

Dolore neuropatico

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2014 - 2015
**GLOBAL
YEAR**
AGAINST
NEUROPATHIC
PAIN

International Association for the Study of Pain

Definizione



**Dolore causato da una lesione o malattia del
sistema nervoso somatosensoriale**

Definizione



Dolore neuropatico NON è una diagnosi ma una descrizione clinica e necessita di una lesione o malattia che soddisfi i criteri diagnostici neurologici stabiliti.

Lesione: dimostrata da indagini diagnostiche o evidente trauma

Malattia: se la causa della lesione è nota (stroke, vasculite, diabete mellito, anomalie genetiche)

Sistema somatosensoriale

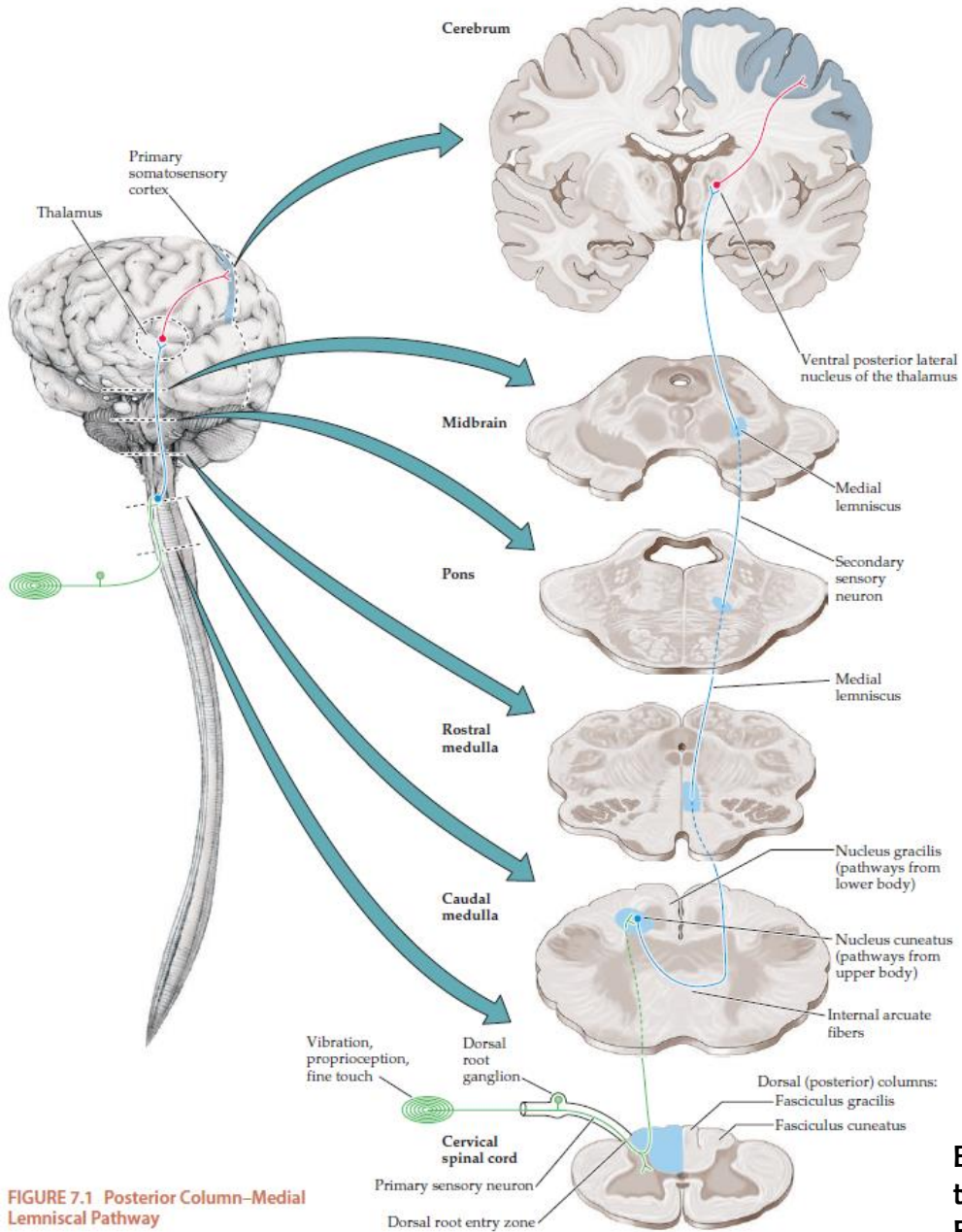


FIGURE 7.1 Posterior Column-Medial Lemniscal Pathway

Blumenfeld H. Neuroanatomy through Clinical Cases with Ebook. Sinauer; 2011.

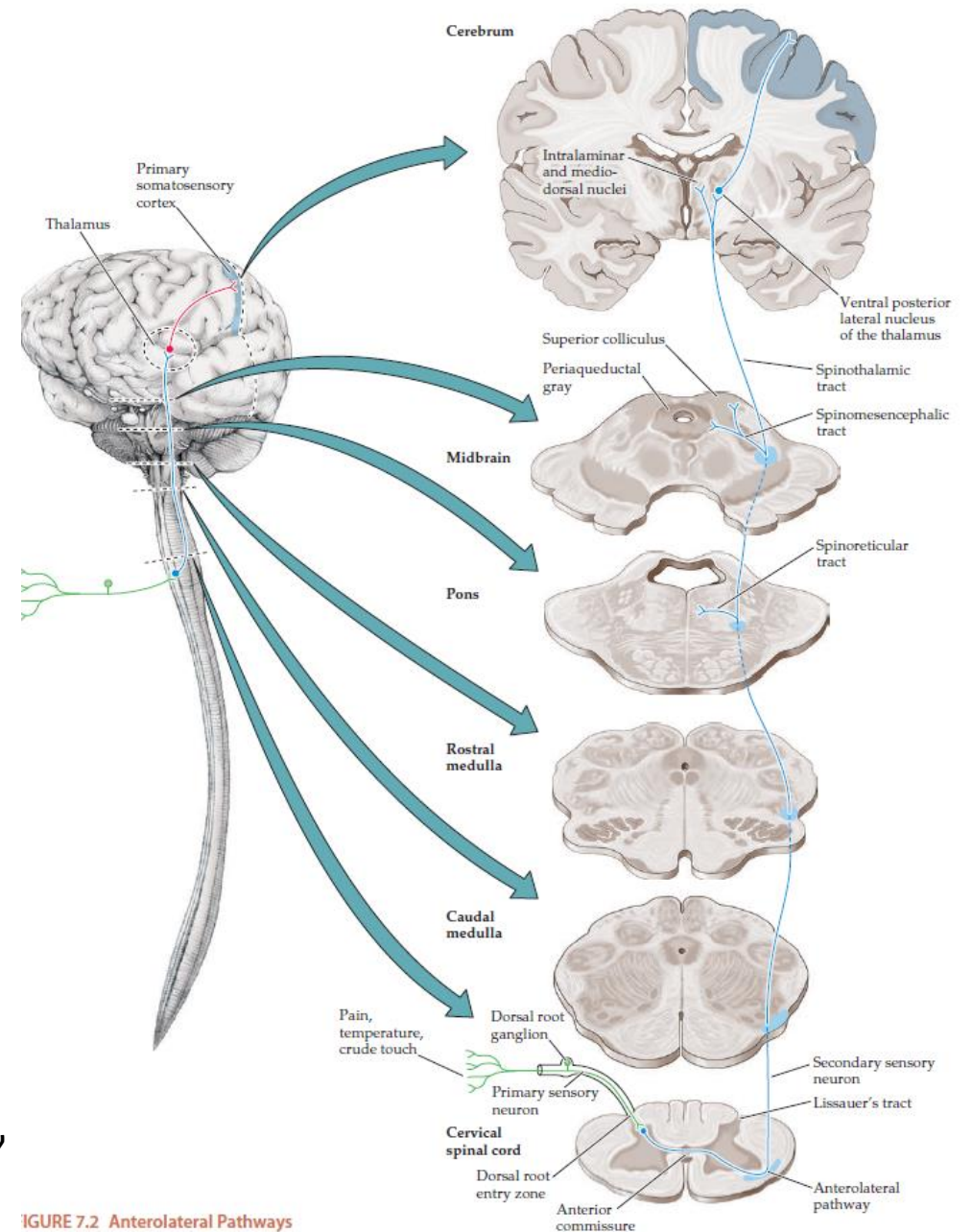


FIGURE 7.2 Anterolateral Pathways

Fisiopatologia e patogenesi

Infiammazione/infezione/neurotossine/chemioterapia

- 1. assonopatia da deficit trasporto assoplasmico a transezione dell'assone (assonotomia)**
- 2. dismielienizzazione o demielinizzazione segmentale**

Danno della fibra nervosa→
Moncone prossimale si chiude→
“end- bulb”

Dopo ore-giorni fini processi si dipartono dal termine dell’assone →
“sprouts”

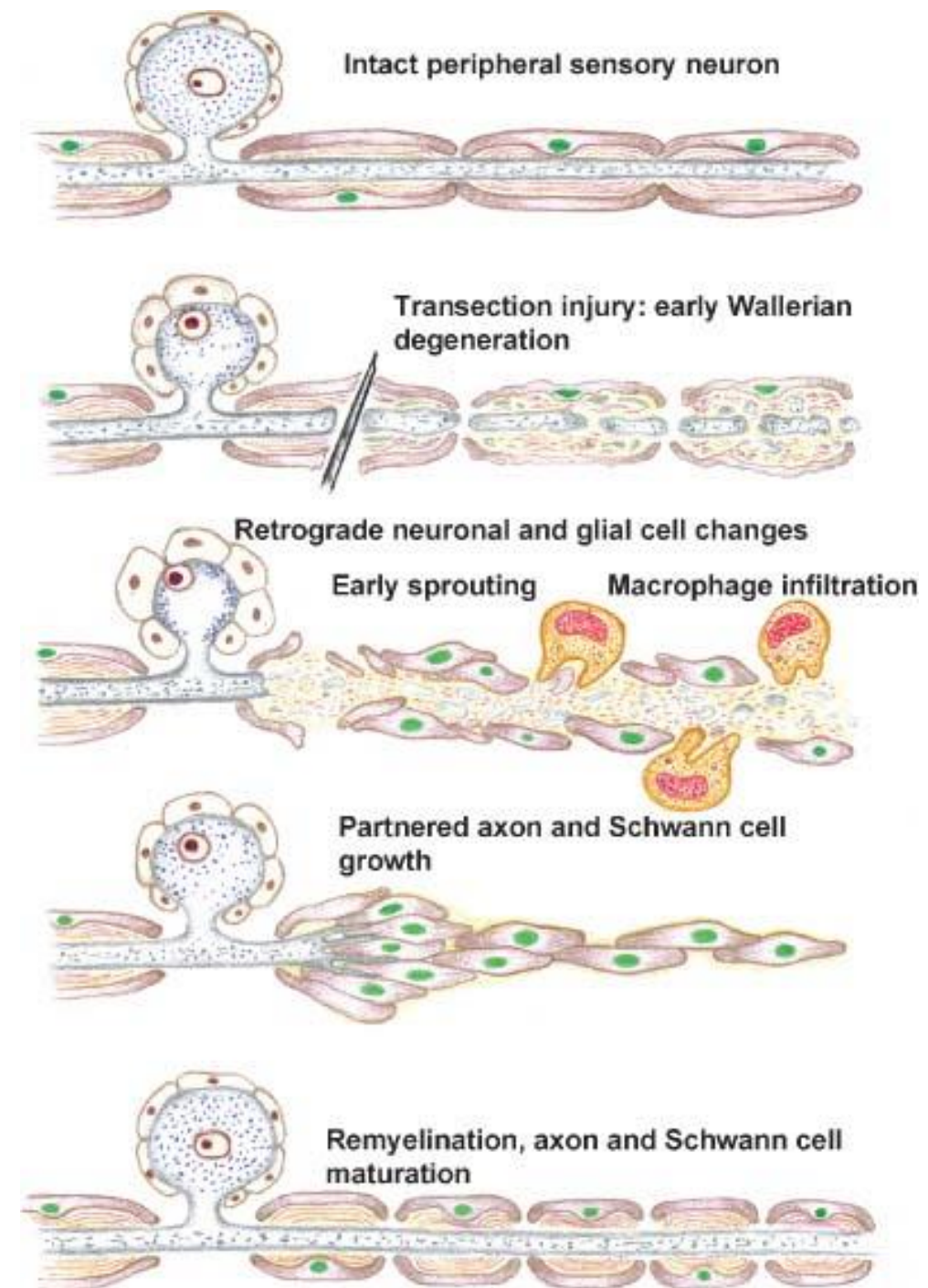
Se non si ricongiungono con estremità distale guidati da endonevrio→
Sprouts si intrecciano→
“nerve-end neuroma”

Stati intermedi:

alcune fibre si ricongiungono e altre formano “neuroma-in-continuity” →
fibre individuali formano “micro-neuroma” dispersi lungo il nervo→

Nell’adulto assonotomia non comporta spesso la morte del soma.

Neuroma, sprouts, aree di demielinizzazione/dismielinizzazione sono
generatori di impulsi ectopici→
Elettrogenesi sia spontanea sia evocata



Fibre A

scariche ectopiche precoci

ritmiche

treni di impulsi 65-35 ms 15-30 Hz con intervalli fissi

Fibre C

scariche irregolari, lente 0.1-10 Hz

Ganglio della radice dorsale DRG fonte predominante di scariche ectopiche

→

Ipereccitabilità →

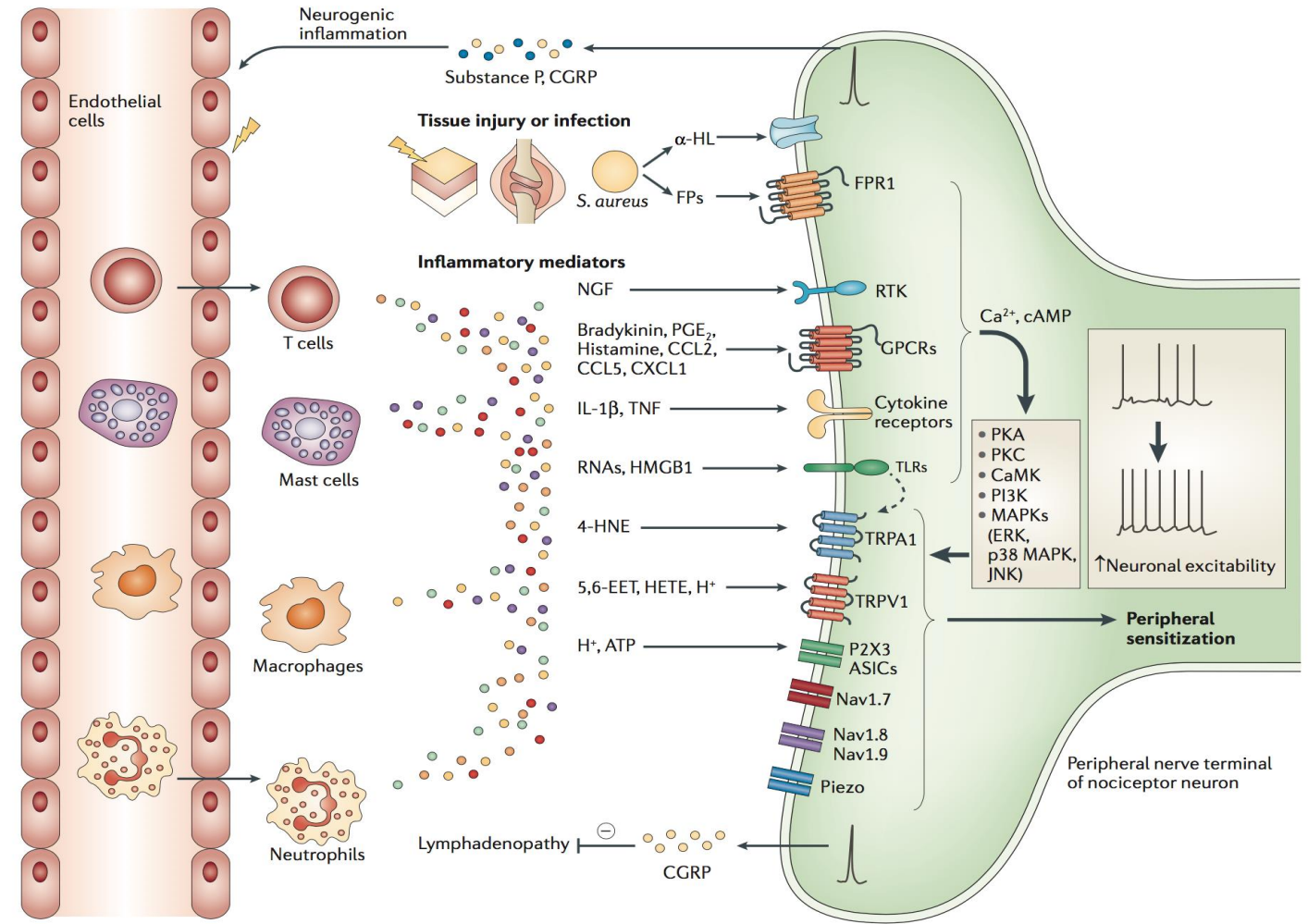
Scariche ectopiche evocate da stimoli chimici e fisici

- **Fisici: stiramento (es Lasegue)**
- **Chimici: cross-excitation da neurotrasmettitori rilasciati da neuroni vicini**
- **Attività ortosimpatica**

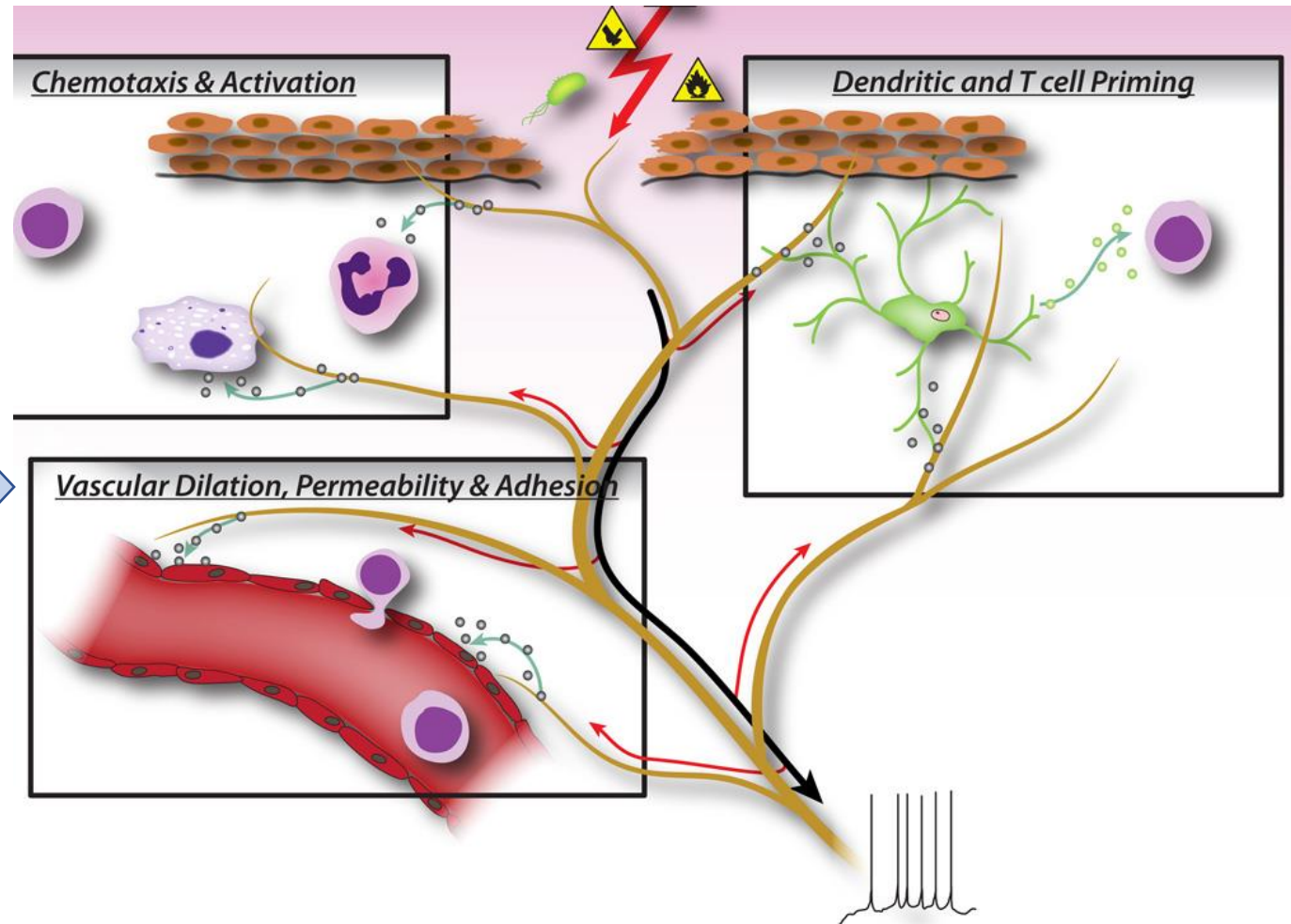
Degenerazione anterograda degli
assoni danneggiati
Prodotti della degradazione
Fibroblasti, mastociti, endotelioцити,
cellule Schwann, cellule immunità,
cheratinociti

Neuroni intatti esposti al processo
infiammatorio
Sensibilizzazione periferica

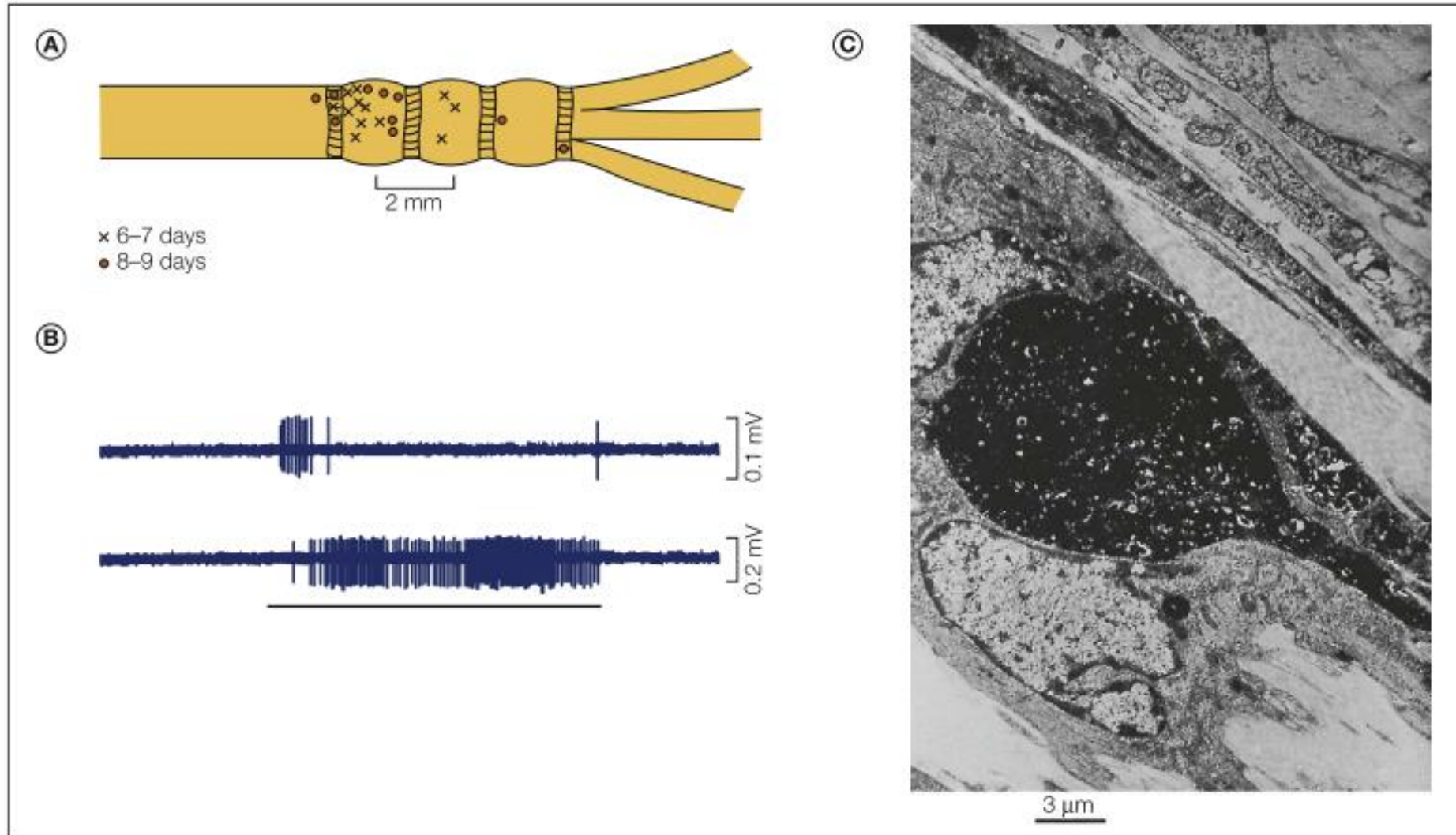
Elettrogenesi spontanea 1 spike/min
Sprouting



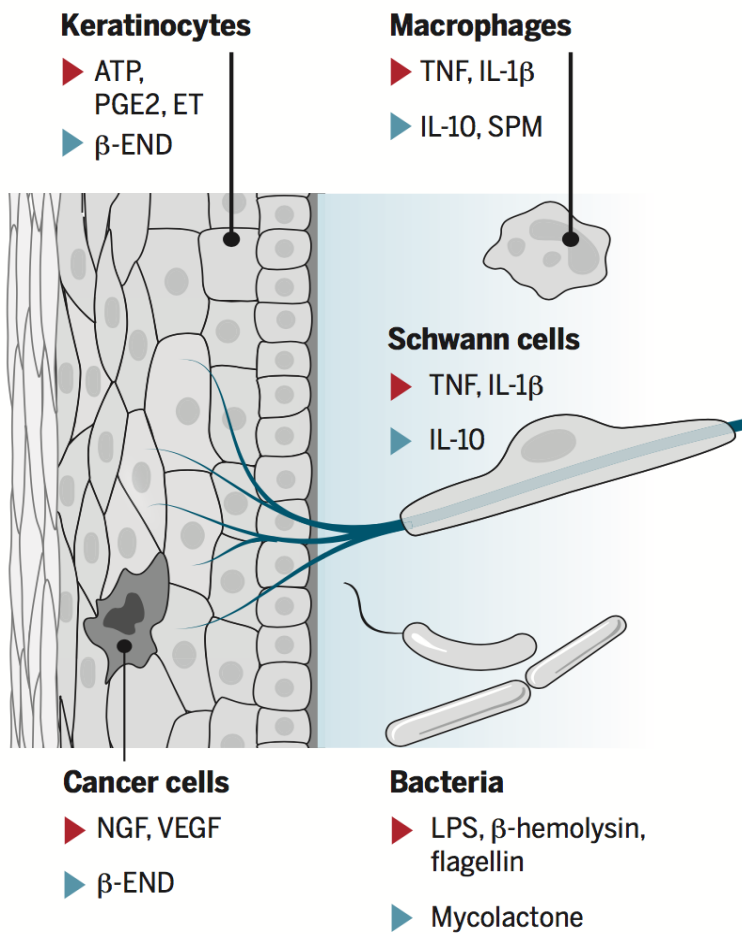
calcitonin gene related peptide (CGRP); substance P (SP);
Adrenomedullin; Neurokinins A and B;
Vasoactive intestinal peptide (VIP);
Neuropeptide Y (NP);
gastrin releasing peptide (GRP)



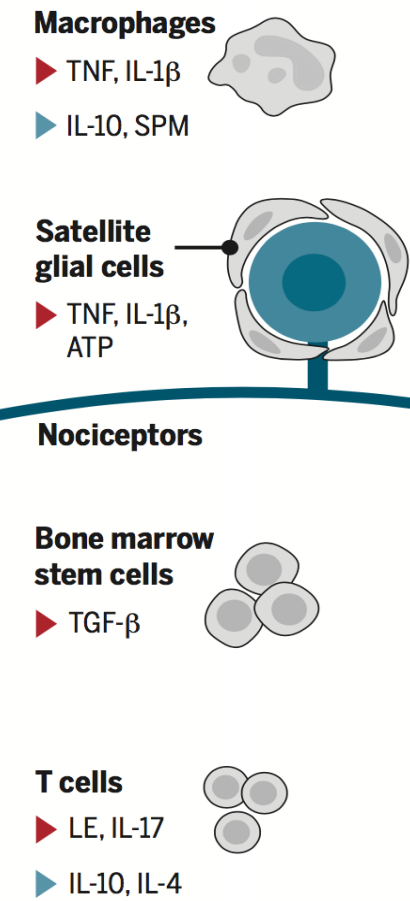
Sul nervo danneggiato si osservano “hot spots” meccanosensibili
Firing persiste oltre la durata dello stimolo
“mechanical afterdischarge”



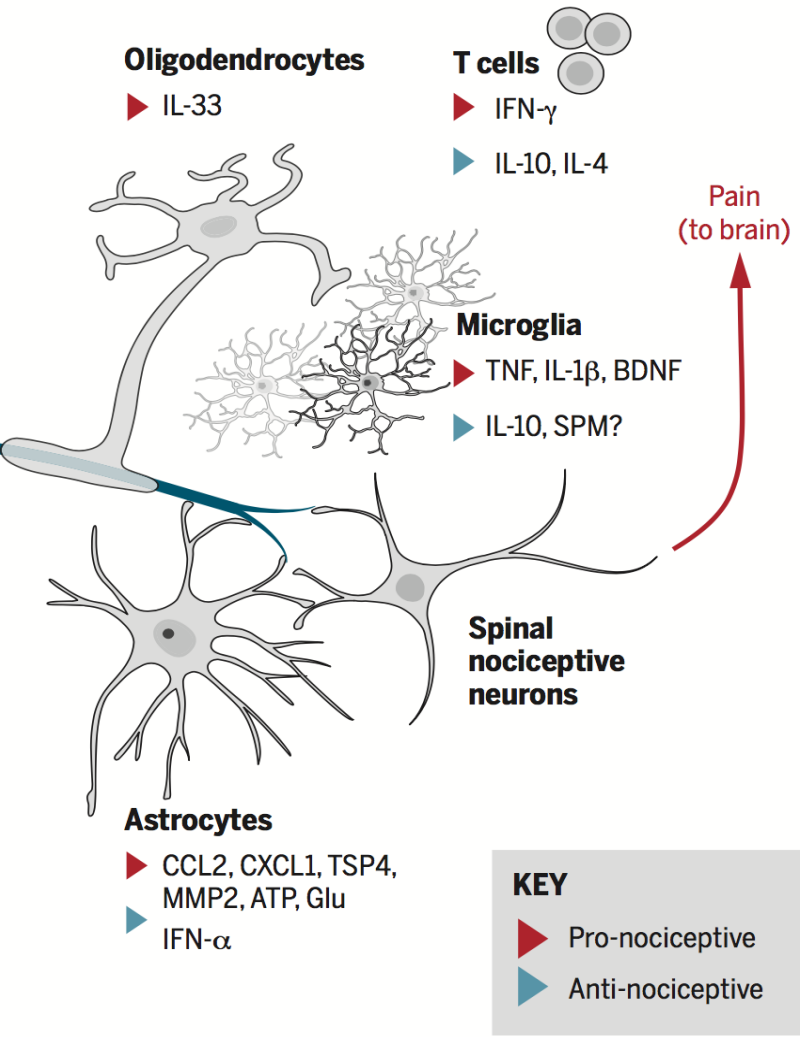
Periphery



Dorsal root ganglion



Spinal cord



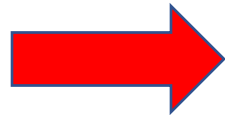
Fibra Afferente Nocicettiva

Rilascio ATP e chemochine (CCL2, CCL21, CX3CL1), Matrix MetalloProtein-9, NeuRegulin-1, Calcitonin-Related-Gene-Peptide



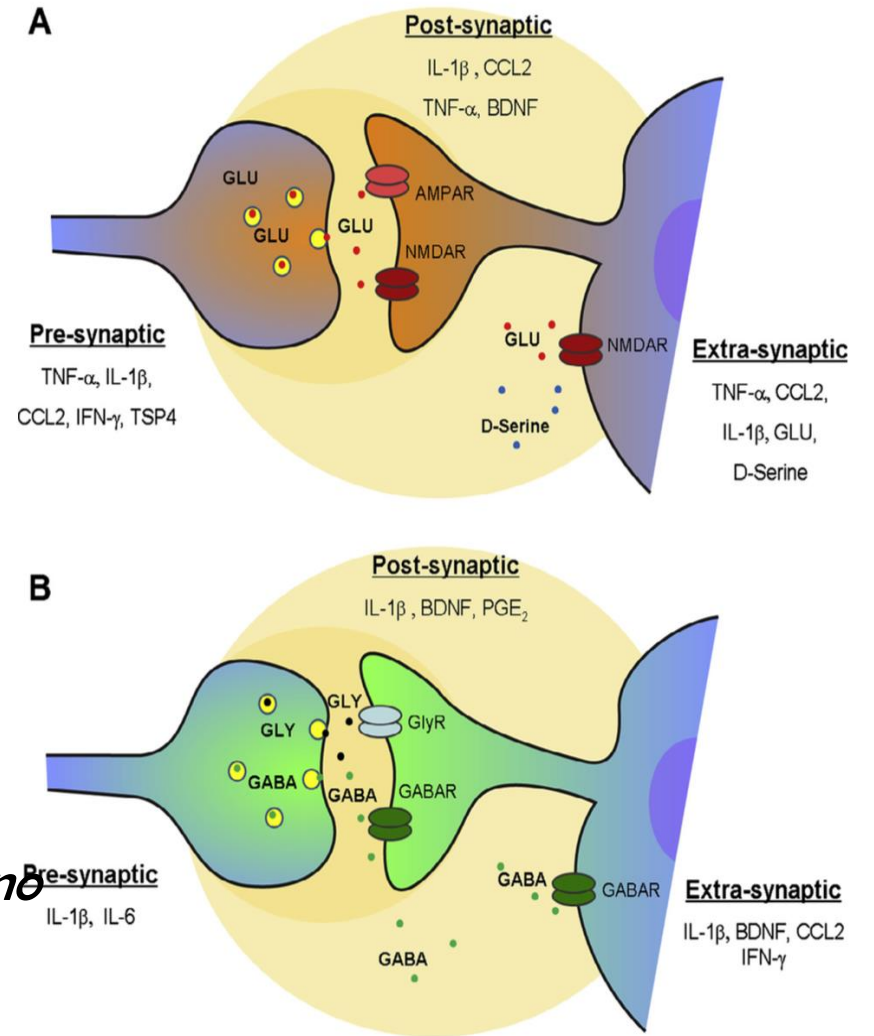
Microglia

- fosforilazione p38 e ERK
- rilascio citochine (TNF- α , IL-1 β , IL-18) e Brain-derived neurotrophic factor



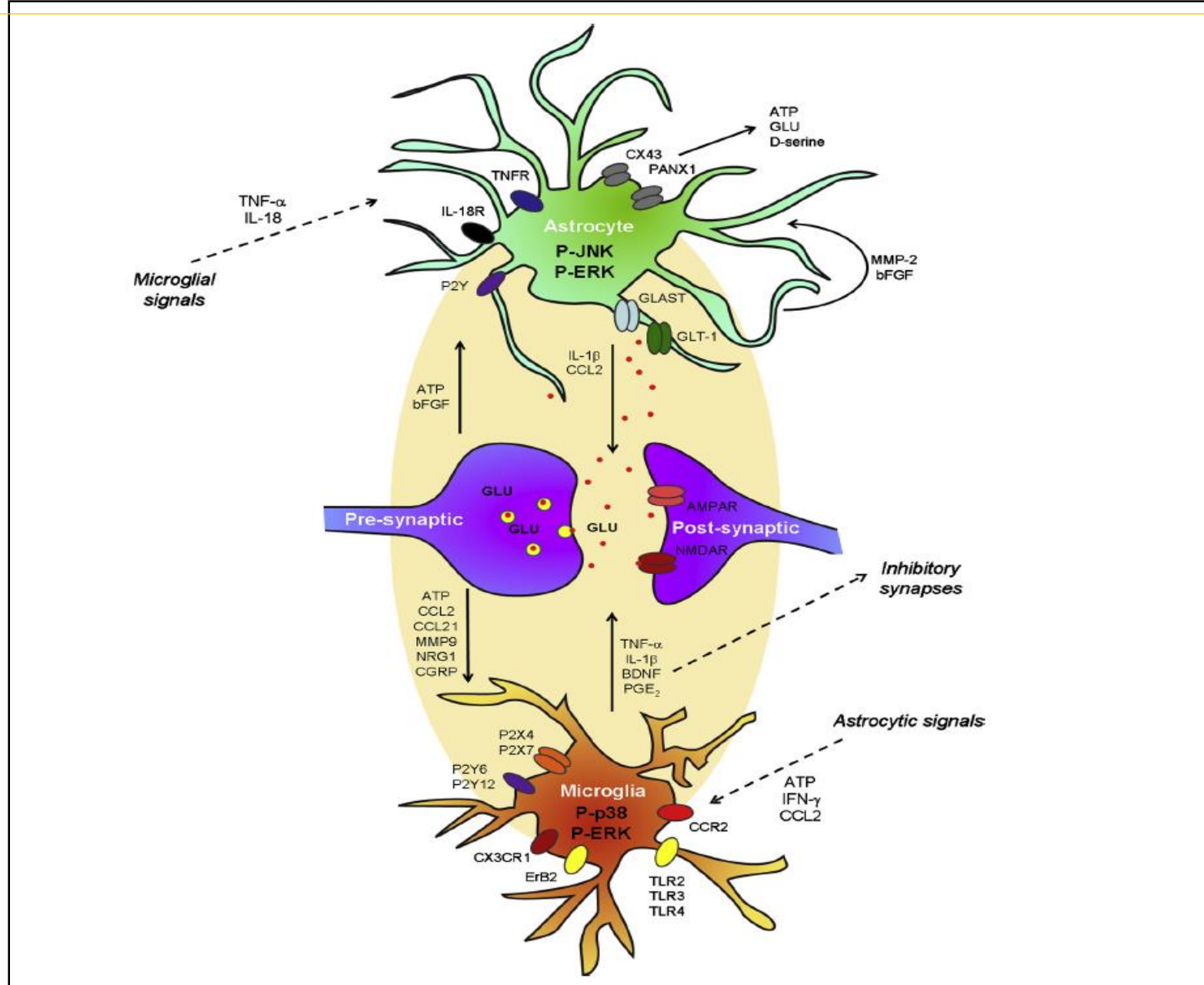
Astrocyti

- fosforilazione JNK e P-ERK
- rilascio chemochine (CCL2), citochine (IL-1 β)
- Rilascio ATP e Glutammato
- Riduzione uptake Glu da danno della fibra nervosa



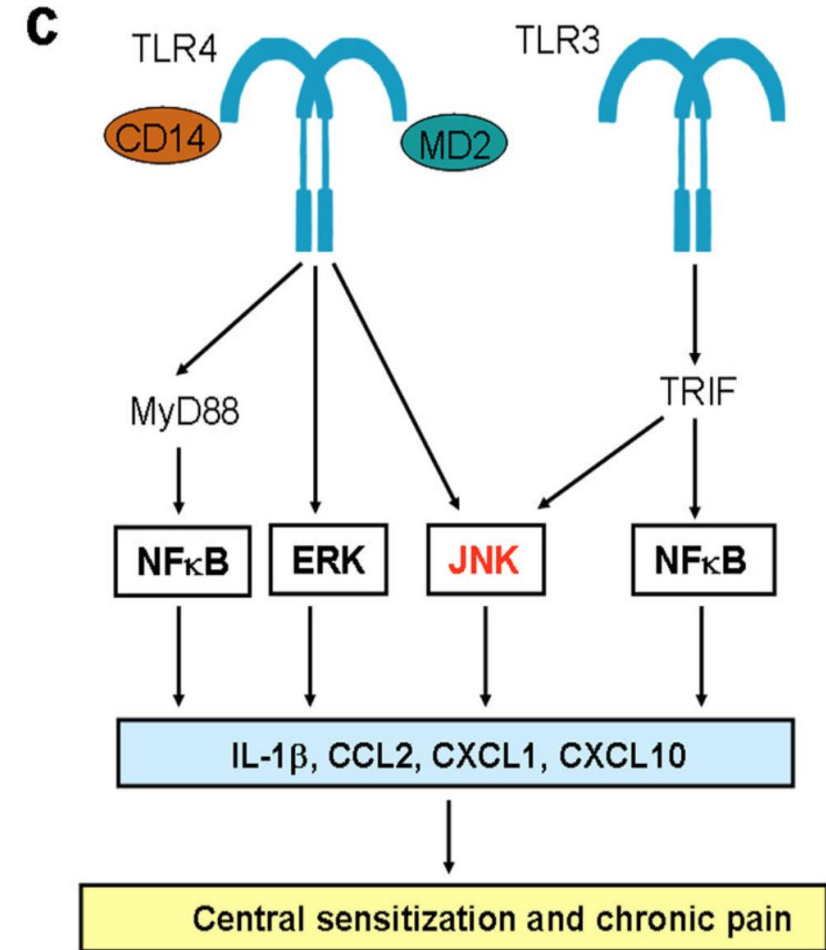
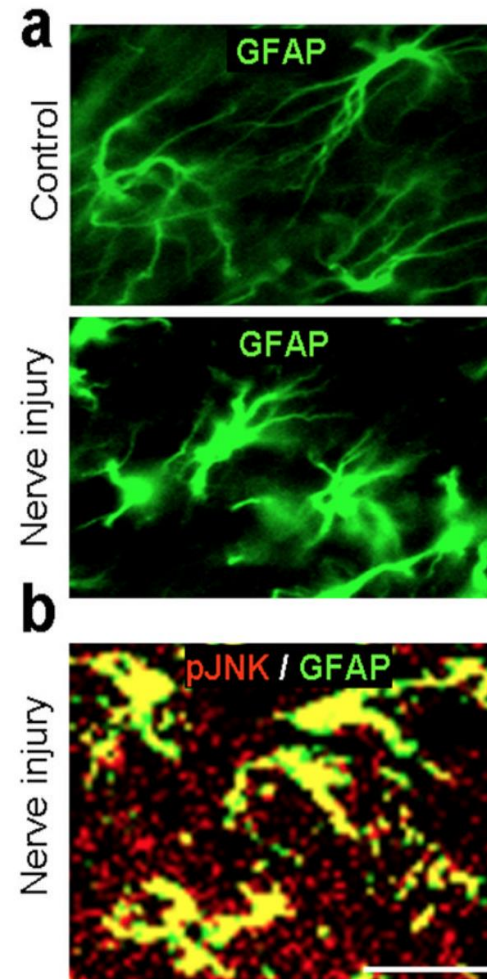
**SENSIBILIZZAZIONE NEURONI DEL CORNO DORSALE
ATTIVAZIONE DELLA MICROGLIA**


Crosstalk Neurone-Glia: Neuroinflammation



Attivazione del Toll Like Receptor 4 necessaria alla reazione microgliale spinale al nerve injury

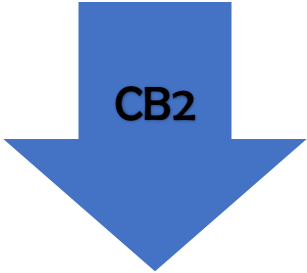
La delezione o l'antagonismo di TLR2, TLR3, TLR4 inibisce lo sviluppo di dolore neuropatico



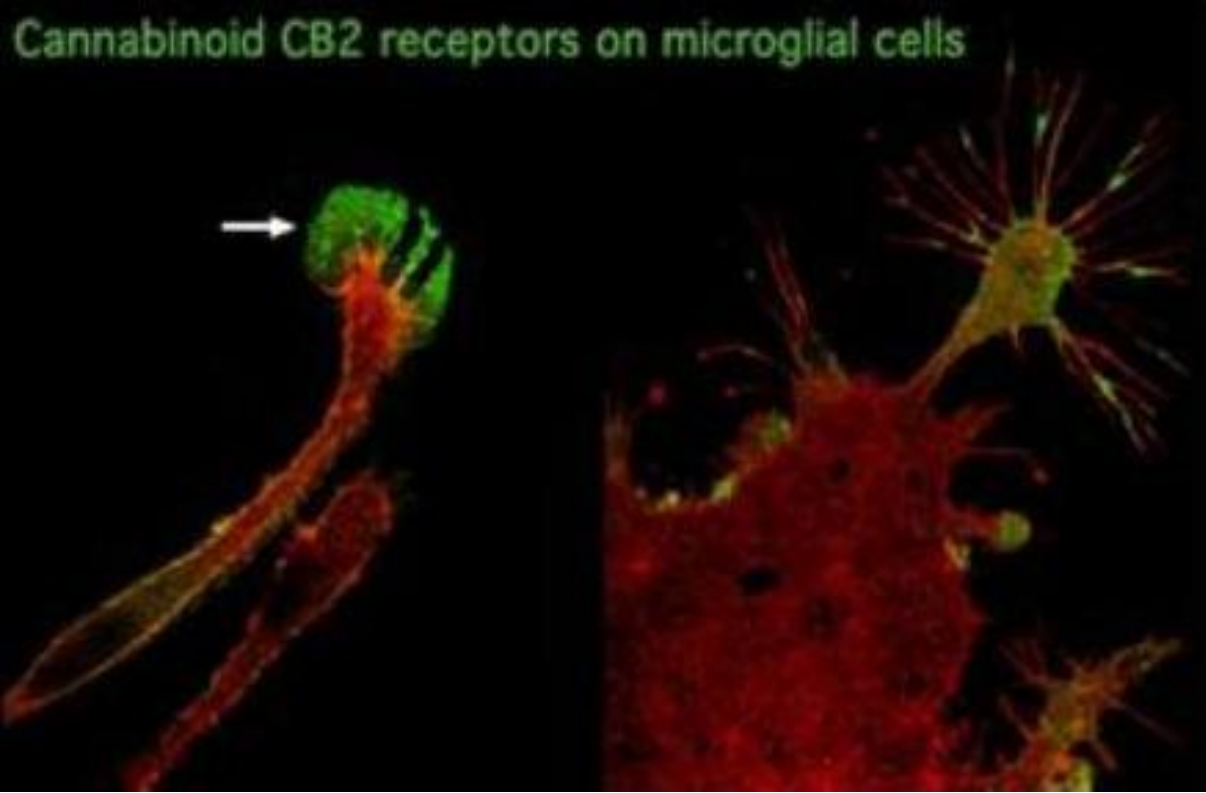


-
- Non-physiological pain signal**
- $Ca_v\alpha2\delta-1 \uparrow$
 $EphrinB1 \uparrow$
- DRG
- Primary afferent
- LPA1
- Demyelination
- SP/NK1 \uparrow
Glu/NMDA-R \uparrow
- GABAergic neuron
- Secondary spinal neuron
- KCC2 \downarrow
- c/i PLA₂ \uparrow
ATX
- LPA
- LPA5
- LPA1/3
- Microglia
- BDNF
- LPA3
- Cytokines (IL-1 β)
- Astrocyte
- Chemokines
- Central Pain
- Spinal Cord

La microglia attivata esprime il recettore CB2



- Riduzione del rilascio di CGRP nel corno dorsale
- Modulazione di ERK-1/2 kinase signalling e del rilascio di NO
- Riduzione del rilascio di TNF
- Aumento del rilascio IL-10
- Prevenzione del dolore neuropatico da taxani



Beltramo M, Bernardini N, Bertorelli R, Campanella M, Nicolussi E, Fredduzzi S, Reggiani A: CB2 receptor-mediated antihyperalgesia: possible direct involvement of neural mechanisms. *Eur J Neurosci* 2006; 23:1530–8

Racz I, Nadal X, Alferink J, Baños JE, Rehnelt J, Martín M, Pintado B, Gutierrez-Adan A, Sanguino E, Manzanares J, Zimmer A, Maldonado R: Crucial role of CB(2) cannabinoid receptor in the regulation of central immune responses during neuropathic pain. *J Neurosci Off J Soc Neurosci* 2008; 28:12125–35

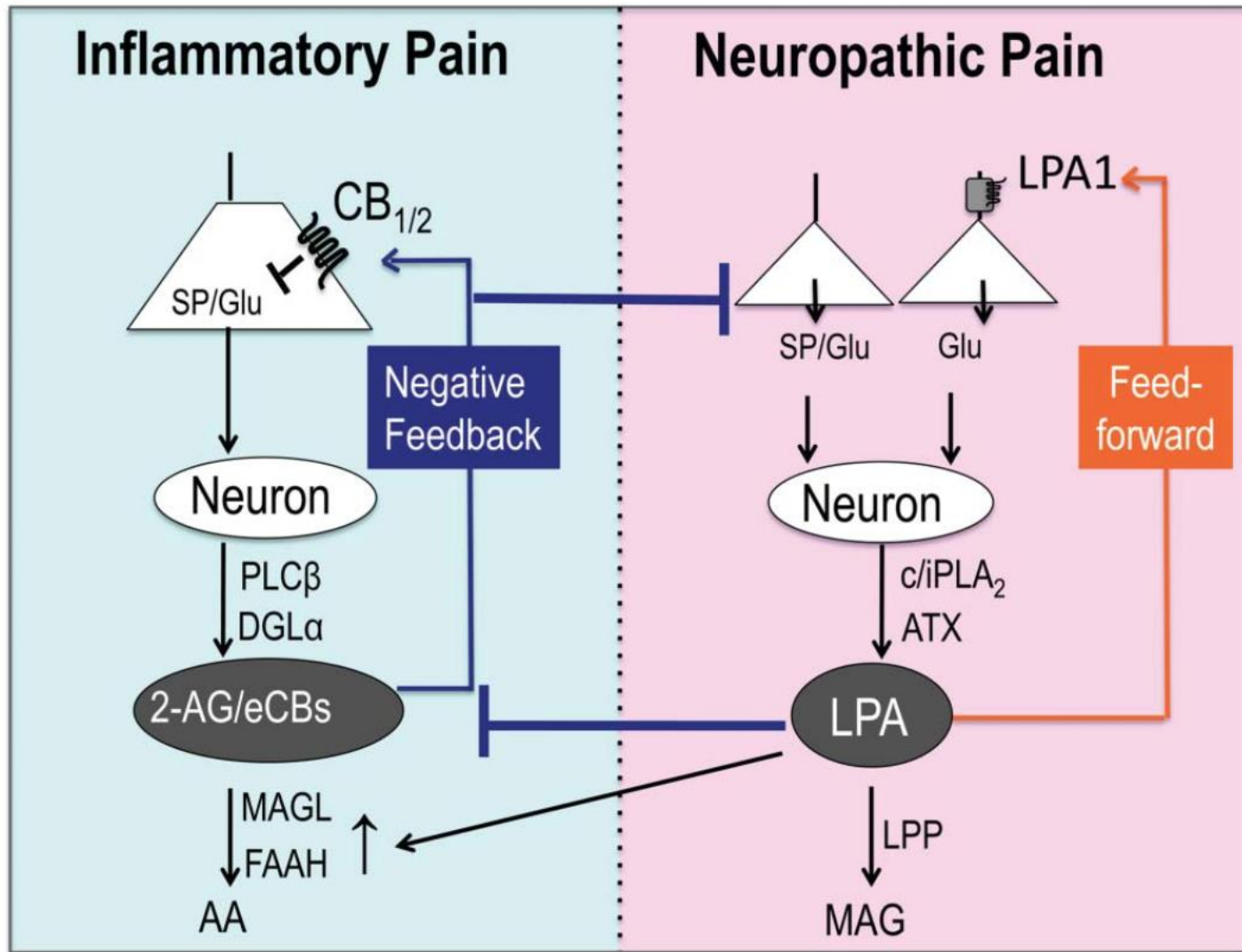
Naguib M, Xu JJ, Diaz P, Brown DL, Cogdell D, Bie B, Hu J, Craig S, Hittelman WN: Prevention of Paclitaxel-Induced Neuropathy Through Activation of the Central Cannabinoid Type 2 Receptor System. *Anesth Analg* 2012; 114:1104–20

Ehrhart J, Obregon D, Mori T, Hou H, Sun N, Bai Y, Klein T, Fernandez F, Tan J, Shytle RD: Stimulation of cannabinoid receptor 2 (CB2) suppresses microglial activation. *J Neuroinflammation* 2005; 2:29

Klegeris A, Bissonnette CJ, McGeer PL: Reduction of human monocytic cell neurotoxicity and cytokine secretion by ligands of the cannabinoid-type CB2 receptor. *Br J Pharmacol* 2003; 139:775–86

Merighi S, Gessi S, Varani K, Simioni C, Fazzi D, Mirandola P, Borea PA: Cannabinoid CB2 receptors modulate ERK-1/2 kinase signalling and NO release in microglial cells stimulated with bacterial lipopolysaccharide. *Br J Pharmacol* 2012; 165:1773–88

<http://depts.washington.edu/stella/b/research.shtml>



LPA induce l'attività dell'enzima
fatty acid amide hydrolase
(FAAH)

Riduzione degli endocannabinoidi LPA mediata

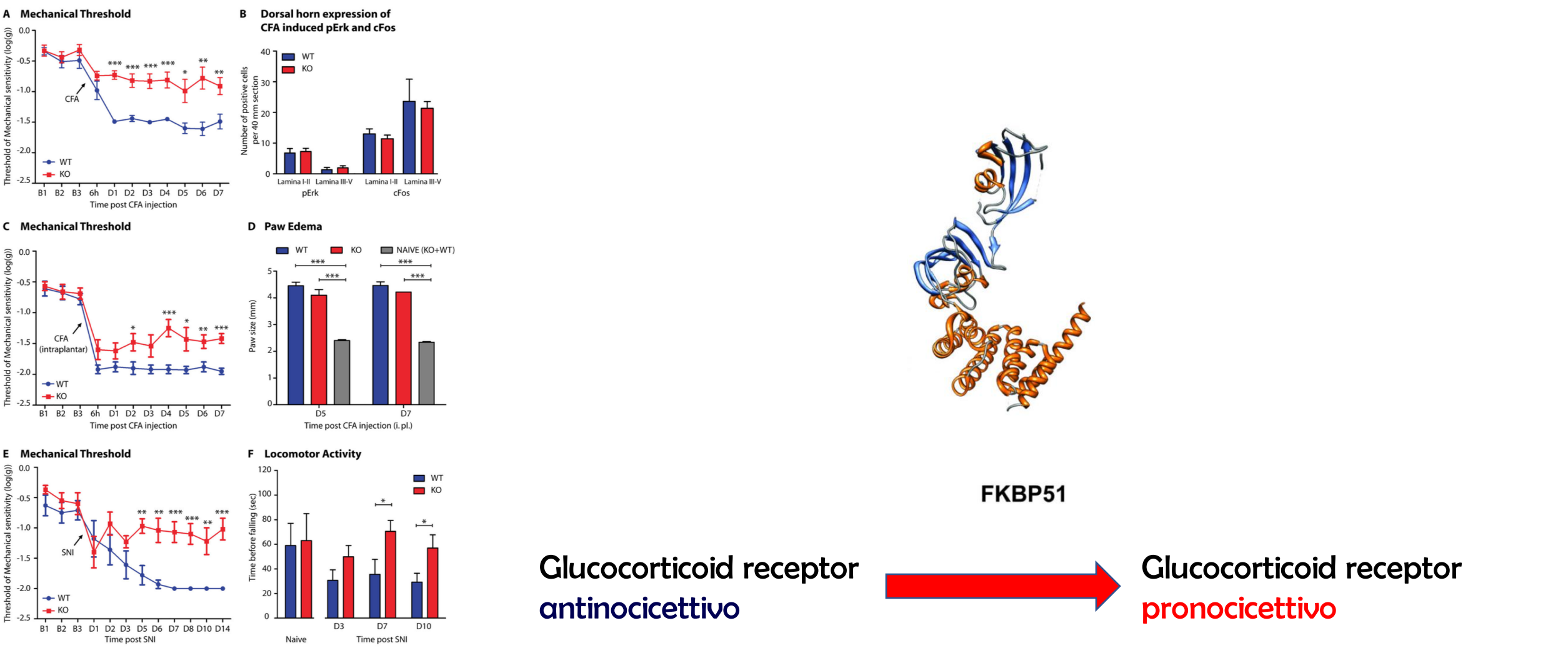


Fig. 4. Global deletion of FKBP51 reduces the mechanical hypersensitivity that develops in long term pain states.

La delezione o l'antagonismo di FKBP51 inibisce l'iperalgesia meccanica indotta dall'adiuvante di Freund

Maiarù M, Tochiki KK, Cox MB, Annan LV, Bell CG, Feng X, Hausch F, Géranton SM: The stress regulator FKBP51 drives chronic pain by modulating spinal glucocorticoid signaling. Sci Transl Med 2016; 8:325ra19

Storer CL, Dickey CA, Galianiga MD, Rein T, Cox MB: FKBP51 and FKBP52 in signaling and disease. Trends Endocrinol Metab. 2011; 22:481-90

Untargeted Metabolomics

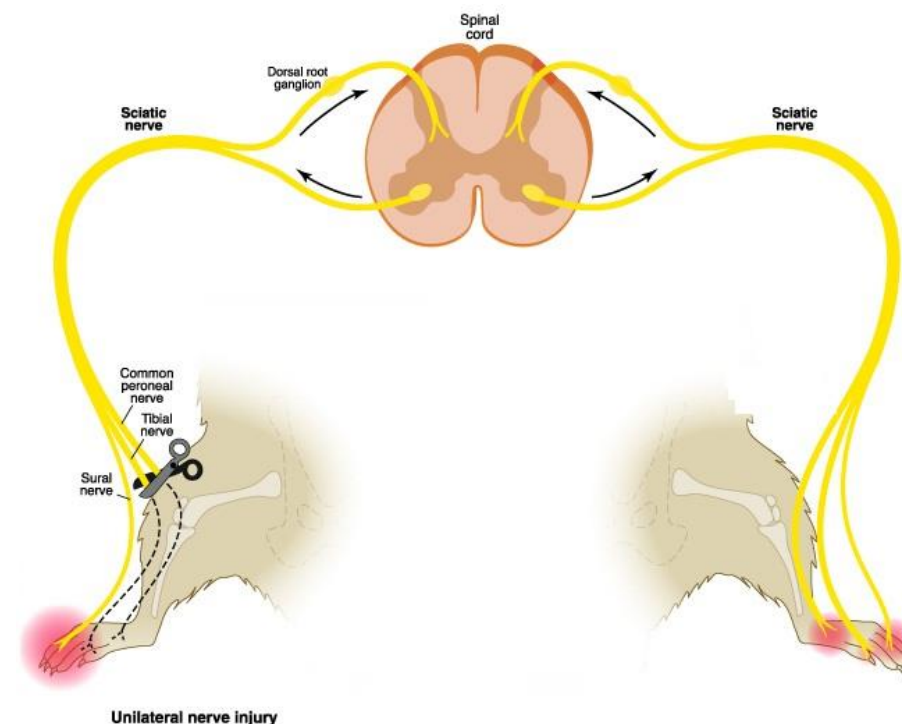
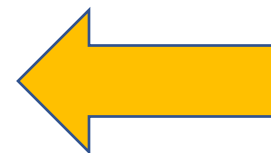
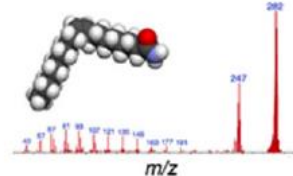
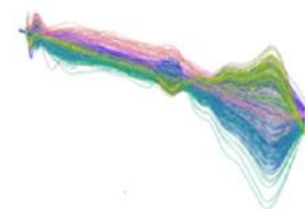
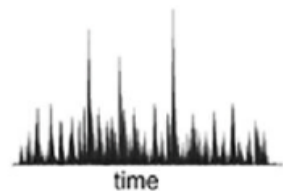
LC/MS of Metabolite Extract

Overlaid
Extracted Ion Chromatograms (EIC)

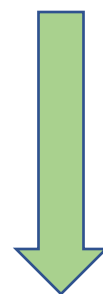
Alignment and Data Analysis

Tandem MS Database

Output



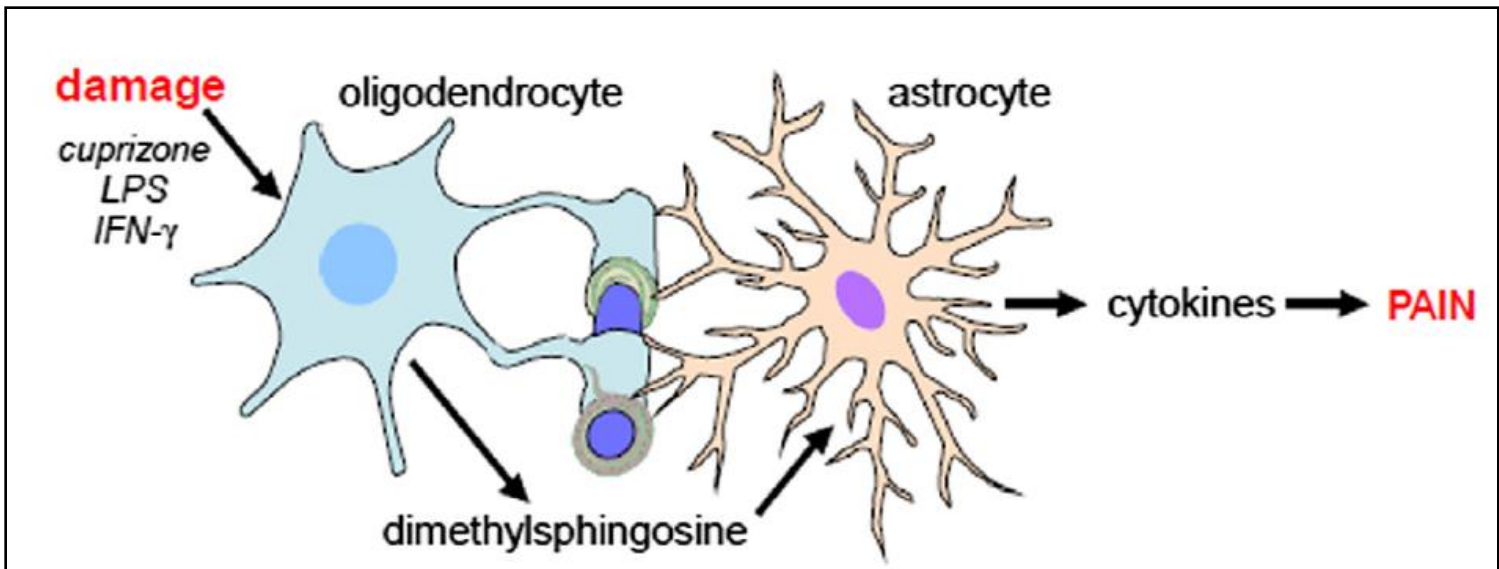
ceramide e fosfatidilcoline
monohexosylceramide
sphinganine
sphingosine
N,N-
dimethylsphingosine



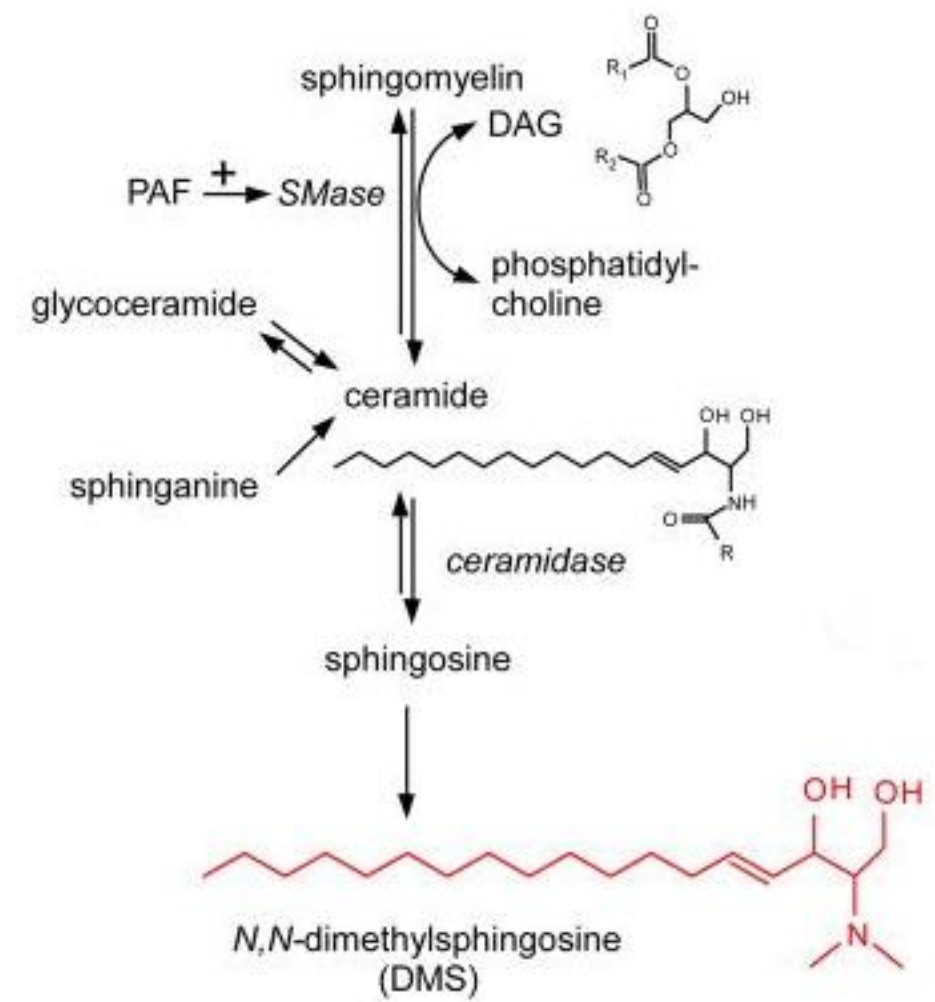
diacilgliceroli

Patti GJ, Yanes O, Siuzdak G. Innovation: Metabolomics: the apogee of the omics trilogy. Nat Rev Mol Cell Biol. 2012 Mar 22;13(4):263-9. doi: 10.1038/nrm3314.

Patti GJ, Yanes O, Shriver LP, Courade JP, Tautenhahn R, Manchester M, Siuzdak G. Metabolomics implicates altered sphingolipids in chronic pain of neuropathic origin. Nat Chem Biol. 2012 Jan 22;8(3):232-4. doi: 10.1038/nchembio.767.



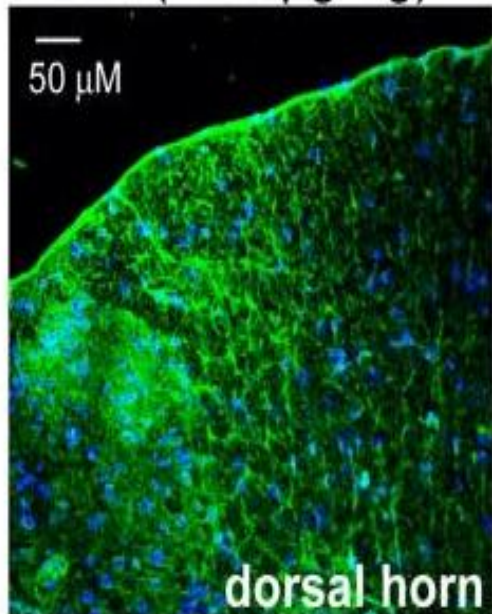
Il danno e gli stimoli infiammatori inducono il rilascio di *N,N*-dimethylsphingosine dagli oligodendrociti



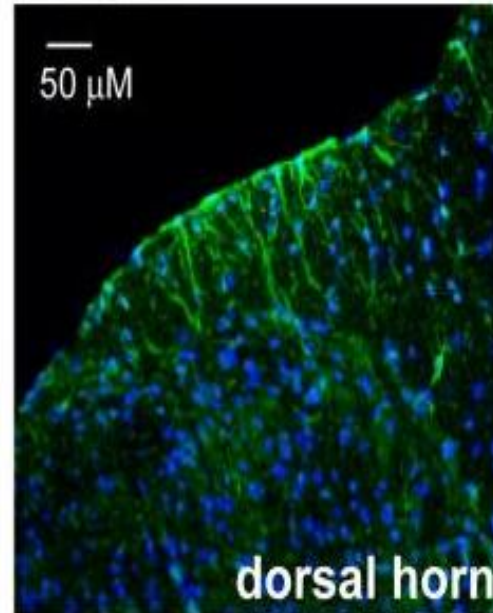
Gli astrociti esposti al N,N-dimethylsphingosine presentano un aumentato rilascio di citochine proinfiammatorie

Immunohistochemistry of DMS-treated animals

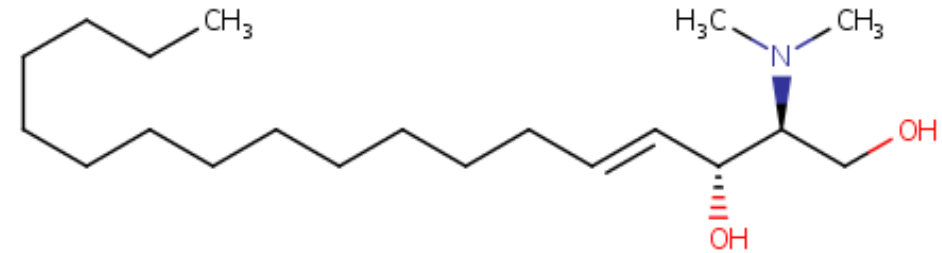
DMS (0.25 µg/Kg)



Vehicle



L'iniezione intratecale di N,N-dimethylsphingosine in ratti sani causa *allodinia meccanica*



1. Aumenta la concentrazione intracellulare di Ca^{2+} negli astrociti
2. Inibisce uptake di glutammato degli astrociti
3. Induce apoptosi
4. Ha proprietà simili alla capsaicina

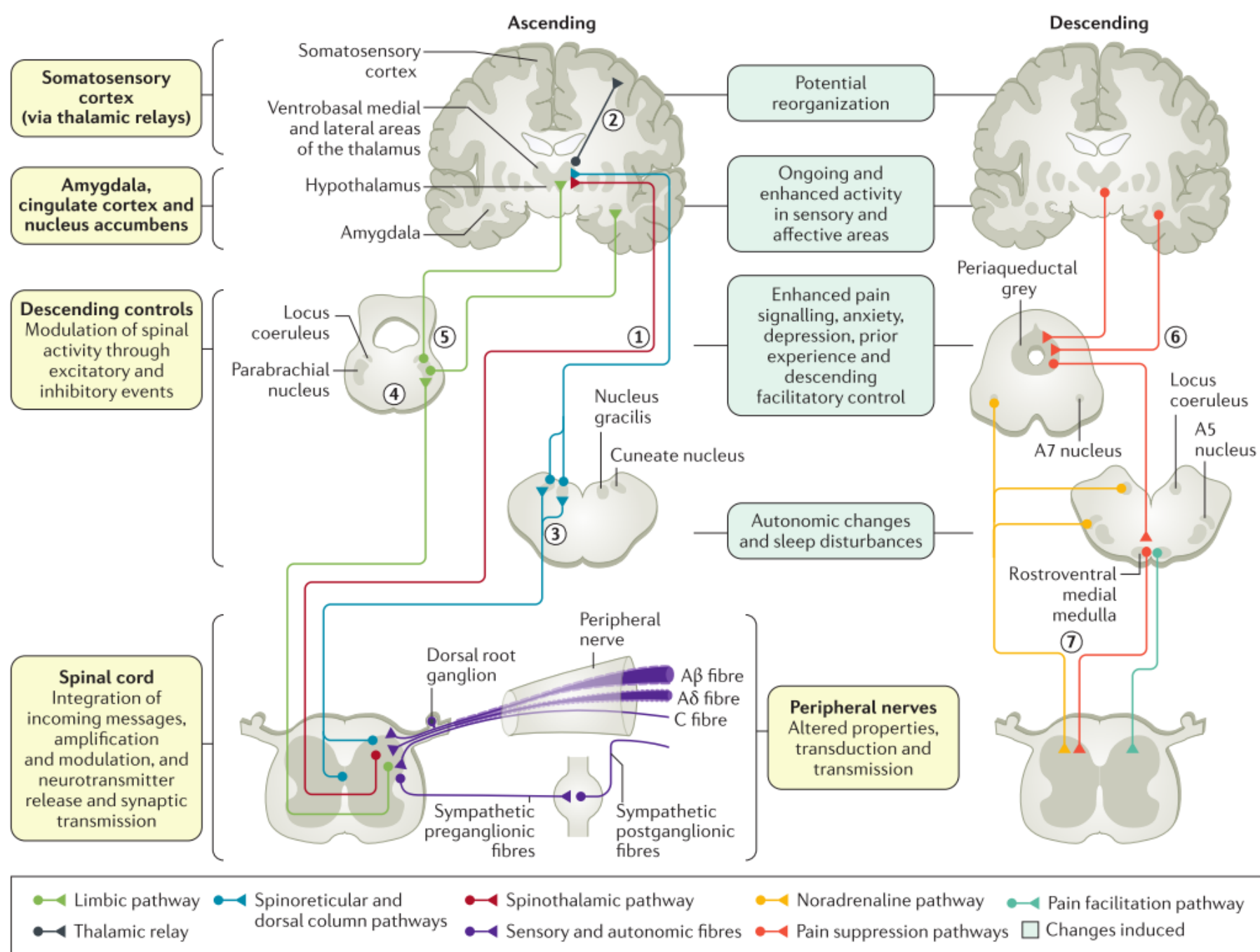
Descrittori verbali

Table 2

Frequency of the items expressed as the percentage of patients who reported a score > 0

	Percentage of patients who reported a score > 0
Burning	70.5
Pressure	60.6
Squeezing	63.4
Electric shocks	61.2
Stabbing	60.1
Evoked by brushing	68.5
Evoked by pressure	67.5
Evoked by cold stimuli	42.5
Pins and needles	63.0
Tingling	66.4

Total intensity score	Subscores	
	Burning (superficial) spontaneous pain:	
1. $Q1 =$	$Q1 =$	/10
	Pressing (deep) spontaneous pain:	
2. $(Q2 + Q3) =$	$(Q2 + Q3)/2 =$	/10
	Paroxysmal pain:	
3. $(Q5 + Q6) =$	$(Q5 + Q6)/2 =$	/10
	Evoked pain:	
4. $(Q8 + Q9 + Q10) =$	$(Q8 + Q9 + Q10)/3 =$	/10
	Paresthesia/dysesthesia:	
5. $(Q11 + Q12) =$	$(Q11 + Q12)/2 =$	/10
<hr/>		
$(1 + 2 + 3 + 4 + 5) =$	/100	



Leading
complaint

Pain

History

History of relevant neurological lesion or disease^a
and
Pain distribution neuroanatomically plausible^b

No

Unlikely to be
neuropathic pain

Yes

Possible
neuropathic pain

Examination

Pain is associated with sensory signs in the same
neuroanatomically plausible distribution^c

Yes

Probable
neuropathic pain

Confirmatory
tests

Diagnostic test confirming a lesion or disease
of the somatosensory nervous system
explaining the pain

Yes

Definite
neuropathic pain^d



NEUROPATHIC
PAIN | NeuPSIG
IASP Special Interest Group

Finnerup NB, Haroutounian S, Kamerman P, et al.
Neuropathic pain: an updated grading system for research
and clinical practice. *PAIN*. 2016;157(8).
https://journals.lww.com/pain/Fulltext/2016/08000/Neuropathic_pain__an_updated_grading_system_for.7.aspx

Topografia del dolore neuropatico

Peripheral



Within the facial or intra-oral trigeminal nerve territory

Trigeminal neuralgia*



Unilateral distribution in one or more spinal dermatome or the trigeminal nerve territory (usually the ophthalmic division)

Postherpetic neuralgia



In the innervation territory of the injured nerve, typically distal to a site of surgery, trauma or compression

Peripheral nerve injury pain



In the missing body part or residual limb

Post-amputation pain



In the feet and often the lower legs, thighs and hands

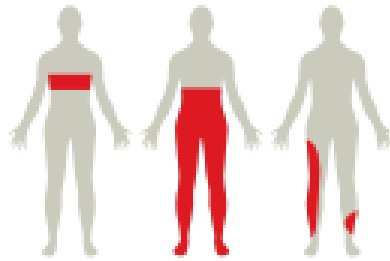
Painful polyneuropathy



In the innervation territory of the affected nerve root

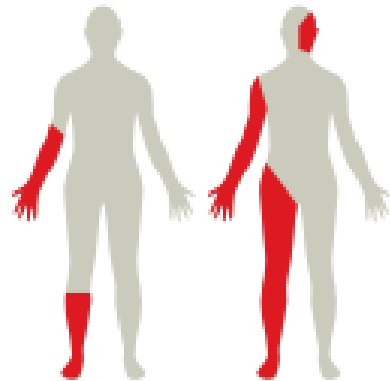
Painful radiculopathy

Central



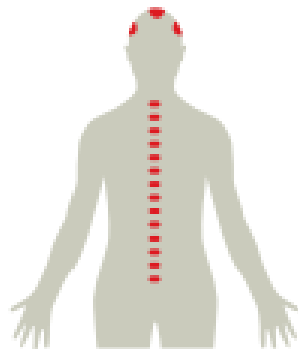
At and/or below
the level of the
spinal cord lesion

Neuropathic pain
associated with
spinal cord injury[‡]



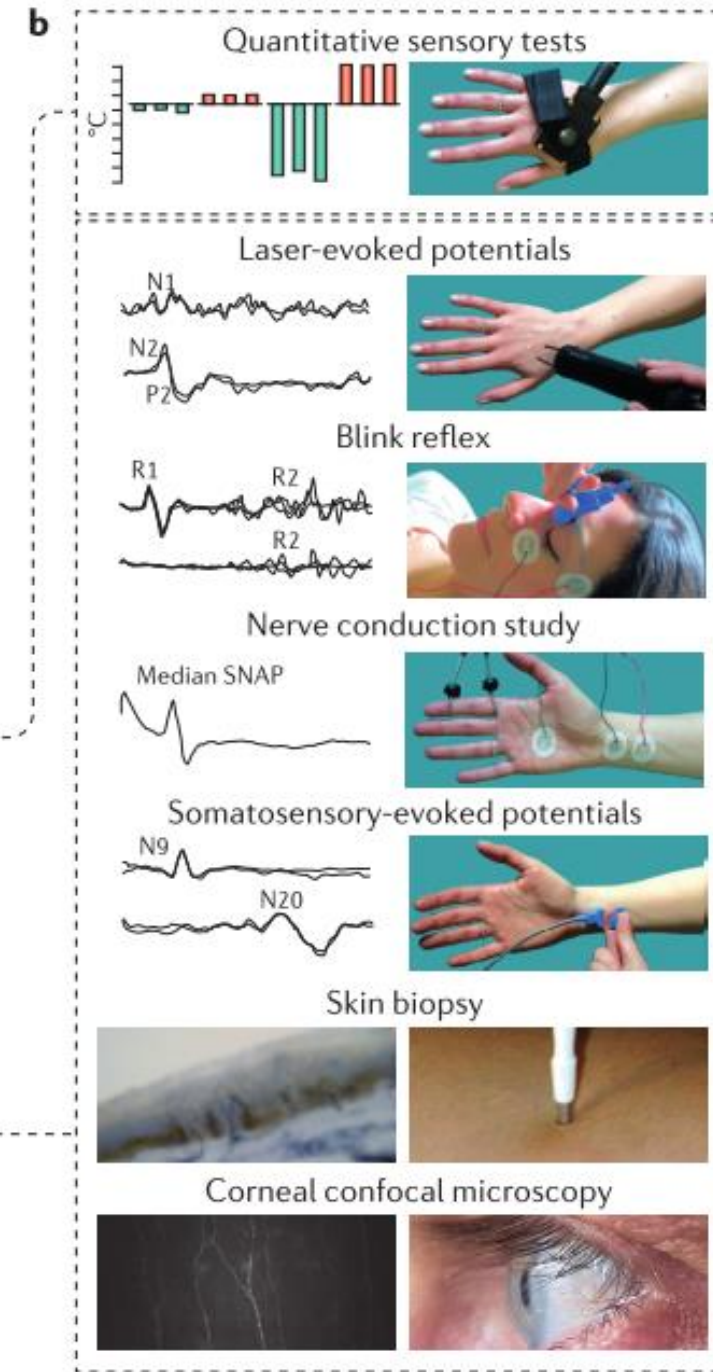
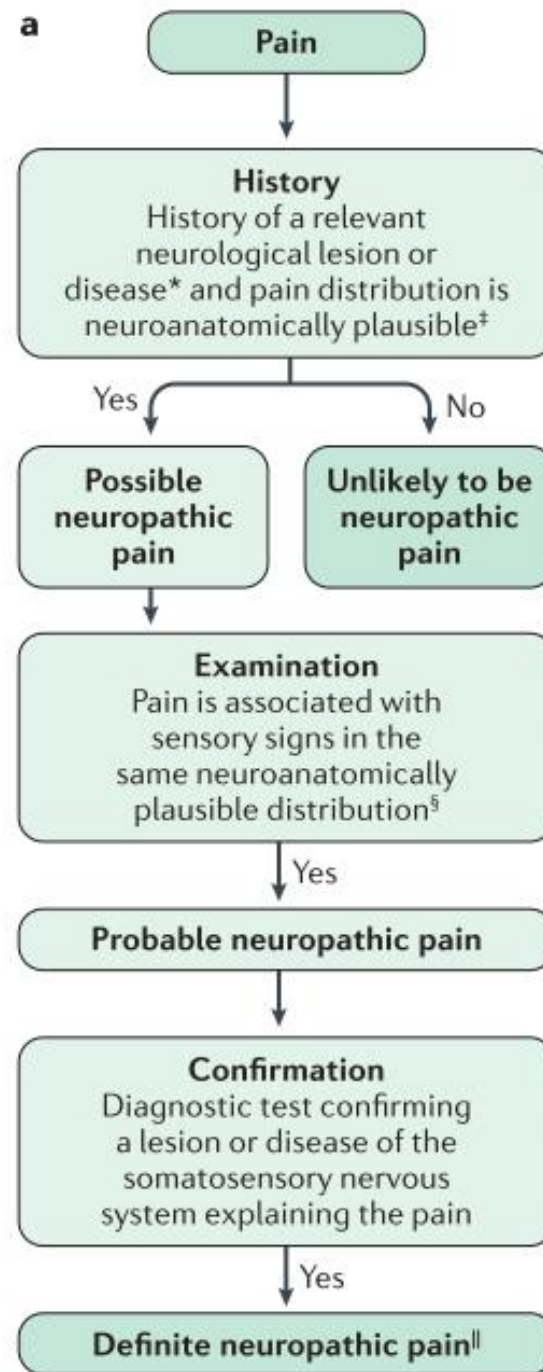
Contralateral to the
stroke; in lateral
medullary infarction,
the distribution can
also involve the
ipsilateral side of
the face

Central
post-stroke
pain



Combined
distributions of
those observed
in spinal cord
injury and stroke

Central neuropathic
pain associated with
multiple sclerosis



Questionari

THE LANSS PAIN SCALE Leeds Assessment of Neuropathic Symptoms and Signs

NAME _____ DATE _____

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

- Think about how your pain has felt over the last week.
 - Please say whether any of the descriptions match your pain exactly.
-
- 1) **Does your pain feel like strange, unpleasant sensations in your skin? Words like pricking, tingling, pins and needles might describe these sensations.**
- a) NO - My pain doesn't really feel like this..... (0)
- b) YES - I get these sensations quite a lot..... (5)
-
- 2) **Does your pain make the skin in the painful area look different from normal? Words like mottled or looking more red or pink might describe the appearance.**
- a) NO - My pain doesn't affect the colour of my skin..... (0)
- b) YES - I've noticed that the pain does make my skin look different from normal (5)

3) Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.

a) NO - My pain doesn't make my skin abnormally sensitive in that area..... (0)

b) YES - My skin seems abnormally sensitive to touch in that area..... (3)

4) Does your pain come on suddenly and in bursts for no apparent reason when you're still. Words like electric shocks, jumping and bursting describe these sensations.

a) NO - My pain doesn't really feel like this (0)

b) YES - I get these sensations quite a lot (2)

5) Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations

a) NO - I don't really get these sensations..... (0)

b) YES - I get these sensations quite a lot (1)

B. SENSORY TESTING

Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pin-prick threshold (PPT).

1) ALLODYNIA

Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

- a) NO, normal sensation in both areas (0)
- b) YES, allodynia in painful area only (5)

2) ALTERED PIN-PRICK THRESHOLD

Determine the pin-prick threshold by comparing the response to a 23 gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently on to the skin in a non-painful and then painful areas.

If a sharp pin prick is felt in the non-painful area, but a different sensation is experienced in the painful area e.g. none / blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

- a) NO, equal sensation in both areas (0)
- b) YES, altered PPT in painful area (3)

SCORING:





Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE (maximum 24)

If score < 12 , neuropathic mechanisms are **unlikely** to be contribution to the patient's pain

If score ≥ 12 , neuropathic mechanisms are **likely** to be contributing to the patient's pain

Table 1. *painDETECT* questionnaire

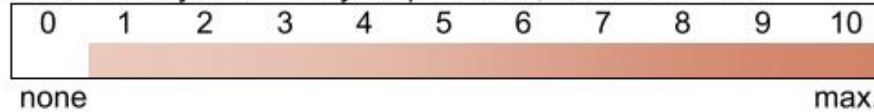
Item	Score
<i>Gradation of pain*</i>	
• Do you suffer from a burning sensation (e.g. stinging nettles) in the marked areas?	0–5
• Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?	0–5
• Is light touching (clothing, a blanket) in this area painful?	0–5
• Do you have sudden pain attacks in the area of your pain, like electric shocks?	0–5
• Is cold or heat (bath water) in this area occasionally painful?	0–5
• Do you suffer from a sensation of numbness in the areas that you marked?	0–5
• Does slight pressure in this area, e.g. with a finger, trigger pain?	0–5
<i>Pain course pattern</i>	
Please select the picture that best describes the course of your pain:	
 Persistent pain with slight fluctuations	0
 Persistent pain with pain attacks	–1
 Pain attacks without pain between them	+1
 Pain attacks with pain between them	+1
<i>Radiating pain</i>	
Does your pain radiate to other regions of your body? Yes/No	+2/0

*For each question: never, 0; hardly noticed, 1; slightly, 2; moderately, 3; strongly, 4; very strongly, 5

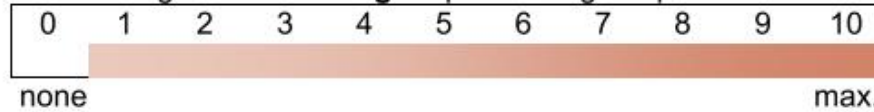
Questions used to document pain, but which were not used in the scoring, are not shown

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

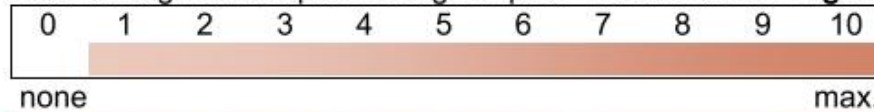
How would you assess your pain **now**, at this moment?



How strong was the **strongest** pain during the past 4 weeks?



How strong was the pain during the past 4 weeks **on average**?



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
<input type="checkbox"/> x 0 = 0	<input type="checkbox"/> x 1 = <input type="text"/>	<input type="checkbox"/> x 2 = <input type="text"/> <input type="text"/>	<input type="checkbox"/> x 3 = <input type="text"/> <input type="text"/>	<input type="checkbox"/> x 4 = <input type="text"/> <input type="text"/>	<input type="checkbox"/> x 5 = <input type="text"/> <input type="text"/>
Total score			<input type="text"/> <input type="text"/>	out of 35	

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

©2005 Pfizer Pharma GmbH

Please transfer the total score from the pain questionnaire:

Total score

Please add up the following numbers, depending on the marked pain behavior pattern and the pain radiation. Then total up the final score:



Persistent pain with slight fluctuations

0



Persistent pain with pain attacks

- 1

if marked, or



Pain attacks without pain between them

+ 1

if marked, or



Pain attacks with pain between them

+ 1

if marked



Radiating pains?

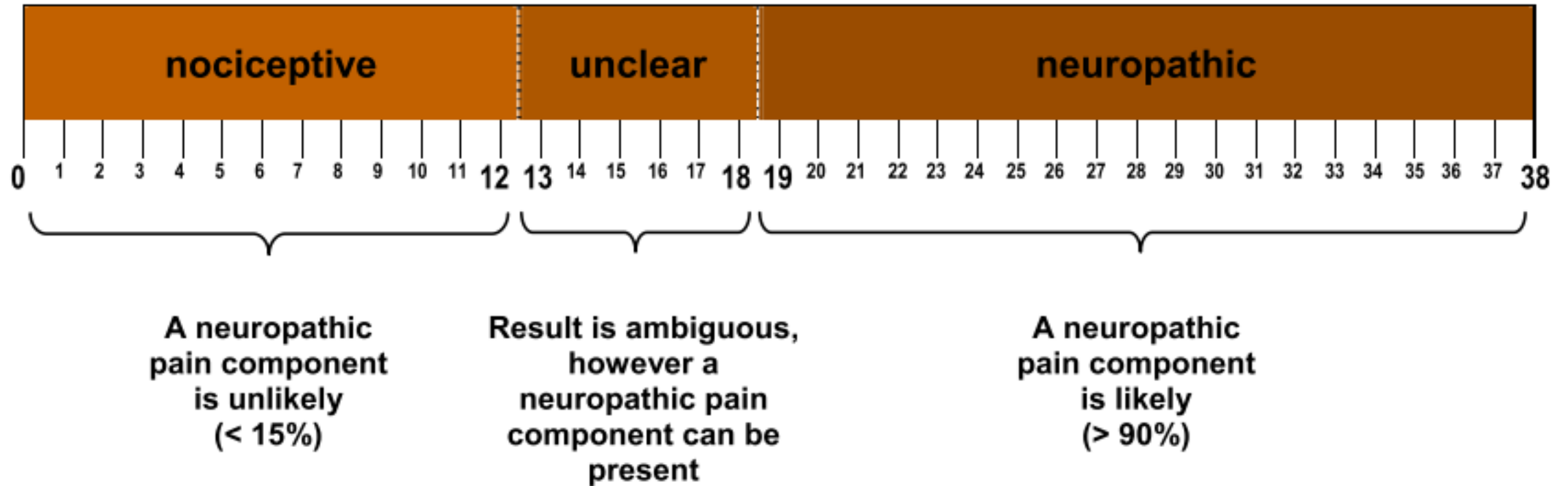
+ 2

if yes

Final score

Screening Result

Final score



Terapia farmacologica EBM

	EFNS [7]				NICE [10]		CPS [2]		NeuPSIG [4]
	Diabetic neuropathy	Post-herpetic neuralgia	Trigeminal neuralgia	Central neuropathic pain	All neuropathic pain	Trigeminal neuralgia	All neuropathic pain	Trigeminal neuralgia	All neuropathic pain
First-line therapy	Duloxetine Gabapentin Pregabalin TCA Venlafaxine ^d	Gabapentin Pregabalin TCA Lidocaine plasters ^a	Carbamazepine Oxcarbazepine	Gabapentin Pregabalin TCA	Amitriptyline Duloxetine Gabapentin Pregabalin Capsaicin cream ^b (localized pain in patients who wish to avoid or who cannot tolerate oral treatments)	Carbamazepine	Gabapentin Pregabalin Duloxetine Venlafaxine ^d TCA	Carbamazepine	Gapabentin Gabapentin ER/enacarbil Pregabalin Duloxetine Venlafaxine ^d TCAs
Second-line therapy	Tramadol	Strong opioids Capsaicin cream		Tramadol Strong opioids	One of the remaining 3 oral drugs of the First-line therapy		Tramadol Strong opioids Lidocaine cream ^c Lidocaine patches ^c		Capsaicin patches ^b Lidocaine patches ^b Tramadol

	EFNS [7]				NICE [10]		CPS [2]		NeuPSIG [4]
	Diabetic neuropathy	Post-herpetic neuralgia	Trigeminal neuralgia	Central neuropathic pain	All neuropathic pain	Trigeminal neuralgia	All neuropathic pain	Trigeminal neuralgia	All neuropathic pain
Third-line therapy	Strong opioids			Strong opioids	One of the remaining 3 oral drugs of the First-line therapy		Cannabinoids		Botulinum toxin type A Strong opioids
Fourth-line therapy				Lamotrigine (in central post-stroke pain) Cannabinoids (in multiple sclerosis)			Other opioids Lacosamide Lamotrigine Botulinum toxin Lidocaine cream Lidocaine patches		

Fenotipizzazione sul profilo sensoriale

B

Validation data set (n=233)

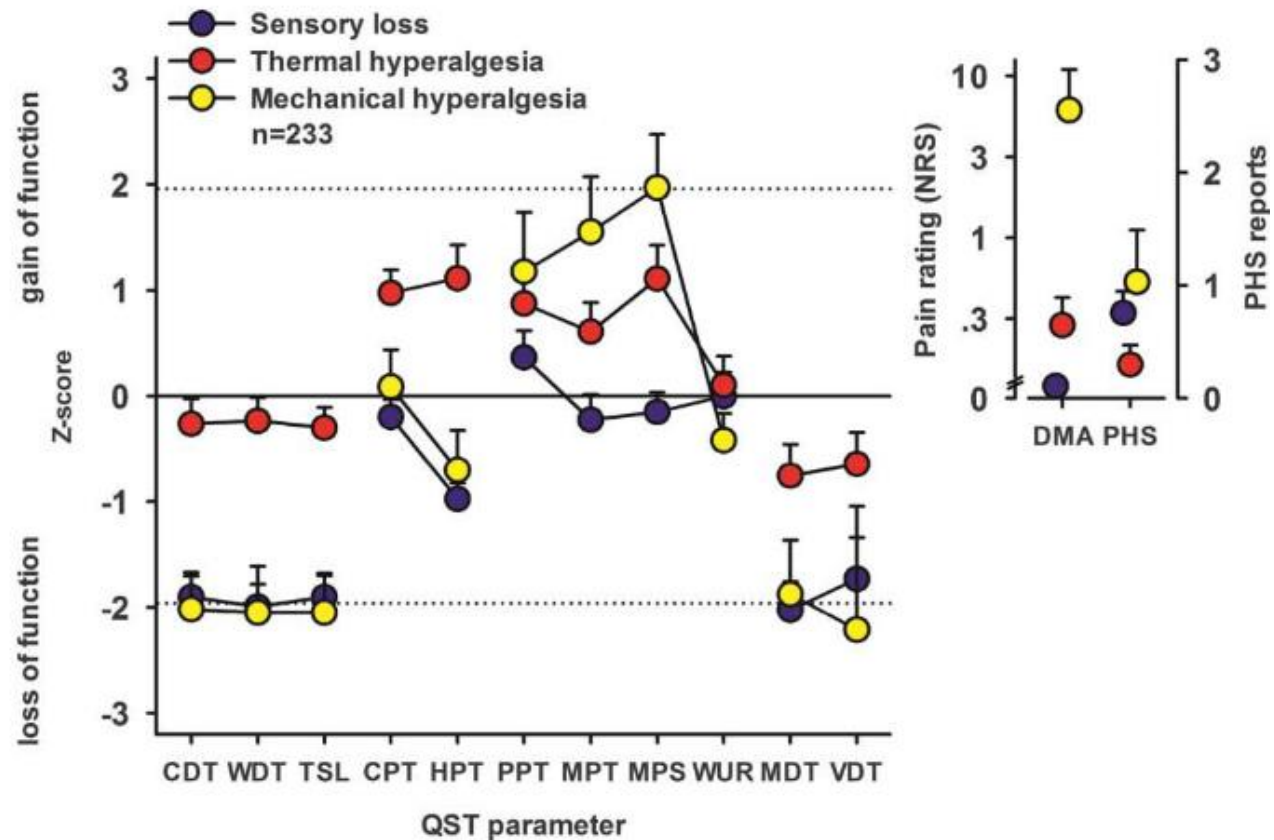


Figure 2. Sensory profiles of the 3-cluster solution for test and replication data sets. Sensory profiles of the 3 clusters presented as mean z scores \pm 95% confidence interval for the test data set (n = 902, A) and the validation data set (n = 233, B). Note that z transformation eliminates differences due to test site, sex, and age. Positive z scores indicate positive sensory signs (hyperalgesia), whereas negative z values indicate negative sensory signs (hypoesthesia and hypoalgesia). Dashed lines: 95% confidence interval for healthy subjects ($-1.96 < z < +1.96$). Note that if the mean of a cluster is within the shaded area, this does not imply that it does not differ from a healthy cohort. Values are significantly different from those of healthy subjects, if their 95% confidence interval does not cross the zero line. Insets show numeric pain ratings for dynamic mechanical allodynia (DMA) on a logarithmic scale (0-100) and frequency of paradoxical heat sensation (PHS) (0-3). Blue symbols: cluster 1 “sensory loss” (42% in A and 53% in B). Red symbols: cluster 2 “thermal hyperalgesia” (33% in A and B). Yellow symbols: cluster 3 “mechanical hyperalgesia” (24% in A and 14% in B). CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; NRS, Numerical Rating Scale; PPT, pressure pain threshold; QST, quantitative sensory testing; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

A Cluster 1 ("sensory loss", n=381)

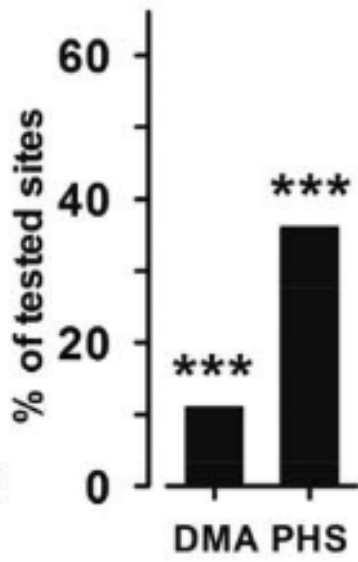
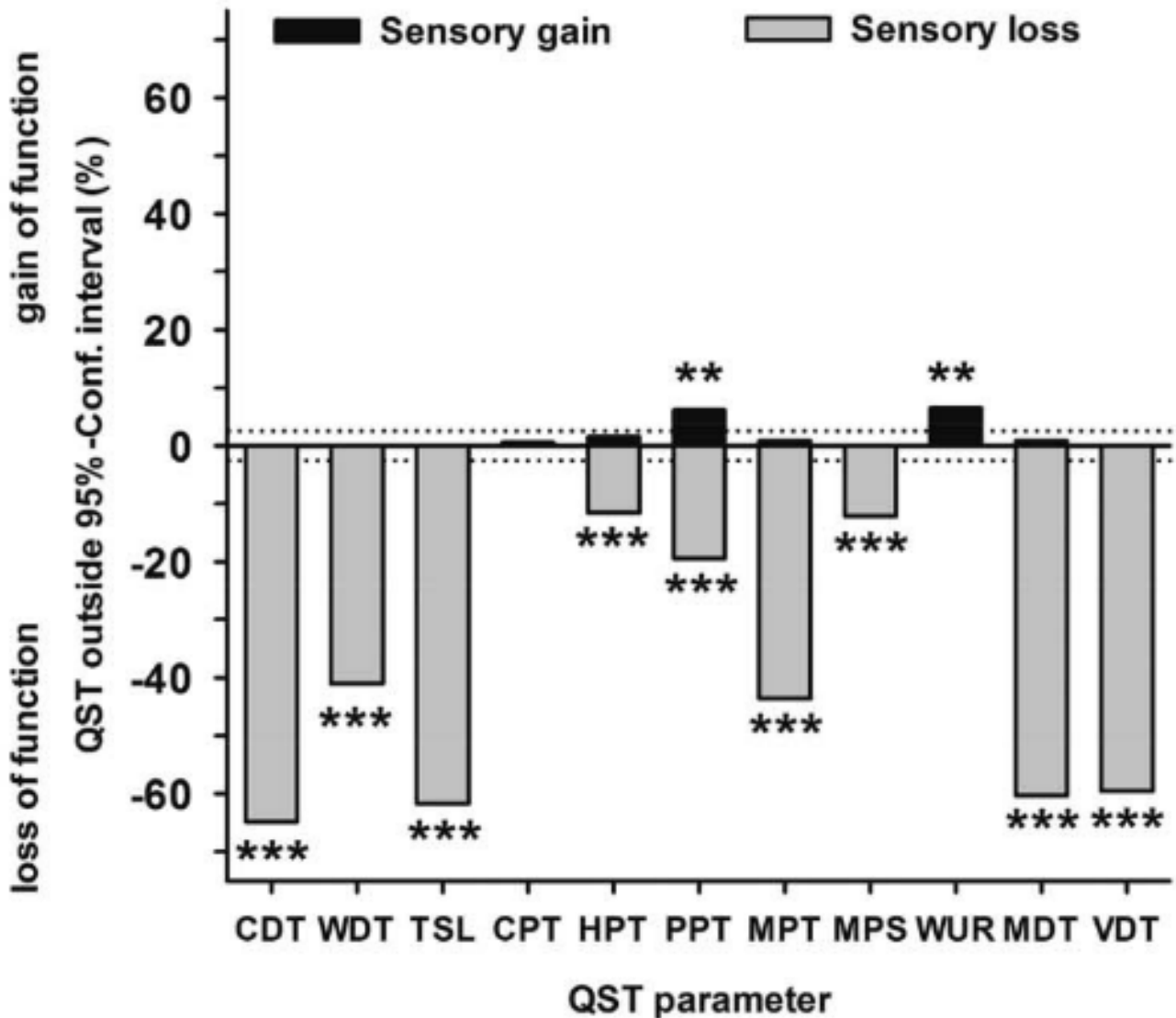


Figure 4. Frequencies of abnormal quantitative sensory testing (QST) findings for the test data set (n = 902). Each column gives the percentage of patients with abnormal findings for that particular QST parameter (outside the 95% CI of healthy subjects). Positive values indicate positive sensory signs (hyperalgesia), whereas negative values indicate negative sensory signs (hypoesthesia and hypoalgesia). Dashed lines: Expected value for healthy subjects ($\pm 2.5\%$). A: cluster 1 "sensory loss" (n = 381 patients), B: cluster 2 "thermal hyperalgesia" (n = 302 patients), C: cluster 3 "mechanical hyperalgesia" (n = 219 patients). Significant compared with the expected value (2.5%) on $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. 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; NRS, Numerical Rating Scale; PHS, paradoxical heat sensation; PPT, pressure pain threshold; QST, quantitative sensory testing; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

4.1. Cluster 1 (sensory loss)

paradoxical heat sensation
(PHS)

Cluster 1 (42%) was characterized by a loss of small and large fiber function and the presence of PHSs (**Table 4**). These patients did not suffer from sensory gain except a mild DMA in few patients. About 52% of patients with polyneuropathies fell into this category indicating dying-back degeneration of nearly all fiber classes. Interestingly, 43% of patients with painful RAD demonstrated this sensory pattern, suggesting severe degeneration of sensory fibers within the affected nerve root. Paradoxical heat sensation was most frequent, which suggests that it is induced by a loss of afferent input although at face value, it is a positive sensory sign possibly related to a central disinhibition process.^{29,69}

The sensory profile is similar to that of a compression nerve block.^{7,24,70} It likely represents the “deafferentation” or “painful hypoesthesia” subgroups described by others.^{7,20,31,61} The spontaneous pain was likely due to ectopic action potentials generated in proximal sites of injured nociceptors,¹⁰ eg, in the dorsal root ganglion or in deafferented central nociceptive neurons.^{16,46,54} Laboratory tests for neuropathic pain assessment are likely to show denervation and loss of function (**Table 4**).²⁸

B Cluster 2 ("thermal hyperalgesia", n=302)

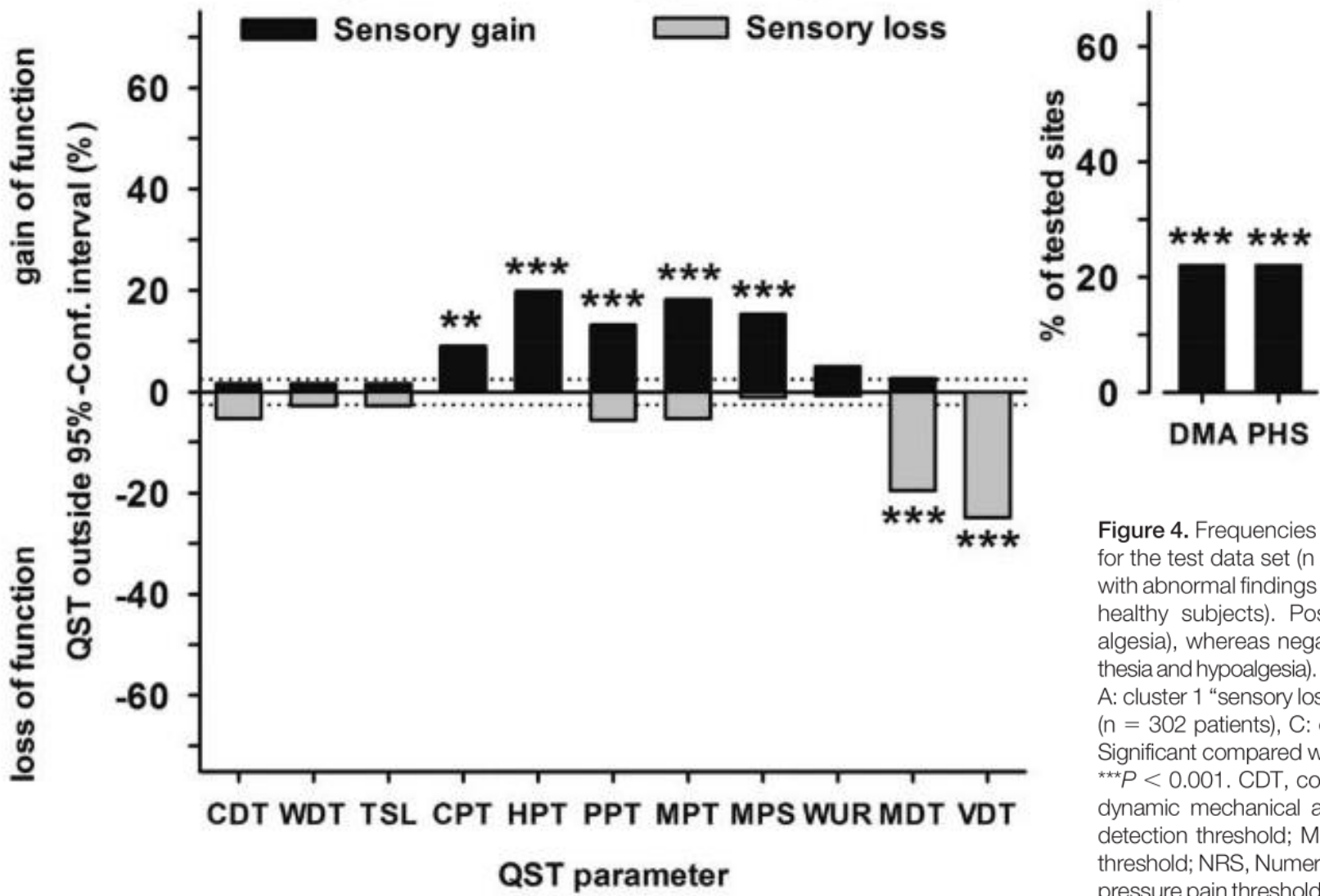


Figure 4. Frequencies of abnormal quantitative sensory testing (QST) findings for the test data set (n = 902). Each column gives the percentage of patients with abnormal findings for that particular QST parameter (outside the 95% CI of healthy subjects). Positive values indicate positive sensory signs (hyperalgesia), whereas negative values indicate negative sensory signs (hypoesthesia and hypoalgesia). Dashed lines: Expected value for healthy subjects ($\pm 2.5\%$). A: cluster 1 "sensory loss" (n = 381 patients), B: cluster 2 "thermal hyperalgesia" (n = 302 patients), C: cluster 3 "mechanical hyperalgesia" (n = 219 patients). Significant compared with the expected value (2.5%) on $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. 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; NRS, Numerical Rating Scale; PHS, paradoxical heat sensation; PPT, pressure pain threshold; QST, quantitative sensory testing; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

dynamic mechanical allodynia
[DMA]

4.2. Cluster 2 (thermal hyperalgesia)

Cluster 2 was characterized by relatively preserved large and small fiber sensory functions in combination with heat and cold hyperalgesia and only low-intensity DMA. This pattern occurred in 33% of all patients with peripheral neuropathic pain regardless of etiology. The fact that in one third of all patients the cutaneous sensory function was relatively well preserved despite documented nerve damage indicates that peripheral neuropathic pain may be associated with effective cutaneous regeneration and sensitized nociceptors.

The sensory profile is similar to that of a UV-B burn lesion²⁷ and is likely due to peripheral sensitization.⁵⁹ It represents the “irritable nociceptor” subgroup described by others.^{13,14,20,45} Sensitized nociceptors are associated with overexpression of channels and receptors leading to pathological spontaneous discharges and a lowered activation threshold for thermal (heat and cold) and mechanical stimuli. Ongoing hyperactivity in surviving nociceptors may be responsible for ongoing pain¹⁰ and may lead to some central sensitization in the spinal cord dorsal horn, so that tactile stimuli conveyed in A-fibers become capable of activating central nociceptive neurons. As a result, mechanical stimuli induce enhanced pain percepts, ie, pinprick hyperalgesia and DMA.⁶⁴ Because these types of mechanical hyperalgesia were only present in about 20% of the patients, peripheral nociceptor drive obviously does not always induce central sensitization.⁶⁰ Structural laboratory tests for

neuropathic pain assessment are likely to be normal, whereas functional tests may show gain of function (**Table 4**).²⁸

C

Cluster 3 ("mechanical hyperalgesia", n=219)

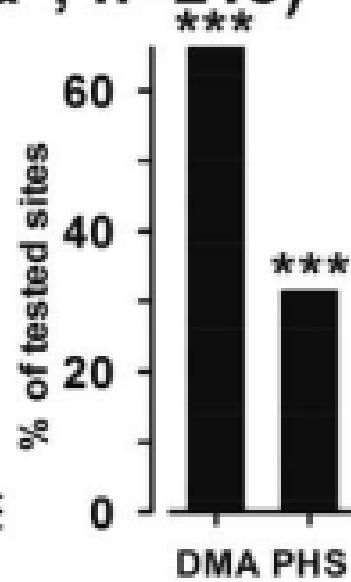
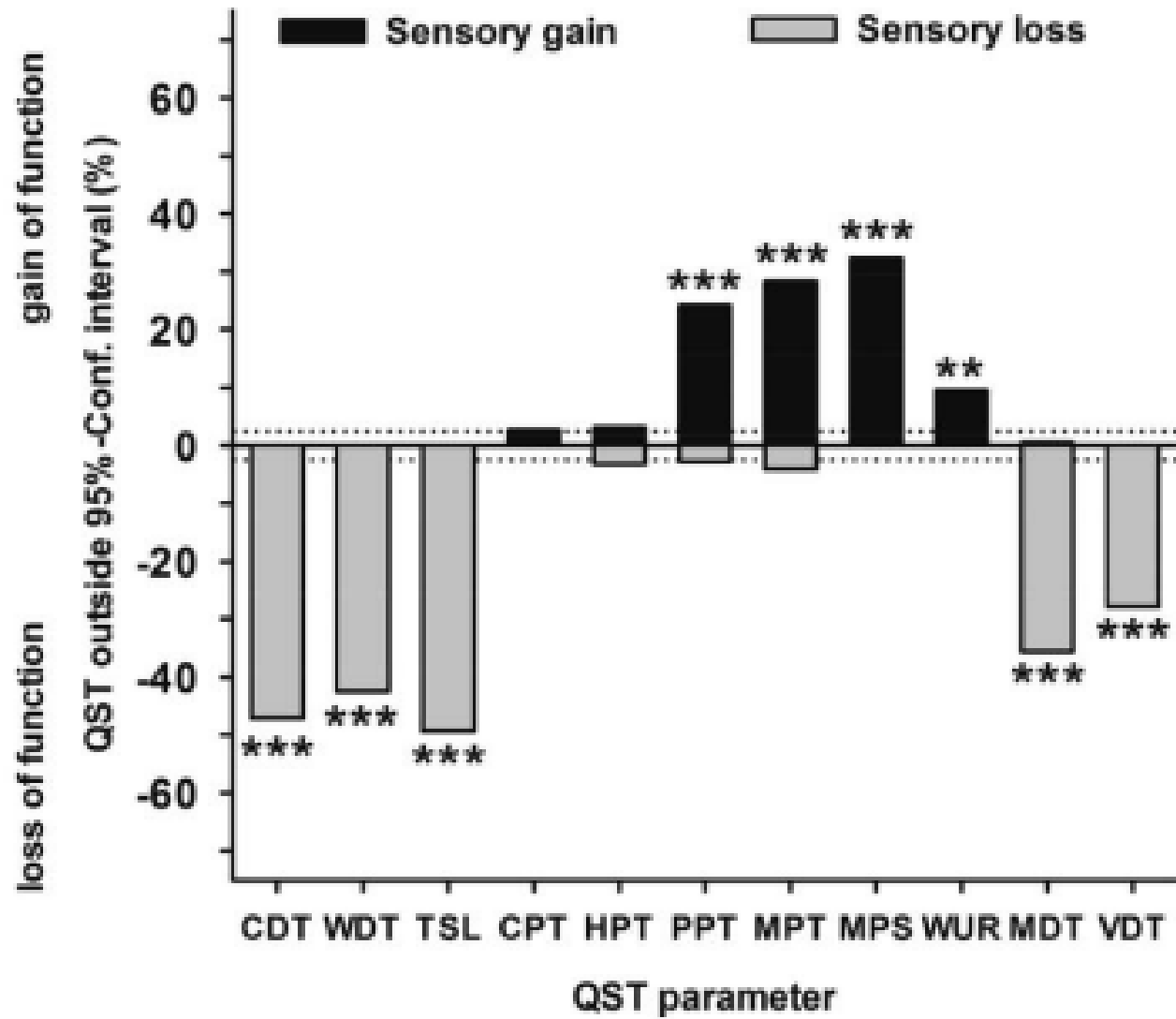


Figure 4. Frequencies of abnormal quantitative sensory testing (QST) findings for the test data set (n = 902). Each column gives the percentage of patients with abnormal findings for that particular QST parameter (outside the 95% CI of healthy subjects). Positive values indicate positive sensory signs (hyperalgesia), whereas negative values indicate negative sensory signs (hypoesthesia and hypoalgesia). Dashed lines: Expected value for healthy subjects ($\pm 2.5\%$). A: cluster 1 "sensory loss" (n = 381 patients), B: cluster 2 "thermal hyperalgesia" (n = 302 patients), C: cluster 3 "mechanical hyperalgesia" (n = 219 patients). Significant compared with the expected value (2.5%) on * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. 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; NRS, Numerical Rating Scale; PHS, paradoxical heat sensation; PPT, pressure pain threshold; QST, quantitative sensory testing; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

dynamic mechanical allodynia
[DMA]
postherpetic neuralgia [PHN]

4.3. Cluster 3 (mechanical hyperalgesia)

Cluster 3 (24%) was characterized by a predominant loss of cold- and heat-sensitive small fiber function in combination with blunt pressure hyperalgesia, pinprick hyperalgesia, and marked and more frequent DMA. Burning pain quality in this cluster was more prominent than in the other groups, consistent with findings in Guillain–Barré syndrome in which burning pain was associated with small fiber deficits⁴³ and with the concept of synthetic heat¹²

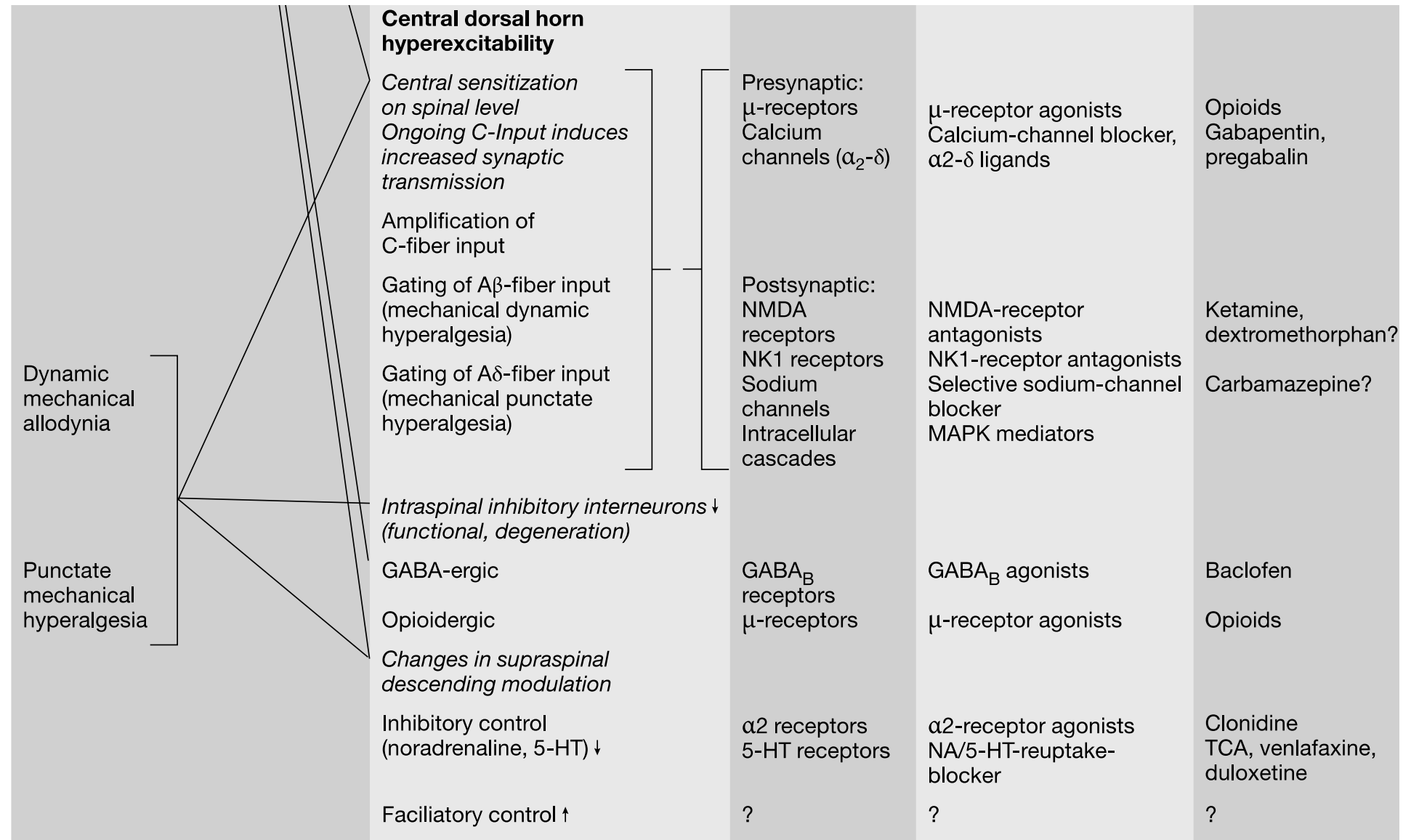
rather than peripheral sensitization to heat. The profile was most commonly present in patients with PHN (47%). It is similar to the one induced by high-frequency electrical stimulation of the skin that is capable of inducing spinal long-term potentiation^{37,50} and likely equivalent to “neurogenic hyperalgesia” or “central sensitization” subgroups described by others.^{7,20} Central sensitization is prominent for mechanical stimuli^{6,55,59} but not thermal stimuli. The dissociation of thermal and mechanical hyperalgesias may be explained by differences in neural signalling of thermal and mechanical pain that starts with peripheral encoding in distinct subsets of nociceptors.^{11,32} Ongoing pain in this subgroup indicates spontaneous activity in the nociceptive system, which may originate in the peripheral and/or central nervous system. Laboratory tests for neuropathic pain assessment are likely to reflect mild loss of function; few tests are sensitive to reflect central sensitization (**Table 4**).²⁸

Cluster characteristics, hypotheses on underlying pathophysiology, and rational pharmaceutical treatment.

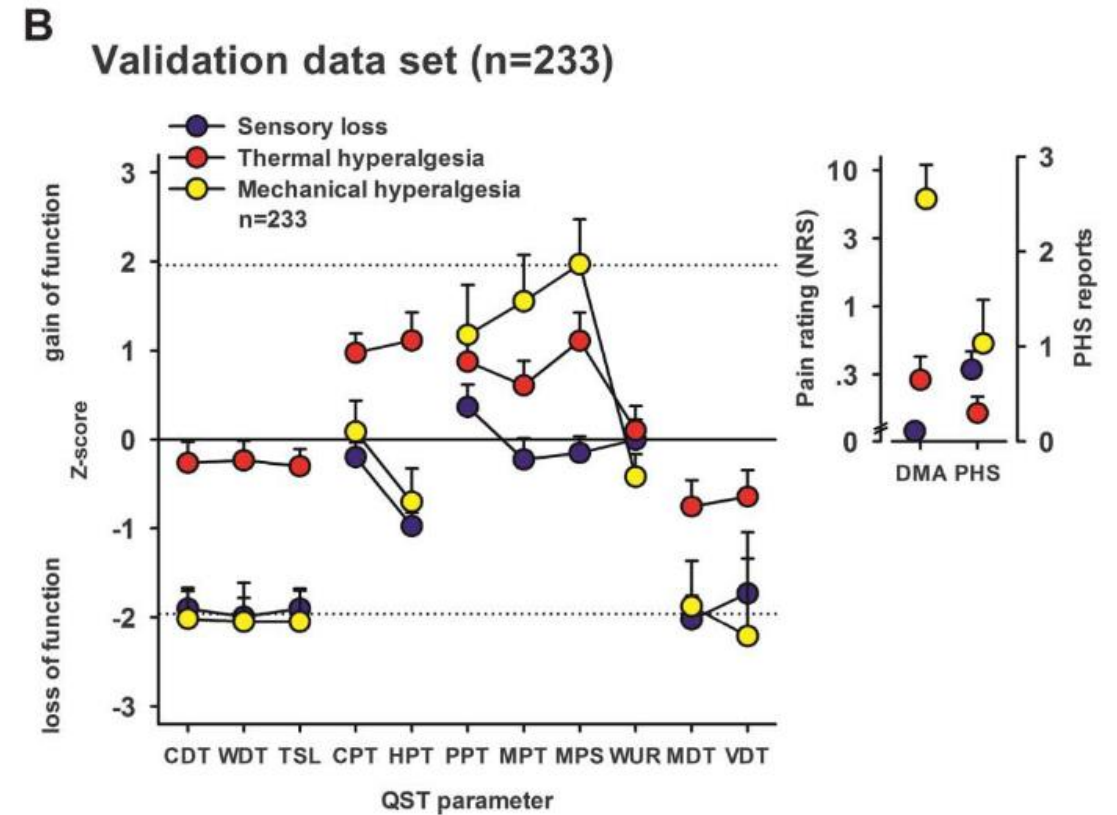
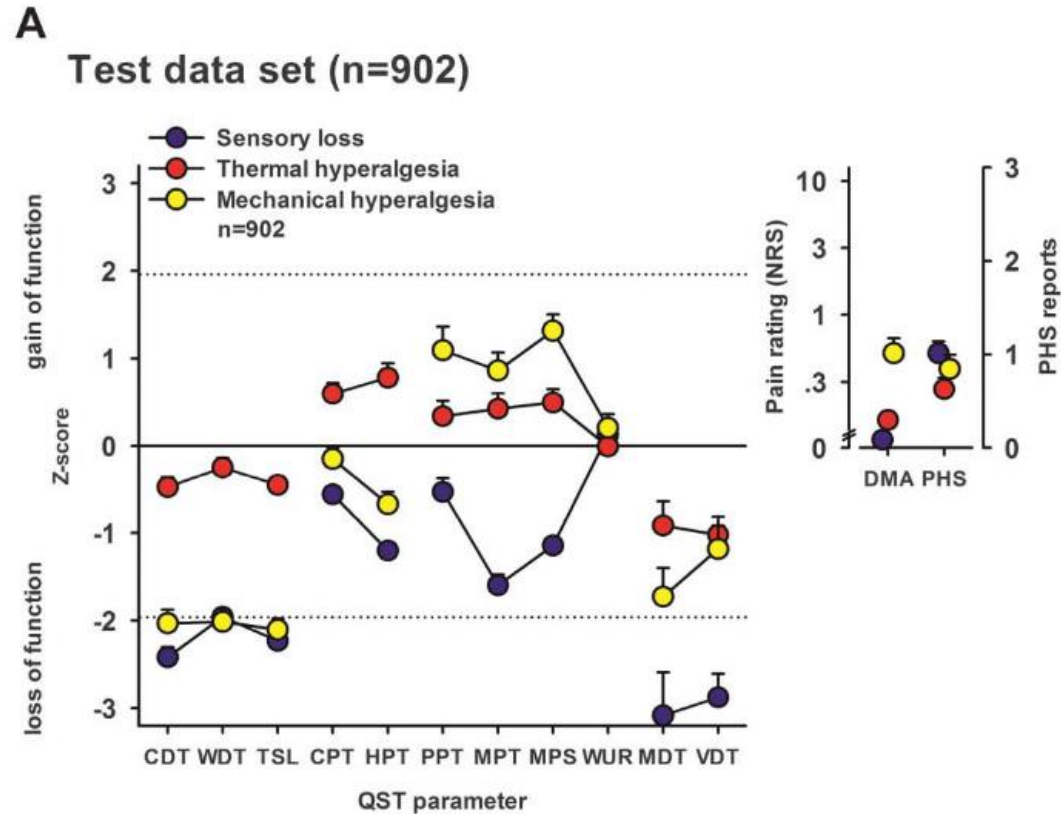
	Sensory loss	Thermal hyperalgesia	Mechanical hyperalgesia
Original data set, n (%)	381 (42)	302 (33)	219 (24)
Validation data set, n (%)	124 (53)	77 (33)	32 (14)
Sensory profile Sensory loss Hyperalgesia DMA PHS	Touch, thermal, pain None Little Much	None Mostly cold and heat Little Little	Mostly thermal Mostly pressure and pin Much Little
Pathophysiology Sensory loss Hyperalgesia Ongoing pain	Small and large fibres — Ectopic activity in damaged nociceptors or in CNS neurons	— Mostly peripheral sensitization Spontaneous activity in surviving nociceptors	Mostly small fibres Mostly central sensitization (Ectopic?) activity in nociceptors
Predicted findings IENFD CCM Peripheral MRI LEP RIII μENG	Loss Loss Damage Reduction Reduction Denervation	None None None Normal or gain Normal or gain Sensitization	Mild loss Mild loss Mild damage Mild reduction Gain Little denervation
Predicted efficacy NSAIDS Botox Topical capsaicin NMDA-antagonist Antidepressant Gabapentinoid Na-channel blocker Opioid	— ++ + + ++	(+) + + + + ++ +	— + + ++ ++ +

CCM, confocal corneal microscopy; CNS, central nervous system; DMA, dynamical mechanical allodynia; IENFD, intraepidermal nerve fiber density; LEP, laser evoked potential; NMDA, *N*-methyl-D-aspartate; PHS, paradoxical heat sensation; RIII, flexor reflex; μENG, microneurography.
MRI, magnetic resonance imaging.

Mechanism-oriented Therapy



Fenotipizzazione sul profilo sensoriale



Neuromodulazione

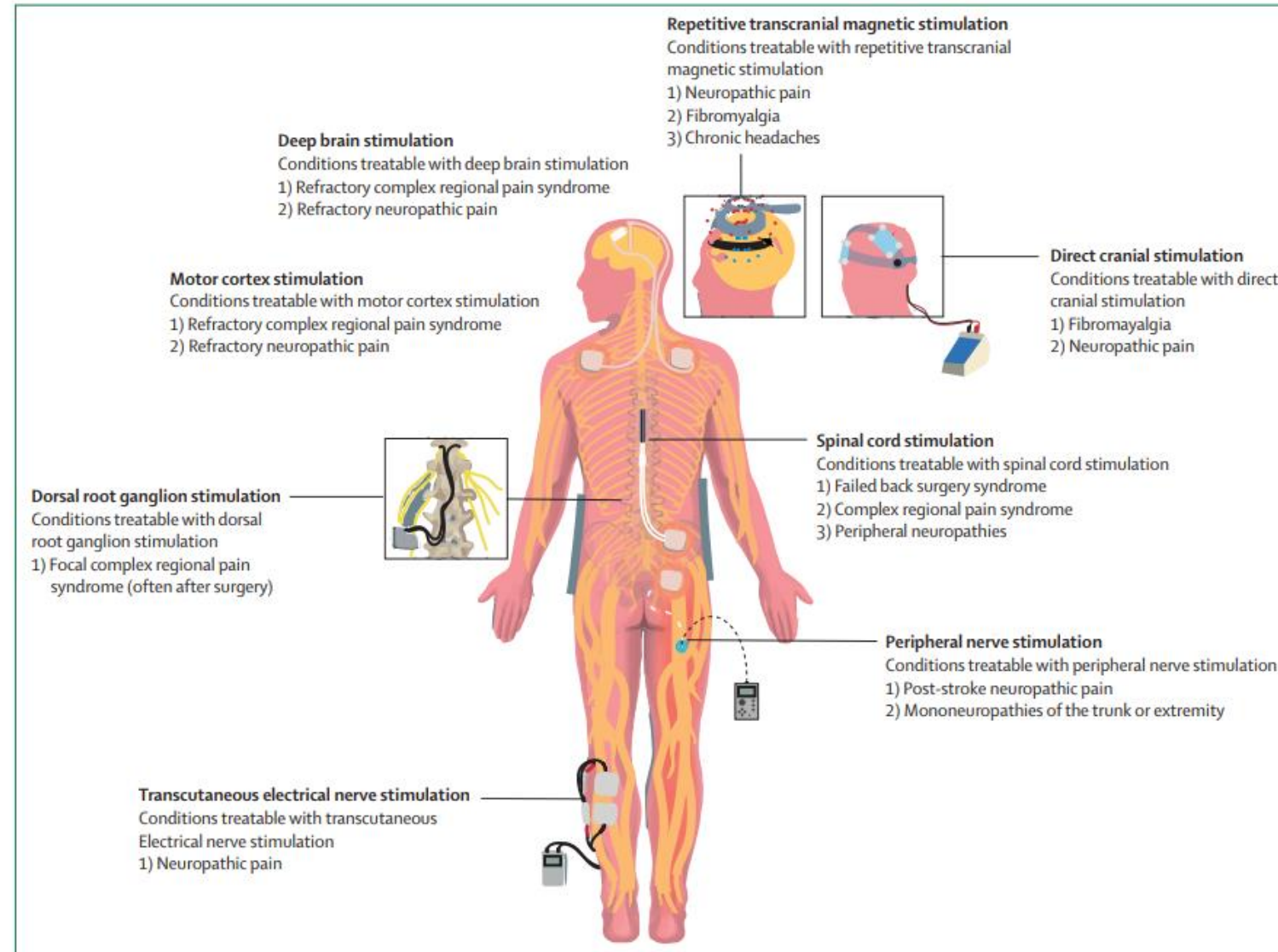
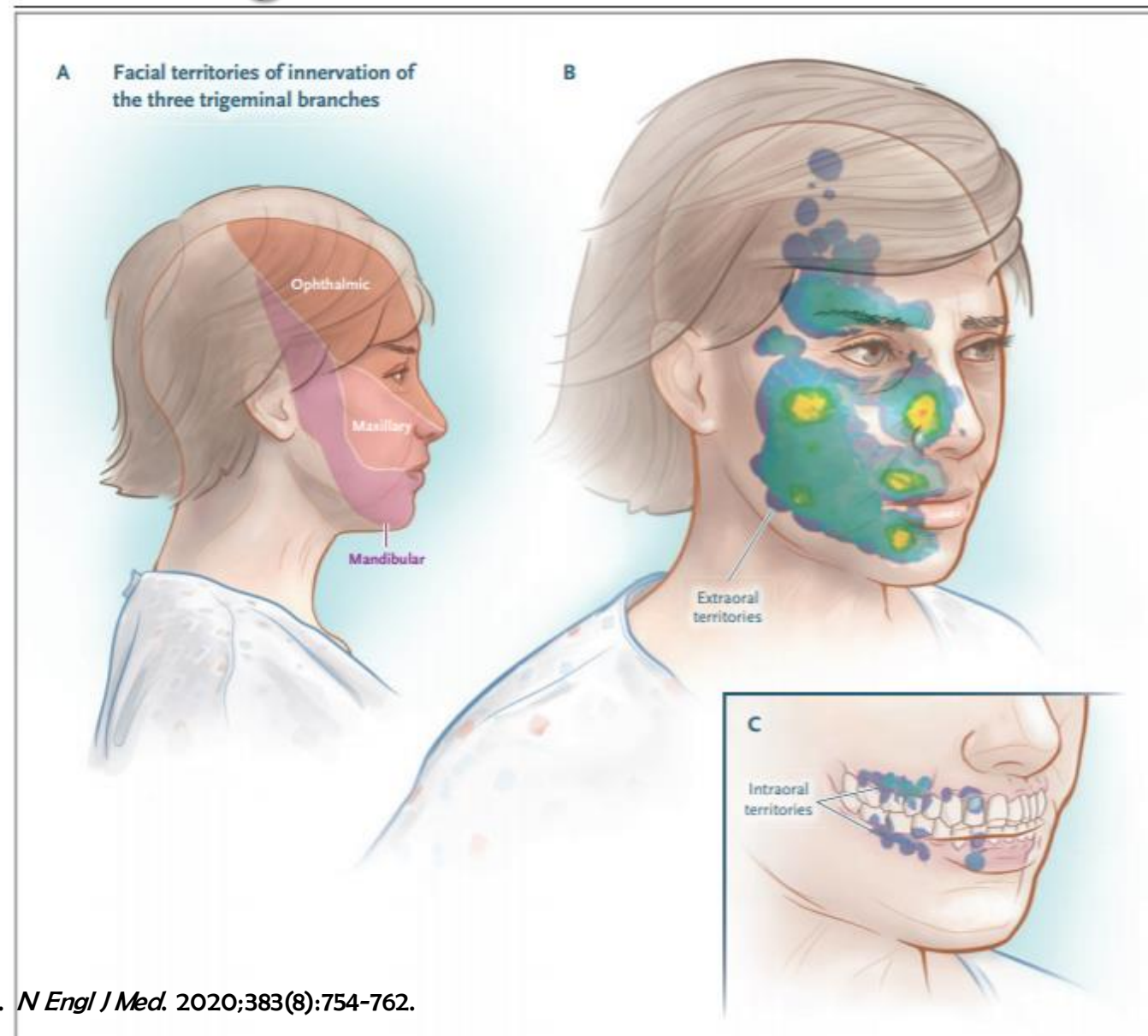


Figure 1: Schematic drawing showing the different forms of neuromodulation and the conditions most amenable to treatment

Peripheral nerve stimulator pulse generators might be implanted or external. Adapted with permission of artist Tricia Park (Cornell University, Ithaca, NY, USA).

Nevralgia del trigemino



1. dolore limitato al territorio di ≥ 1 divisioni del trigemino
2. dolore parossistico, intenso, breve (<1 s- 2 min)
3. dolore descritto scossa elettrica o shock
4. dolore innescato da stimoli innocui sul viso, area trigeminale intraorale- presenza di trigger 91-99%
5. 24-49% dolore persistente tra crisi dolorose (bruciante, pulsante, *aching*)

Triggers	No. of Patients (%)
Activities of daily living	
Talking	71 (59)
Washing face	52 (43)
Chewing	49 (41)
Brushing teeth	43 (36)
Drying face	43 (36)
Eating	23 (19)
Drinking	17 (14)
Shaving	16 (13)
Applying makeup	7 (6)
Combing hair	2 (2)
Washing hair	2 (2)

Specific movements	
Swallowing	13 (11)
Blowing nose	11 (9)
Gently touching face	106 (88)
Jaw movement	7 (6)
Head movement	7 (6)
Yawning	7 (6)
Flexing the trunk forward	5 (4)
Pronouncing labial letters	5 (4)
Raising voice	5 (4)
Laughing	3 (3)
Eye movement	2 (2)
Tongue movement	2 (2)

Compressione vascolare/Sclerosi multipla cause più comuni →

Demielinizzazione all'ingresso del Ponte →

Vulnerabilità alla Transizione cellule di Schwann Oligodendrociti →

Ipereccitabilità → Scariche spontanee → Frequenti after-discharge →

Trasmissione efaptica →

Riorganizzazione corticale

Primary demyelinating disorders

Multiple sclerosis (major risk factor)

Charcot-Marie-Tooth disease

Tumors (eg, schwannoma, cholesteatoma, acoustic neuroma, meningioma)

Arteriovenous malformation

Saccular aneurysm

Nondemyelinating lesions

Small infarct or angioma in brainstem

Infiltrative disorders

Trigeminal amyloidoma

Epidermoid cyst



ClinicalKey®

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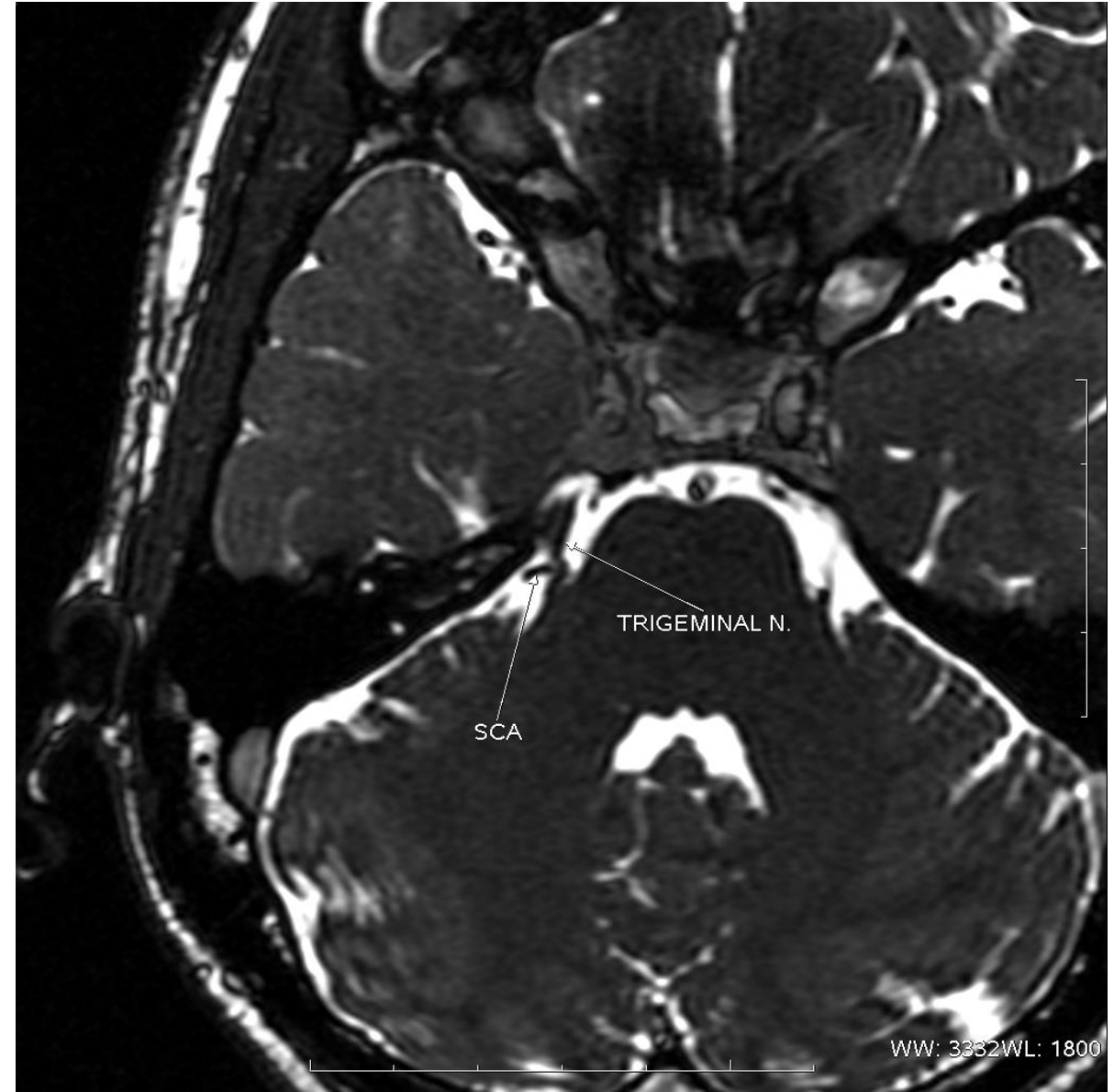
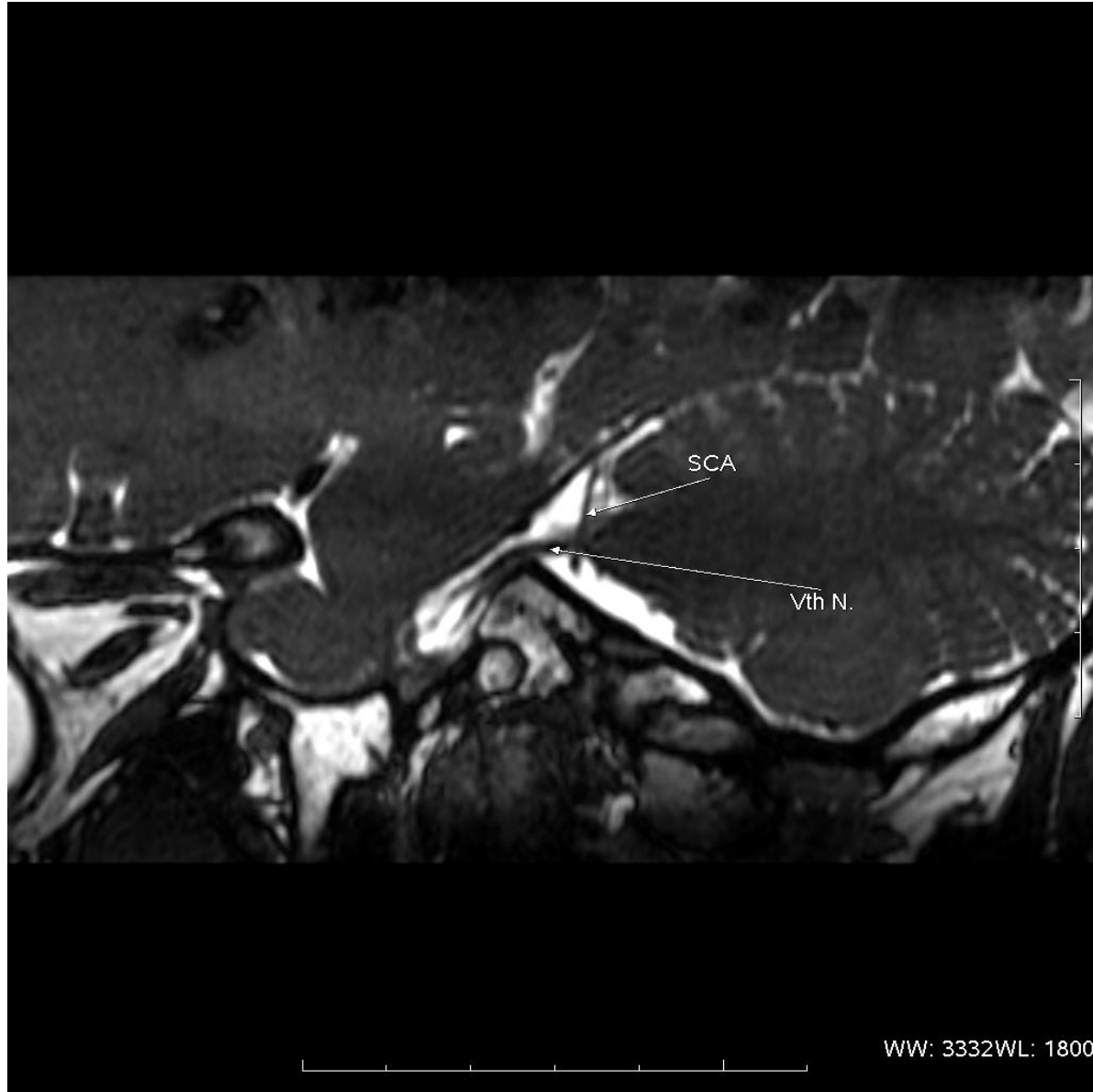
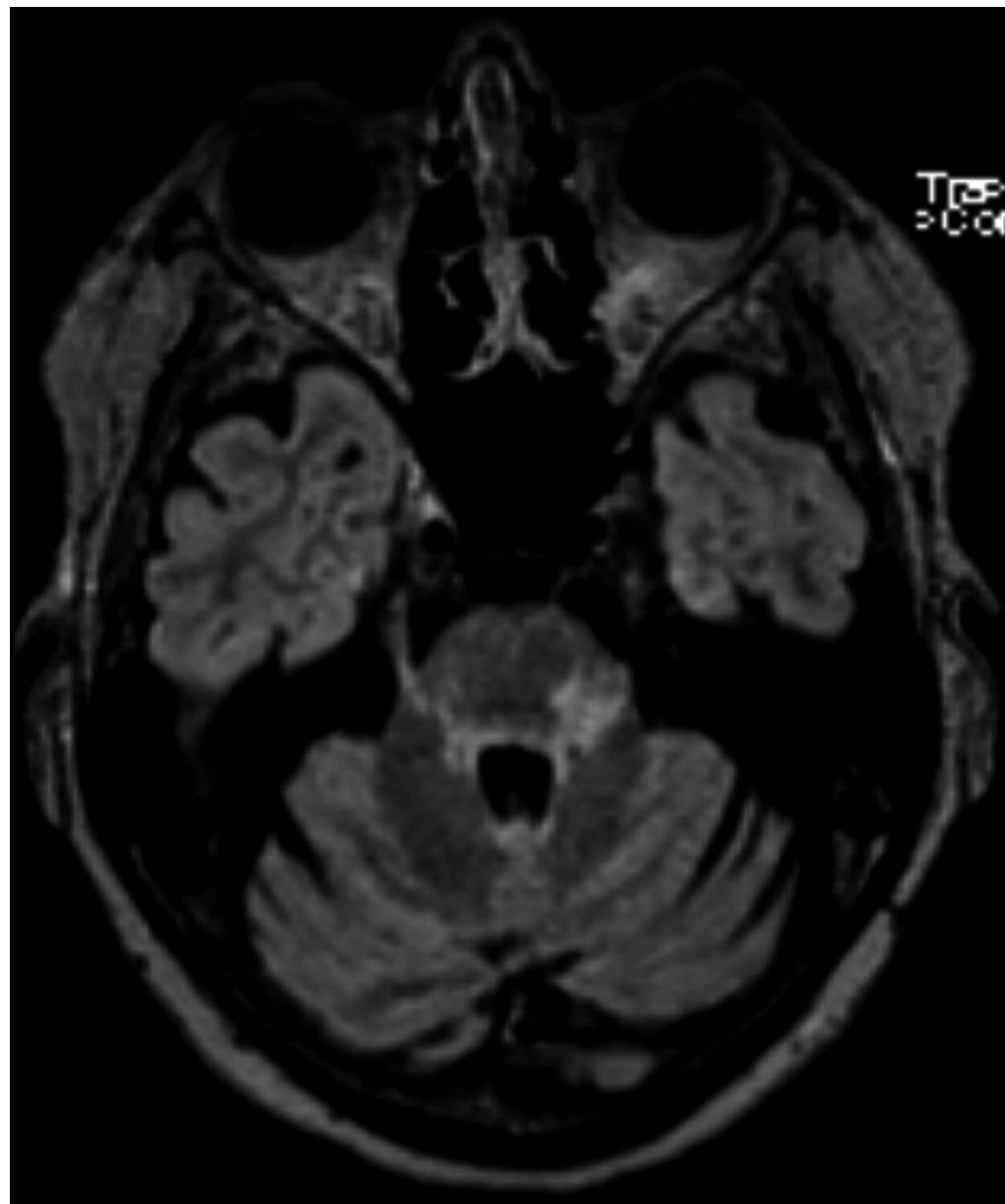


FIGURE 3 A representative MRI scan showing a demyelinating lesion near the trigeminal ganglion. A 52-y-old female patient with MS had the onset of left-sided TN at the age of 40 y. An MRI taken 10 y later, when the TN was clinically very active, showed a relatively large demyelinating lesion on the left in the pons, near the trigeminal ganglion. MRI field strength was 1.5T (T2 flair sequence)



The prevalence of TN was 2.1% for MS patients in our cohort, which is in line with previous studies reporting prevalences between 1.1% and 6.3%.¹¹⁻¹⁶ In our study, the incidence of TN in MS patients was 15-fold higher compared to the general neurological outpatient population. MS was diagnosed at a mean age of 36.4 years in our cohort, which does not differ from the usual age of MS onset.²² The age of onset of TN symptoms, mean 46.6 years in our study, is comparable to the age of TN onset in other studies on MS patients.^{12,17} Although our

A Location of surgical incision



B

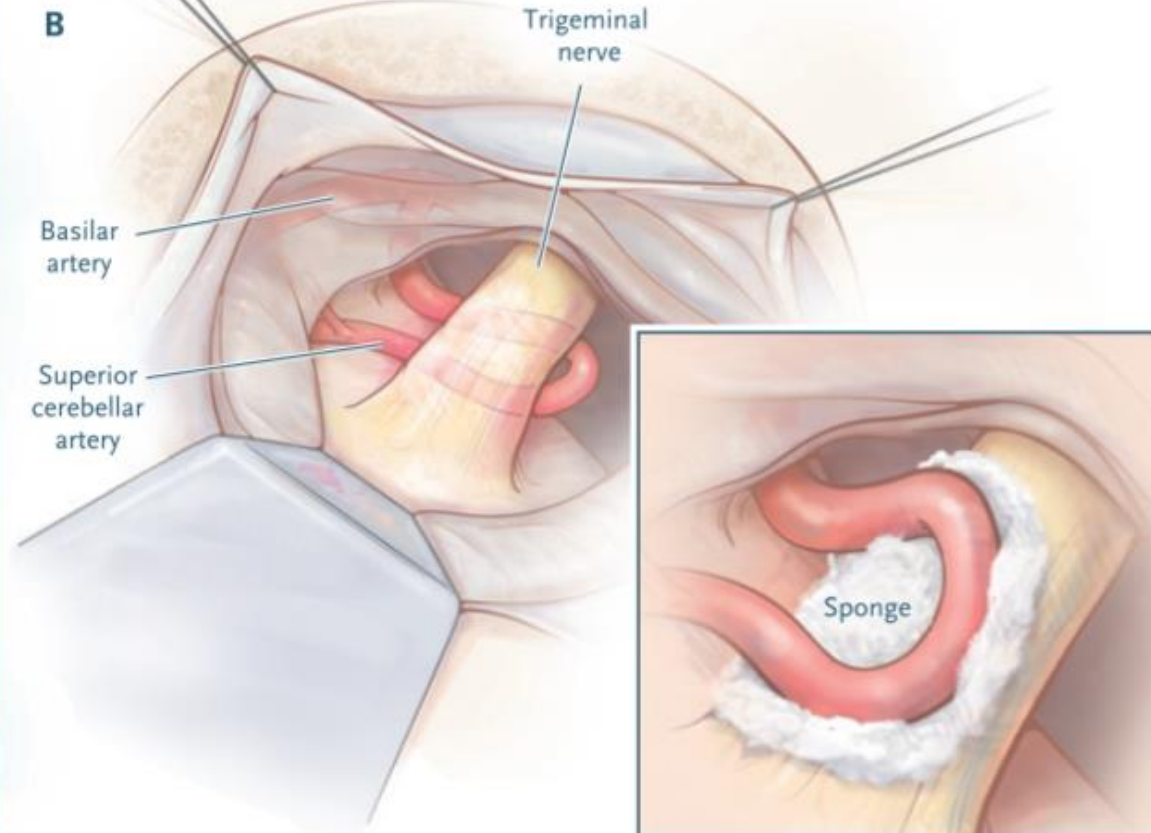


Figure 3. Microvascular Decompression.

In microvascular decompression, after craniotomy, the neurosurgeon cuts the dura mater, shifts the cerebellar hemisphere, and uses microscopy to visualize the nerves emerging from the ventral pons. The vessel that is compressing the trigeminal nerve root is identified and moved if necessary, and a small sponge is inserted to keep the pulsating artery separated from the root.

John Y.K. Lee, MD

Assistant Professor of Neurosurgery
Medical Director, Penn Gamma Knife Center

Penn Neurosurgery



Penn Medicine

Terapia farmacologica

carbamazepine 200 - 1200 mg/die

oxcarbazepine 300 - 1800 mg/die

Shock pain



Clinical guide. Carbamazepine is considered the gold standard for the initial medical treatment of TN. Carbamazepine has been shown to increase pain relief compared with placebo, but also causes adverse effects such as drowsiness, dizziness, rash, liver damage and ataxia and has the potential for multiple drug interactions. Consensus expert opinion suggests that carbamazepine may have a 50% failure rate for long-term (5–10 years) pain control [58,60]. Based on the strength of published evidence, carbamazepine remains the best supported standard medical treatment for TN.

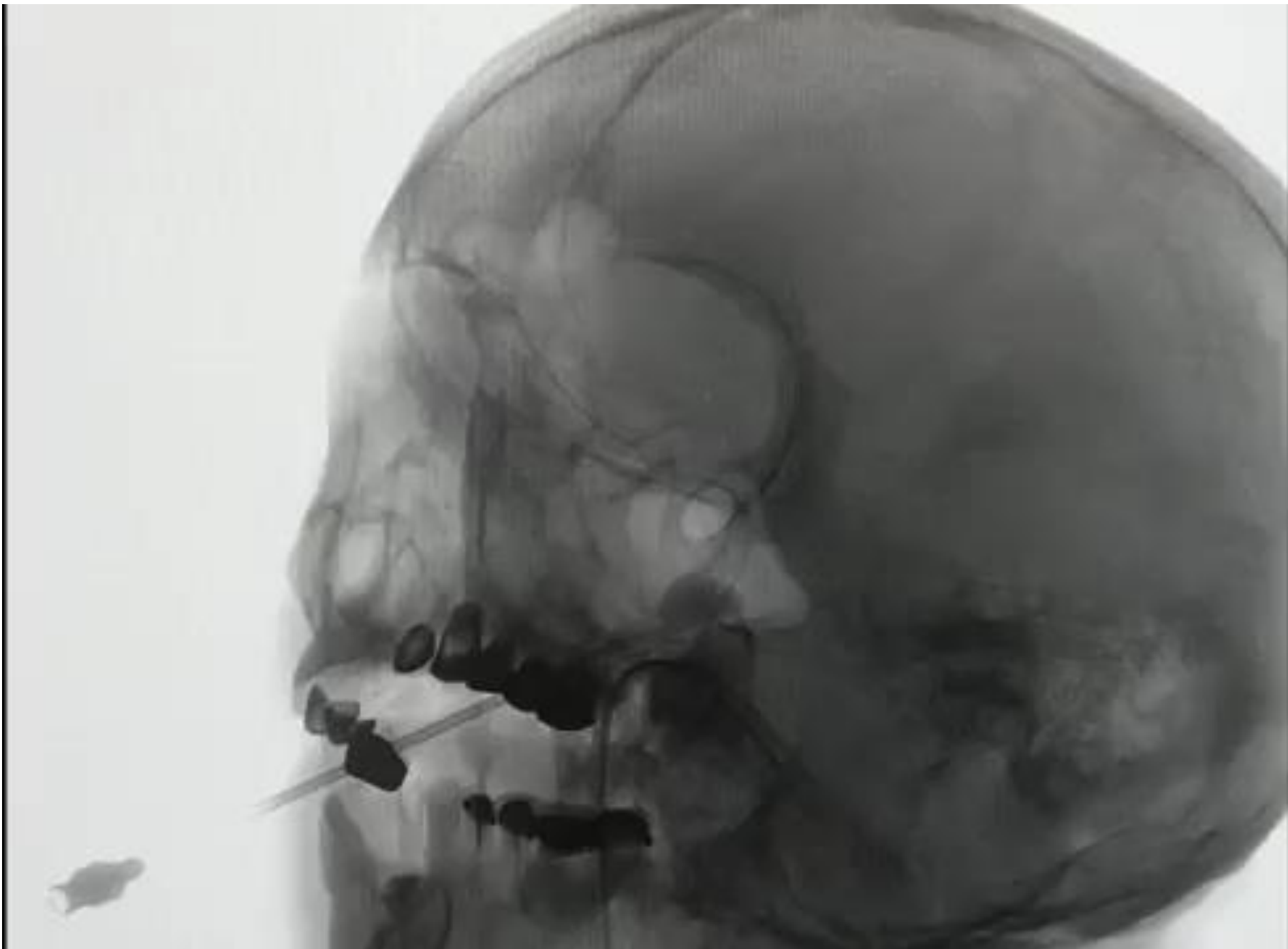


Table 2
Procedural details reported by the included studies.

Study	Balloon Compression-Compression time	Glycerol Rhizolysis - Dose	Radiofrequency Thermocoagulation
Lee 1998	-	0.3 ml	– 5 lesions for 60 sec -1 st lesion at 60 °C -Next at 70 °C-80 °C
Udupi 2012	-	0.3 ml	– 5 lesions for 60 sec -1 st lesion at 60 °C -Next at 70 °C-80 °C
Bender 2013	-	0.3-0.4 ml	60 °C for 60 sec
Haridas 2008	-	0.4-0.8 ml	70 °C for 60 sec
Tan 1995	-	0.2-0.4 ml	70 °C for 60sec
Fraoli 1989	3-10 min (majority for 5-7 min)	0.2-0.4 ml	47-108 °C
Mohammad 2013	60 sec*	0.5 ml	NR
Noorani 2016	60 sec x3 times	0.36 ml	60-80 °C for 60sec
Asplund 2016	90-180 sec	-	-
Kouzounias 2010	60-120 sec	-	-
Mallory 2012	60-300sec	-	-
Broggi 1993	-	-	-
Meglio 1989	-	-	-
Frank 1989	-	-	-

* For repeated procedures, each extra compression was extended for 30 sec for each previous lesion; NR: not reported.

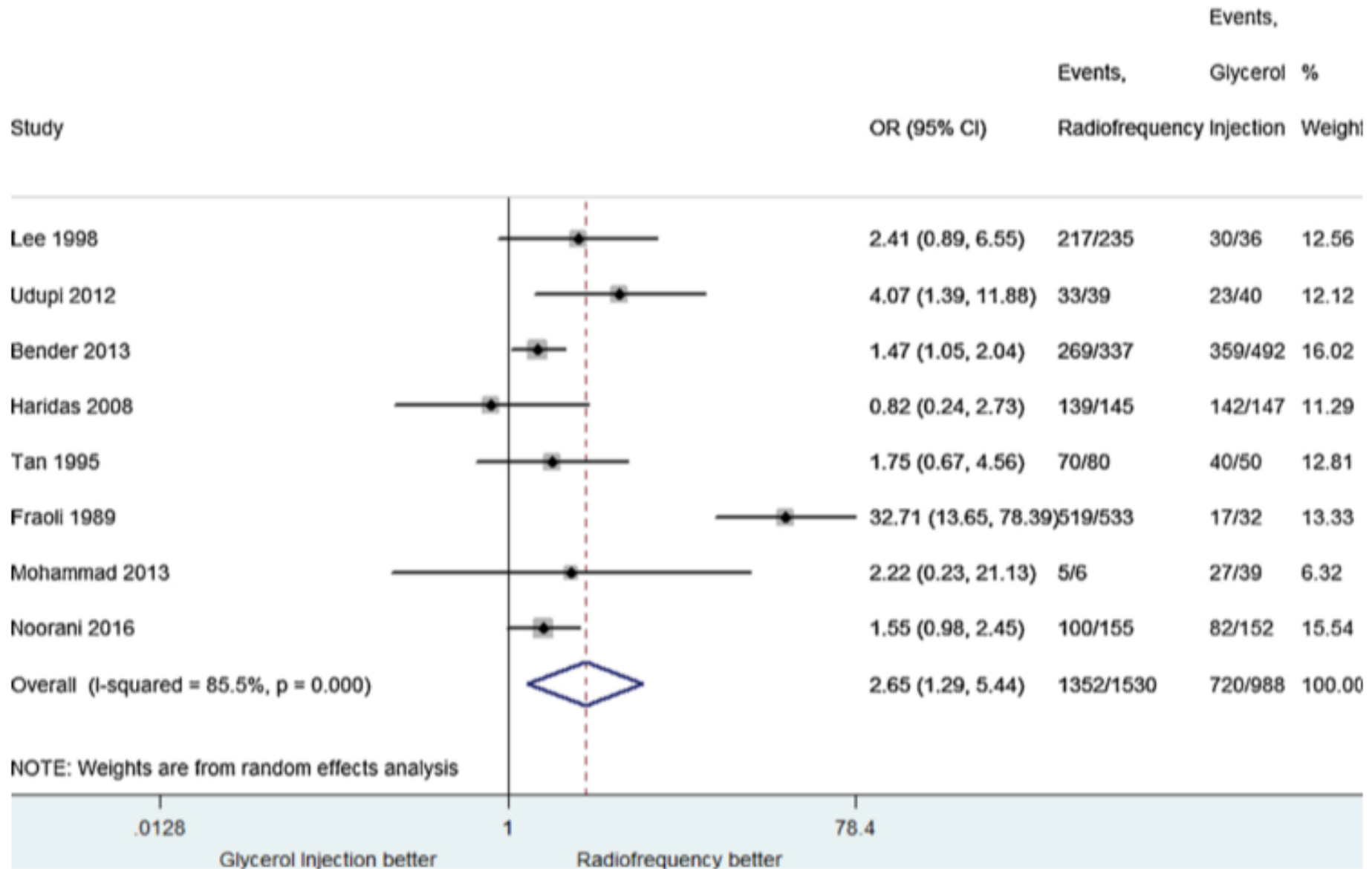
Table 3

Relative frequencies of all available outcomes in each group.

Outcome	RF vs GR (%)	BC vs GR (%)	BC vs RF
Immediate pain relief	88.3 vs 72.8*	79.1 vs 63.4	81.9 vs 92.7
Pain recurrence	28.5 vs 43.2	23.7 vs 43.8	22.8 vs 17.4
Anesthesia	18.2 vs 30.4*	NR	NR
Herpes eruption	2.4 vs 8*	5.2 vs 6.5	NR
Anesthesia dolorosa	0.75 vs 0.29	0.4 vs 0.2	0.4 vs 1.3
Dysesthesia	4.7 vs 2.5	6.6 vs 10.7	10.3 vs 8
Hypoesthesia	93.5 vs 94.5	68.6 vs 45.5	
Paresthesia	8.9 vs 3.2	8.1 vs 4.3	8.1 vs 12.9
Reduced corneal reflex/keratitis	12.5 vs 4.8	4.9 vs 6.5	NR
Mastication weakness	1.1 vs 0.3	6.3 vs 0*	7.1 vs 5.3
Diplopia	NR	4 vs 0.4*	1.3 vs 0.2
Numbness	NR	18 vs 59.6	NR

* designates statistical significance.

Immediate Pain Relief



Nevralgia posterpetica

4.1.1.4 Postherpetic neuralgia: Postherpetic neuralgia is defined as pain persisting for ≥ 3 months following the onset or healing of herpes zoster. The innervation territory of the first (ophthalmic) branch of the trigeminal nerve and thoracic dermatomes are the locations most frequently affected by chronic pain after herpes zoster. Postherpetic neuralgia may emerge in continuation of the acute pain associated with the skin rash or develop after a painless interval. Negative and positive sensory symptoms or signs must be compatible with the innervation territory of the affected cranial nerve or peripheral dermatome (or dermatomes).



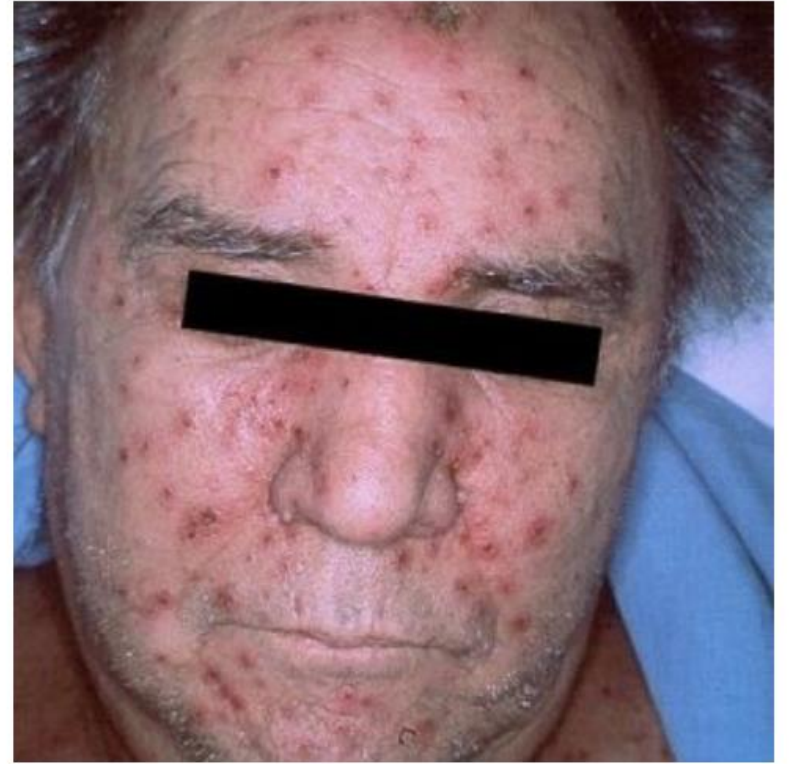


TABLE 27.2 Factors Associated with an Increased Incidence of Herpes Zoster

1. Increasing age
2. Disease states
 - HIV
 - Lymphoproliferative disorders
3. Immunosuppressive therapy
 - After organ transplant
 - Chemotherapy
 - Steroid treatment
4. Possible association with
 - Caucasian vs. African American racial group
 - Psychological stress
 - Physical trauma

Fisiopatologia

Riattivazione dell'infezione latente da VZV → Herpes zoster

- Virioni trasportati per via assonale anterograda e retrograda
- Replicazione virale infiammazione e danno del tessuto nervoso
- Necrosi emorragica
- Neuroni nel ganglio sensitivo ↓↓↓
- Fibrosi
- assoni mielinizzati ↓
- assoni non mielinizzati ↑

Patologia

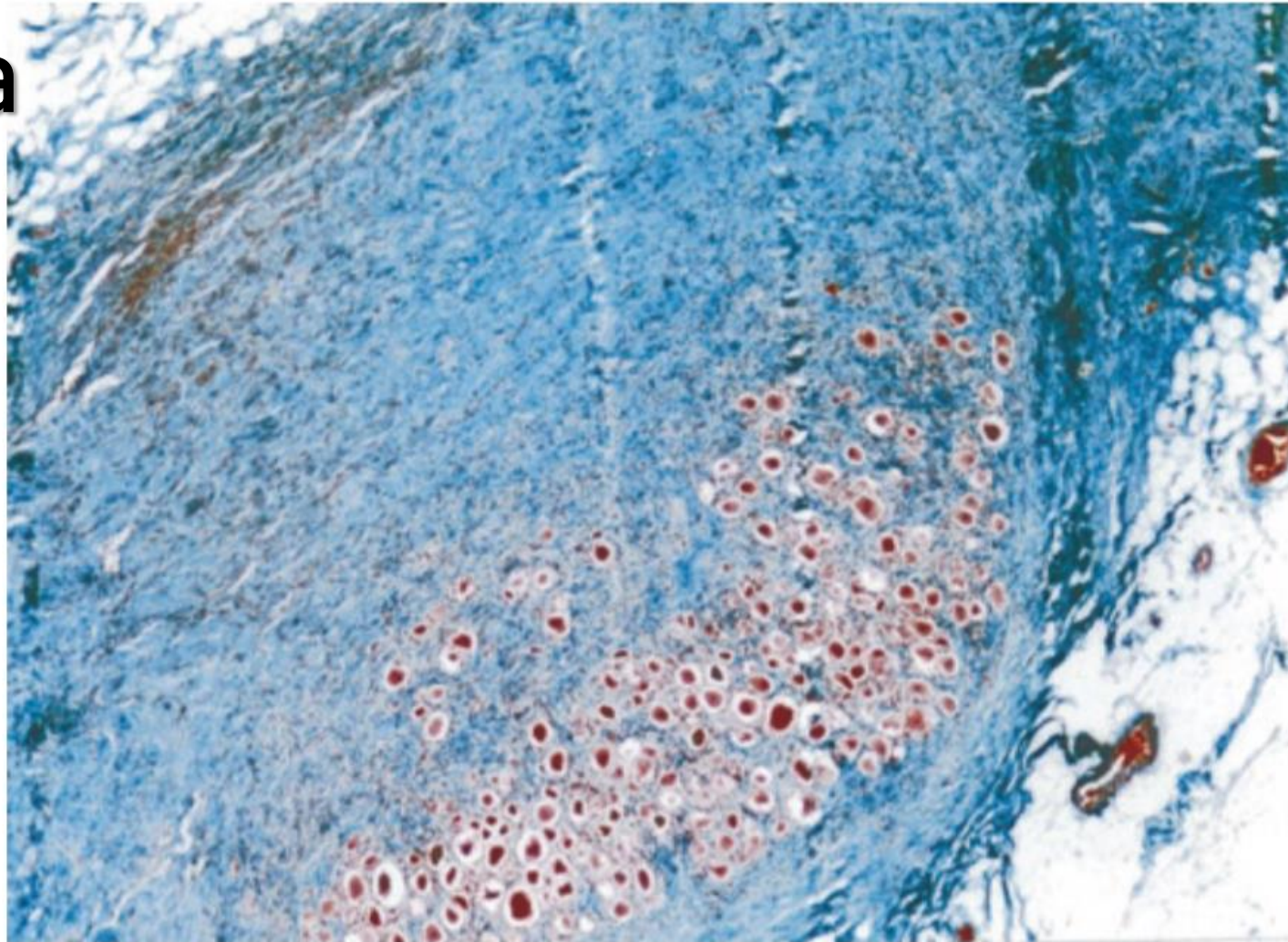


Fig. 12.3 This right T8 dorsal root ganglion from a patient with 5 years of PHN shows a large area of pan-cellular necrosis and fibrosis (scarring) in only this one DRG (*upper left*). Residual normal-appearing ganglion is at lower right (Masson trichrome $\times 10$) (From: Watson et al. [50])

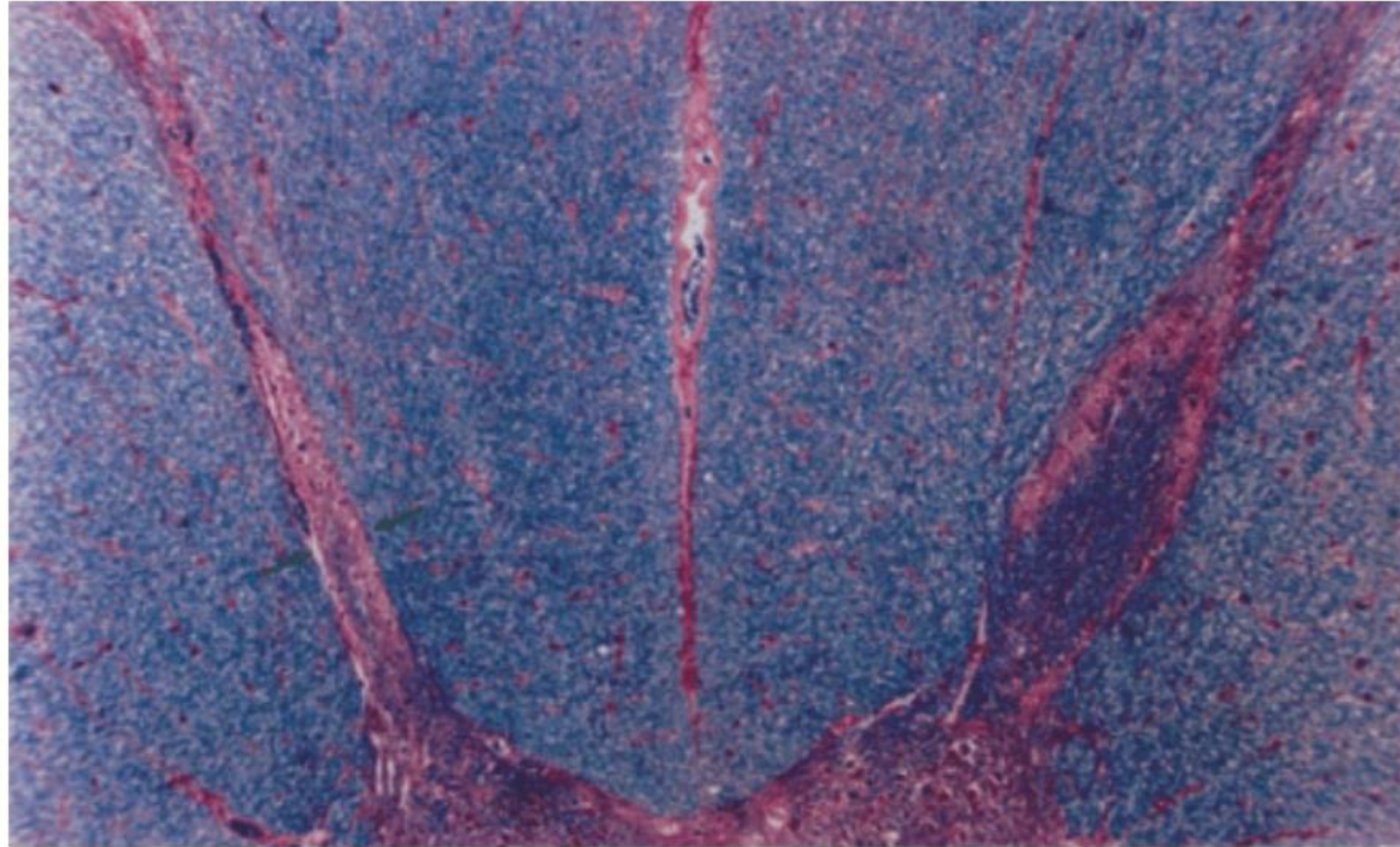


Fig. 12.4 Atrophy of the dorsal horn of the spinal cord on the shingles-affected side (*left side*). This involves loss of myelin as evidenced by the reduced darker staining of the central dorsal horn compared with the contralesional control side) (MBP $\times 2.5$). In contrast to the single DRG affected, dorsal horn atrophy and cell, axon, and myelin loss with DRG fibrosis were found only in patients with persistent PHN (From: Watson et al. [50])

Table 1. Pharmacologic Therapies for Postherpetic Neuralgia.*

Agent	Average Effective Dose in Clinical Trials	Starting Dose	Dose Adjustment	Number Needed to Treat (95% CI) [†]	Side Effects	Precautions
Topical treatments						
Lidocaine patch	5%; up to 3 patches/day	Maximum of 3 patches/day for a maximum of 12 hr		2.0 (1.4–3.3) ²⁰	Local erythema	
Capsaicin cream	0.075%; 4 applications/day	NA		3.3 (2.3–5.8) ²⁰	Pain on application, local erythema, rash	Avoid eyes and nose
Capsaicin patch	8%; application time of 30–90 min	NA		11.0 (6.1–62.0) ²²	Pain on application, local erythema, rash; systemic adverse events in <5% of study participants‡	
Oral treatments						
Gabapentin	2572 mg/day	100 mg 3 times daily	Increase each of the 3 daily doses by 100–300 mg every 3–7 days as tolerated; maximum dose is 1800 mg/day, but unlicensed dose of up to 3600 mg/day is used by some clinicians	4.4 (3.3–6.1) ²⁰	Sedation, dizziness, peripheral edema	Avoid in patients with renal insufficiency
Pregabalin	398 mg/day	50–75 mg twice daily	Increase to 300 mg daily after 3–7 days, then by an additional 150 mg daily every 3–7 days as tolerated, to a maximum dose of 600 mg daily	4.2 (3.4–5.4) ^{20,23}	Same as with gabapentin	Same as with gabapentin
Tricyclic antidepressants (off-label use)	Amitriptyline, 95 mg/day; or nortriptyline, 122 mg/day	10–25 mg at bedtime	Increase by 10–25 mg every 3–7 days as tolerated to 75–150 mg/day with caution as side effects permit; if blood level of active drug and its metabolite is >100 ng/ml, continue dose adjustment very cautiously	2.6 (2.1–3.5) ²⁰	Sedation, dry mouth, blurred vision, weight gain, urinary retention	Avoid in patients with cardiac disease, glaucoma, or seizure disorder; avoid concomitant use of tramadol
Morphine and oxycodone	Morphine, 90 mg/day; oxycodone, 45 mg/day	5–15 mg every 4 hr as needed	After 1–2 wk, convert total daily dose to long-acting opioid and continue short-acting formulation as rescue medication	Morphine, 2.8 (2.0–4.6) ²⁰ ; oxycodone, 2.5 (1.7–4.4) ²⁰	Nausea, vomiting, constipation, drowsiness, dizziness, mood change, disorientation	There is risk of abuse and uncertainty over long-term effectiveness and safety§
Tramadol	298 mg/day	50 mg every 4–6 hr	Increase by 50–100 mg/day in divided doses every 3–7 days as tolerated, to maximum dose of 400 mg/day (300 mg/day in patients >75 yr of age)	4.8 (2.6–27.0) ²⁰	Nausea, vomiting, constipation, drowsiness, dizziness, seizures	Same as with morphine and oxycodone; also, avoid concomitant use of SSRIs, SSNRIs, tricyclic antidepressants

* Data are primarily from Hempenstall et al.²⁰ and Dworkin et al.²¹ NA denotes not available, SSNRIs selective serotonin- and norepinephrine-reuptake inhibitors, and SSRIs selective serotonin-reuptake inhibitors.

[†] This is the number needed to treat for one person to have at least 50% pain relief.

[‡] Systemic adverse events include diarrhea, nausea, vomiting, fatigue, infections, musculoskeletal disorders, hypertension, dizziness, and headache.

[§] See also national guidelines on opioid use for chronic pain.^{24,25}

Neuropati(e) diabetic(he)

In addition to these studies evaluating the incidence and prevalence of diabetic neuropathy in the entire population, many epidemiological studies are confined to patients with either type 1 diabetes mellitus (T1DM) or T2DM. The incidence of neuropathy is higher in individuals with T2DM (6,100 per 100,000 person-years) than in those with T1DM (2,800 per 100,000 person-years)^{9,15-17}. By contrast, the prevalence of neuropathy is similar in those with T2DM (8-51%¹⁸⁻²⁰) to those with T1DM (11-50%²⁰⁻²²). Importantly, the prevalence is even higher when asymptomatic neuropathy is included, with 45% of patients with T2DM and 54% of those with T1DM developing neuropathy²⁰. The higher incidence of neuropathy in patients with T2DM, with a similar prevalence in those with T2DM or T1DM, is probably secondary to multiple factors, including differences in age of onset of diabetes and differences in the underlying pathophysiology.

The prevalence of diabetic neuropathy also changes with disease duration. Indeed, the prevalence of diabetic neuropathy increased from 8% to 42% in patients with T2DM when patients were monitored for 10 years¹⁹.

Table 1—Classification for diabetic neuropathies

Diabetic neuropathies
A. Diffuse neuropathy
DSPN
<ul style="list-style-type: none">• Primarily small-fiber neuropathy• Primarily large-fiber neuropathy• Mixed small- and large-fiber neuropathy (most common)
Autonomic
Cardiovascular
<ul style="list-style-type: none">• Reduced HRV• Resting tachycardia• Orthostatic hypotension• Sudden death (malignant arrhythmia)
Gastrointestinal
<ul style="list-style-type: none">• Diabetic gastroparesis (gastropathy)• Diabetic enteropathy (diarrhea)• Colonic hypomotility (constipation)
Urogenital
<ul style="list-style-type: none">• Diabetic cystopathy (neurogenic bladder)• Erectile dysfunction• Female sexual dysfunction
Sudomotor dysfunction
<ul style="list-style-type: none">• Distal hypohydrosis/anhidrosis,• Gustatory sweating
Hypoglycemia unawareness
Abnormal pupillary function
B. Mononeuropathy (mononeuritis multiplex) (atypical forms)
Isolated cranial or peripheral nerve (e.g., CN III, ulnar, median, femoral, peroneal)
Mononeuritis multiplex (if confluent may resemble polyneuropathy)
C. Radiculopathy or polyradiculopathy (atypical forms)
Radiculoplexus neuropathy (a.k.a. lumbosacral polyradiculopathy, proximal motor amyotrophy)
Thoracic radiculopathy
Nondiabetic neuropathies common in diabetes
Pressure palsies
Chronic inflammatory demyelinating polyneuropathy
Radiculoplexus neuropathy
Acute painful small-fiber neuropathies (treatment-induced)

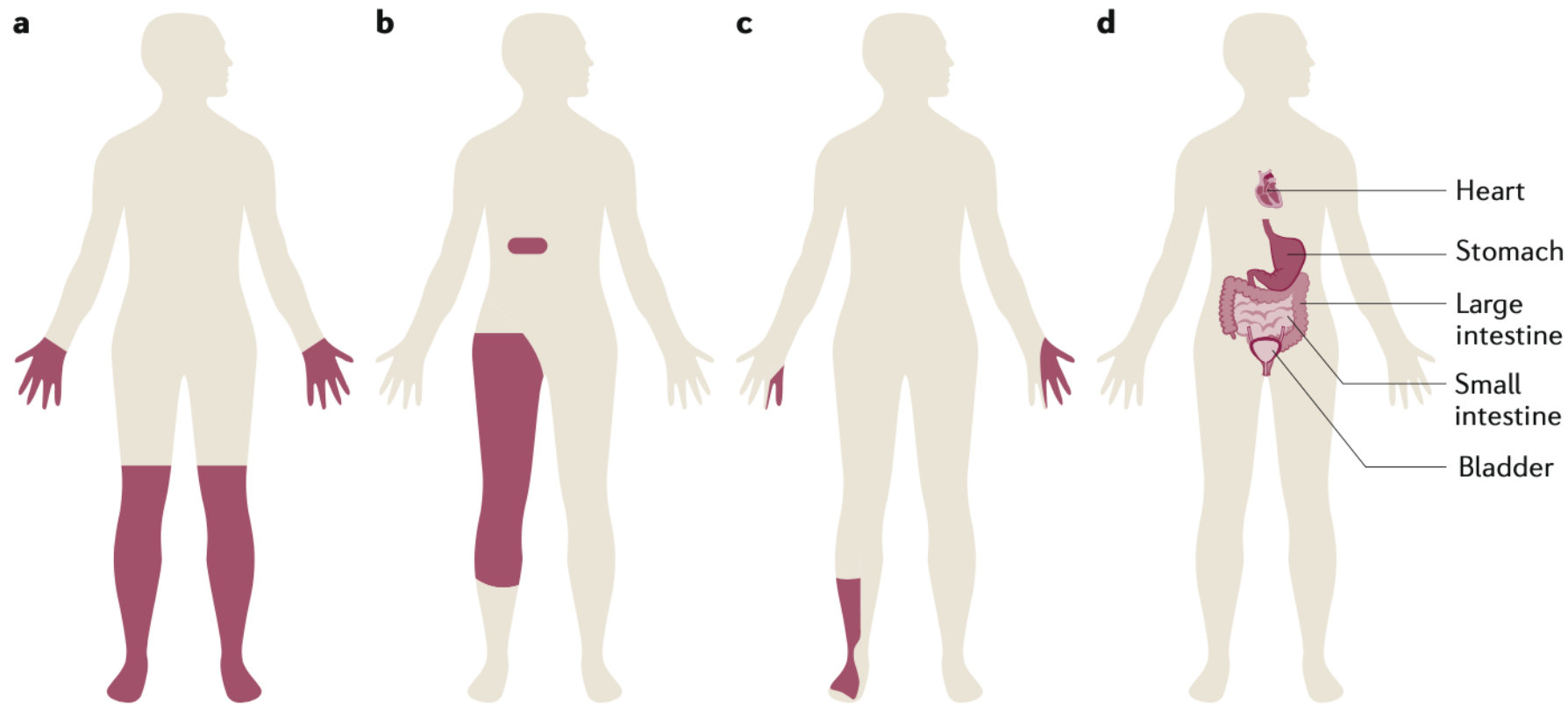


Fig. 1 | Patterns of nerve injury in diabetic neuropathy. Several different patterns of neuropathy can present in individuals with diabetes. Of these, the most common is distal symmetric polyneuropathy (DSP). Examples of patterns of neuropathy are DSP, small-fibre-predominant neuropathy or treatment-induced neuropathy (part **a**); radiculoplexopathy or radiculopathy (part **b**); mononeuropathy (part **c**); and autonomic neuropathy or treatment-induced neuropathy (part **d**). Small-fibre-predominant neuropathy has the same distribution as DSP, although the neurological examination and results from nerve conduction velocity studies are different. Diabetic radiculoplexopathy or radiculopathy can respond to immunotherapy and usually improves with time, unlike other types of nerve injury in individuals with diabetes. Treatment-induced neuropathy is under-recognized, is caused by overaggressive glycaemic control and can present in multiple forms (parts **a** and **d**). Adapted by permission from BMJ Publishing Group Limited. *BMJ* Peltier, A., Goutman, S. A. & Callaghan, B. C. **348**, (2014)²³⁰.

Reduction in neurofilament, GAP43 and β -tubulin synthesis and increased HSP and PARP expression

DRG

Motor neurons

Remak bundle

Spinal nerve

Ischaemia

C fibres

Schwann cell or myelin

Axon

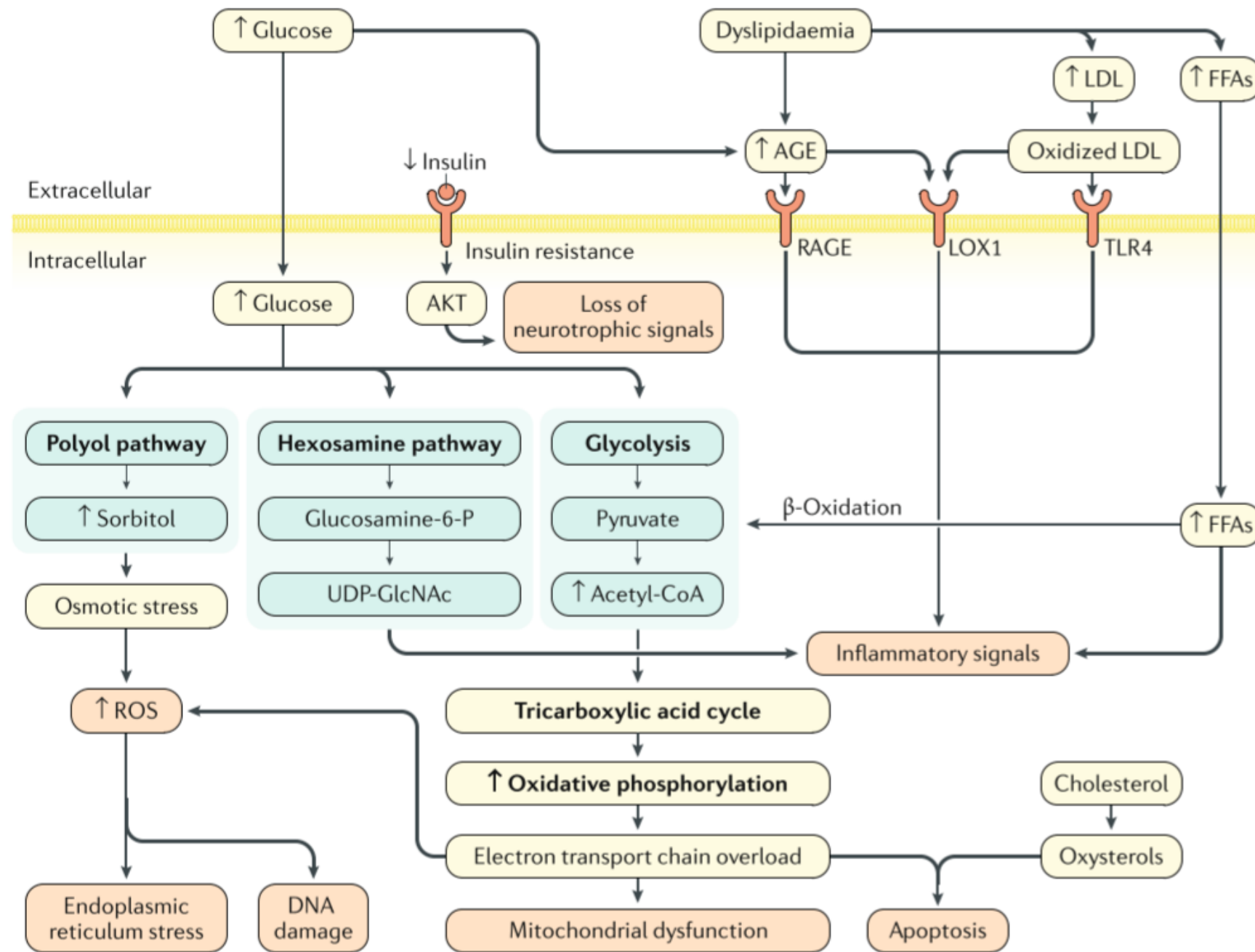
Demyelination (in more severe cases)

Degeneration

Reduced Schwann cell-axon transport

Fig. 2 | **The peripheral nervous system and alterations in diabetic neuropathy.**

Sensory neurons relay sensory information from their nerve terminals (which are located throughout the periphery) to the dorsal horn of the spinal cord. The cell bodies of these sensory neurons are located in the dorsal root ganglia (DRG). Conversely, the cell bodies of motor neurons reside in the spinal cord ventral horn and transmit information from here to the periphery. Thin and unmyelinated sensory axons (C fibres or small fibres) are grouped together by non-myelinating Schwann cells into Remak bundles and represent a large portion of neurons of the peripheral nervous system. By comparison, other sensory axons are myelinated by associated Schwann cells, which have an important role in preserving axonal function. The precise order of cellular injury (whether, for example, damage to Schwann cells or axons occurs before damage to neuronal cell bodies) in diabetes is currently unknown. These changes include alterations in Schwann cell-axon transport, alterations in protein expression in the DRG, demyelination and degeneration. GAP43, growth-associated protein 43; HSP, heat shock protein; PARP, poly(ADP-ribose) polymerase. Adapted with permission from REF.³⁷, Elsevier.



AGE, advanced glycation end-product;

FFAs, free fatty acids;

Glucosamine-6-P, glucosamine 6-phosphate;

LDL, low-density lipoprotein;

LOX1, oxidized LDL receptor 1;

RAGE, AGE-specific receptor;

ROS, reactive oxygen species;

TLR4, Toll-like receptor 4;

UDP-GlcNAc, uridine diphosphate N-acetylglucosamine.

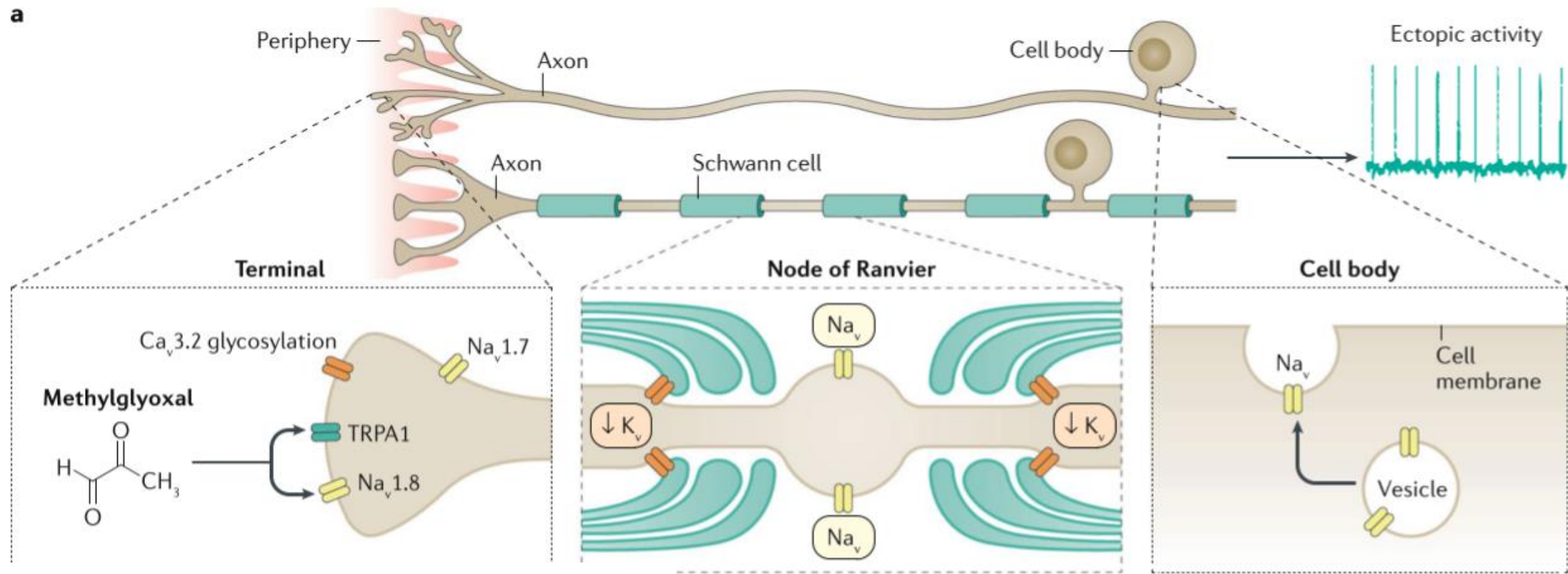
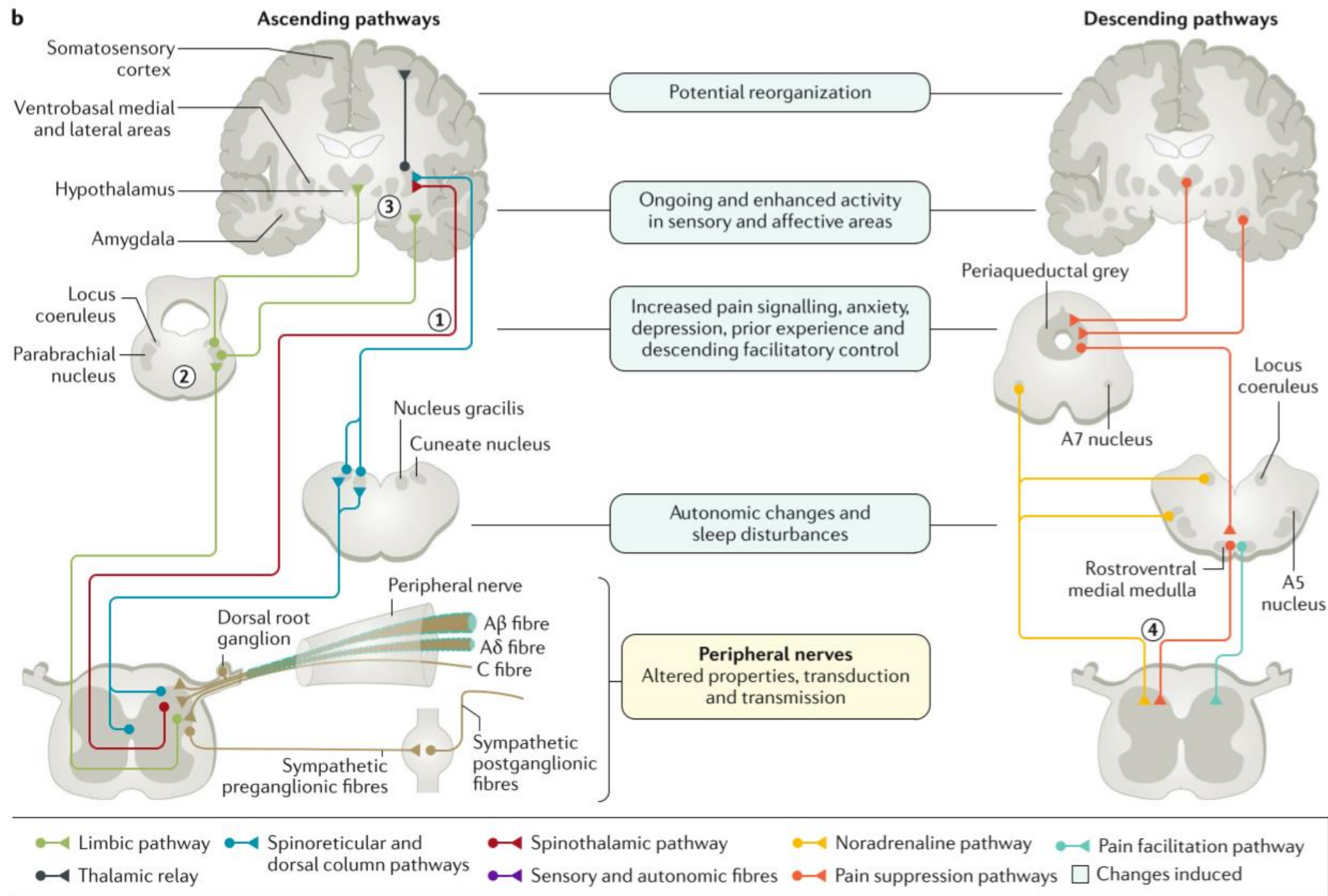


Fig. 4 | Central and peripheral mechanisms contributing to neuropathic pain in diabetic neuropathy. a | Several alterations to peripheral and central neurons contribute to the pathophysiology of painful diabetic neuropathy. Ion channels at the terminals of nociceptors can undergo glycation through the addition of methylglyoxal to form advanced glycation end-products (AGEs), which can contribute to gain of function of these channels and neuronal hyperexcitability. Changes at the perikaryon include increased expression of voltage-gated sodium channels, such as Na_v1.8, which can lead to hyperexcitability. In myelinated axons, the expression of shaker-type potassium (K_v) channels is reduced, which can also contribute to hyperexcitability. Hyperexcitability of neurons leads to increased stimulus responses and ectopic neuronal activity, leading to excessive nociceptive input to the spinal cord. In the spinal cord, microglia become



Mechanisms of pain

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system. Approximately 30–50% of patients with diabetic neuropathy develop neuropathic pain⁹², which most commonly takes the form of spontaneous (that is, stimulus-independent) burning pain of the feet. Patients can also report other positive sensory symptoms, such as brush-evoked allodynia (when a normally non-noxious stimulus evokes pain) and paresthesias. These positive sensory symptoms are often accompanied by sensory loss, and patients will comment on the paradox that their feet are continuously painful yet insensate to touch. Why only some patients with diabetic neuropathy develop neuropathic pain whereas others do not remains unclear, although this likely reflects a complex interplay of vulnerabilities, including genetic factors, the somatosensory circuitry and psychological factors in the face of stressors, such as the metabolic dysfunction of diabetes and neuropathy severity⁹³.

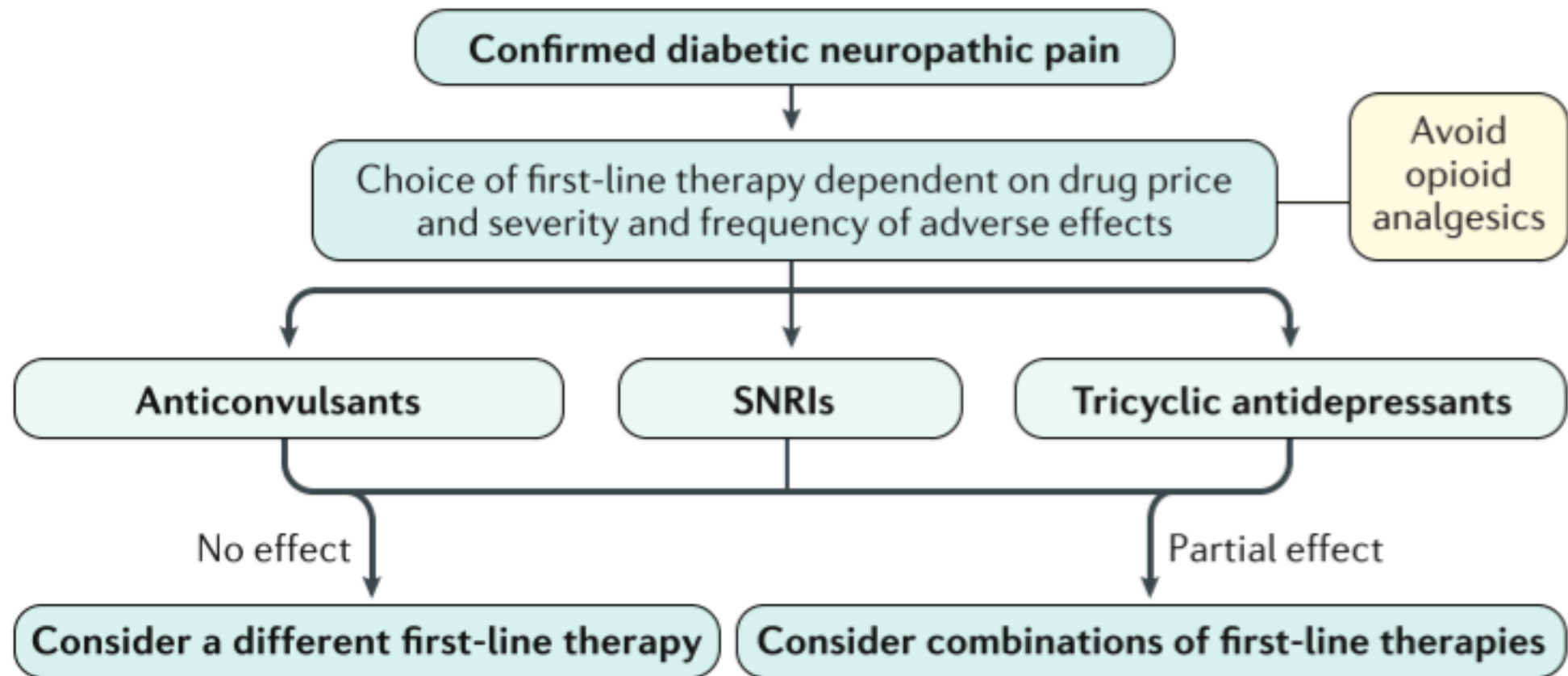


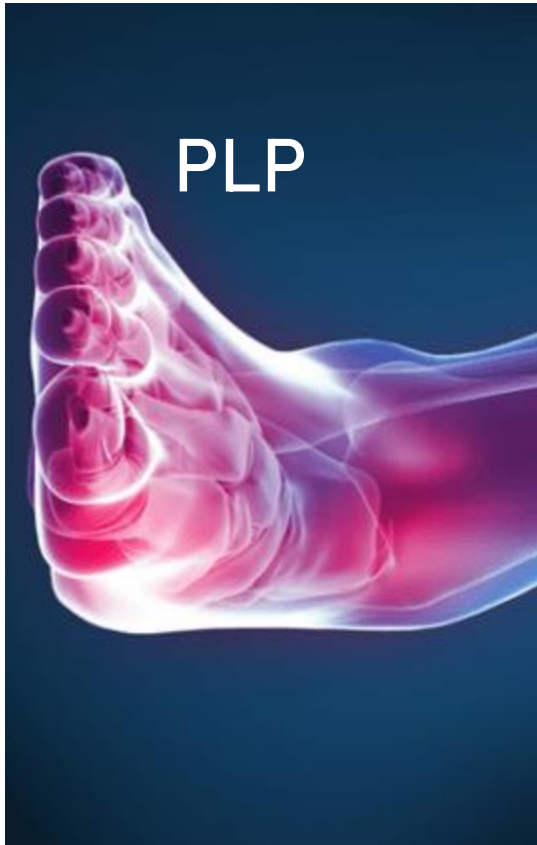
Fig. 6 | **Treatment of painful diabetic neuropathy.** First-line and second-line treatments for painful diabetic neuropathy include several drug classes, such as anticonvulsants (gabapentin or pregabalin), serotonin and noradrenaline reuptake inhibitors (SNRIs; duloxetine or venlafaxine) and tricyclic antidepressants (amitriptyline, nortriptyline, desipramine or imipramine). Opioids should be avoided owing to their serious adverse effects and association with addiction.

Phantom limb pain

- Dolore che si presenta in una parte del corpo rimossa traumaticamente o chirurgicamente
- 85% dei pazienti amputati, spesso con autorisoluzione in 2-3 anni
- Incidenza 3 settimane-1 anno dopo amputazione (75% 1° settimana)
- Arto fantasma ha spesso le stesse dimensioni e caratteristiche dell'arto mancante
- Nel tempo è possibile che si modifichi per dimensione e caratteristiche (*telescoping*)
- Dolore più intenso a livello distale
- Qualità: a coltellata, pulsante, bruciante, crampiforme/ punture spillo, prurito, numbness
- **Esacerbato** da: movimento dell'arto fantasma, meteo, pressione sul moncone, tosse, minzione, attività sessuale, defecazione, anestesia (ALR e AG), emozioni

Residual limb pain (RLP)=stump pain

- Dolore del moncone, DIVERSO da phantom limb pain
- Avvertito in una parte del corpo esistente



Fisiopatologia e patogenesi

Amputazione →

- degenerazione dell'estremità distale delle fibre
- sprouting rigenerativo
- formazione del neuroma
 - attività spontanea ectopica
 - attività evocata da stimoli fisici (pressione) e chimici (noradrenalina)

proliferazione canali eterotopici NaV (1.3, 1.7, 1.8)

↓↓ soglia scarica

→ attività ectopica

scariche spontanee ectopiche dal DRG

Degenerazione delle fibre C non mielinizzate → denervazione funzionale della lamina II

→ sprouting di fibre A β e A δ

→ switch fenotipico di A β → espressione di sostanza P

→ Allodinia meccanica

Aumento scariche midollo → Apoptosi degli interneuroni glicinerfici e GABAergici

Neuroinfiammazione e switch microglia

Downregulation oppioidi Upregulation CCK

Upregulation NaV 1.3 2° e 3° neurone

Remapping sovraspinale e della corteccia somatosensoriale

Remapping topografico → Stimoli di altre zone possono scatenare PLP

Fallimento della neuromatrix nel coping con amputazione

Uso della protesi ed esercizi immaginari/mirror therapy possono rimodulare la topografia corticale



Limakatso K, Parker R. Treatment Recommendations for Phantom Limb Pain in People with Amputations: An Expert Consensus Delphi Study. PM R. 2021;13(11):1216-1226.

Proposed treatments	Percentage of experts who endorsed each treatment in round 2	Percentage of experts who endorsed each treatment in round 3	Consensus reached? (Yes/No)	Level of consensus [*]
Nonpharmacological treatments				
Mirror therapy	75	80	Yes	High
Graded motor imagery	70	75	Yes	High
Cognitive behavioral therapy	70	75	Yes	High
Use of a functional prosthesis	70	75	Yes	High
Sensory discrimination training	60	60	Yes	Low
Virtual reality training	60	75	Yes	High

Limakatso K, Parker R. Treatment Recommendations for Phantom Limb Pain in People with Amputations: An Expert Consensus Delphi Study. PM R. 2021;13(11):1216-1226.

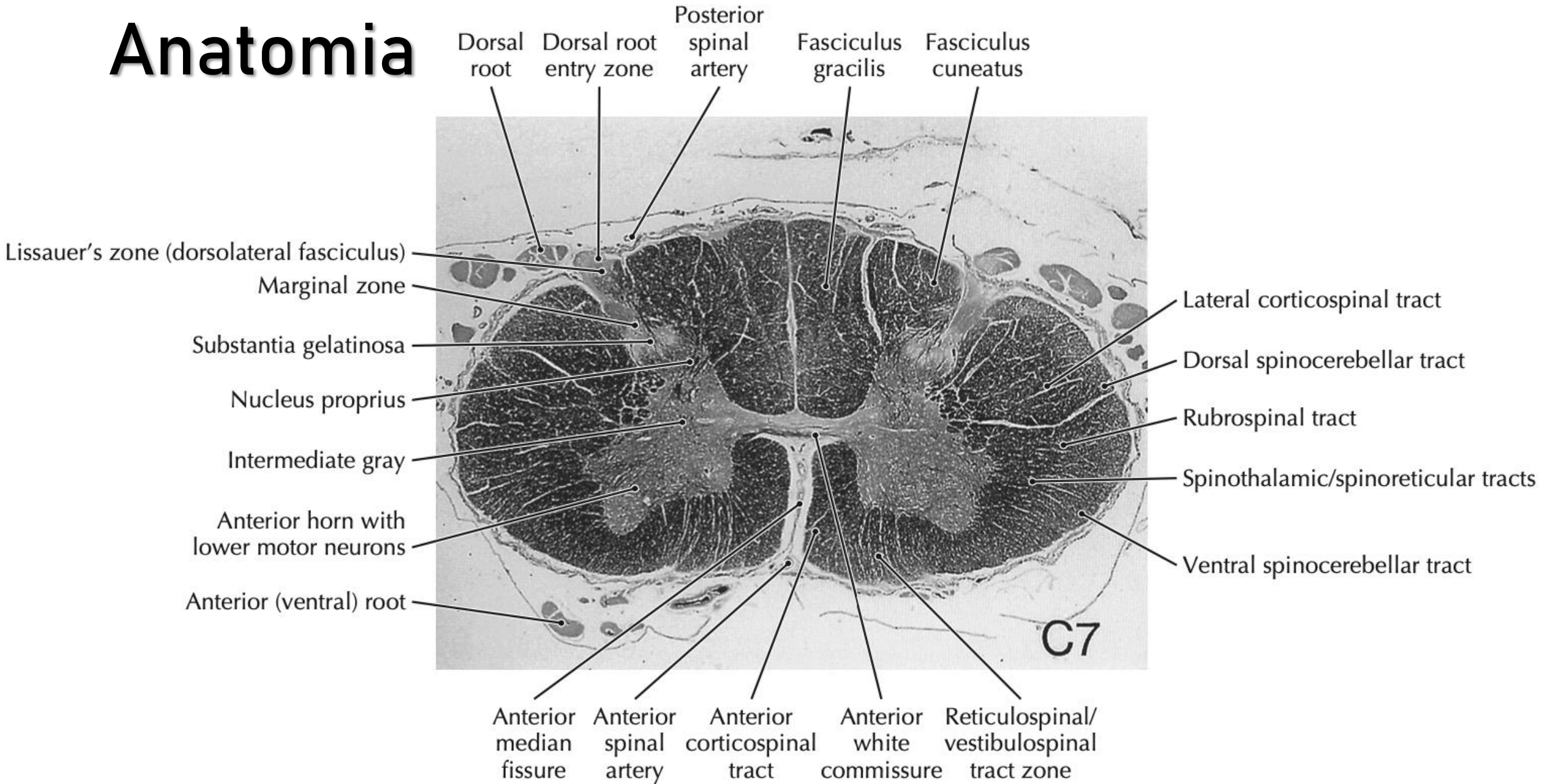
Proposed treatments	Percentage of experts who endorsed each treatment in round 2	Percentage of experts who endorsed each treatment in round 3	Consensus reached? (Yes/No)	Level of consensus *
Pharmacological treatments				
Amitriptyline	50	65	Yes	Moderate
Pregabalin	45	-	No	-
Gabapentin	40	-	No	-
Morphine	35	-	No	-
Ketamine	30	-	No	-
Intraforaminal infusion of dilute lidocaine	30	-	No	-
Fluoxetine	15	-	No	-
NSAIDs	15	-	No	-
Surgery				
Peripheral nerve surgeries	35	-	No	-

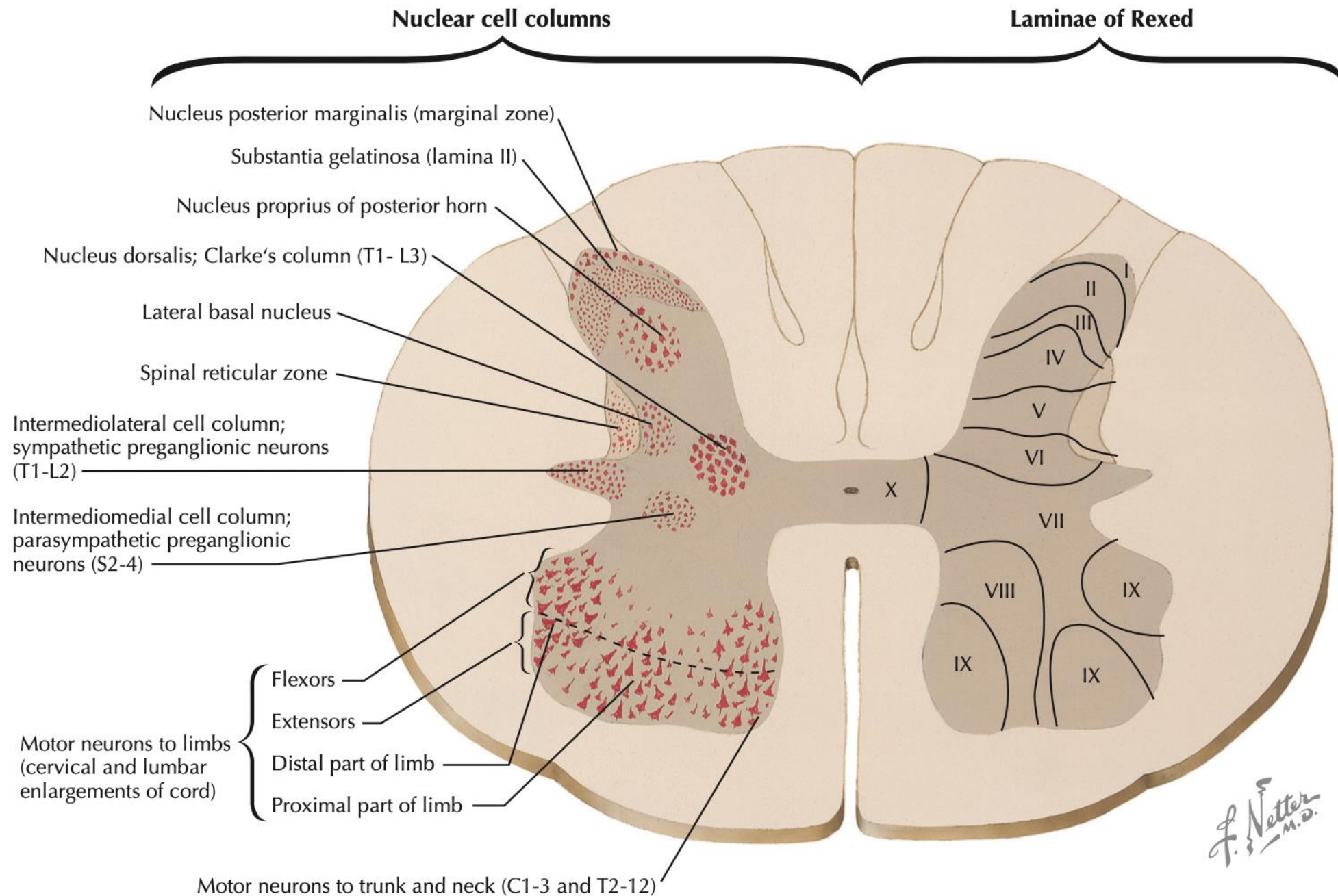
Spinal Cord Central Pain

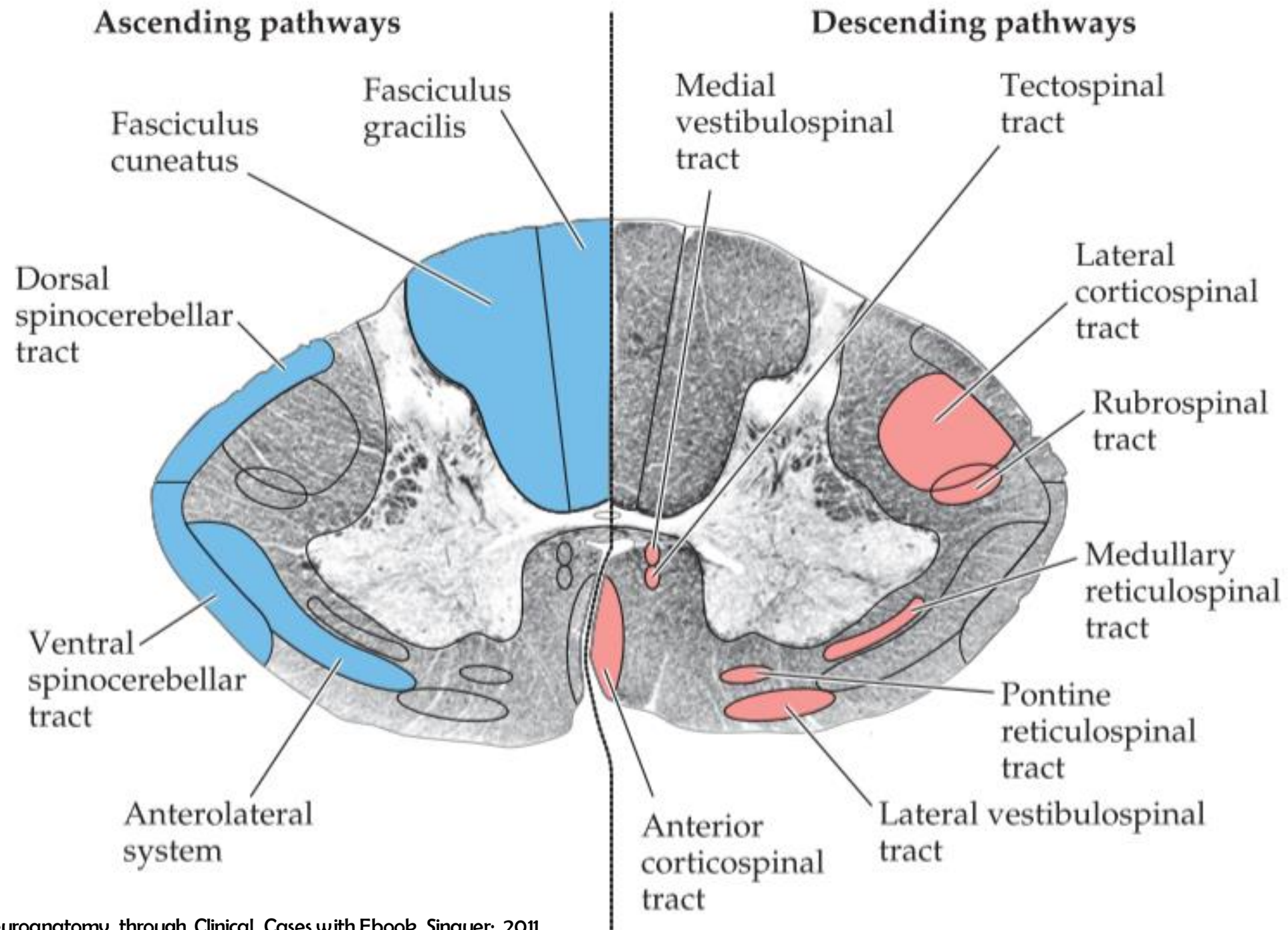
Prevalenza di dolore centrale nei pazienti mielolesi 20-40%

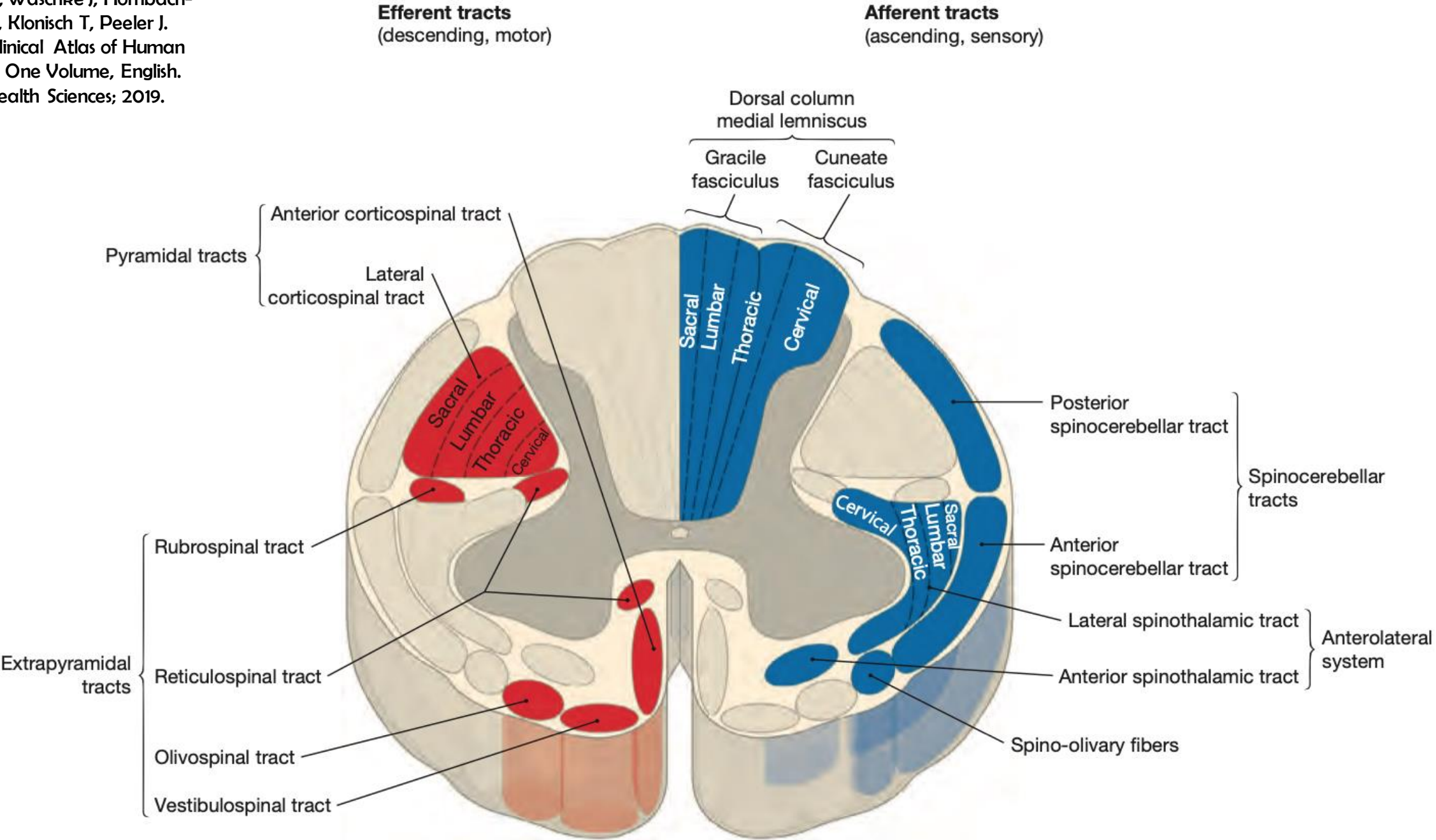
La lesione del Sistema somatosensoriale, in particolare del tratto spinotalamico, sono condizione necessaria ma non sufficiente per sviluppo del dolore centrale

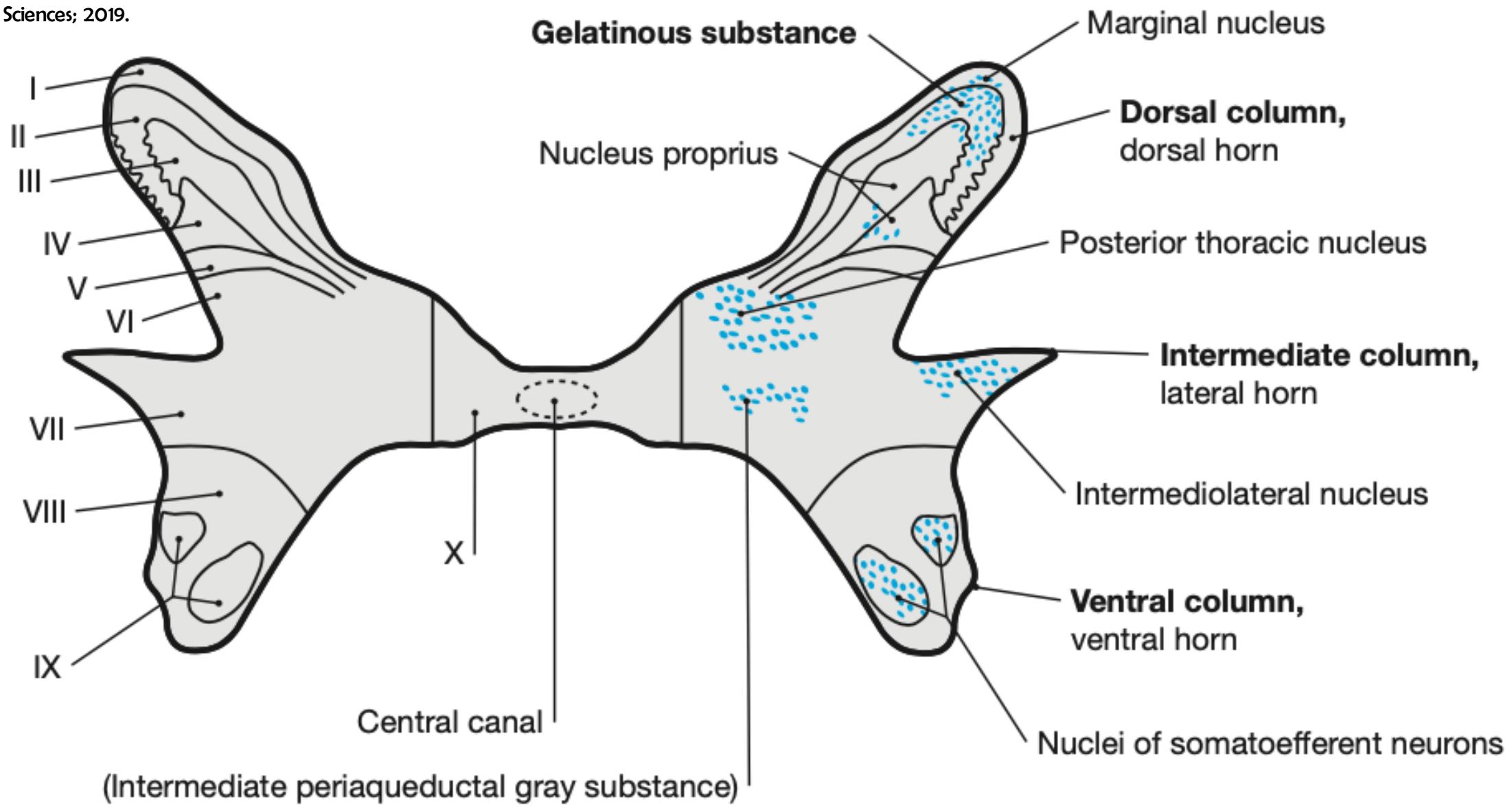
Anatomia











Spinal Cord Crosssection: Detailed Anantomy

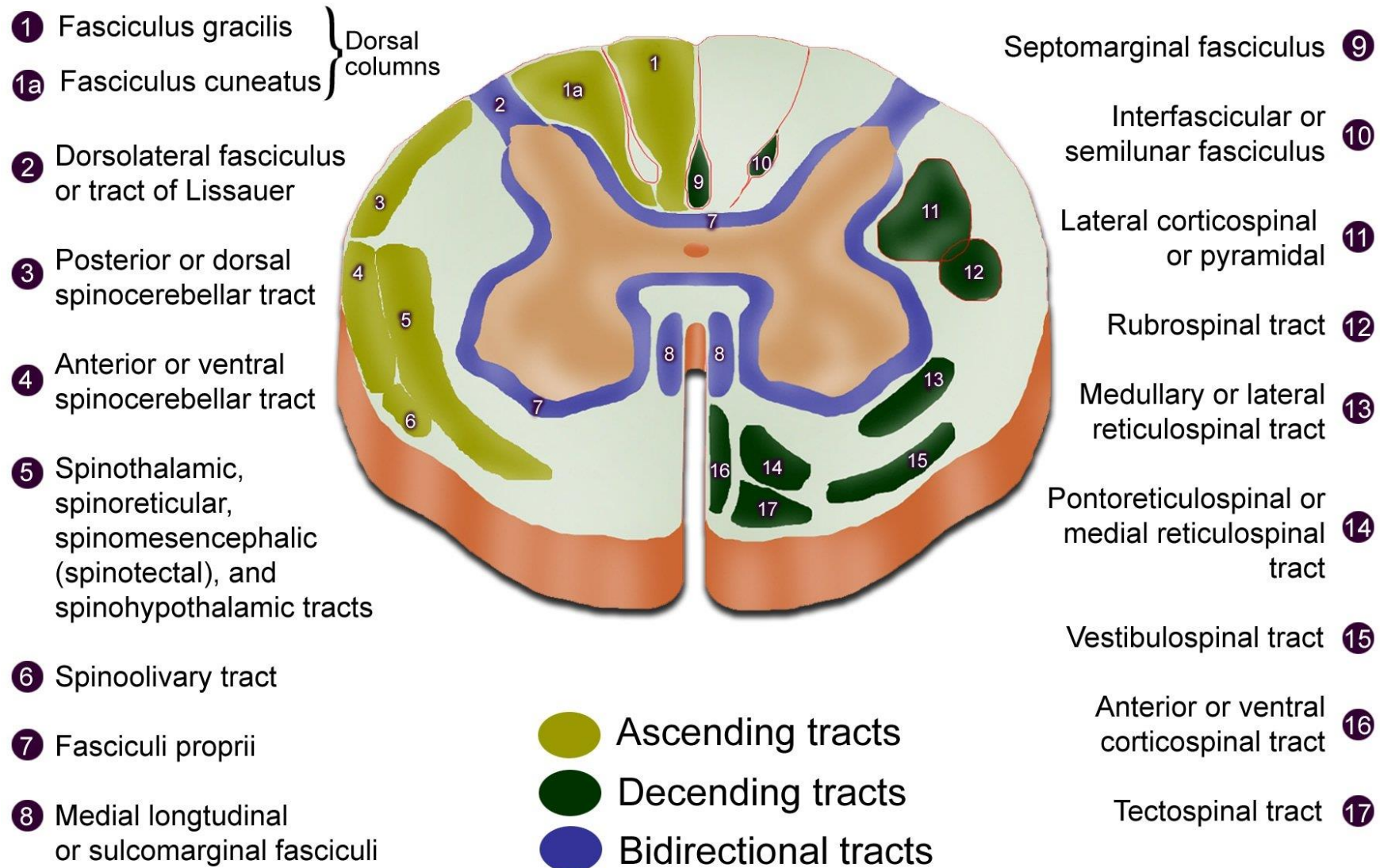


Fig. 27.4 Routes by which noxious (purple) and non-noxious (blue) primary afferent inputs may engage spinothalamic projection neurones in laminae I–IV of the dorsal horn. Nociceptive C and A δ fibres (purple) activate neurokinin 1 (NK1)-expressing spinothalamic projection neurones of lamina I directly, and through the vertical cells (V) of the outer part of lamina II (Ilo) indirectly (green axon). Nociceptive C fibres also activate central cells (C) of lamina II (Ili); the C cells contact, and probably excite, V cells in lamina Ilo.

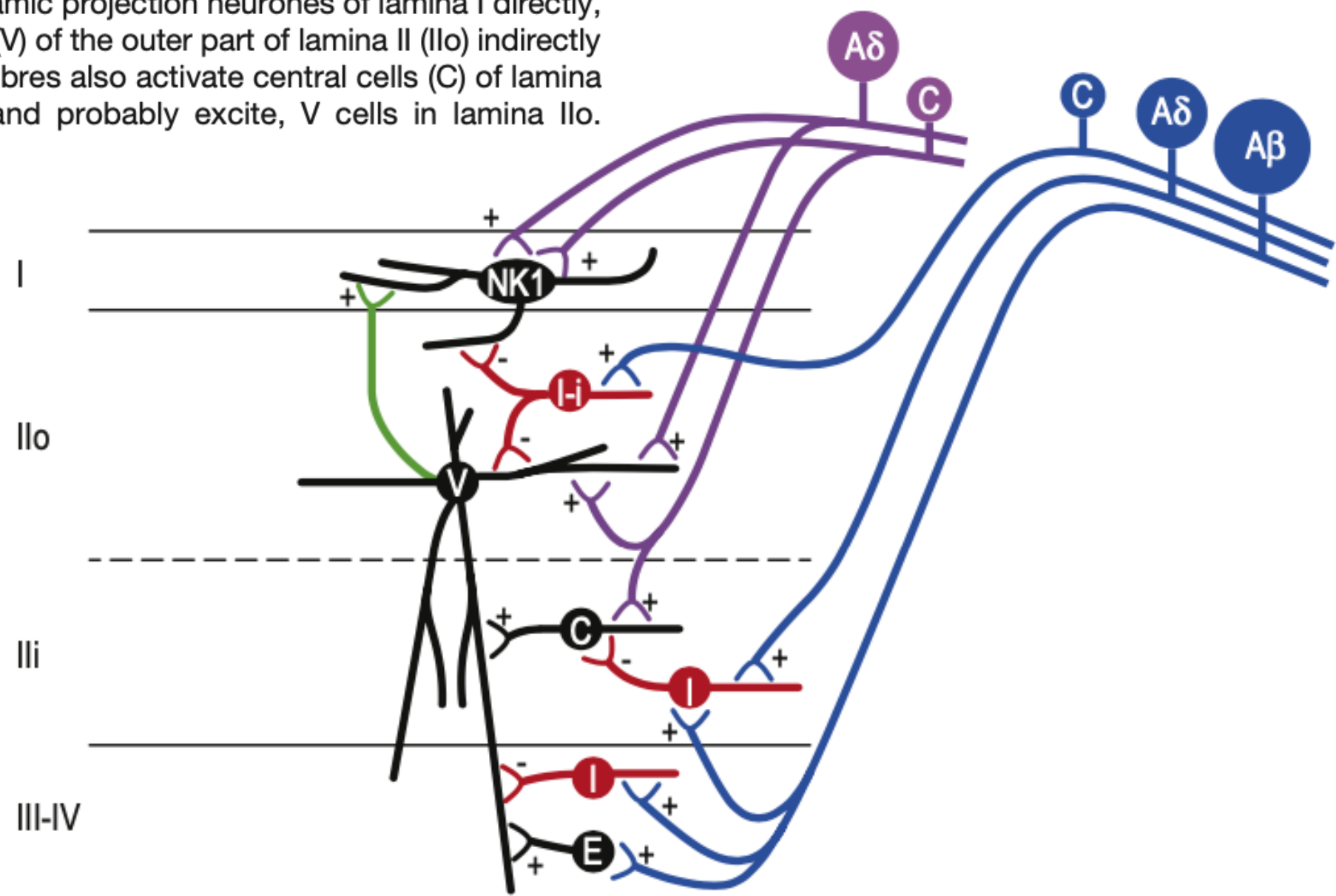


FIGURE 7.10 Spinal Cord

Syndromes (Spinal section from DeArmond SJ, Fusco MM, Maynard MD. 1989. *Structure of the Human Brain: A Photographic Atlas*. 3rd Ed. Oxford, New York.)

KEY

▨ Lesion

SENSORY/MOTOR LOSS:

- Vibration and position sense loss
- Pain and temperature sense loss
- Motor loss

SPINAL CORD STRUCTURES

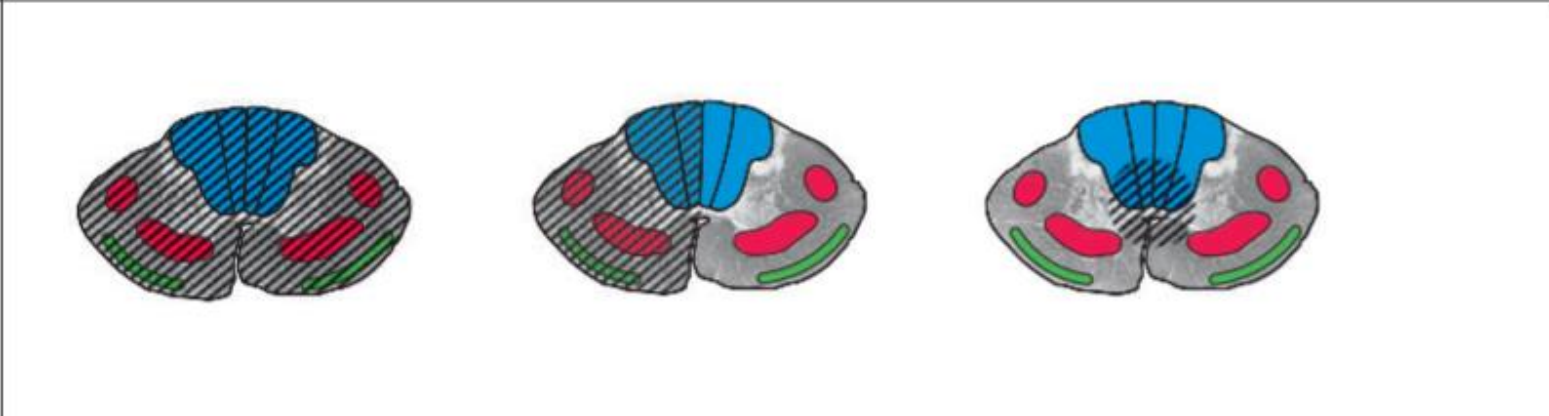
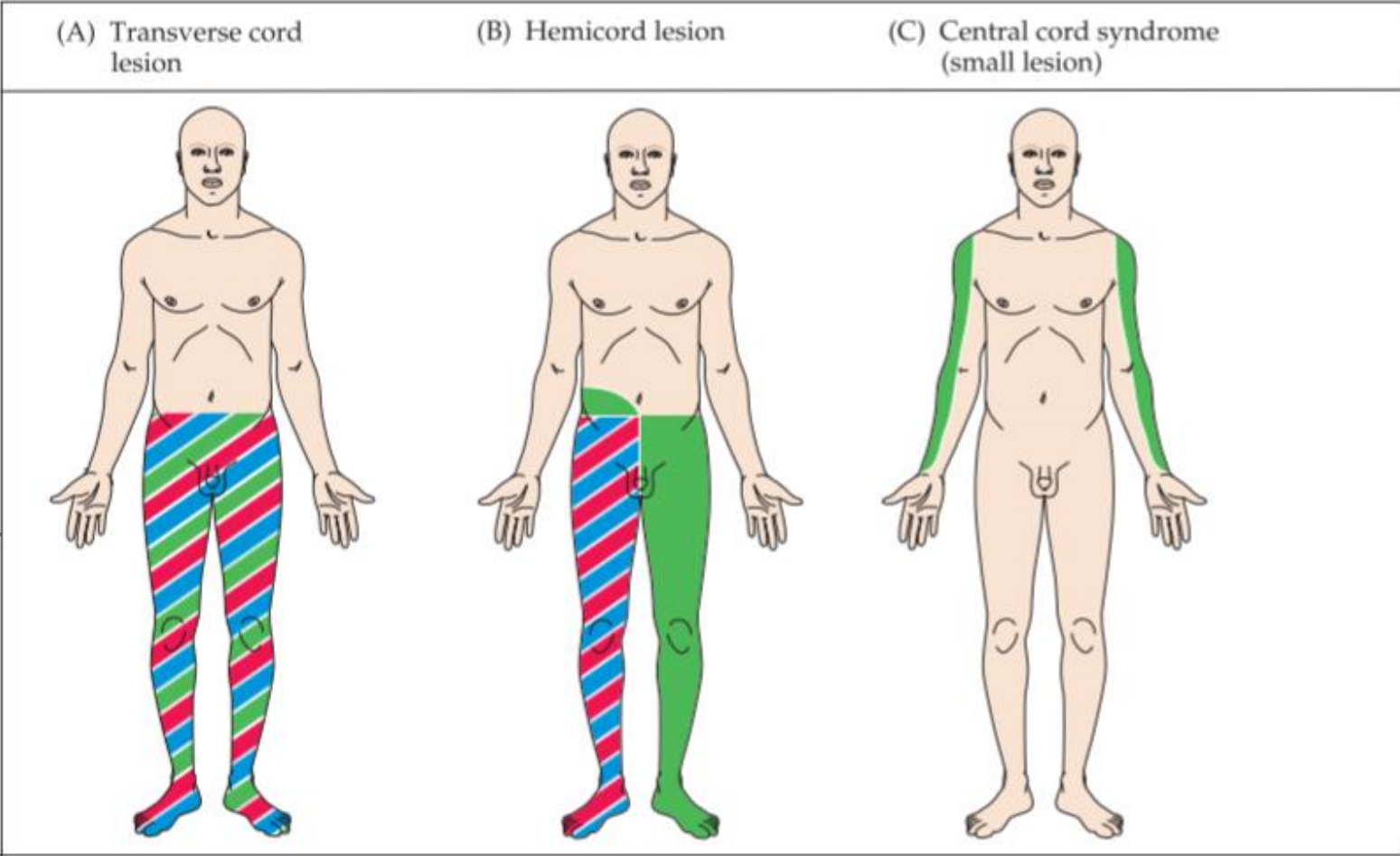
Posterior columns (vibration and position sense)

Lateral corticospinal tract (UMN)

Anterior horn cells (LMN)

Anterolateral pathways (pain and temperature sense)

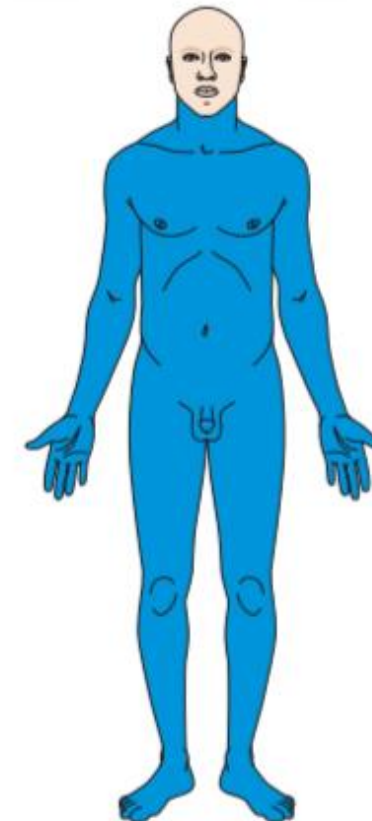
Ventral commissure



(D) Central cord syndrome
(large lesion)



(E) Posterior cord syndrome



(F) Anterior cord syndrome



KEY

▨ Lesion

SENSORY/MOTOR LOSS:

■ Vibration and position sense loss

■ Pain and temperature sense loss

■ Motor loss

**SPINAL CORD
STRUCTURES**

Posterior columns
(vibration and
position sense)

Lateral corticospinal
tract (UMN)

Anterior horn
cells (LMN)

Anterolateral
pathways (pain and
temperature sense)

Ventral
commissure

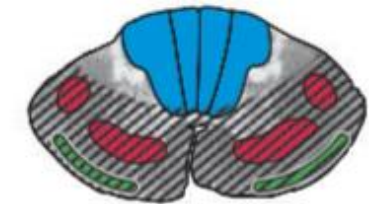
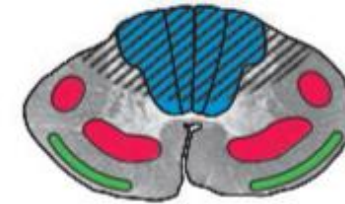
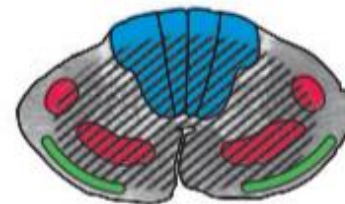


Table 3.2 Lesions associated with cord central pain (CCP)

1. Spinal trauma with fracture and/or dislocations producing complete or partial transection or concussion of the spinal cord (Schneider's syndrome)
2. Ischemic/hemorrhagic: e.g., aortic dissection, systemic hypotension, atherosclerosis/thromboembolism/infarcts, hematomyelia^a/subarachnoid hemorrhage due to arteriovenous malformation^b, cavernomas*, spinal epidural hematoma**, dural fistula, traumatic/nontraumatic/iatrogenic cervical anterior spinal cord syndrome, spontaneous abdominal compartment syndrome, etc.
3. Rheumatological and degenerative disorders: e.g., myelopathy due to cervical spinal stenosis–spondylosis and cervical discal hernia, ankylosing spondylitis with conus lesions, Paget's disease, rheumatoid arthritis, posterior longitudinal ligament ossification, sarcoidosis, etc.
4. Intra- and extramedullary tumors^c
5. Congenital and developmental: nontumoral cysts, syringomyelia, dysraphism, diastematomyelia, spina bifida, myelomeningocele, etc.
6. Inflammatory/infective: multiple sclerosis, transverse myelitis, viral (e.g., herpes zoster, cytomegalovirus, HIV, poliovirus), bacterial (e.g., mycobacteria/Pott's disease, luetic gummad), fungal (e.g., cryptococcus), or parasitic infections/abscesses (e.g., toxoplasma, schistosoma), infective transverse myelitis
7. Degenerative CNS disorders
8. Toxic: antineoplastic agents, radiation, etc.
9. Genetic and metabolic
10. Iatrogenic: cordotomy, aortic repair surgery, surgery for spinal angiomas/fistulas/hernias/spondylosis/intra- and extramedullary tumors, spinal fusion surgery, myelography, anticoagulant therapy with epidural/subdural hematomas

Fisiopatologia del *below-level pain*

Trauma della sostanza grigia

- Eccitotossicità
- Upregulation Nav1.3 → Scariche anomale
- Attività spontanea parossistica dal corno dorsa
- ↑↑ risposte agli input nel segment lesionato e vicino

Rimodellamento corticale S1

connessioni tra neuroni at-level e below-level

Iperattività spinoreticolare → ↑↑ arousal

Trauma della sostanza bianca

60% pazienti ASIA A cercine di assoni funzionanti attorno alla lesione

- Parziale deafferentazione talamica
- Trasmissione dell'attività dei neuroni nocicettivi tra mielomeri contigui tramite sistemi propriospinali e al talamo/corteccia via fibre ascendenti risparmiate
- Demielinizzazione → attività spontanea
- Iperattività delle fibre C

Neuroinfiammazione e attivazione della glia

Clinica

Canavero S, Bonicalzi V. *Central Pain Syndrome*.
Springer International Publishing; 2018.

La lesione del Sistema somatosensoriale, in particolare del tratto spinotalamico, sono condizione necessaria ma non sufficiente per sviluppo del dolore centrale

- SCCP può coinvolgere l'intera regione corporea sotto il livello della lesione (dolore diffuso)
- MAI distribuzione dermatomerica
- Generalmente più intenso nei dermatomeri sacrali (natiche, genitali, piedi)
- Spesso profondo
- Talora se localizzato, distribuzione a sella
- In sdr Brown-Séquard dolore controlaterale alla lesione, talora allochiria
- Picco notturno

Qualità bizzarre

Canavero S, Bonicalzi V. *Central Pain Syndrome*.
Springer International Publishing; 2018.

- Diversi tipi di dolore simultaneamente o in successione
- Dolore intermittente shock elettrico o lancinante più frequente nel torso anteriore, genitali, natiche, aa inferiori
- Dolore aching “indolenzimento” nel collo, spalle, dorso

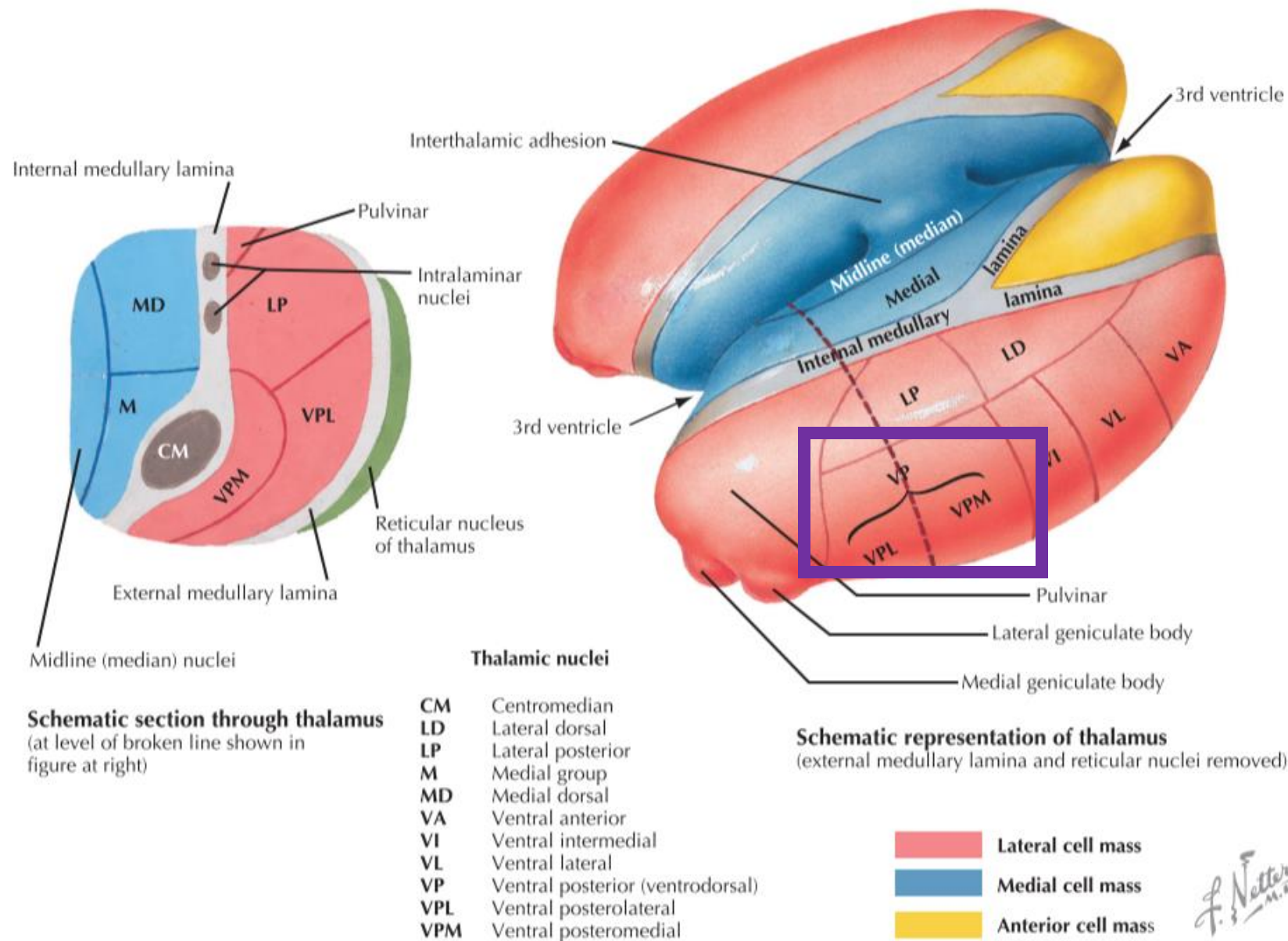
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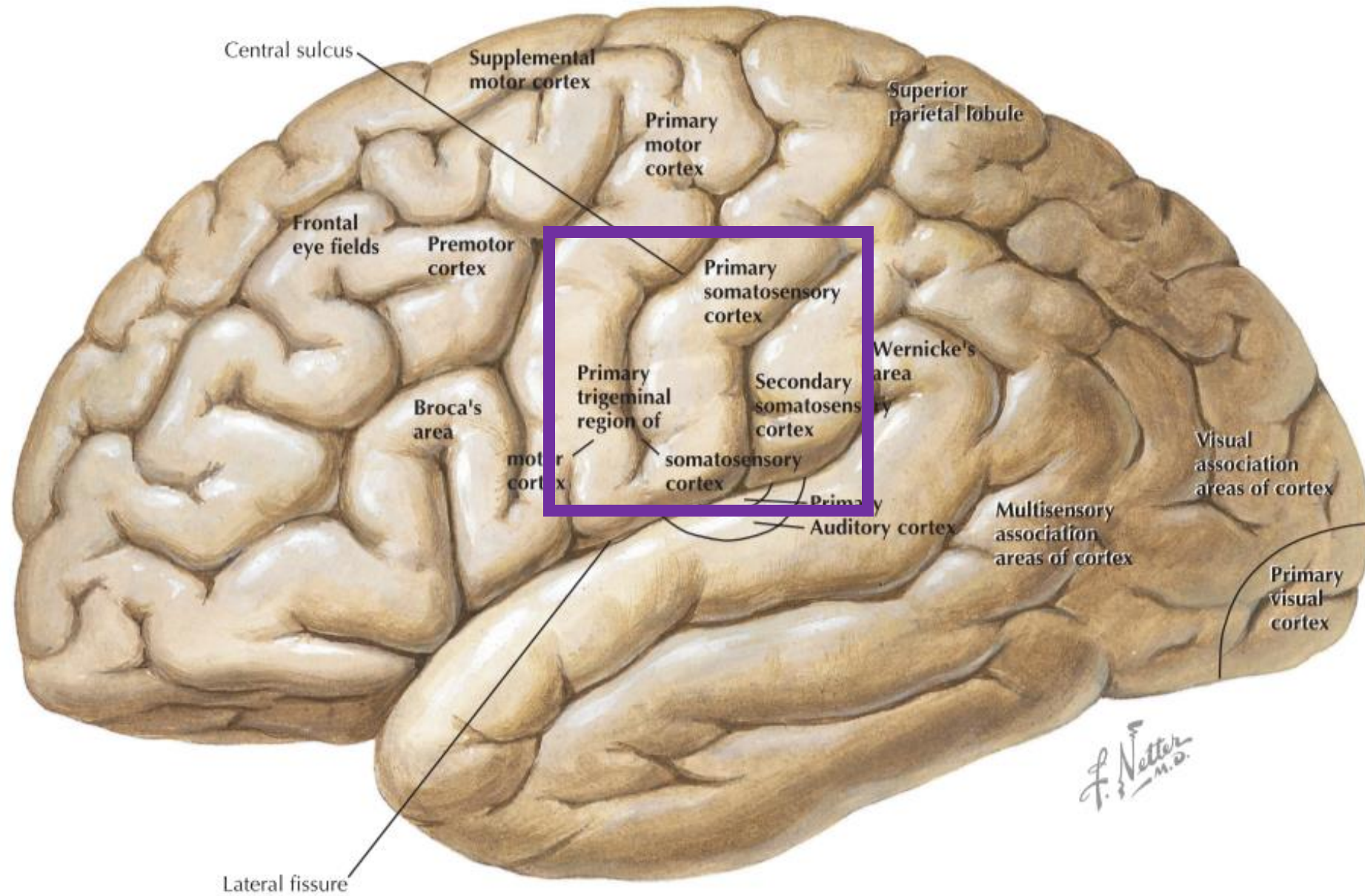
- Tagliente, a pugnata, puntorio, crampiforme, formicolio doloroso, folgorante, pulsante, freddo/congelamento, vibrante, irradiante, costrittivo...

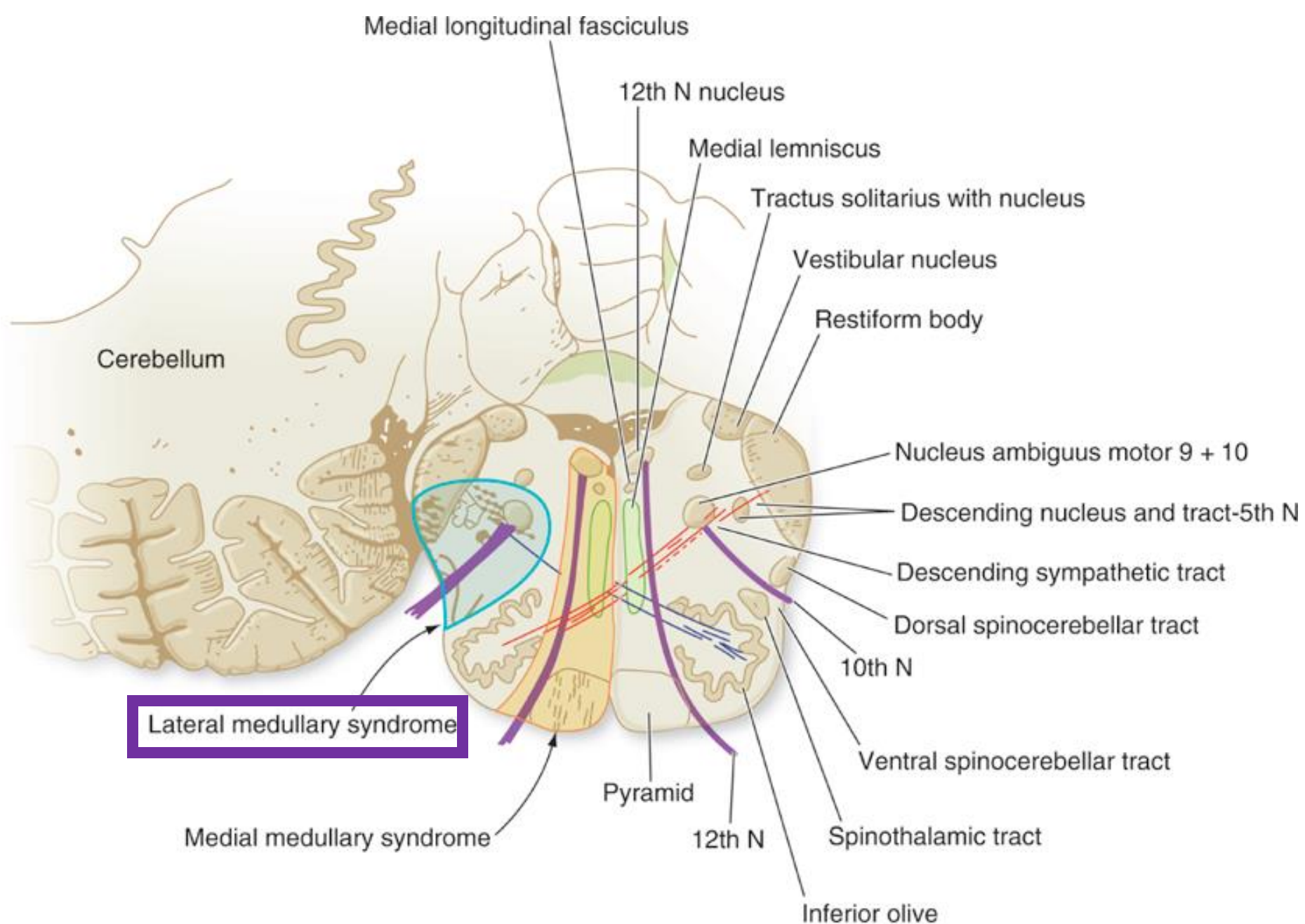
Table 3.1 Lesions associated with brain central pain (BCP)

1. Vascular lesion: ischemia/infarct; hemorrhage, including intracerebral; and subarachnoid (independent of surgery, due to spasm and infarction, or direct brain injury); vascular malformations (arteriovenous malformation through compression, ischemia by steal, or hemorrhage, cavernomas through hemorrhage and perhaps compression, compressing nonhemorrhagic saccular aneurysm, venous angioma), migraine-induced vasospasm [est. 85%]
2. Penetrating trauma [est. 1–2%] and non-penetrating trauma*
3. Inflammation: MS, primary Sjögren syndrome
4. Infection: abscess (e.g., toxoplasma), gumma, tuberculoma, encephalitis, etc. [est. 4%]
5. Tumor: glioma, meningioma, etc., including intratumoral hemorrhage [est. 1–2%], neuroepithelial cyst (**), ruptured epidermoid cyst (***) at brainstem, thalamic, or parietal level
6. Iatrogenic

- **Talamo nucleus ventrocaudalis (Vc) sempre coinvolto**
- **Cortico-subcorticali tutte le lesioni corticali responsabili coinvolgono lobo parietale**
- **Capsulotalamiche**
- **Lenticolocapsulari**
- **Tronco, più spesso bulbo**
- **Diffuse**







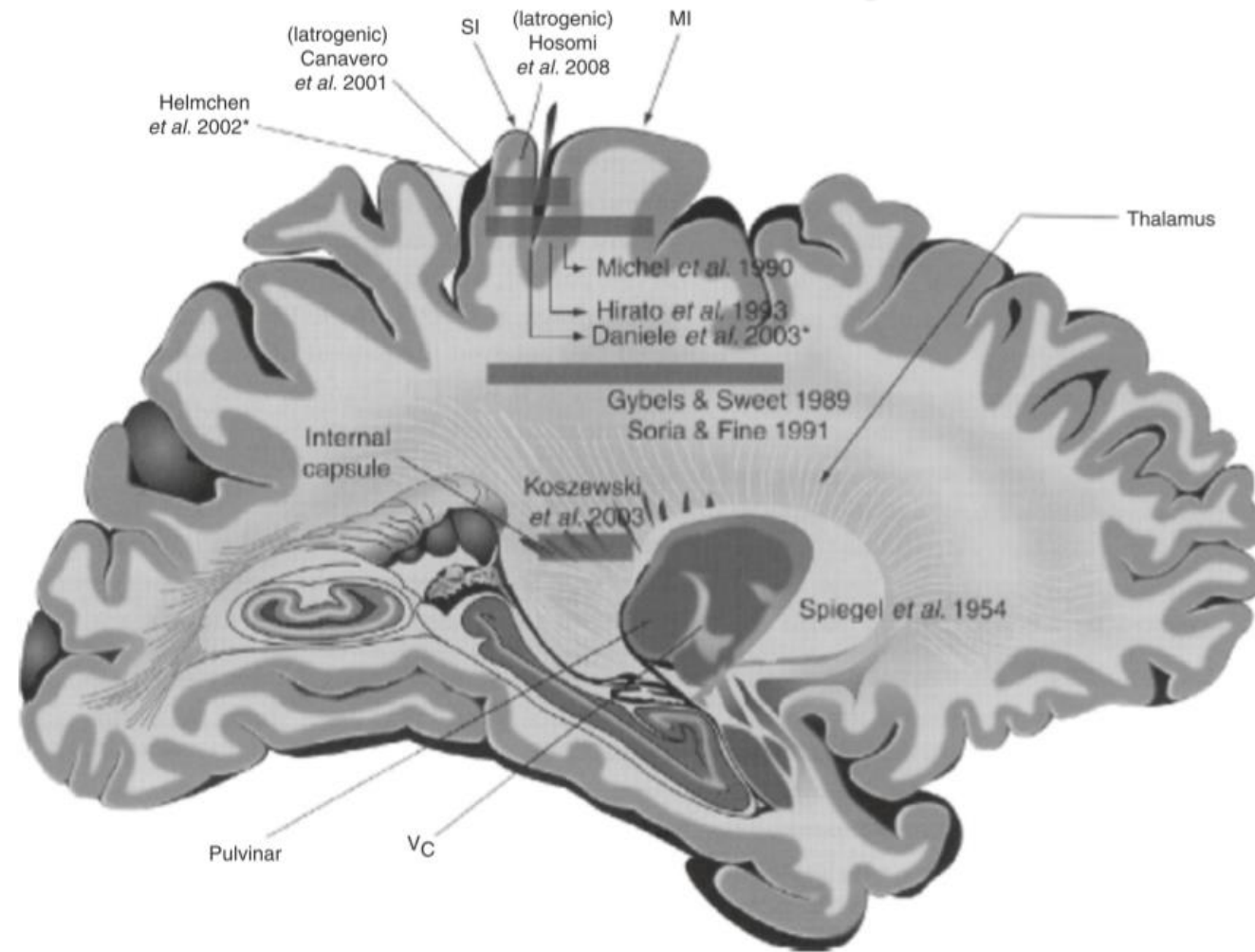
Clinica

- Distribuzione somatotopica
- 40% dolore all'emisoma \pm emivolto
- Negli altri casi parti del corpo (spt viso, braccio), quadranti, combinazioni di parti senza zone di transizione
- Dolore può vagare
- Può localizzarsi ai visceri (retto, vagina...)
- Può presentarsi a chiazze
- Qualità varie (2-4) e talora distribuite nelle regioni colpite
- Picco pomeridiano o serale

Componenti del dolore in BCP

1. **Componente spontanea costante (85-100%)**
2. **Componente intermittente (15%)**
 - Quotidiano
 - Intervalli di alcune ore
 - Breve (secondi-minuti)
 - Intenso
 - Spontaneo
 - Folgorante, lancinante, terebrante
3. **Dolore evocato (iperpatia, iperalgesia, allodinia)**

Dynamic Reverberation Theory



Canavero S, Bonicalzi V. *Central Pain Syndrome*. Springer International Publishing; 2018.

Fig. 8.1 Plot of lesions that abolished central pain. Notice that all lesions align on a trajectory that joins the sensory cortex and the thalamus (from: Helmchen et al. *Pain* 2002; 98: 325–330; Canavero et al. *Acta Neurol Belg* 2001; 101: 221–223; Hosomi et al. *Clin Neurophysiol* 2008; 119: 993–1001; Michel et al. *Rev Neurol* 1990; 146: 405–414;

Hirato et al. *Acta Neurochir (Wien) Suppl.* 58, 141–144; Daniele et al. *Funct neurol* 2003; 18: 95–96; Gybels Jand Sweet WH. *Neurosurgical treatment of persistent pain*. Karger, 1989; Soria and Fine. *Pain* 1991; 44: 285–288; Spiegel et al. *Neurology* 1954; 4:735–751; Kozewski et al. *Pain clin* 2003; 15 :115–123)

Corteccia output glutamatergico discendente sul talamo
Sistema talamocorticale ascendente 10x più debole

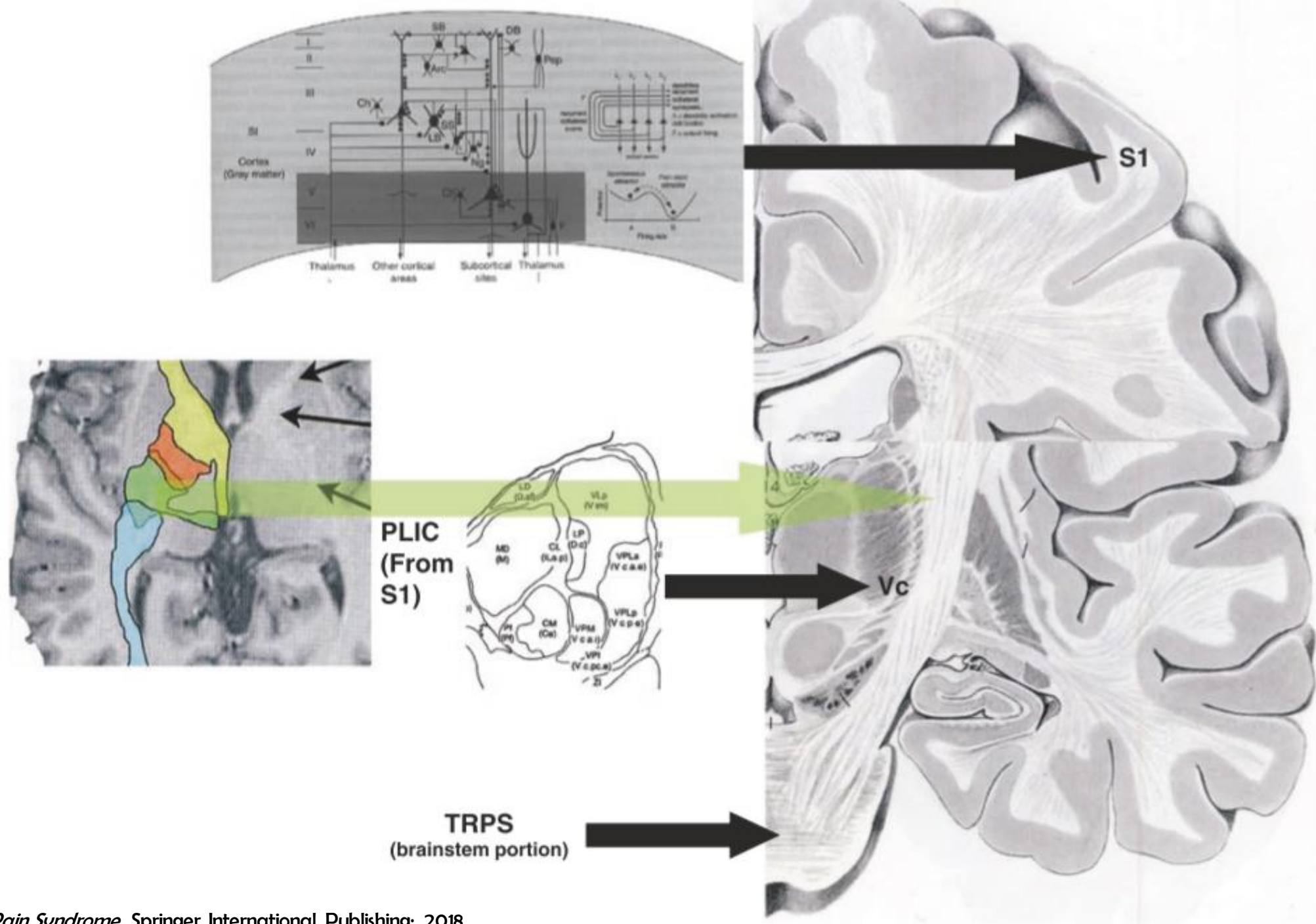
Danno del tratto spinotalamico + Deficit Sistema GABAergico? →
Squilibrio outflow glutamatergico corticotalamico
Iperattività del sistema troncoretico-proprio-spinale
Facilitazione bottom-up del loop corticotalamico

S1 attractor state (locked S1) (e.g., layer 4 ⇒ (layer 2/3 ⇒) layer 5 ⇒ layer 6 ⇒ layer 4+corticothalamic outflow).

Se distruzione completa di S1 o talamo il loop si sviluppa nell'emisfero opposto via corpo calloso e nucleo reticolare talamico

→ **Alterazione del connettoma**

Canavero S, Bonicalzi V. Pain Myths and the Genesis of Central Pain. *Pain Med.* 2015;16(2):240-248. doi:10.1111/pme.12509



Farmacoterapia del Dolore Centrale

Propofol

0.2 mg/kg (iv)

Ketamina

0.05 - 0.5 mg/kg/h (iv-sc)

0.2–0.5 mg/kg/dose PO BID/TID

Lidocaina

1 mg/kg (iv 10 min) - 5 mg/kg (30 min–6 h)

(test per Mexiletina orale)

Lamotrigina

**25 mg QD (14 giorni), + 50 mg QD (14 giorni)
+ 50-100 mg QD fino a 500 mg**

**Amitriptilina (efficace sul dolore continuo
lancinante e sull'evocato dalla temperatura)**

10-25 mg QD fino a 150 mg QD

**Gabapentin (dolore pulsante, formicolio
doloroso, dolore evocato?)**

Poco efficace in monoterapia

Fino a 3600 mg/die

Neurostimolazione

- Neurostimolazione NON invasiva
- Neurostimolazione invasiva e Deep Brain Stimulation
- Spinal Cord Stimulation



Box 30.1: Palliation of Central Pain: The 2016 TANG Guidelines

Step 1

Amitriptyline (cardiologic assessment before starting)
(Start at 10 mg die at night and slowly increase up to 150 mg, benefit or intolerable side effects.) *Timeline: maximum 3 months*

+TENS (or scrambler therapy if available)

+CAM (e.g., virtual reality hypnosis)

If pain is not satisfactorily controlled, add (or replace with):

Lamotrigine

(Start at 25 mg and increase by 25 mg every week until benefit or intolerable side effects, up to 600–800 mg; *timeline: 3 months*)

If pain is not satisfactorily controlled:

Step 2

Therapeutic Dissection (on separate days):

(a) IV propofol test (0.2 mg/kg IV; placebo, Intralipid®)

(b) IV ketamine (5 mg up to 25 mg max; consider a benzodiazepine, e.g., midazolam 5 mg, before test)

(c) rTMS: M1 and S1 test stimulation (low and high frequency) over at least 5 days

If at least one positive:

Invasive (neurosurgical) cortical stimulation (ICS)

(For CCP, start with a trial of SCS first, and move to ICS if pain uncontrolled.)

If negative:

(d) IV lidocaine (1–5 mg/kg over 30'–6 h; placebo, saline; warning: may transiently worsen MS)

If positive:

Mexiletine (cardiologic assessment before starting; may not be available in some countries)

(Start at 200 mg on a full stomach and increase every 3 days as needed or until intolerable side effects, up to 1000 mg; *timeline: 3 weeks*)

If pain is not satisfactorily controlled:

Step 3

IT midazolam/clonidine (+ baclofen+, e.g., bupivacaine)