Trattamento farmacologico: dal dolore neuropatico al dolore nociplastico

Diego Fornasari
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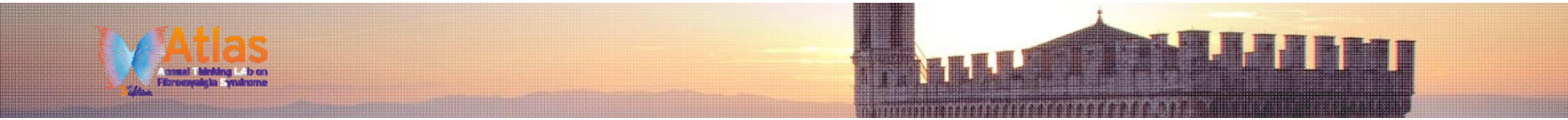

Atlas
Annual Meeting Lab on
Fibromyalgia Syndrome

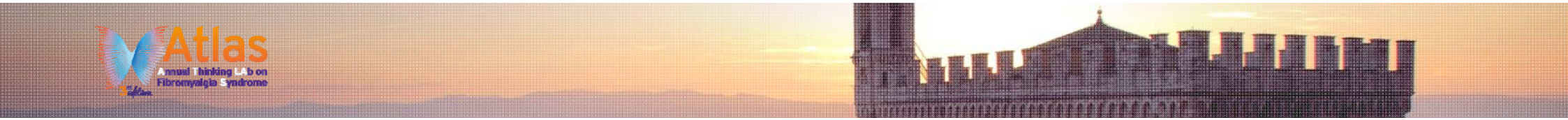
Narrative Review

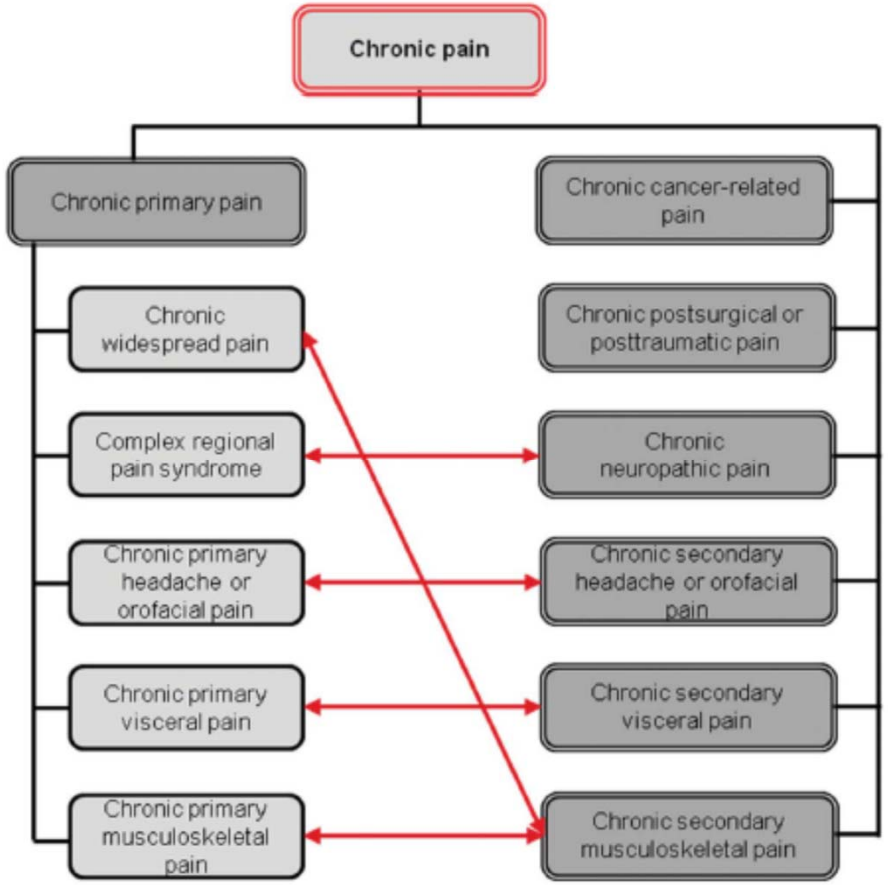
PAIN®

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

January 2019 • Volume 160 • Number 1





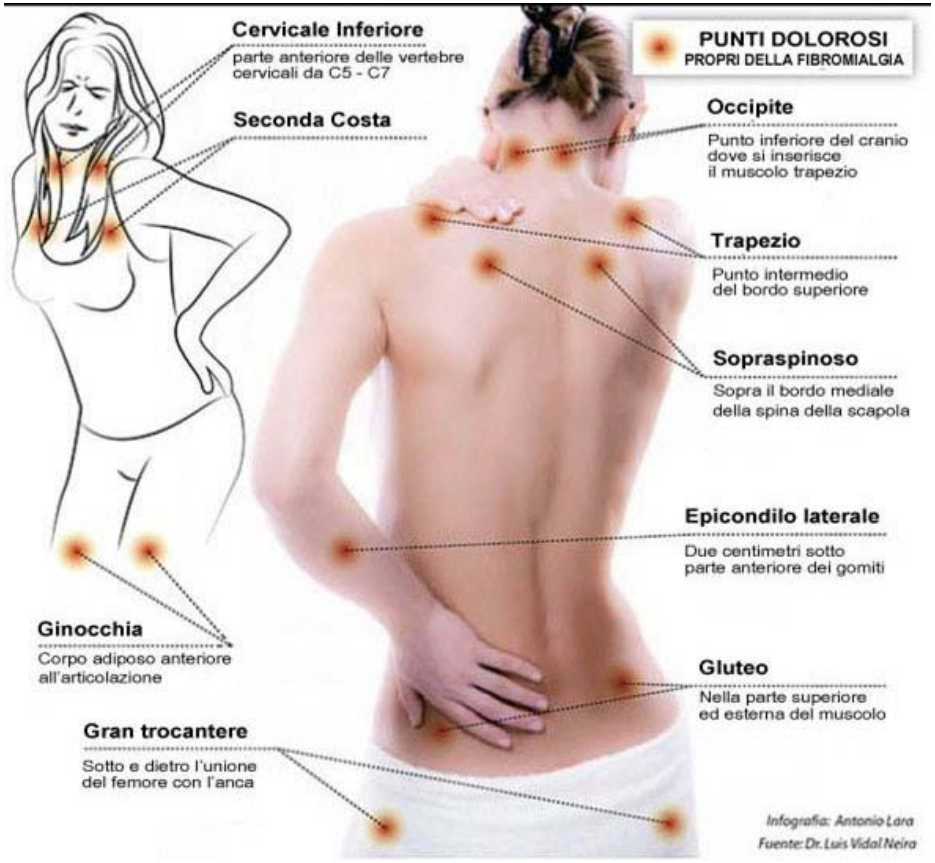
Chronic secondary pain syndromes

Fibromialgia – definizione della sindrome

La fibromialgia è una sindrome caratterizzata da **dolore muscoloscheletrico cronico e diffuso (tender points)**

associata a:

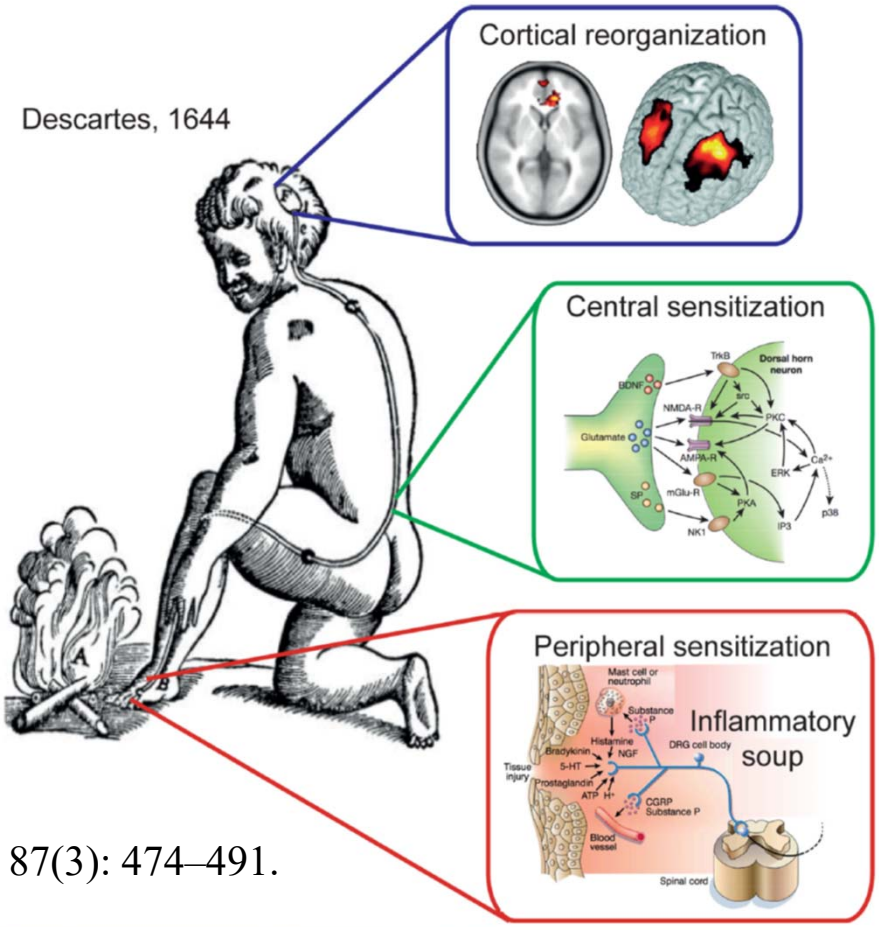
- **Astenia/affaticamento**
- **Disturbi del sonno**
- **Depressione**
- **Disturbi cognitivi** («fibro-fog» deficit di attenzione e memoria)



DEFINITION OF NOCIPLASTIC PAIN

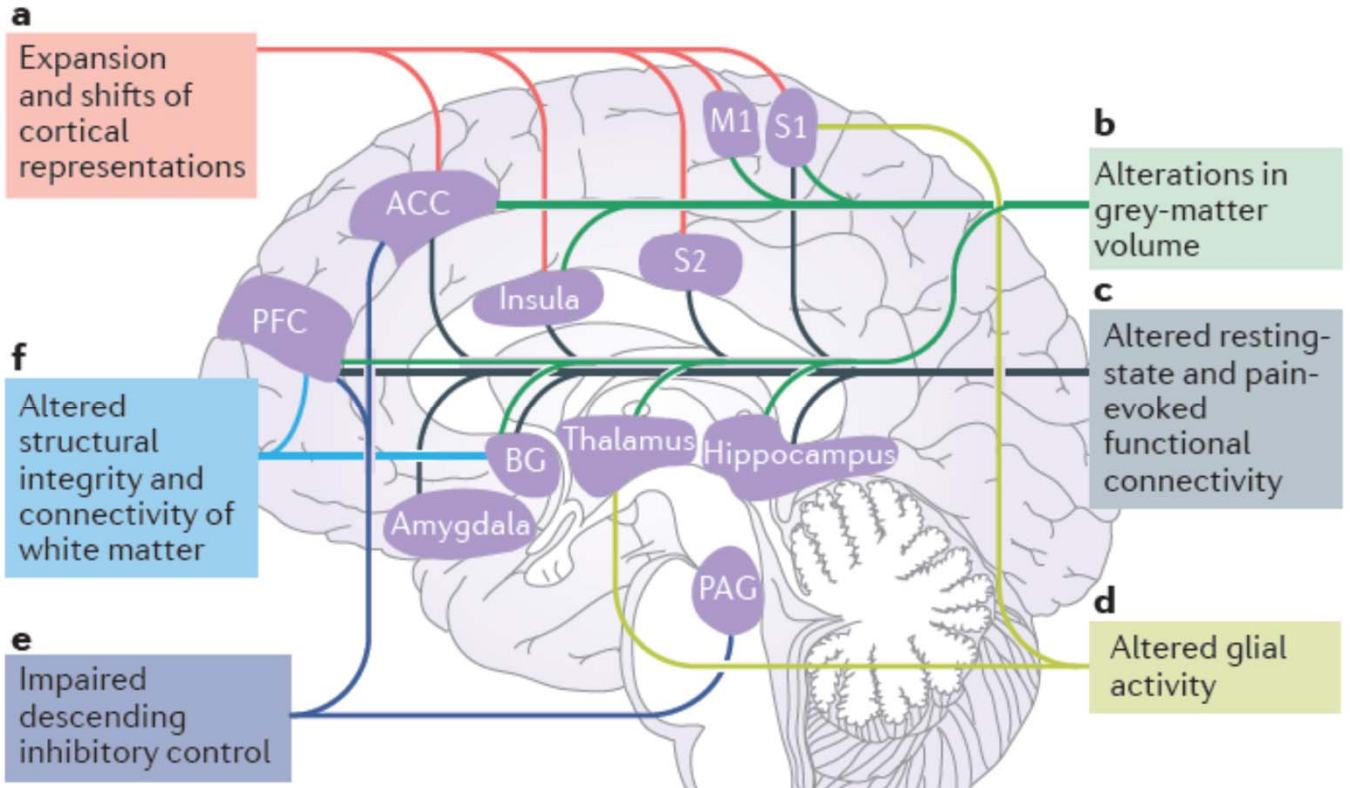
Nociplastic pain is defined as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.”

PAIN 2016;157:1382–6.



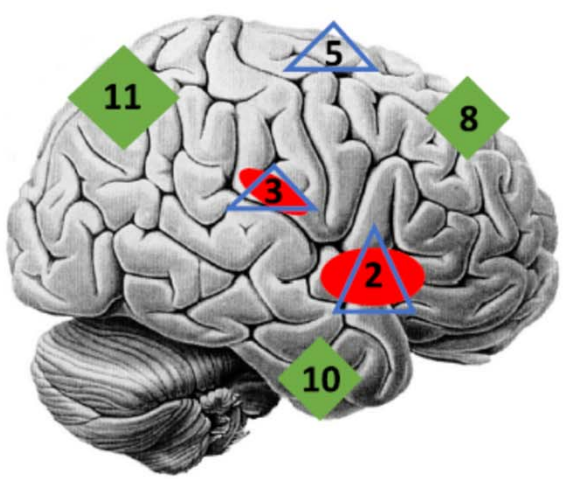
Neuron. 2015 August 5; 87(3): 474–491.

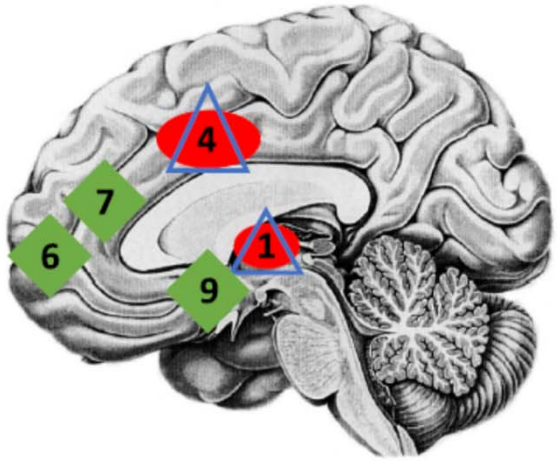
Structural and functional changes in the human brain in chronic pain conditions.



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

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.

Research Paper

PAIN®

OPEN

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

Angelica Sandström[a,b,*], Isabel Ellerbrock[a,b], Monika Löfgren[c], Reem Altawil[d], Indre Bileviciute-Ljungar[c], Jon Lampa[d], Eva Kosek[a,b,e]

PAIN 163 (2022) 538–547

PRINCIPAL FIBROMYALGIA SYMPTOMS

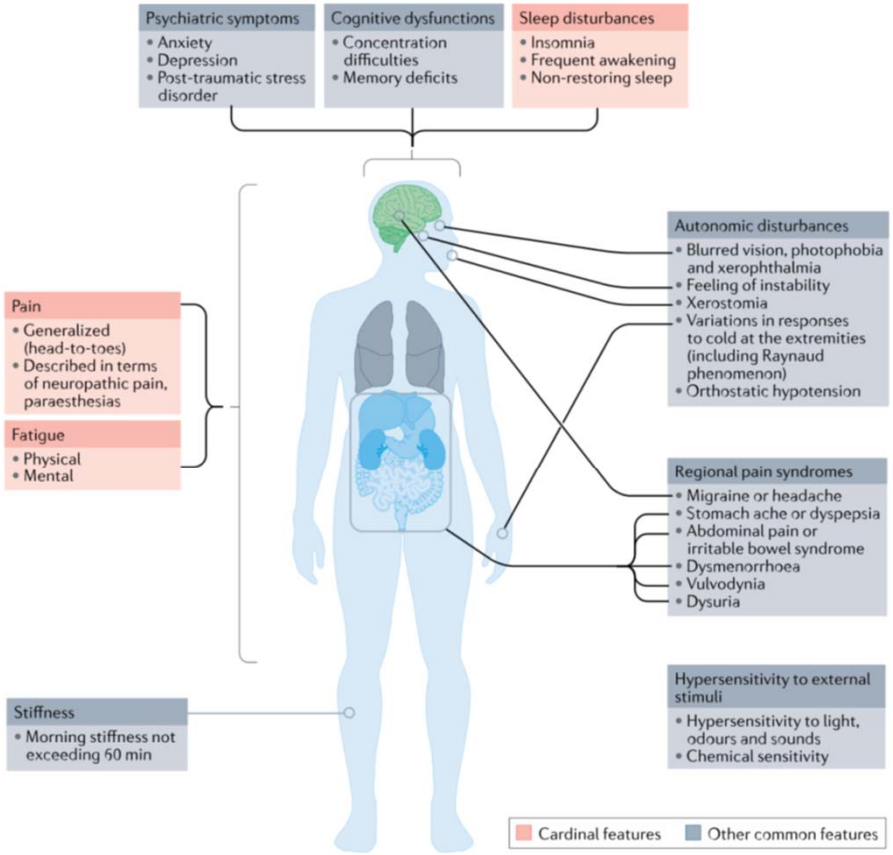


Fig. 2 | **Principal fibromyalgia symptoms.** Fibromyalgia has a complex symptomatology. Symptoms can be are divided in two groups: cardinal features (shown in pink), which include the most characteristic fibromyalgia symptoms that are pivotal for a diagnosis according to the latest criteria, and other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

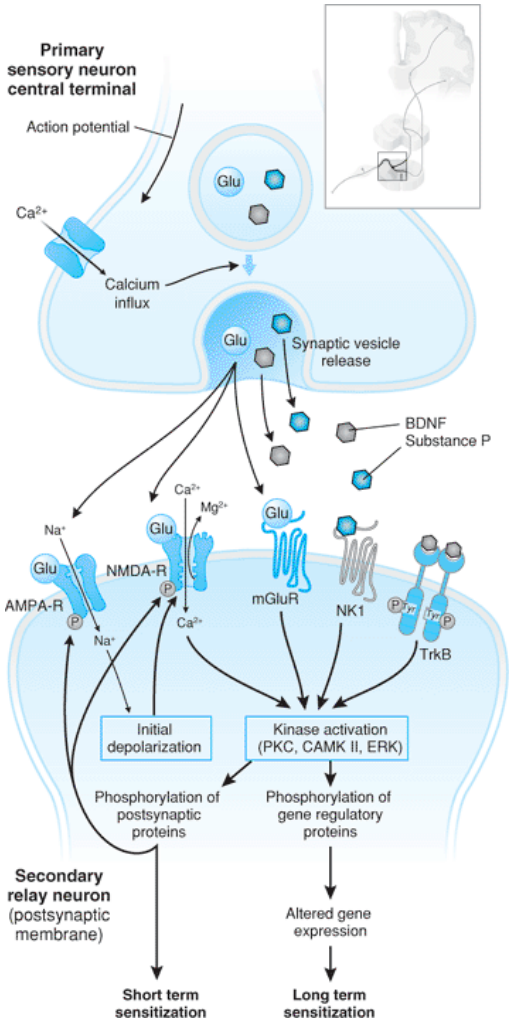
Sarzi-Puttini P *et al.* *Nature Rev Rheumatol* 2020 16: 645-660

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.

SPINAL SENSITIZATION

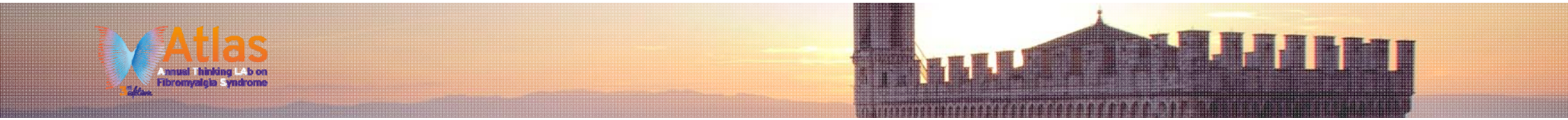


Biennial Review of Pain

PAIN®

Central sensitization: clinical utility of a physiological concept for the International Statistical Classification of Diseases and Related Health Problems and for nociplastic pain

Rolf-Detlef Treede*, Ulrich Hoheisel, Dan Wang, Walter Magerl



Nociplastic pain—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—is a new concept that calls for a history of pain hypersensitivity in the region of pain to be diagnosed. The pain is conceptualized as chronic, regional in distribution, and not explainable by a nociceptive or neuropathic process. The regional pain and hyperalgesia distribution is consistent with deficits in endogenous pain modulation. Hence, this subtype of central sensitization is believed to be the key mechanism behind nociplastic types of pain, but this subtype of central sensitization differs from the activity-dependent spinal central sensitization in nociceptive or neuropathic pain….

Comorbid anxiety or depression may rather be indicators of a third type of central sensitization in thalamocortical circuits.

Narrative Review

PAIN

ICD-11

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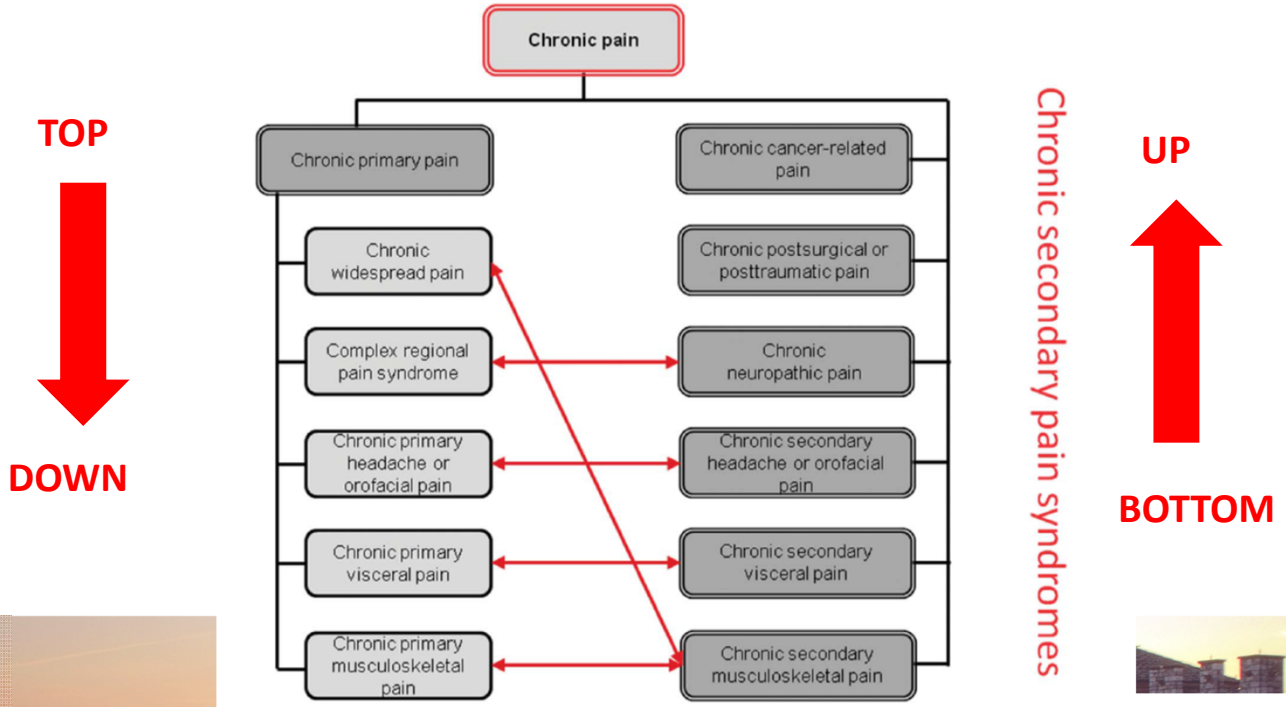


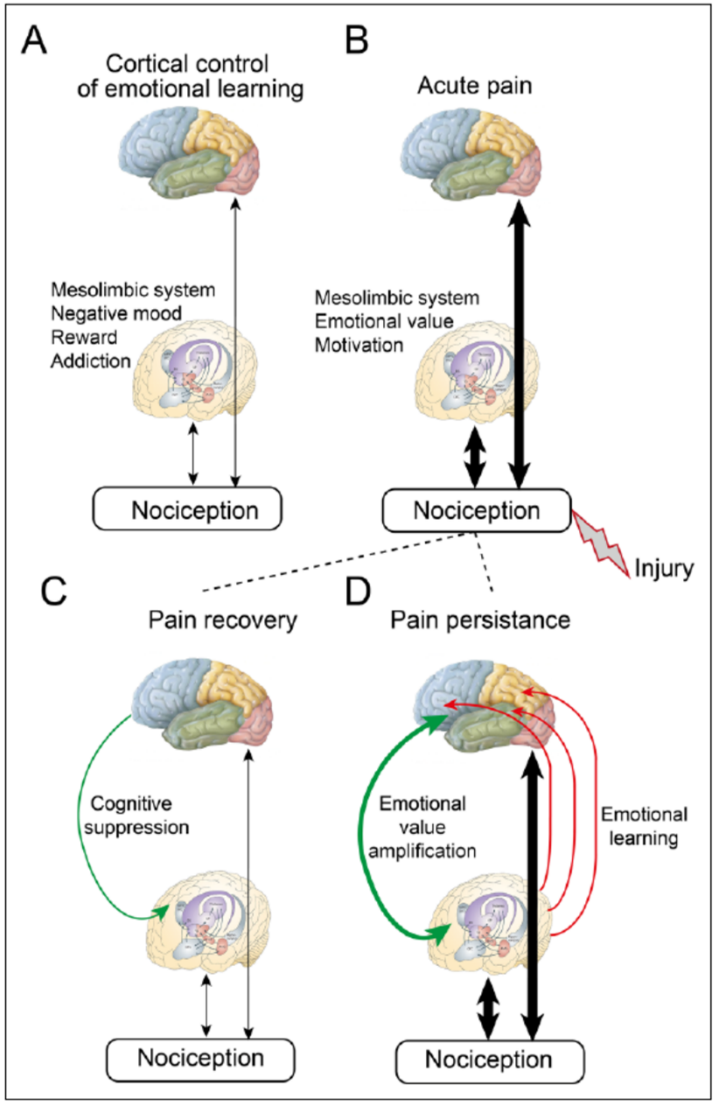
TOP

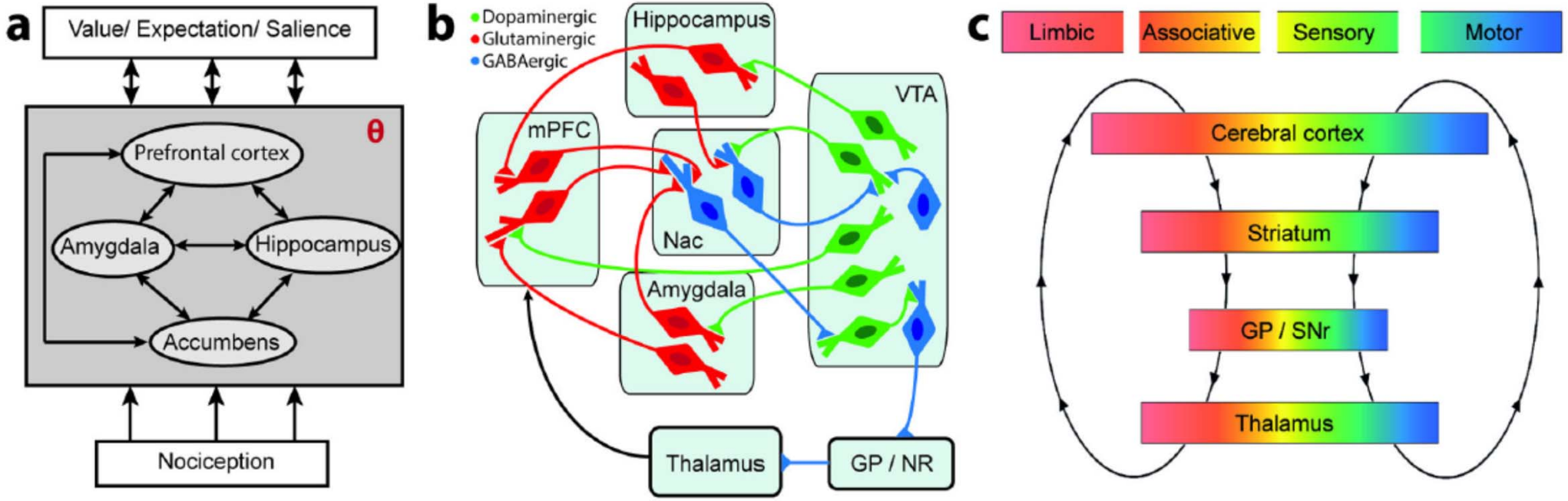
DOWN

UP

BOTTOM

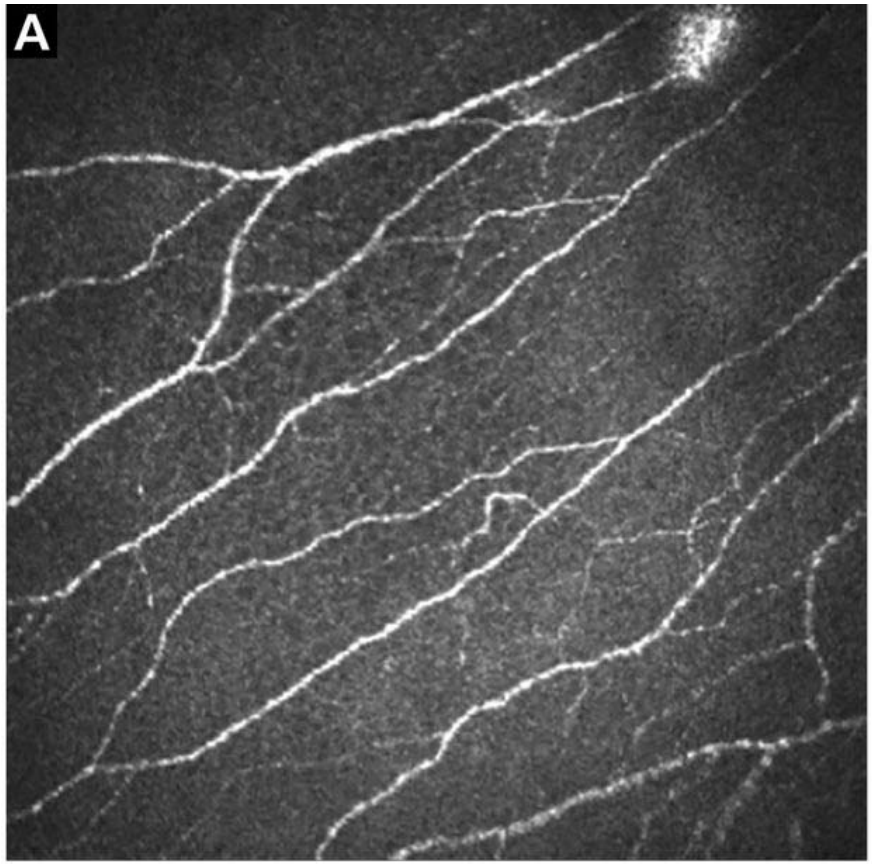
Chronic pain depends on the corticolimbic properties interacting with nociceptive inputs.

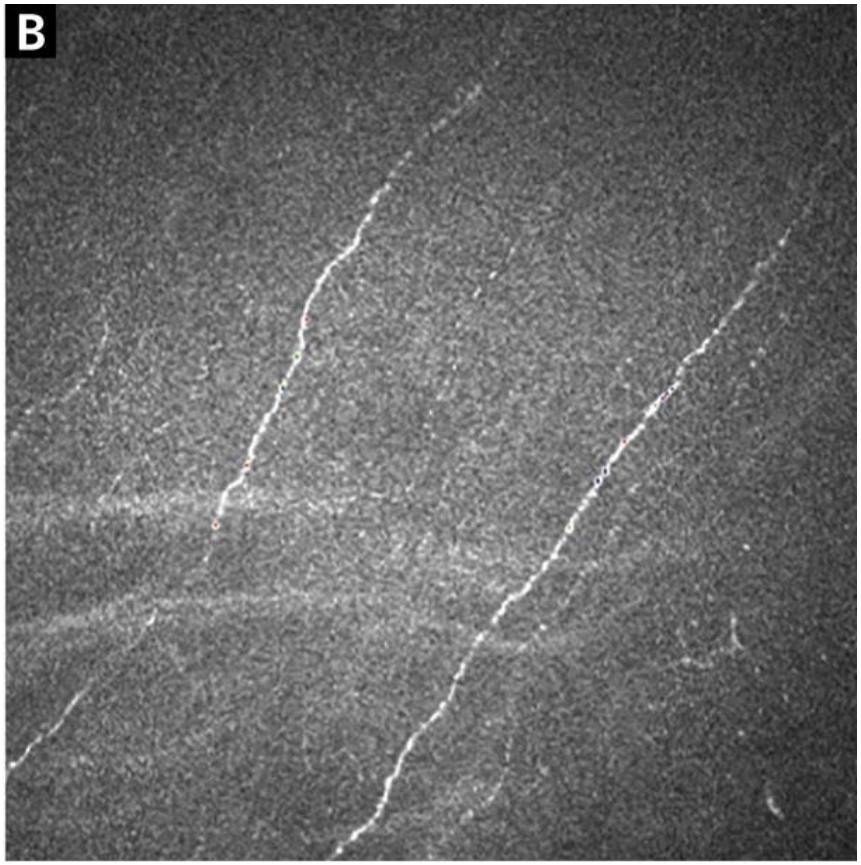




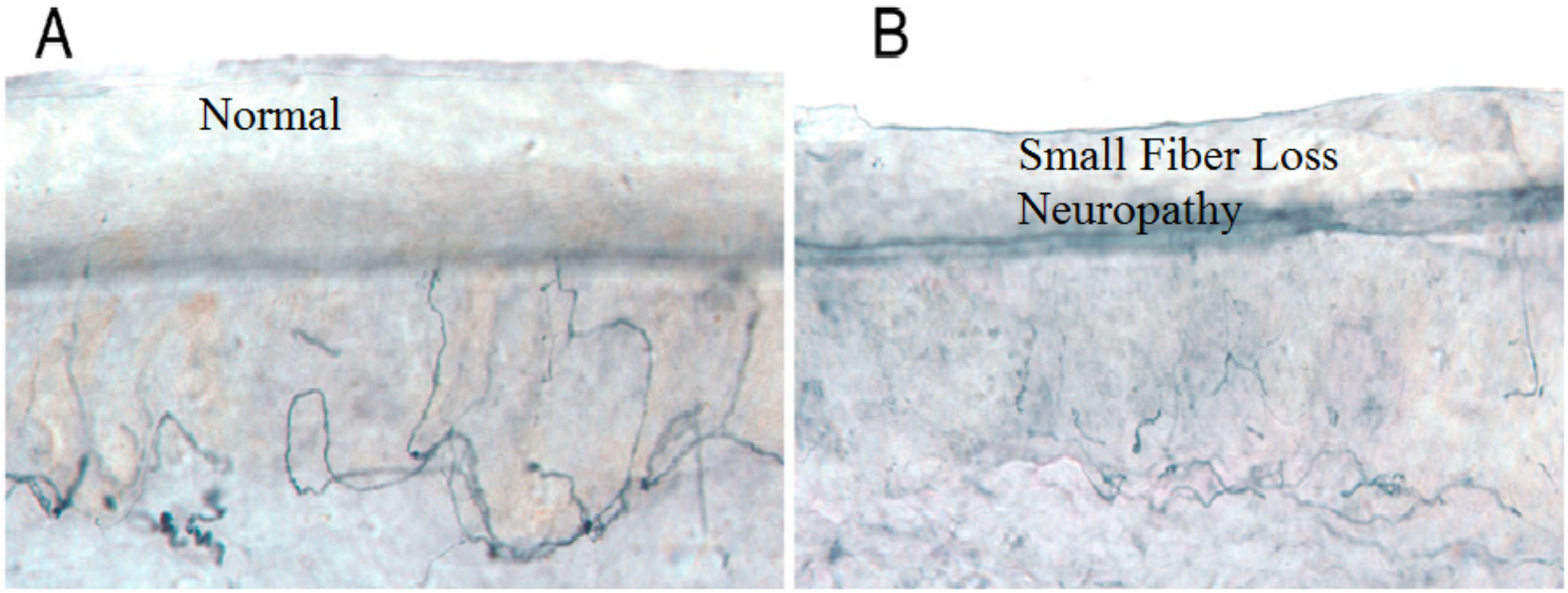
Neuron. 2015 August 5; 87(3): 474–491.

SMALL FIBER NEUROPATHY

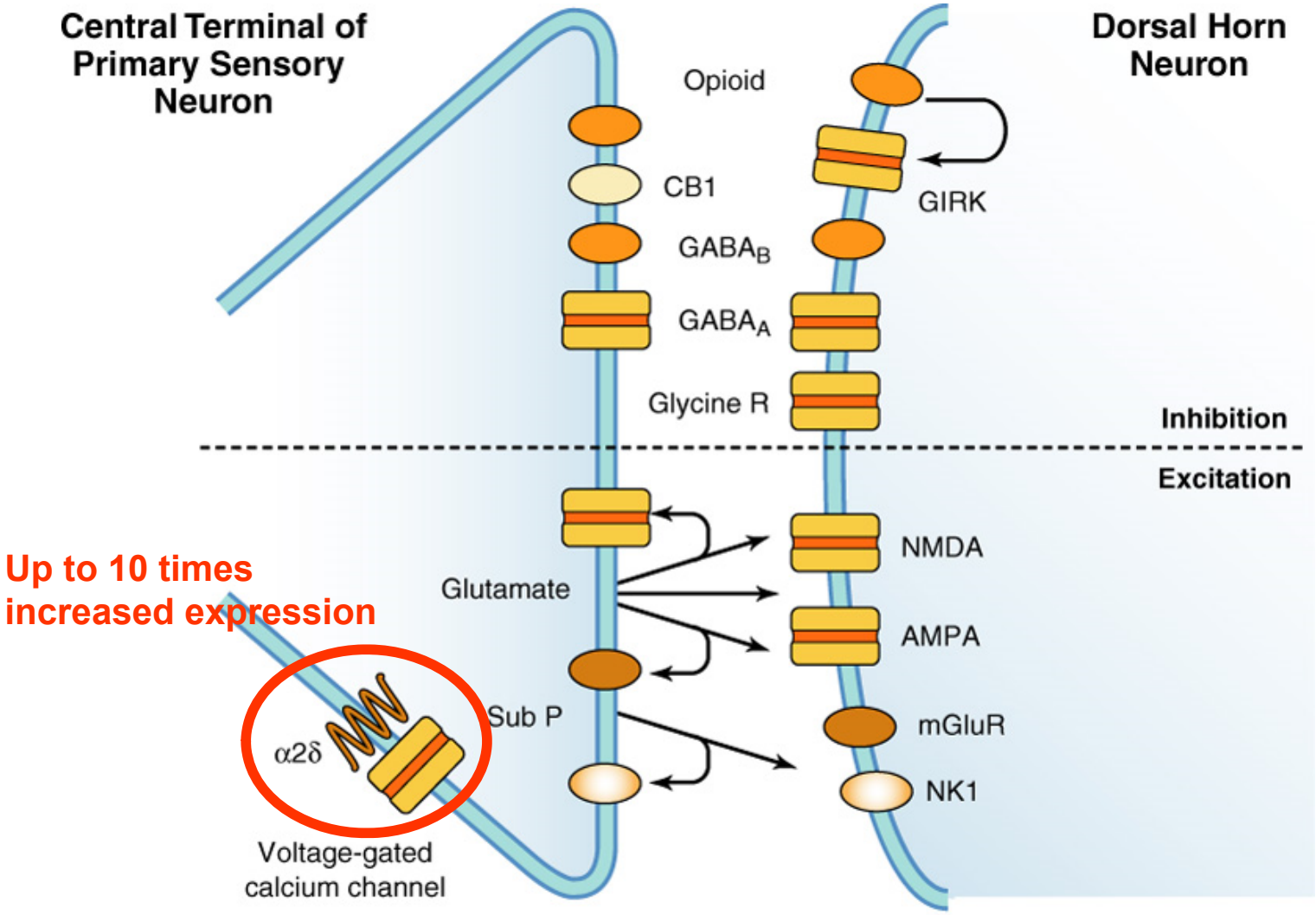




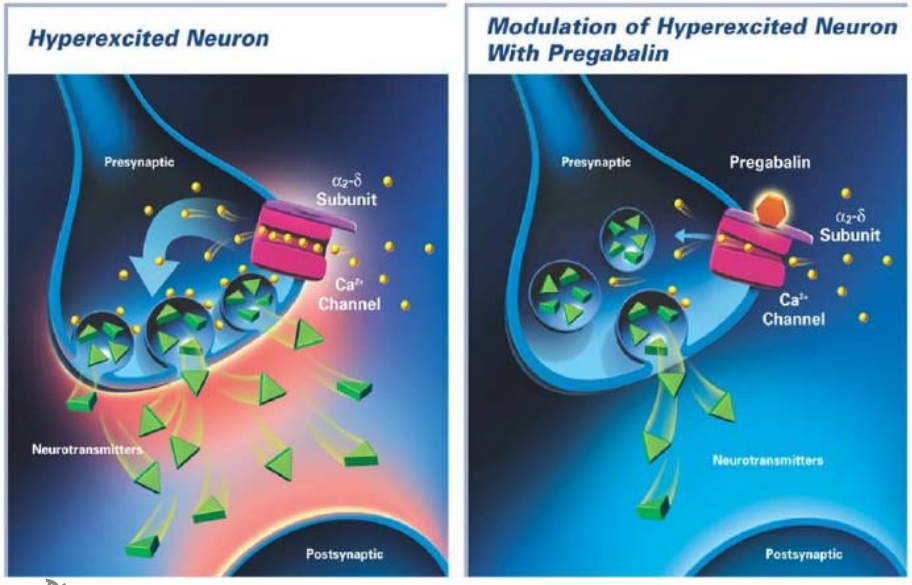
Fibromialgia e neuropatia delle piccole fibre



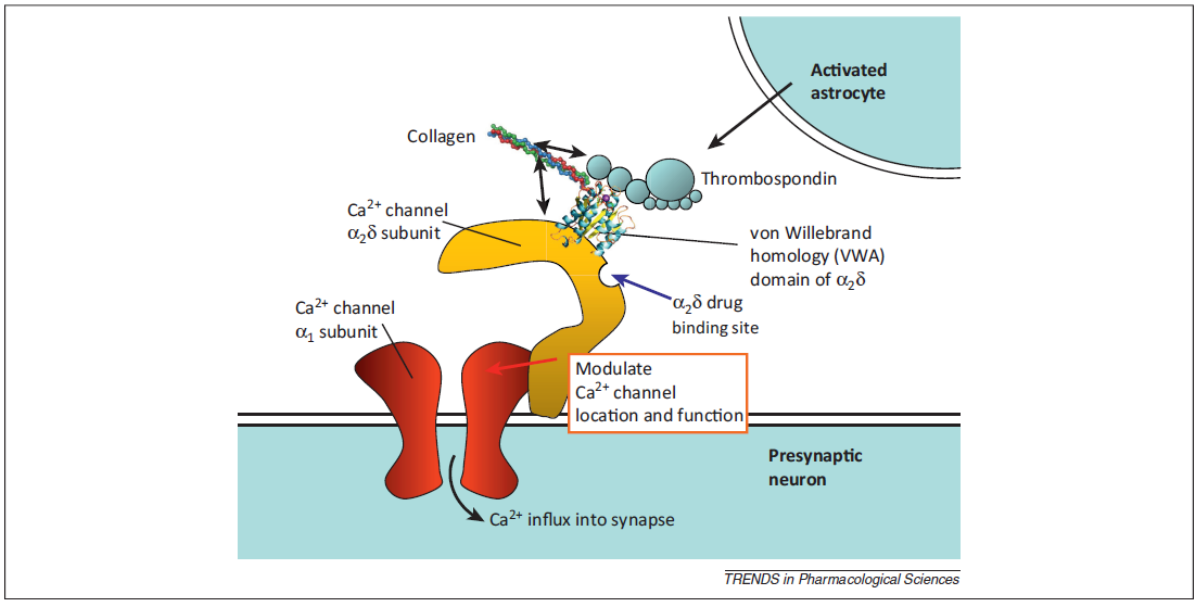
Pediatrics. 2013 Mar 11.in press. Evidence of Small-Fiber Polyneuropathy in Unexplained, Juvenile-Onset, WidespreadPain Syndromes.
Oaklander AL, Klein MM.



Up to 10 times increased expression



Diego Fornasari



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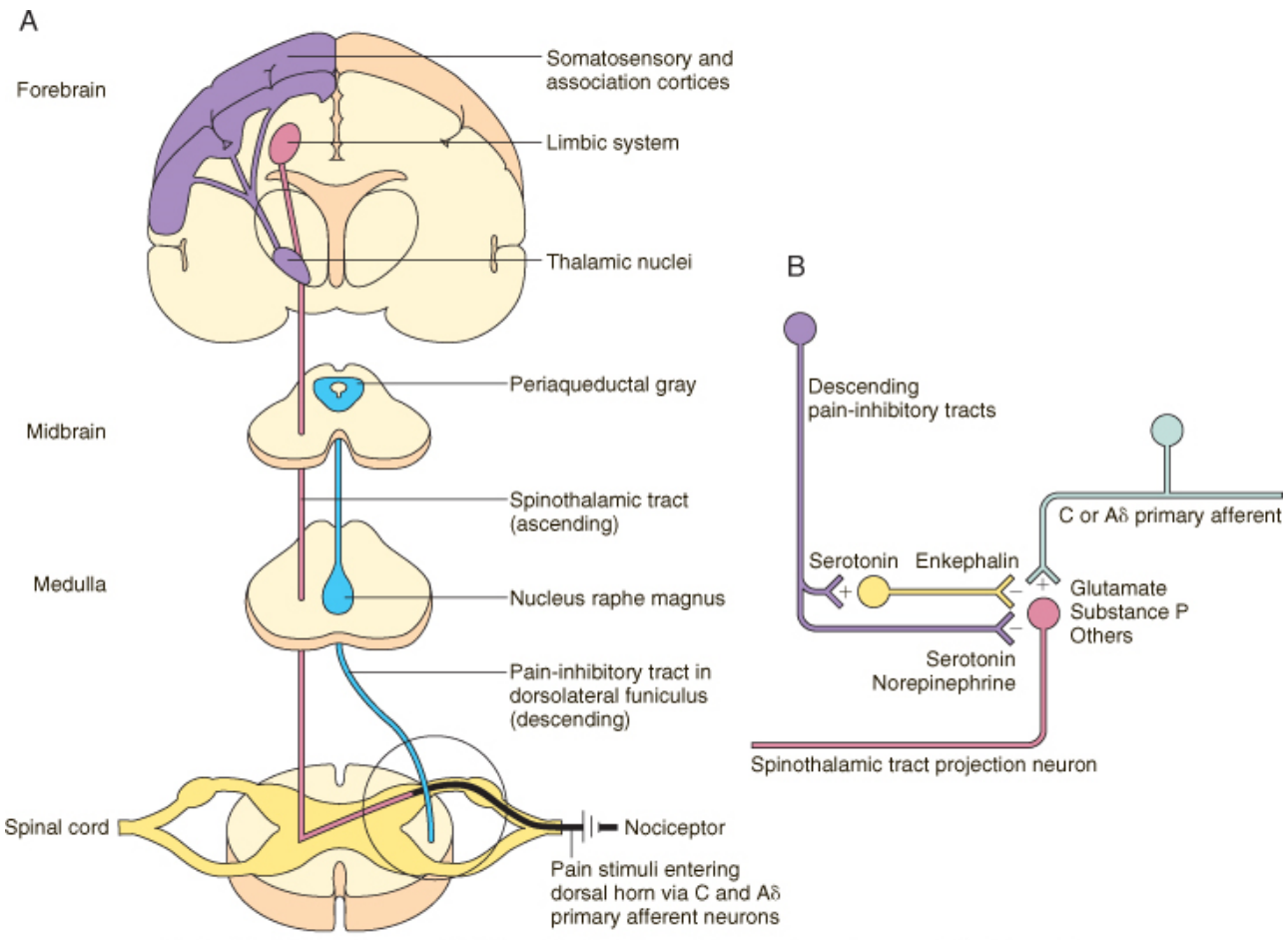
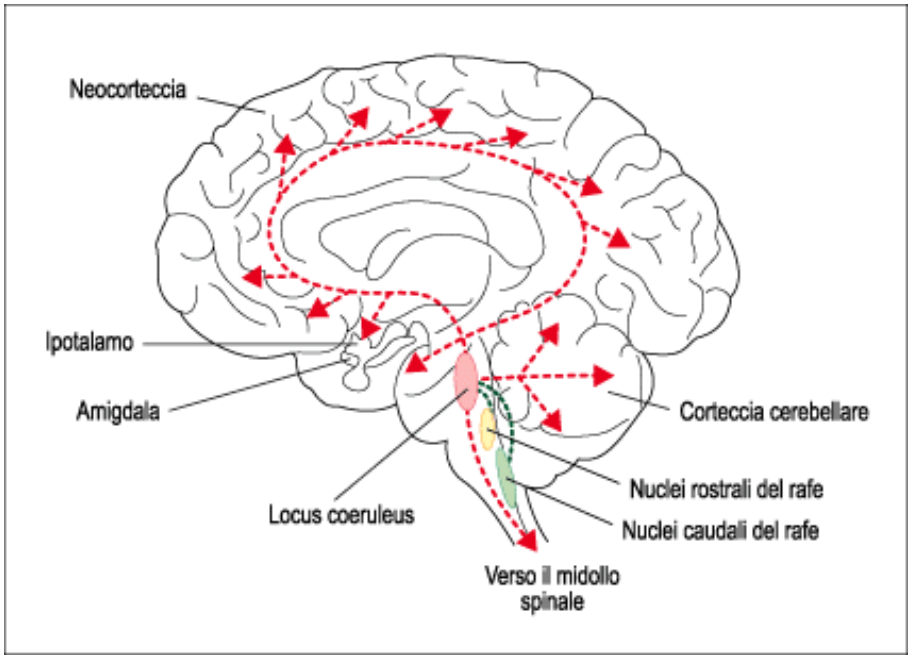
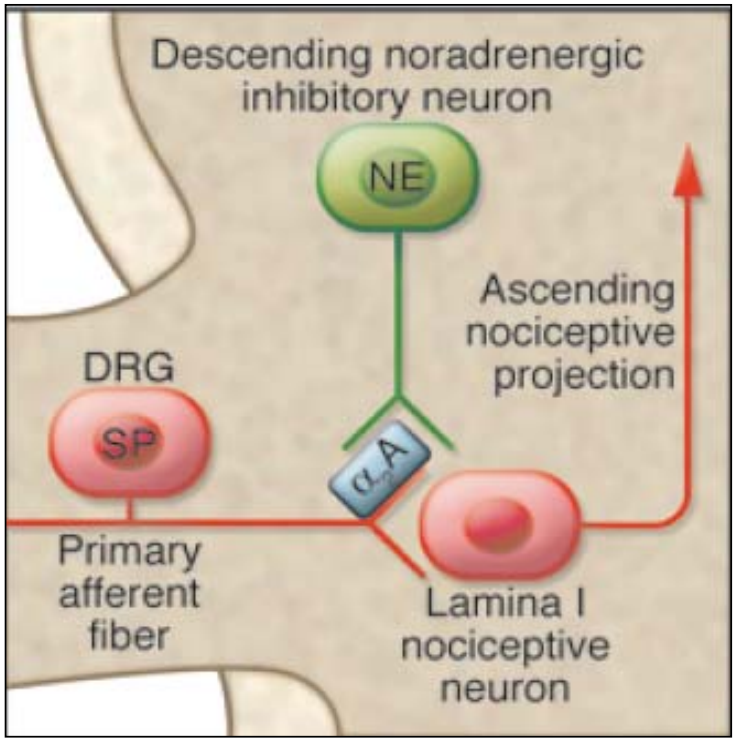
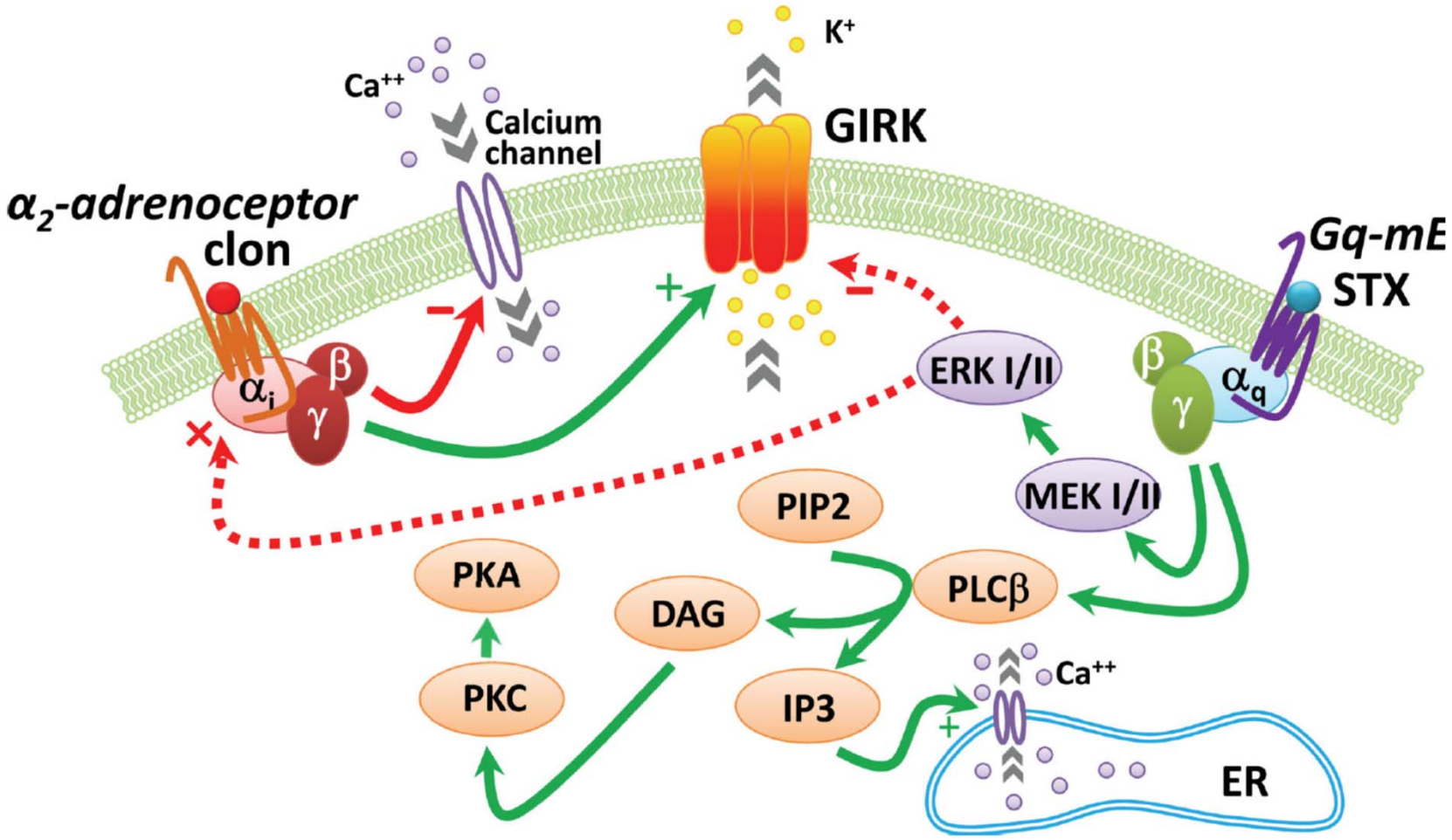
Ann Intern Med. 2007;146:726-734.

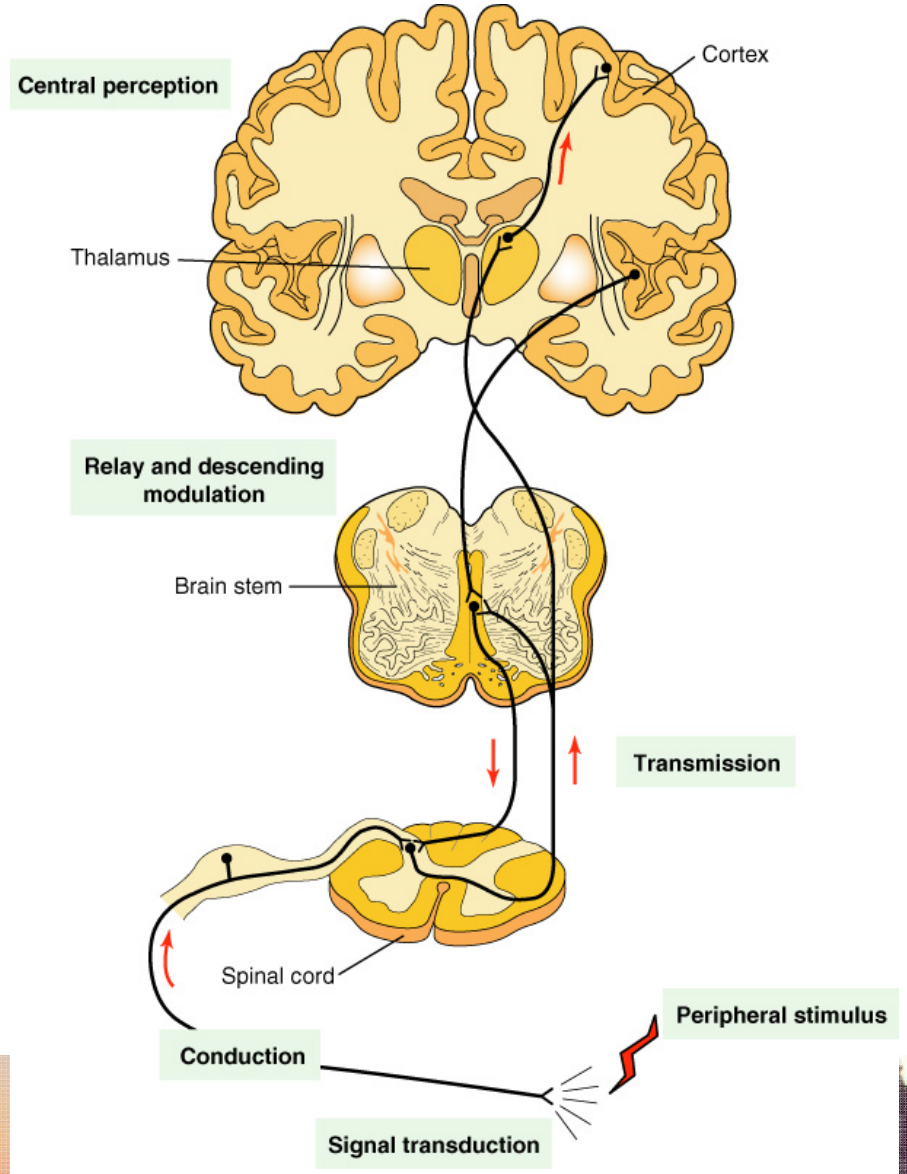


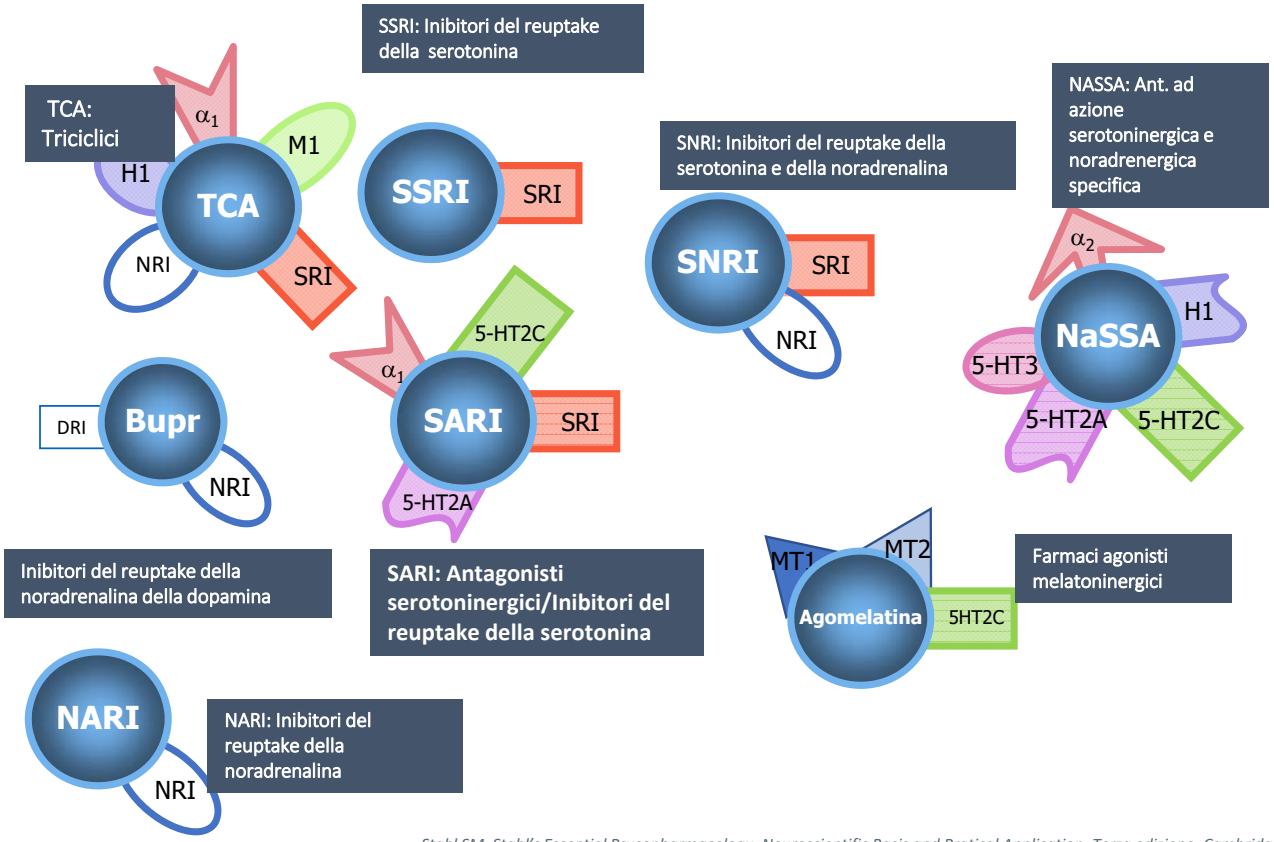

Neocorteccia
Ipotalamo
Amigdala
Locus coeruleus
Corteccia cerebellare
Nuclei rostrali del rafe
Nuclei caudali del rafe
Verso il midollo spinale


Descending noradrenergic inhibitory neuron
NE
Ascending nociceptive projection
DRG
SP
α_2A
Primary afferent fiber
Lamina I nociceptive neuron



Neuroscience. 2014 May 16; 267: 122–134

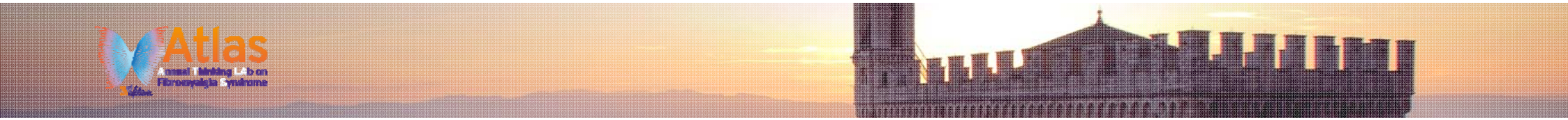




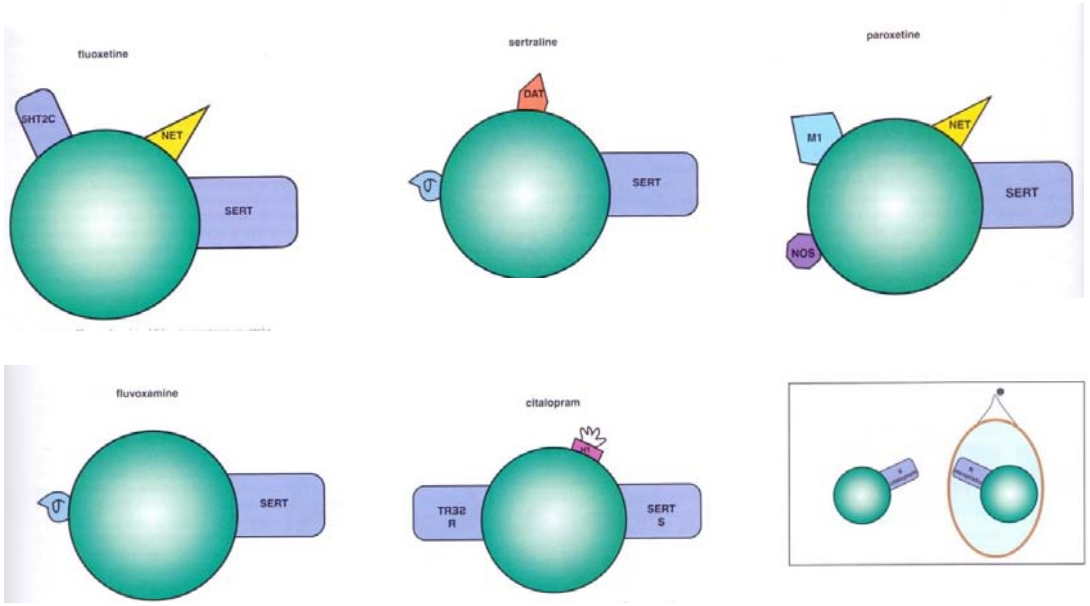
Stahl SM. Stahl's Essential Psycopharmacology. Neuroscientific Basis and Pratical Application. Terza edizione. Cambridge University Press. 2008

ANTIDEPRESSIVI

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

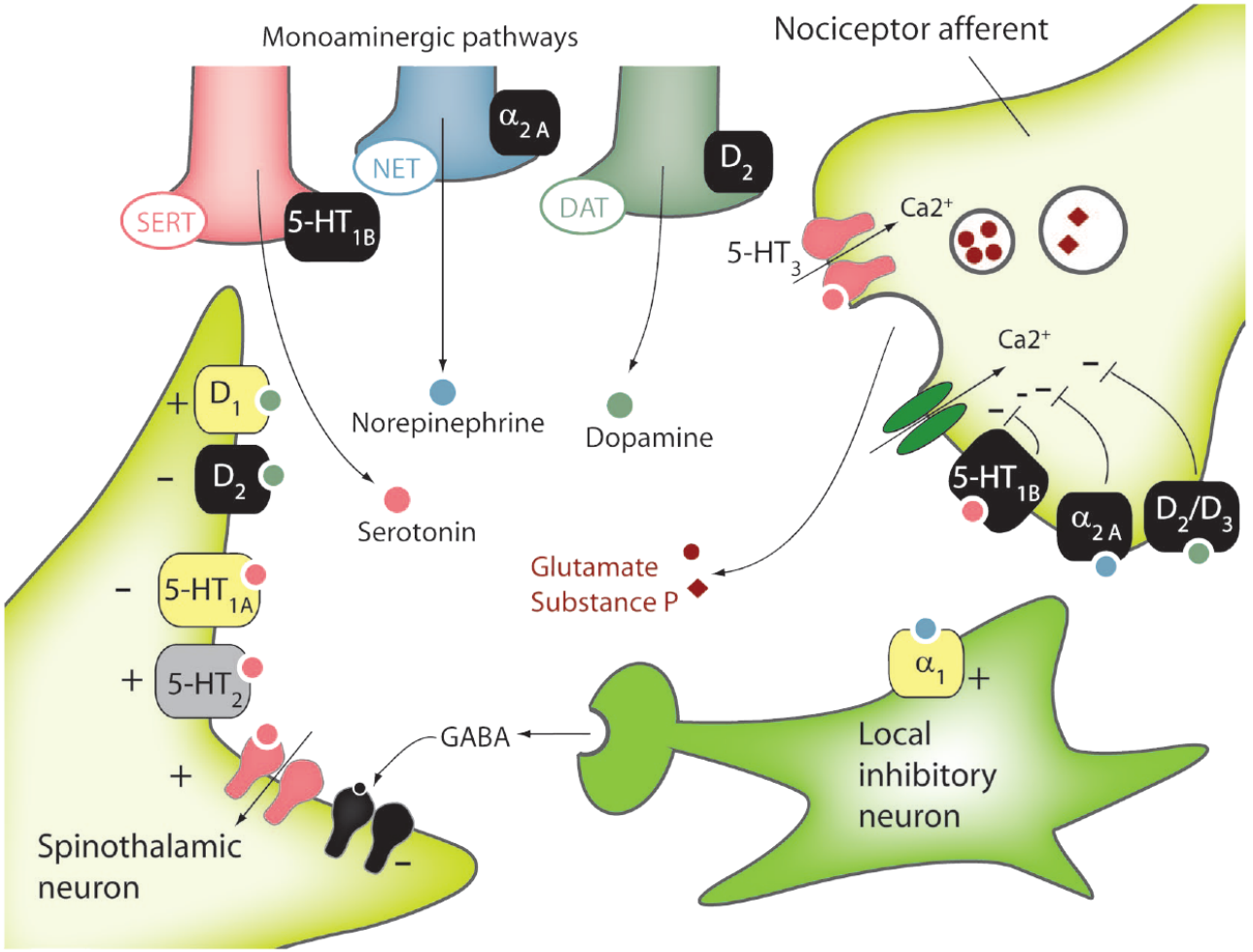


SSRI

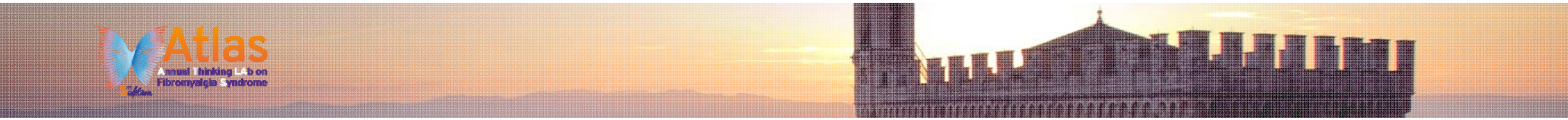


Stahl SM. St[illegible]al Psycopharmacology. Neuroscientific Basis and Pratical Application. Terza [illegible]

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



Pharmacological treatments				
Selective serotonin-norepinephrine reuptake inhibitors (SNRIs)		Alleviate pain, fatigue, and sleep disturbances associated with fibromyalgia	Demonstrated effectiveness in reducing pain and fatigue and improving quality of life. Well-tolerated and effective for managing multiple symptoms.	Arnold LM et al. (2008) [16]; Clauw DJ et al. (2008) [17]; Mease PJ et al. (2009) [18]; Arnold LM et al. (2005) [19]; Arnold LM et al. (2010) [20]; Murakami M et al. (2015) [21]; Arnold LM et al. (2009) [22]
Anticonvulsants	Pregabalin	Reduce pain, sleep disturbances, and anxiety associated with fibromyalgia	Demonstrated effectiveness in reducing pain, improving sleep patterns, and reducing fatigue. Adverse effects include dizziness and somnolence.	Ohta H et al. (2012) [23]; Crofford LJ et al. (2005) [24]; Derry S et al. (2016) [25]
	Mirogabalin	Potential treatment for fibromyalgia	Effective in reducing pain and improving sleep quality. Associated with central nervous system side effects.	Arnold LM et al. (2019) [26]; Chen EY et al. (2021) [27]
	Lacosamide	Potential analgesic effects	More effective than the placebo in reducing pain and improving sleep quality. Adverse effects include dizziness, nausea, and tremor.	Hearn L et al. (2012) [28]; Zaccara G et al. (2013) [29]
Cannabidiol (CBD) and tetrahydrocannabinol (THC)		Interact with the endocannabinoid system to regulate pain, mood, and sleep	Effective in reducing pain, improving sleep quality, and reducing anxiety and depression. Potential side effects include dizziness and dry mouth.	Khurshid H et al. (2021) [30]; Habib G, Artul S (2018) [31]; Sagy I et al. (2019) [32]; Walitt B et al. (2016) [33]; Bourke SL et al. (2022) [34]; Chaves et al. (2020) [35] Bhaskar A et al. (2021) [36]
Tropisetron		5-HT3 receptor antagonist	More effective than placebo in reducing pain and fatigue, and improving sleep quality.	Haus U et al. (2000) [37]; Stratz T et al. (2001) [38]; Späth M et al. (2004) [39]; Arnold LM (2006) [40]
Sodium oxybate		Central nervous system depressant	Effective in reducing pain, fatigue, and sleep disturbance. Common side effects include nausea, dizziness, and vomiting.	Staud R (2011) [41]; Russell JI et al. (2011) [42]; Spaeth M et al. (2012) [43]; Spaeth M et al. (2013) [44]



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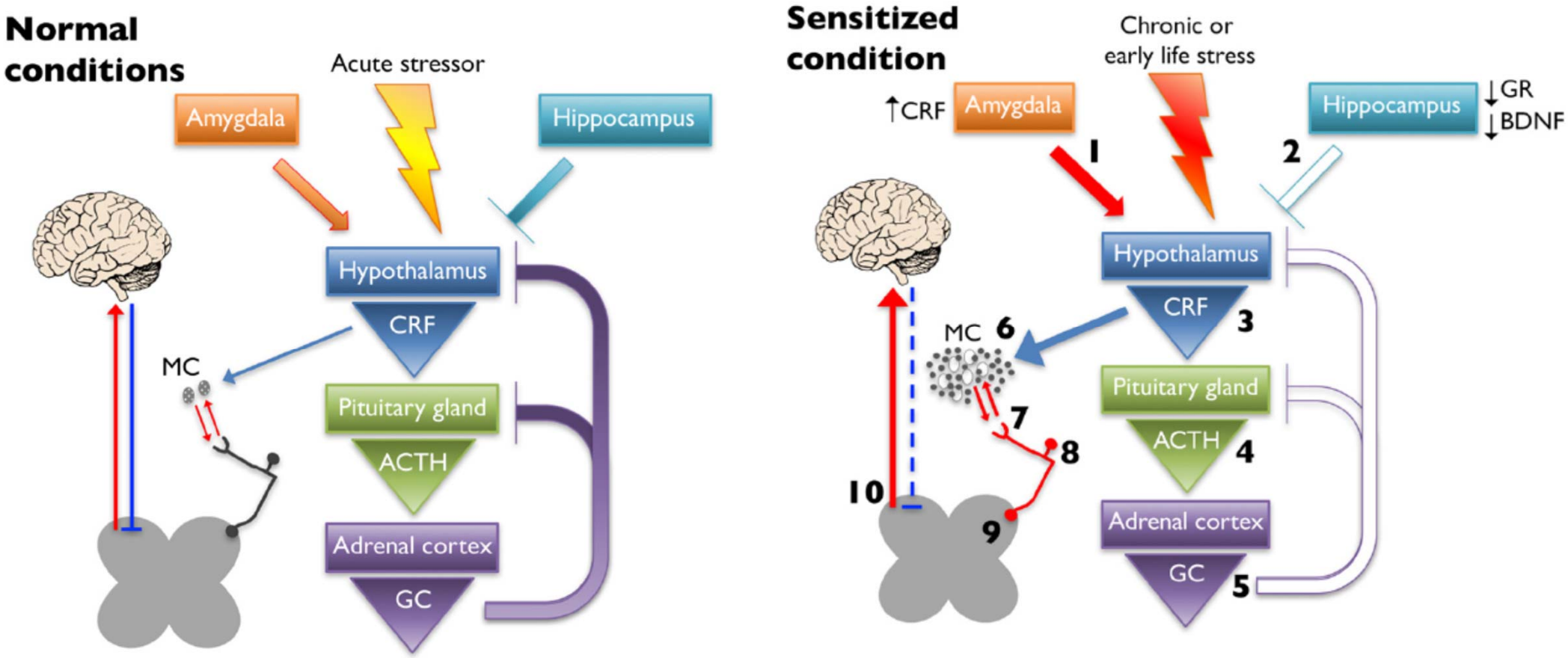
Ann Intern Med. 2007;146:726-734.

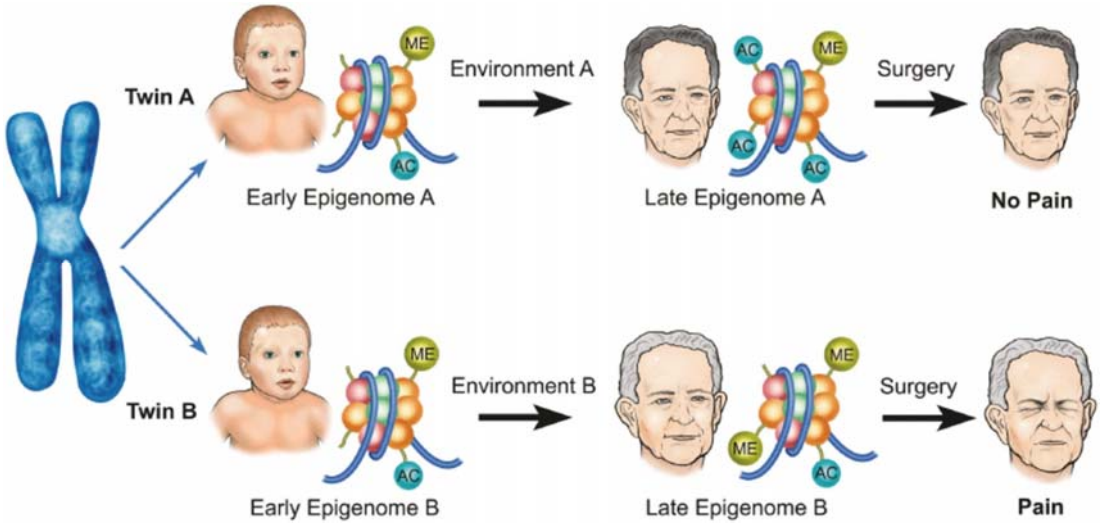
CENTRALIZED PAIN



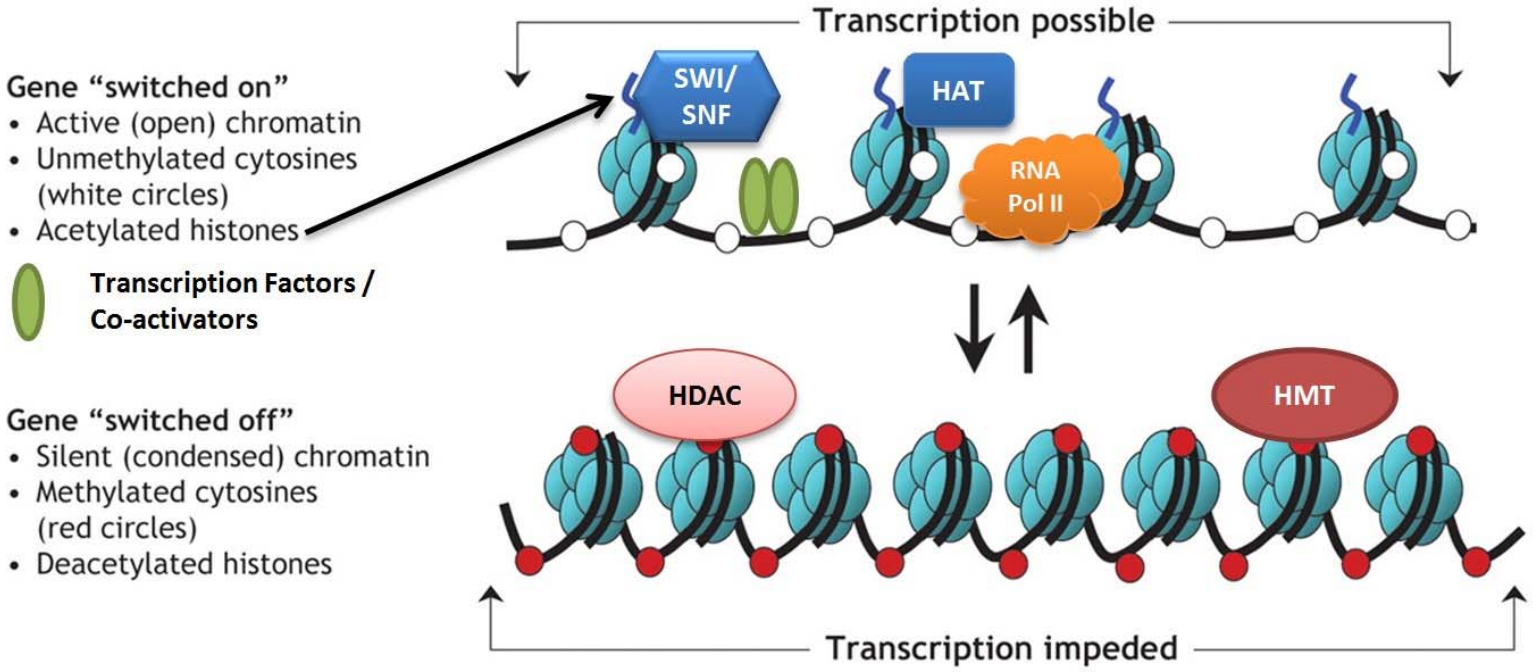
Front. Cell. Neurosci. 12: art. 35, 2018

Figure 7-87 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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



Pain Medicine, Volume 13, Issue 11, November 2012, Pages 1474–1490, https://doi.org/10.1111/j.1526-4637.2012.01488.x

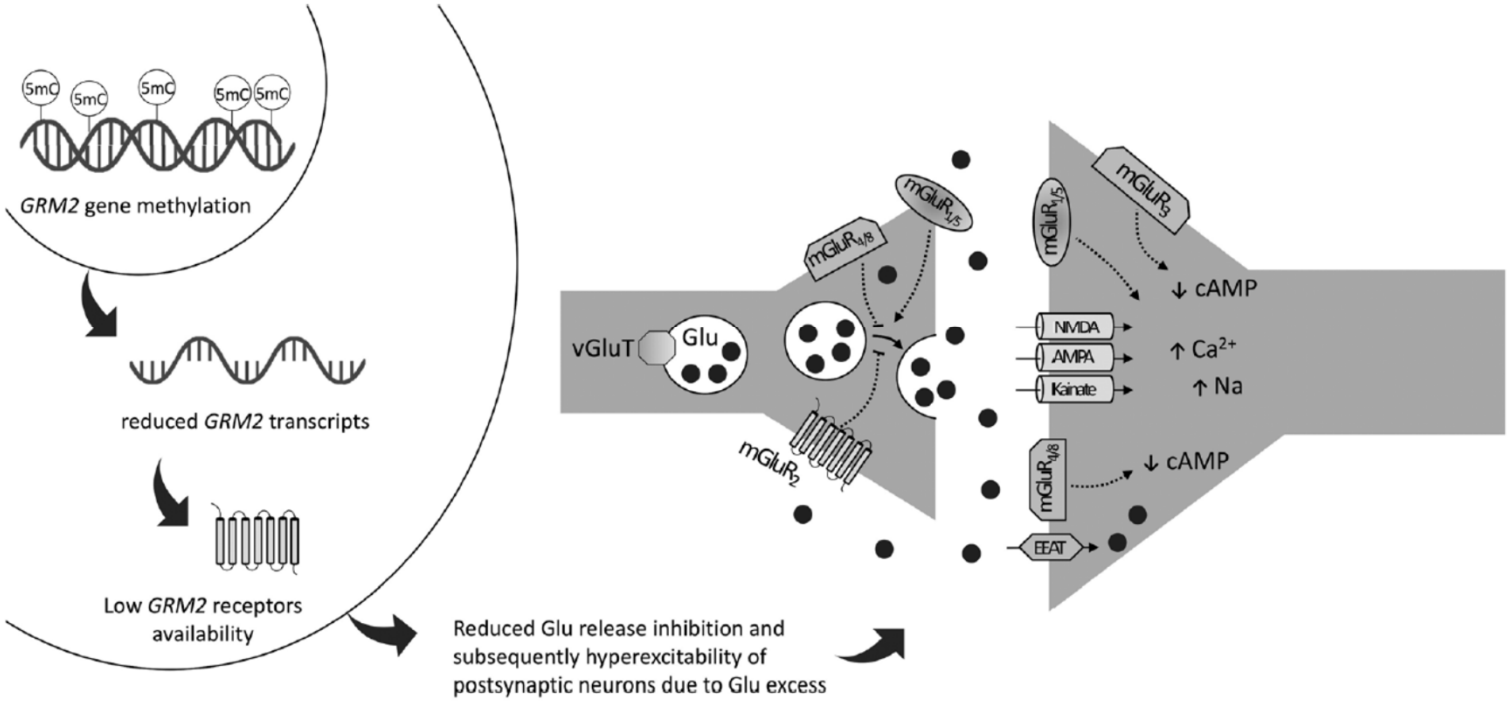

Transcription possible
Gene "switched on"
• Active (open) chromatin
• Unmethylated cytosines (white circles)
• Acetylated histones
Transcription Factors / Co-activators
SWI/ SNF
HAT
RNA Pol II
Gene "switched off"
• Silent (condensed) chromatin
• Methylated cytosines (red circles)
• Deacetylated histones
HDAC
HMT
Transcription impeded

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



Scand J Pain 2021; 21(2): 372–383

Pharmacological Research 173 (2021) 105874

Contents lists available at ScienceDirect

Pharmacological Research

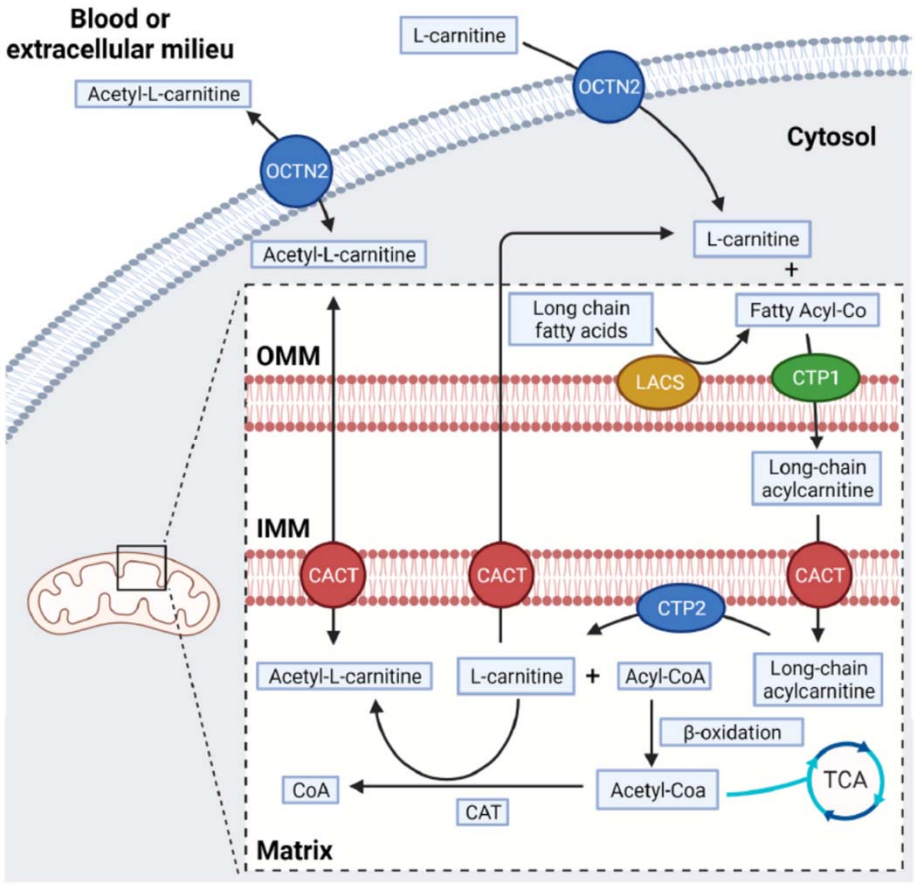
journal homepage: www.elsevier.com/locate/yphrs

Review

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

Piercarlo Sarzi-Puttini [a], Valeria Giorgi [a,*], Simona Di Lascio [b], Diego Fornasari [b]

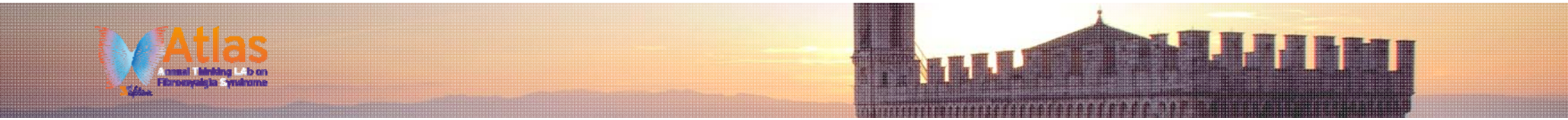
[a] Rheumatology Unit, ASST Fatebenefratelli Luigi Sacco University Hospital, Milan, Italy
[b] Department of Medical Biotechnology and Molecular Medicine, Università degli Studi di Milano, Milan, Italy



Pharmacol Res. 2021 Nov;173:105874.

INDICAZIONI TERAPEUTICHE DELLA LAC (da scheda tecnica):

Lesioni meccaniche e infiammatorie tronculari e radicolari del nervo periferico



MAYO CLINIC: TRATTAMENTO NEL DOLORE NEUROPATICO

Trattamenti di 1° linea

orali

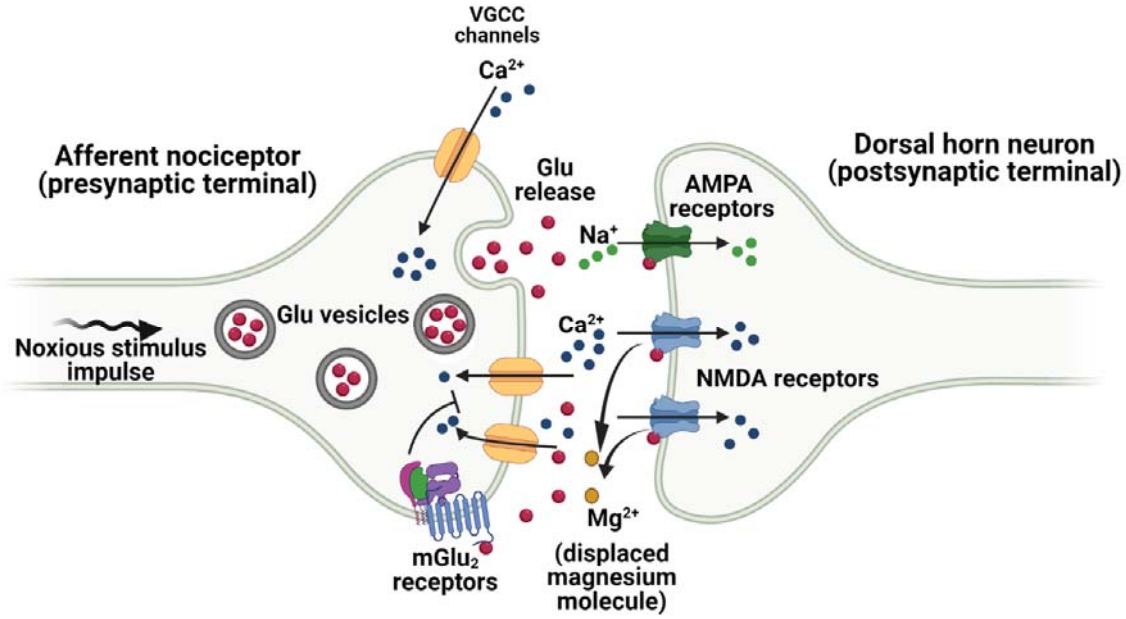
Anticonvulsants		
Gabapentin[b]	300 mg at bedtime, increase every 4-7 d by 300-mg increments initially to 3 times daily, then to goal of 1800 mg/d as necessary to 3600 mg/d	3600 mg/ d (split TID)
Pregabalin[b]	75 mg twice daily; after 4-7 d, increase by same dosage to goal of 300 mg/d as necessary to 600 mg/d	600 mg/d (split BID)
Antidepressants		
Amitriptyline, nortriptyline[b]	10-25 mg at bedtime, increase every 4-7 d to goal of 100 mg at bedtime	150 mg/d
Duloxetine[b]	20-30 mg once daily, then increase weekly by same dosage to goal of 60 mg/d	120 mg/d (split BID)
Supplements		
α-Lipoic acid	600 mg once daily	600 mg/d
Acetyl-L-carnitine	1000 mg 3 times per day	3000 mg/d (split TID)

Capsaicin (8%) patch	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

Fra i trattamenti di PRIMA LINEA è raccomandata:

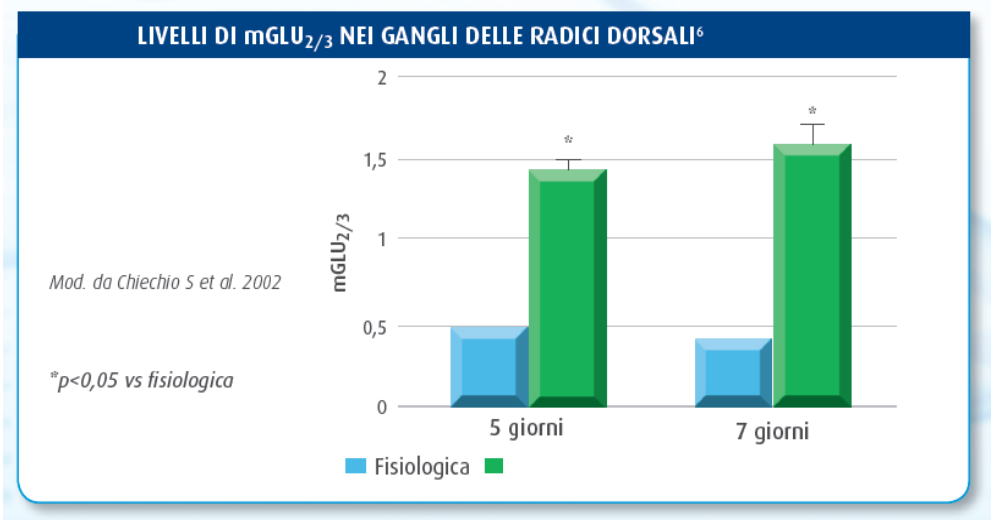
❖**ALC 3 g/die (negli US non è disponibile ALC im)**

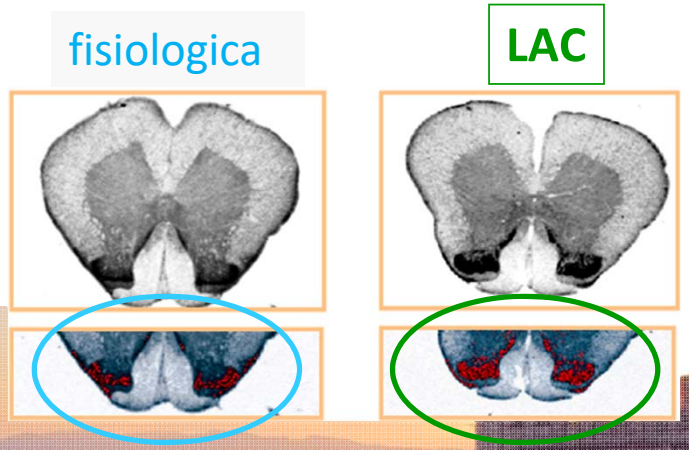
 ■ Mayo Clin Proc. 2015;90(7):940-951



Pharmacol Res. 2021 Nov;173:105874.

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





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

Mol Pharmacol. 2002 May;61(5):989-96.

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

Research Article

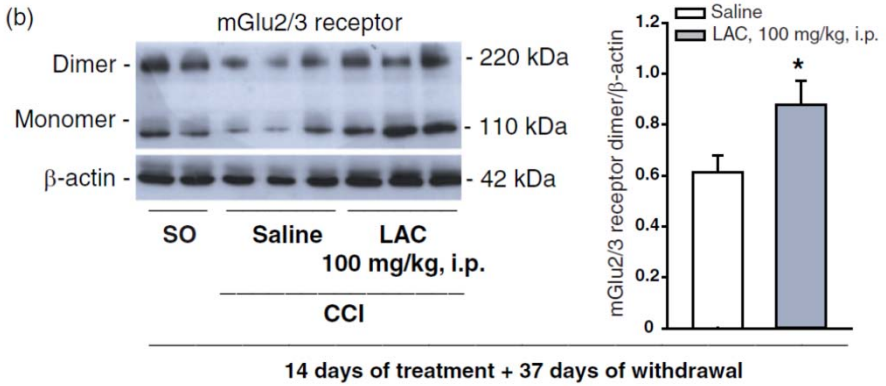
MOLECULAR PAIN

Molecular Pain
Volume 13: 1–12

DOI: 10.1177/1744806917697009
journals.sagepub.com/home/mpx
SAGE

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

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

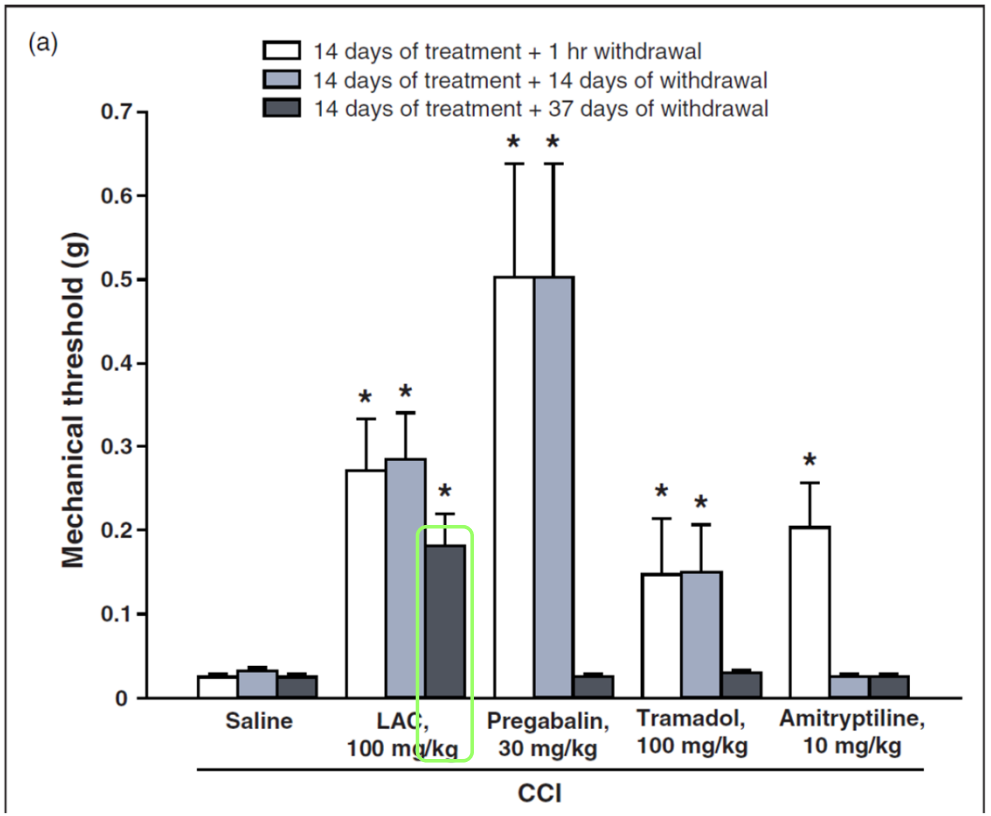


Studio su modello di Dolore Neuropatico da compressione cronica (CCI).

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

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 ALC ha ancora effetto antiallodinico.

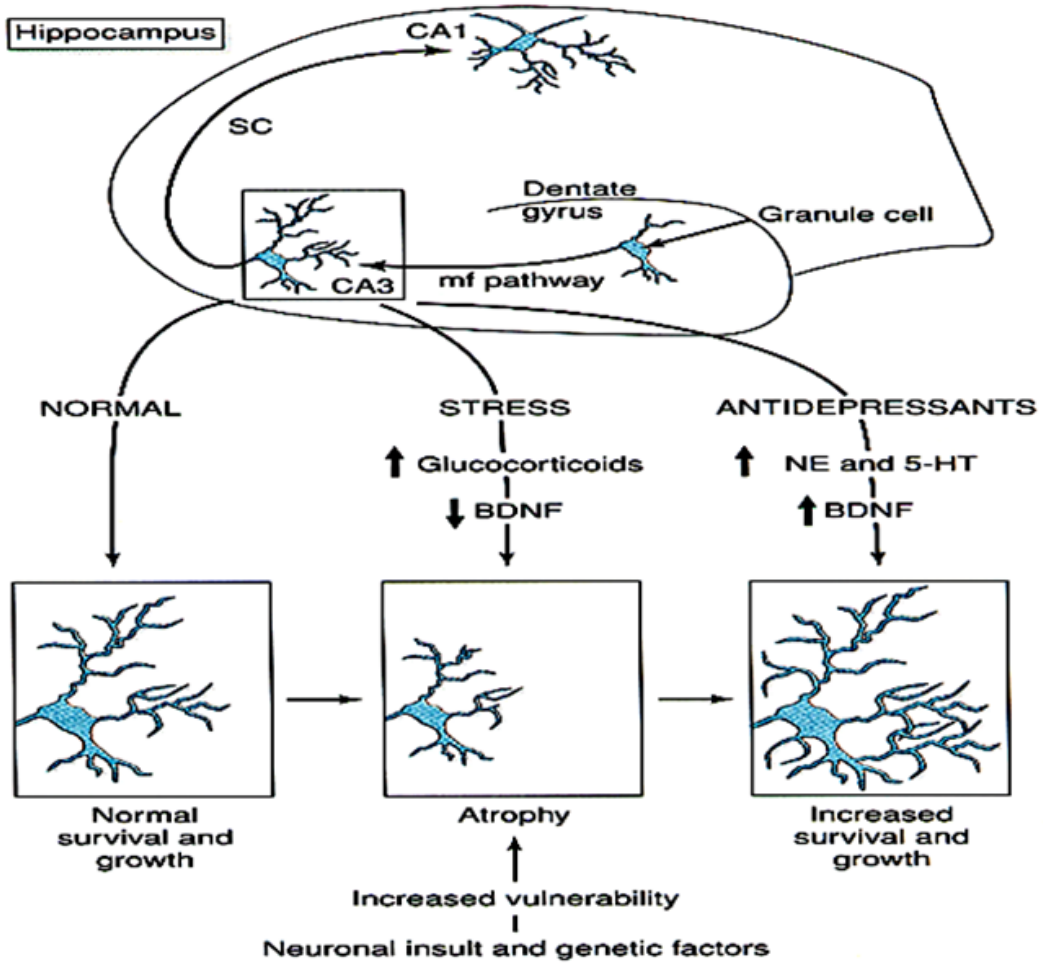
Notartomaso, Molecular Pain 2017

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.

Azione antidepressiva di LAC


Hippocampus
CA1
SC
Dentate gyrus
Granule cell
CA3
mf pathway
NORMAL
STRESS
ANTIDEPRESSANTS
Glucocorticoids
BDNF
NE and 5-HT
BDNF
Normal survival and growth
Atrophy
Increased survival and growth
Increased vulnerability
Neuronal insult and genetic factors

PRINCIPAL FIBROMYALGIA SYMPTOMS

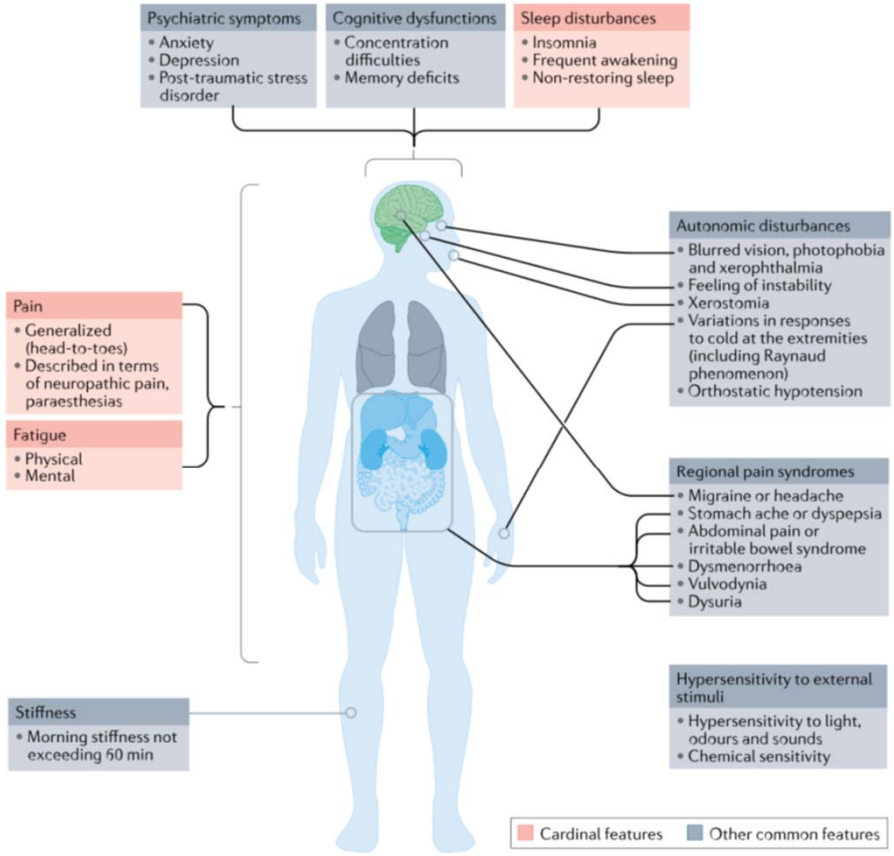
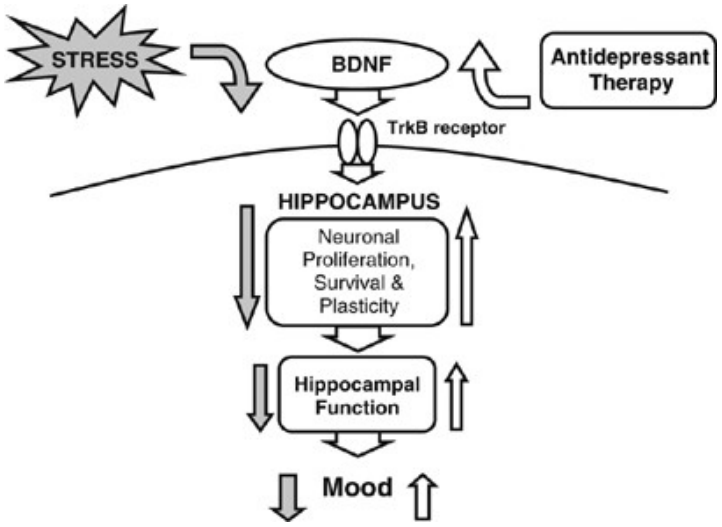


Fig. 2 | **Principal fibromyalgia symptoms.** Fibromyalgia has a complex symptomatology. Symptoms can be are divided in two groups: cardinal features (shown in pink), which include the most characteristic fibromyalgia symptoms that are pivotal for a diagnosis according to the latest criteria, and other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

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


STRESS
BDNF
Antidepressant Therapy
TrkB receptor
HIPPOCAMPUS
Neuronal Proliferation, Survival & Plasticity
Hippocampal Function
Mood

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

Neuropsychopharmacology (2013) 38, 2220–2230

www.neuropsychopharmacology.org

Upregulation of mGlu2 Receptors via NF-κB p65 Acetylation Is Involved in the Proneurogenic and Antidepressant Effects of Acetyl-L-Carnitine

Bruna Cuccurazzu[1,2,4], Valeria Bortolotto[1,2,4], Maria Maddalena Valente[1,2], Federica Ubezio[1,2], Aleardo Koverech[3], Pier Luigi Canonico[2] and Mariagrazia Grilli*[,1,2]

[1]Laboratory of Neuroplasticity and Pain, University of Piemonte Orientale “A. Avogadro”, Novara, Italy; [2]Department of Pharmaceutical Sciences, University of Piemonte Orientale “A. Avogadro”, Novara, Italy; [3]University of Rome Sapienza, Rome, Italy

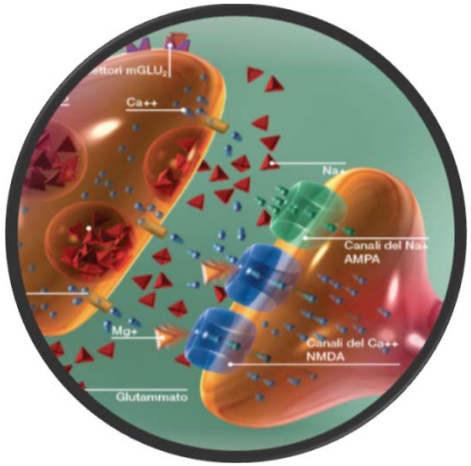
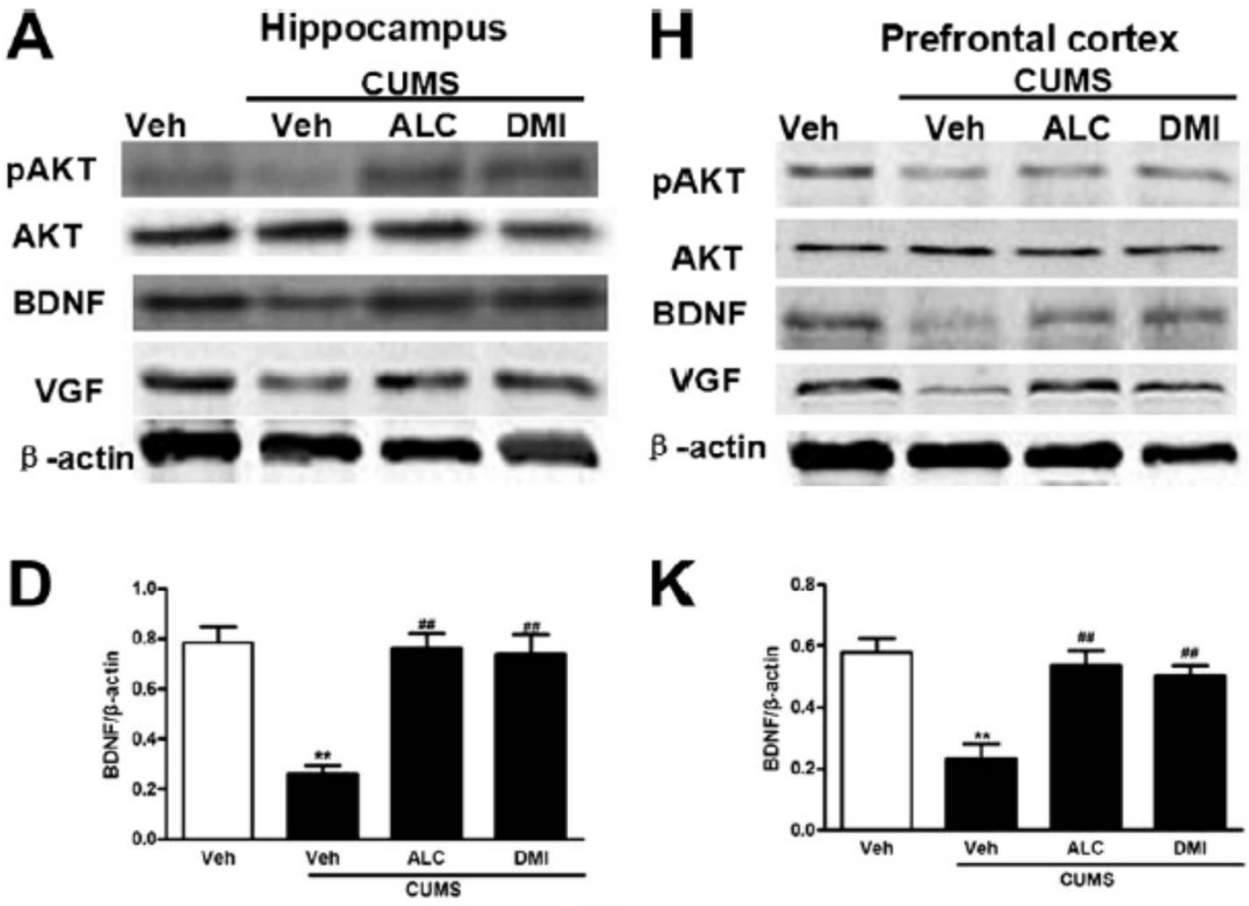


Table 1. Schedule of stressors used in the 21 days of CUMS procedure

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



Atlas
Annual Thinking LAb on Fibromyalgia Syndrome

Neuroscience 285 (2015) 281–291

L-acetil-carnitina in pazienti con dolore cronico:

effetti su depressione e tono dell'umore

International Journal of *Molecular Sciences*

MDPI

Review

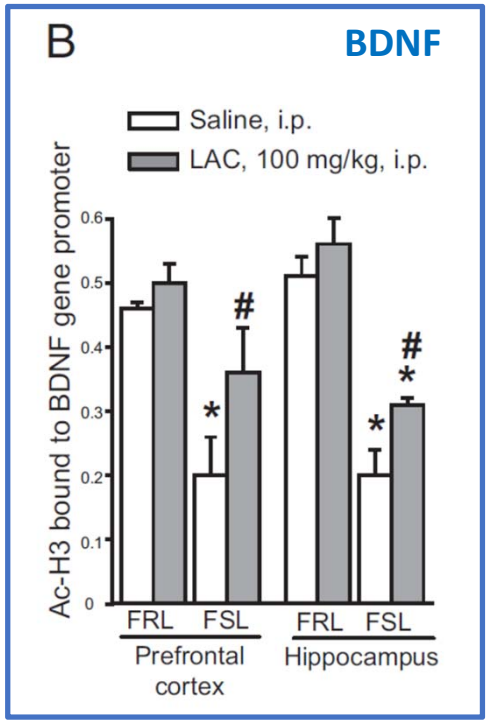
L-Acetylcarnitine: A Mechanistically Distinctive and Potentially Rapid-Acting Antidepressant Drug

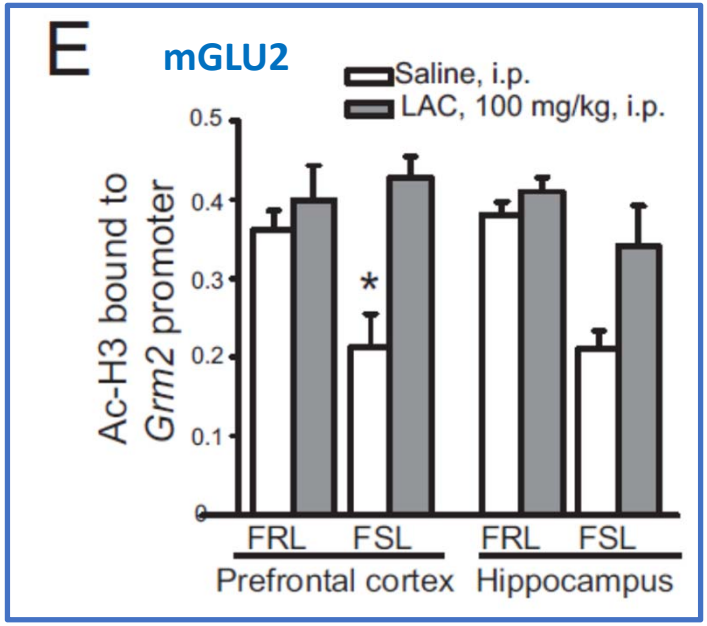
Santina Chiechio [1], Pier Luigi Canonico [2] and Mariagrazia Grilli [3,*]

[1] Department of Drug Sciences, Section of Pharmacology and Toxicology, University of Catania, 95125 Catania, Italy; chiechio@unict.it
[2] Department of Pharmaceutical Sciences, University of Piemonte Orientale, 28100 Novara, Italy; pierluigi.canonico@uniupo.it
[3] 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.

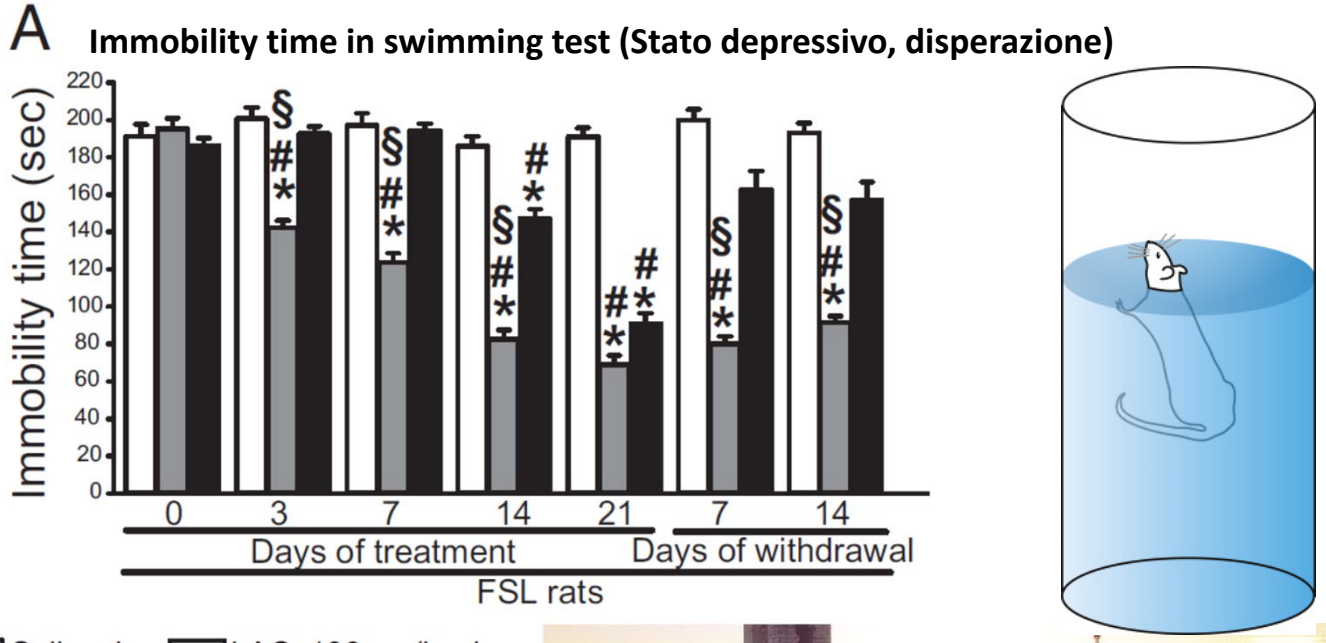




Nasca C et al. L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. Proc Natl Acad Sci U S A. 2013 Mar 19;110(12):4804-9.

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

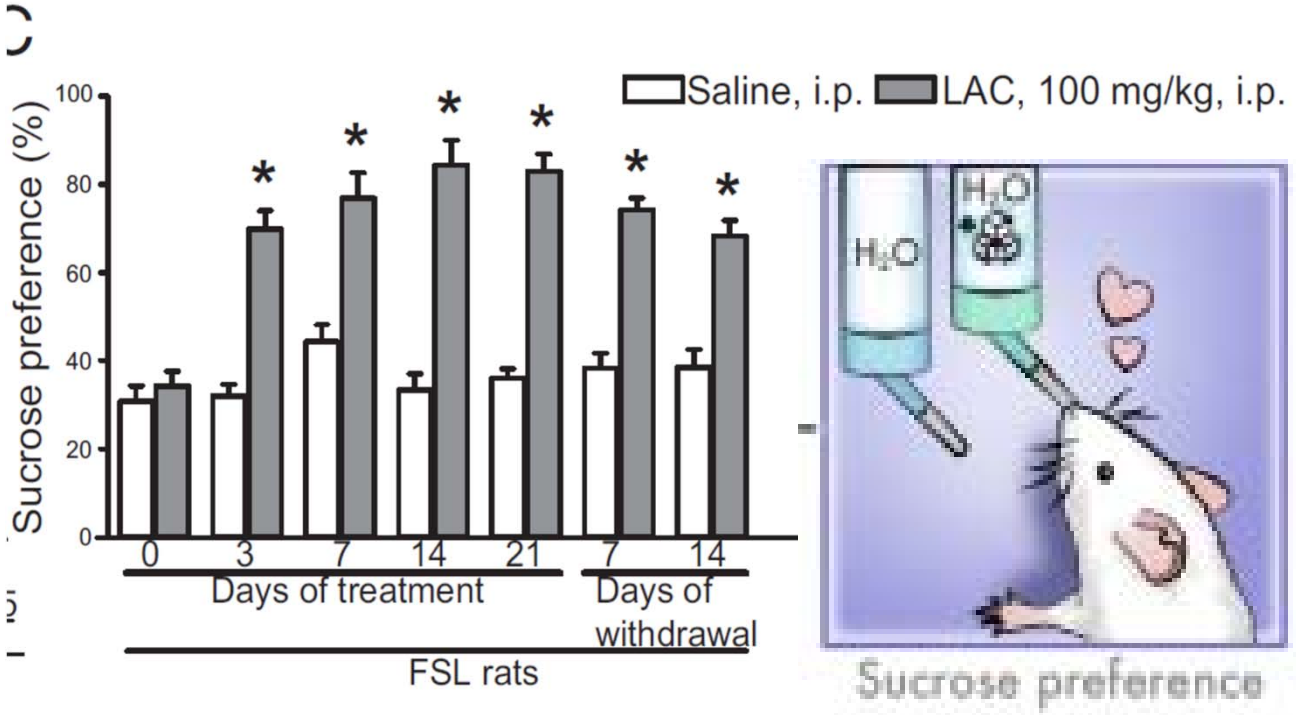


Clomipramina: antidepressivo triciclico (es. Anafranil)

Nasca C et al. Proc Natl Acad Sci U S A. 2013 Mar 19;110(12):4804-9

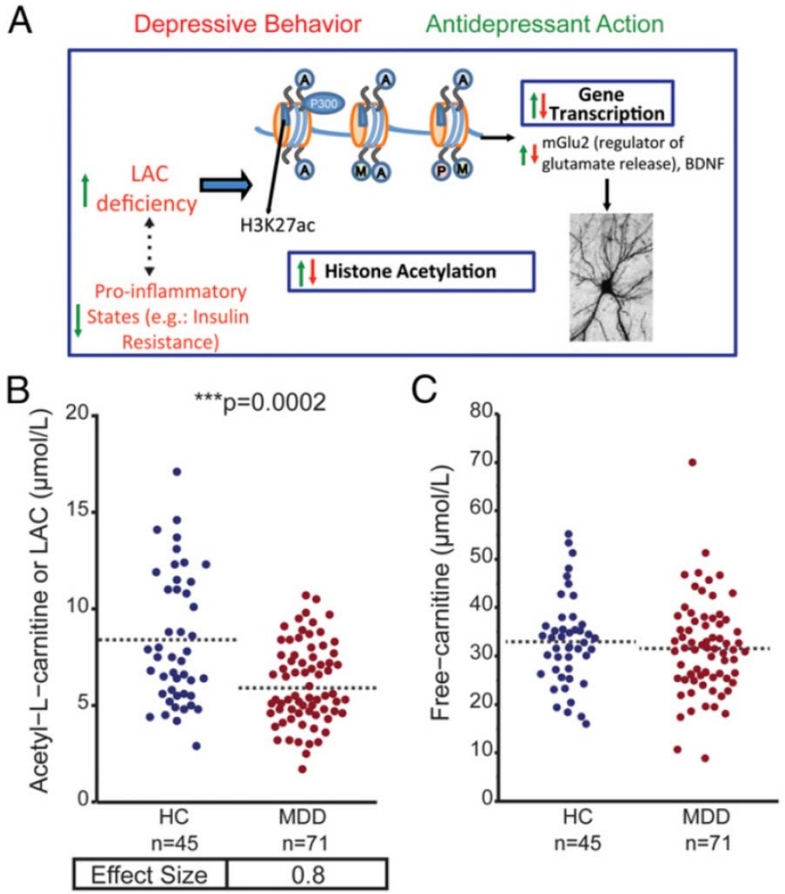
LAC migliora rapidamente e in modo marcato e prolungato lo stato di anedonia

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



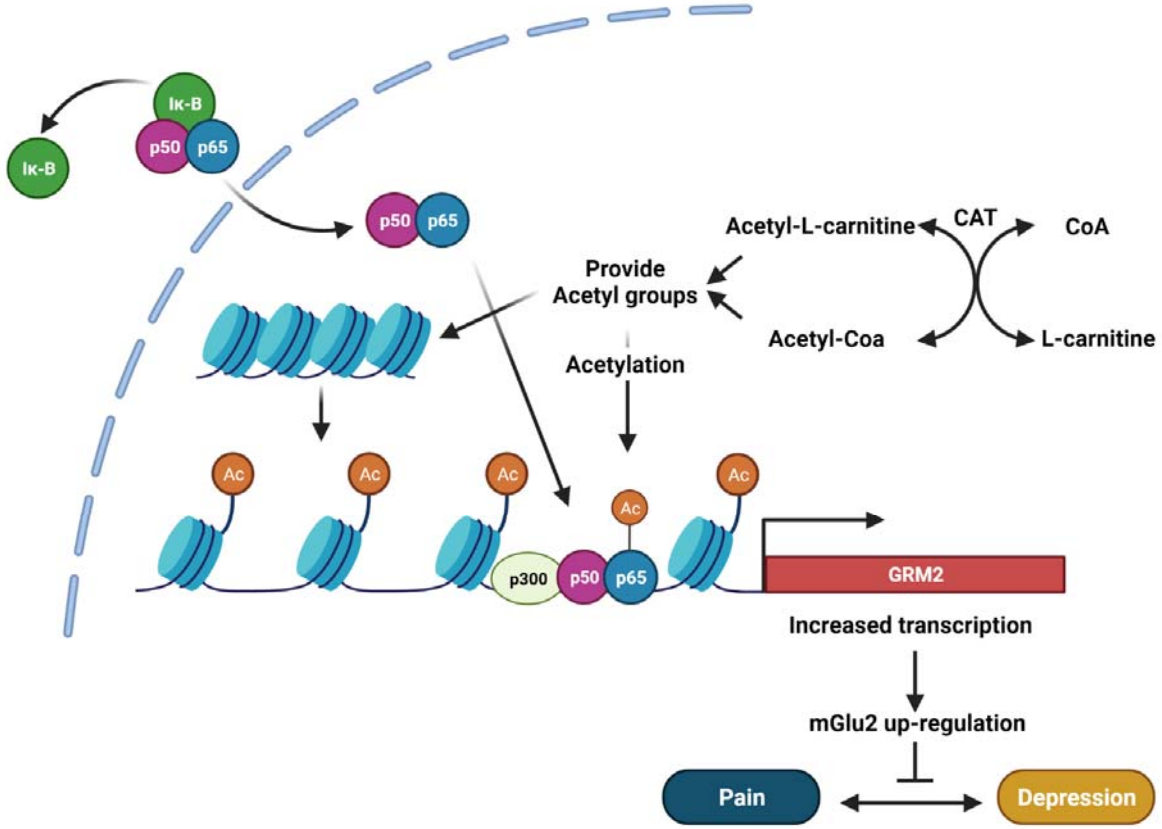
Nasca C et al. Acetyl-L-carnitine deficiency in patients with major depressive disorder. PNAS 2018;115(34):8627-8632

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 *et al.* (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 *et al.* (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 *et al.* (1993)	MDD	6	ALC (1.5 g); n = 14	PBO	ALC > PBO in HDS***	[24]
Gecele *et al.* (1991)	MDD (elderly)	6	ALC (2 g); n = 14	PBO; n = 14	ALC > PBO in HDS-17*	[27]
Fulgente *et al.* (1990)	Dysthymic disorder	8	ALC (3 g); n = 30	PBO; n = 30	ALC > PBO in HDS-17***	[30]
Garzya *et al.* (1990)	MDD (elderly)	8	ALC (1.5 g); n = 14	PBO; n = 14	ALC > PBO in HDS-17**	[26]
Bella *et al.* (1990)	Dysthymic disorder (elderly)	8	ALC (3 g); n = 30	PBO; n = 30	ALC > PBO in HDS-17****	[29]
Nasca *et al.* (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.

Wang S et al. Expert Rev Neurother 15(9), 1015–1029 (2015)



Pharmacol. Rev. 2021 *in press*

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	Decreased dopamine transmission in the brain may lead to chronic pain through unclear mechanisms
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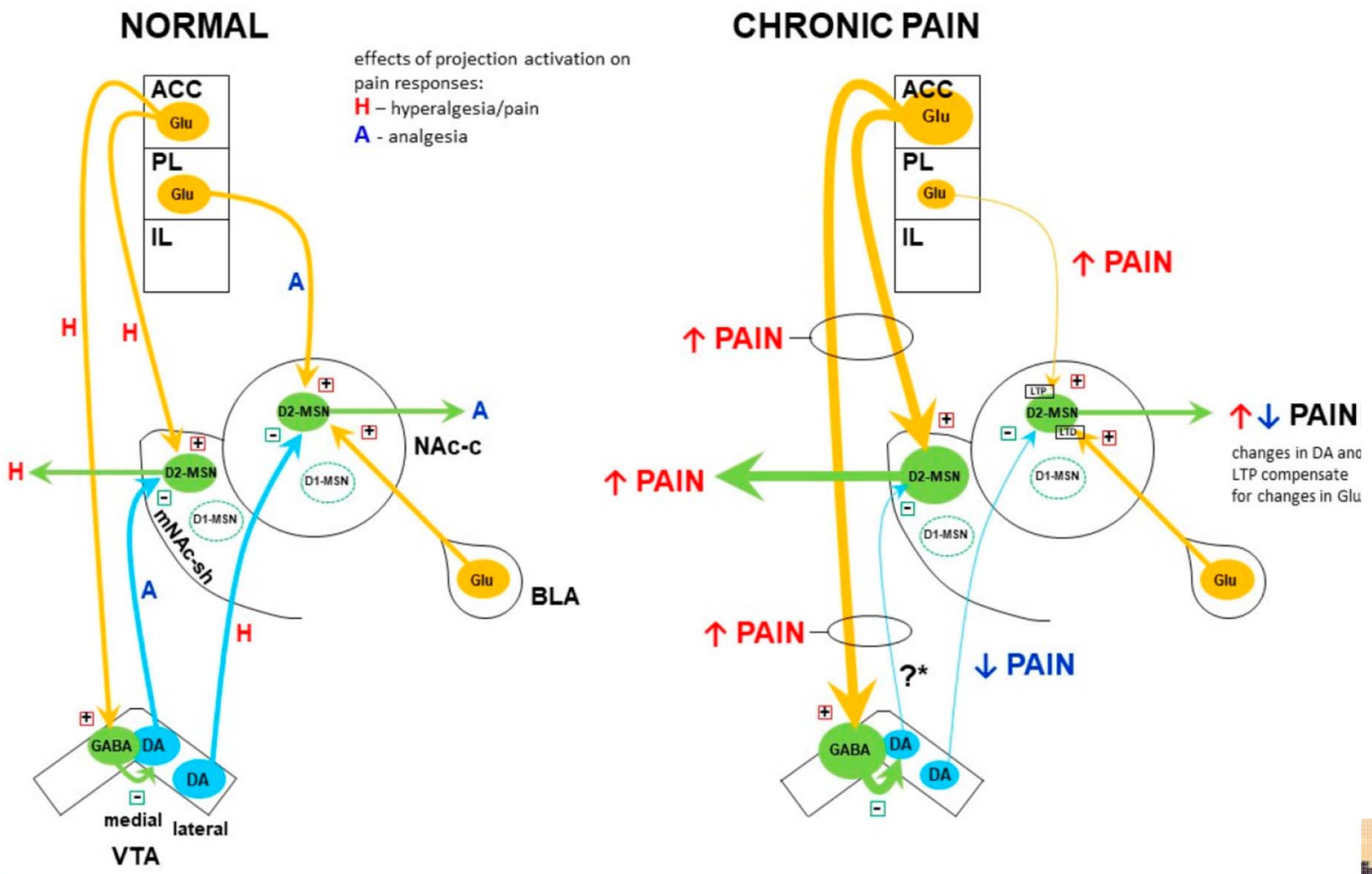
Ann Intern Med. 2007;146:726-734.

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

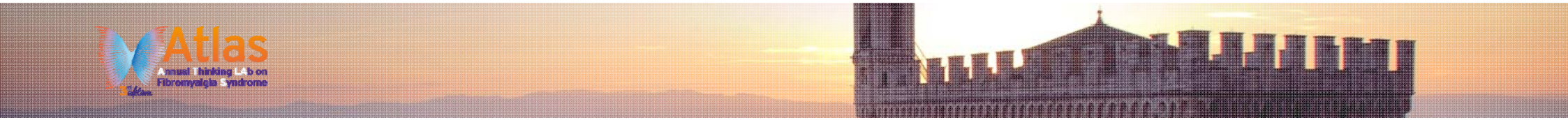


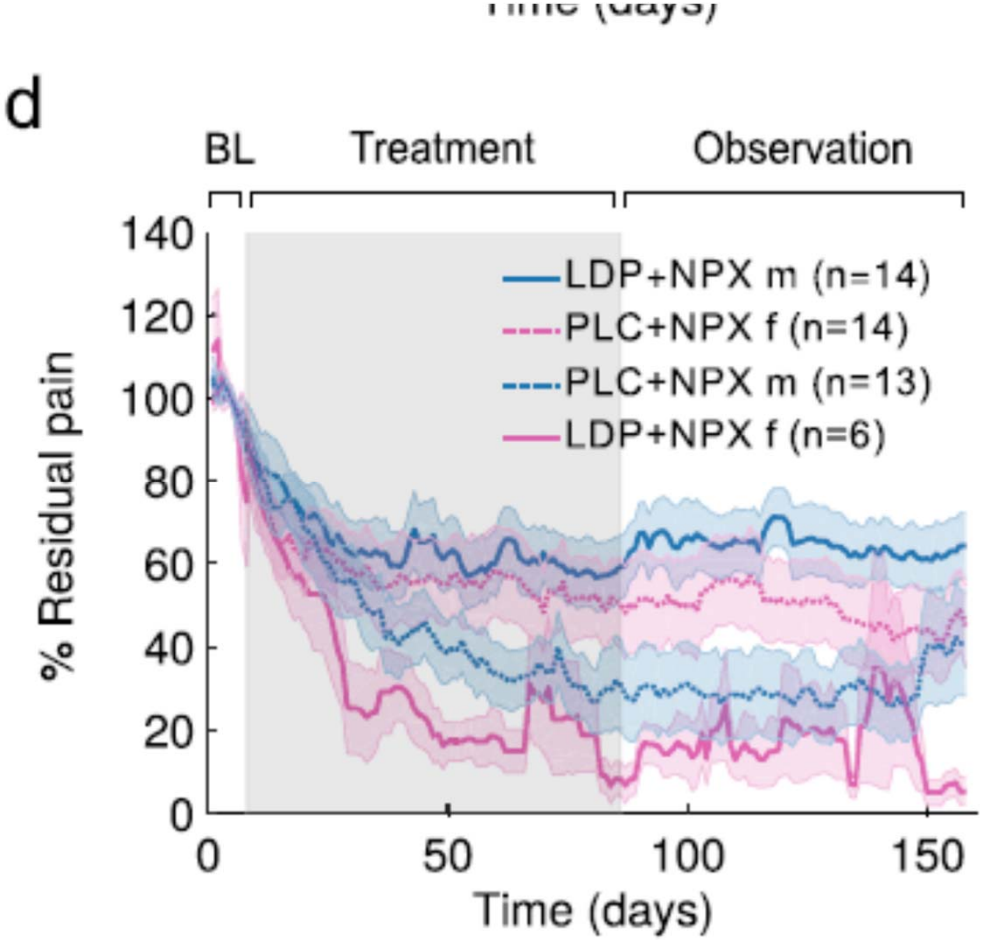
Pain Ther
https://doi.org/10.1007/s40122-021-00297-2

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-Presseau · Sara Berger · Alexis Baria · James W. Griffith · Marwan N. Baliki · Thomas J. Schnitzer · A. Vania Apkarian




d
BL
Treatment
Observation
140
120
100
80
60
40
20
0
% Residual pain
LDP+NPX m (n=14)
PLC+NPX f (n=14)
PLC+NPX m (n=13)
LDP+NPX f (n=6)
0
50
100
150
Time (days)