

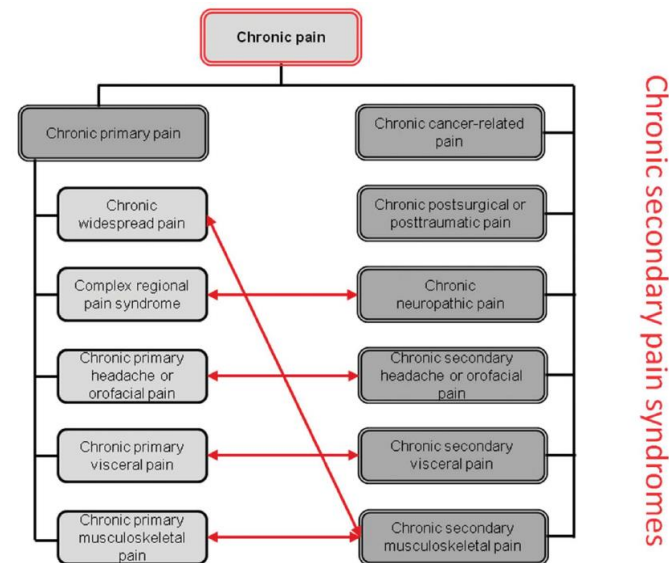


# Meccanismi d'azione dei farmaci nella fibromialgia

Diego Fornasari

## Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the *International Classification of Diseases (ICD-11)*

Rolf-Detlef Treede<sup>a,\*</sup>, Winfried Rief<sup>b</sup>, Antonia Barke<sup>b</sup>, Qasim Aziz<sup>c</sup>, Michael I. Bennett<sup>d</sup>, Rafael Benoliel<sup>e</sup>, Milton Cohen<sup>f</sup>, Stefan Evers<sup>g</sup>, Nanna B. Finnerup<sup>h,i</sup>, Michael B. First<sup>l</sup>, Maria Adele Giamberardino<sup>k</sup>, Stein Kaasa<sup>l,m,n</sup>, Beatrice Korwisi<sup>b</sup>, Eva Kosek<sup>o</sup>, Patricia Lavand'homme<sup>p</sup>, Michael Nicholas<sup>q</sup>, Serge Perrot<sup>r</sup>, Joachim Scholz<sup>s</sup>, Stephan Schug<sup>t,u</sup>, Blair H. Smith<sup>v</sup>, Peter Svensson<sup>w,x</sup>, Johan W.S. Vlaeyen<sup>y,z,aa</sup>, Shuu-Jiun Wang<sup>bb,cc</sup>

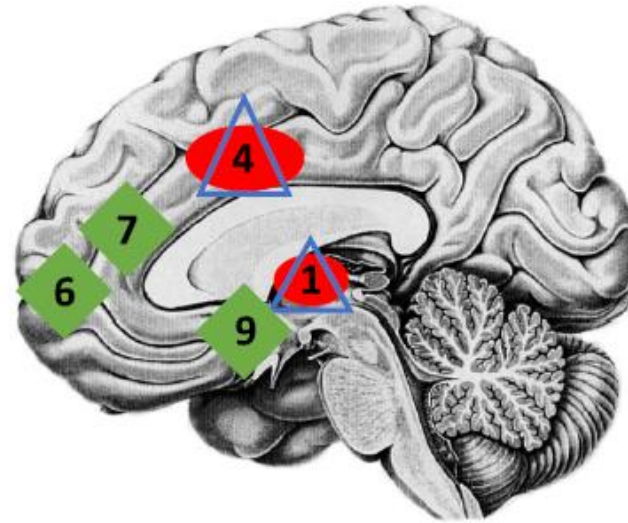
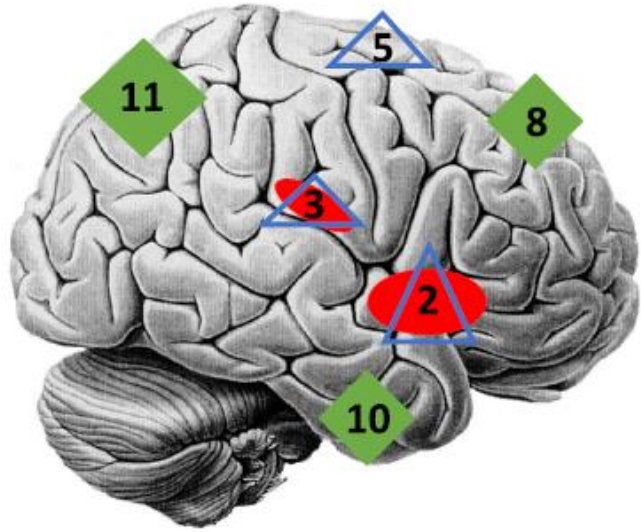


PAIN 160 (2019) 19–27

# DEFINITION OF NOCIPLASTIC PAIN

Nociplastic pain is defined as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.”

# PAIN IN THE BRAIN



## Acute Pain

1. thalamus
2. insula
3. SII
4. dACC



## Nociceptive Pain

1. thalamus
2. insula
3. SII
4. dACC
5. SMA



## Nociplastic Pain

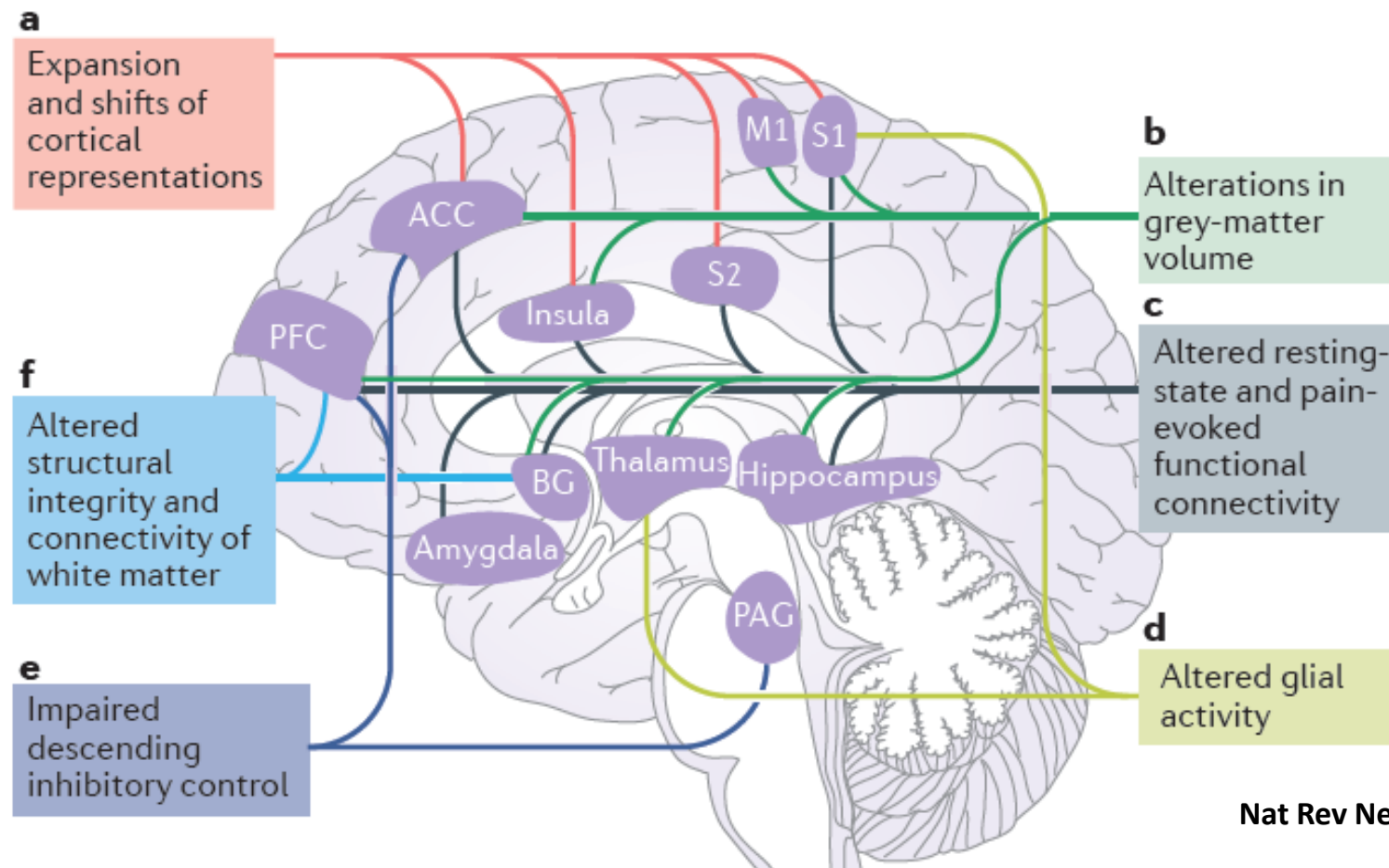
6. mPFC
7. rACC
8. SFG
9. NAc
10. ITG
11. PPC

Fig. 1. Pain in the brain. Neural networks associated with three causally discrete types of pain: acute, nociceptive, and nociplastic. Note the high degree of overlap between the acute pain and nociceptive pain networks, which include both sensory and affective regions. In contrast, the nociplastic pain network includes relatively distinct affective regions. Abbreviations: SII, secondary somatosensory cortex; SMA, supplementary motor area; mPFC, medial prefrontal cortex; rACC, rostral anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; SFG, superior frontal gyrus; NAc, nucleus accumbens; ITG, inferior temporal gyrus; PPC, posterior parietal cortex.

## Distinct aberrations in cerebral pain processing differentiating patients with fibromyalgia from patients with rheumatoid arthritis

Angelica Sandström<sup>a,b,\*</sup>, Isabel Ellerbrock<sup>a,b</sup>, Monika Löfgren<sup>c</sup>, Reem Altawil<sup>d</sup>, Indre Bileviciute-Ljungar<sup>c</sup>, Jon Lampa<sup>d</sup>, Eva Kosek<sup>a,b,e</sup>

# Structural and functional changes in the human brain in chronic pain conditions.



Nat Rev Neurosci 2017 Jan 20; 18 (2): 113

**Table. Pathophysiology of Fibromyalgia: Potential Mechanisms**

Mechanism	Description
Central sensitization	Amplification of pain in the spinal cord via spontaneous nerve activity, expanded receptive fields, and augmented stimulus responses
Abnormalities of descending inhibitory pain pathways	Dysfunction in brain centers (or the pathways from these centers) that normally downregulate pain signaling in the spinal cord
Neurotransmitter abnormalities	Decreased serotonin in the central nervous system may lead to aberrant pain signaling; this may partly be explained by a serotonin transporter polymorphism Decreased dopamine transmission in the brain may lead to chronic pain through unclear mechanisms
Neurohumoral abnormalities	Dysfunction in the hypothalamic–pituitary–adrenal axis, including blunted cortisol responses and lack of cortisol diurnal variation, is associated with (but is not specific for) fibromyalgia
Psychiatric comorbid conditions	Patients with fibromyalgia have increased rates of psychiatric comorbid conditions, including depression, anxiety, posttraumatic stress, and somatization; these may predispose to the development of fibromyalgia

*Ann Intern Med.* 2007;146:726-734.

# PRINCIPAL FIBROMYALGIA SYMPTOMS

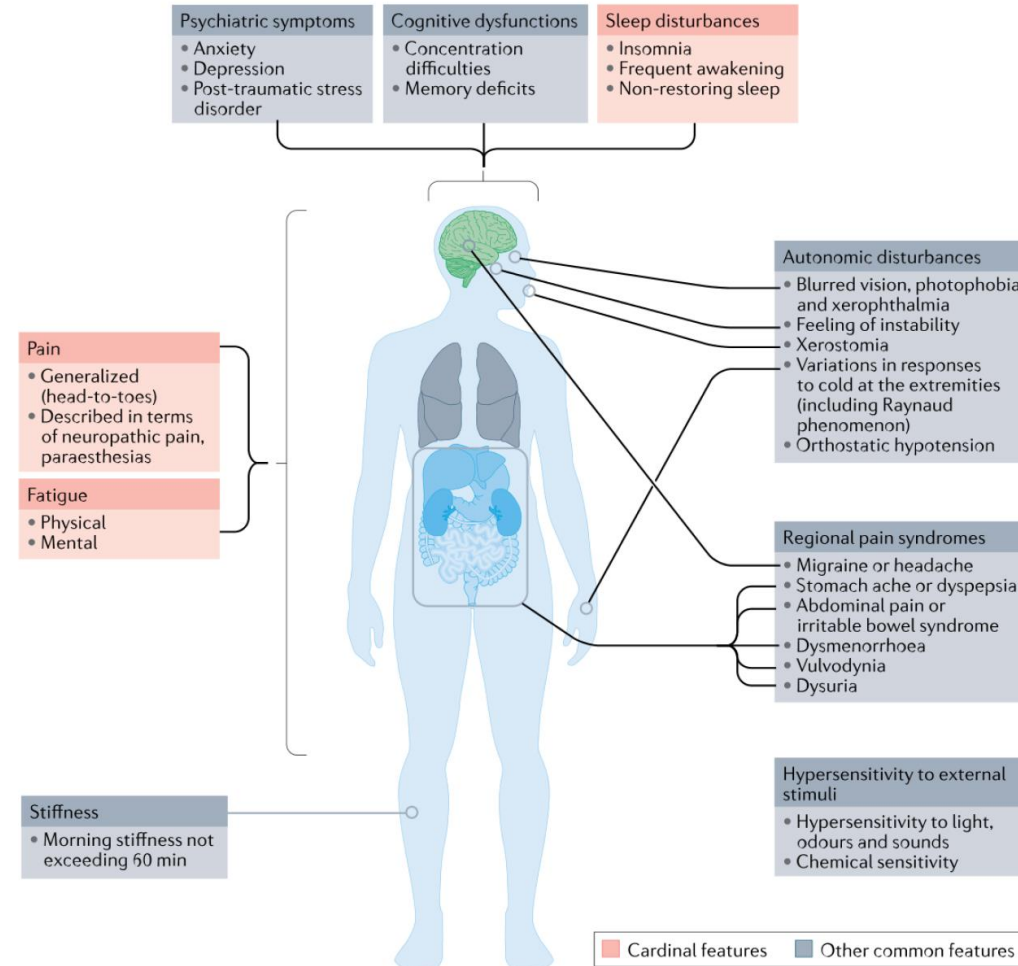
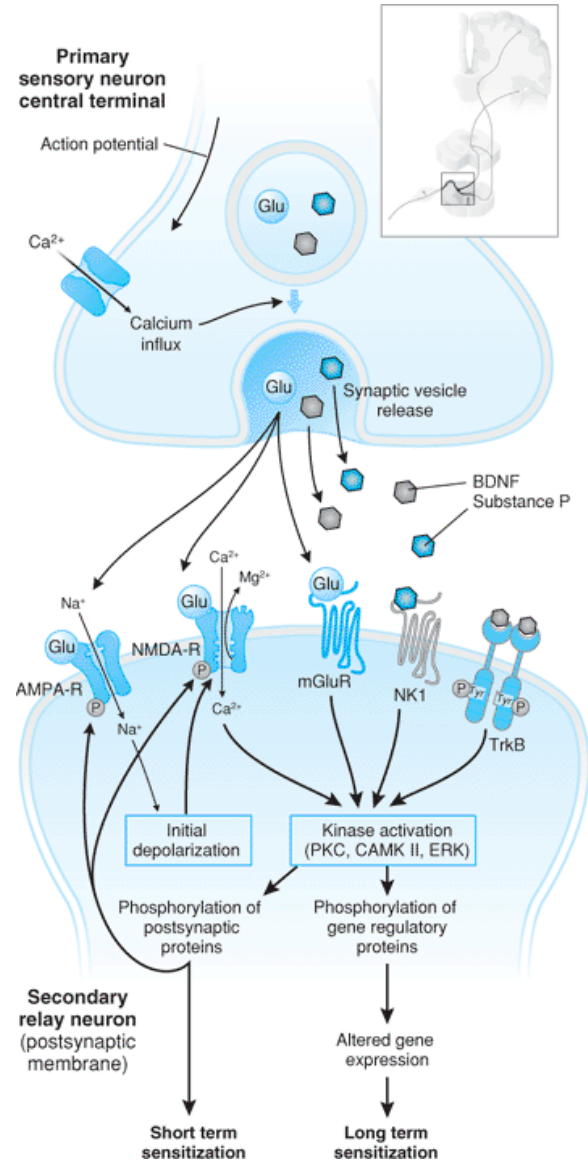


Fig. 2 | **Principal fibromyalgia symptoms.** Fibromyalgia has a complex symptomatology. Symptoms can be divided in two groups: cardinal features (shown in pink), which include the most characteristic fibromyalgia symptoms that are pivotal for a diagnosis according to the latest criteria, and other common features (shown in grey).

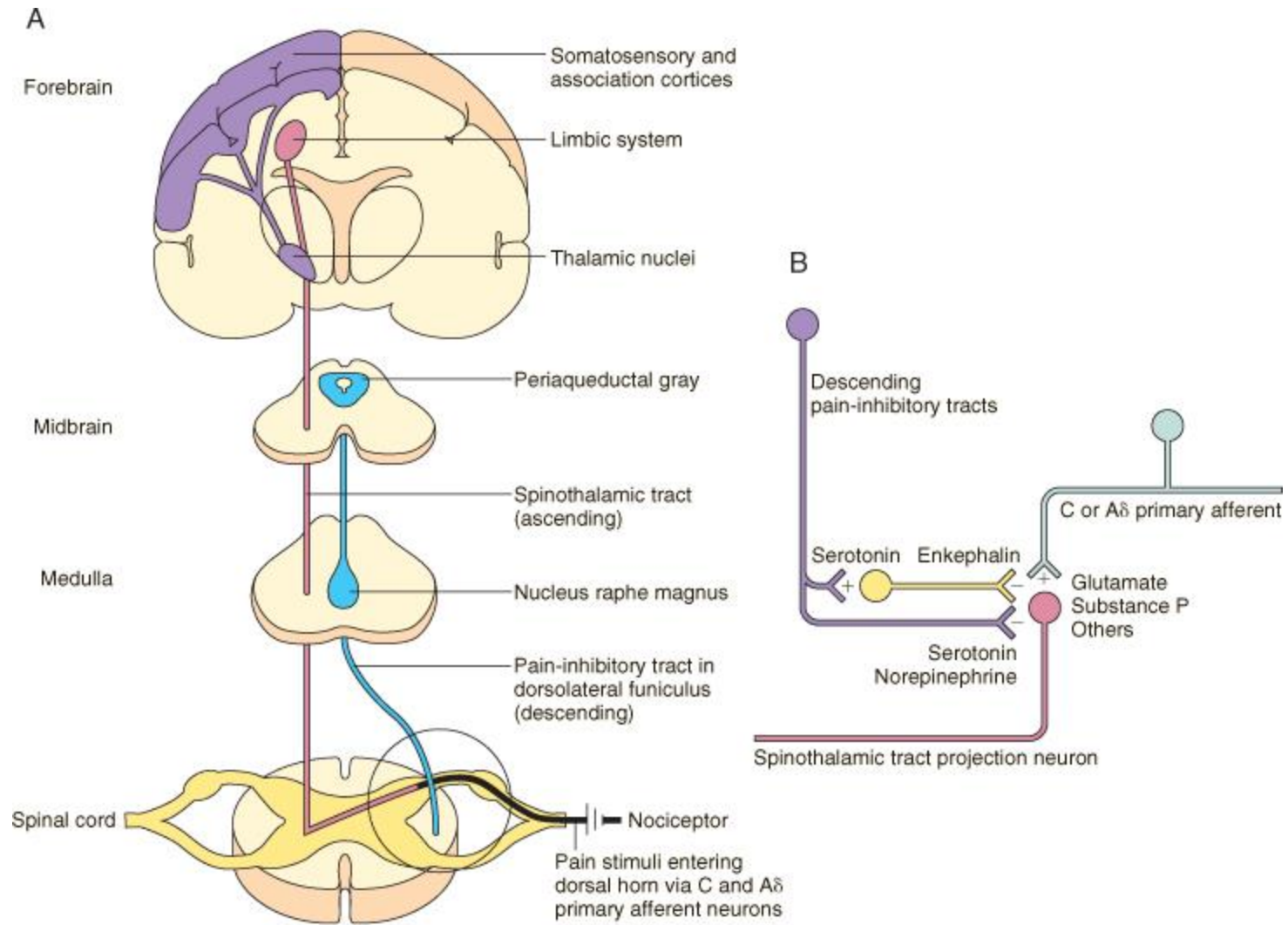
Sarzi-Puttini P *et al.* *Nature Rev Rheumatol* 2020 16: 645-660



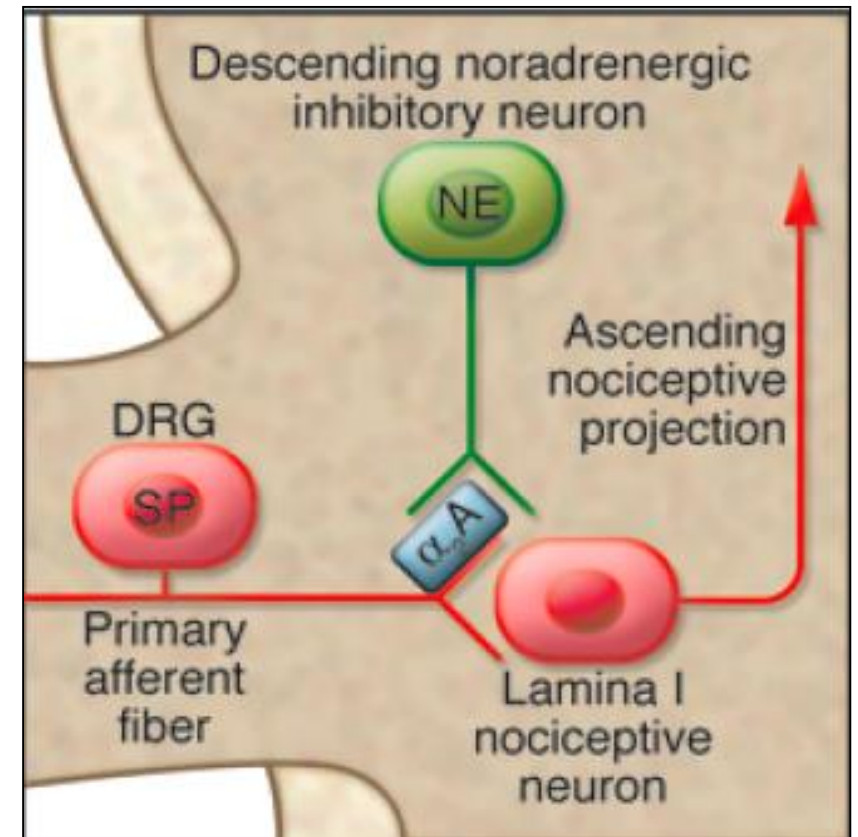
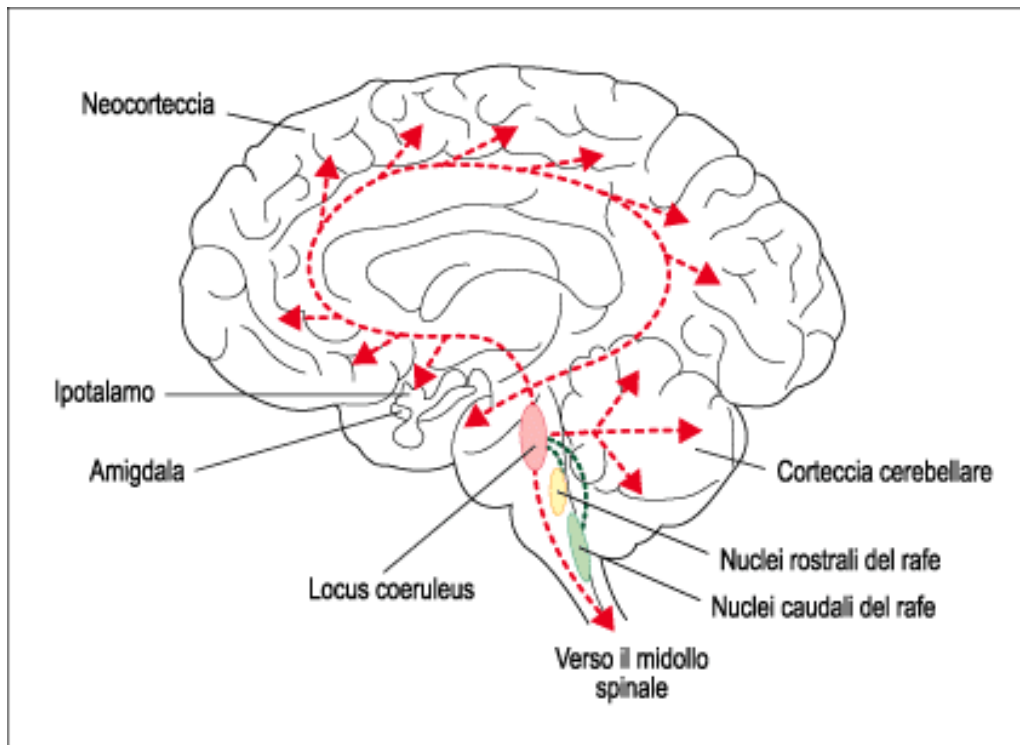
# SENSIBILIZZAZIONE SPINALE



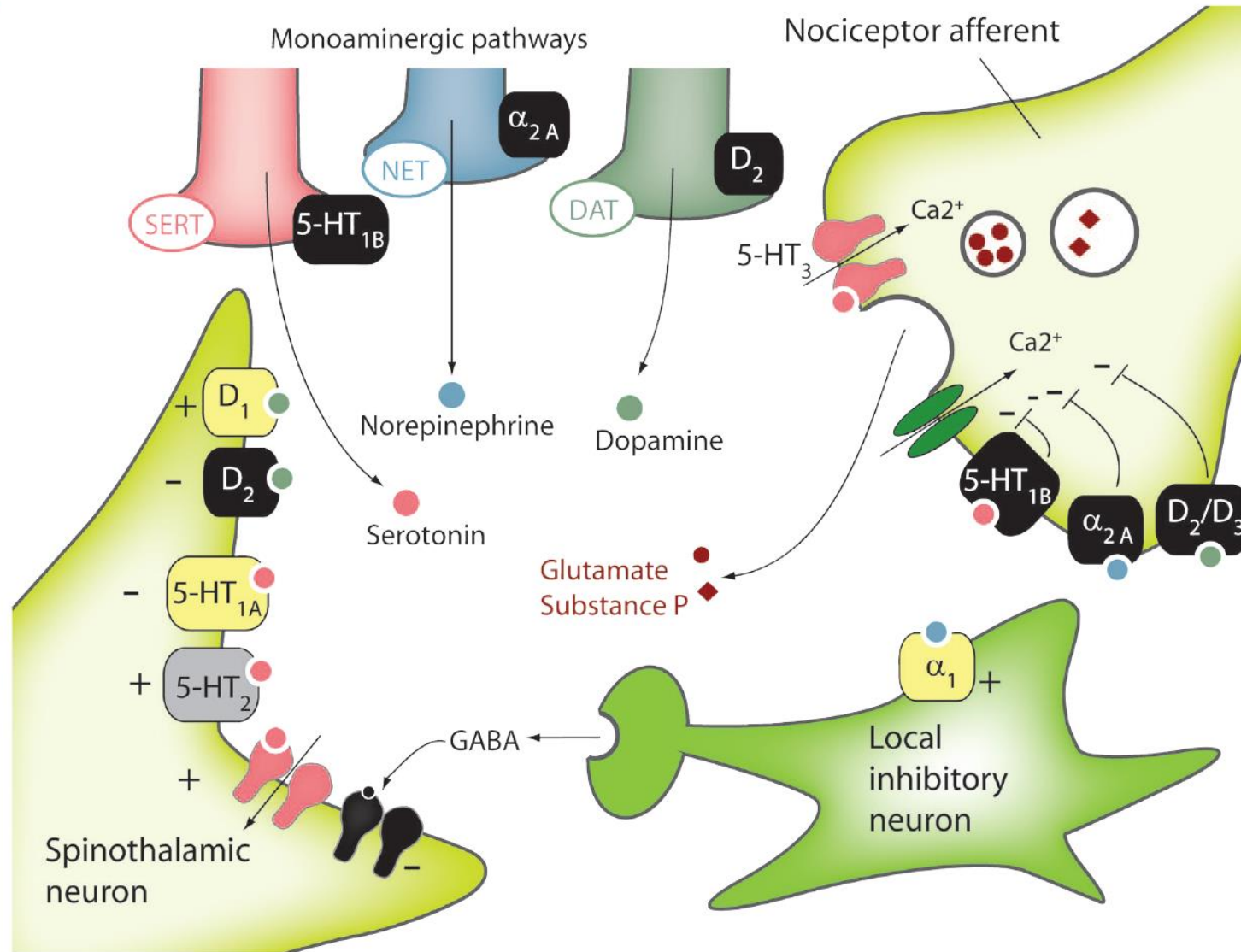
Diego Fornasari



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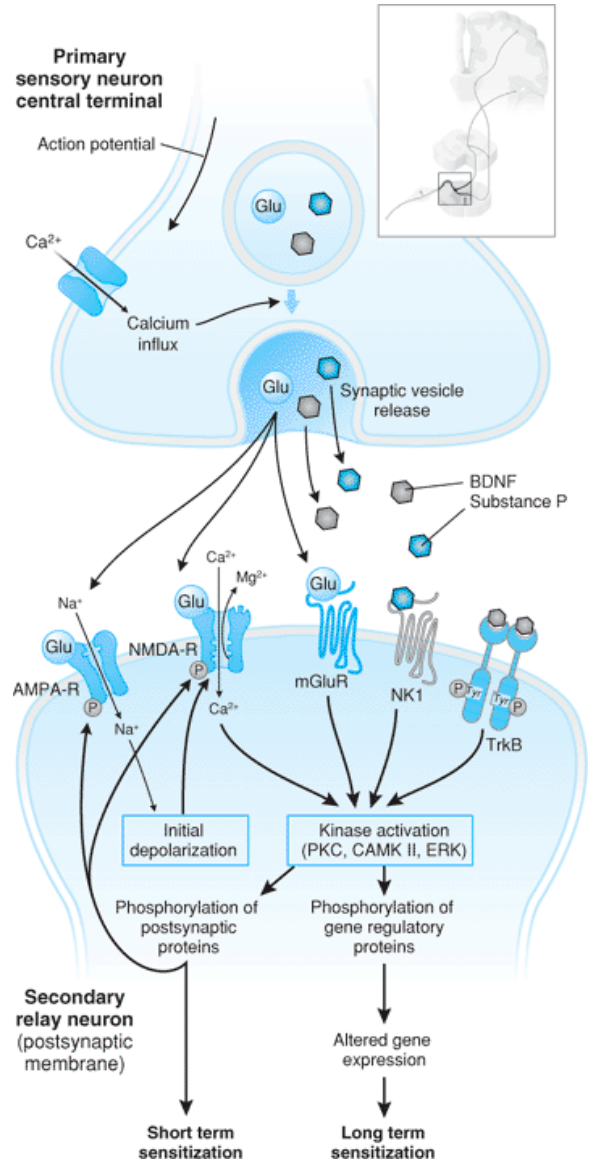
**Figure 2** Potential targets and receptor mechanism mediating the pain modulatory effects of monoamines in the dorsal horn



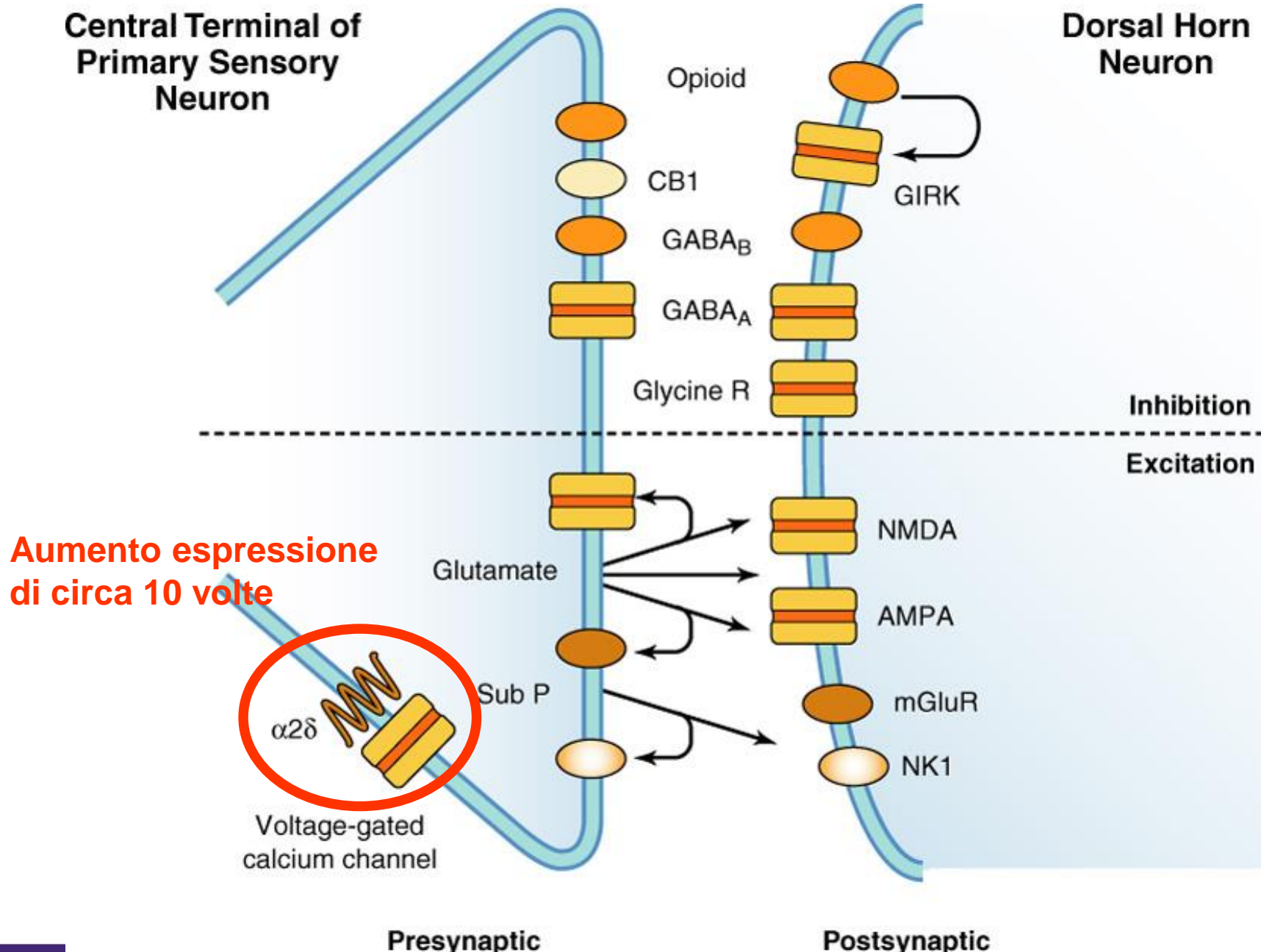
## ANTIDEPRESSIVI

FARMACO	APPLICAZIONE CLINICA	REAZIONI AVVERSE	CONTROINDICAZIONI	CONSIDERAZIONI TERAPEUTICHE
<b>IMIPRAMINA</b>	DOLORE NEUROPATICO	CARDIOTOSSICITA'	CONCOMITANTE USO DI INIBITORI DELLE MAO, DIFETTI DI CONDUZIONE CARDIACA	
<b>DULOXETINA</b>	DOLORE NEUROPATICO LOW-BACK PAIN	COME IMIPRAMINA	COME IMIPRAMINA	
<b>VENLAFAXINA</b>	DOLORE NEUROPATICO	COME IMIPRAMINA	COME IMIPRAMINA	

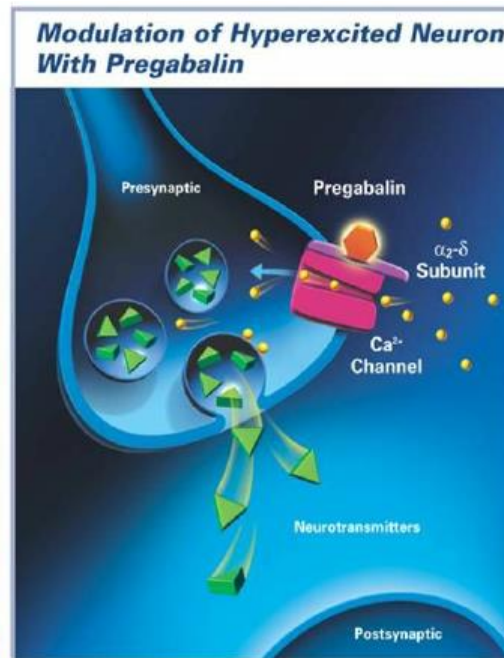
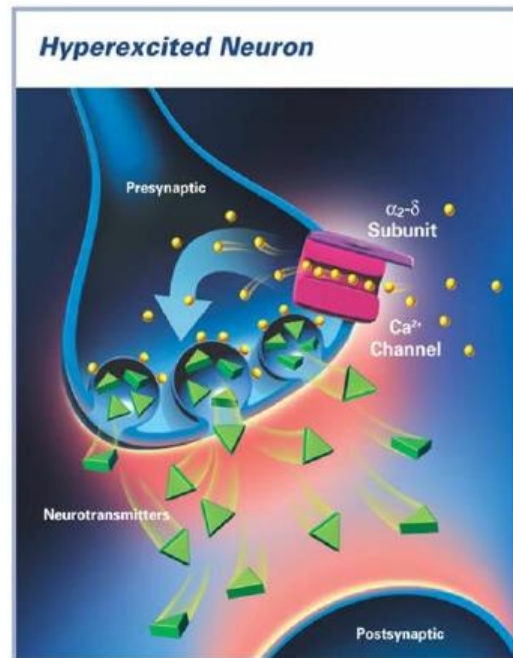
# SENSIBILIZZAZIONE SPINALE



Diego Fornasari

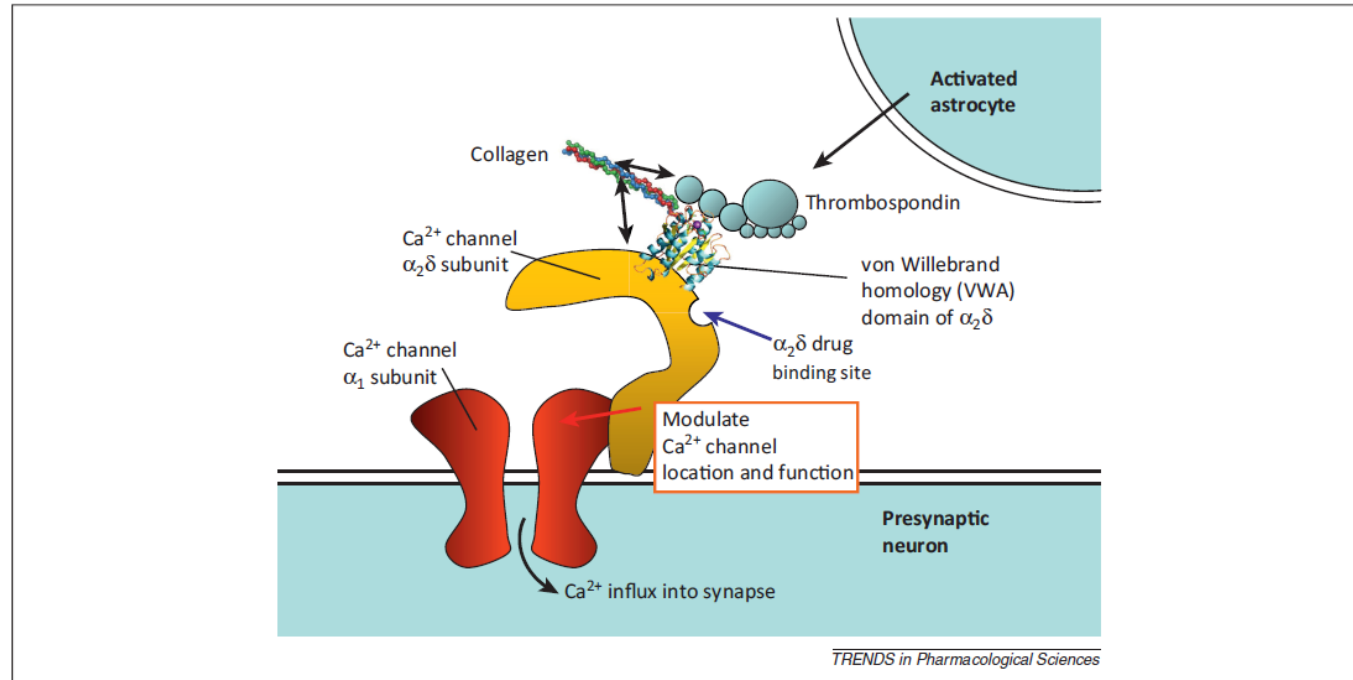


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Diego  
Fennarari

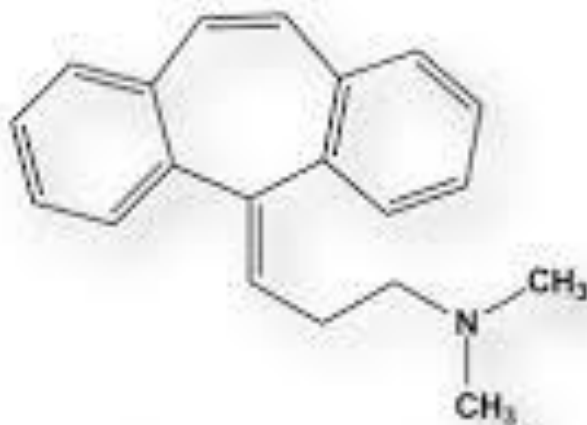




Diego Fornasari

## BLOCCANTI CANALI PER IL CALCIO (SUBUNITA' $\alpha 2\delta$ )

FARMACO	APPLICAZIONE CLINICA	REAZIONI AVVERSE	CONTROINDICAZIONI	CONSIDERAZIONI TERAPEUTICHE
<b>GABAPENTINA</b>	DOLORE NEUROPATICO (NEUROPATIA DIABETICA PERIFERICA DOLOROSA, NEUROPATIA POST-ERPETICA)	SONNOLENZA, VERTIGINI, FATICA. QUESTI EFFETTI, DI GRADO MODERATO, SI ESAURISCONO SPESSO DOPO 2 SETTIMANE DI TRATTAMENTO		SCARSE INTERAZIONI FARMACOLOGICHE CON ALTRI FARMACI. NON VIENE METABOLIZZATA MA ELIMINATA CON LE URINE IMMODIFICATA
<b>PREGABALIN</b>	COME GABAPENTINA	COME GABAPENTINA		PIU' POTENTE DI GABAPENTINA SCARSE INTERAZIONI FARMACOLOGICHE CON ALTRI FARMACI. NON VIENE METABOLIZZATO MA ELIMINATO CON LE URINE IMMODIFICATA

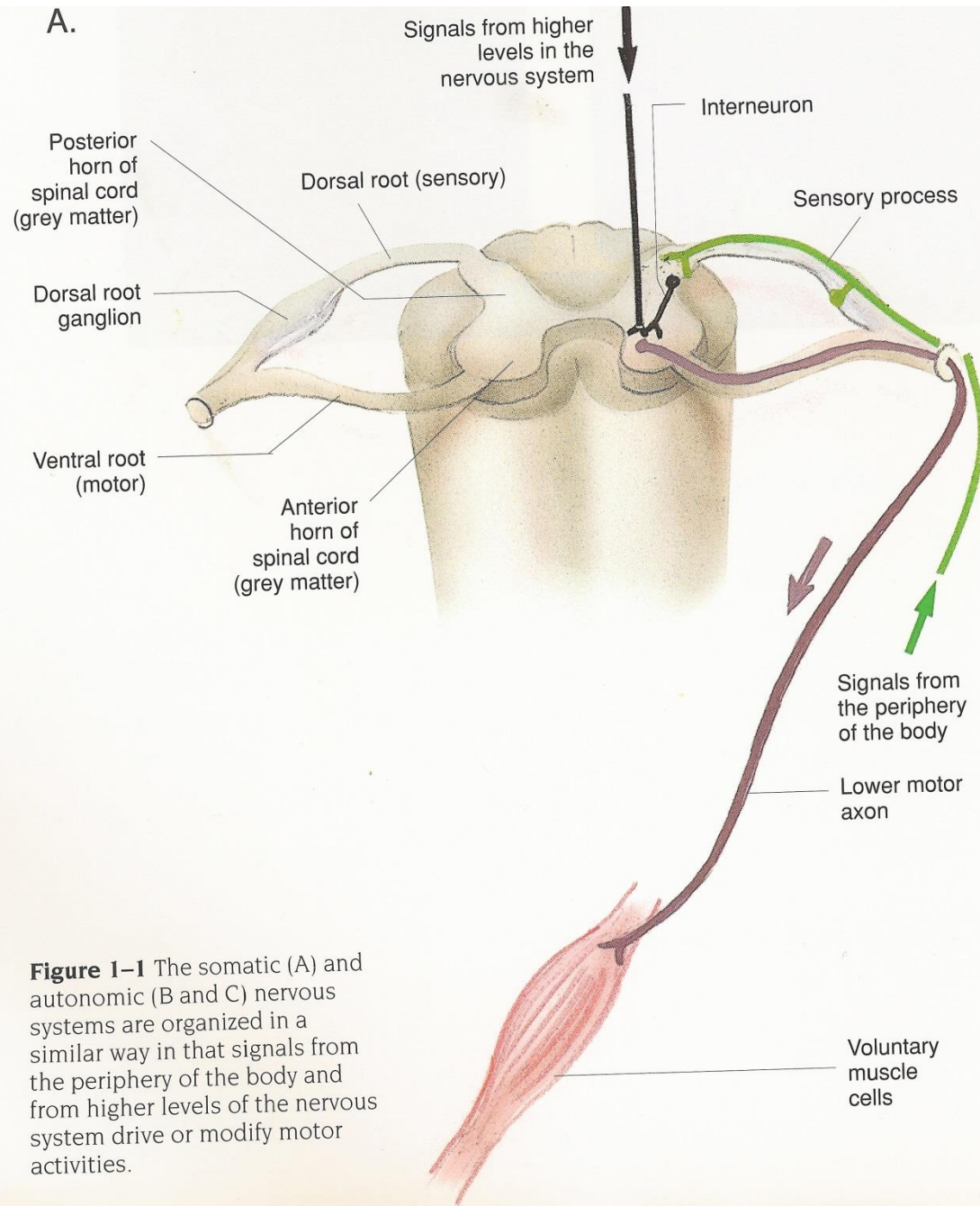


Ciclobenzaprina (Yurelax®)

3-(5H-dibenzo[a,d]anulen-5-iliden)-N,N-dimetilpropan-1-amina

Sinonimia:

3-(5H-dibenzo[a,d]diciclohepten-5-iliden)-N,N-dimetilpropilamina



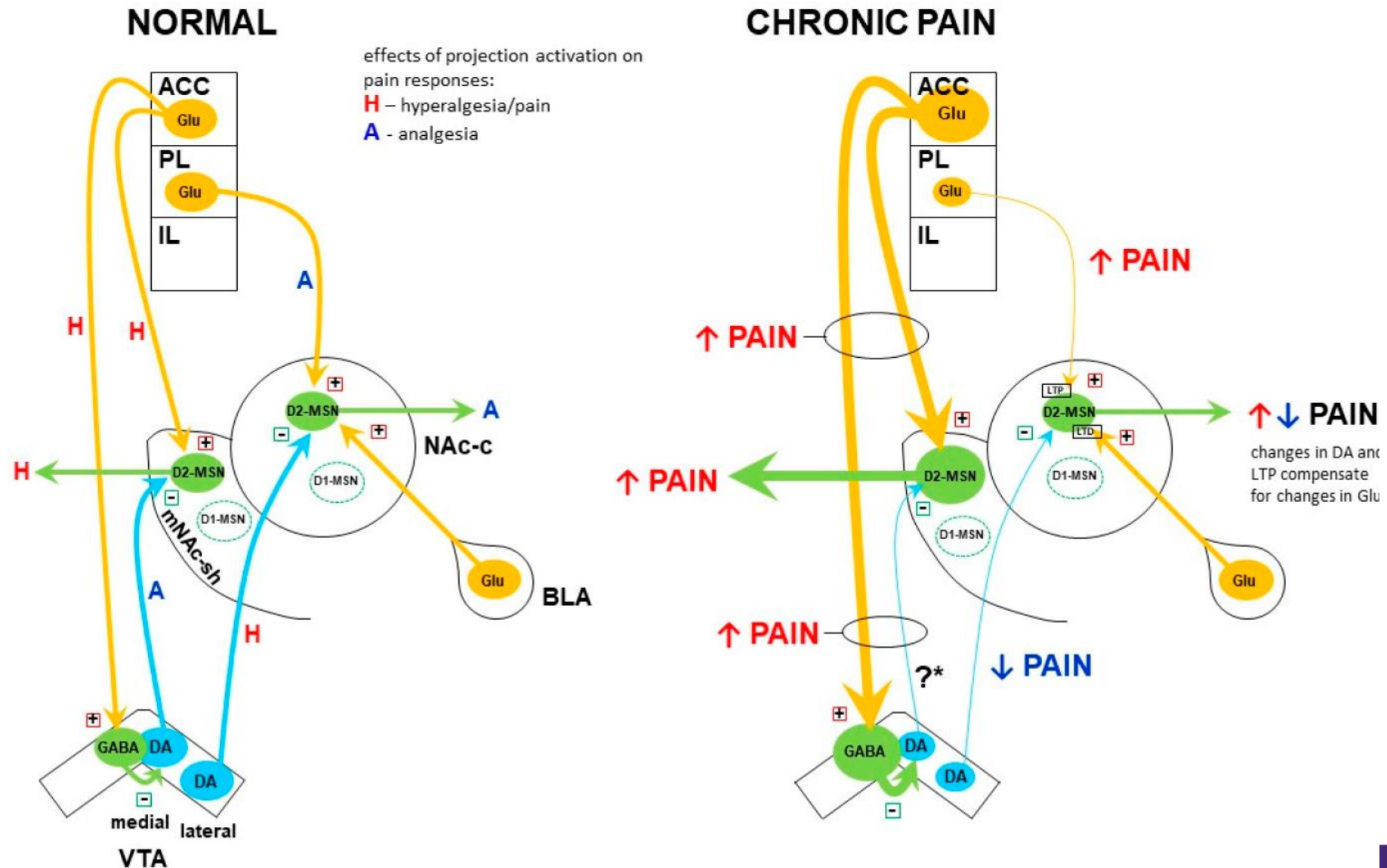
**Figure 1-1** The somatic (A) and autonomic (B and C) nervous systems are organized in a similar way in that signals from the periphery of the body and from higher levels of the nervous system drive or modify motor activities.

**Table. Pathophysiology of Fibromyalgia: Potential Mechanisms**

<b>Mechanism</b>	<b>Description</b>
Central sensitization	Amplification of pain in the spinal cord via spontaneous nerve activity, expanded receptive fields, and augmented stimulus responses
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*Ann Intern Med.* 2007;146:726-734.

# Interactions between the Ventral Mesostriatal Dopaminergic Pathway and Corticostriatal Glutamatergic Afferents in chronic pain



Pain Ther

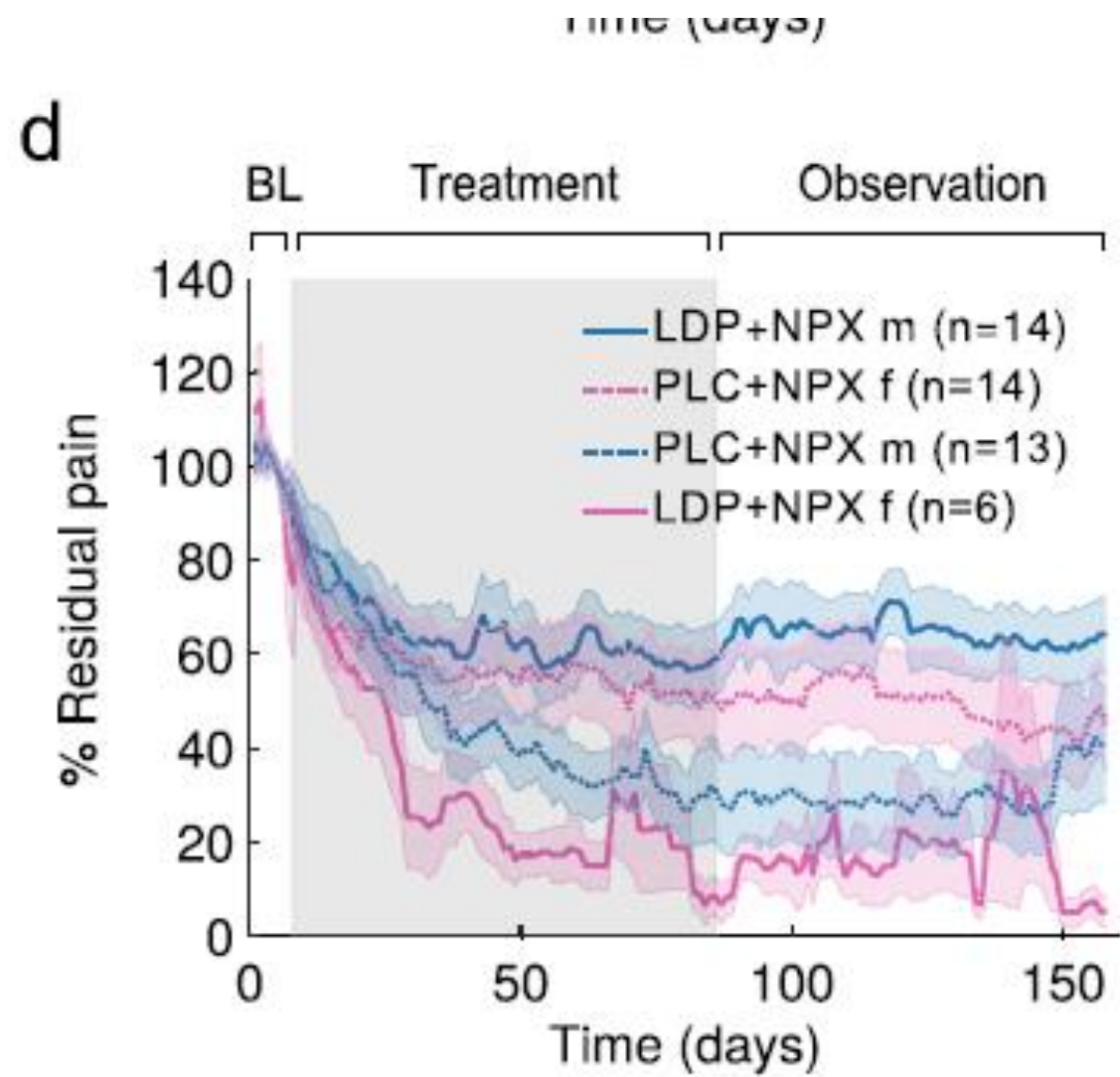
<https://doi.org/10.1007/s40122-021-00297-2>



ORIGINAL RESEARCH

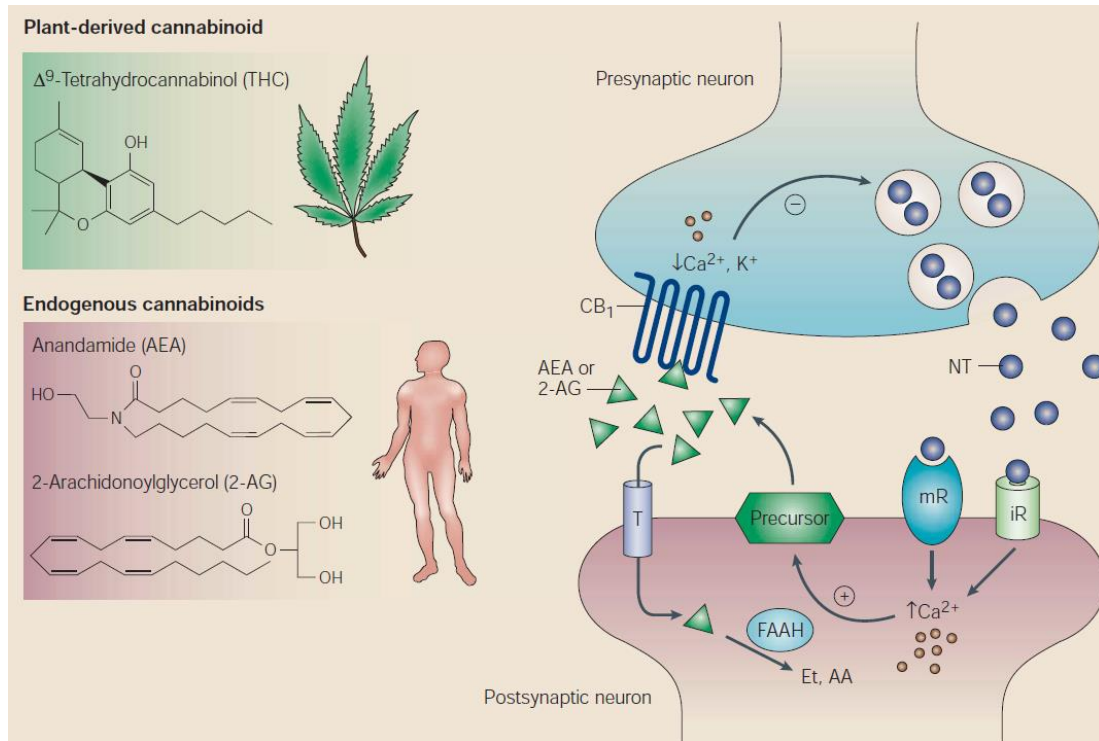
# Sex-Specific Pharmacotherapy for Back Pain: A Proof-of-Concept Randomized Trial

Diane Reckziegel · Pascal Tétreault · Mariam Ghantous · Kenta Wakaizumi · Bogdan Petre · Lejian Huang · Rami Jabakhanji · Taha Abdullah · Etienne Vachon-Preseau · Sara Berger · Alexis Baria · James W. Griffith · Marwan N. Baliki · Thomas J. Schnitzer · A. Vania Apkarian

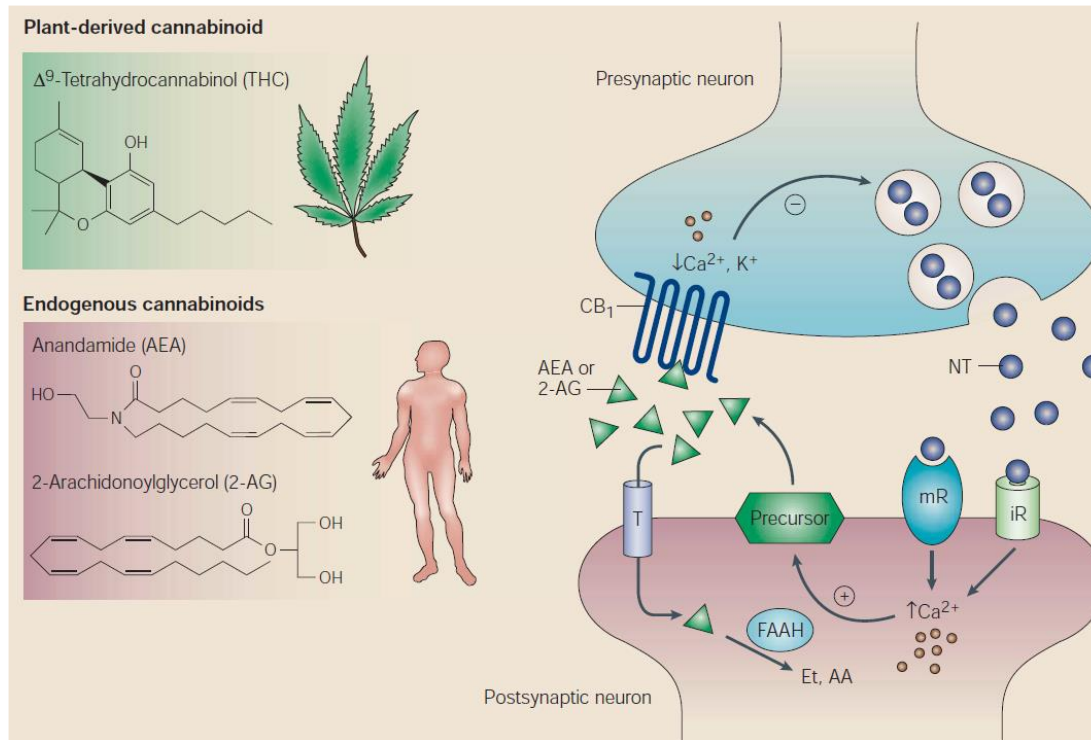




# Systematic Review and Meta-analysis Seem to Indicate that Cannabinoids for Chronic Primary Pain Treatment Have Limited Benefit



Giossi R, Carrara F, Padroni M, Bilancio MC, Mazzari M, Enisci S, Romio MS, Boni G, Corrà F, Fittipaldo VA, Tramacere I, Pani A, Scaglione F, Fornasari D. **Pain Ther.** 2022 Sep 21. doi: 10.1007/s40122-022-00434-5. Online ahead of print. PMID: 36129666



## Key Summary Points

Chronic primary pain (CPP) is a new ICD-11 diagnostic definition including several painful conditions such as fibromyalgia, chronic regional pain syndrome, irritable bowel syndrome, and chronic migraine among others.

While interest in the potential role of cannabinoids in painful conditions has increased and previous systematic reviews found they are effective in treatment of chronic, especially secondary, non-cancer pain, limited evidence is available on the effects of cannabinoids on CPP and for this reason we performed a systematic review and a meta-analysis to evaluate the role of cannabinoids in CPP.

We found limited benefit of cannabinoids compared to placebo on pain relief in patients with CPP in the overall analysis, while we observed a significant reduction of pain in clinical trials with a long-term treatment.

Cannabinoids might improve pain and quality of life in patients with fibromyalgia.

The quality of the available evidence for cannabinoids use in CPP is generally low and future, long-term trials are needed.

# MAYO CLINIC: TRATTAMENTO NEL DOLORE NEUROPATICO

## Trattamenti di 1° linea

### orali

Anticonvulsants			Supplements		
Gabapentin <sup>b</sup>	300 mg at bedtime, increase every 4-7 d by 300-mg increments initially to 3 times daily, then to goal of 1800 mg/d as necessary to 3600 mg/d	3600 mg/ d (split TID)	α-Lipoic acid	600 mg once daily	600 mg/d
Pregabalin <sup>b</sup>	75 mg twice daily; after 4-7 d, increase by same dosage to goal of 300 mg/d as necessary to 600 mg/d	600 mg/d (split BID)	Acetyl-L-carnitine	1000 mg 3 times per day	3000 mg/d (split TID)
Antidepressants			Capsaicin (8%) patch		
Amitriptyline, nortriptyline <sup>b</sup>	10-25 mg at bedtime, increase every 4-7 d to goal of 100 mg at bedtime	150 mg/d	Should be placed by medical staff trained in its usage using nonlatex gloves; pretreat area with 4% topical lidocaine for 60 min, confirm anesthesia, apply patch(es) to affected area (may cut to shape) for 60 min, wipe clean with provided soap	4 patches per application	
Duloxetine <sup>b</sup>	20-30 mg once daily, then increase weekly by same dosage to goal of 60 mg/d	120 mg/d (split BID)			

Fra i trattamenti di PRIMA LINEA è raccomandata:

❖ ALC 3 g/die (negli US non è disponibile ALC im)

© 2015 Mayo Foundation for Medical Education and Research ■ Mayo Clin Proc. 2015;90(7):940-951



Contents lists available at [ScienceDirect](#)

## Pharmacological Research

journal homepage: [www.elsevier.com/locate/yphrs](http://www.elsevier.com/locate/yphrs)



Review

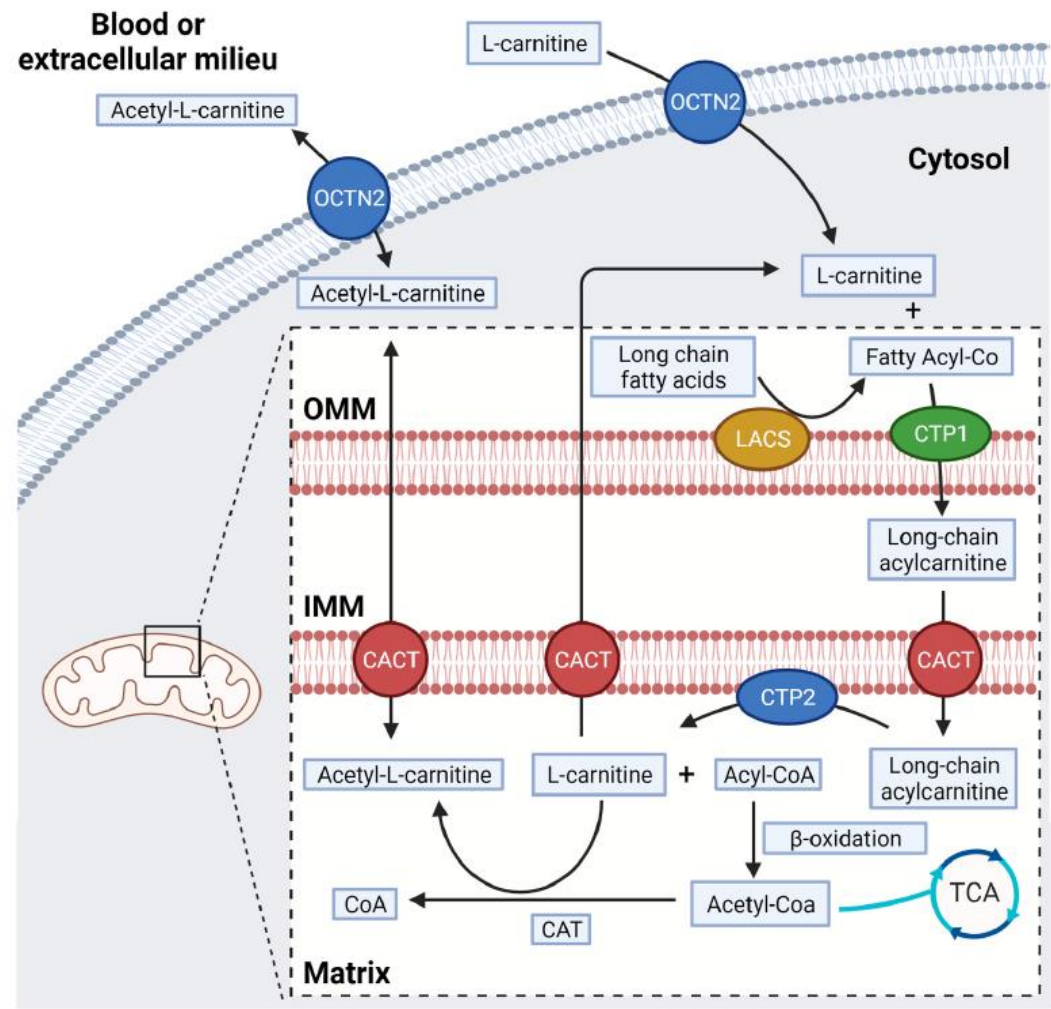
### Acetyl-L-carnitine in chronic pain: A narrative review

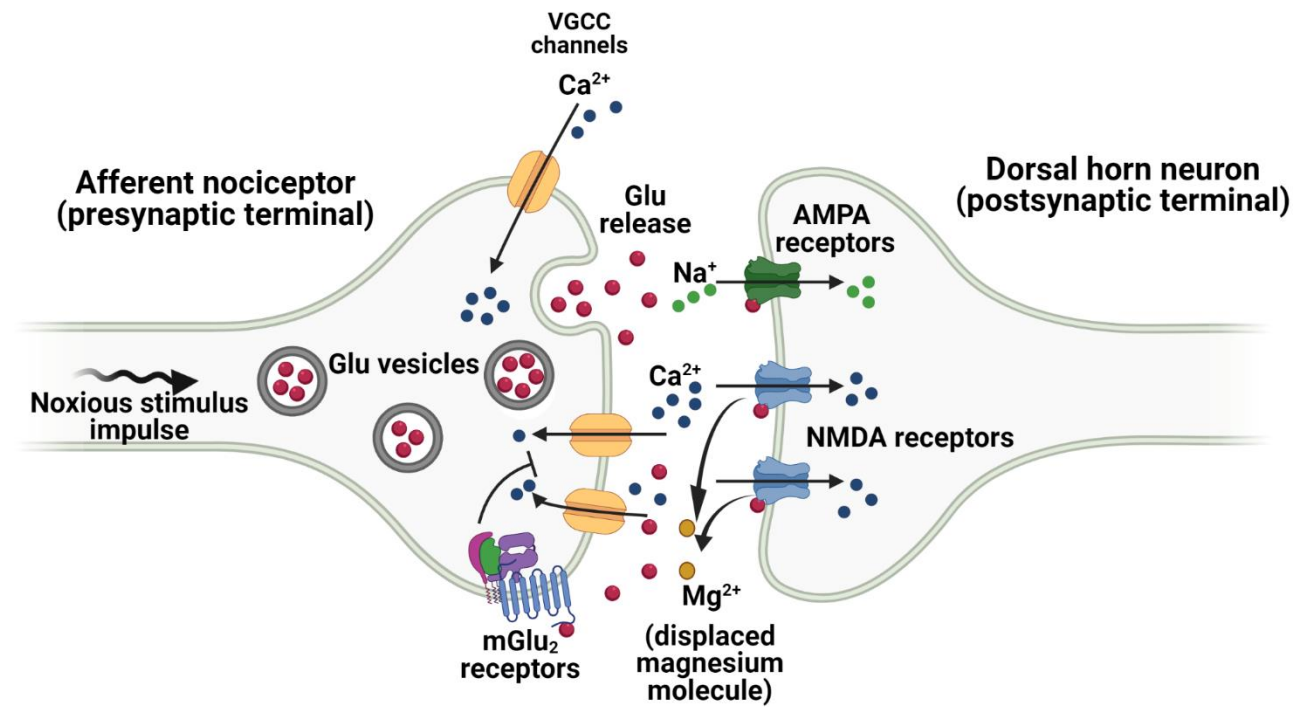
Piercarlo Sarzi-Puttini<sup>a</sup>, Valeria Giorgi<sup>a,\*</sup>, Simona Di Lascio<sup>b</sup>, Diego Fornasari<sup>b</sup>

<sup>a</sup> Rheumatology Unit, ASST Fatebenefratelli Luigi Sacco University Hospital, Milan, Italy

<sup>b</sup> Department of Medical Biotechnology and Molecular Medicine, Università degli Studi di Milano, Milan, Italy

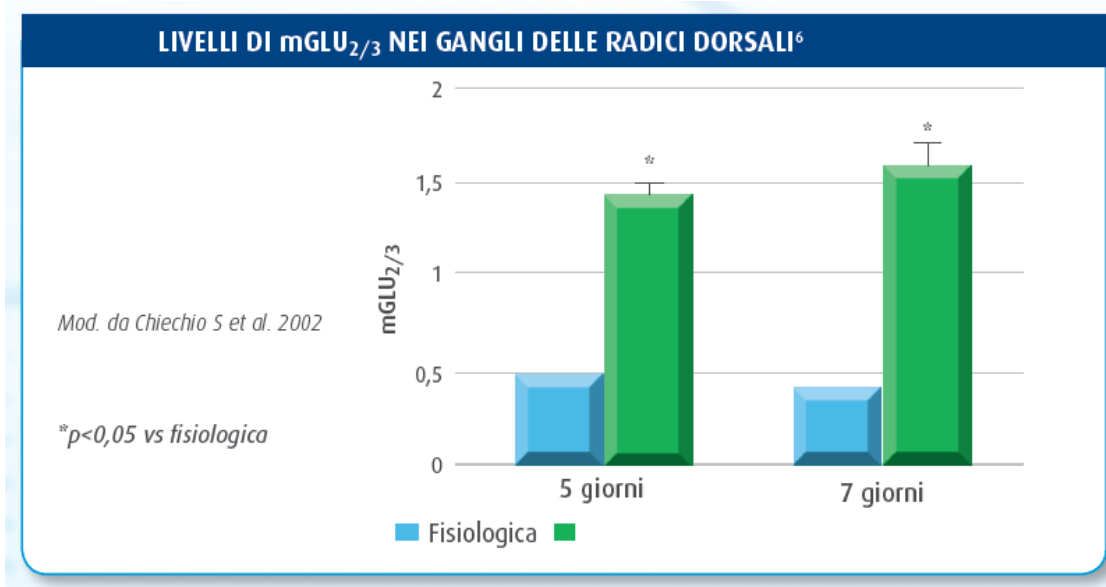






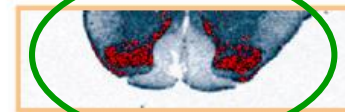
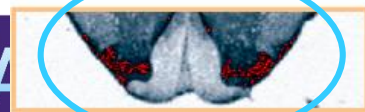
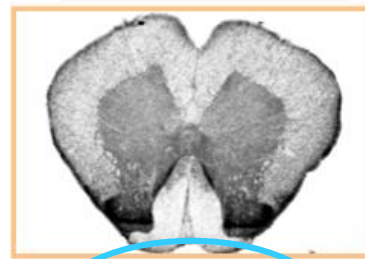
Pharmacol Res. 2021  
Nov;173:105874.

## Effetto di LAC sull'espressione del recettore mGLU-2 nelle corna dorsali del midollo

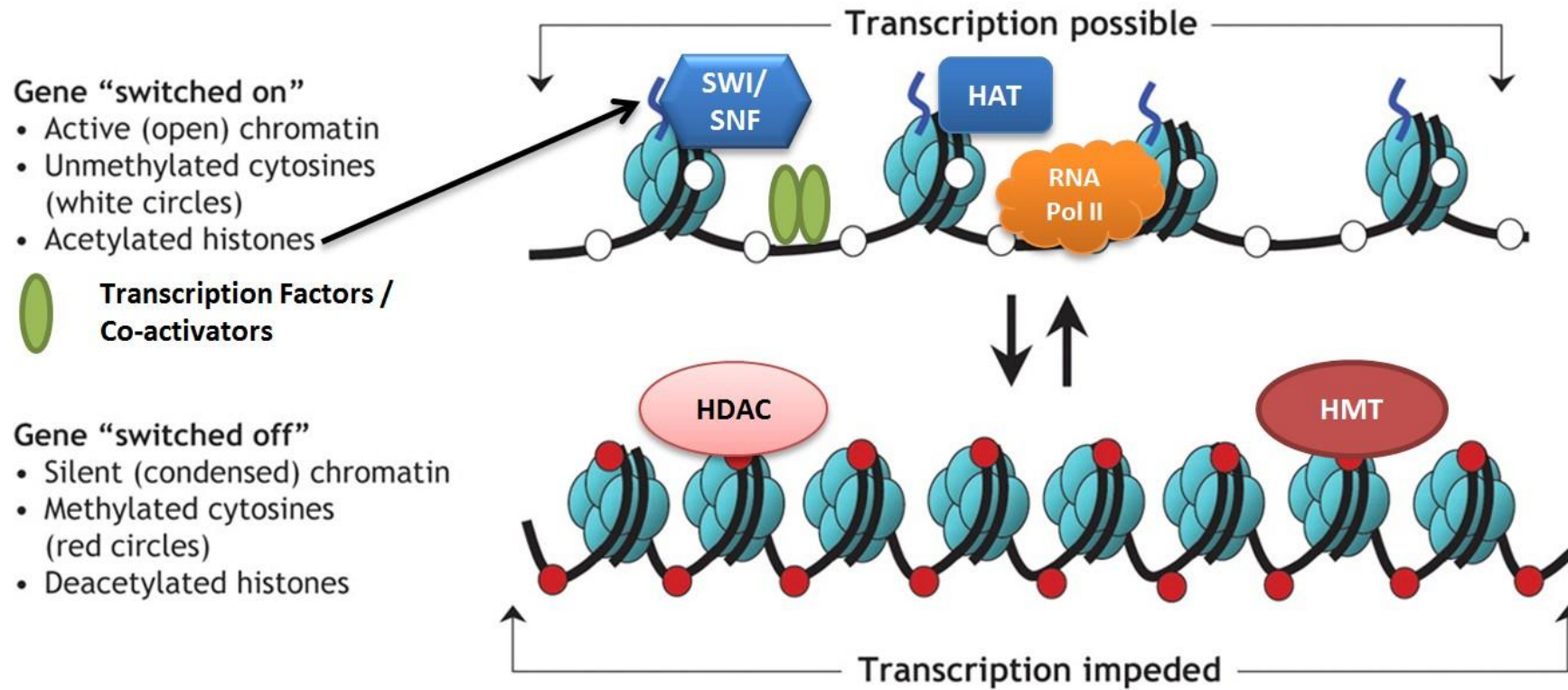


fisiologica

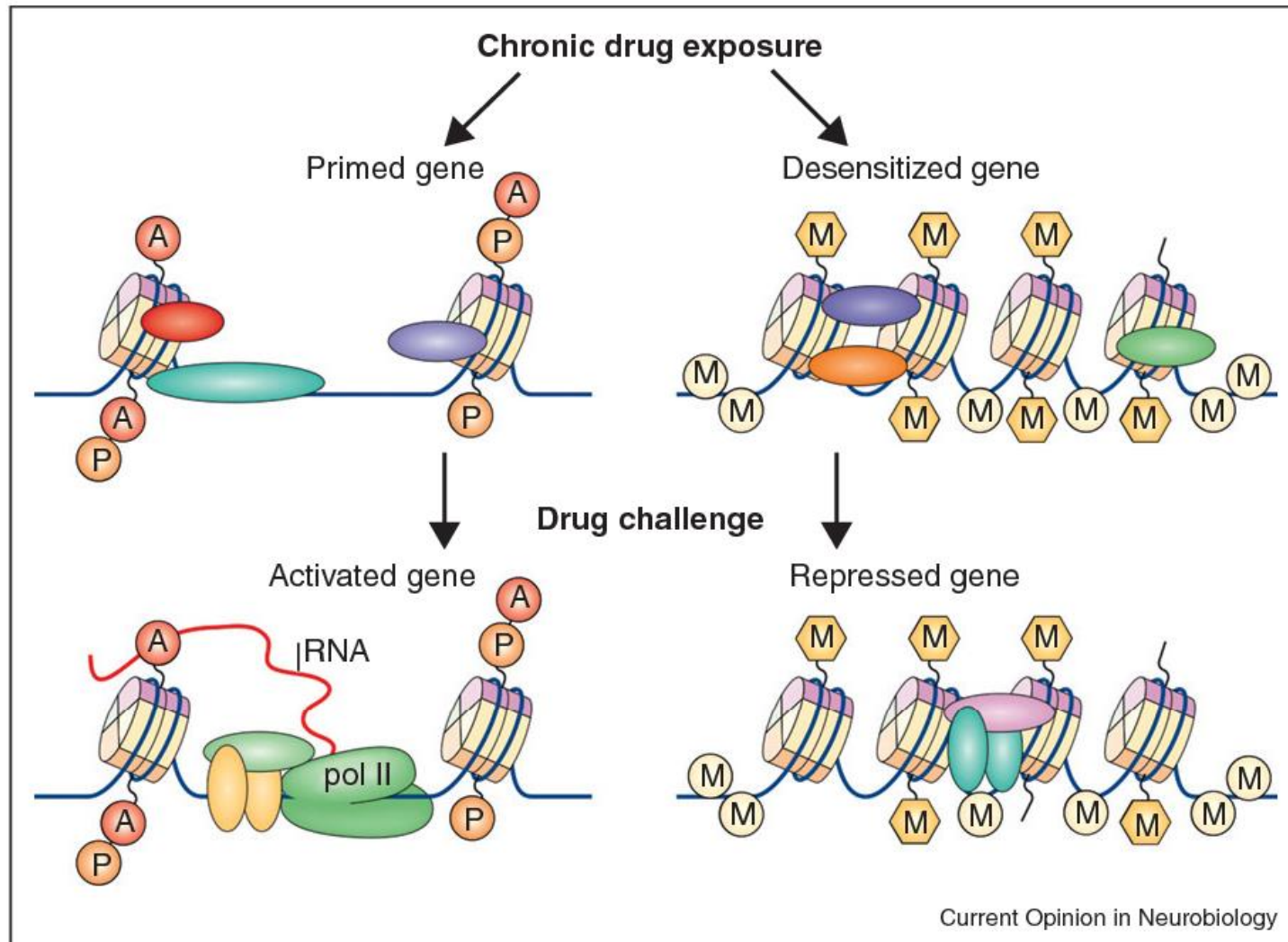
LAC



**Aumento della densità di recettori mGlu-2 indotta da LAC sulle corna posteriori del midollo spinale**

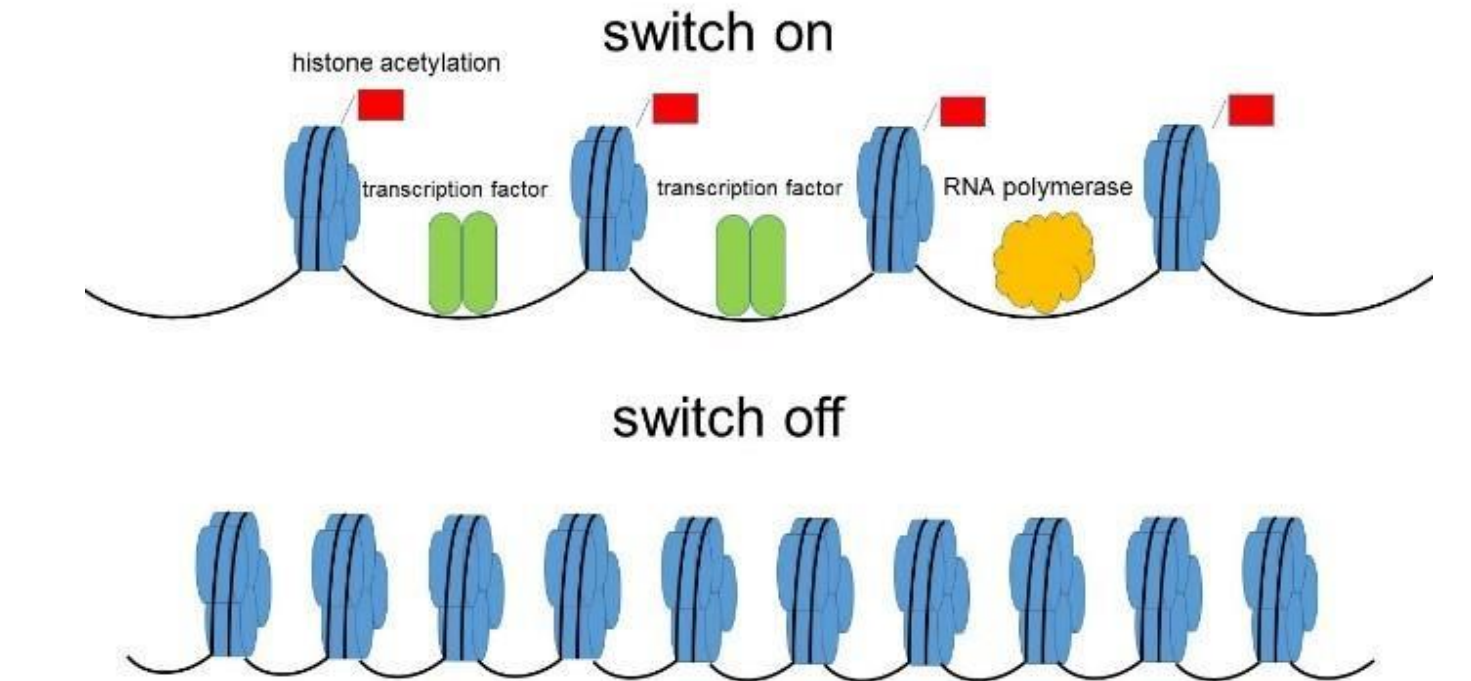






# L-ACETIL-CARNITINA: donatore di gruppi acetilici

LAC regola l'espressione di geni  $\uparrow$  mGlu2,  $\uparrow$  Fattori di crescita nervosa,  $\uparrow$  SOD



mGLU2



azione analgesica

Fattori di crescita nervosa

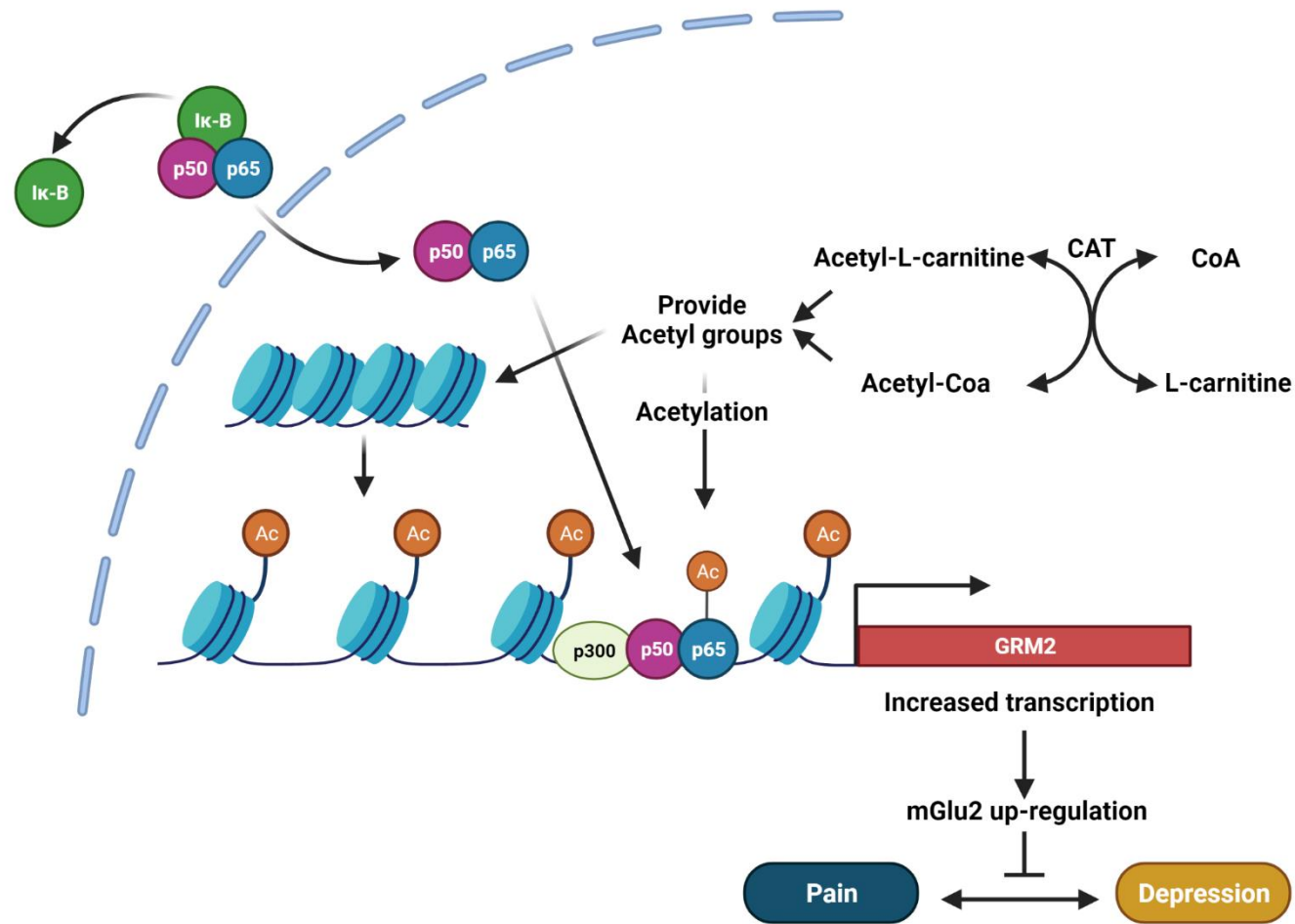


azione neurotrofica

SOD (Superoxide Dismutase)  
Atlas  
Fibromyalgia Syndrome



Nhow Milano, 30 settembre - 1 ottobre 2022  
azione antiossidante/neuroprotettiva



# L'Azione analgesica di LAC perdura oltre il termine del trattamento

Research Article

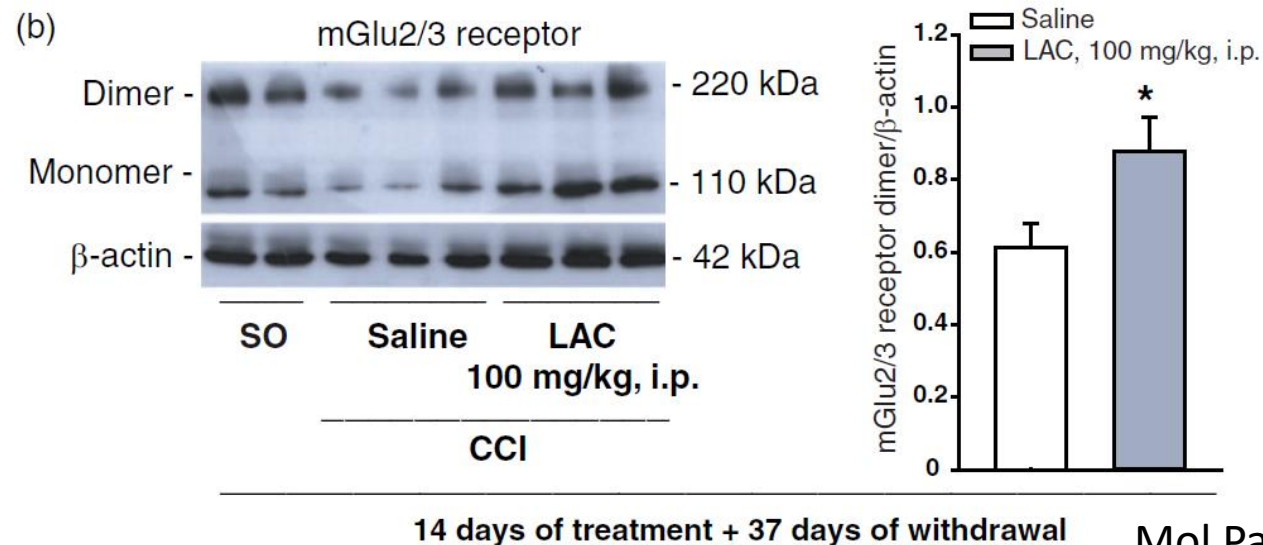
MOLECULAR  
PAIN

Molecular Pain  
Volume 13: 1–12  
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sagepub.com/journalsPermissions.nav  
DOI: 10.1177/1744806917697009  
journals.sagepub.com/home/mpx



## Analgesia induced by the epigenetic drug, L-acetylcarnitine, outlasts the end of treatment in mouse models of chronic inflammatory and neuropathic pain

Serena Notartomaso<sup>1</sup>, Giada Mascio<sup>1</sup>, Matteo Bernabucci<sup>1</sup>, Cristina Zappulla<sup>1</sup>, Pamela Scarselli<sup>1</sup>, Milena Cannella<sup>1</sup>, Tiziana Imbriglio<sup>1</sup>, Roberto Gradini<sup>1,2</sup>, Giuseppe Battaglia<sup>1</sup>, Valeria Bruno<sup>1,3</sup> and Ferdinando Nicoletti<sup>1,3</sup>



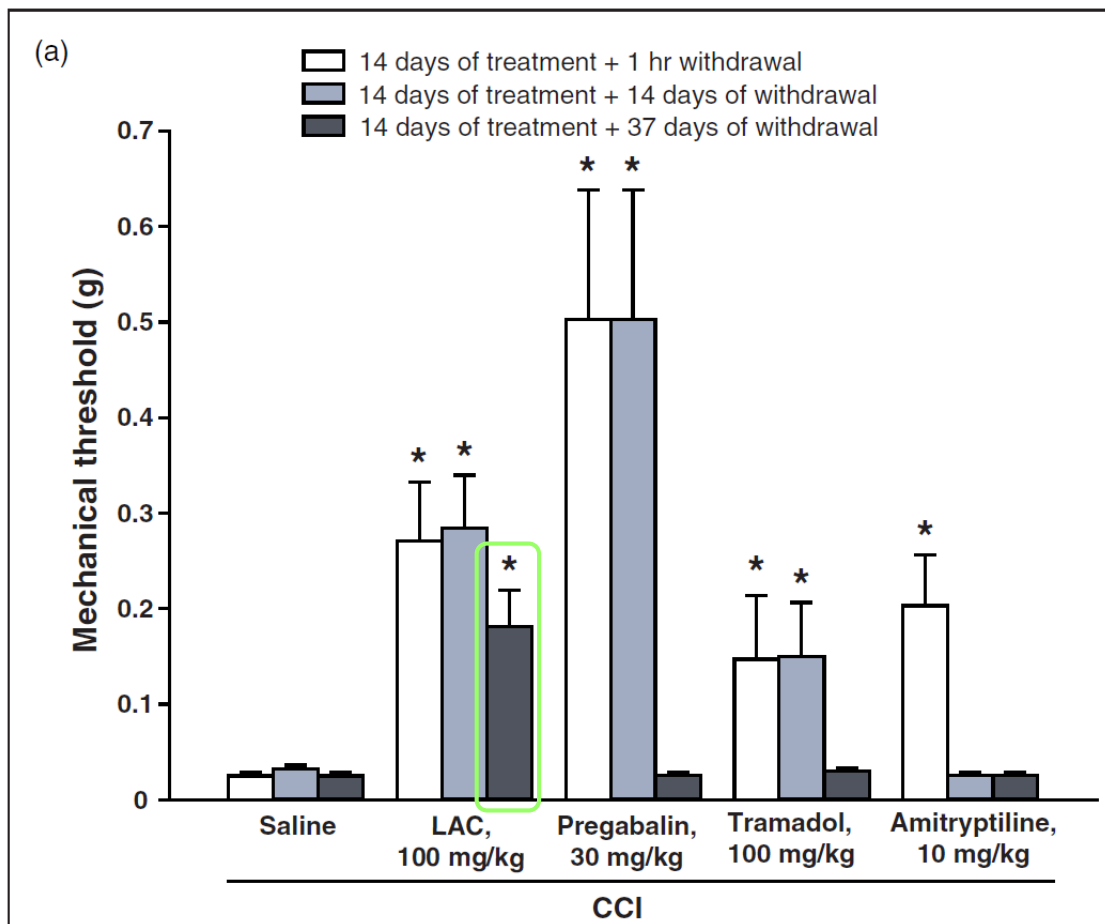
Studio su modello di Dolore Neuropatico da compressione cronica (CCI).

**Dopo 37 gg dal termine del trattamento nel gruppo trattato con ALC si osserva ancora una sovra-espressione di mGLU2.**

1 ottobre 2022

Mol Pain. 2017 Jan;13:1744806917697009

## L'Azione analgesica di LAC perdura oltre il termine del trattamento



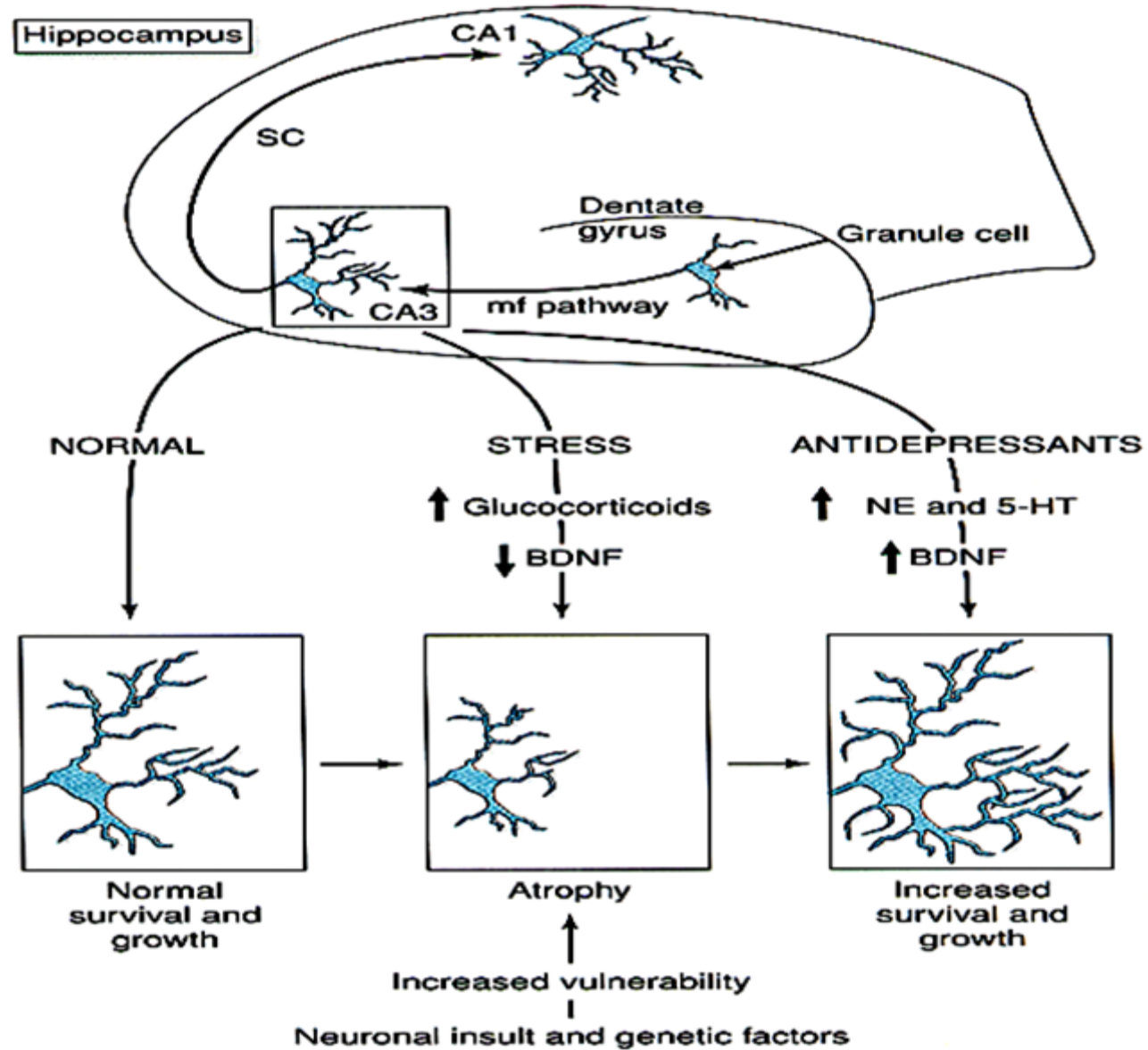
Soglia del dolore in modello di Dolore Neuropatico da compressione cronica (CCI).

**Dopo 37 gg dal termine del trattamento solo LAC ha ancora effetto antiallodinico.**

Comparative effects of LAC and other analgesic drugs on pain thresholds in the CCI model of neuropathic pain. Mice were subjected to CCI of the sciatic nerve and then treated i.p. once a day for 14 days with either saline, LAC (100 mg/kg), pregabalin (30 mg/kg), tramadol (100 mg/kg), or amitryptiline (10 mg/kg). Pain thresholds were measured under basal conditions, at the end of drug treatments, and then after 7 or 37 days.



## Azione antidepressiva di LAC



# PRINCIPAL FIBROMYALGIA SYMPTOMS

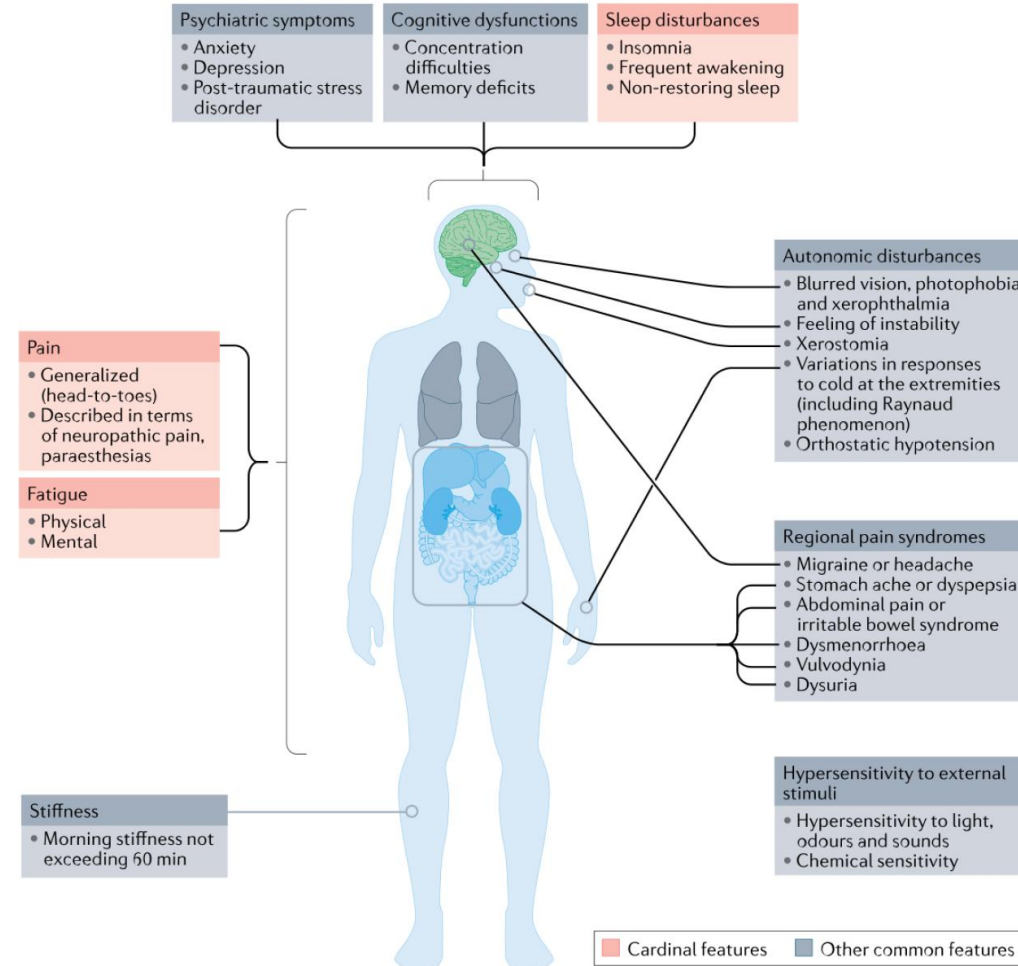
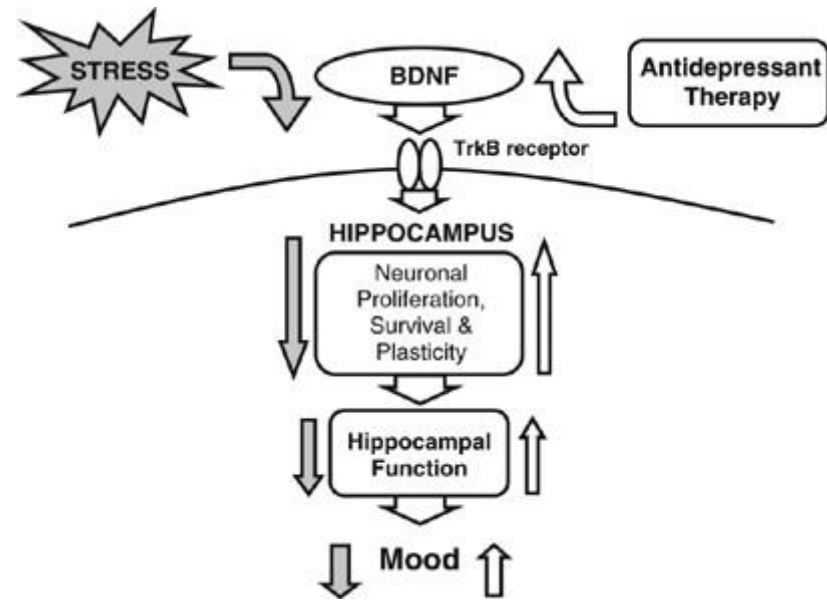


Fig. 2 | **Principal fibromyalgia symptoms.** Fibromyalgia has a complex symptomatology. Symptoms can be divided into two groups: cardinal features (shown in pink), which include the most characteristic fibromyalgia symptoms that are pivotal for a diagnosis according to the latest criteria, and other common features (shown in grey).

Sarzi-Puttini P *et al.* *Nature Rev Rheumatol* 2020 16: 645-660





# L'upregulation degli m-GLU2 potrebbe essere coinvolta negli effetti antidepressivi di LAC



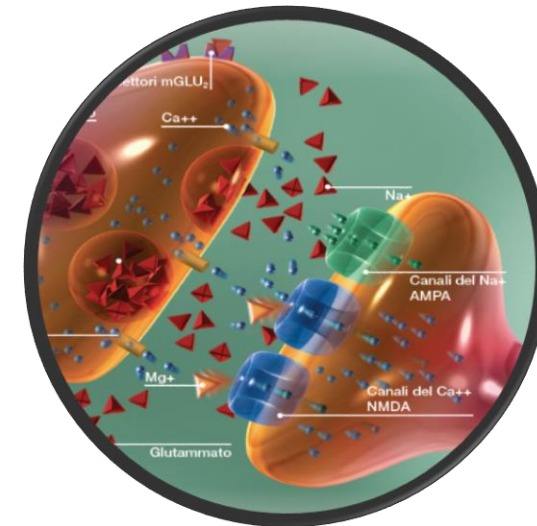
Neuropsychopharmacology (2013) 38, 2220–2230  
© 2013 American College of Neuropsychopharmacology. All rights reserved 0893-133X/13

www.neuropsychopharmacology.org

## Upregulation of mGlu2 Receptors via NF- $\kappa$ B p65 Acetylation Is Involved in the Proneurogenic and Antidepressant Effects of Acetyl-L-Carnitine

**Bruna Cuccurazzu<sup>1,2,4</sup>, Valeria Bortolotto<sup>1,2,4</sup>, Maria Maddalena Valente<sup>1,2</sup>, Federica Ubezio<sup>1,2</sup>, Aleardo Koverech<sup>3</sup>, Pier Luigi Canonico<sup>2</sup> and Mariagrazia Grilli<sup>\*,1,2</sup>**

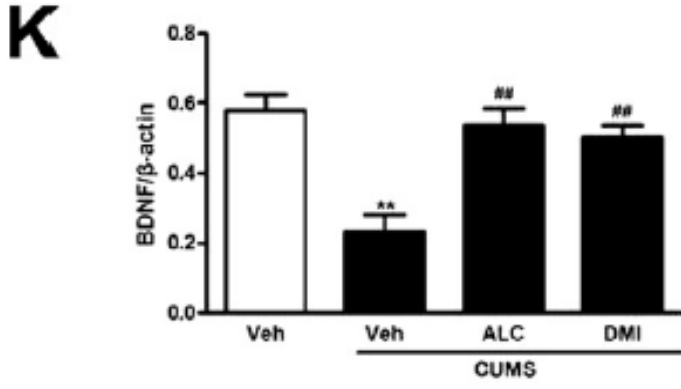
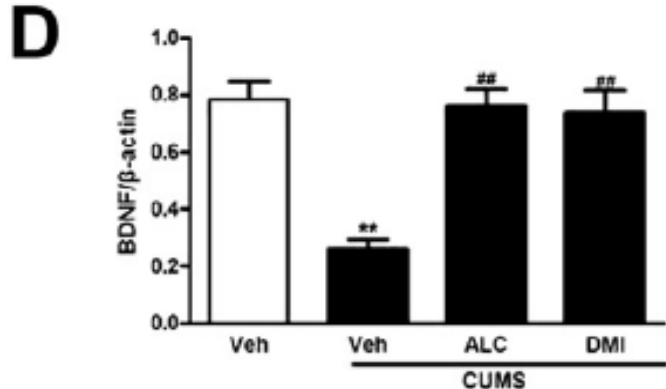
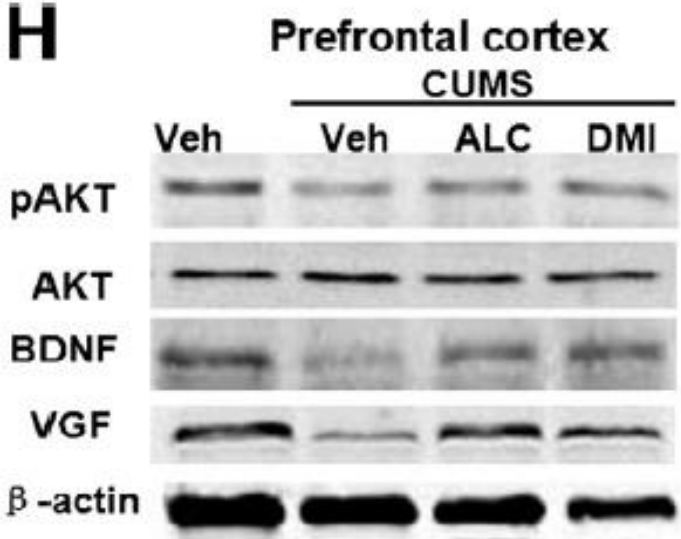
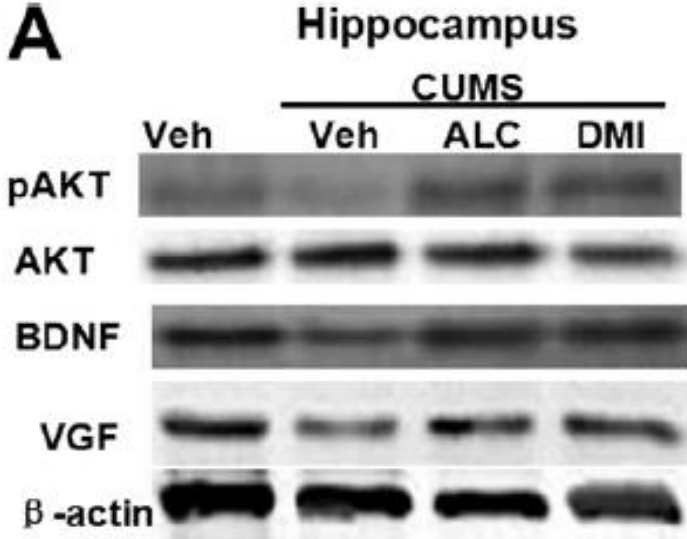
<sup>1</sup>Laboratory of Neuroplasticity and Pain, University of Piemonte Orientale "A. Avogadro", Novara, Italy; <sup>2</sup>Department of Pharmaceutical Sciences, University of Piemonte Orientale "A. Avogadro", Novara, Italy; <sup>3</sup>University of Rome Sapienza, Rome, Italy



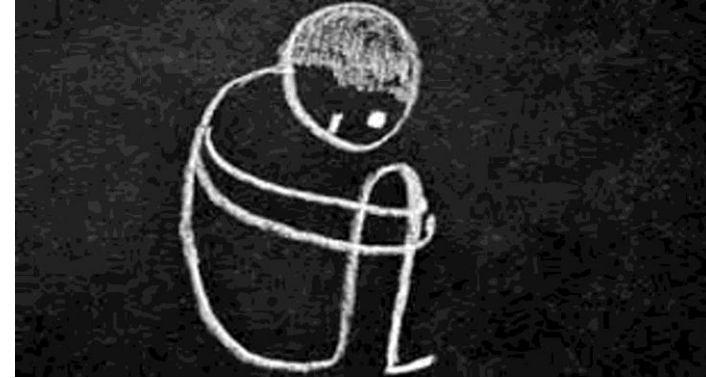
**Table 1.** Schedule of stressors used in the 21 days of CUMS procedure

Stressor	Duration	Day
Food deprivation	24-h	Monday
Exposure to a foreign object	24-h	
Water deprivation	24-h	
Forced swimming at 12 °C	6-min	Tuesday
Soiled cage	24-h	
Overnight illumination	Overnight	
Food deprivation	24-h	Wednesday
Cage tilt (45 °C)	7-h	
Physical restraint	2-h	
Exposure to an empty bottle	1-h	Thursday
Cage tilt (45 °C)	7-h	
Overnight illumination	Overnight	
Soiled cage	24-h	Friday
Forced swimming at 12 °C	6-min	
Physical restraint	2-h	
Exposure to a foreign object	24-h	Saturday
Forced swimming at 12 °C	6-min	
Cage tilt (45 °C)	7-h	
Soiled cage	24-h	Sunday
Exposure to an empty bottle	1-h	
Overnight illumination	Overnight	

# EFFETTI DELLA LAC SULL'ESPRESSIONE DEL BDNF




L-acetil-carnitina in  
pazienti con dolore  
cronico:  
effetti su depressione e  
tono dell'umore



*Review*

## **L-Acetylcarnitine: A Mechanistically Distinctive and Potentially Rapid-Acting Antidepressant Drug**

Santina Chiechio <sup>1</sup>, Pier Luigi Canonico <sup>2</sup> and Mariagrazia Grilli <sup>3,\*</sup> 

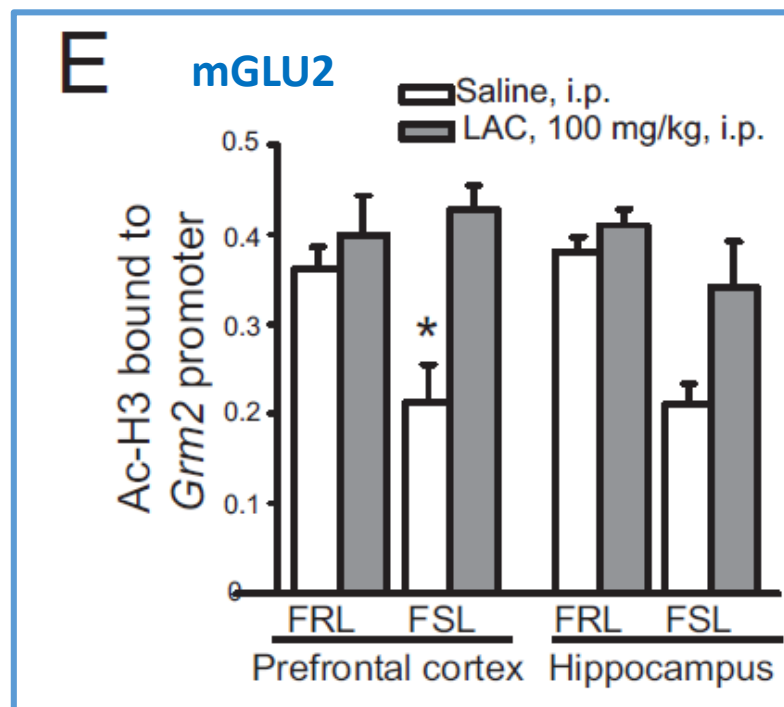
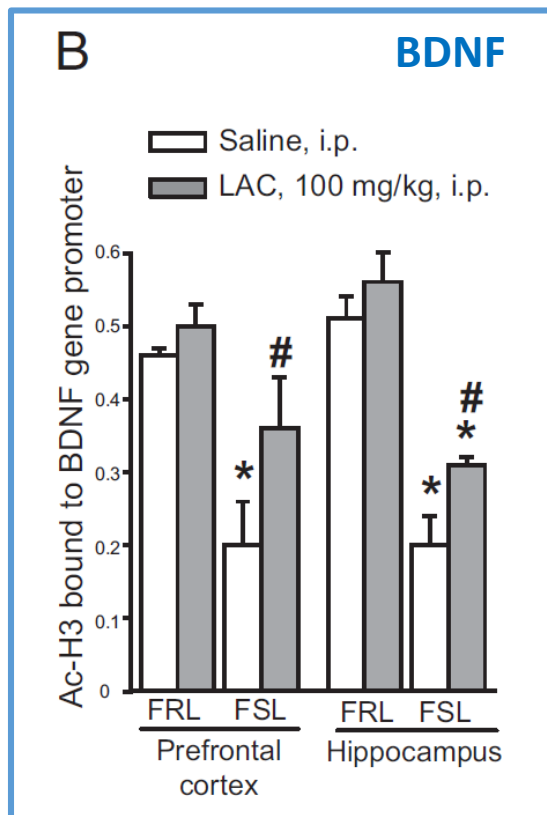
<sup>1</sup> Department of Drug Sciences, Section of Pharmacology and Toxicology, University of Catania, 95125 Catania, Italy; chiechio@unict.it

<sup>2</sup> Department of Pharmaceutical Sciences, University of Piemonte Orientale, 28100 Novara, Italy; pierluigi.canonico@uniupo.it

<sup>3</sup> Laboratory of Neuroplasticity, Department of Pharmaceutical Sciences, University of Piemonte Orientale, 28100 Novara, Italy

## EFFETTO EPIGENETICO

LAC aumenta i livelli di **acetilazione degli istoni** in corrispondenza delle sequenze promoter per i geni che codificano per **BDNF e mGLU2** nella corteccia prefrontale e nell'ippocampo.

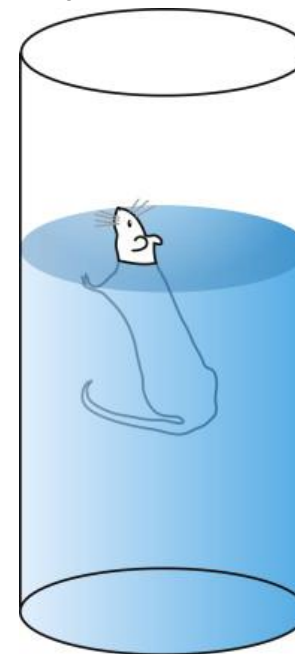
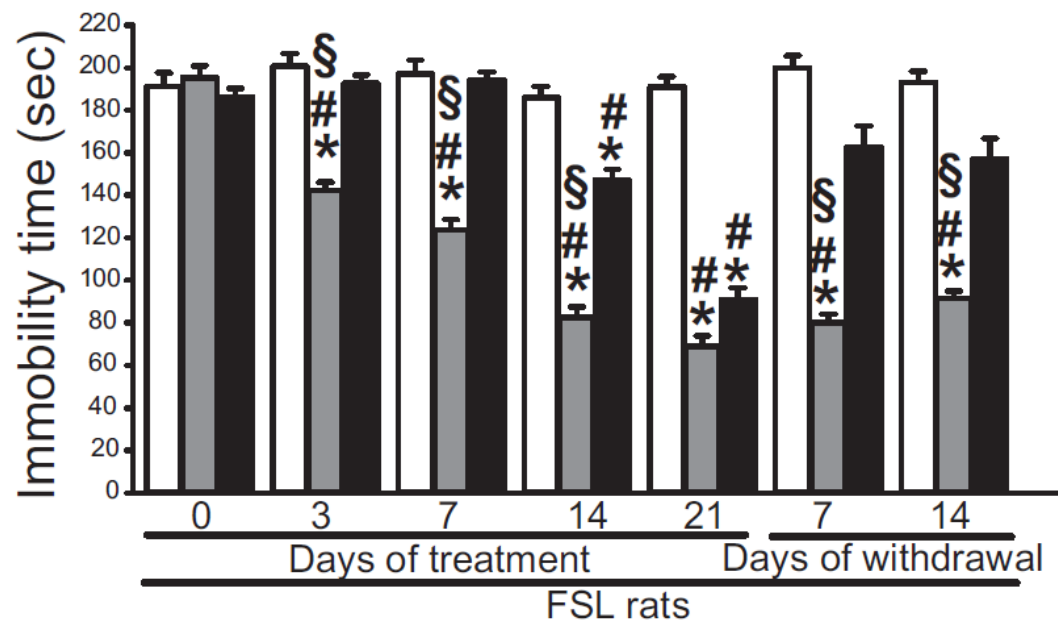


Nasca C et al. L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. Proc Natl Acad Sci U S A. 2013 Mar 19;110(12):4804-9.

# LAC migliora **rapidamente** lo stato depressivo in modello animale di depressione

- LAC migliora lo stato depressivo già **dopo 3 giorni** di trattamento, clomipramina dopo 14 giorni.
- LAC mantiene l'effetto **fino a 14 gg dopo il termine del trattamento**, mentre clomipramina lo perde appena il trattamento viene interrotto

**A** Immobility time in swimming test (Stato depressivo, disperazione)



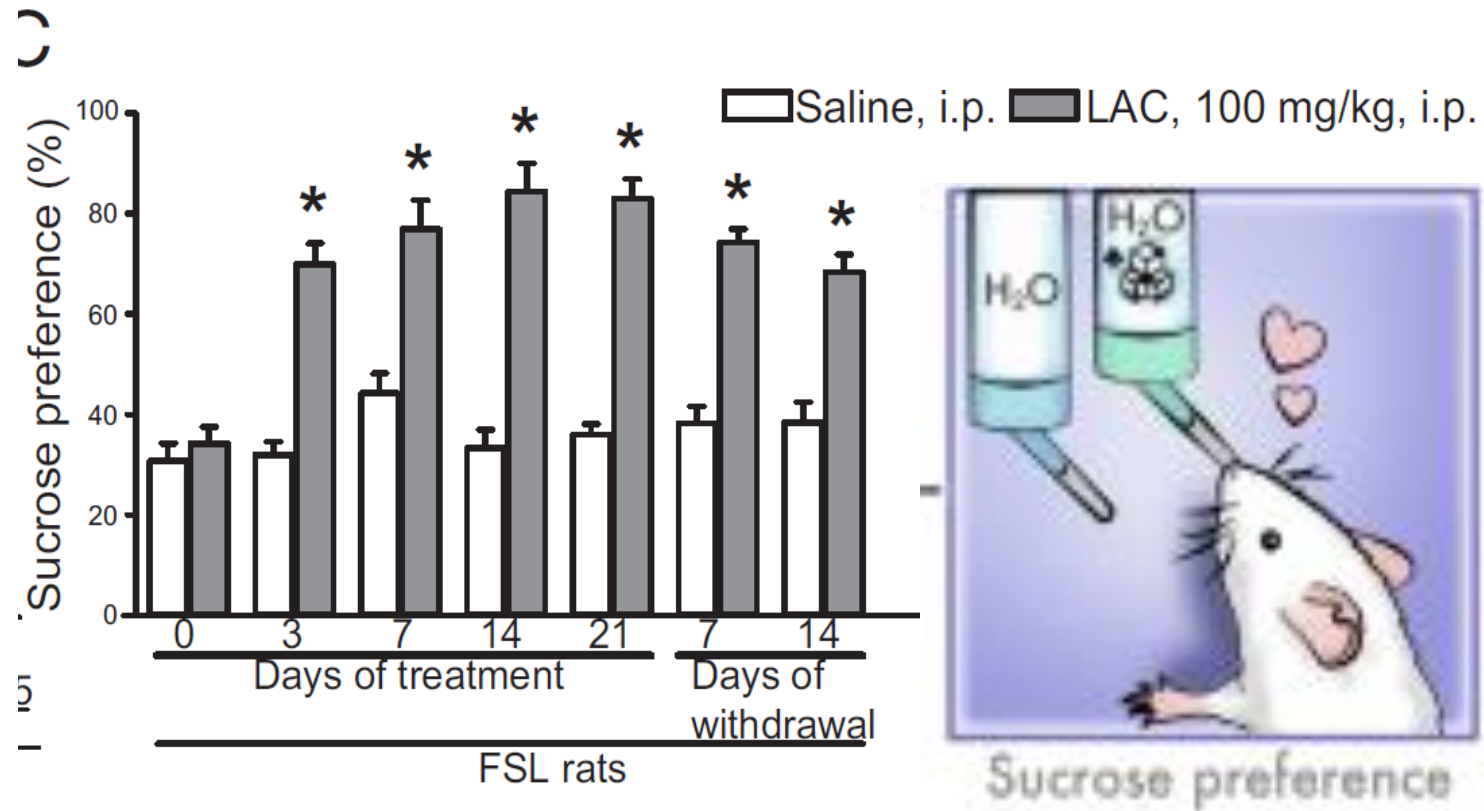
Saline, i.p.
  LAC, 100 mg/kg, i.p.
  Chlorimipramine, 10 mg/kg, i.p.

Clomipramina: antidepressivo triciclico (es. Anafranil)

Know Milano, 30 settembre - 1 ottobre 2022

# LAC migliora rapidamente e in modo marcato e prolungato lo stato di **anedonia**

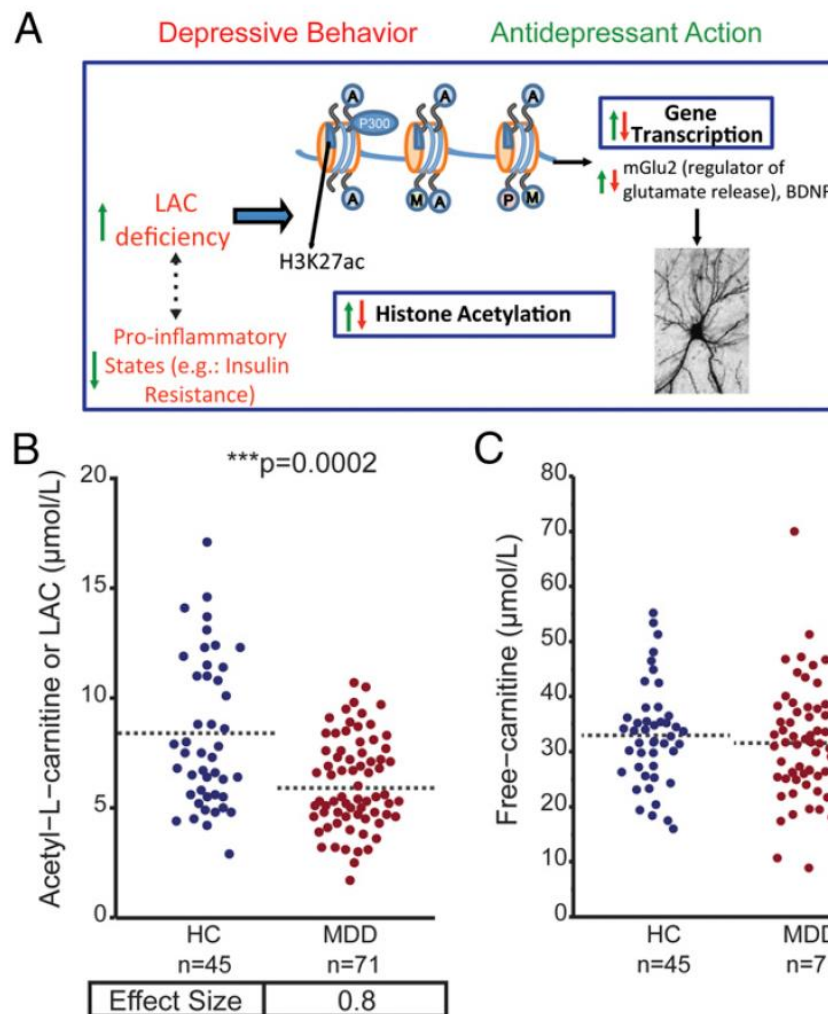
Sucrose preference test (anedonia)



Nasca C et al. L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. Proc Natl Acad Sci U S A. 2013 Mar 19;110(12):4804-9.



# L-Acetil-Carnitina risulta carente nel plasma di pazienti con depressione maggiore



Nasca C et al. Acetyl-L-carnitine deficiency in patients with major depressive disorder. PNAS 2018;115(34):8627-8632

**Table 1. Summary of randomized, placebo or comparator controlled, clinical trials of acetyl-L-carnitine in treatment of depression.**

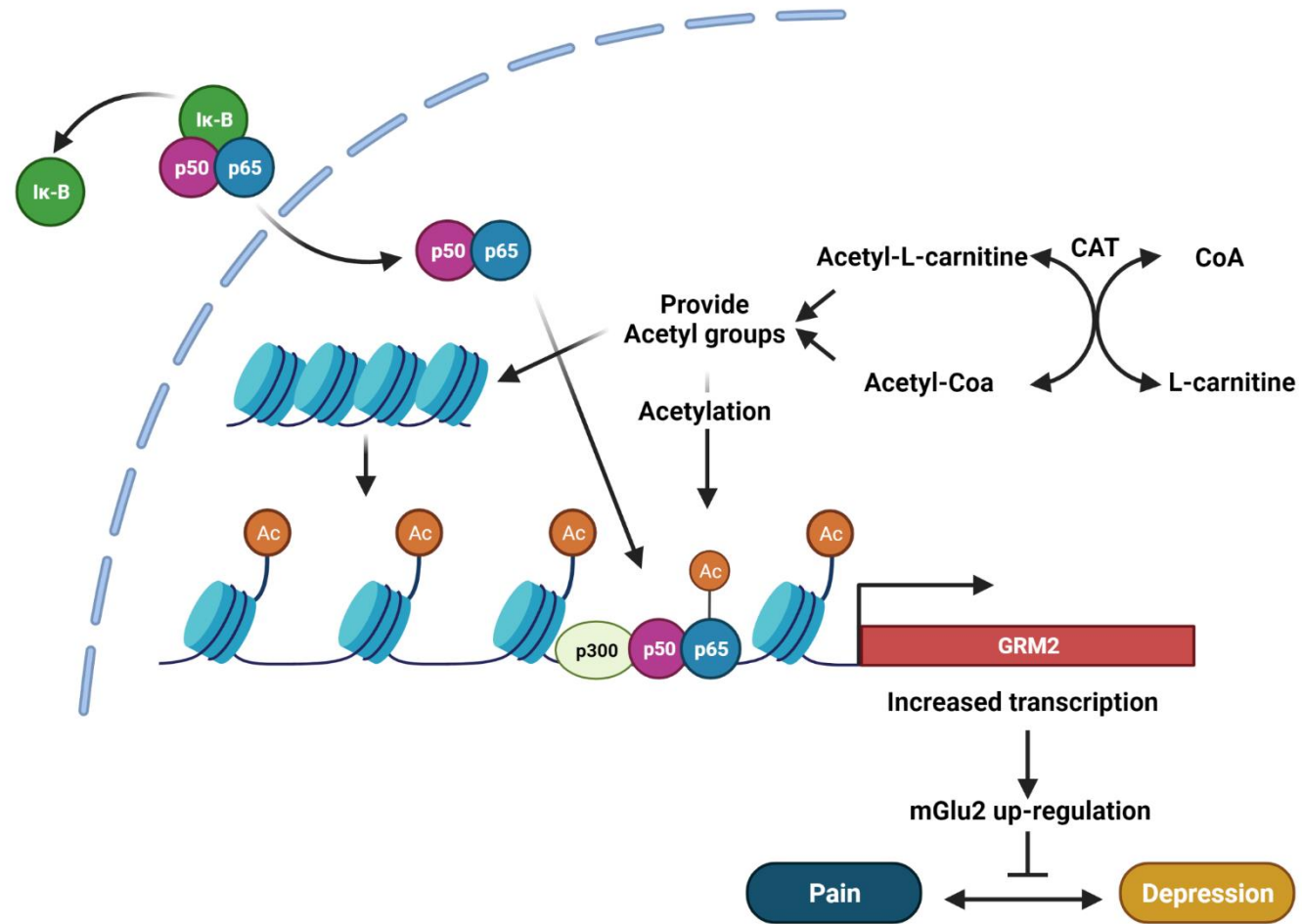
Author (year)	Primary diagnosis	Length (weeks)	Type and dosage of ALC	Type and dosage of comparator	Efficacy results	Ref.
Bersani <i>et al.</i> (2013)	Dysthymic disorder (elderly)	7	ALC (3 g); n = 41	FOX (20 mg); n = 39	ALC = FOX in HDS-21, HAM-A, and BDI	[32]
Brennan <i>et al.</i> (2013)	Bipolar depression	12	ALC (1–3 g) + ALA (0.61.8 g); n = 20	PBO; n = 20	ALC + ALA = PBO in MADRS, HDS-21, YMRS, and CGI	[28]
Zanardi & Smeraldi (2006)	Dysthymic disorder	12	ALC (1 g); n = 99	ASP (100 mg); n = 94	ALC comparable to ASP in HDS-21, MADRS, CDRS, and CGI	[31]
Villardita <i>et al.</i> (1993)	MDD	6	ALC (1.5 g); n = 14	PBO	ALC > PBO in HDS***	[24]
Gecele <i>et al.</i> (1991)	MDD (elderly)	6	ALC (2 g); n = 14	PBO; n = 14	ALC > PBO in HDS-17*	[27]
Fulgente <i>et al.</i> (1990)	Dysthymic disorder	8	ALC (3 g); n = 30	PBO; n = 30	ALC > PBO in HDS-17***	[30]
Garzya <i>et al.</i> (1990)	MDD (elderly)	8	ALC (1.5 g); n = 14	PBO; n = 14	ALC > PBO in HDS-17**	[26]
Bella <i>et al.</i> (1990)	Dysthymic disorder (elderly)	8	ALC (3 g); n = 30	PBO; n = 30	ALC > PBO in HDS-17****	[29]
Nasca <i>et al.</i> (1989)	Depression	8	MIA + ALC (2 g); n = 10 MIA + PBO	MIA + PBO; n = 10	MIA + ALC > MIA + PBO in HDS***	[25]

\*p < 0.05.

\*\*p < 0.01.

\*\*\*p < 0.001 versus comparator.

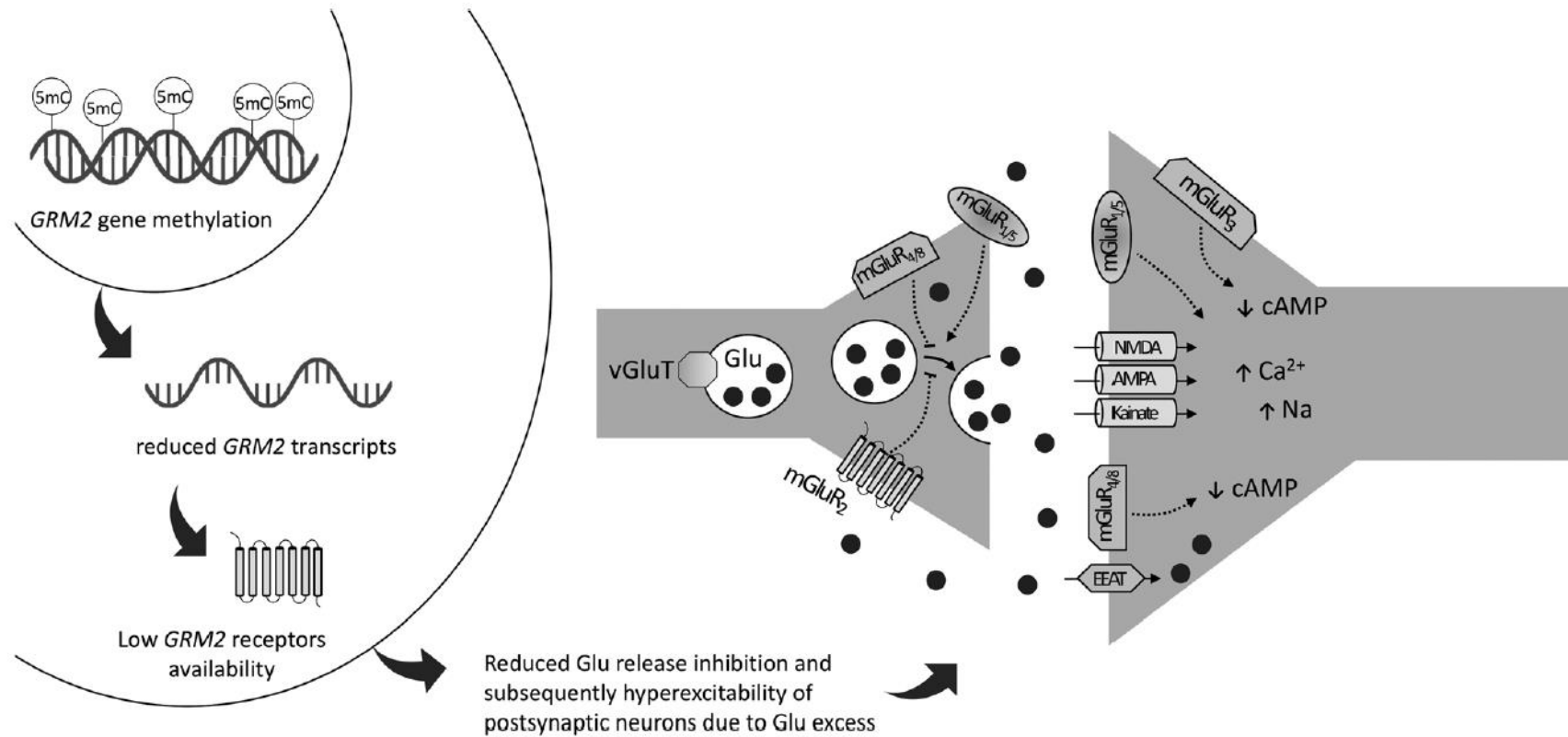
ALC: Acetyl-L-carnitine; ASP: Amisulpride; BDI: Beck depression inventory; CDRS: Cornell dysthymia rating scale; CGI: Clinical global impression scale; FOX: Fluoxetine; HAM-A: Hamilton anxiety rating scale; HDMS: Hamilton depression and melancholia scale; HDS: Hamilton depression rating scale; MADRS: Montgomery-Åsberg depression rating scale; MDD: Major depressive disorder; MIA: Mianserine.



## Original Experimental

Maria Carla Gerra\*, Davide Carnevali, Inge Søkilde Pedersen, Claudia Donnini, Matteo Manfredini, Alberto González-Villar, Yolanda Triñanes, Marina Pidal-Miranda, Lars Arendt-Nielsen and Maria Teresa Carrillo-de-la-Peña

# **DNA methylation changes in genes involved in inflammation and depression in fibromyalgia: a pilot study**



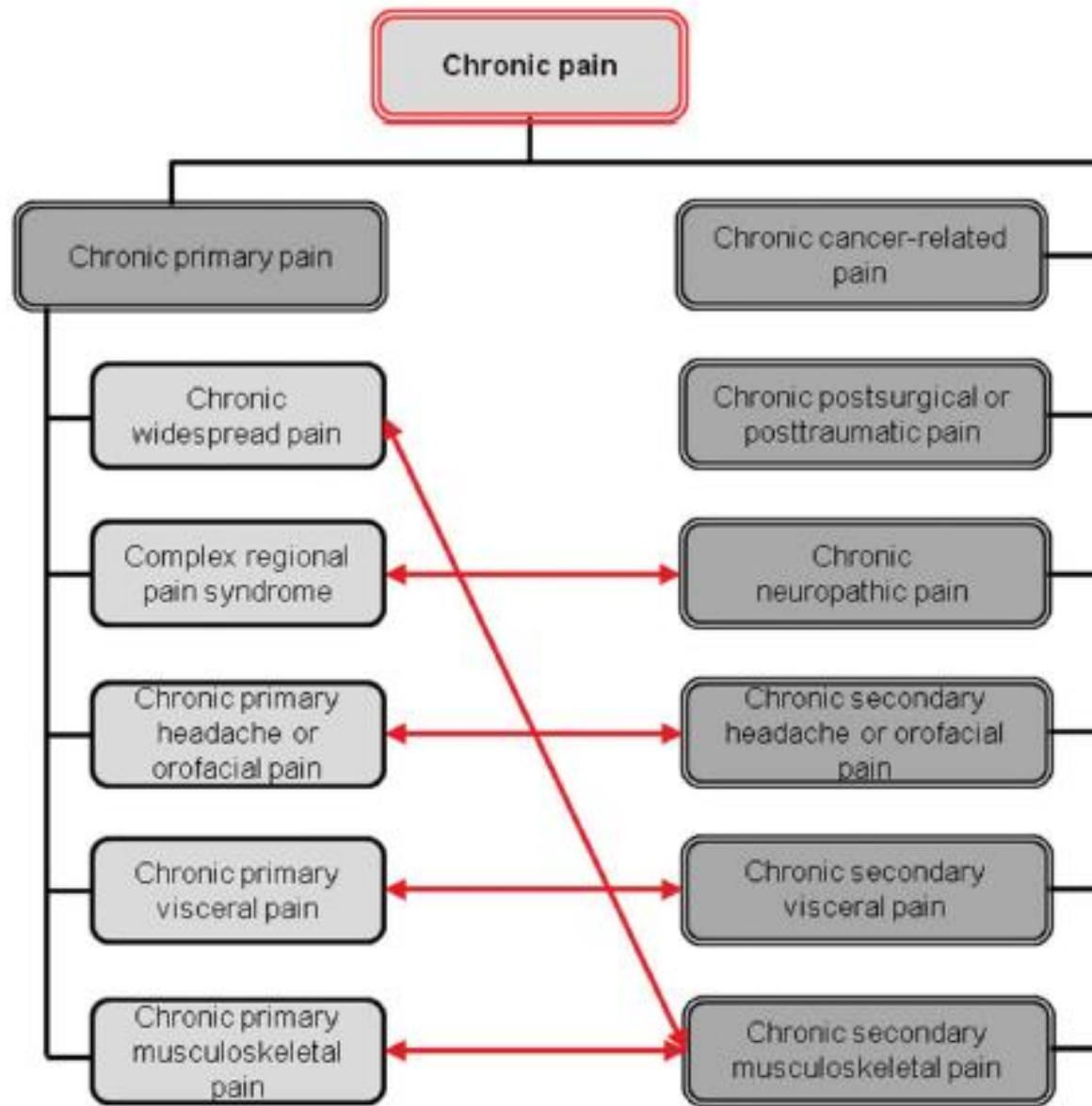
Scand J Pain 2021; 21(2): 372–383



*Patrizia Romualdi*

*Diego Fornasari*

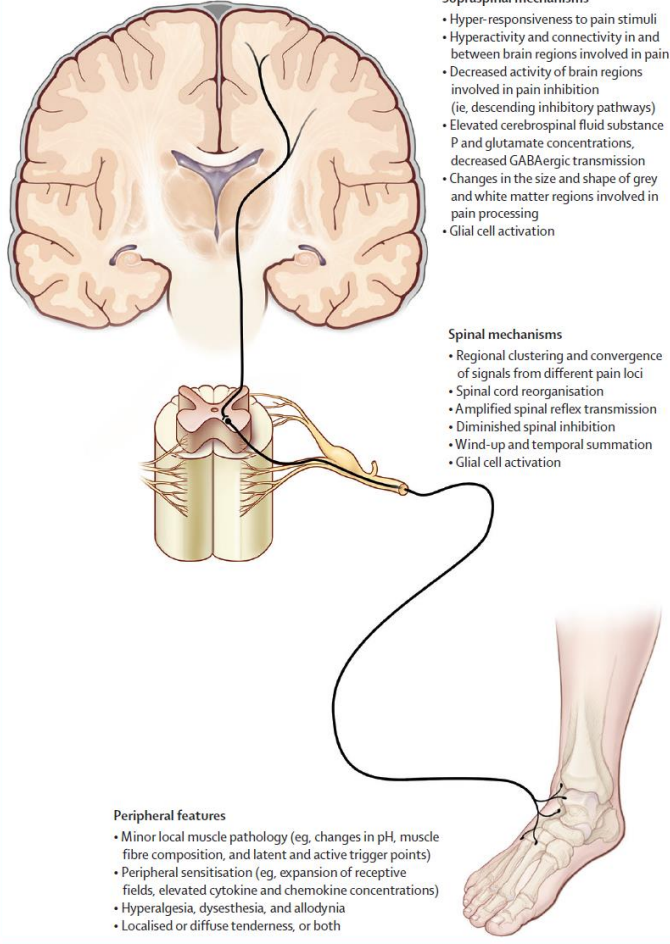
2022



Chronic secondary pain syndromes

#### Features of nociplastic pain conditions

- Combined peripheral and central pain sensitisation
- Hyper-responsiveness to painful and non-painful sensory stimuli
- Associated features
  - Fatigue
  - Sleep disturbance
  - Cognitive disturbances
  - Hypersensitivity to environmental stimuli
  - Anxiety and depressed mood



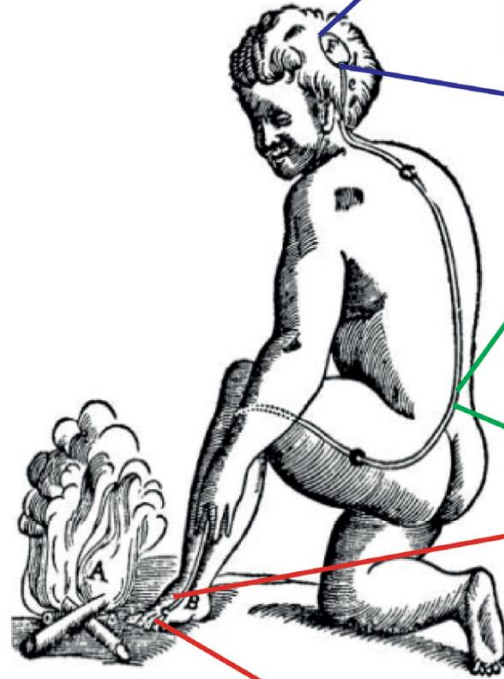
#### Features of nociplastic pain conditions

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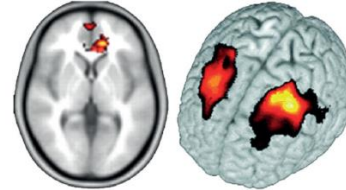
Figure: Mechanisms and features of nociplastic pain  
Figure created by Joe Kanasz.



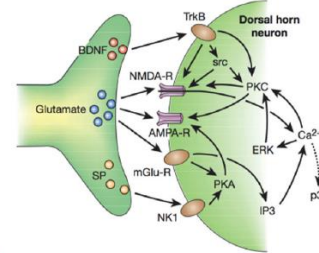
Descartes, 1644



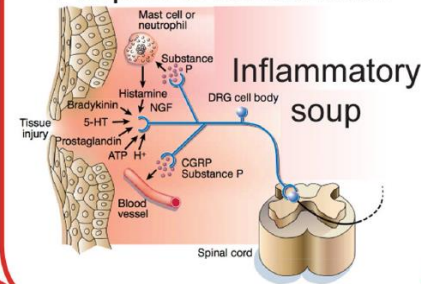
### Cortical reorganization



### Central sensitization



### Peripheral sensitization



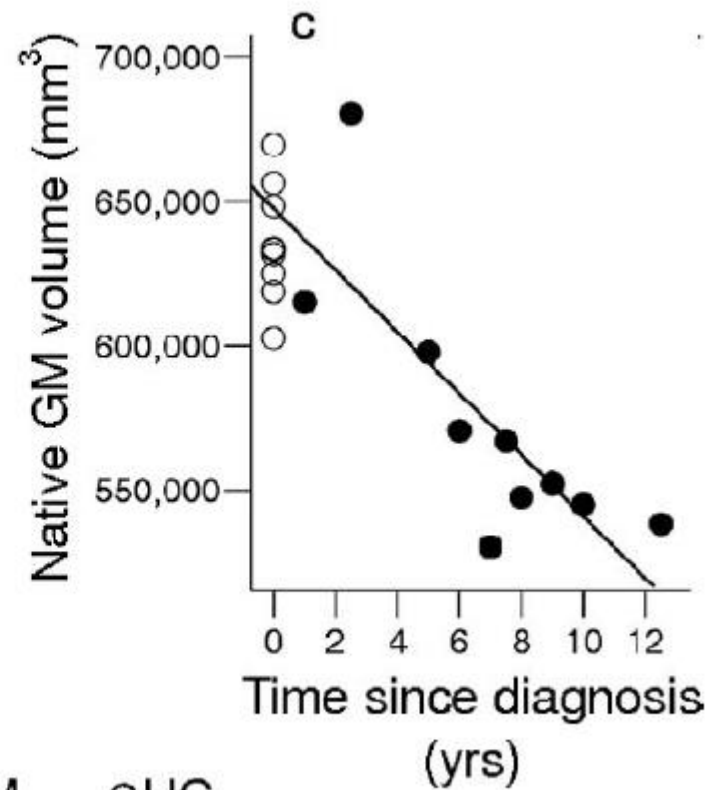
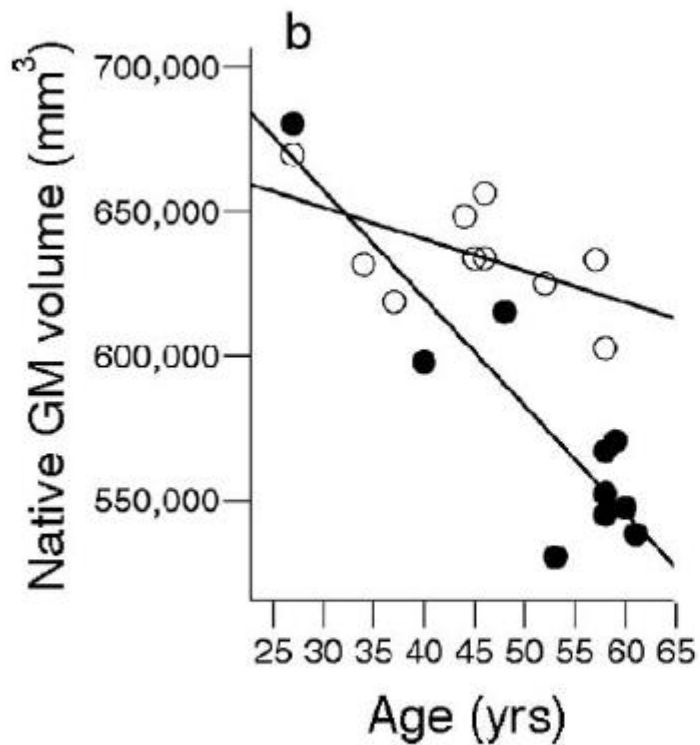
*Neuron*. 2015 August 5; 87(3): 474–491.

Brief Communications

# Accelerated Brain Gray Matter Loss in Fibromyalgia Patients: Premature Aging of the Brain?

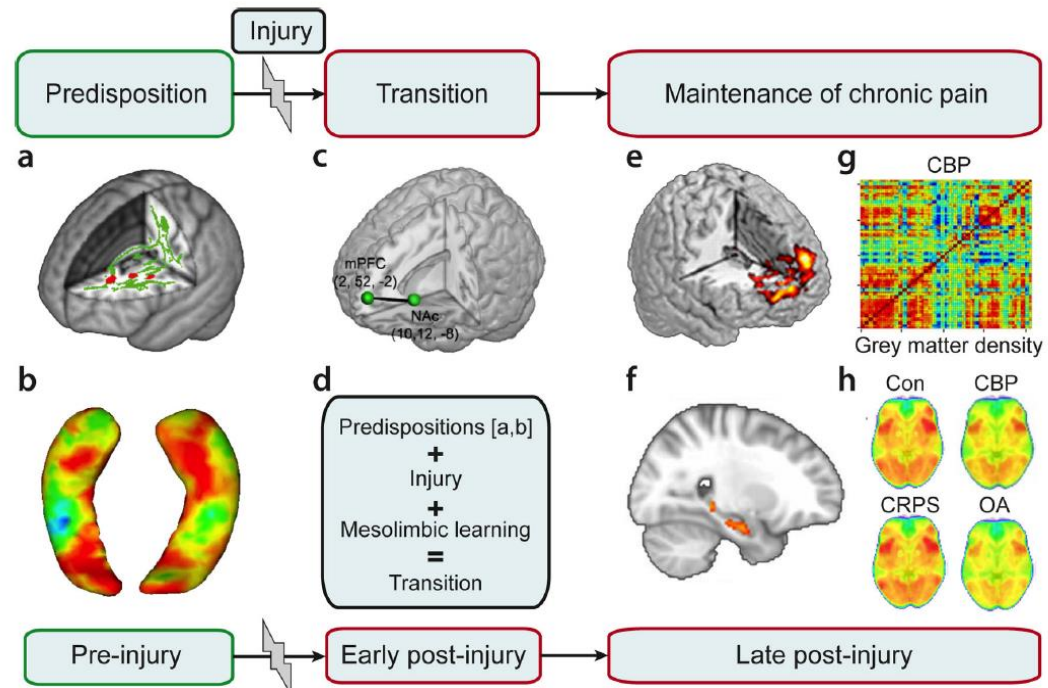
**Anil Kuchinad,<sup>1,2</sup> Petra Schweinhardt,<sup>1</sup> David A. Seminowicz,<sup>1</sup> Patrick B. Wood,<sup>1</sup> Boris A. Chizh,<sup>4</sup> and M. Catherine Bushnell<sup>1,2,3</sup>**

<sup>1</sup>McGill Centre for Research on Pain, <sup>2</sup>Department of Neurology and Neurosurgery, and <sup>3</sup>Department of Anesthesia and Faculty of Dentistry, McGill University, Montreal, Quebec, Canada H3A 2B2, and <sup>4</sup>GlaxoSmithKline, Addenbrooke's Centre for Clinical Investigation, Addenbrooke's Hospital, Cambridge CB2 2GG, United Kingdom



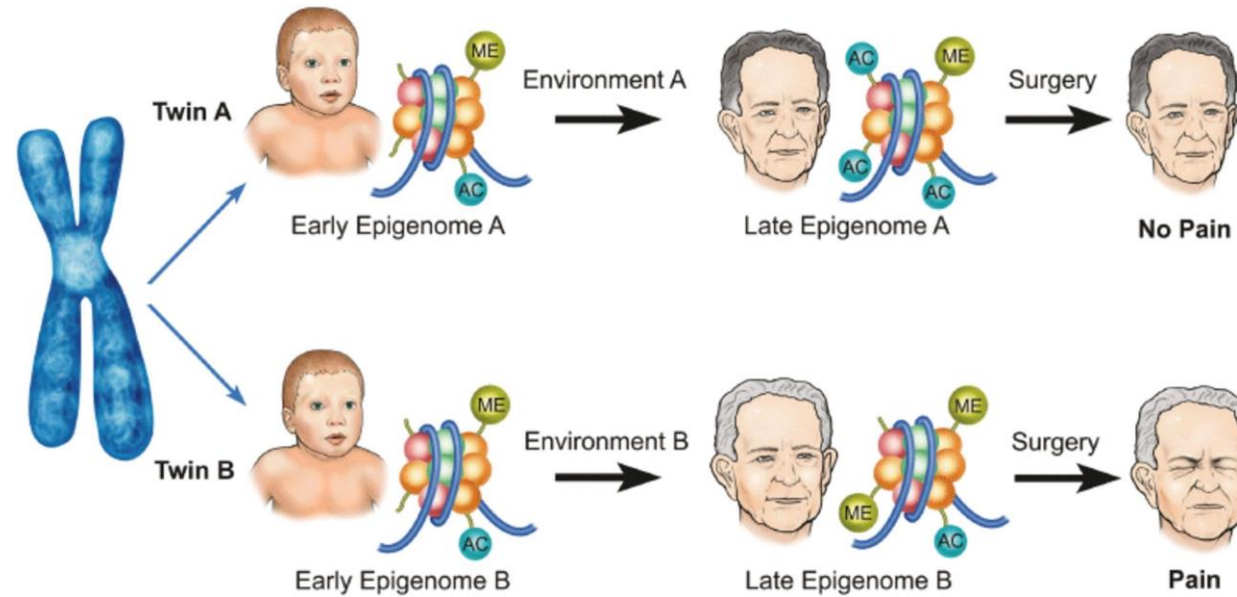
● FM ○ HC

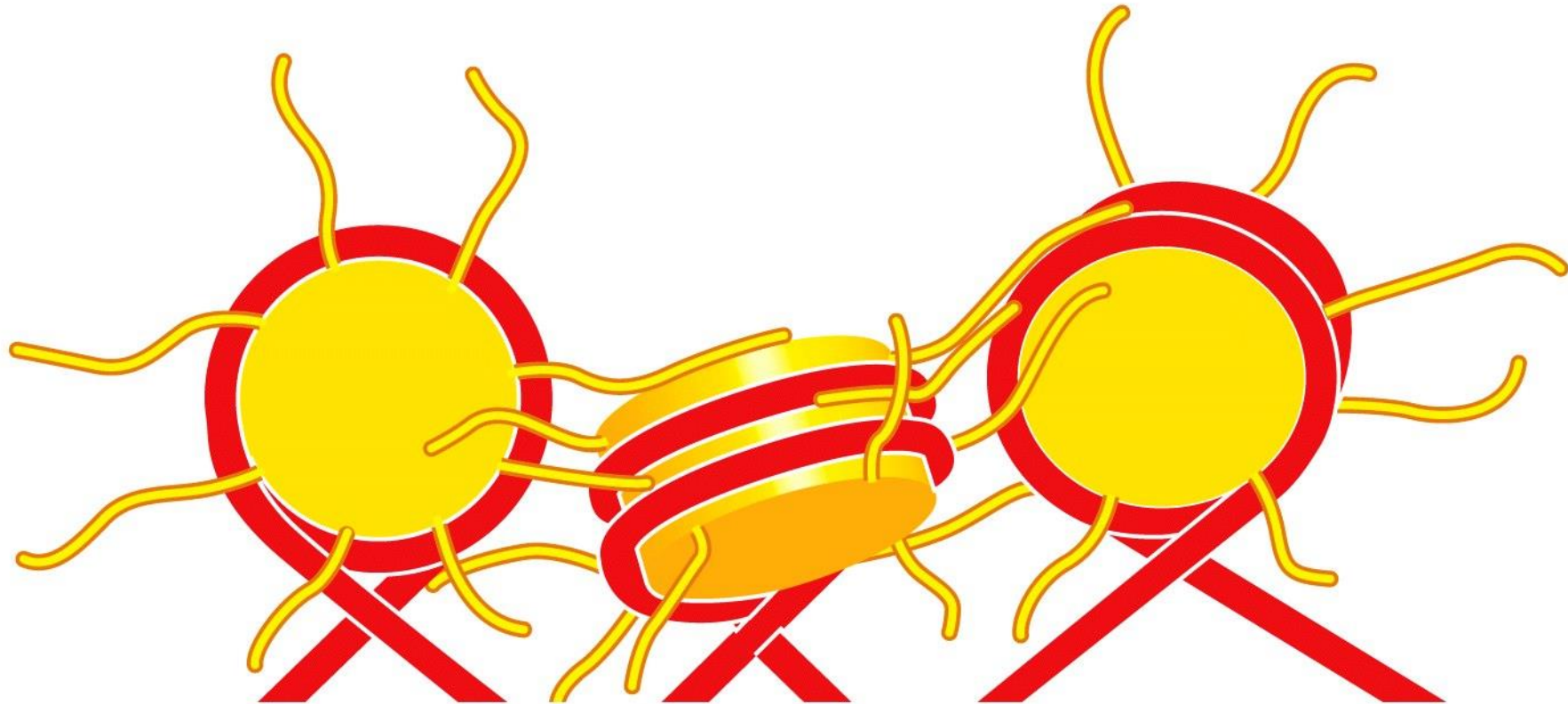
The Journal of Neuroscience, April 11, 2007 • 27(15):4004–4007

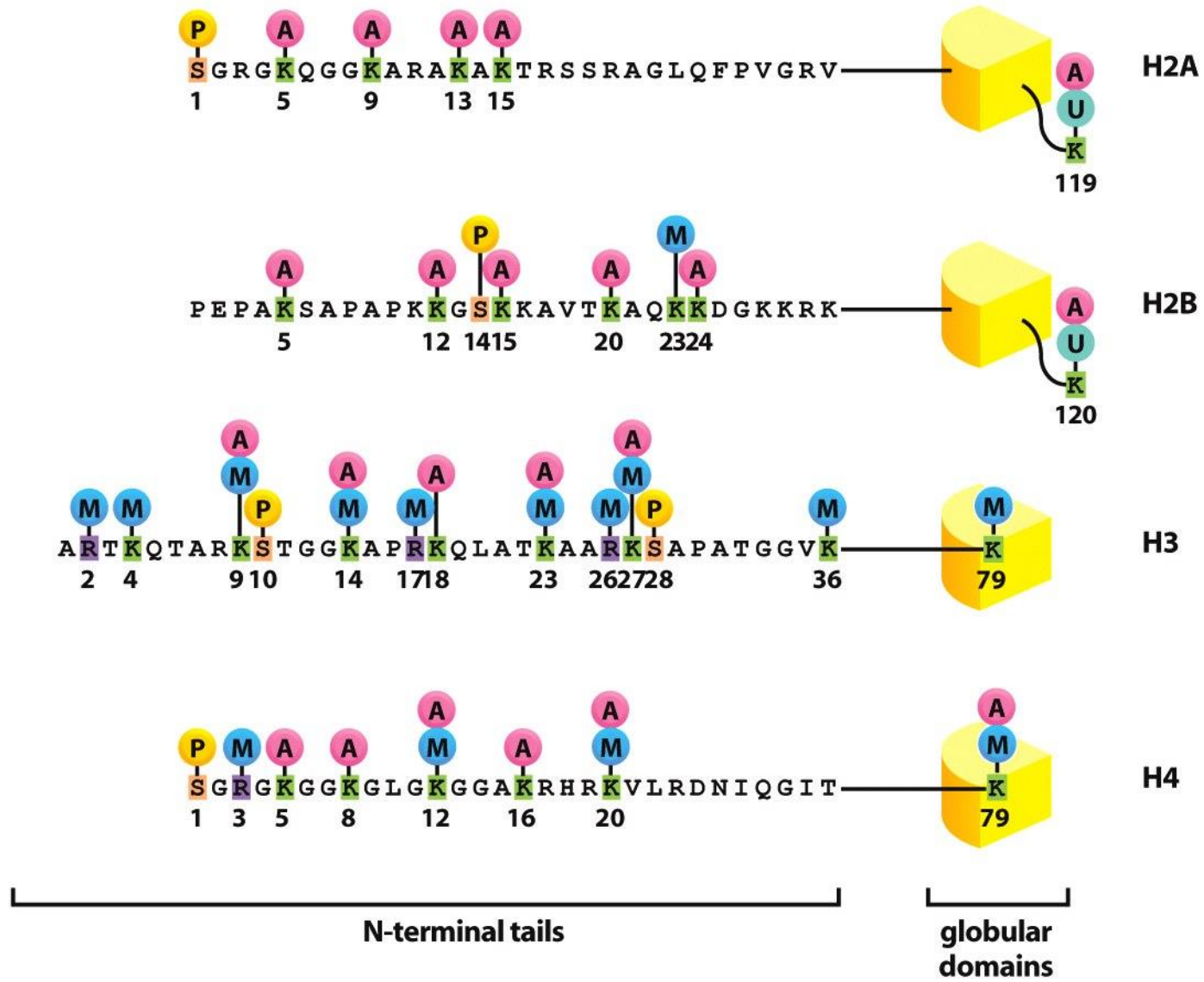


*Neuron.* 2015 August 5; 87(3): 474–491.

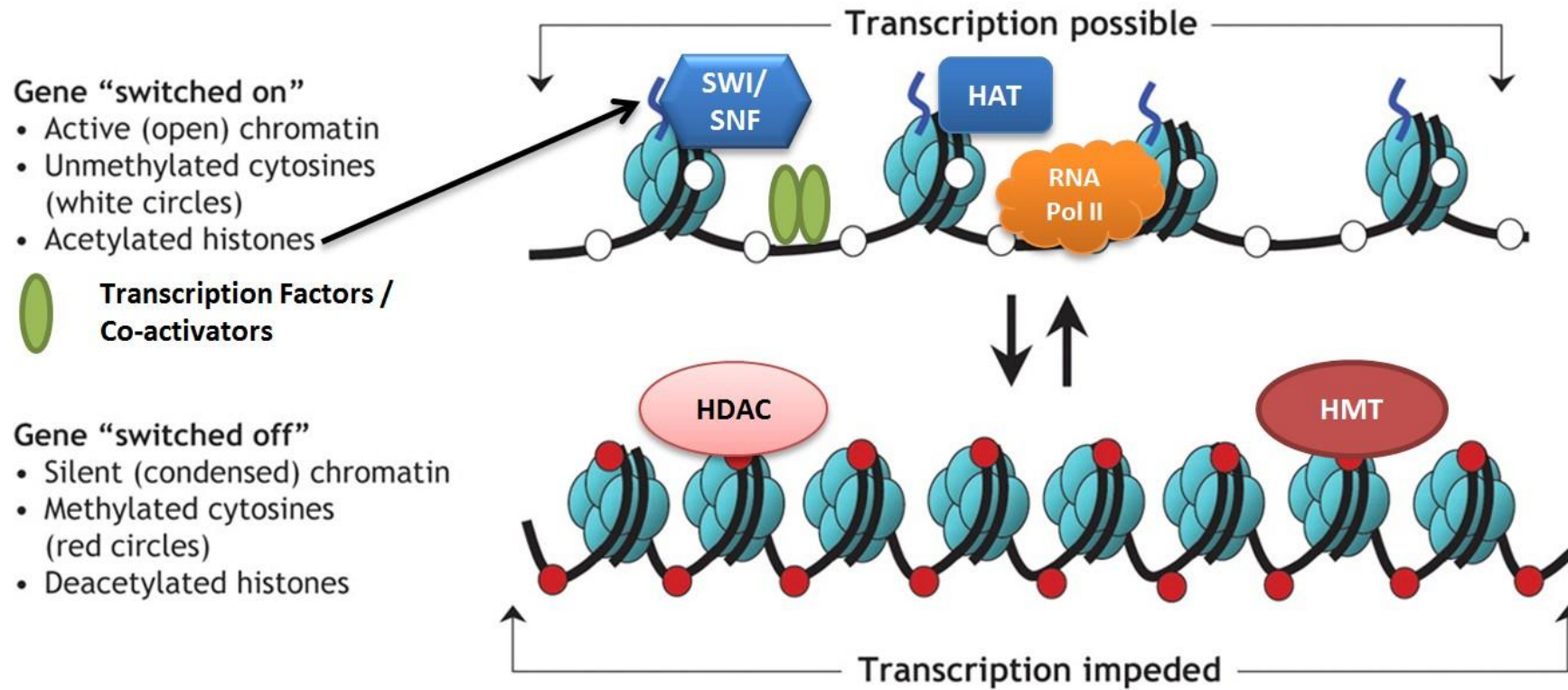
**Figure 1** Epigenome and chronic pain. Twin A and Twin B demonstrate similar “epigenomes” at birth with few (if any) ...





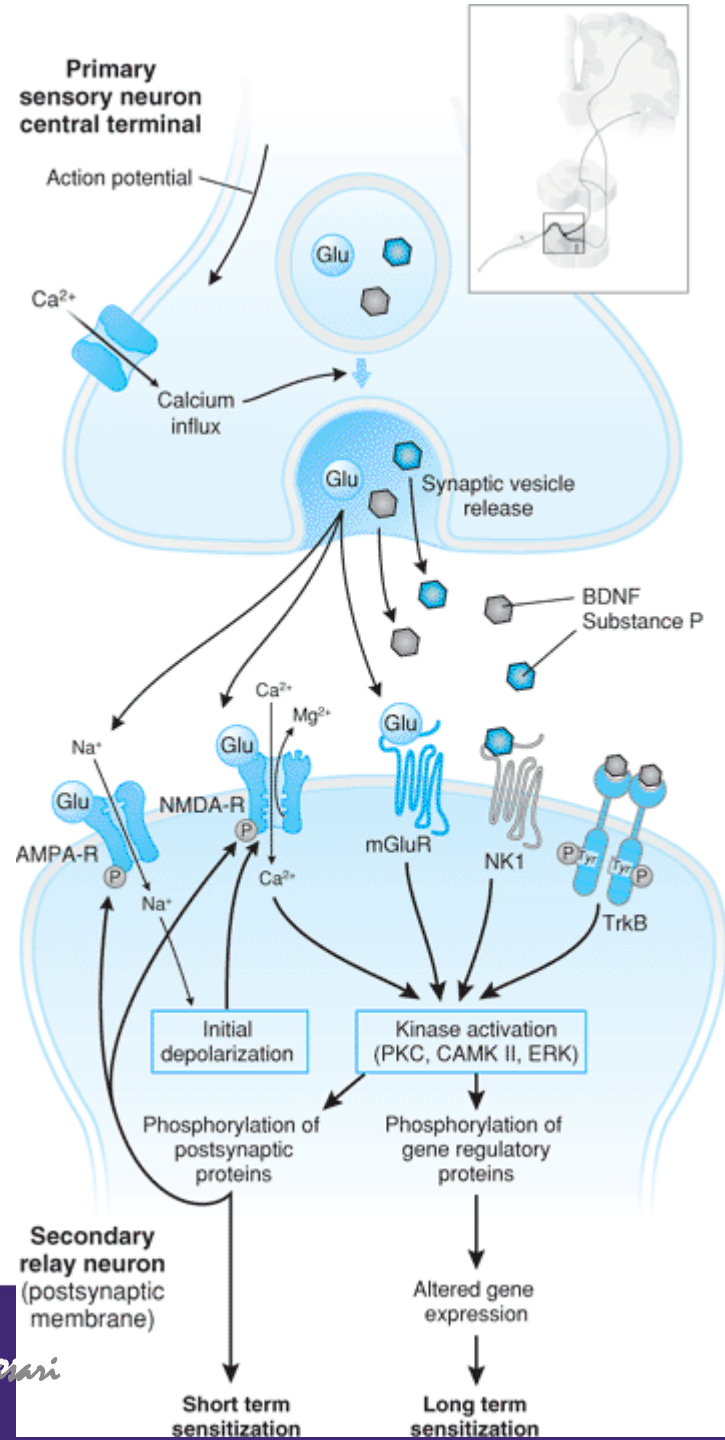


M methylation   
 P phosphorylation   
 A acetylation   
 U ubiquitylation





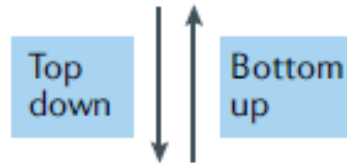
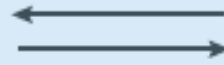
# SENSIBILIZZAZIONE SPINALE



## Central nervous system

- Activation of pain areas
- Altered brain connectivity
- ↓ Pain inhibitory signals and paradoxical stimulation
- ↓ Noradrenaline, 5HT, dopamine and opioid receptors
- ↑ Substance P and excitatory neurotransmitters (such as glutamate)

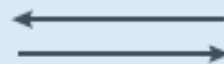
- Low resilience
- Maladaptive stress coping
- Sleep alterations
- Depression and anxiety
- Autonomic alterations
- Genetic factors



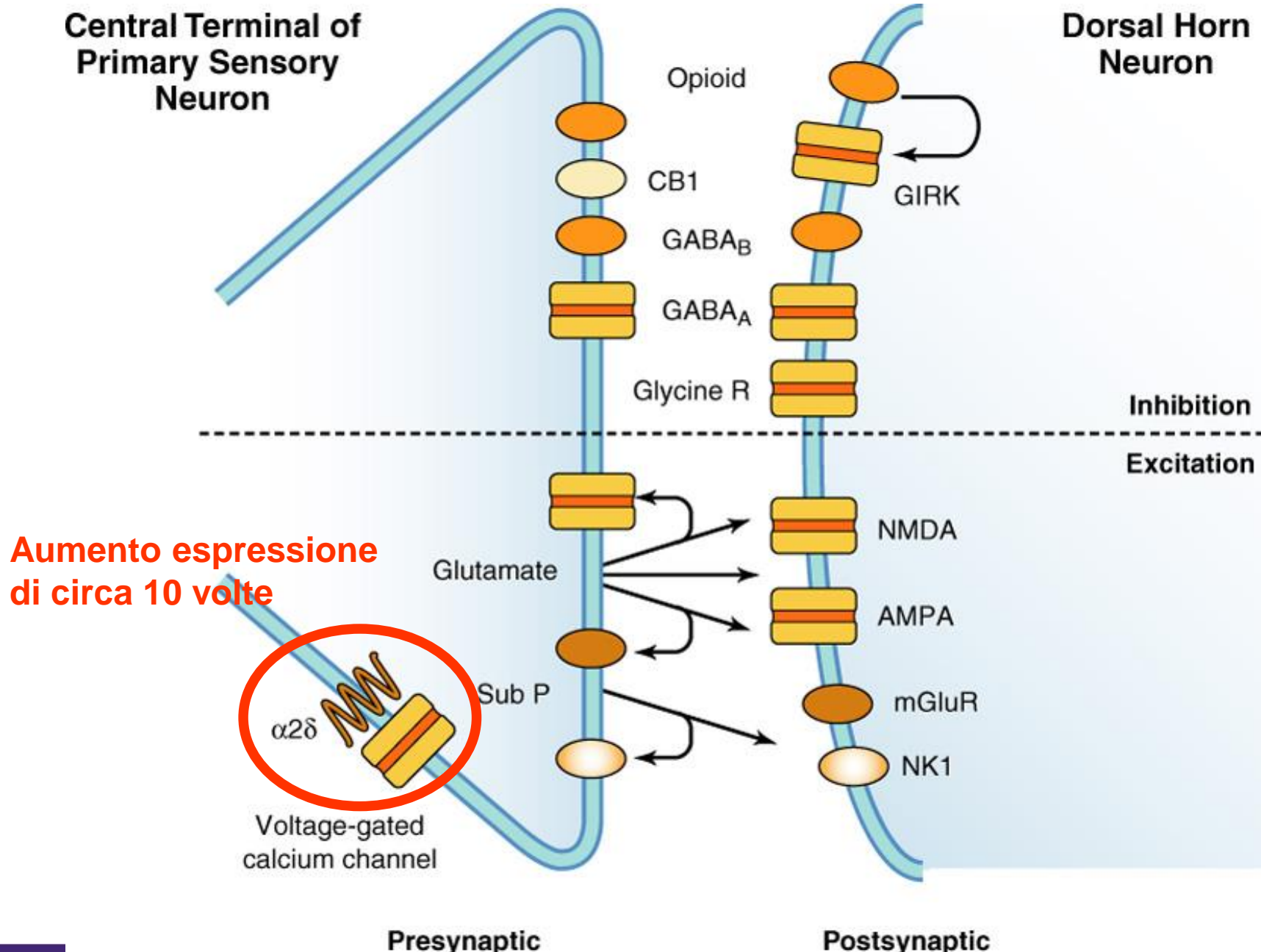
## Body periphery (sensory neurons, joints, viscera and immune cells)

Peripheral sensitization  
(↓ nociceptive threshold)

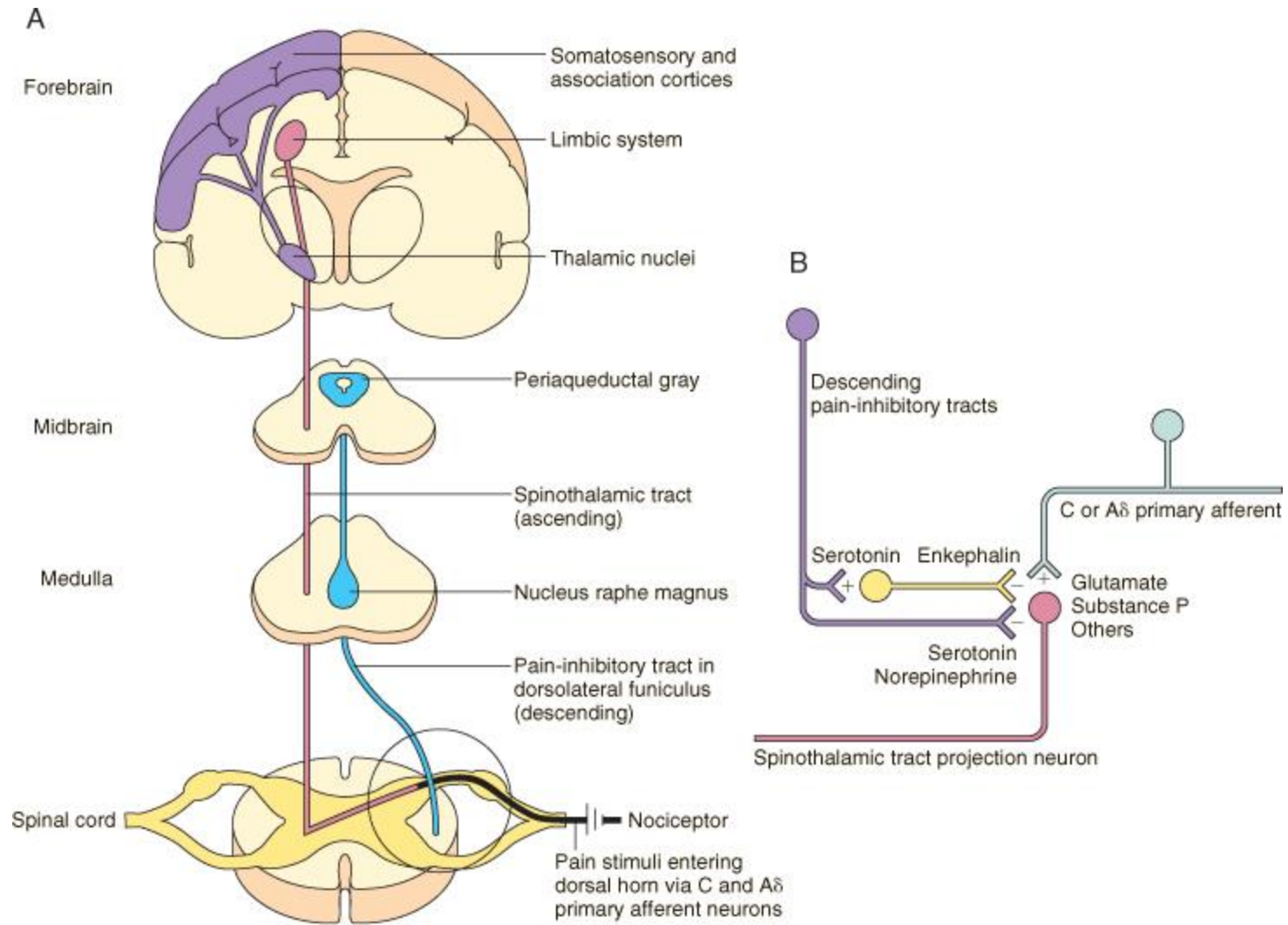
- Neuroinflammation
- Small fibre neuropathy
- Peripheral nociceptive stimuli or any chronic painful disease
- Genetic factors



■ Nociceptive alterations    ■ Pathogenic mechanisms



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