Il dolore nocicettivo neuropatico

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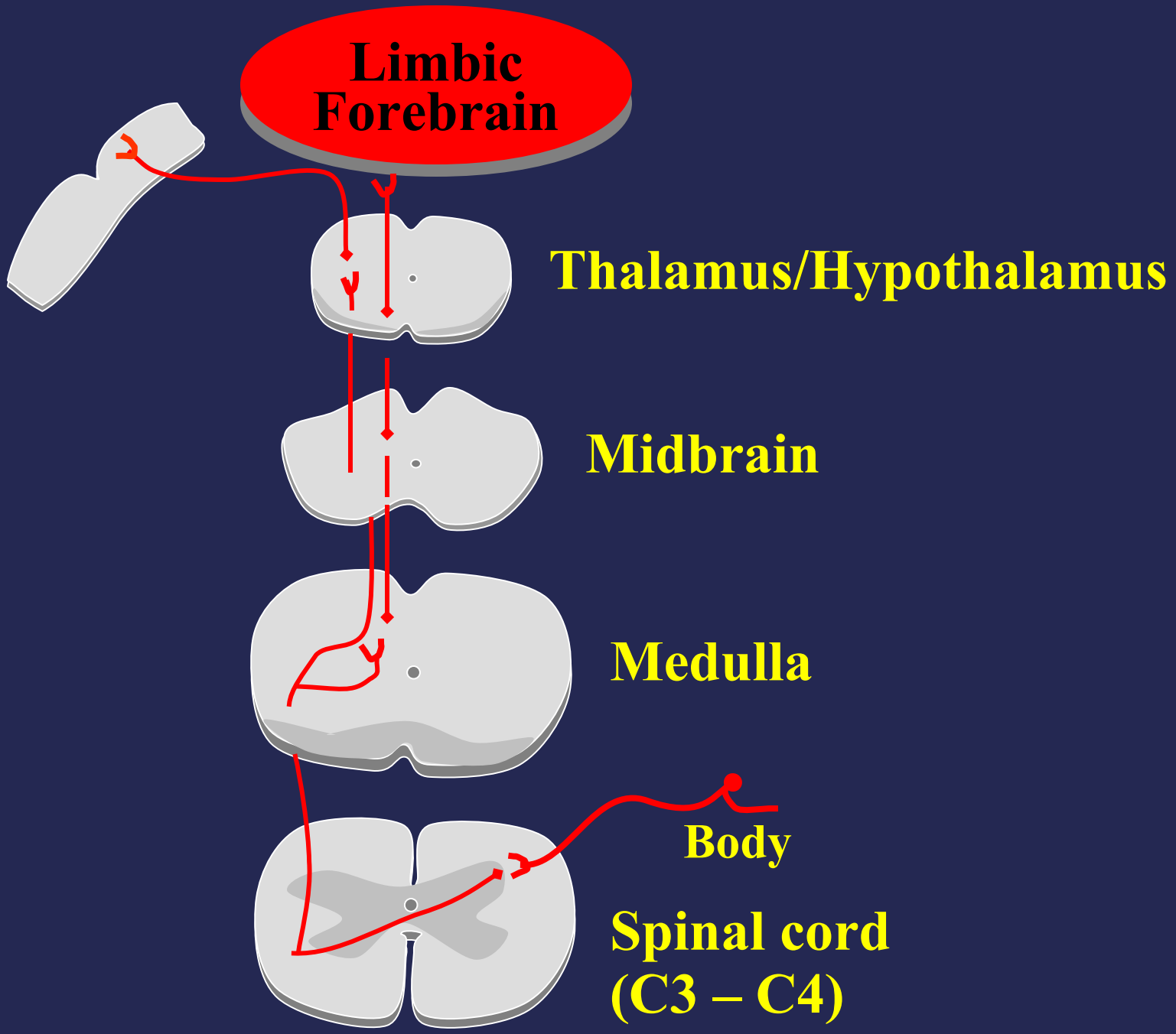
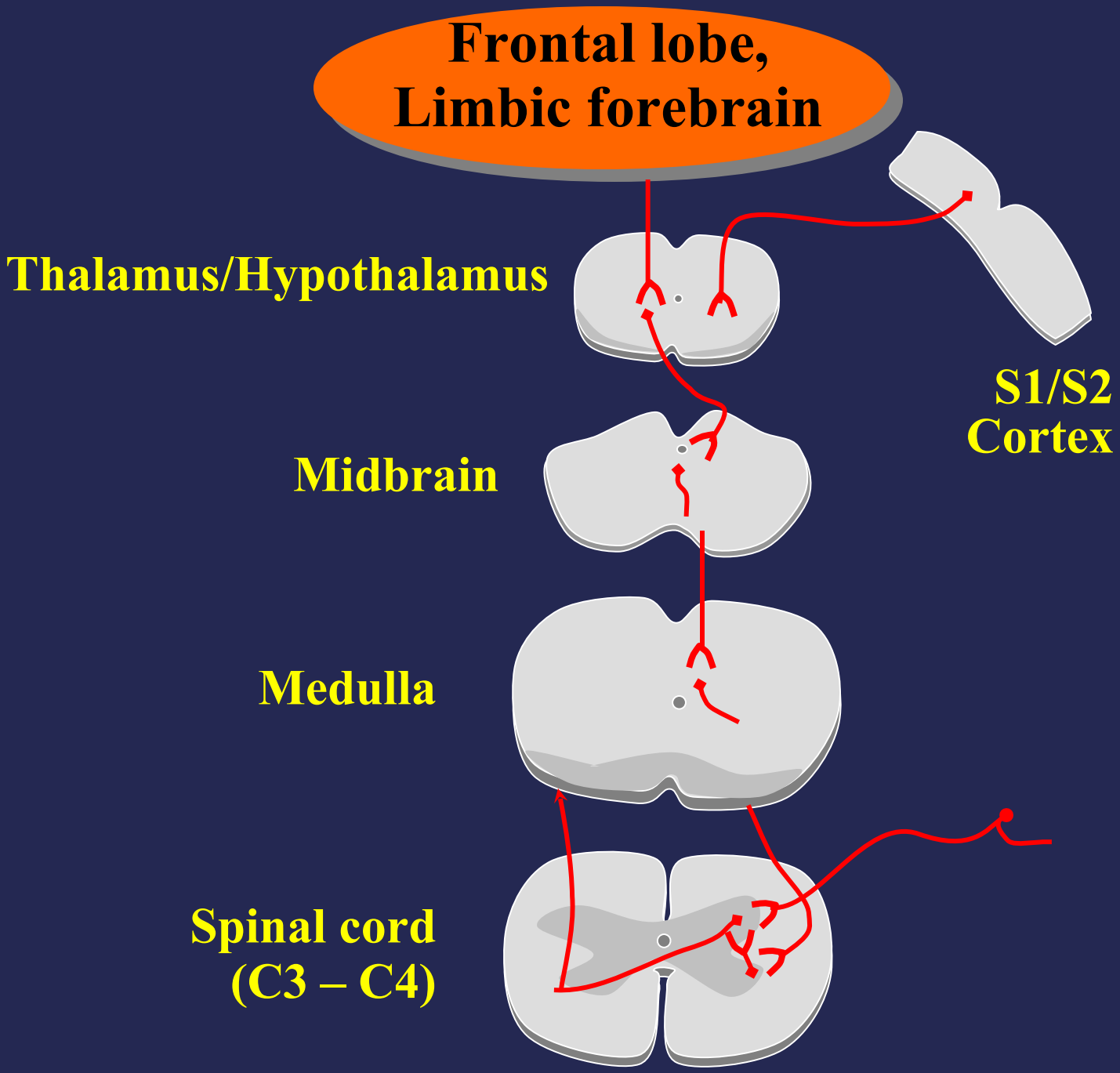
Il dolore è una esperienza sensoriale ed emozionale spiacevole

associata ad un danno tessutale

Nocicezione: fenomeno sensoriale

Dolore: interpretazione emozionale e cognitiva dello stimolo


Limbic Forebrain
Thalamus/Hypothalamus
Midbrain
Medulla
Body
Spinal cord (C3 – C4)


Frontal lobe,
Limbic forebrain
Thalamus/Hypothalamus
S1/S2
Cortex
Midbrain
Medulla
Spinal cord
(C3 – C4)

CLASSIFICATION

Pain syndromes have been classified as:

nociceptive

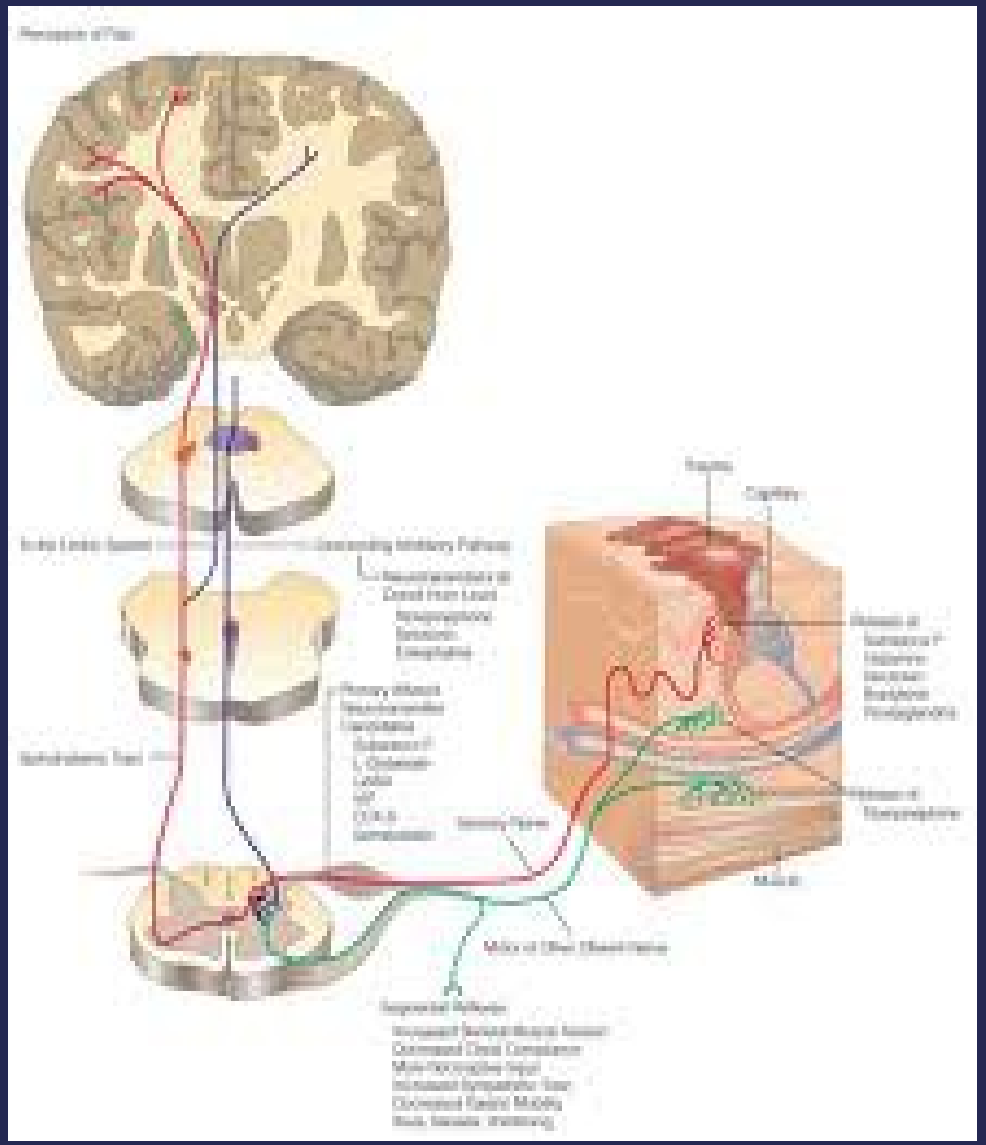
neuropathic

psycogenic pain

Idiopathic

Mixed pain

DOLORE NOCICETTIVO

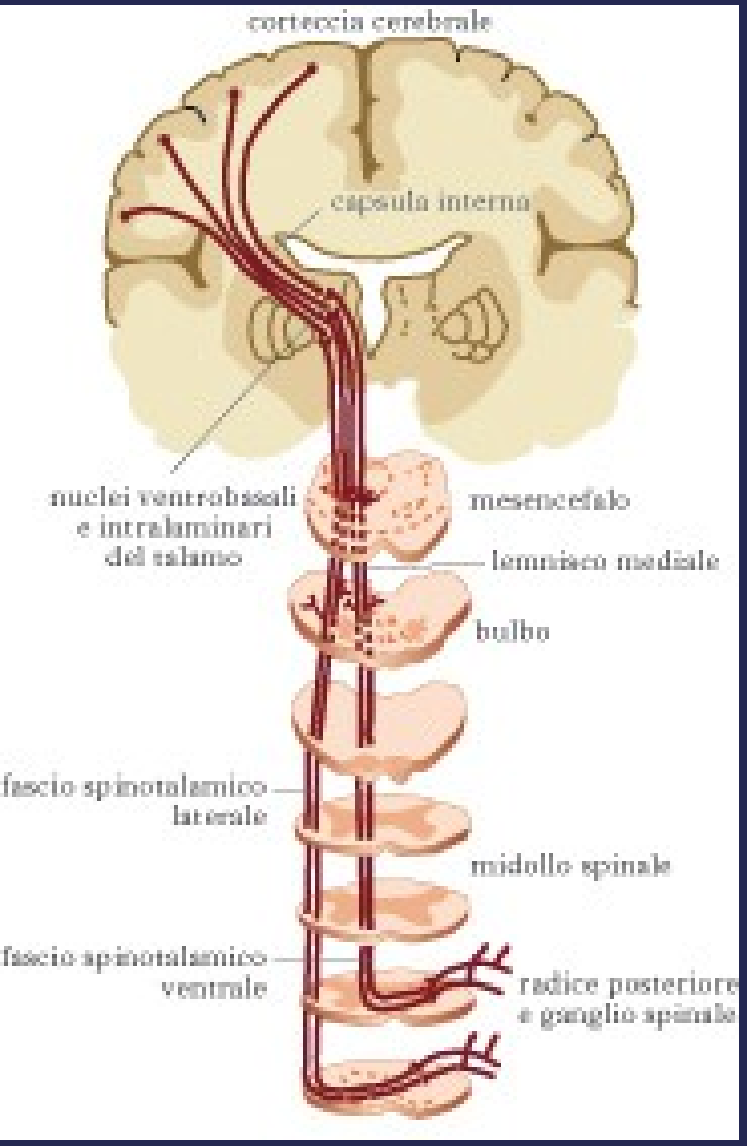


Risposta appropriata a stimoli dolorosi

Espressione della fisiologica attivazione dei nocicettori

- intenso, continuo
- spesso pulsante
- ad andamento crescente
- generalmente circoscritto ad aree anatomiche ben definite

DOLORE NEUROPATICO



- Fenomeno non appropriato, secondario a disfunzione o lesione nervosa: deriva dalla stimolazione diretta delle fibre nervose o da modificazioni sinaptiche di tipo eccitatorio
- E' spontaneo ovvero insorge senza uno stimolo
- È ectopico, non è innescato da una scarica dei nocicettori (insorge in sede anomala)

Sintomi del dolore neuropatico

Dolore spontaneo, indipendente da stimoli (Sintomi descritti dal paziente)

dolore bruciante continuo

parossistico

urente

dolore intermittente lancinante, a fitta

dolore a scossa elettrica

alcune parestesie/disestesie

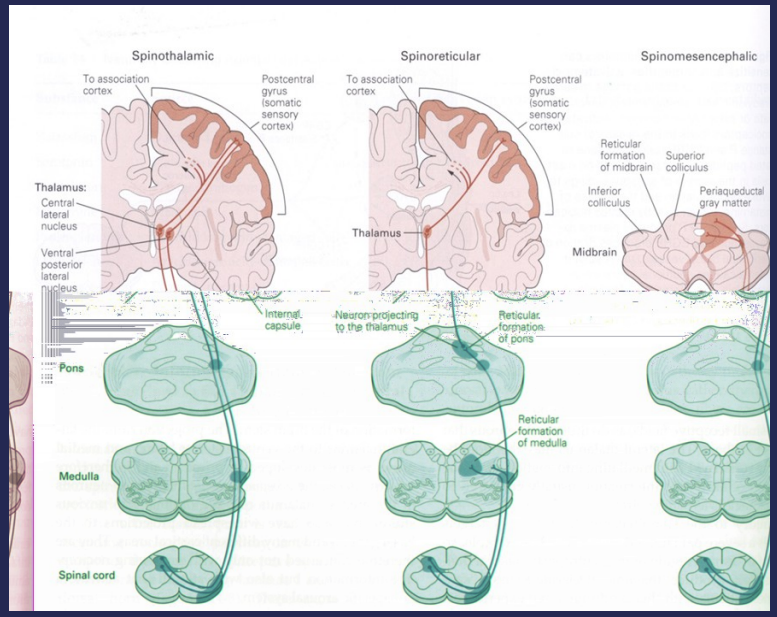
Patogenesi

Periferici Nevralgia trigeminale

Centrali Disconessione

Danno diretto

Demielinizzazione



Percezione del dolore somatico

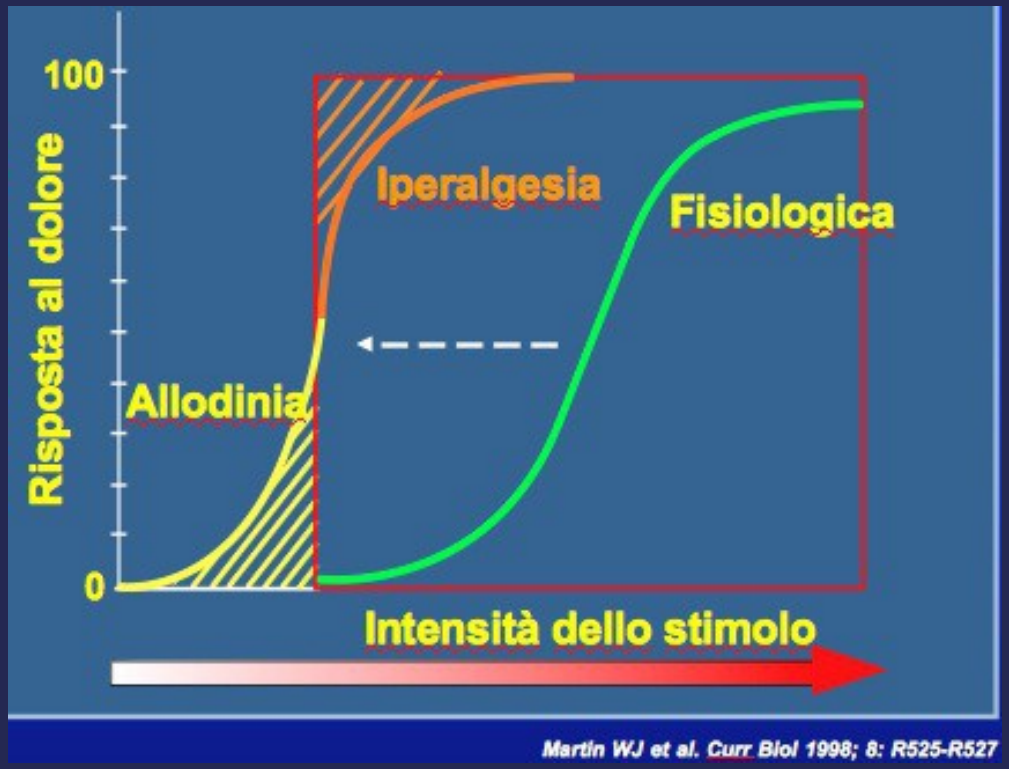
Disturbi cognitivi-depressivi

Iperalgesia

Una risposta dolorosa incrementata e sproporzionata verso stimoli che sono *di solito dolorosi*

Allodinia

Una risposta dolorosa conseguente a stimoli *di solito* *non* *dolorosi*



Review

Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms

Troels S Jensen, Nanna B Finnerup

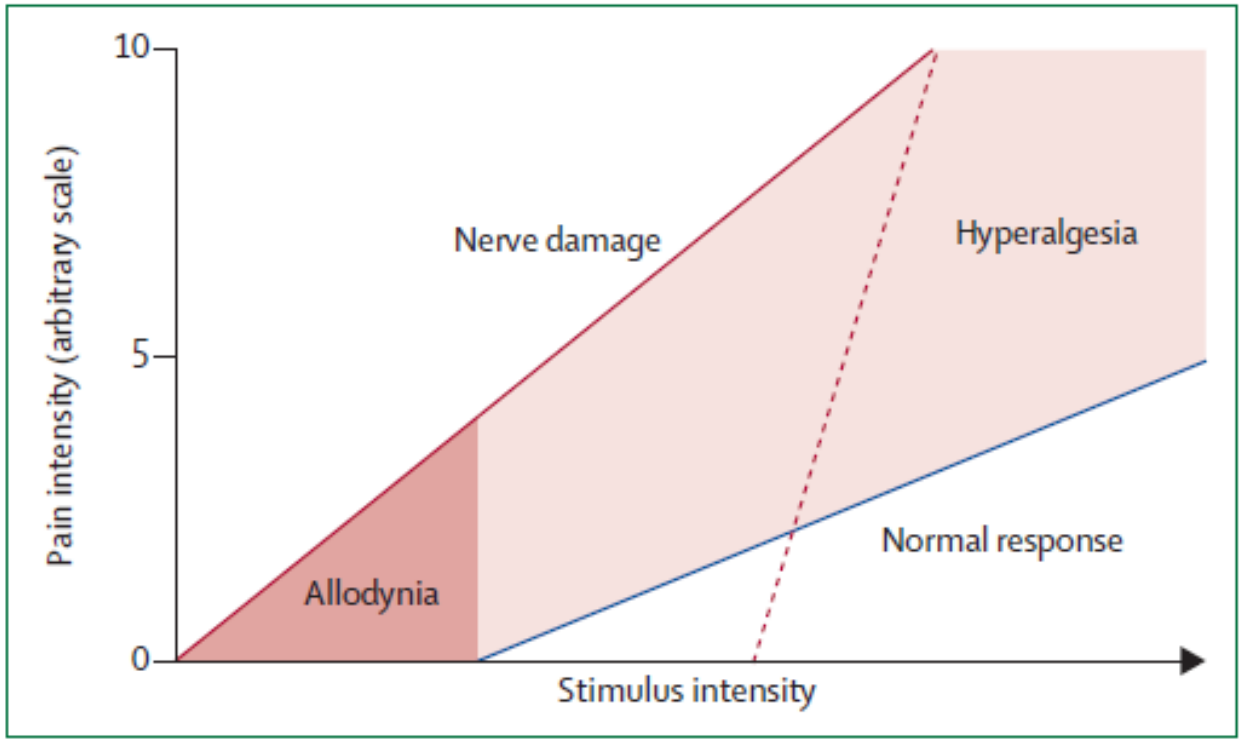


Figure 1: Stimulus–response function illustrating allodynia and hyperalgesia following nerve damage

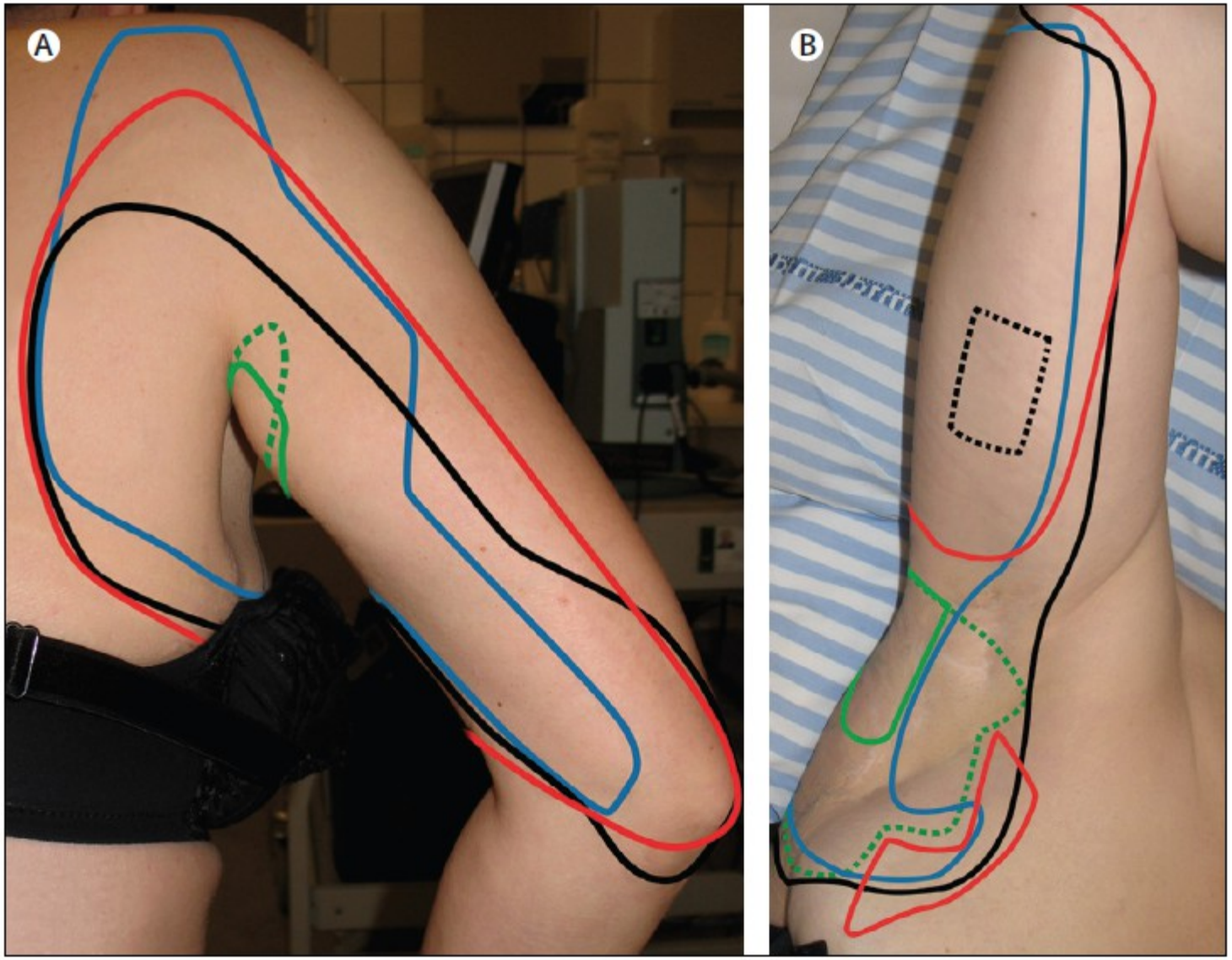


Figure 2: Mapping of allodynia and hyperalgesia

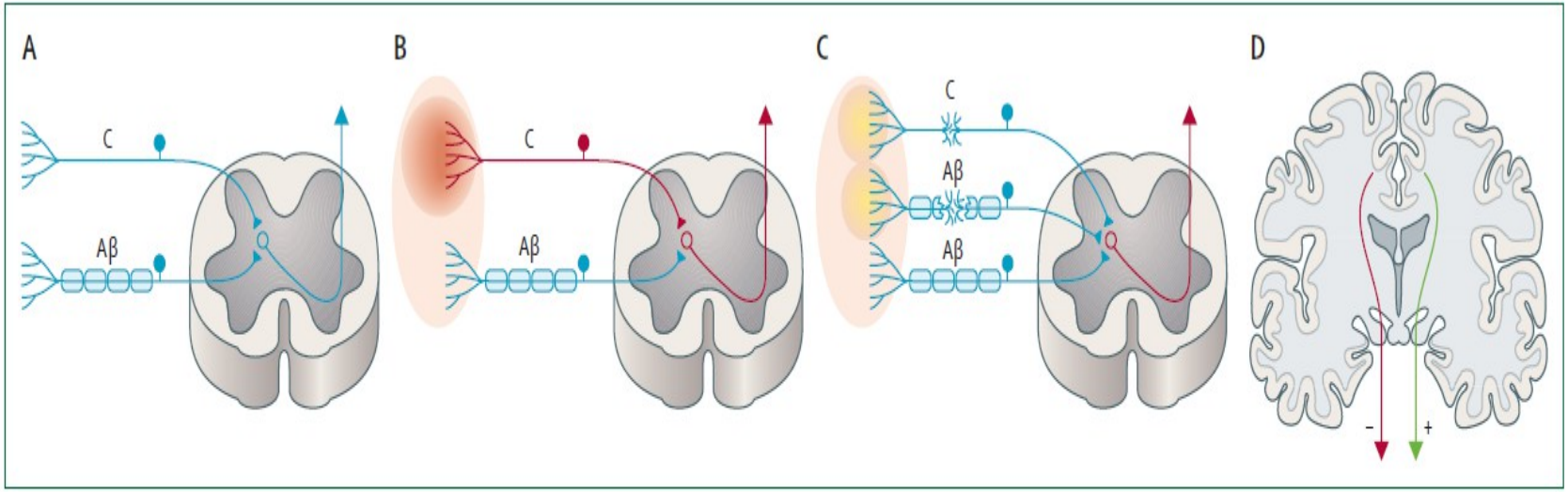


Figure 3: Mechanism for development of central sensitisation

(A) Diagram of noxious (C fibres) and non-noxious (Aβ fibres) input to second-order projection neurons in the spinal cord. (B) Following stimulation of C fibres (red area)—eg, by capsaicin amplification of spinal cord signalling systems—central sensitisation develops and non-noxious stimulation outside the injured area is sufficient to elicit a painful sensation. (C) After injury to nerves, second-order neurons are excited by abnormal and increased input form the periphery, causing central sensitisation and non-noxious input from damaged or undamaged Aβ fibres, which may now elicit activity sufficient to cause pain. Because of injury, there are also areas with a loss of sensitivity (yellow areas). (D) Additionally, a change in the balance of descending inhibitory (–) and facilitating (+) pathways from the brain to the spinal cord can affect dorsal horn neuronal activity and can therefore cause central sensitisation. Red represents sensitisation of fibres and blue represents normal fibres in A–C.

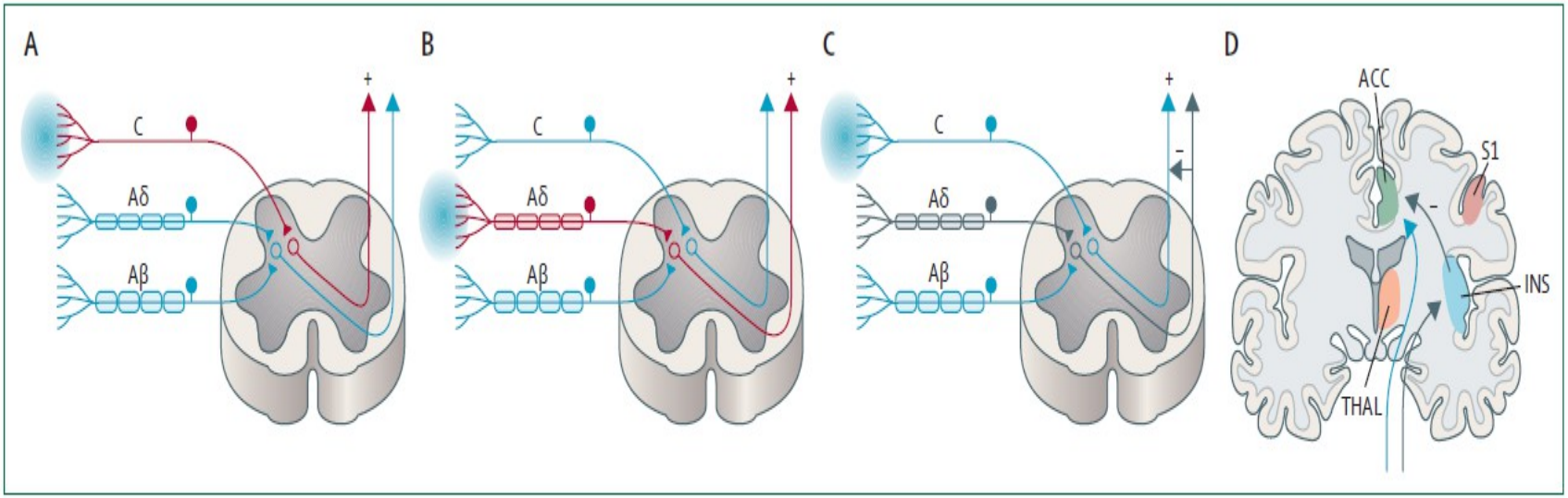


Figure 5: Potential mechanisms for cold allodynia and hyperalgesia

(A) Peripheral sensitisation of cold-sensitive C fibres through abnormal expression or function of, for example, TRPM8 and TRPV1 receptors, or sodium, potassium, or calcium channels, can cause decreased thresholds and exaggerated responses to cold. (B) Peripheral sensitisation of Aδ fibres might likewise cause cold allodynia and hyperalgesia. (C) Loss of peripheral Aδ fibres or (D) of central innocuous cold pathways (eg, by disruption of a thermosensory area in the insular cortex) might disinhibit cold-sensitive polymodal nociceptive heat-pinch-cold-sensitive pathways, causing cold to be experienced as burning pain. Red represents sensitisation of fibres, grey represents loss of fibres, and blue represents normal fibres in A–D. Blue areas show where a cold stimulus is applied. ACC=anterior cingulate cortex. INS=insular cortex. S1=primary somatosensory area. THAL=thalamus.

Rapid Review

Subgrouping of patients with neuropathic pain according to pain-related sensory abnormalities: a first step to a stratified treatment approach

Ralf Baron, Matti Förster, Andreas Binder

Components of pain history

Somatic aspects

- Onset
- Location
- Quality
- Quantity
- Duration
- Aggravating/alleviating factors

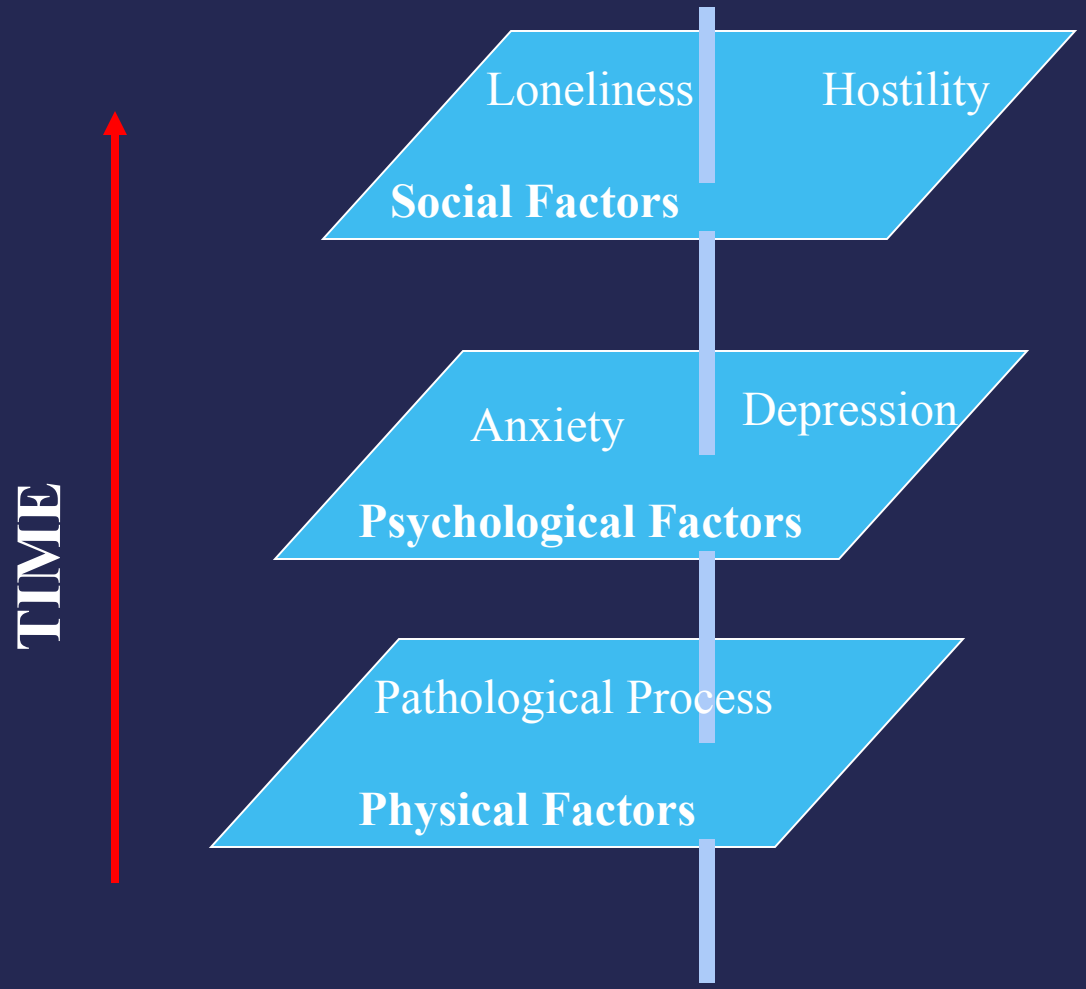
Psychological aspects

- Mood
- Cognitive
- Coping styles
- Beliefs on pain

Social aspects

- Impact on relationship
- Capacity for intimacy
- Activities of daily living
- Vocational
- recreational

Dimensions of Chronic Pain



Traditional *vs.* biopsychosocial models of pain

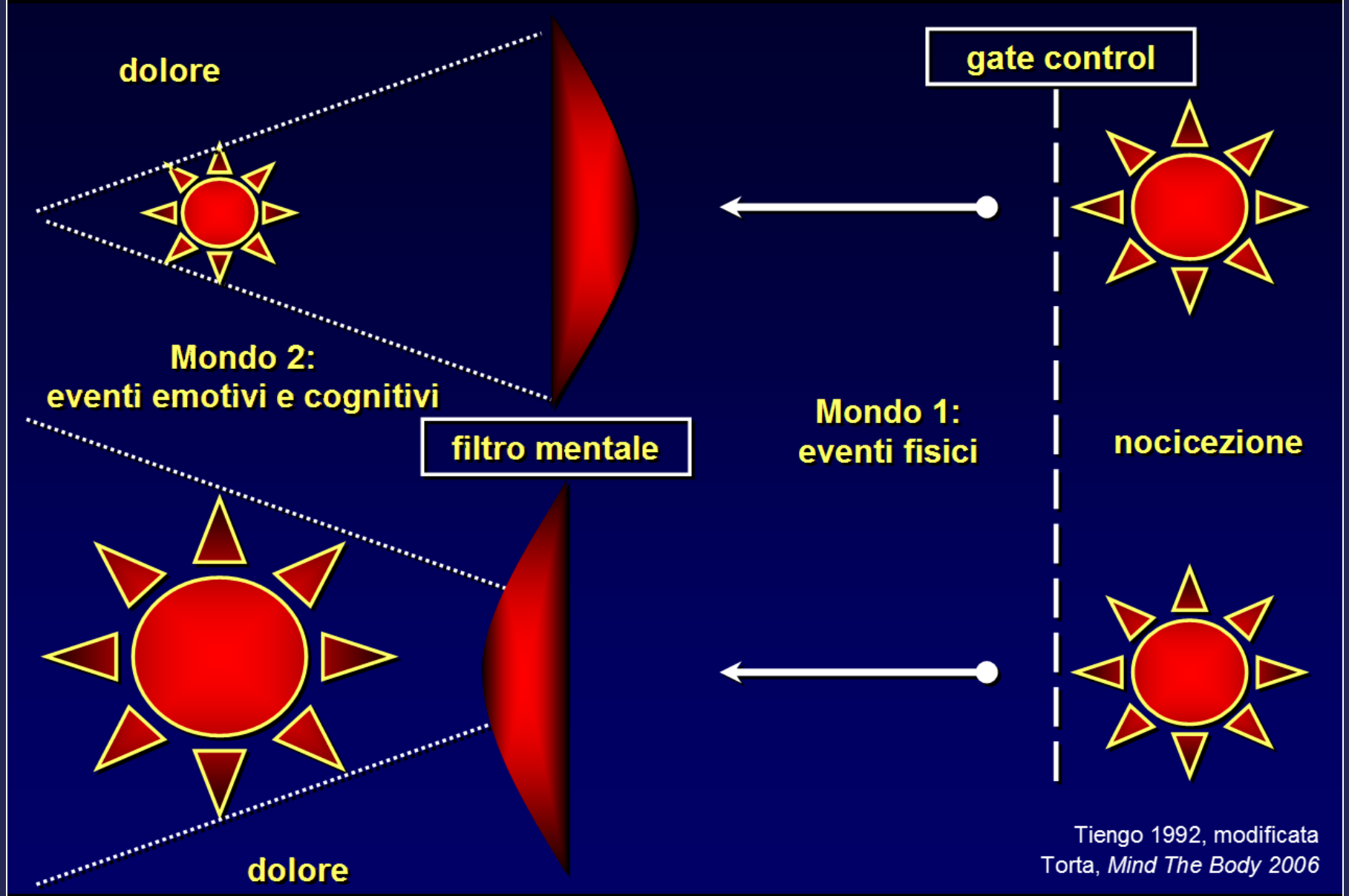
	Traditional	*Biopsychosocial*
View of pain	as an illness	as an experience
Determinants	Disease	Biopsychosocial factors
Management	Physician only	Physician + patient
Role of patient	Passive	Active
Goal	Pain relief	Quality of life
Focus of attention	Somatic complaints	Patient's beliefs

Osborne TL, Jensen MP, Ehde DM, Hanley MA, Kraft G: Psychosocial factors associated with pain intensity, pain-related interference, and psychologial functioning in persons with multiple sclerosis and pain *Pain 2007; 127: 52 - 62*

Co-morbidity of central pain in MS

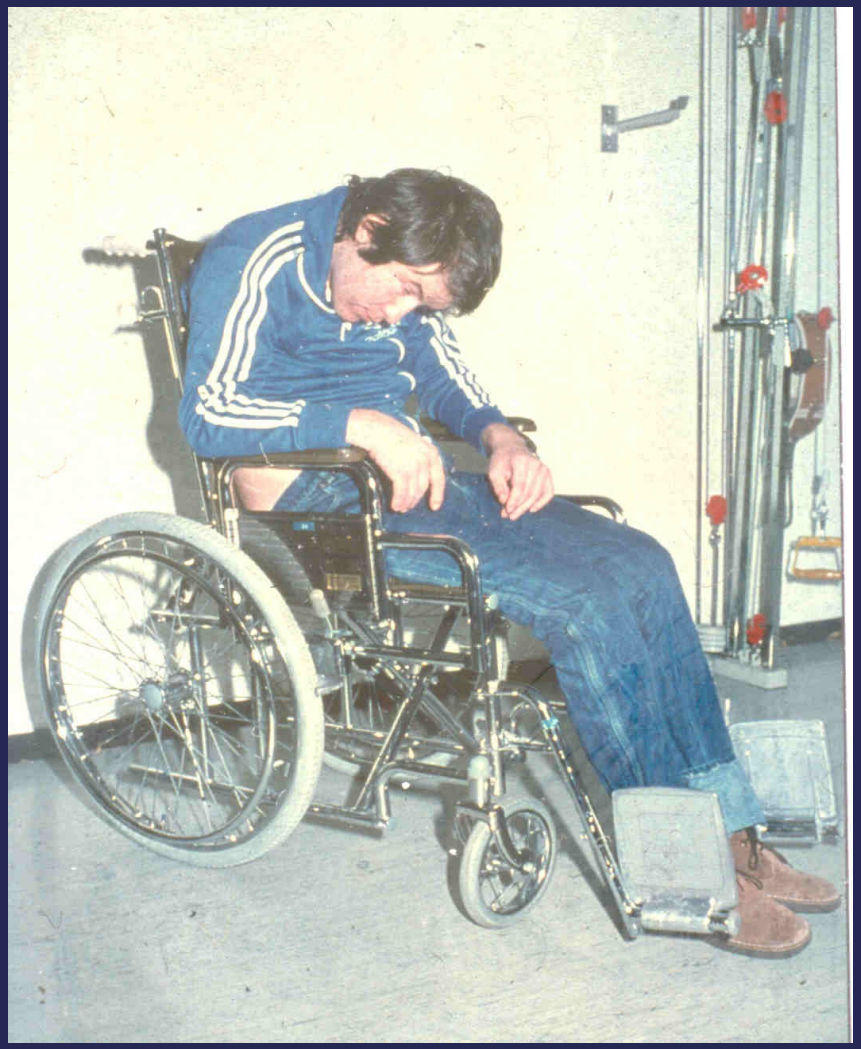
- Sleep disturbance 71%
- Fatigue 63%
- Attentional deficit 39%
- Depression 38%
- Anxiety 26%
- Anorexia 19%

Meyer A: Pain and sensory complaints in multiple sclerosis Eur J Neurol 2004; 11: 479–82


dolore
gate control
Mondo 2:
eventi emotivi e cognitivi
filtro mentale
Mondo 1:
eventi fisici
nocicezione
dolore
Tiengo 1992, modificata
Torta, *Mind The Body 2006*

Pain: related to disability and treatment

- Neck pain in wheelchair users
- Osteoporosis
- Peripheral nerve lesions
- (Injection sites)



Problematiche diagnostiche

Difficolta da parte del paziente a riferire la sintomatologia depressiva (aspetti culturali, insight, sesso, eta)

Difficolta da parte del medico (prevalenza della malattia di base sugli aspetti psicologici, scarsita di risorse diagnostiche, difficolta delle gestione delle co-morbilita)

Clinical Journal of Pain
May 2012 – Volume 28 – Issue 4 – p 300-308

Pain in Individuals With Multiple Sclerosis, Knee Prosthesis, and Post-herpetic Neuralgia: Learning From Focus Group Patients' Experience

Saverino Alessia MD and Solaro Claudio MD

Original spontaneous descriptors, possibly pathology-specific, emerged in all groups not included in the MGPQ and pointed out the need to use assessment tools based on people experience.

PatientsLikeMe: Consumer Health Vocabulary as a Folksonomy

Review

Pain assessment in elderly adults with dementia

Thomas Hadjistavropoulos, Keela Herr, Kenneth M Prkachin, Kenneth D Craig, Stephen J Gibson, Albert Lukas, Jonathan H Smith

DN4 QUESTIONNAIRE

DN4 Questionnaire

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

INTERVIEW OF THE PATIENT

Question 1: Does the pain have one or more of the following characteristics?

	yes	no
1 - **Burning**		
2 - **Painful cold**		
3 - **Electric Shocks**		

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

	yes	no
4 - **Tingling**		
5 - **Pins and Needles**		
6 - **Numbness**		
7 - **Itching**		

EXAMINATION OF THE PATIENT

Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

	yes	no
8 - **Hypoesthesia to touch**		
9 - **Hypoesthesia to prick**		

Question 4: In the painful area, can the pain be caused or increased by:

	yes	no
10 - **Brushing**		

NPSI

Q1. Il dolore assomiglia a una sensazione di bruciore?												
Nessuna sensazione di bruciore	0	1	2	3	4	5	6	7	8	9	10	La peggiore sensazione di bruciore che si possa immaginare
Q2. Il dolore assomiglia ad una stretta?												
Nessuna stretta	0	1	2	3	4	5	6	7	8	9	10	La stretta più forte che si possa immaginare
Q3. Il dolore assomiglia a una sensazione di compressione?												
Nessuna sensazione di compressione	0	1	2	3	4	5	6	7	8	9	10	La peggiore sensazione di compressione che si possa immaginare

Q4. *Nelle ultime 24 ore*, il dolore spontaneo è stato presente:
Scelga *la risposta* che descrive meglio il suo caso.

In continuazione	|__|
Da 8 a 12 ore	|__|
Da 4 a 7 ore	|__|
Da 1 a 3 ore	|__|
Meno di 1 ora	|__|

Vorremmo sapere se ha brevi attacchi di dolore. Per ciascuna delle seguenti domande, la preghiamo di scegliere il numero che descrive meglio *l'intensità media dei suoi attacchi di dolore nelle ultime 24 ore*. Scelga il numero 0 se non ha provato questo tipo di dolore (faccia un cerchietto attorno a un solo numero).

Q5. Il dolore è simile a delle scosse elettriche?

Nessun dolore simile a scosse elettriche	0	1	2	3	4	5	6	7	8	9	10	Il peggiore dolore simile a scosse elettriche che si possa

Q6. Il dolore è simile a una pugnalata?

Nessun dolore simile a una pugnalata	0	1	2	3	4	5	6	7	8	9	10	Il peggiore dolore simile a una pugnalata che si possa immaginare

Q7. *Nelle ultime 24 ore*, quanti di questi attacchi di dolore ha avuto?
Scelga *la risposta* che descrive meglio il suo caso.

Più di 20	|__|
Da 11 a 20	|__|
Da 6 a 10	|__|
Da 1 a 5	|__|
Nessun attacco di dolore	|__|

Vorremmo sapere se avverte dolore provocato o accentuato dallo sfioramento, dalla pressione o dal contatto della parte dolorante con il freddo o con il caldo. Per ciascuna delle seguenti domande, la preghiamo di scegliere il numero che descrive meglio *l'intensità media del dolore provocato nelle ultime 24 ore*. Scelga il numero 0 se non ha provato questo tipo di dolore (faccia un cerchietto attorno a un solo numero).

Q8. Il dolore è provocato o accentuato dallo sfioramento della parte dolorante?

Nessun dolore	0	1	2	3	4	5	6	7	8	9	10	Il peggiore dolore che si possa immaginare

Q9. Il suo dolore è provocato o accentuato dalla pressione sulla parte dolorante?

Nessun dolore	0	1	2	3	4	5	6	7	8	9	10	Il peggiore dolore che si possa immaginare

Q10. Il dolore è provocato o accentuato dal *contatto* della parte dolorante con il freddo?

Nessun dolore	0	1	2	3	4	5	6	7	8	9	10	Il peggiore dolore che si possa immaginare

Vorremmo sapere se ha delle sensazioni insolite *nella parte dolorante*. Per ciascuna delle seguenti domande, la preghiamo di scegliere il numero che descrive meglio *l'intensità media delle sensazioni insolite nelle ultime 24 ore*. Scelga il numero 0 se non ha avuto questo tipo di sensazione.

Q11. Ha una sensazione di aghi o spilli?

Nessuna sensazione di aghi o spilli	0	1	2	3	4	5	6	7	8	9	10	La peggiore sensazione di aghi o spilli che si possa immaginare

Q12. Avverte un formicolio?

Nessun formicolio	0	1	2	3	4	5	6	7	8	9	10	Il peggiore formicolio che si possa immaginare

The international Classification of headache disorders

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
33(9) 629–808

DOI: 10.1177/0333102413485658
cep.sagepub.com
SAGE

Headache Classification Committee of the International Headache Society (IHS)

The International Classification of Headache Disorders, 3rd edition (beta version)

13. Painful cranial neuropathies and other facial pains

13.1 Trigeminal neuralgia

- 13.1.1 Classical trigeminal neuralgia
  - 13.1.1.1 Classical trigeminal neuralgia, purely paroxysmal
  - 13.1.1.2 Classical trigeminal neuralgia with concomitant persistent facial pain
- 13.1.2 Painful trigeminal neuropathy
  - 13.1.2.1 Painful trigeminal neuropathy attributed to acute Herpes zoster
  - 13.1.2.2 Post-herpetic trigeminal neuropathy
  - 13.1.2.3 Painful post-traumatic trigeminal neuropathy
  - 13.1.2.4 Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque
  - 13.1.2.5 Painful trigeminal neuropathy attributed to space-occupying lesion
  - 13.1.2.6 Painful trigeminal neuropathy attributed to other disorder

Painful trigeminal neuropathy attributes to MS plaque

13.1.2.4 Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque

Description:
Unilateral head and/or facial pain in the distribution of a trigeminal nerve and with the characteristics of classical trigeminal neuralgia, induced by a multiple sclerosis plaque affecting the trigeminal nerve root and associated with other symptoms and/or clinical signs of multiple sclerosis.

Diagnostic criteria:

A. Head and/or facial pain with the characteristics of 13.1.1 *Classical trigeminal neuralgia* with or without concomitant persistent facial pain, but not necessarily unilateral
B. Multiple sclerosis (MS) has been diagnosed
C. An MS plaque affecting the trigeminal nerve root has been demonstrated by MRI or by routine electrophysiological studies (blink reflex or trigeminal evoked potentials) indicating impairment of the affected trigeminal nerve(s)
D. Not better accounted for by another ICHD-3 diagnosis.

Comments:
Current studies indicate that about 7% of MS patients have a syndrome that is similar to 13.1.1 *Classical trigeminal neuralgia*. However, symptoms of trigeminal neuralgia are very rarely a presenting feature of MS.

Symptoms of 13.1.2.4 *Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque* are more likely to be bilateral than those of 13.1.1 *Classical trigeminal neuralgia.*

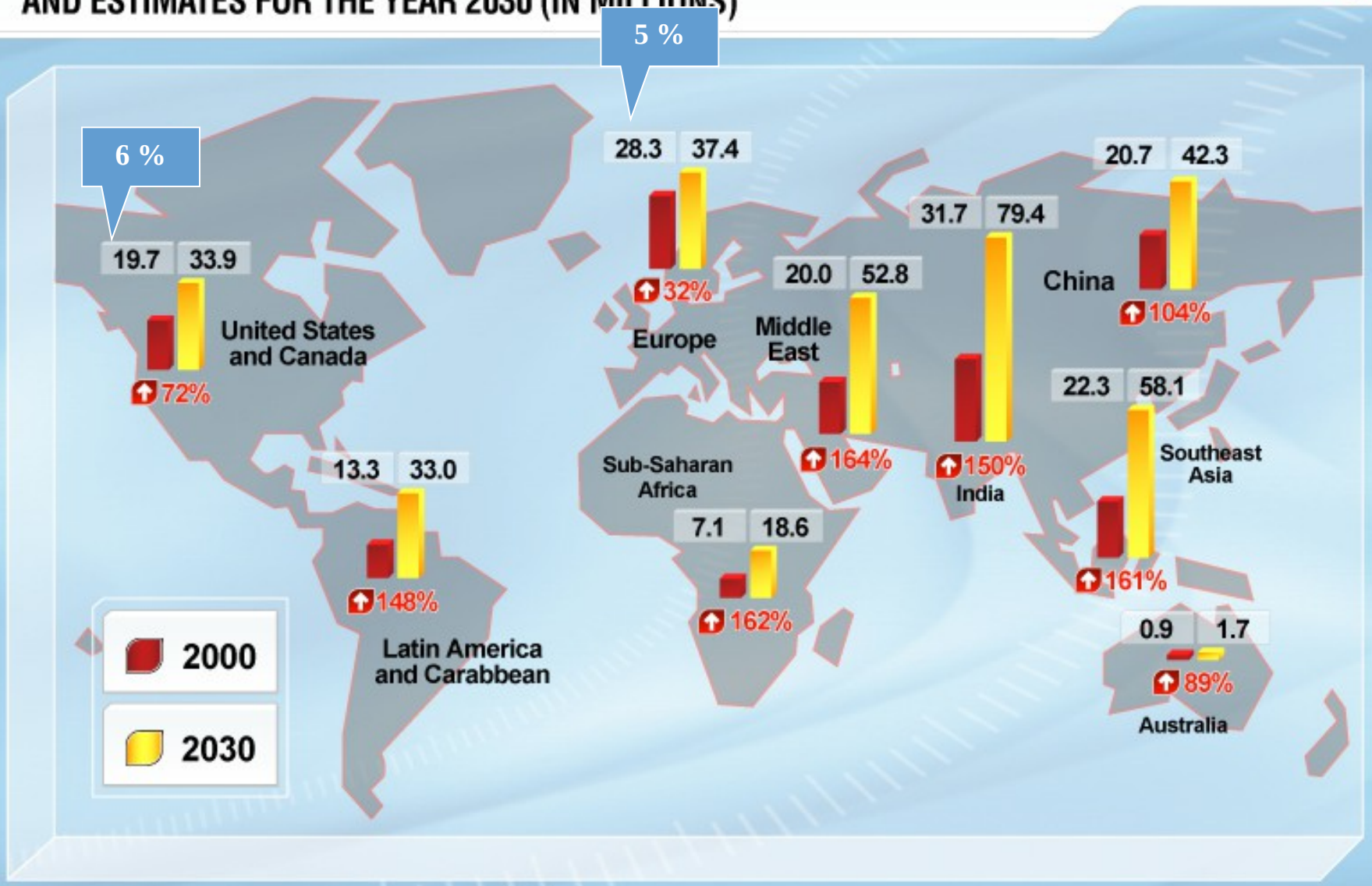
Patients with 13.1.2.4 *Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque* benefit less from pharmacological interventions than those with 13.1.1 *Classical trigeminal neuralgia.*

Neuropathic Pain is a Frequent Complication of Diabetes

- **30–60% of patients with diabetes develop long-term complications of diabetic peripheral neuropathy and up to 10–20% of these experience pain[1–3]**
- **Increased risk with longer duration of diabetes and with poor glucose control[4]**
- **Diabetic peripheral neuropathic pain (DPNP) interferes with patients' functioning and quality of life[4]**
- **Patients' quality of life and level of daily function decrease further with increasing disease severity[4,5]**

1. Clark CM, et al. *N Engl J Med.* 1995;332:1210–1217;
2. Boulton AJM, et al. *Diabetes Care.* 2004;27:1458–1486;
3. Eastman RC. Neuropathy in Diabetes. In: Diabetes Data Group, eds. *Diabetes in America*, 2nd ed. NIH Publication: Washington, DC;1995:339–348.
4. Argoff CE, et al. *Mayo Clin Proc.* 2006; 81(4):S3–11; 5. Sullivan SD, et al. *Pharmacoeconomics.* 2002;20:1079–1089.

WORLDWIDE PREVALENCE OF DIABETES IN 2000 AND ESTIMATES FOR THE YEAR 2030 (IN MILLIONS)



Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org

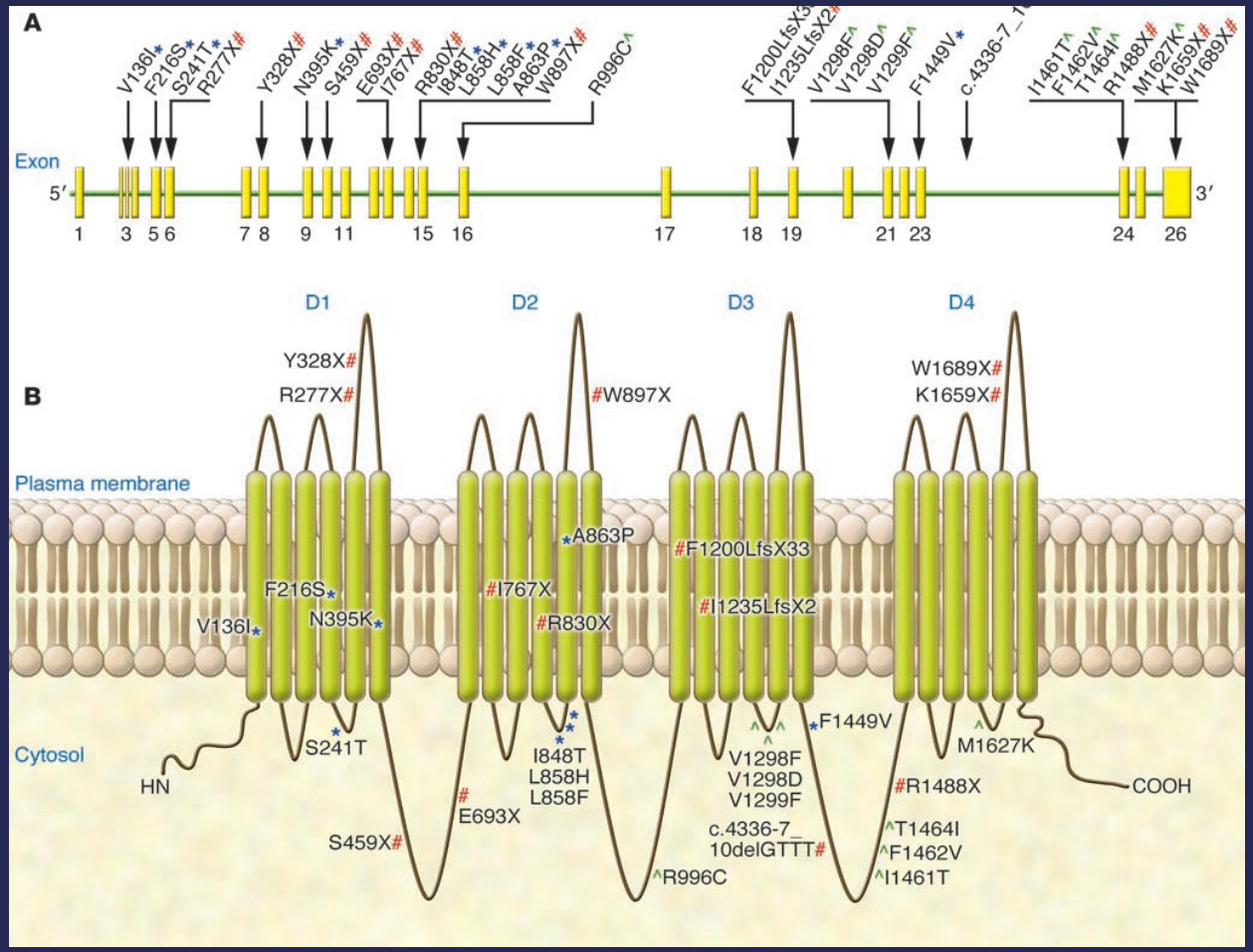
Adapted from Hossain P et al. N Engl J Med 2007; 356: 213-5

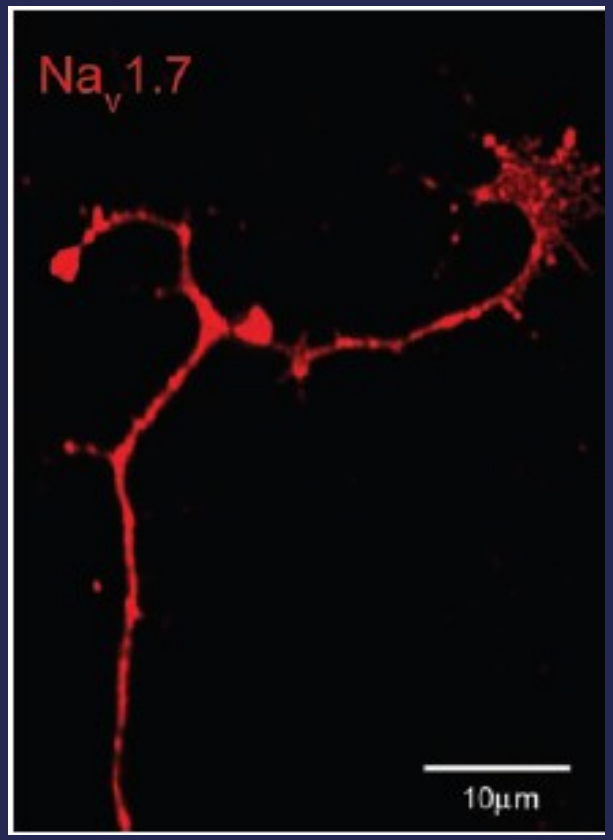
Premessa

It is still unclear why neuropathies of apparently equal aetiology can be painful or painless. Prototypes of painful polyneuropathies are those with the prominent involvement of small unmyelinated fibres (C-fibres), such as the amyloid neuropathies and Fabry disease. However, neuropathies with nonselective fibre loss such as the alcoholic, dysproteinaemic, and some toxic neuropathies can be equally painful, as well as some neuropathies with selective large fibre loss.

Sommer, 2003

Gene SCN9A (Nav 1.7)

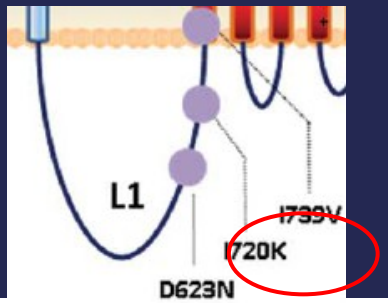


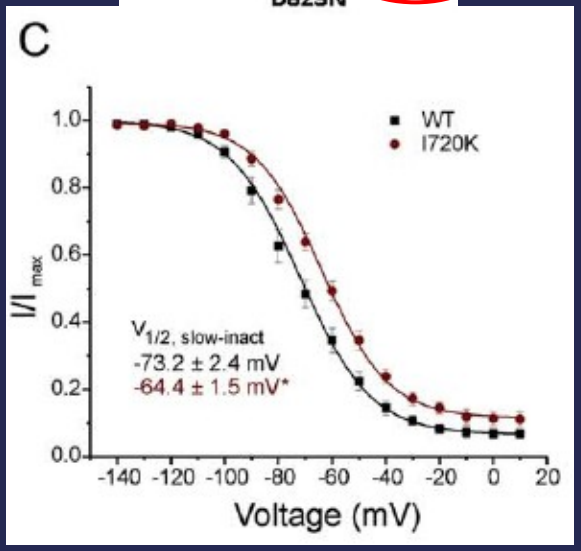


JPH Drenth and SG Waxman J Clin Invest, 2007

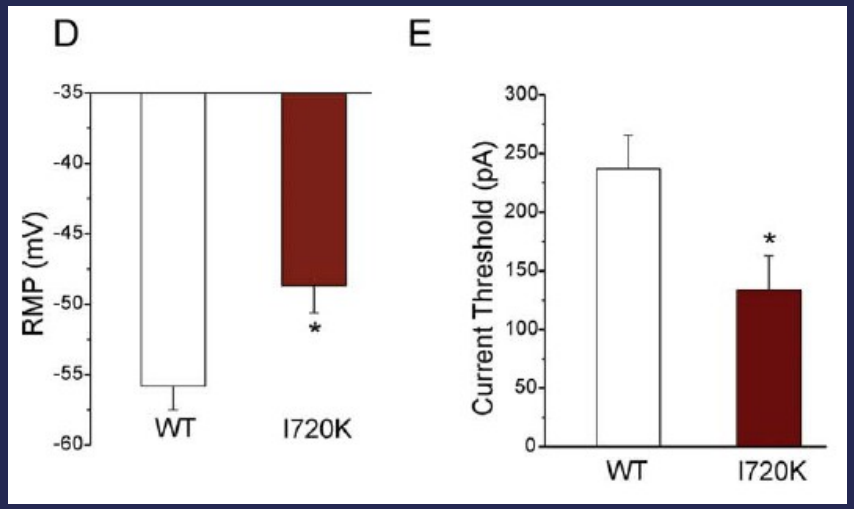
Functional Characterization of $Na_V1.7$ Mutations

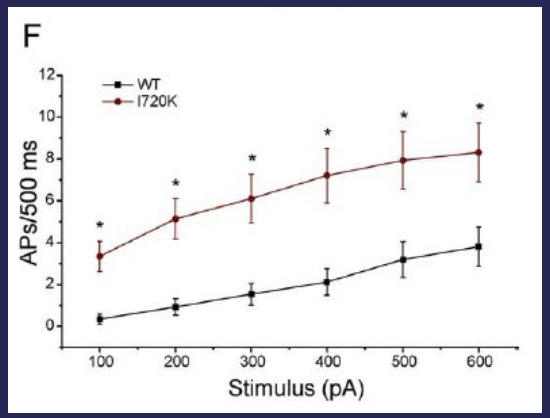
Voltage clamp analysis of the mutant channels from patients with I-SFN showed that they were all gain of function, and that they impaired slow inactivation (p.I720K, p.M1532I, p.I228M, p.I739V), depolarized slow and fast inactivation (p.D623N), or enhanced resurgent currents (p.M932L/V991L, p.R185H). None of these mutations exhibited the hyperpolarized activation or enhanced ramp currents characteristic of IEM[15] or the incomplete fast inactivation characteristic of PEPD[17] mutations of $Na_V1.7$. Current clamp analysis demonstrated that all 7 mutations rendered DRG neurons hyperexcitable. Here we present the





HEK 293





DRG NEUR

Gain-of-function $Na_v1.8$ mutations in painful neuropathy

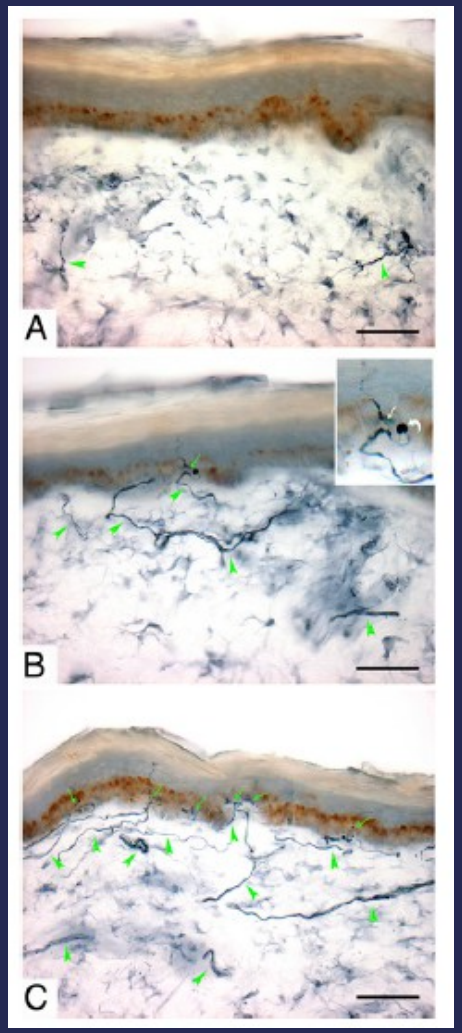
Catharina G. Faber[a,1], Giuseppe Lauria[b,1], Ingemar S. J. Merkies[a,c,1], Xiaoyang Cheng[d,e], Chongyang Han[d,e], Hye-Sook Ahn[d,e], Anna-Karin Persson[d,e], Janneke G. J. Hoeijmakers[a], Monique M. Gerrits[f], Tiziana Pierro[b], Raffaella Lombardi[b], Dimos Kapetis[b,g], Sulayman D. Dib-Hajj[d,e], and Stephen G. Waxman[d,e,2]

19444–19449 | PNAS | November 20, 2012 | vol. 109 | no. 47

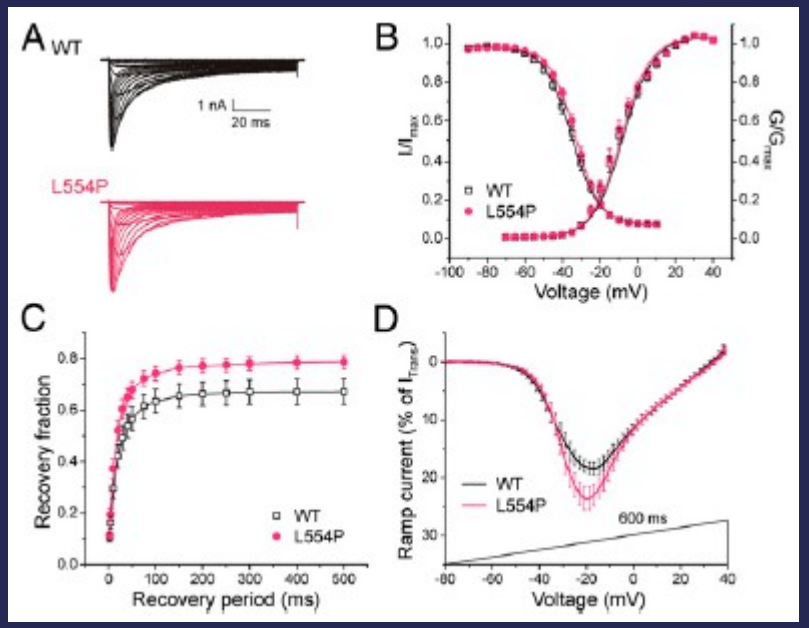
Father

Son

Control



L554P mutation alters $hNa_v1.8$ channel properties.



Gain-of-function mutations in sodium channel $Na_V1.9$ in painful neuropathy

Jianying Huang,[1,*] Chongyang Han,[1,*] Mark Estacion,[1,*] Dymtro Vasylyev,[1,*] Janneke G. J. Hoeijmakers,[2] Monique M. Gerrits,[3] Lynda Tyrrell,[1] Giuseppe Lauria,[4] Catharina G. Faber,[2] Sulayman D. Dib-Hajj,[1] Ingemar S. J. Merkies[2,5] and Stephen G. Waxman[1] on behalf of the PROPANE Study Group

Brain 2014: 137; 1627–1642

Sodium channel $Na_v1.9$ is expressed in peripheral nociceptive neurons, as well as visceral afferents, and has been shown to act as a threshold channel. Painful peripheral neuropathy represents a significant public health challenge and may involve gain-of-function variants in sodium channels that are preferentially expressed in peripheral sensory neurons. Although gain-of-function variants of peripheral sodium channels $Na_v1.7$ and $Na_v1.8$ have recently been found in painful small fibre neuropathy, the aetiology of peripheral neuropathy in many cases remains unknown. We evaluated 459 patients who were referred for possible painful peripheral neuropathy, and confirmed the diagnosis of small fibre neuropathy in a cohort of 393 patients (369 patients with pure small fibre neuropathy, and small fibre neuropathy together with large fibre involvement in an additional 24 patients). From this cohort of 393 patients with peripheral neuropathy, we sequenced *SCN11A* in 345 patients without mutations in *SCN9A* and *SCN10A*, and found eight variants in 12 patients. Functional profiling by electrophysiological recordings showed that these $Na_v1.9$ mutations confer gain-of-function attributes to the channel, depolarize resting membrane potential of dorsal root ganglion neurons, enhance spontaneous firing, and increase evoked firing of these neurons. Our data show, for the first time, missense mutations of $Na_v1.9$ in individuals with painful peripheral neuropathy. These genetic and functional observations identify missense mutations of $Na_v1.9$ as a cause of painful peripheral neuropathy.

DOLORE NEUROPATICO
E SINDROMI ALGICHE
CRONICHE

Coordinatore: Dott. Claudio Solaro

ore 9.00 - 11.00

Dolore e neuropatie periferiche: farmacogenetica

?

Angelo Schenone

Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno Infantili, Università di Genova

Treatment of $Na_v1.7$-mediated pain in inherited erythromelalgia using a novel sodium channel blocker

Yigal Paul Goldberg [a,*], Nicola Price [a], Rostam Namdari [a], Charles Jay Cohen [a], Mieke H. Lamers [b], Conrad Winters [a], James Price [c], Clint E. Young [a], Henry Verschoof [a], Robin Sherrington [a], Simon Neil Pimstone [a], Michael Reuben Hayden [a,d]

PAIN® 153 (2012) 80–85

We have developed a novel compound (XEN402) that exhibits potent, voltage-dependent block of $Na_v1.7$ (IC_{50} 80 nM). Here we report an exploratory trial performed to evaluate the efficacy of XEN402 in mutation-proven erythromelalgia patients, with the primary aim of demonstrating that $Na_v1.7$ antagonism alleviates pain associated with IEM. Our novel approach uses a rare genetic

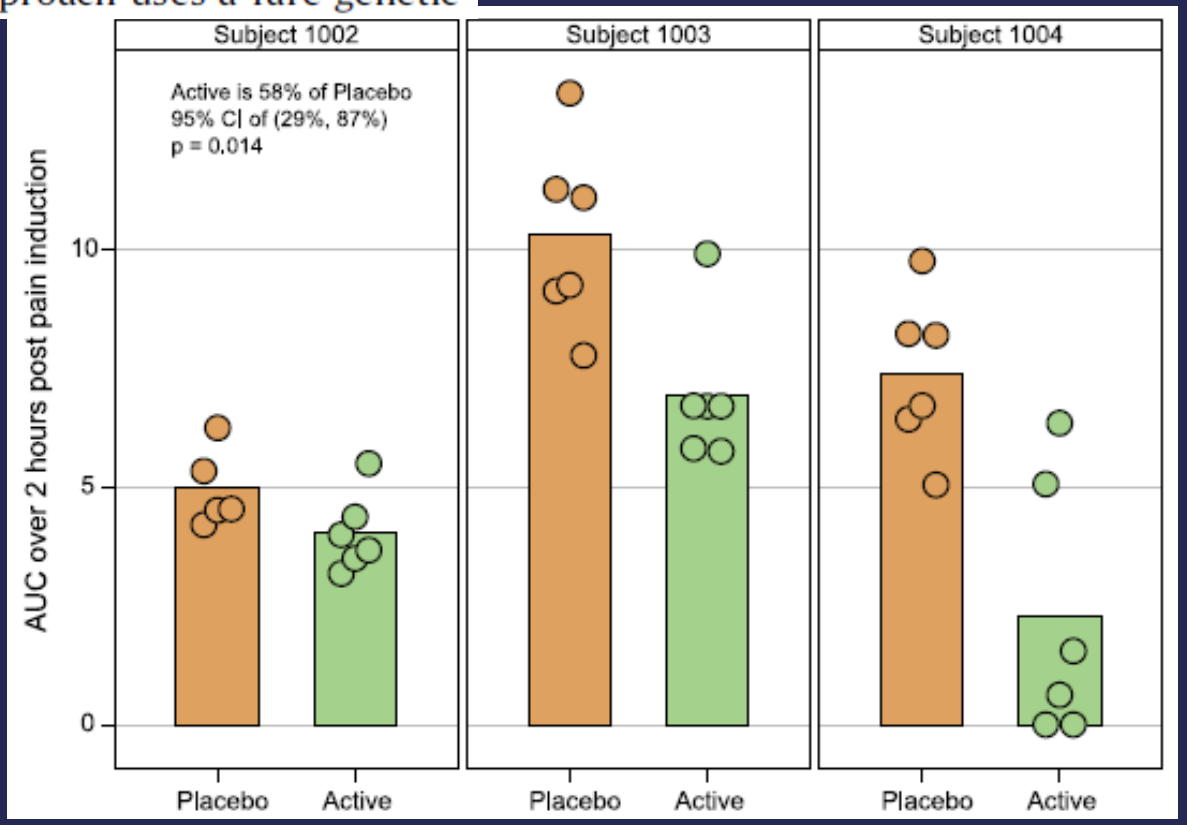


Fig. 1. Reduction in total pain in the 2 hours after each pain induction by treatment for subjects 1002, 1003, and 1004.

Pharmacogenetic

Pharmacokinetics
Pharmacodynamics

- Pharmacokinetic: factors that affect drug metabolism and/or elimination, altering the relationship between drug dose and steady state serum concentrations
- Pharmacodinamic: based on variations in drug target receptors and downstream signal transduction

Review

Pharmacogenetics of chronic pain management

Bhushan M. Kapur [a,b,c,*], Prateek K. Lala [b], Julie L.V. Shaw [c]

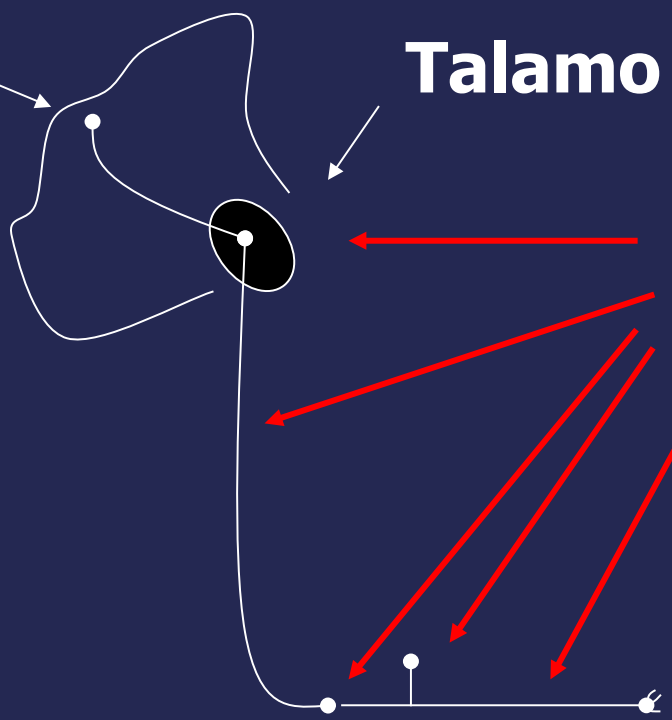
Clinical Biochemistry 47 (2014) 1169–1187

- **Genes affecting pharmacokinetic: cytochrome p450 family of enzymes, enzymes responsible for glucoronidation, drug transporter proteins**

- **Genes affecting pharmacodinamic: cyclooxigenase enzymes, catecholamine methyltransferase enzyme, the opioid receptors**

Kapur MB et al, 2014

La via del dolore



Corteccia sensitiva

Talamo

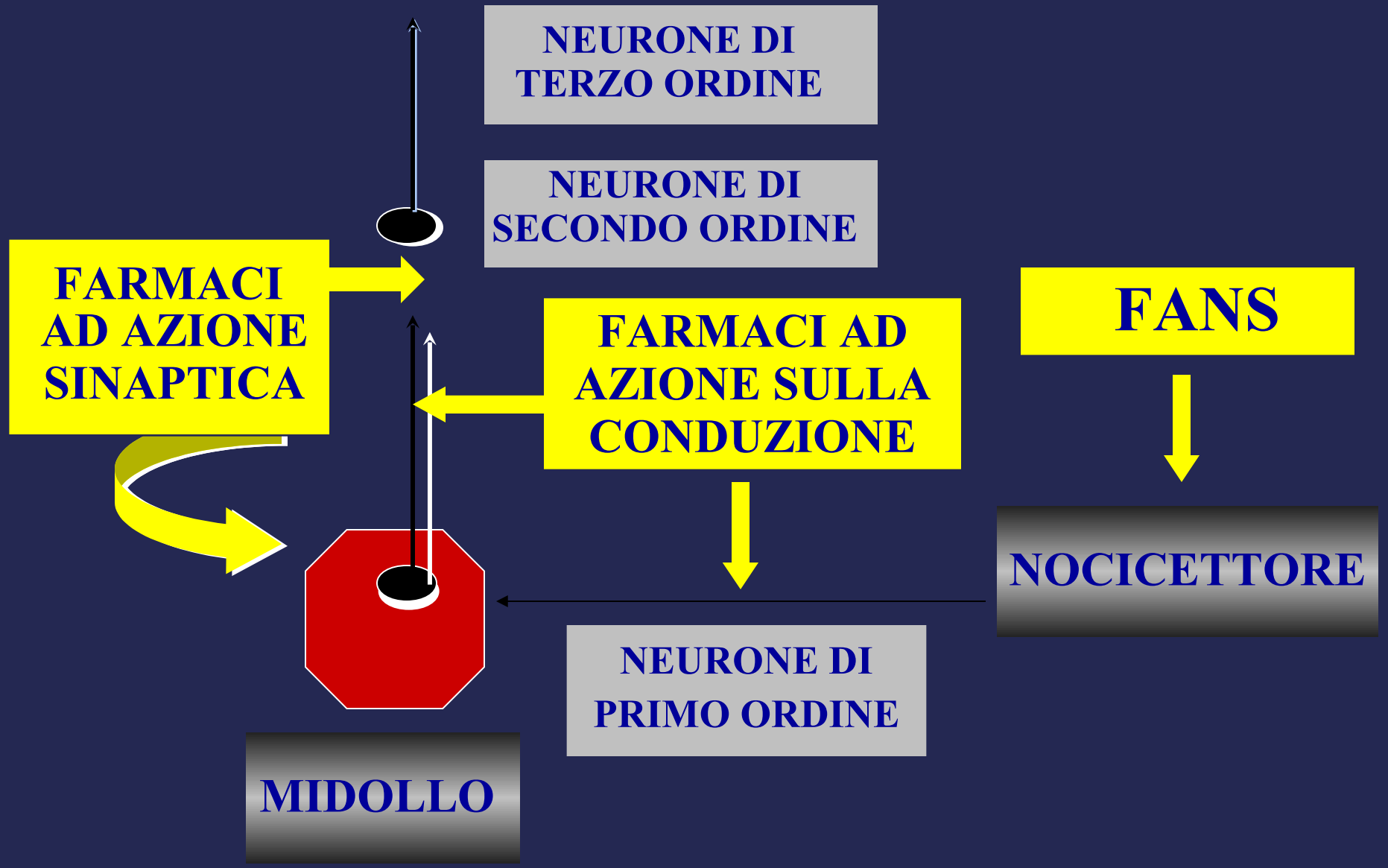
DOLORE NEUROPATICO

DOLORE PSICOGENO

Nocicettore

DOLORE NOCICETTIVO

Siti d'azione dei farmaci sulle vie di conduzione del massaggio nocicettivo



Raccolta anamnestica
Esame neurologico

Dolore SI

Classificazione del dolore
(DN4)
Valutazione delle co-morbilità

TERAPIA

- Terapia medica
- Valutazione ausilii
- Trattamenti
- Valutazione terapista del dolore
- Infusione intra-tecale
- Stimolazione midollare