Atlas
Annual Thinking LAb on Fibromyalgia Syndrome

Il concetto di sensibilizzazione centrale

Prof. Enrico POLATI

DIRETTORE DIPARTIMENTO ANESTESIA, TERAPIA INTENSIVA E TERAPIA DEL DOLORE

Università degli Studi di Verona

Nhow Milano, 30 settembre - 1 ottobre 2022

Conference Report

Novel insights on the management of pain: highlights from the 'Science of Relief' meeting

Praveen Anand[1], Anthony Dickenson[2], Gabriele Finco[3], Franco Marinangeli[4], Enrico Polati[5], Patrizia Romualdi[6], Thomas M Tzschentke[7] & Pier Luigi Canonico*[,8]
[1]Department of Neurology, Imperial College London, Hammersmith Hospital, London, UK
[2]Division of Biosciences, UCL, London, UK
[3]Dipartimento di Scienze Mediche e Sanità Pubblica, Università degli Studi di Cagliari. UOC Anestesia e Rianimazione, Centro Terapia del Dolore Azienda Ospedaliero-Universitaria di Cagliari
[4]Dipartimento di Medicina clinica, Università degli Studi, Sanità pubblica, Scienza della vita e dell'ambiente dell'Aquila
[5]Anestesia, Rianimazione e Terapia del Dolore, Università di Verona, Verona, Italy
[6]Dipartimento di Farmacia e Biotecnologie, Università di Bologna, Bologna
[7]Grünenthal GmbH, Aachen, Germany
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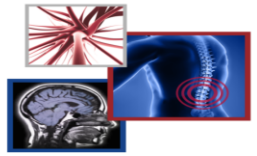
Pain Management



Anand P, Dickenson A, Finco G, Marinangeli F, **Polati E**, Romualdi P, Tzschentke TM, Canonico PL.

Pain Manag 2019;9:521-33

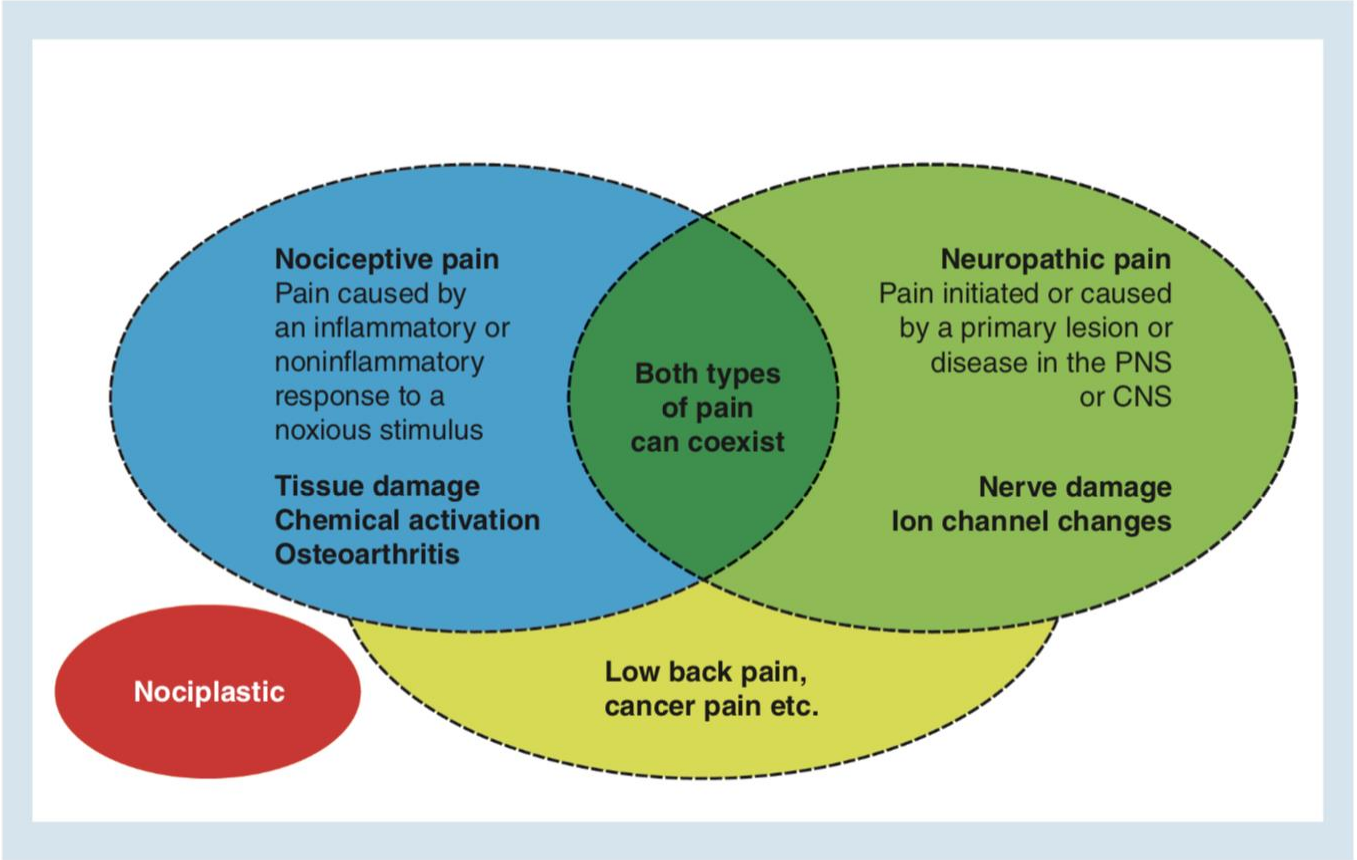
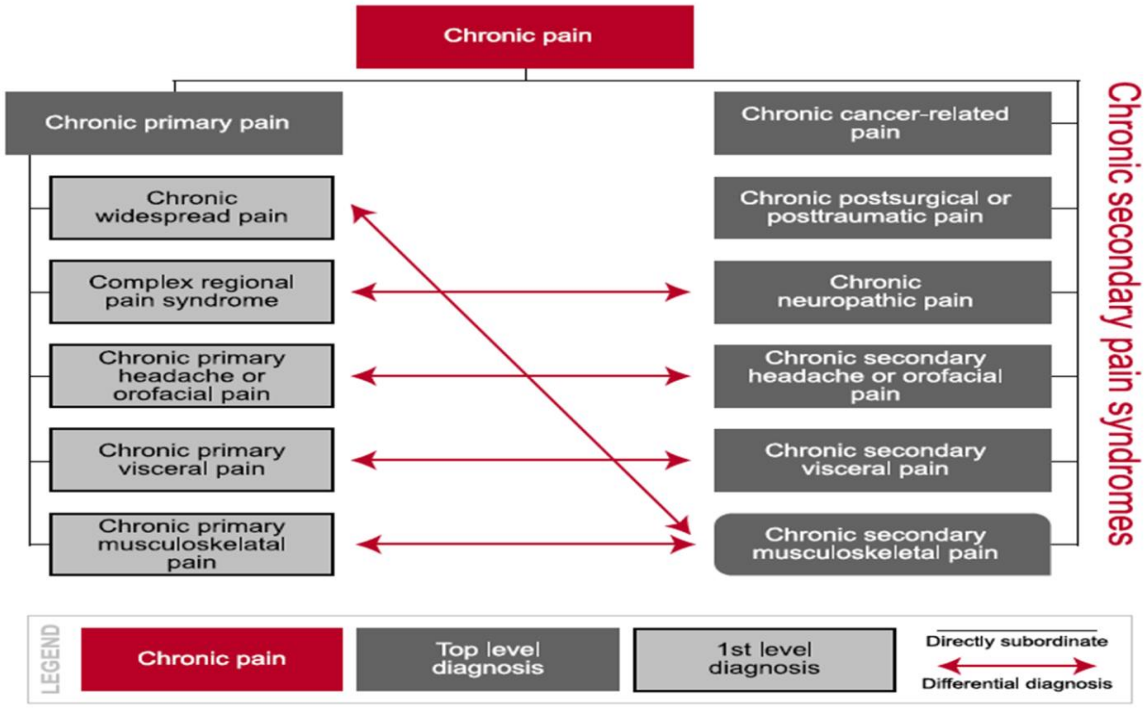


Figure 1. Key types of pain.
CNS: Central nervous system; PNS: Peripheral nervous system.



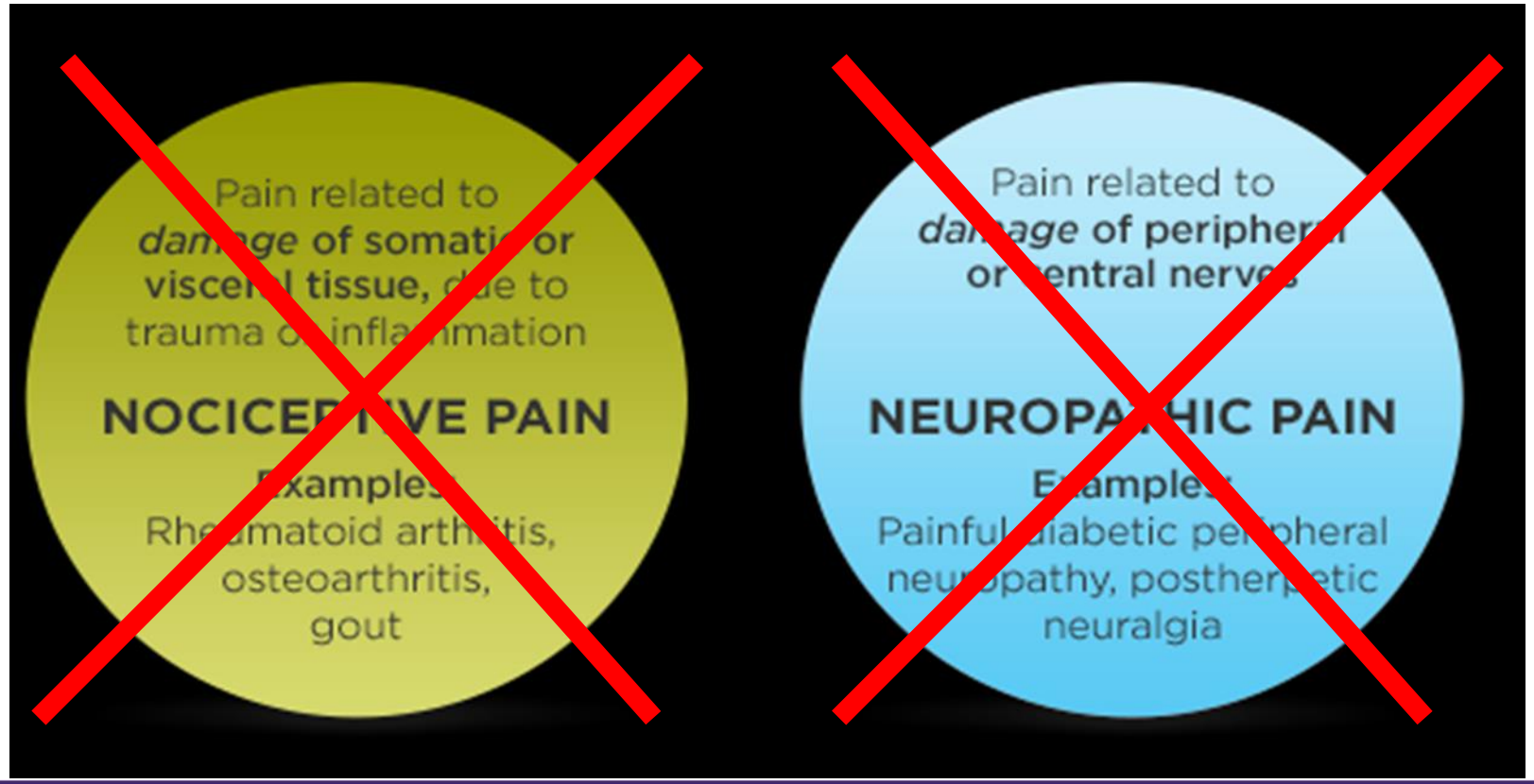
Sindromi di dolore cronico

SENSIBILIZZAZIONE PERIFERICA

NII

SENSIBILIZZAZIONE CENTRALE

FIBROMIALGIA:
“paradigma del dolore nociplastico”



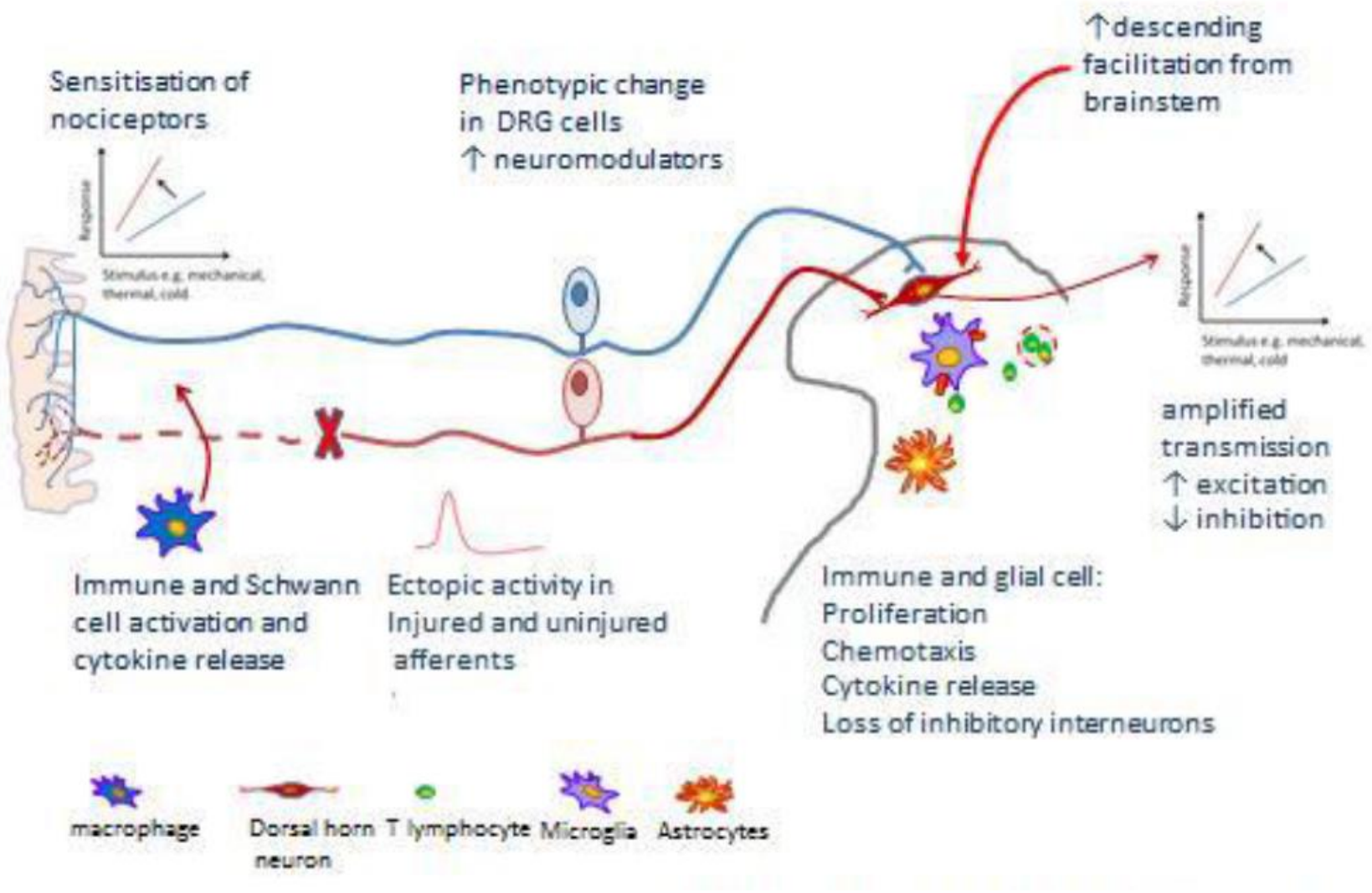
FMS: disnocicezione

- Lo sviluppo della FMS è dovuto ad **alterazioni nei principali processi responsabili dell'elaborazione e nella modulazione dello stimolo doloroso**

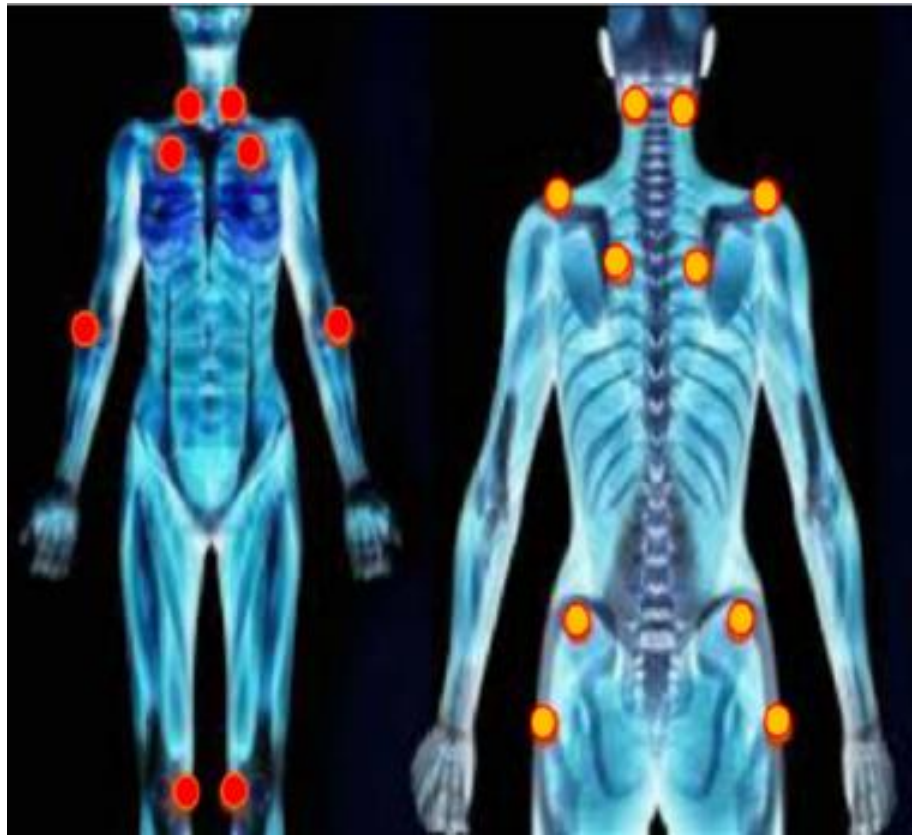
Chinn S et al, 2016

MECCANISMI PERIFERICI

MECCANISMI CENTRALI



FIBROMIALGIA: sensibilizzazione centrale



International Journal of *Molecular Sciences*

MDPI

Review

Fibromyalgia: Pathogenesis, Mechanisms, Diagnosis and Treatment Options Update

Rosalba Siracusa [1], Rosanna Di Paola [1,*], Salvatore Cuzzocrea [1,2,*] and Daniela Impellizzeri [1]

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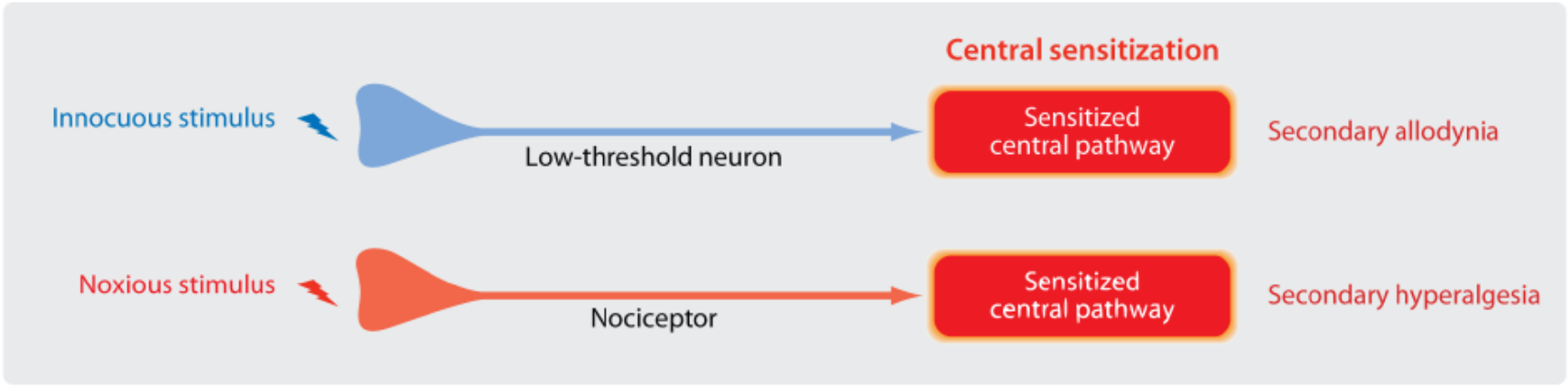
Siracusa R, et al. Int J Mol Sci 2021;22:3891

MECCANISMI CENTRALI DI ALTERATA NOCICEZIONE

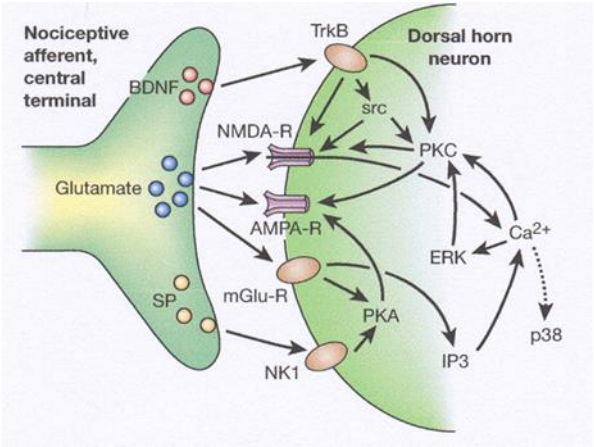
- SENSIBILIZZAZIONE CENTRALE
- PERDITA DI INIBIZIONE DISCENDENTE
- DISINIBIZIONE SPINALE
- RIORGANIZZAZIONE STRUTTURALE
- ATTIVITA' NEURONI A-β LOW-THERSHOLD
- NEURODEGENERAZIONE

MECCANISMI CENTRALI: Sensibilizzazione centrale



Amplificazione centrale del segnale periferico dovuta a **facilitazione sinaptica** a livello del corno posteriore del midollo spinale. Tale fenomeno è presente sia nel dolore neuropatico periferico che in quello centrale e contribuisce a sviluppare allodinia e iperalgesia secondaria

MECCANISMI CENTRALI: Sensibilizzazione centrale



- Alterazione **PRESINAPTICHE** includono alterazione nella sintesi di neurotrasmettitori e neuromodulatori e nella densità dei canali del calcio

- Alterazione **POSTSINAPTICHE** includono fosforilazione delle subunità NMDA e aumento della densità recettoriale e della sintesi di canali ionici e di proteine di membrana

- Tali alterazioni si verificano anche in strutture coinvolte nella processazione emozionale del dolore quali amigdala, giro cingolato anteriore e corteccia prefrontale (alterazioni comportamentali)

MECCANISMI CENTRALI: Sensibilizzazione centrale

• **L'effetto netto della SC** è il reclutamento di input provenienti dal sistema nocicettivo che normalmente sarebbero sotto-soglia, con generazione di potenziali d'azione in uscita anche in maniera rilevante

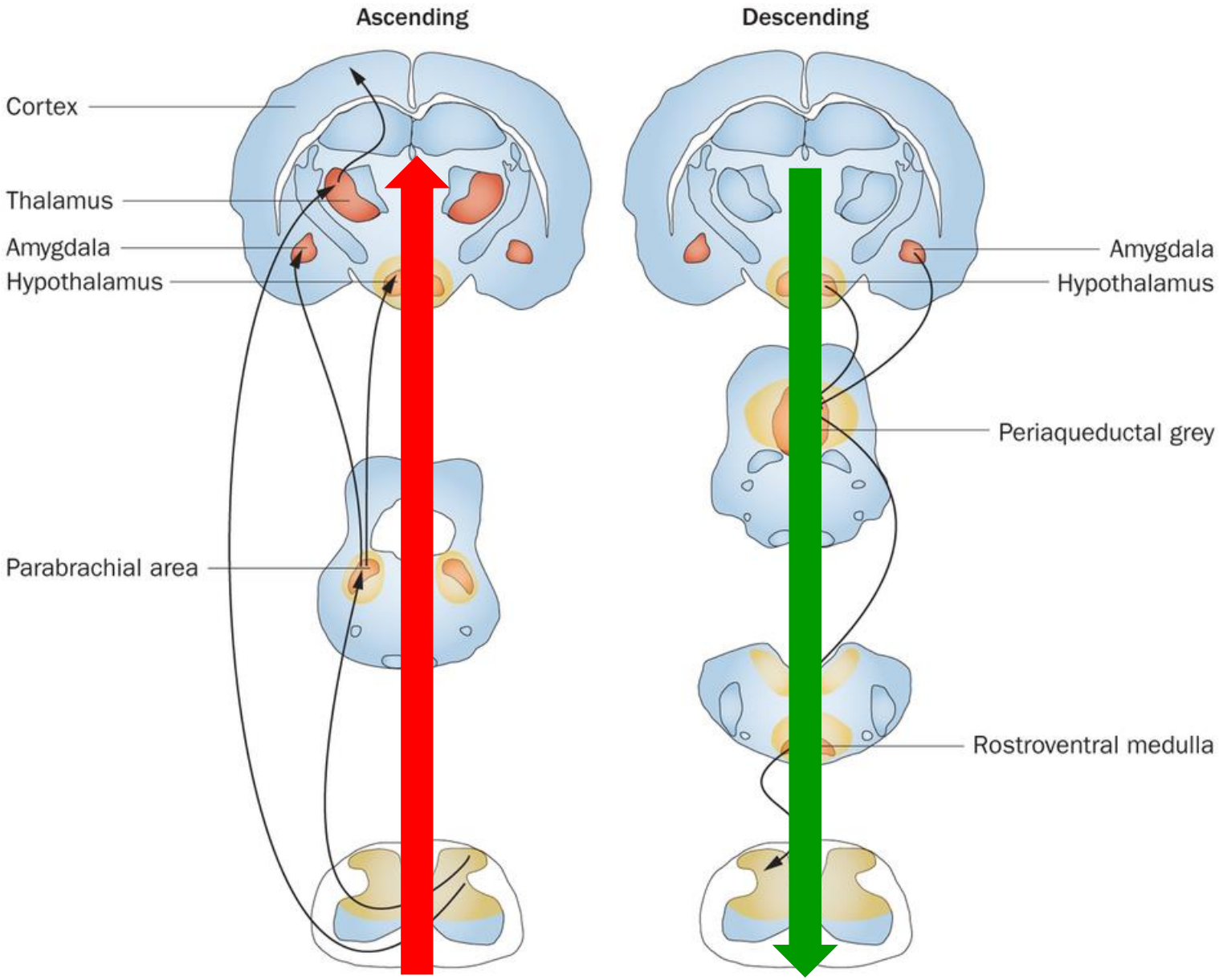
• La **SC provoca dolore** quindi modificando la risposta sensoriale indotta da normali input, compresi quelli che normalmente non sono in grado di indurre sensazioni dolorose

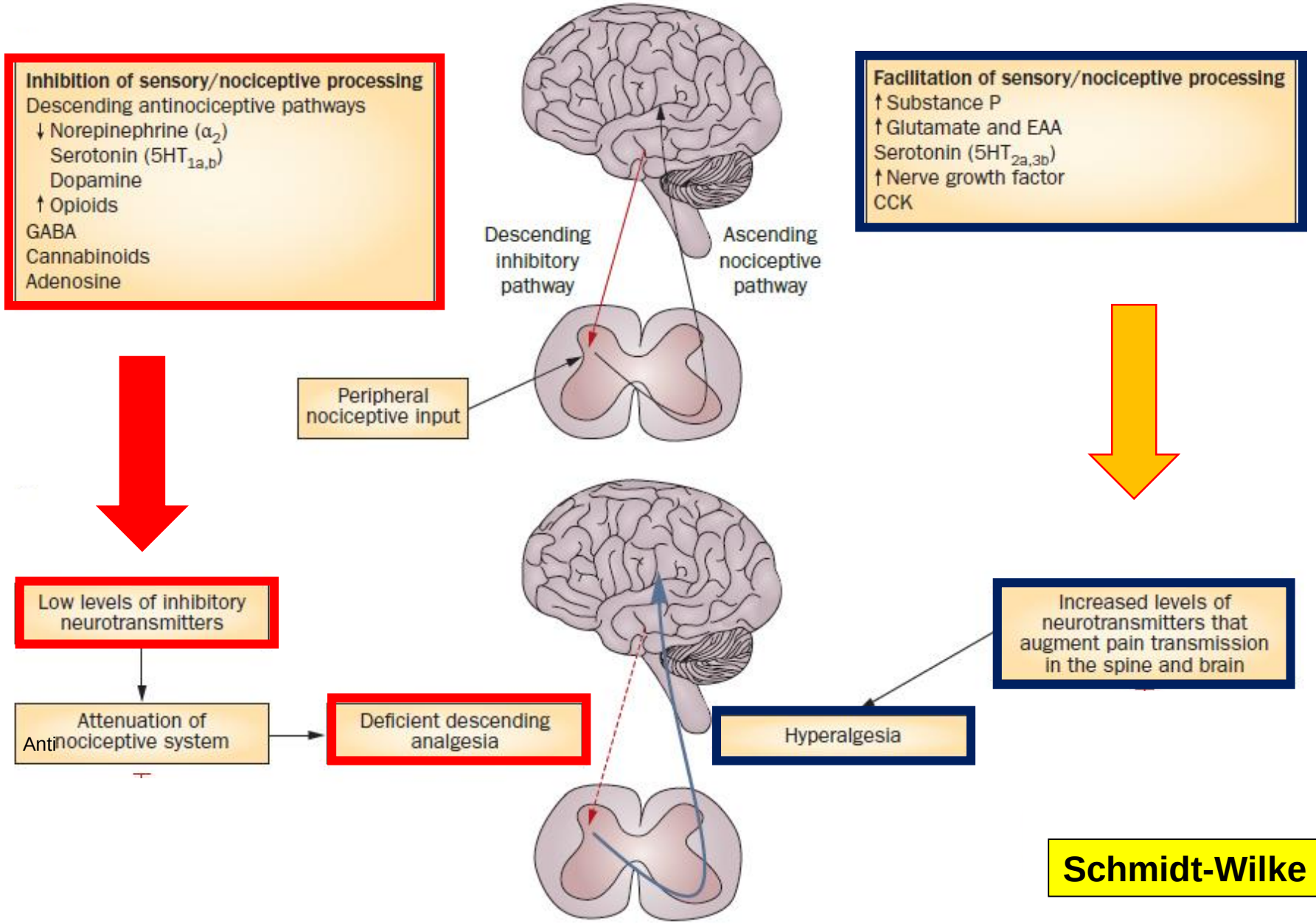
The Journal of Pain, Vol 10, No 9 (September), 2009: pp 895-926

MECCANISMI CENTRALI: perdita di inibizione discendente

- L’ inibizione tonica noradrenergica viene persa
- L’effetto inibitorio serotoninergico diviene facilitatore
- L’espressione dei recettori μ per gli oppioidi si riduce, e con esso la sensibilità dei neuroni del corno posteriore agli oppiacei
- L’attività del sistema GABAergico inibitorio (pre e postsinaptico) viene perduta, con prevalenza di stimoli eccitatori di membrana

Costigan M et al, 2009

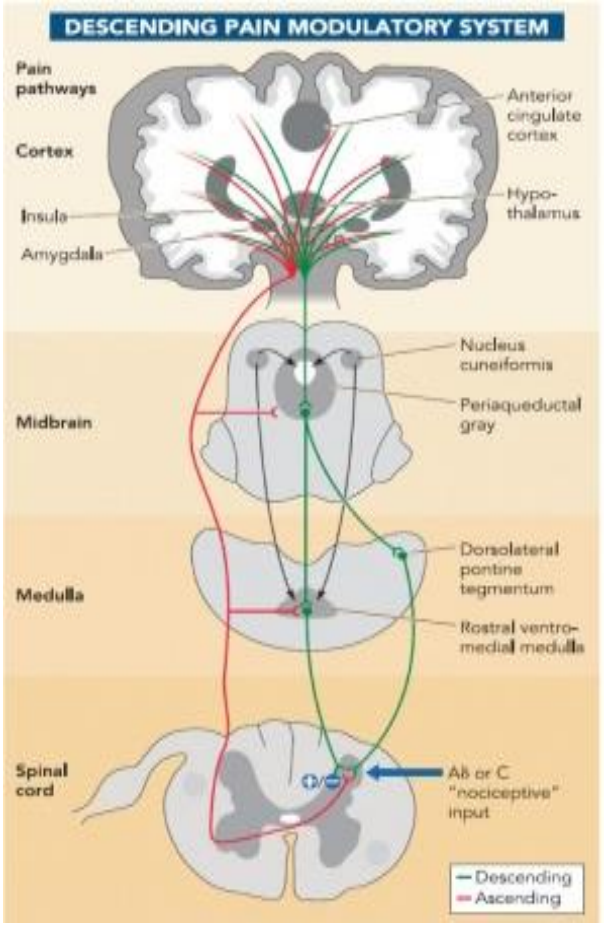

Ascending
Descending
Cortex
Thalamus
Amygdala
Hypothalamus
Parabrachial area
Amygdala
Hypothalamus
Periaqueductal grey
Rostroventral medulla



Schmidt-Wilke T et al, 2011

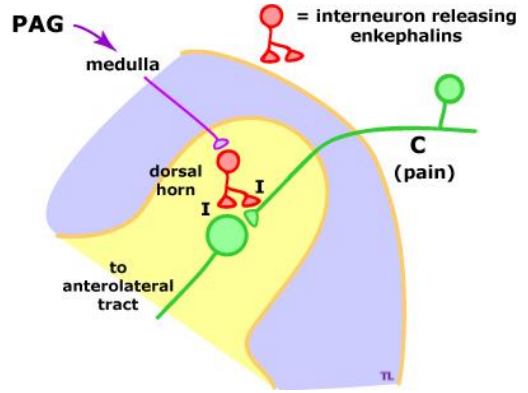
MECCANISMI CENTRALI: perdita di inibizione discendente

One of the descending inhibitory pathways originates from the rostral ventromedial medulla (RVM) and nuclear raphe magnus and contains serotonergic (5-hydroxytryptaminergic, 5-$HT_{1,2}$) and GABAergic neurons, which synapse in the spinal cord to inhibit transmission in the dorsal horn [16]. A second pathway originates from the dorsolateral posterior tegmentum (DLPT) containing noradrenergic (containing norepinephrine) neurons that send inhibitory signals [2•]. Cerebrospinal fluid (CSF) analysis in fibromyalgia patients has consistently found decreased levels of serotonin and norepinephrine.



Chinn S et al, 2016

MECCANISMI CENTRALI: Disinibizione spinale

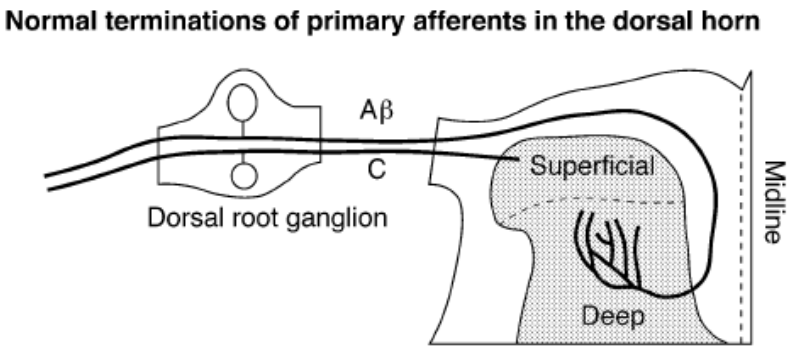


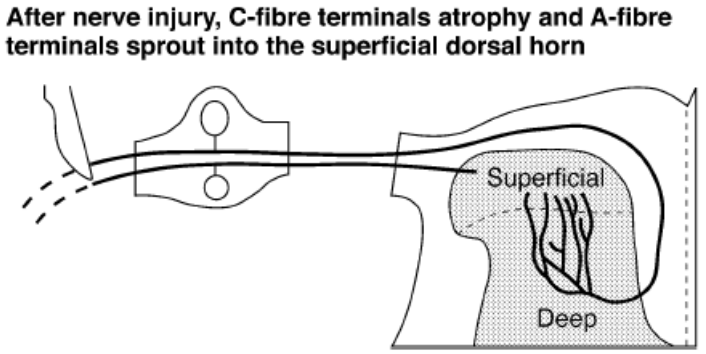
Consiste in:

- Riduzione nell'espressione di recettori inibitori
- Down-regulation di trasportatori di membrana (KCC2) con tendenza a ridurre il potenziale negativo e innescare eccitazione
- Apoptosi danno-indotta di neuroni inibitori GABAergici

Campbell JN et al, 2006

MECCANISMI CENTRALI: Riorganizzazione strutturale

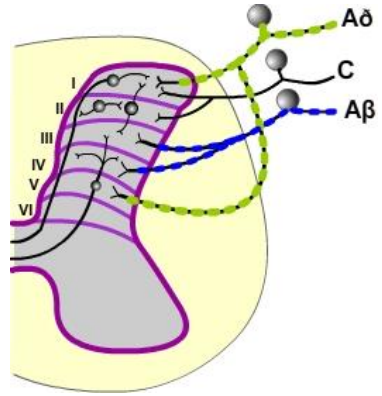




I terminali dei grandi neuroni mielinizzati (fibre A-beta) si infiltrano negli strati superficiali del corno posteriore. Tali alterazioni strutturali potrebbero essere substrato di ingresso di stimoli a bassa soglia nei circuiti nocicettivi

Wolf CJ et al, 1992

MECCANISMI CENTRALI: Attività neuroni A-β low-threshold



- Le fibre A-β a bassa soglia, che normalmente veicolano sensazioni innocue di tipo propriocettivo divengono in grado di produrre dolore se stimolate

- Evidenze sperimentali hanno dimostrato che in alcuni pazienti aumentano gli input di tali neuroni sulle lamine superficiali del corno posteriore trasformando l'informazione da non-nocicettiva a nocicettiva

- Tale plasticità e i suoi meccanismi sono ancora non del tutto conosciuti

Costigan M et al, 2009

FIBROMIALGIA E PLASTICITA' SOPRASPINALE

Seminars in Arthritis and Rheumatism 44 (2014) 68–75

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

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

Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI

Barbara Cagnie, PT, PhD[a,*,1], Iris Coppieters, PT[a,*,1], Sien Denecker, PT[a], Jasmien Six, PT[a], Lieven Danneels, PT, PhD[a], Mira Meeus, PT, PhD[a,b,c]

[a] Department of Rehabilitation Sciences and Physiotherapy, Ghent University, De Pintelaan 185 3B3, Ghent 9000, Belgium
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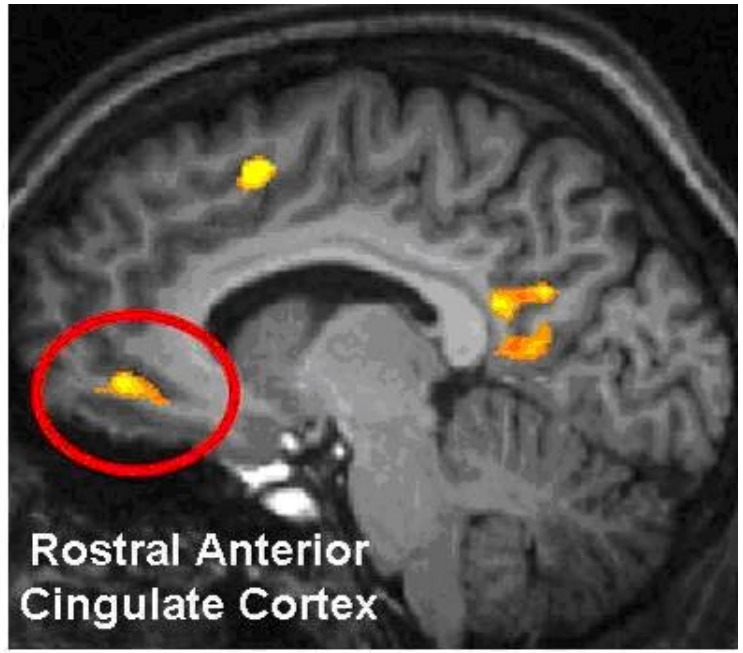
ARTICLE INFO

Keywords:
Central sensitization
(rs)-fMRI
VBM
Chronic pain
Hyperalgesia
Temporal summation
Pain matrix
Gray matter
Brain activity
Functional connectivity

ABSTRACT

Objectives: The aim of the present study was to systematically review the literature addressing pain-induced changes in the brain related to central sensitization in patients with fibromyalgia (FM) using specific functional (rs-fMRI and fMRI) and structural (voxel-based morphometry—VBM) brain MRI techniques.
Methods: PubMed and Web of Science were searched for relevant literature using different key word combinations related to FM, brain MRI, and central sensitization. Full-text reports fulfilling the inclusion criteria were assessed on risk of bias and reviewed by two independent reviewers.
Results: From the 61 articles that were identified, 22 met the inclusion criteria and achieved sufficient methodological quality. Overall, eight articles examined structural brain (VBM) changes in patients with FM, showing moderate evidence that central sensitization is correlated with gray matter volume decrease in specific brain regions (mainly anterior cingulate cortex and prefrontal cortex). However, global gray matter volume remains unchanged. A total of 13 articles evaluated brain activity (fMRI) in response to a nociceptive stimulus. Findings suggest a higher but similar pattern of activation of the pain matrix in FM patients compared to controls. There is also evidence of decreased functional connectivity in the descending pain-modulating system in FM patients. Overall, two articles examined intrinsic brain connectivity in FM patients with rs-fMRI. In conclusion, there is moderate evidence for a significant imbalance of the connectivity within the pain network during rest in patients with FM.
Conclusions: The included studies showed a moderate evidence for region-specific changes in gray matter volume, a decreased functional connectivity in the descending pain-modulating system, and an increased activity in the pain matrix related to central sensitization. More research is needed to evaluate the cause–effect relationship.



Cagnie B et al, 2014

MECCANISMI CENTRALI: Neurodegenerazione

10410 • The Journal of Neuroscience, November 17, 2004 • 24(46):10410–10415

Behavioral/Systems/Cognitive

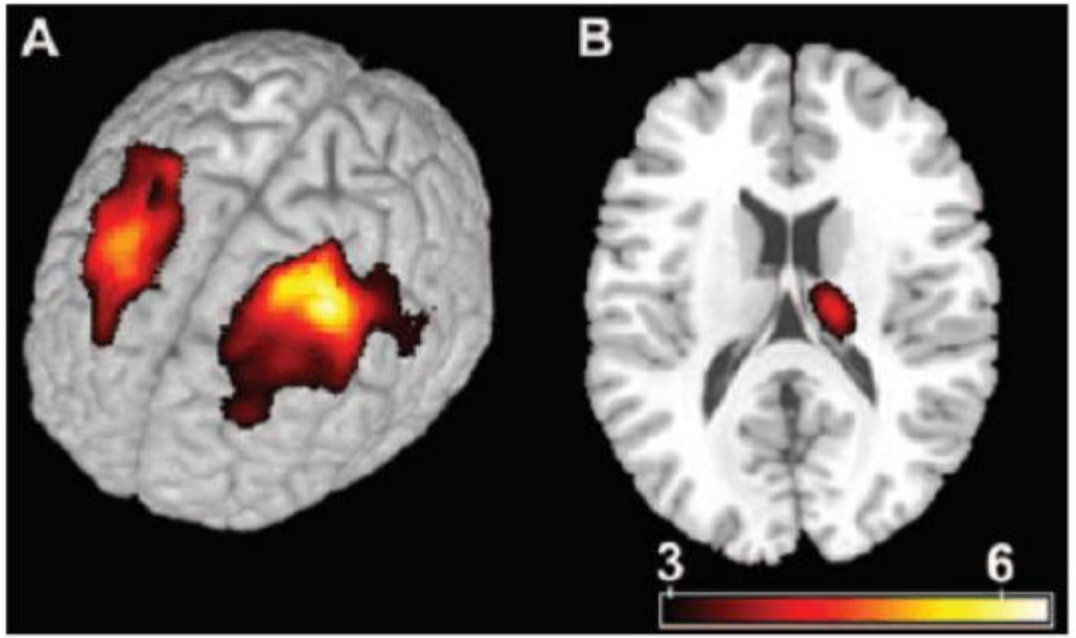
Chronic Back Pain Is Associated with Decreased Prefrontal and Thalamic Gray Matter Density

A. Vania Apkarian,[1] Yamaya Sosa,[1] Sreepadma Sonty,[2] Robert M. Levy,[3] R. Norman Harden,[5] Todd B. Parrish,[4] and Darren R. Gitelman[2,4]

[1]Department of Physiology and Institute of Neuroscience, and Departments of [2]Neurology, [3]Neurosurgery, and [4]Radiology, and [5]Rehabilitation Institute of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Illinois 60611

The role of the brain in chronic pain conditions remains speculative. We compared brain morphology of 26 chronic back pain (CBP) patients to matched control subjects, using magnetic resonance imaging brain scan data and automated analysis techniques. CBP patients were divided into neuropathic, exhibiting pain because of sciatic nerve damage, and non-neuropathic groups. Pain-related characteristics were correlated to morphometric measures. Neocortical gray matter volume was compared after skull normalization. Patients with CBP showed 5–11% less neocortical gray matter volume than control subjects. The magnitude of this decrease is equivalent to the gray matter volume lost in 10–20 years of normal aging. The decreased volume was related to pain duration, indicating a 1.3 cm^3 loss of gray matter for every year of chronic pain. Regional gray matter density in 17 CBP patients was compared with matched controls using voxel-based morphometry and nonparametric statistics. Gray matter density was reduced in bilateral dorsolateral prefrontal cortex and right thalamus and was strongly related to pain characteristics in a pattern distinct for neuropathic and non-neuropathic CBP. Our results imply that CBP is accompanied by brain atrophy and suggest that the pathophysiology of chronic pain includes thalamocortical processes.

Key words: chronic pain; morphometry; frontal cortex; thalamus; neuropathic back pain; aging



APKARIAN AV et al, 2004

MECCANISMI CENTRALI: Neurodegenerazione

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Conclusions: The included studies showed a moderate evidence for region-specific changes in gray matter volume, a decreased functional connectivity in the descending pain-modulating system, and an increased activity in the pain matrix related to central sensitization. More research is needed to evaluate the cause–effect relationship.

- Nei pazienti fibromialgici vi sono prove di una diminuzione del volume della materia grigia in alcune specifiche regioni cerebrali
- Tale degenerazione è probabilmente diretta conseguenza dell'attività ectopica protratta e incontrollata e/o da citotossicità mediata da glutammato
- La natura di queste alterazioni strutturali rimane poco determinata, ma potrebbe giustificare la ricerca su trattamenti preventivi la neurodegenerazione

Cagnie B et al, 2014

CLINICAL TRIAL STUDY

Ultramicronized Palmitoylethanolamide (um-PEA) as Add-on Treatment in Fibromyalgia Syndrome (FMS): Retrospective Observational Study on 407 Patients

Vittorio Schweiger[1,*], Alvise Martini[1], Paola Bellamoli[1], Katia Donadello [1], Carlo Schievano[2], Giovanna Del Balzo[3], Piercarlo Sarzi-Puttini[4], Massimo Parolini[1] and Enrico Polati[1]

1Department of Surgery, Dentistry, Maternal and Infant Sciences, Pain Therapy Centre, Verona University Hospital, Policlinico GB Rossi, Verona; [2]Innovative Statistical Research, Padua, Italy; [3]Department of Medicine and Public Health, Section of Forensic Medicine, Verona University Hospital, Policlinico GB Rossi, Verona; [4]Rheumatology Unit, ASST-Fatebenefratelli- L. Sacco University Hospital, Milan, Italy

ARTICLE HISTORY

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10.2174/1871527318666190227205359

Abstract: ***Background***: Fibromyalgia syndrome is a chronic multifaceted disease characterized by widespread pain, muscle stiffness, fatigue, unrefreshing sleep and cognitive disorders. To date, no medication has been shown to significantly improve pain, associated symptoms and Quality of Life in fibromyalgic patients.

Methods: In this retrospective observational study, we analyzed data regarding 407 patients with diagnosis of fibromyalgia syndrome who between 2013 and 2016 have been prescribed orally ultramicronized palmitoylethanolamide tablets (Normast® Epitech Group SpA, Saccolongo, Italy) regardless of the concomitant pharmacological therapy (add-on treatment).

Results: Regarding efficacy, in the 359 analyzed patients, the change over time in Visual Analogue Scale pain score was statistically significant, ranging from 75.84 (±15.15) to 52.49 (±16.73) ($p<0.001$). Regarding quality of life, the change over time in Fibromyalgia Impact Questionnaire score was statistically significant, ranging from 68.4 (±14.1) to 49.1 (±19.6) ($p<0.001$). In the treated population, only 36 patients (13,7%) reported Adverse Events predominantly of gastrointestinal type (diarrhea, dyspepsia, bloating, constipation, vomiting). Globally, 151 patients (57,63%) left the treatment due to inefficacy.

Conclusion: The results of ultramicronized palmitoylethanolamide treatment in this retrospective analysis represent an important step for the development of a new and well-tolerated therapy for fibromyalgia syndrome, mostly suitable for these patients who need long-term treatments. Further methodologically stronger studies will be necessary to validate our observation.

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Deconstructing the Neuropathic Pain Phenotype to Reveal Neural Mechanisms

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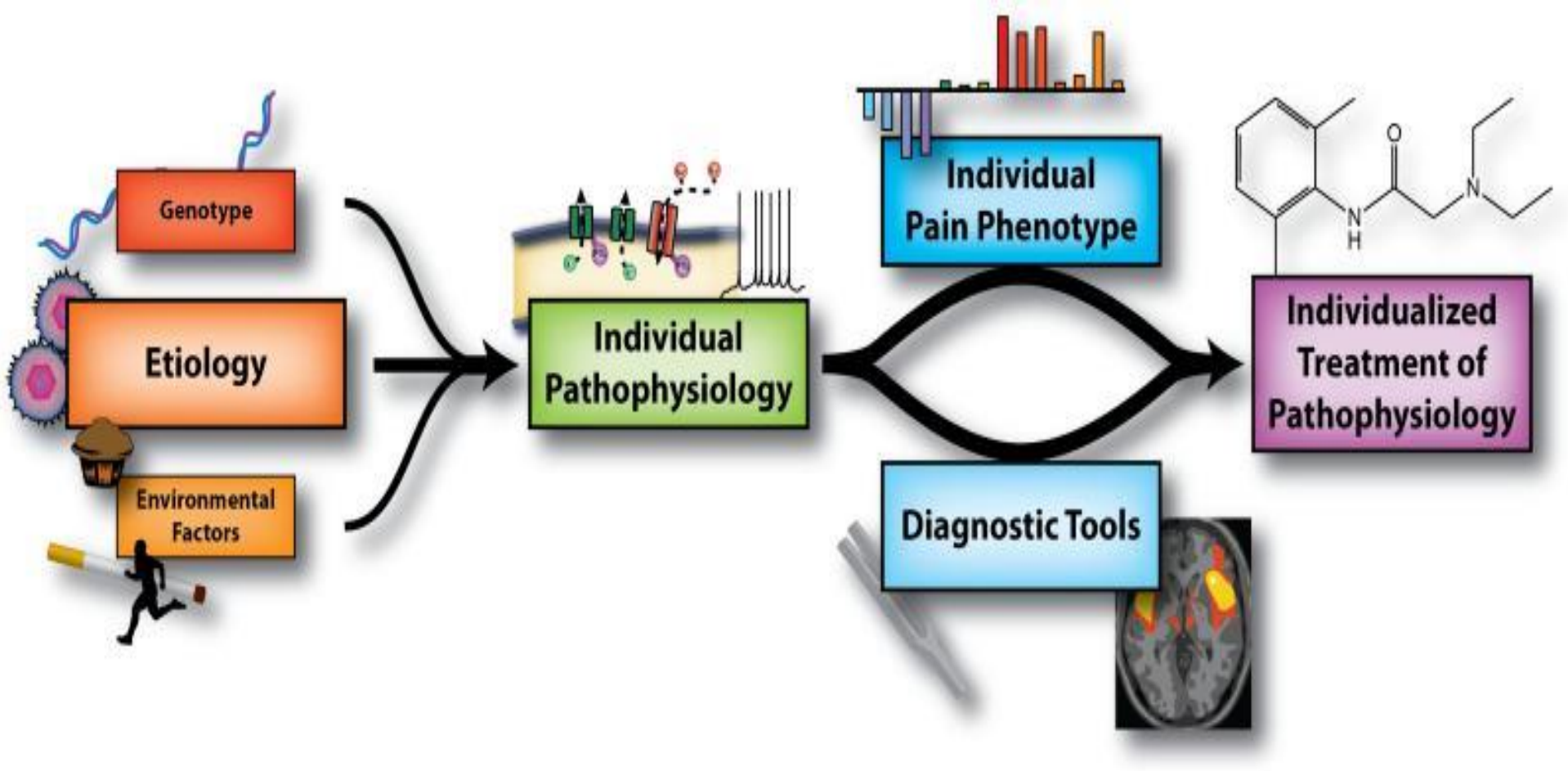

Bodily Illusions and Motor Imagery in Fibromyalgia

Michele Scandola[1], Giorgia Pietroni[1], Gabriella Landuzzi[2], Enrico Polati[3], Vittorio Schweiger[3] and Valentina Moro[1]**

- L'**immaginazione motoria** (simulazione mentale degli atti motori volontari) è compromessa e la gravità dei deficit riscontrati è correlata al grado di compromissione funzionale. Ciò indicherebbe che i disturbi nella creazione delle immagini motorie fanno parte dell'espressione clinica della FM come prodotti della ridotta autonomia e dei deficit funzionali

- Le **illusioni corporee** (illusioni relative ai movimenti e ai cambiamenti delle parti e nelle dimensioni del corpo, sensazioni di estraneità e di parti del corpo non appartenenti a sé), **sono indipendenti dal dato funzionale e rappresentano potenzialmente un marker cognitivo tipico della FM**

Front. Hum. Neurosci. 15:798912.
doi: 10.3389/fnhum.2021.798912

FIBROMIALGIA: prospettive future

LINGUISTICA COMPUTAZIONALE

Centro HUB Terapia del Dolore
Università di Verona (Italy)

Prof. Guillermo Cecchi e coll.
IBM Watson Research Center
New York City (USA)

FMS: disnocicezione e terapia

Diagnostic and therapeutic care pathway for fibromyalgia

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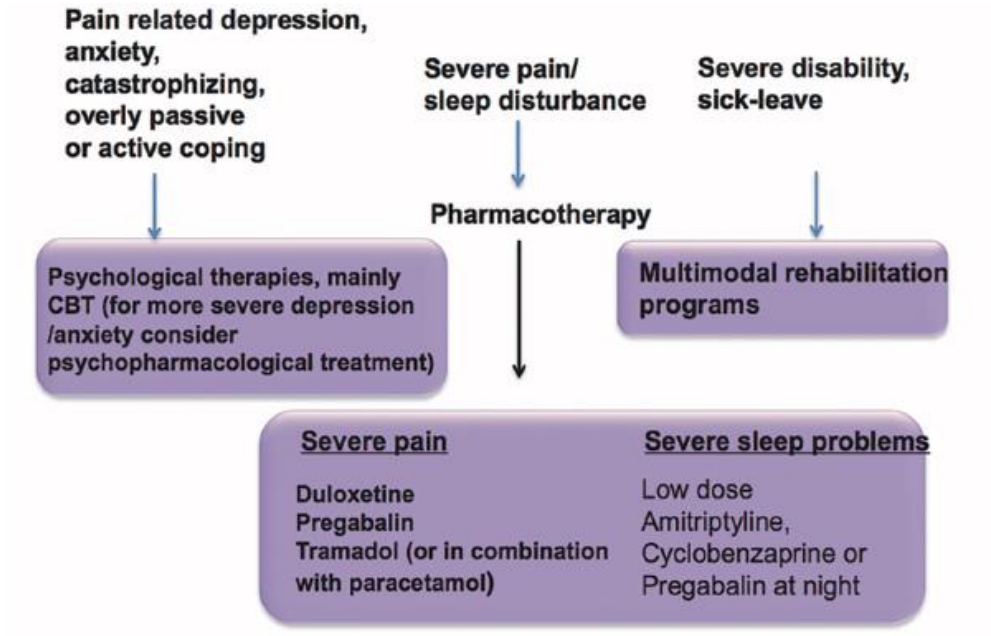

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