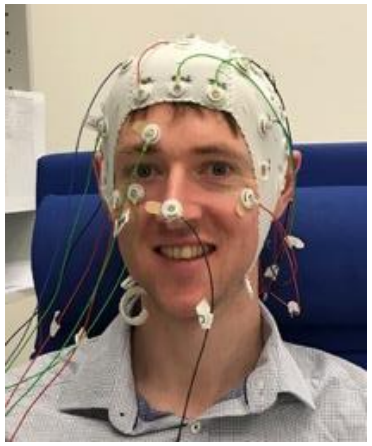
- Event-related brain potentials
- Stimulus-evoked fMRI-BOLD responses
- …

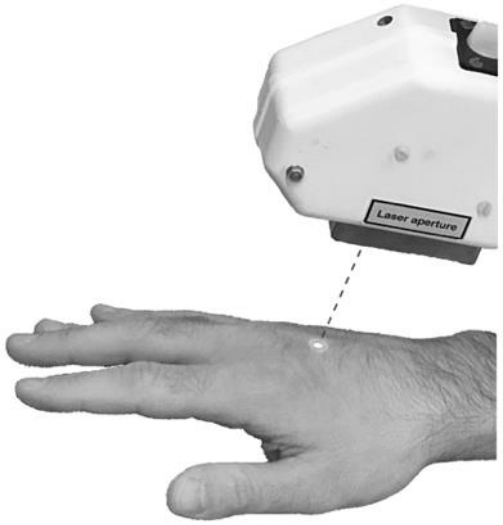
Nociceptive heat-evoked brain potentials

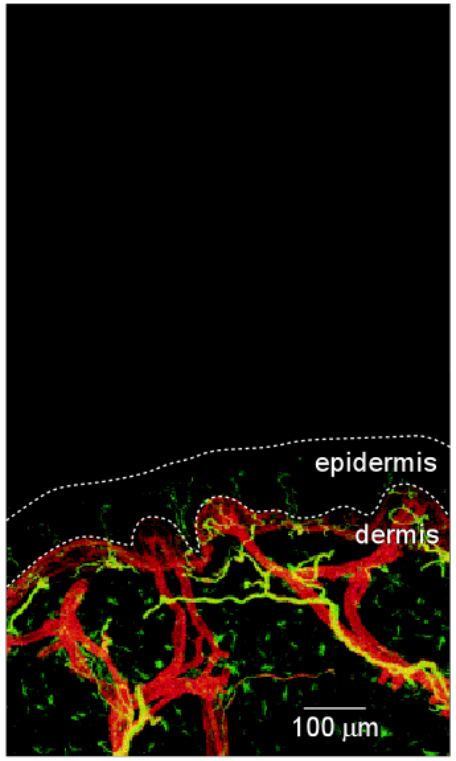


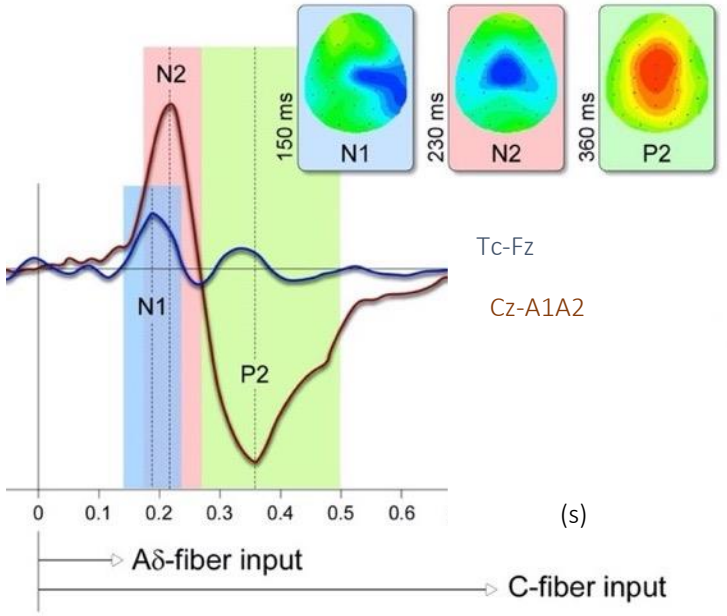
Brain biomarkers

Laser-evoked brain potentials

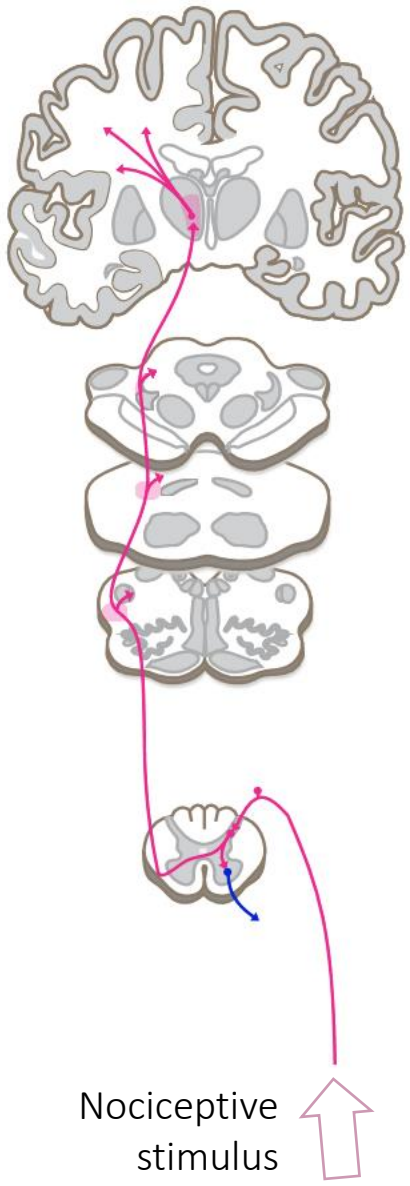






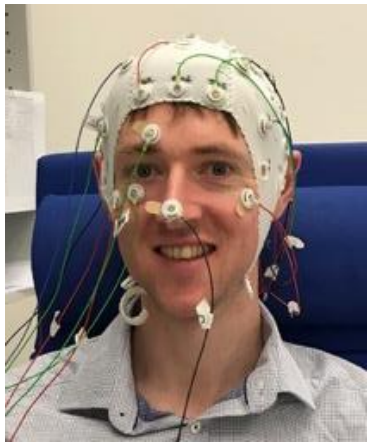


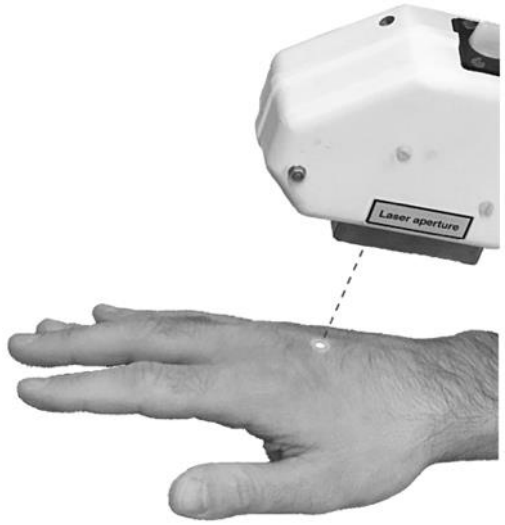
Nociceptive heat-evoked brain potentials



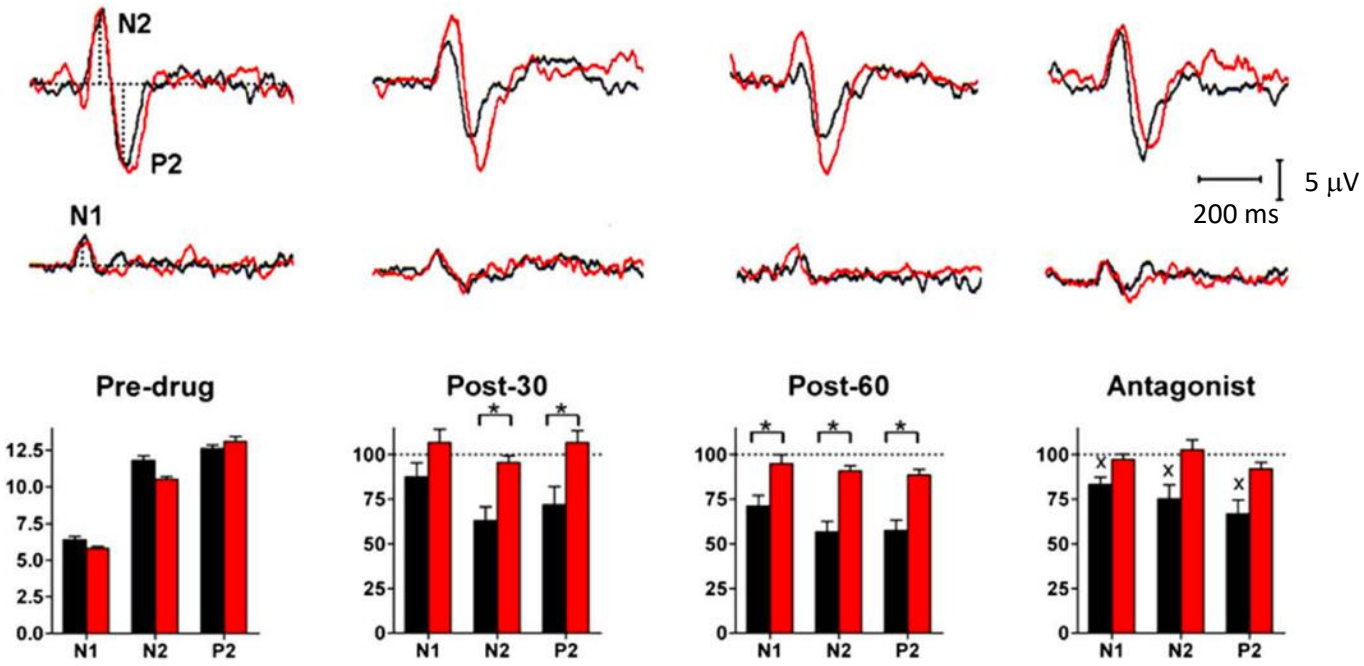
Brain biomarkers

Laser-evoked brain potentials



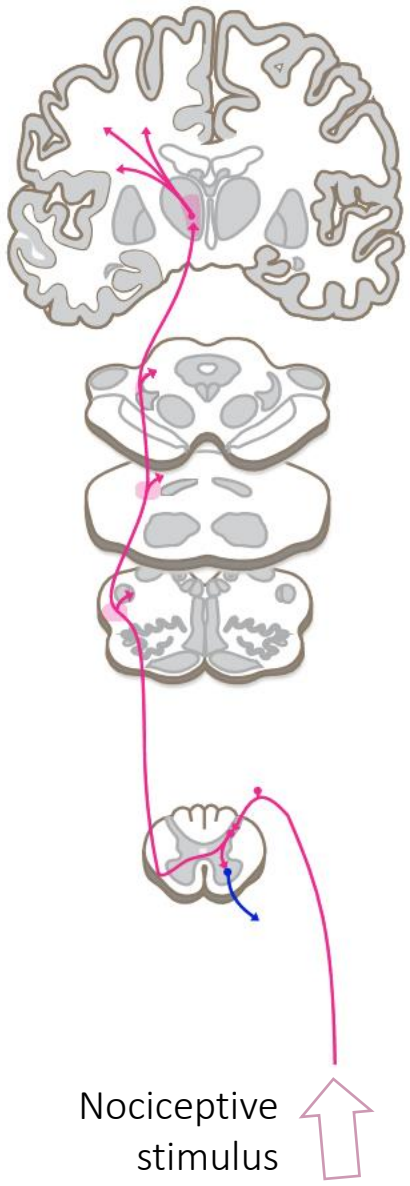


Truini et al. (Eur J Pain. 2010)



Single dose of tramadol (IM, 100 mg) vs. placebo in healthy volunteers

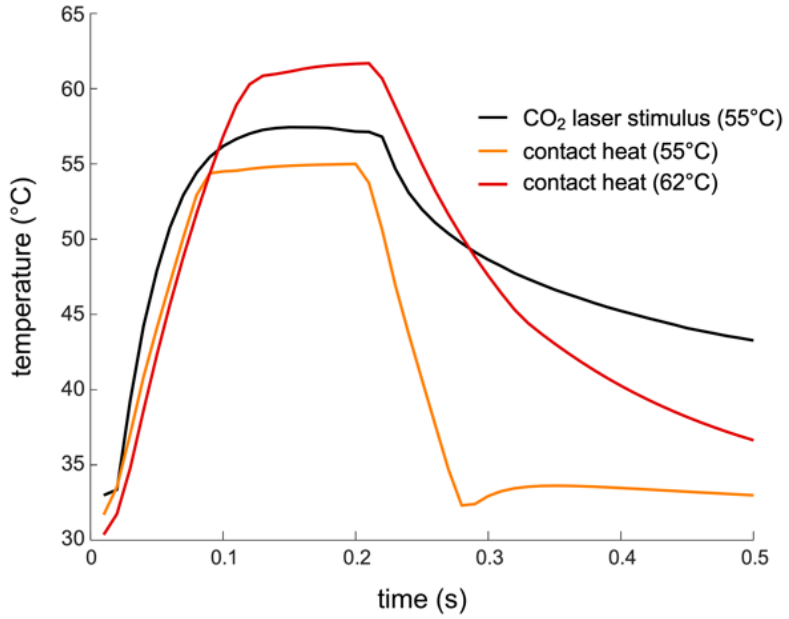
Nociceptive heat-evoked brain potentials

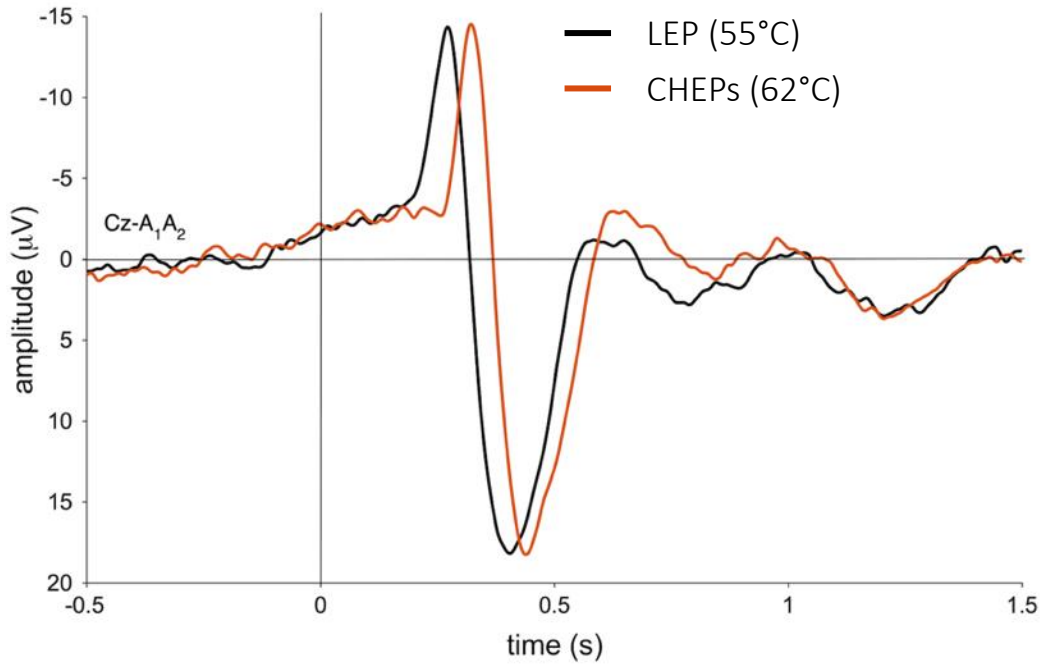


Brain biomarkers

Contact heat-evoked potentials

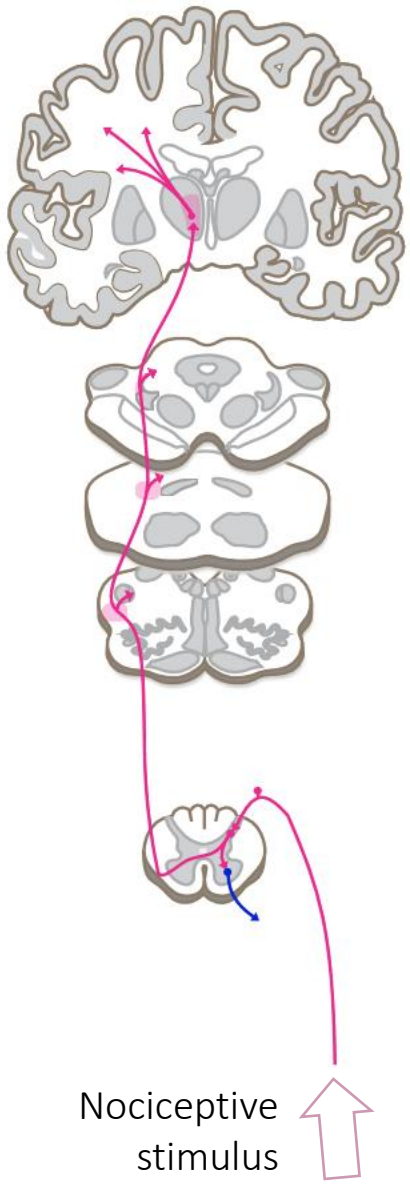
Micro-Peltier elements able to achieve heating ramps up to 300°C/s





Lejeune et al. (Clin Neurophysiol, in press)
see also De Schoenmacker et al. (Sci Rep, 2021; Sci Rep, 2022)

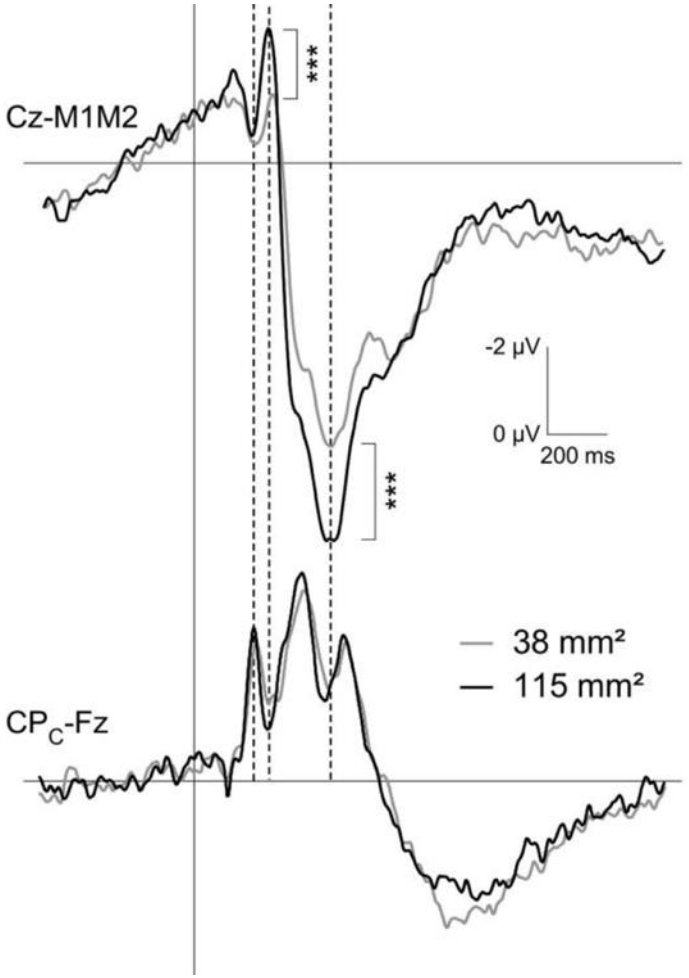
Cold-evoked brain potentials

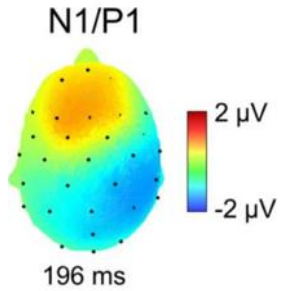


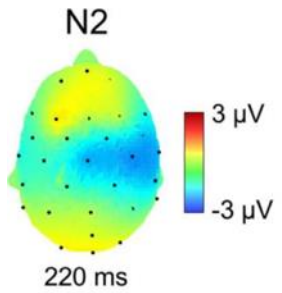
Brain biomarkers

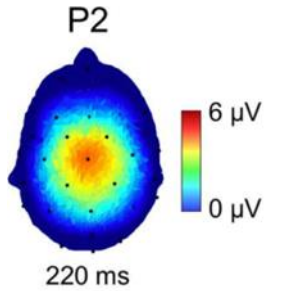
Contact cold-evoked potentials

Micro-Peltier elements able to achieve cooling ramps up to 300°C/s



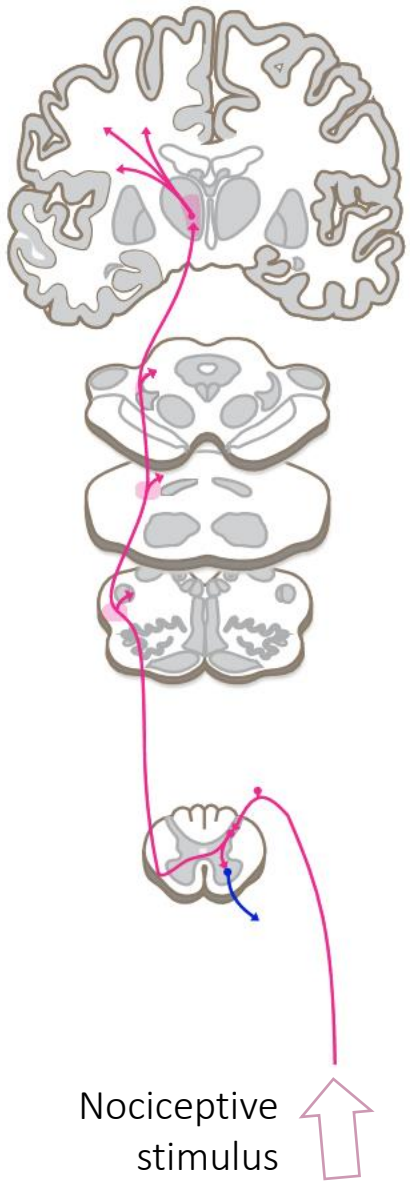




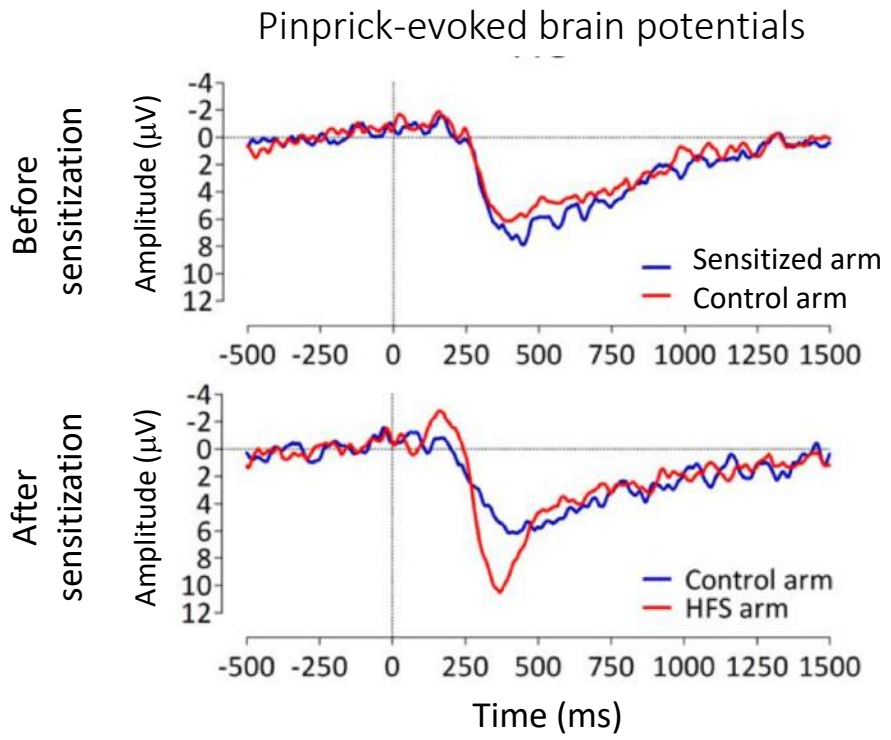


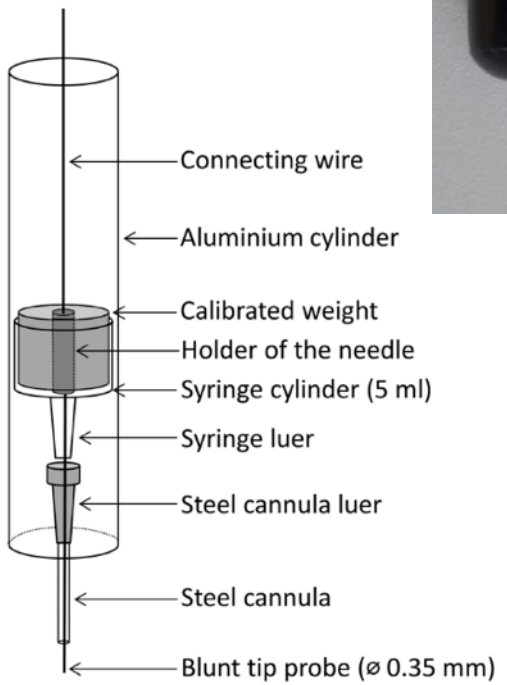
De Keyser et al. (Clin Neurophysiol, 2018)
see also Courtin & Mouraux (J Pain, 2022)

Mechanical pinprick-evoked brain potentials



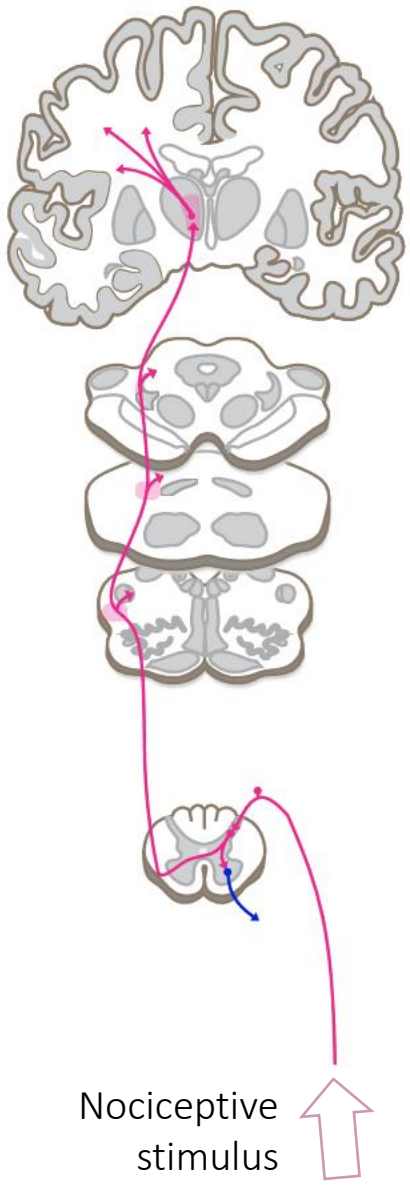
Brain biomarkers



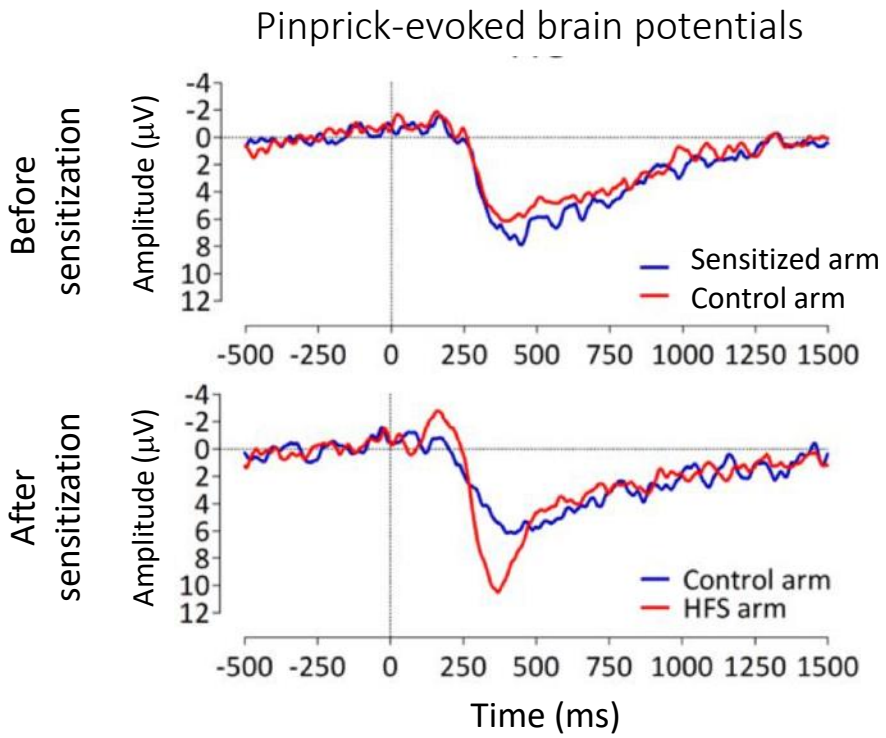


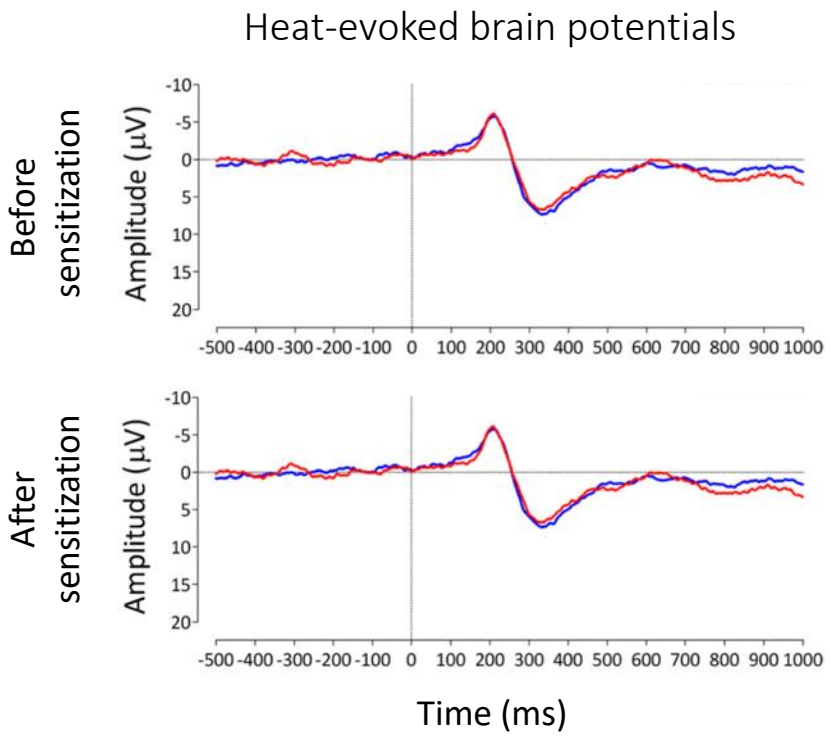
van den Broeke et al. (J Neurophysiol 2014)
Van den Broeke et al. (Clin Neurophysiol 2020)

Mechanical pinprick-evoked brain potentials



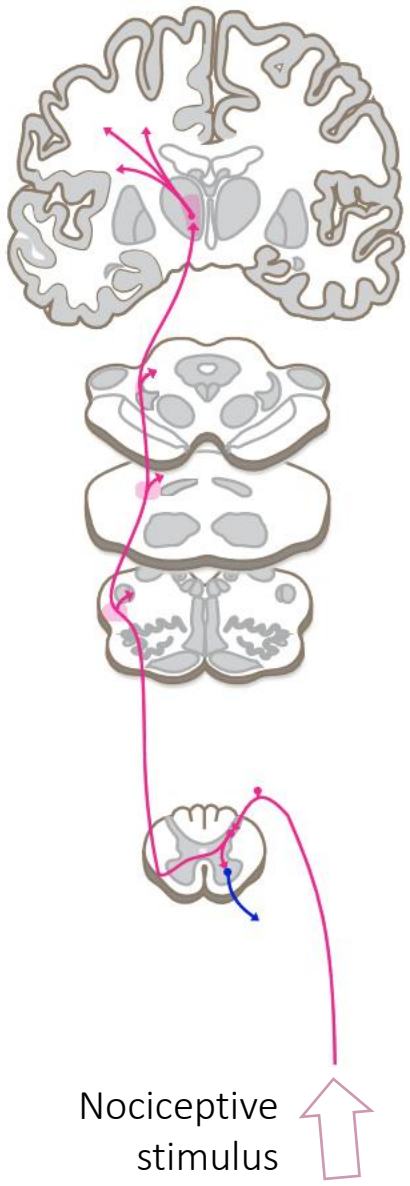
Brain biomarkers

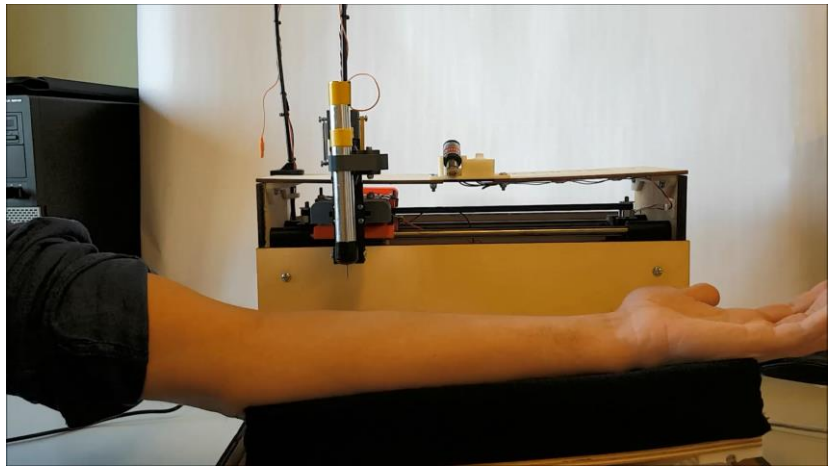




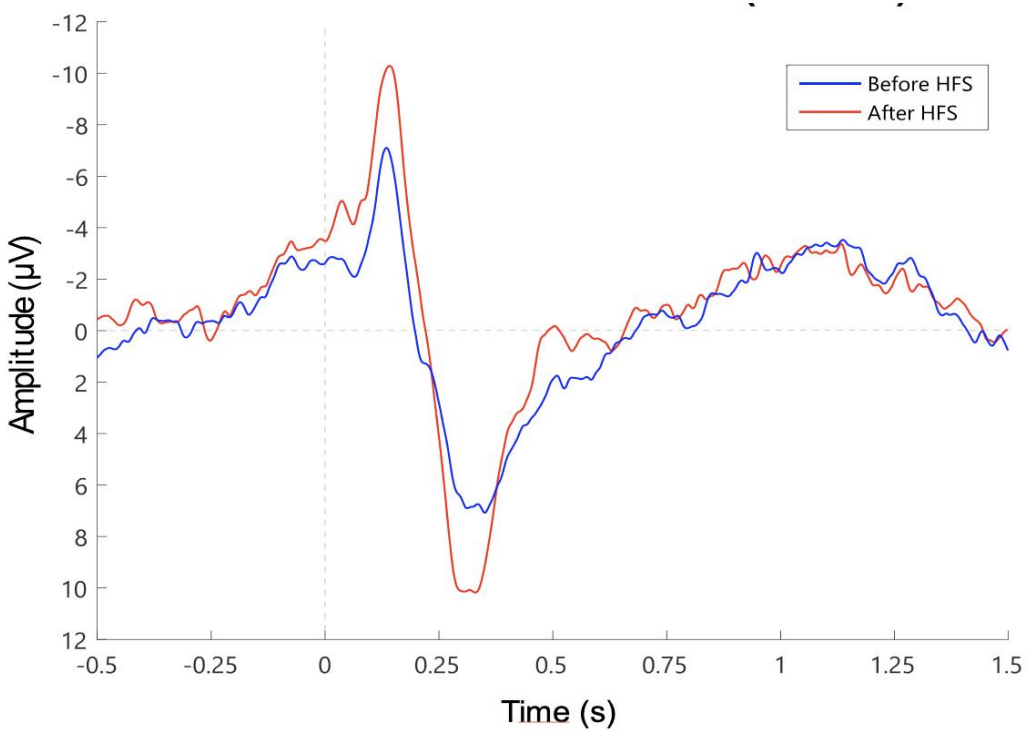
van den Broeke et al. (J Neurophysiol 2014)
Van den Broeke et al. (Clin Neurophysiol 2020)

Mechanical pinprick-evoked brain potentials





Gousset et al. (in preparation)



Human biomarkers of nociceptive processing and its modulation

Understanding nociception and pain

- Explore nociceptive processing in humans and its modulation

Tools for the pharmacological development of novel pain treatments

- Pharmacodynamic biomarkers to evaluate target engagement in early-stage clinical trials?
- (Surrogate) biomarkers of clinical efficacy?

Clinical diagnosis and personalized medicine

- Neuropathic pain : *“pain caused by a lesion or disease of the somatosensory nervous system”*
- Mechanism-based diagnosis, patient selection and stratification, predicting response to treatment?

Preventing chronic pain

- Early diagnosis for potential preventive treatments
- Biomarkers of the susceptibility to develop chronic pain?

Human biomarkers of nociceptive processing and its modulation

Understanding nociception and pain

- Explore nociceptive processing in humans and its modulation

Tools for the pharmacological development of novel pain treatments

- Pharmacodynamic biomarkers to evaluate target engagement in early-stage clinical trials?
- (Surrogate) biomarkers of clinical efficacy?

Clinical diagnosis and personalized medicine

- Neuropathic pain : *“pain caused by a lesion or disease of the somatosensory nervous system”*
- Mechanism-based diagnosis, patient selection and stratification, predicting response to treatment?

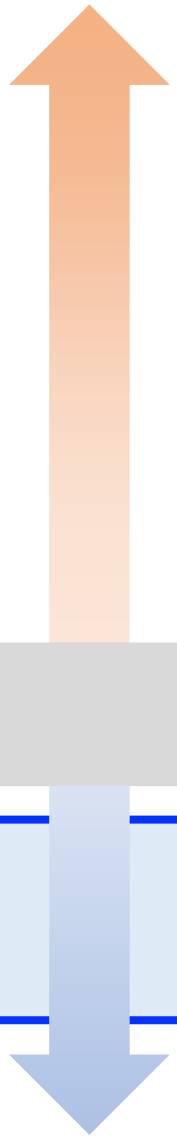
Preventing chronic pain

- Early diagnosis for potential preventive treatments
- Biomarkers of the susceptibility to develop chronic pain?

Clinical diagnosis of neuropathic pain

IASP definition of neuropathic pain (2019)

"(…) pain caused by a lesion or disease of the somatosensory nervous system"



Positive symptoms

Ongoing or intermittent spontaneous pain
Intermittent electric-shock-like pain paroxysms
Touch-evoked or cold-evoked allodynia
Mechanical and/or thermal hyperalgesia
Aftersensations
Hyperpathia
Referred pain to denervated area

Neuropathic pain

Loss of function

Negative symptoms

Sensory loss

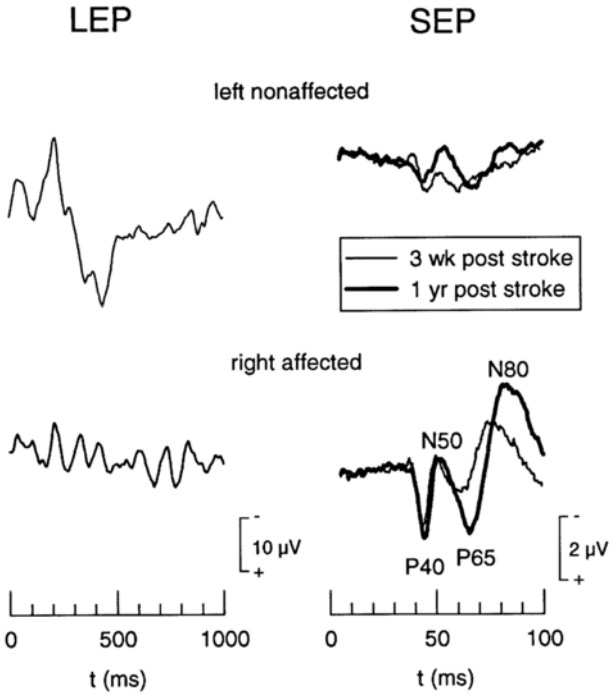
diagnosis of neuropathic pain

NeuPSIG guidelines on neuropathic pain assessment (Pain, 2011)

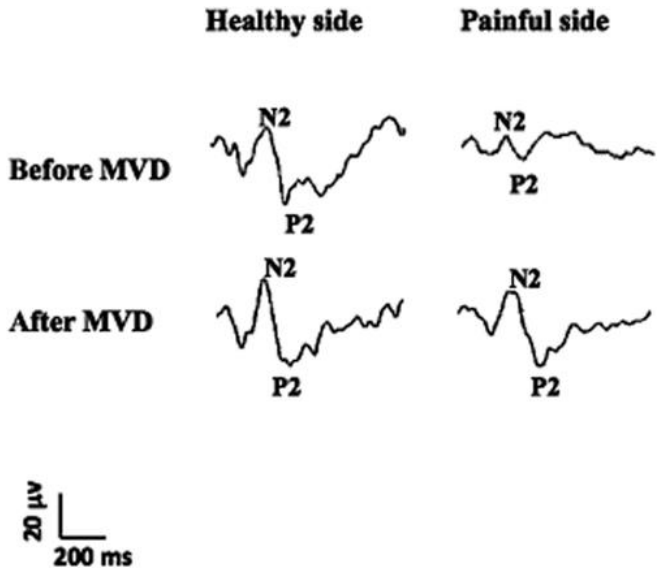
"Laser-evoked potentials are established as useful for assessing function of the A-delta fiber subcortical pathways in patients with neuropathic pain."

Cruccu et al. (Eur J Neurol 2010)

Lorenz et al.
(Neuroreport 1998)
Central post-stroke pain following lateral brainstem infarction



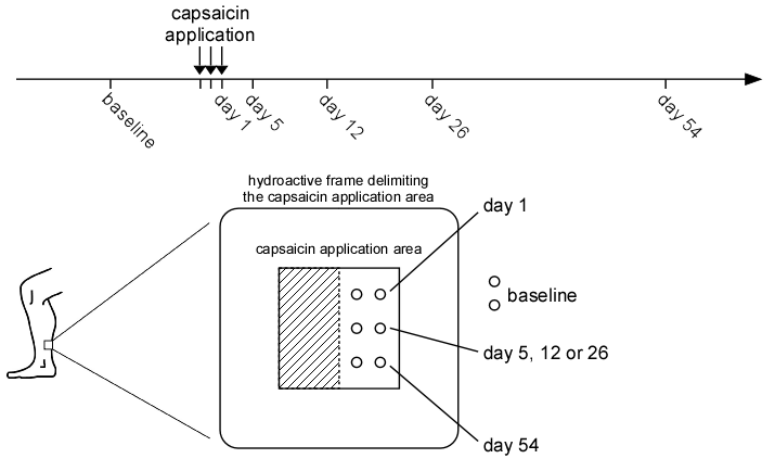
Squintani et al.
(EJP 2014)
Trigeminal contact neuralgia before and after microvascular decompression (MVD)

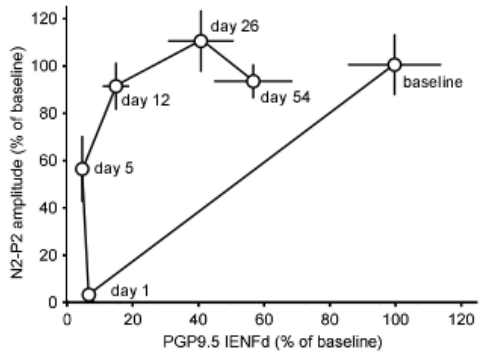


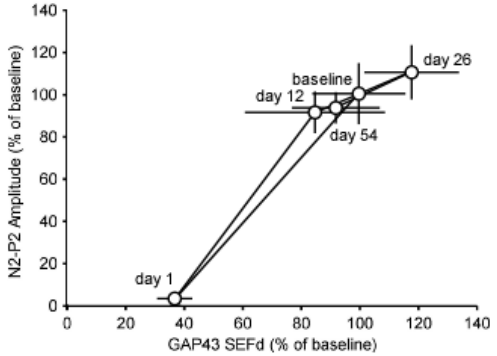
Correlation between LEP magnitude and IENF density

Capsaicin-induced IENF ablation

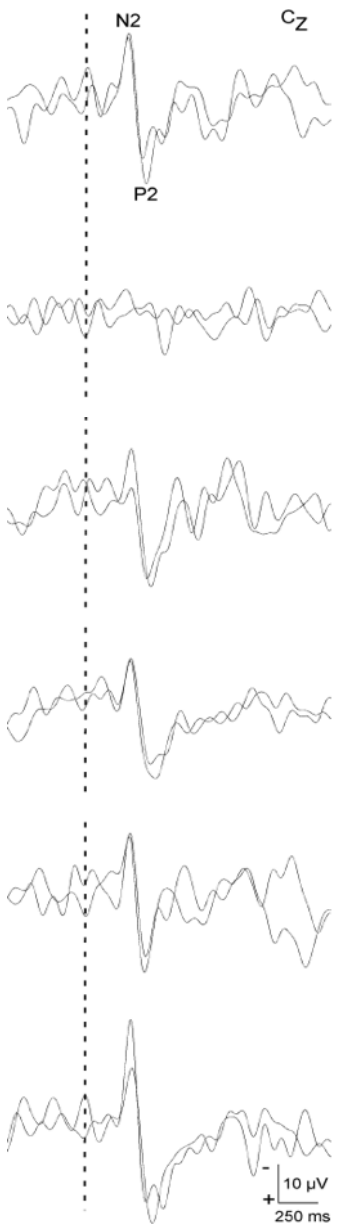
Correlation between LEP magnitude and IENF density



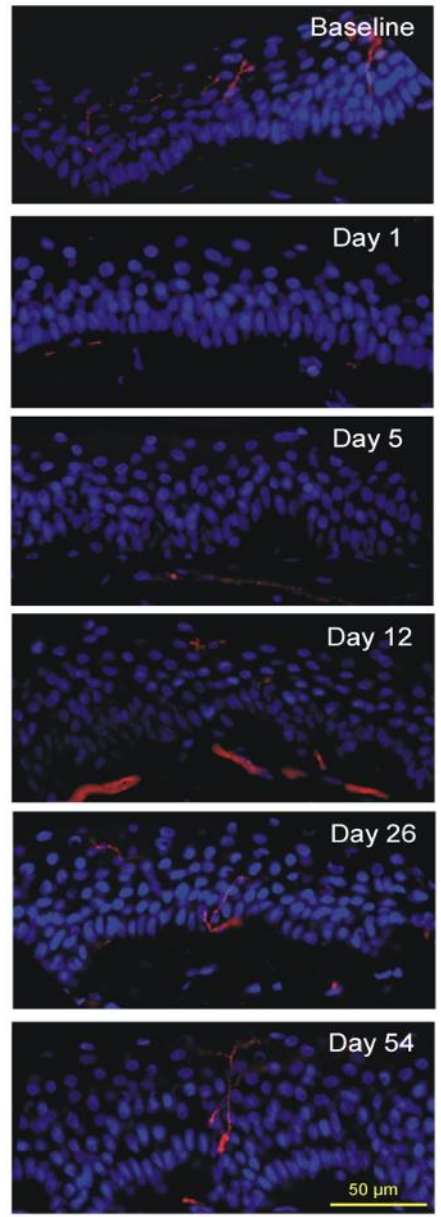




Aδ-LEP



IENFd



Ragé et al. (Clin Neurophysiol 2010)

Human biomarkers of nociceptive processing and its modulation

Understanding nociception and pain

- Explore nociceptive processing in humans and its modulation

Tools for the pharmacological development of novel pain treatments

- Pharmacodynamic biomarkers to evaluate target engagement in early-stage clinical trials?
- (Surrogate) biomarkers of clinical efficacy?

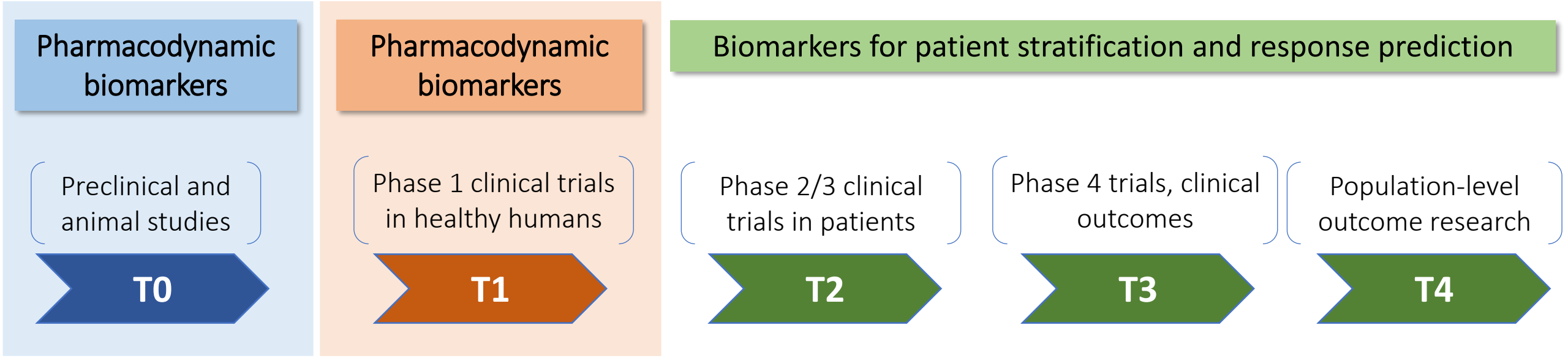
Clinical diagnosis and personalized medicine

- Neuropathic pain : *“pain caused by a lesion or disease of the somatosensory nervous system”*
- Mechanism-based diagnosis, patient selection and stratification, predicting response to treatment?

Preventing chronic pain

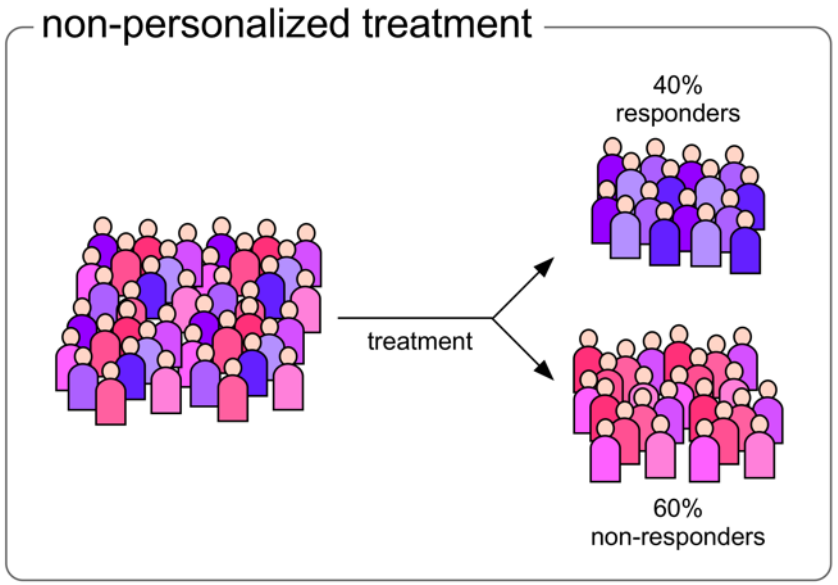
- Biomarkers of the susceptibility to develop chronic pain?

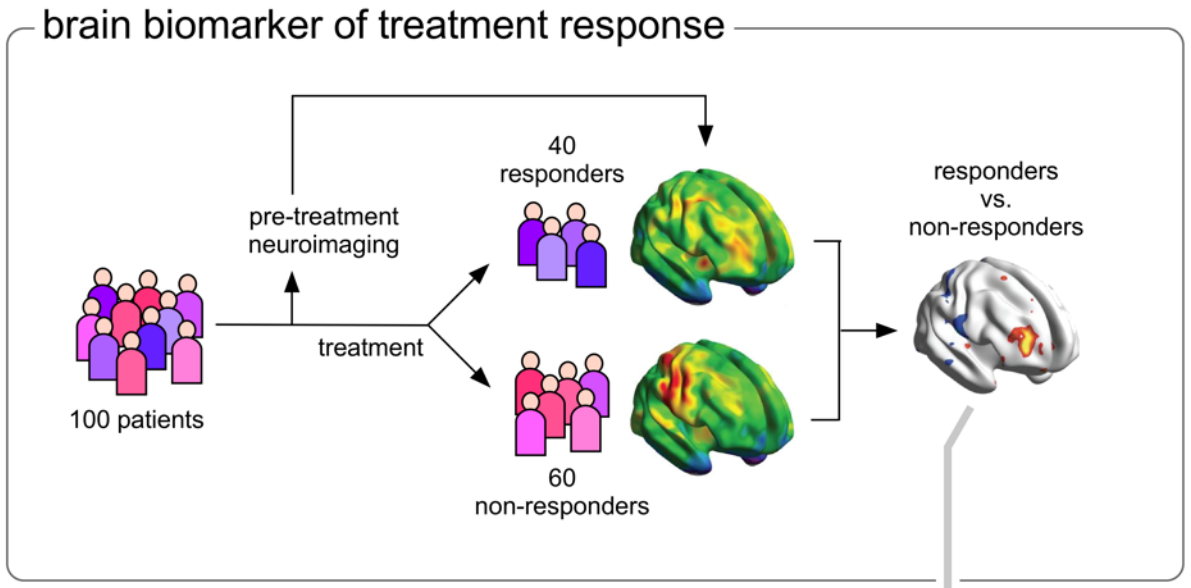
Biomarkers for patient selection and response prediction

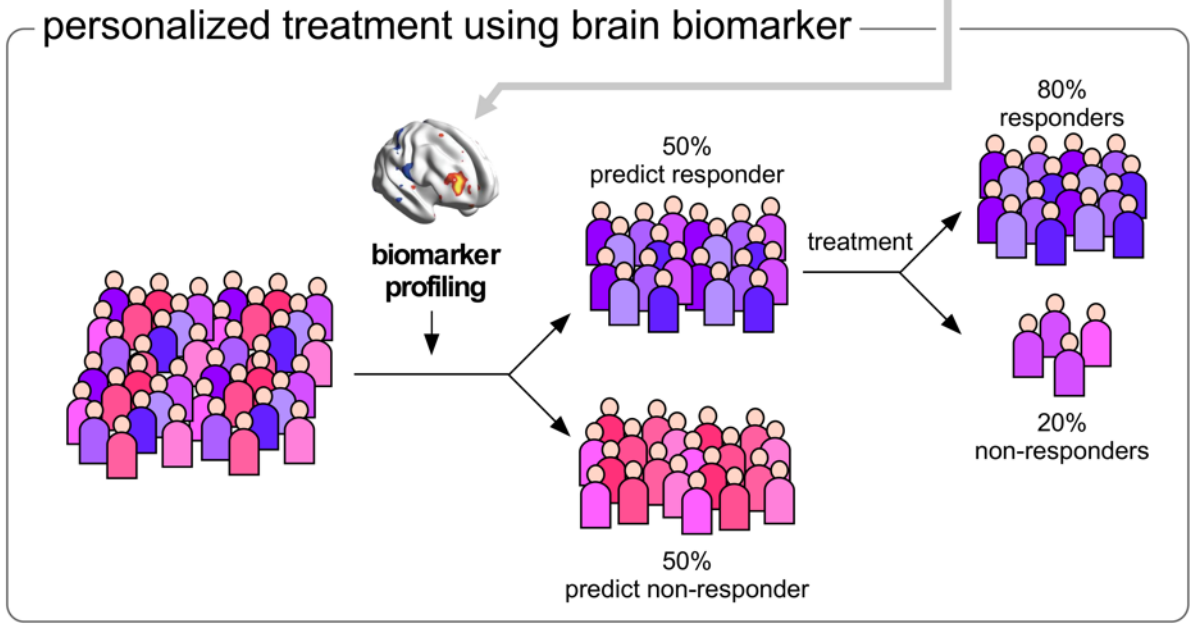


Biomarkers for patient selection and response prediction

Mouraux & Iannetti (Brain, 2018)







Predicting response to treatment : ”irritable nociceptor” phenotype

97 patients with peripheral neuropathic pain, treated with oxcarbazepine vs placebo
(polyneuropathy, surgical/ traumatic nerve injury, postherpetic neuralgia)
QST : 31 patients with “irritable nociceptor phenotype” vs 52 patients with “non-irritable nociceptor phenotype”

“Irritable nociceptor” phenotype

- dynamic mechanical allodynia

or

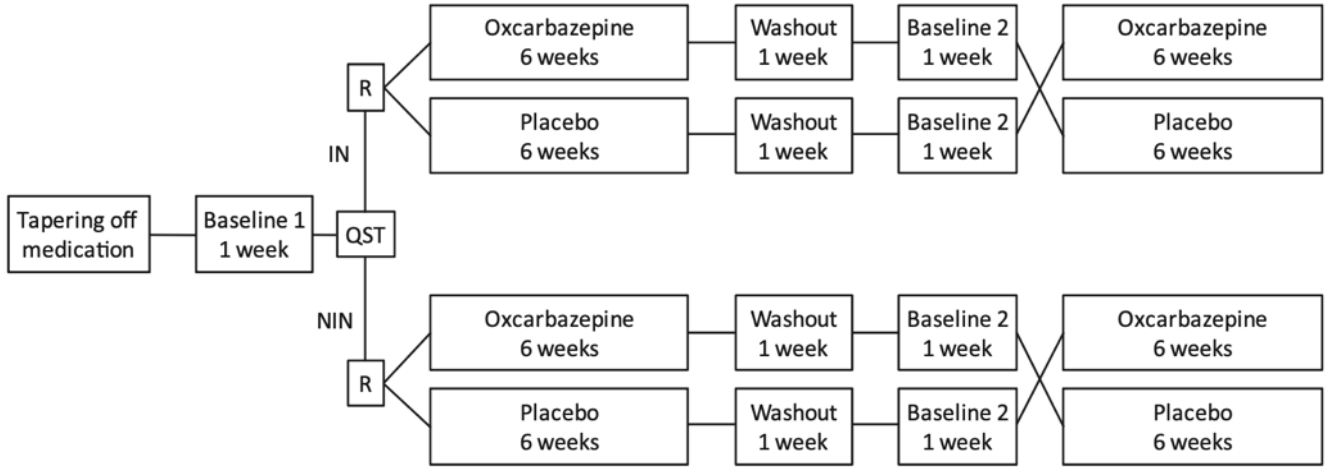
- reduced mechanical or pressure threshold

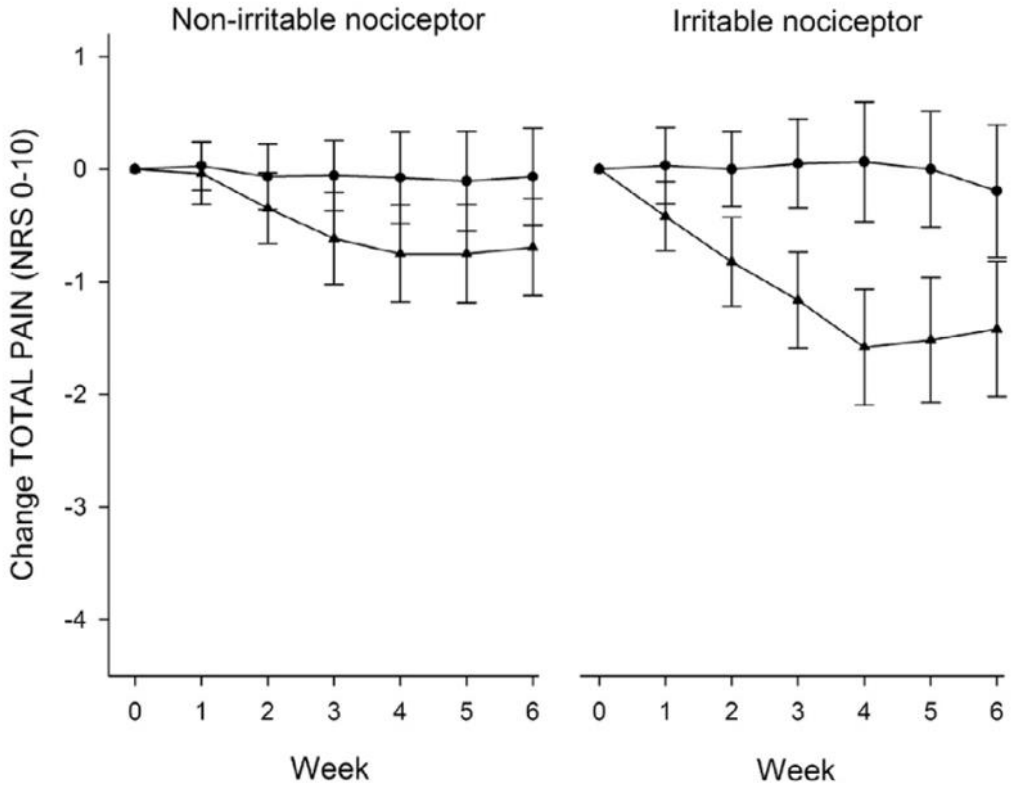
or

- increased mechanical pain sensitivity

or

- reduced cold or heat pain threshold





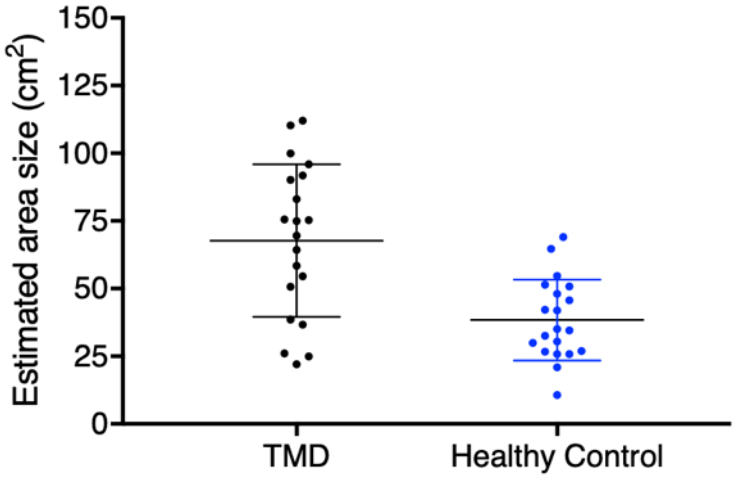
placebo (●) and oxcarbazepine (▲)

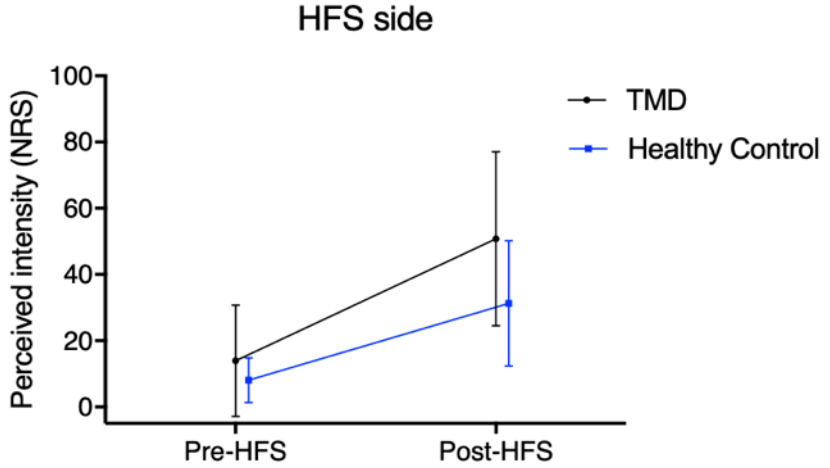
Mechanism-based diagnosis : central sensitization

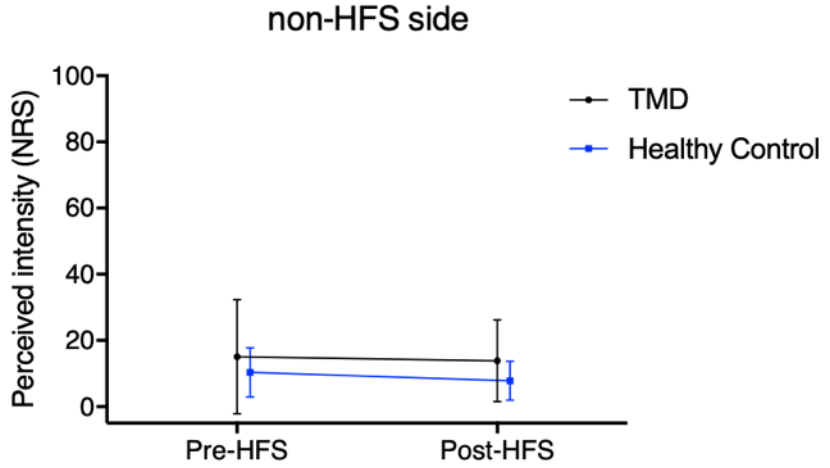
HFS to evaluate the susceptibility to develop central sensitization

Patients with painful temporo-mandibular disorder (TMD)

Cayrol et al. (Pain 2022)







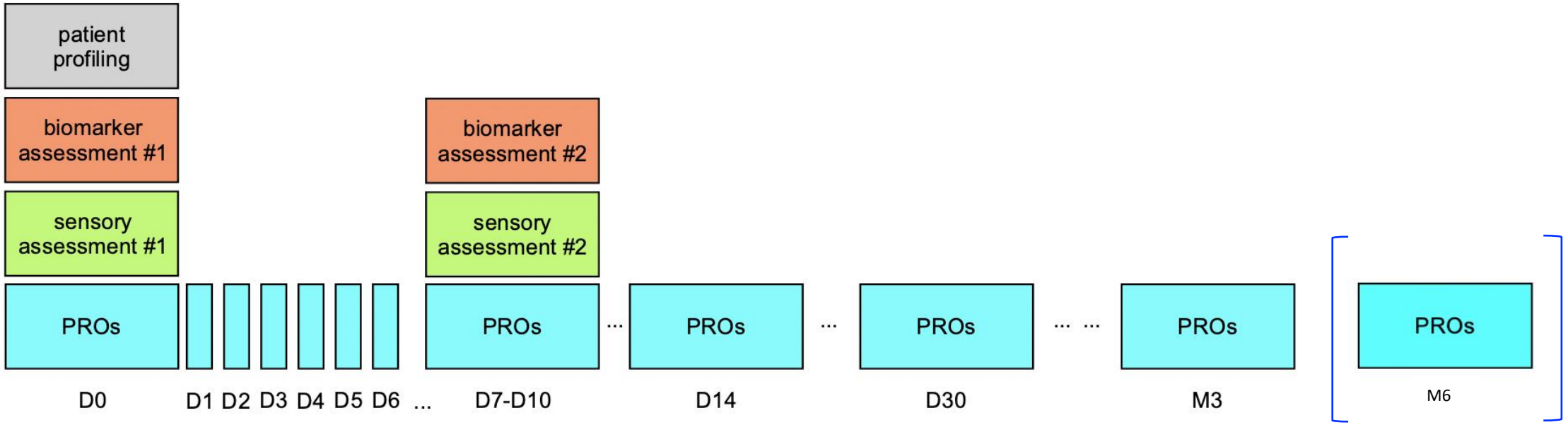
	TMD (n=20)		Healthy controls (n=20)		
	n	%	n	%	*p*
Cotton allodynia	9	45	3	15	.038
Brush allodynia	5	25	2	10	.407
Q-tip allodynia	8	40	3	15	.077

n, number of occurrences of allodynia. %, percentage of individuals within a group.

Predicting response to treatment : QSPainrelief-patientCNS study

H2020 QSPainRelief

Drug effects on CNS biomarkers to be compared with clinical therapeutic effects in patients initiating pharmacological treatment for persistent post-surgical pain.



Human biomarkers of nociceptive processing and its modulation

Understanding nociception and pain

- Explore nociceptive processing in humans and its modulation

Tools for the pharmacological development of novel pain treatments

- Pharmacodynamic biomarkers to evaluate target engagement in early-stage clinical trials?
- (Surrogate) biomarkers of clinical efficacy?

Clinical diagnosis and personalized medicine

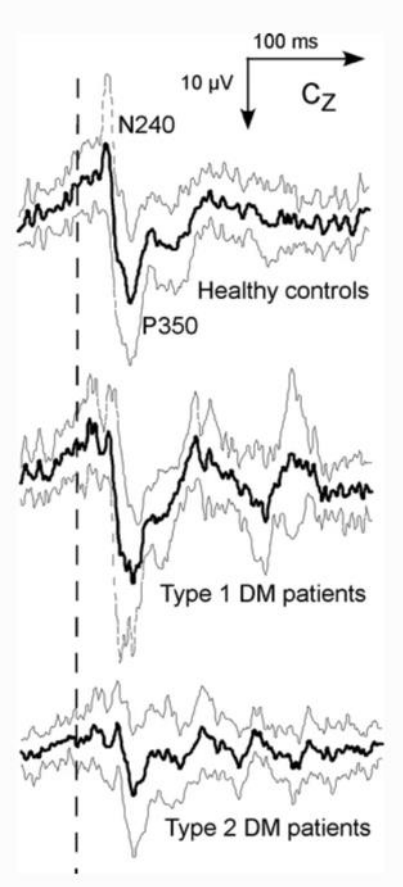
- Neuropathic pain : *“pain caused by a lesion or disease of the somatosensory nervous system”*
- Mechanism-based diagnosis, patient selection and stratification, predicting response to treatment?

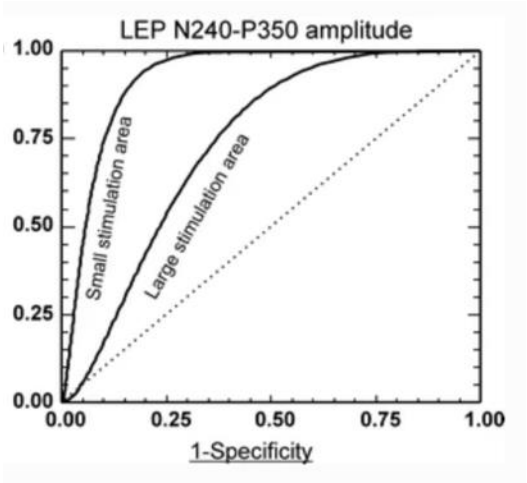
Preventing chronic pain

- Early diagnosis for potential preventive treatments
- Biomarkers of the susceptibility to develop chronic pain?

Preventing chronic pain : early diagnosis

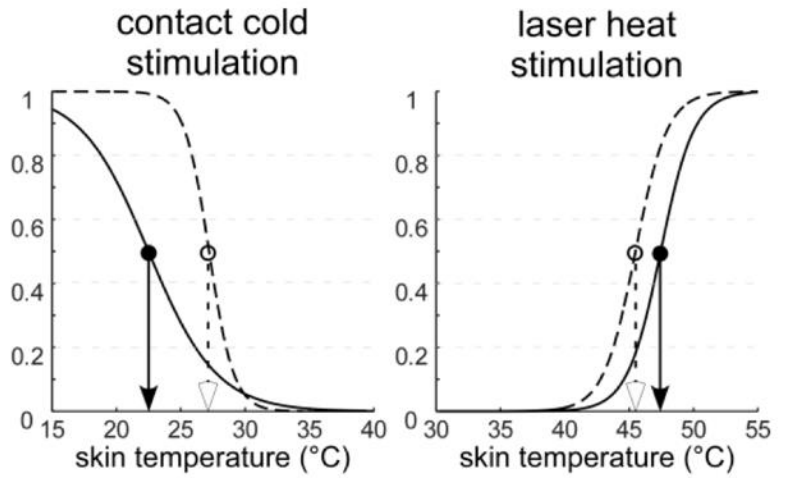
Biomarkers to identify patients at risk of developing small fiber neuropathy?

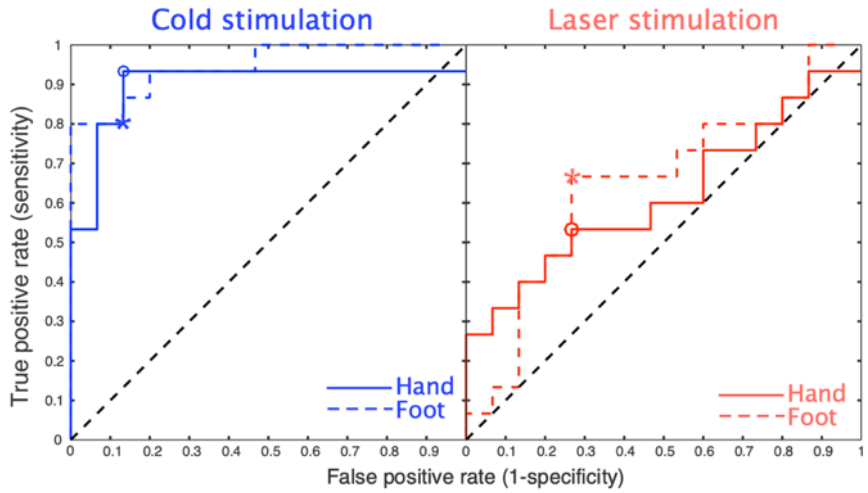




ROC analysis for "critical small-fiber loss" defined (log-IENF density ≤−2 z scores).

Ragé et al. (J Neurol 2011)



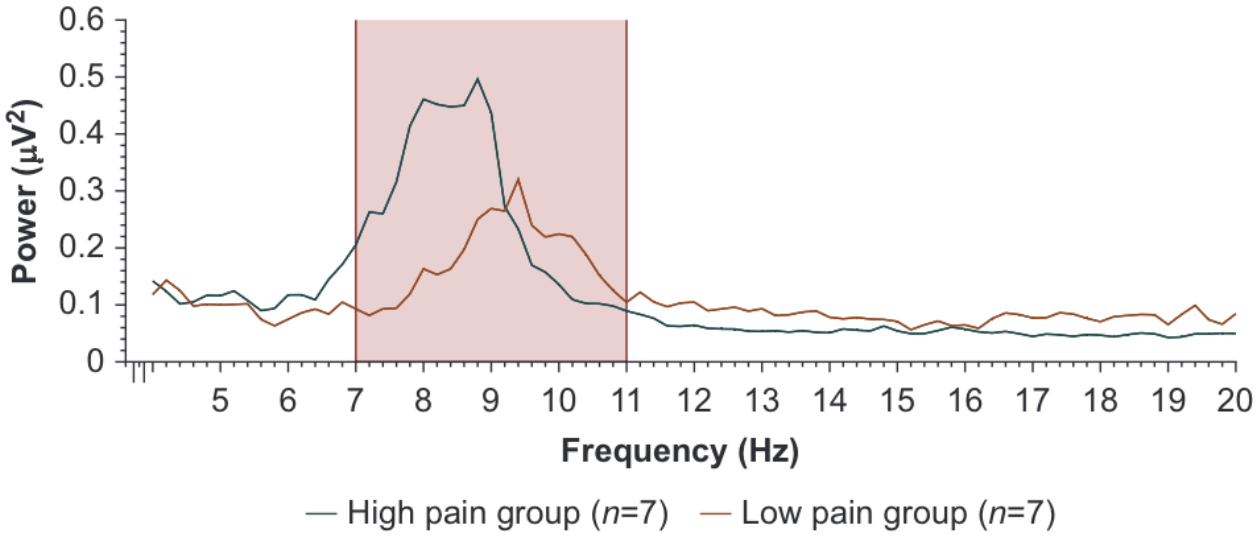


Courtin et al. (Neurosci Lett 2020)

Preventing chronic pain : susceptibility to develop persistent PSP

Millard et al. (Br J Anesth, 2022)

Pilot study in 16 patients undergoing surgery (thoracotomy) for lung cancer
Median split: « low » vs « high » pain based on post-operative pain ratings <72h after surgery



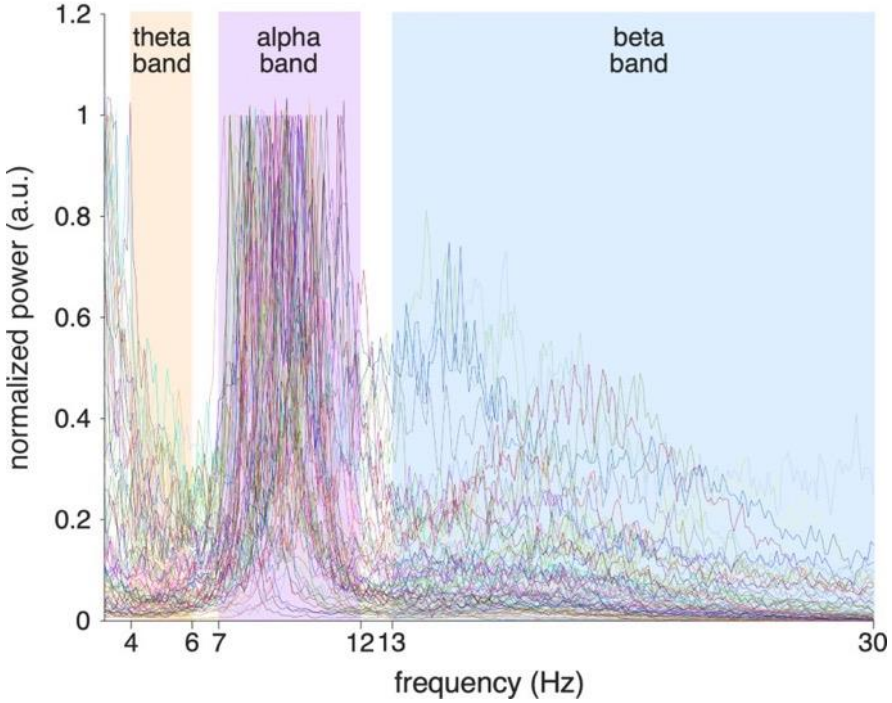
Peak alpha frequency (PAF) is reduced in high pain group compared to low pain group

Preventing chronic pain : susceptibility to develop persistent PSP

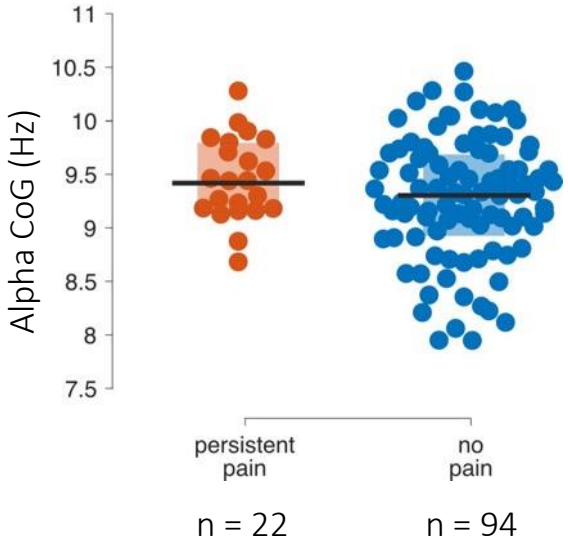
Lenoir et al. (ongoing study)

116 pain-free patients, aged 66.4 ±10.2 years (17 women)
Planned for median sternotomy

Resting-state EEG (eyes closed)
before surgery

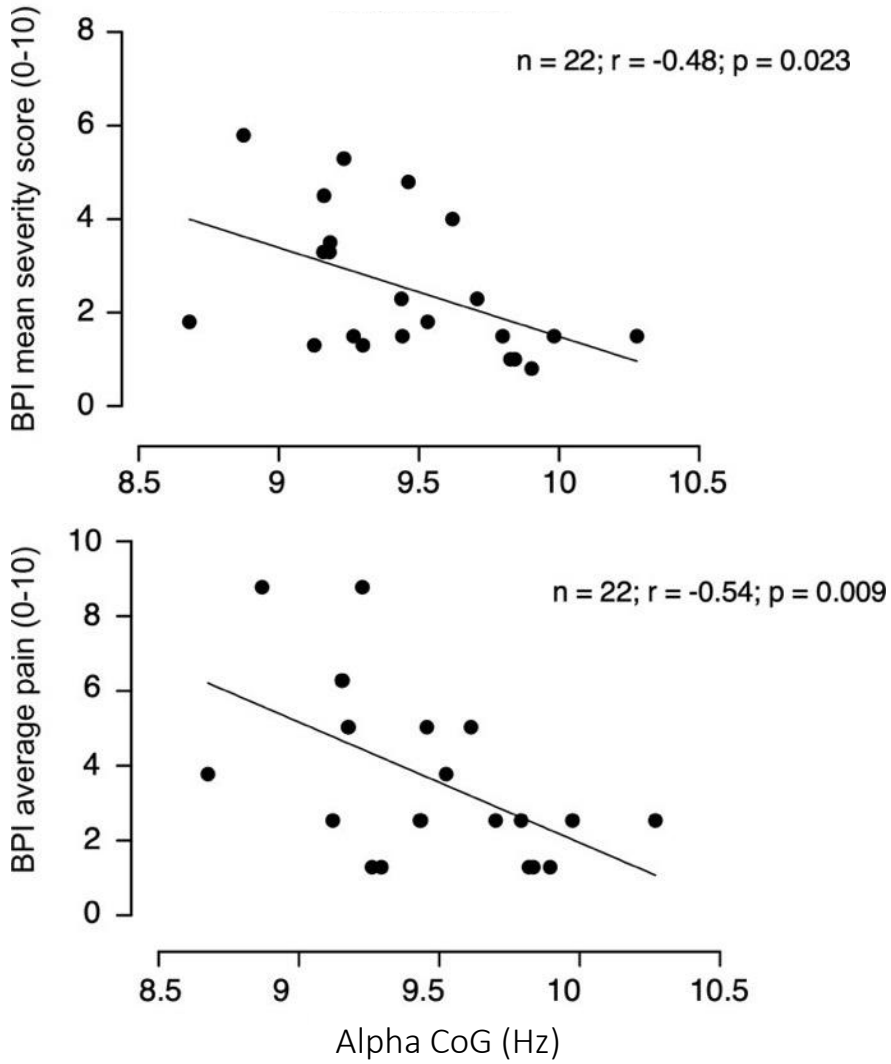


Peak alpha frequency
(PAF)



n = 22 n = 94

Patients with persistent PSP
(3 months)



Preventing chronic pain : susceptibility to develop persistent PSP

Martinez et al. (Pain, 2012)

Table 2
Factors predictive of neuropathic CPSP in univariate analysis. [a]

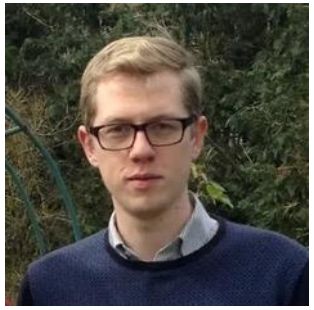
Characteristic	Patients **without** Neuropathic CPSP, *N* = 63 (76.8%)	Patients **with** Neuropathic CPSP, *N* = 19 (23.1%)	*P*
Area of secondary hyperalgesia 24h postoperative (cm^2)	**33.3 ± 44**	**88 ± 54**	**.001**

van den Broeke et al. (ongoing study)

Ongoing clinical study to evaluate whether pre-operative susceptibility to develop HFS-induced secondary mechanical hyperalgesia predicts the severity of post-surgical pain and/or the subsequent development of persistent post-surgical pain.

ClinicalTrials.gov Identifier: NCT04220697


Vladimir Aron


Arthur Courtin


Dellia Della Porta


Giulia Esposito


Lieve Filbrich


Solenn Gousset


Roberta Gualdani


Monika Halicka


Emmanuel Hermans


Julien Lambert


Louisien Lebrun


Valéry Legrain


Nicolas Lejeune


Cédric Lenoir


Chiara Leu


Giulia Liberati


Marc-Henri Louis


Gwenaëlle Mievis


André Mouraux


Dounia Mulders


Léon Plaghki


Arnaud Steyaert


Carlo Matej


Dominikla Sulcova


Emanuel van den Broeke


Amélie Van Caekenberghe

http://nocions.org