



UNIVERSITÀ DEGLI STUDI
DI CAGLIARI



AISD Associazione Italiana
per lo Studio del Dolore

La fibromialgia: una sindrome di dolore atipico

Salvatore Sardo
Ricercatore in Anestesiologia
UNICA

My first encounter with FM

Rheumatol Int (2014) 34:1047–1052

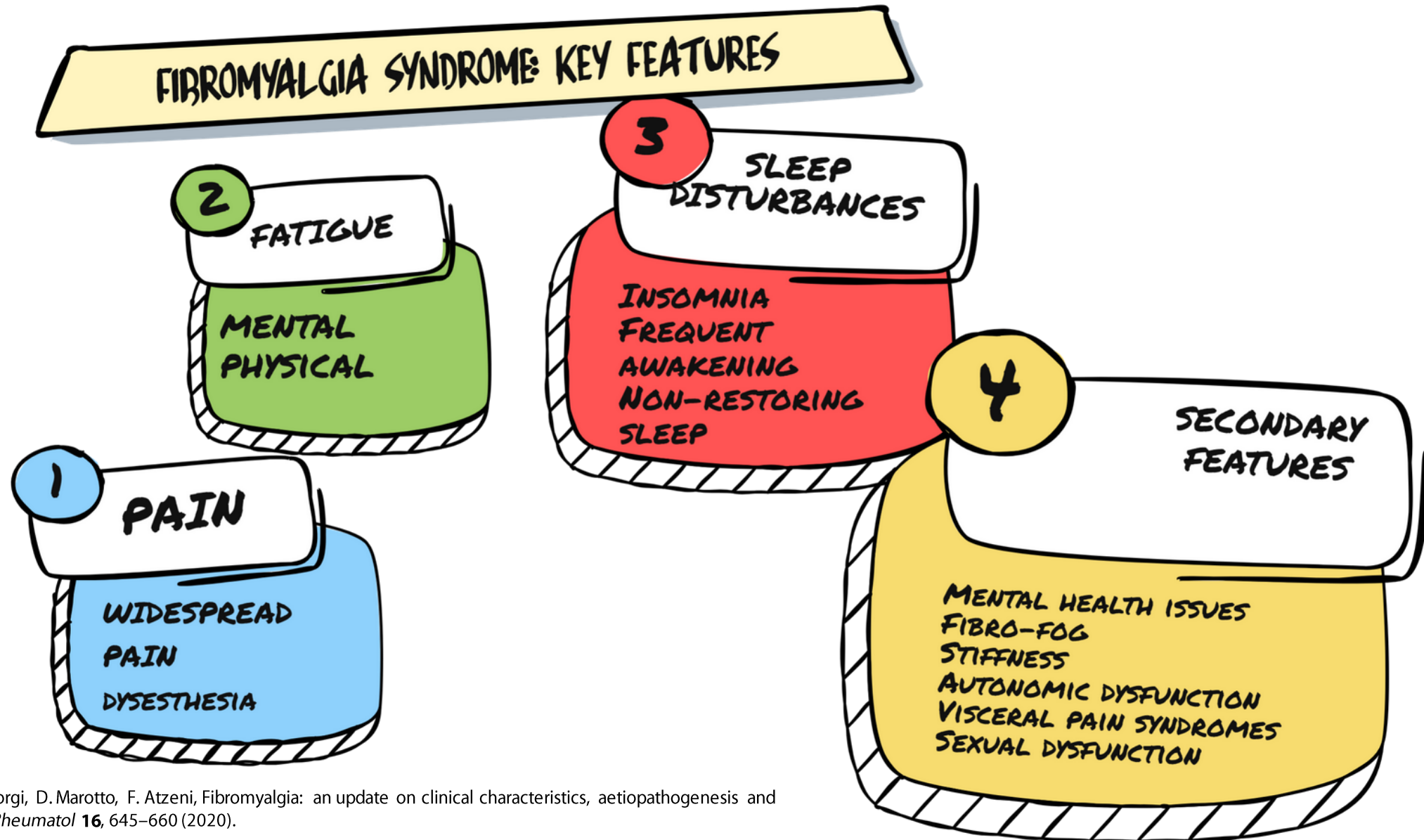
DOI 10.1007/s00296-014-2953-y

SHORT COMMUNICATION

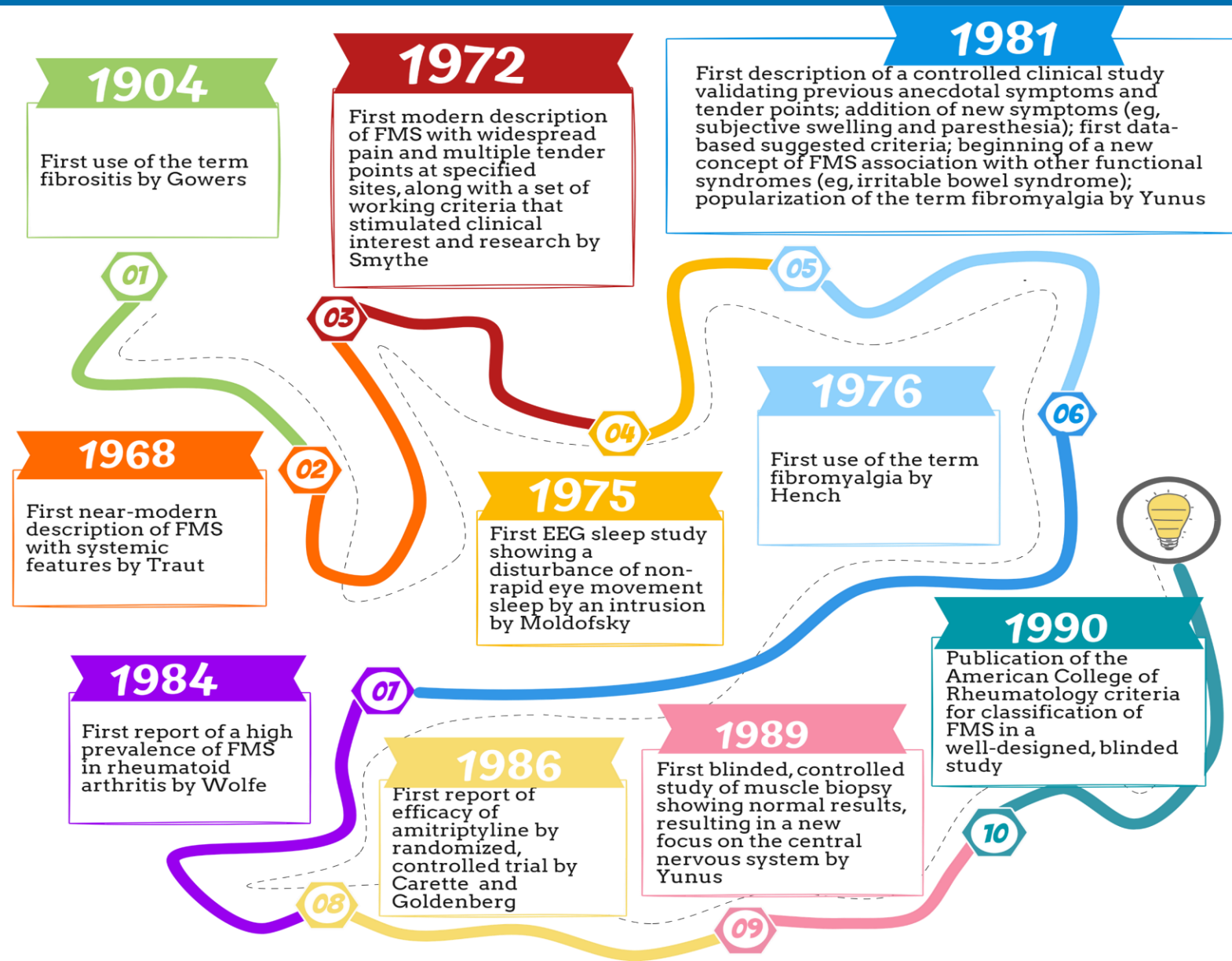
Oxytocin nasal spray in fibromyalgic patients

**S. Mameli · G. M. Pisanu · S. Sardo · A. Marchi ·
A. Pili · M. Carboni · L. Minerba · G. Trincas ·
M. G. Carta · M. R. Melis · R. Agabio**

What is fibromyalgia?



The birth of Fibromyalgia

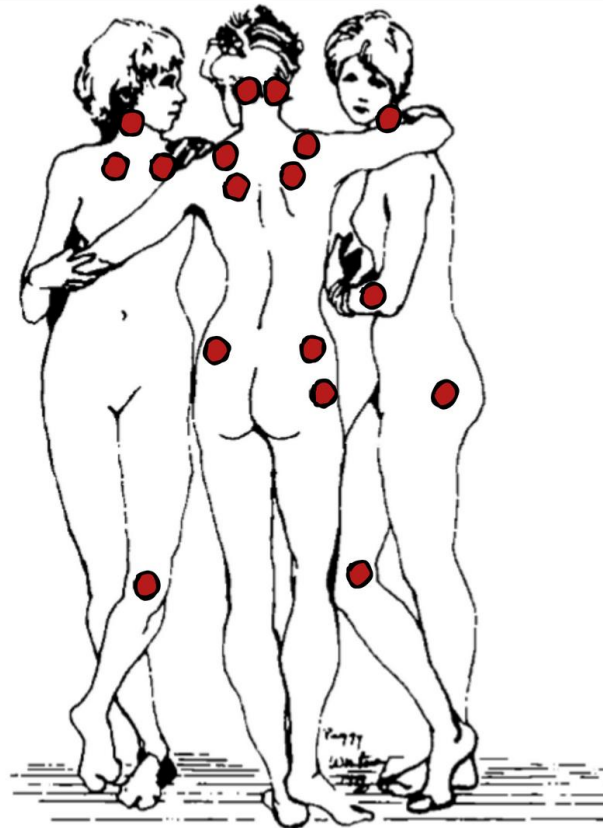


F. F. Inanici, M. B. Yunus, History of fibromyalgia: Past to present. Current Science Inc 8, 369–378 (2004).

1990 criteria

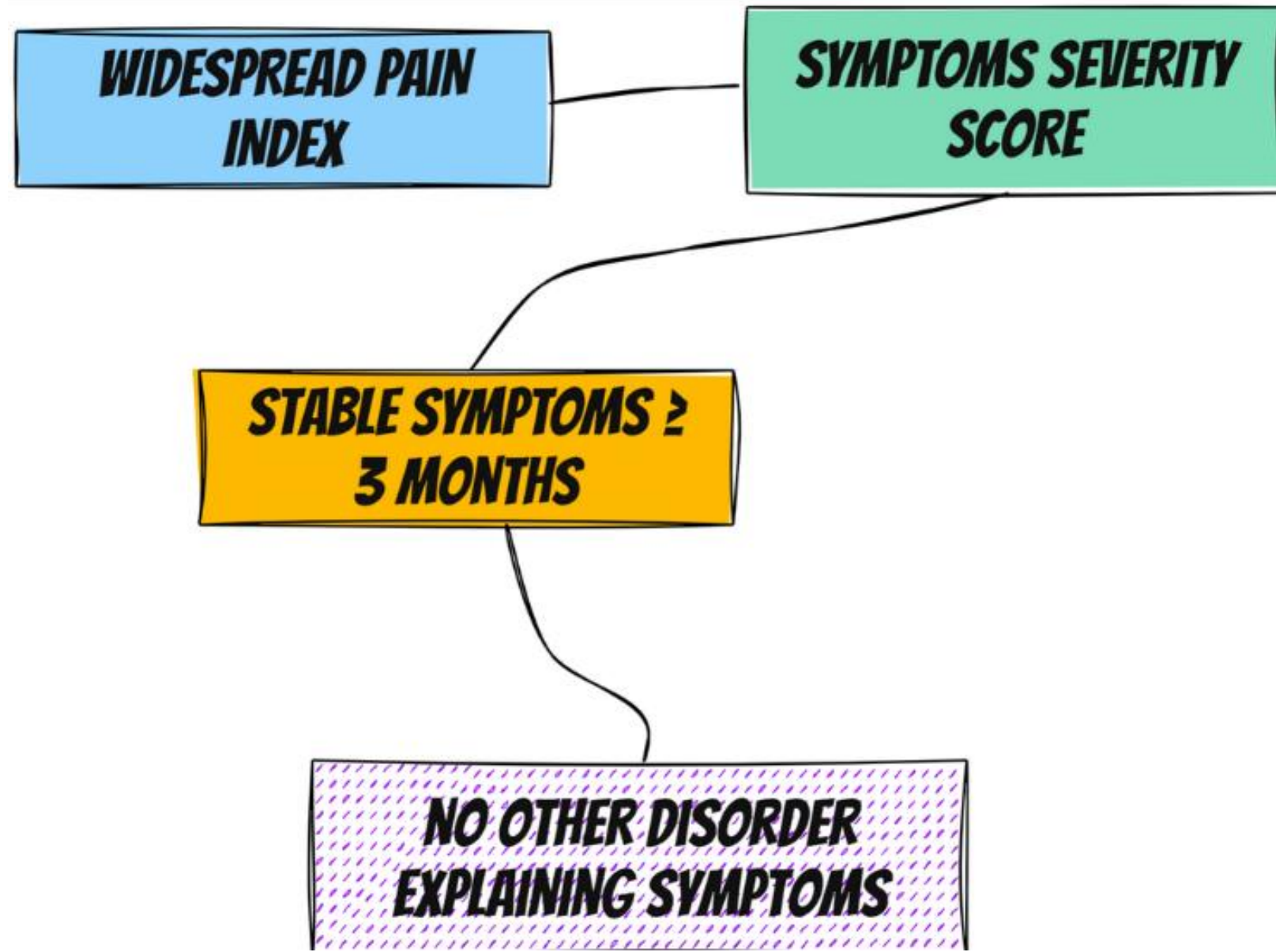
**1. HISTORY OF
WIDESPREAD PAIN
≥ 3 MONTHS**

**2. 11/18 TENDER
POINTS
4 KG PRESSURE**

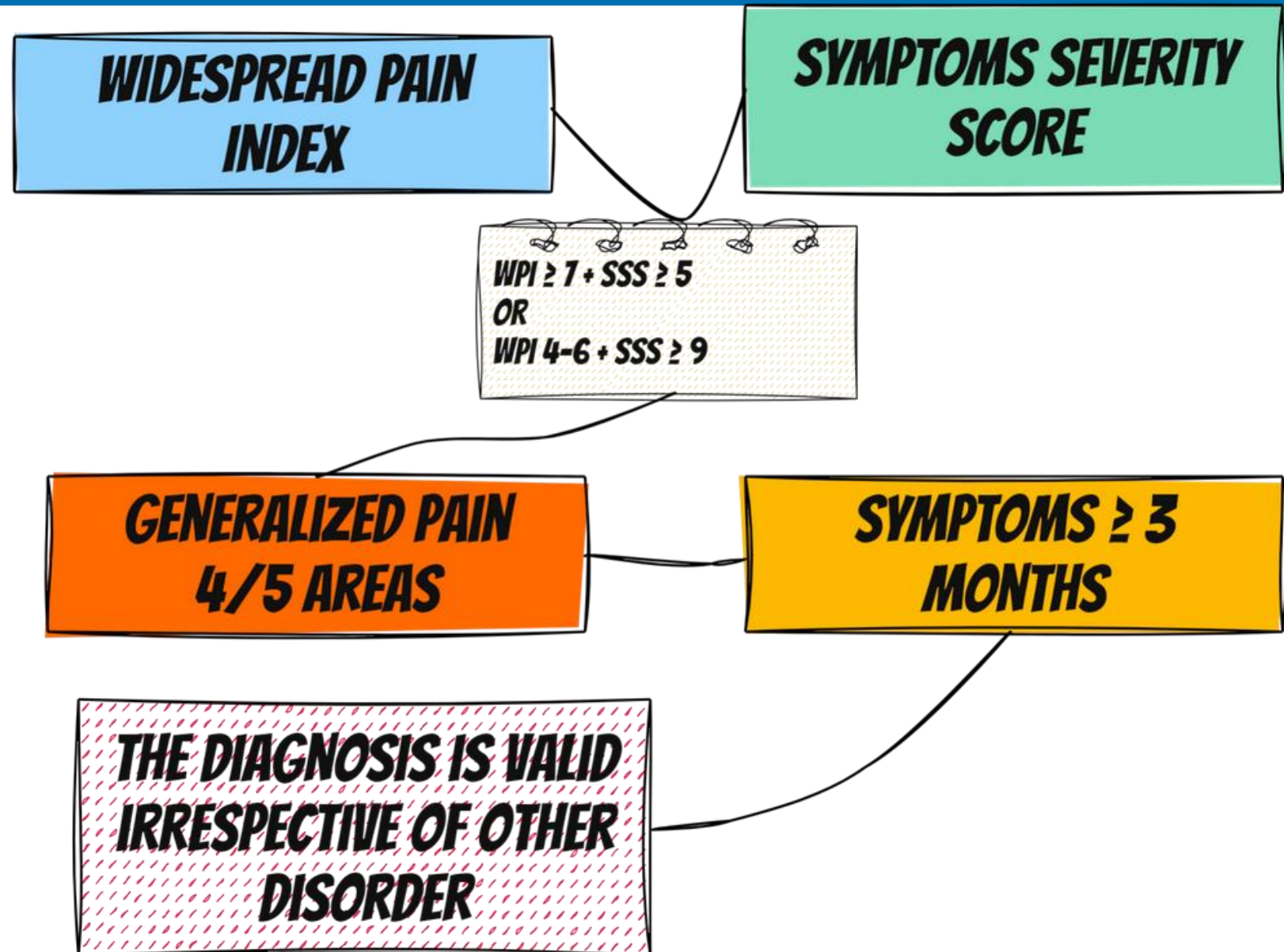


F. Wolfe, H. A. Smythe, M. B. Yunus, R. M. Bennett, C. Bombardier, D. L. Goldenberg, P. Tugwell, S. M. Campbell, M. Abeles, P. Clark, The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* **33**, 160–172 (1990).

2010 criteria



2016 criteria



Widespread Pain Index WPI

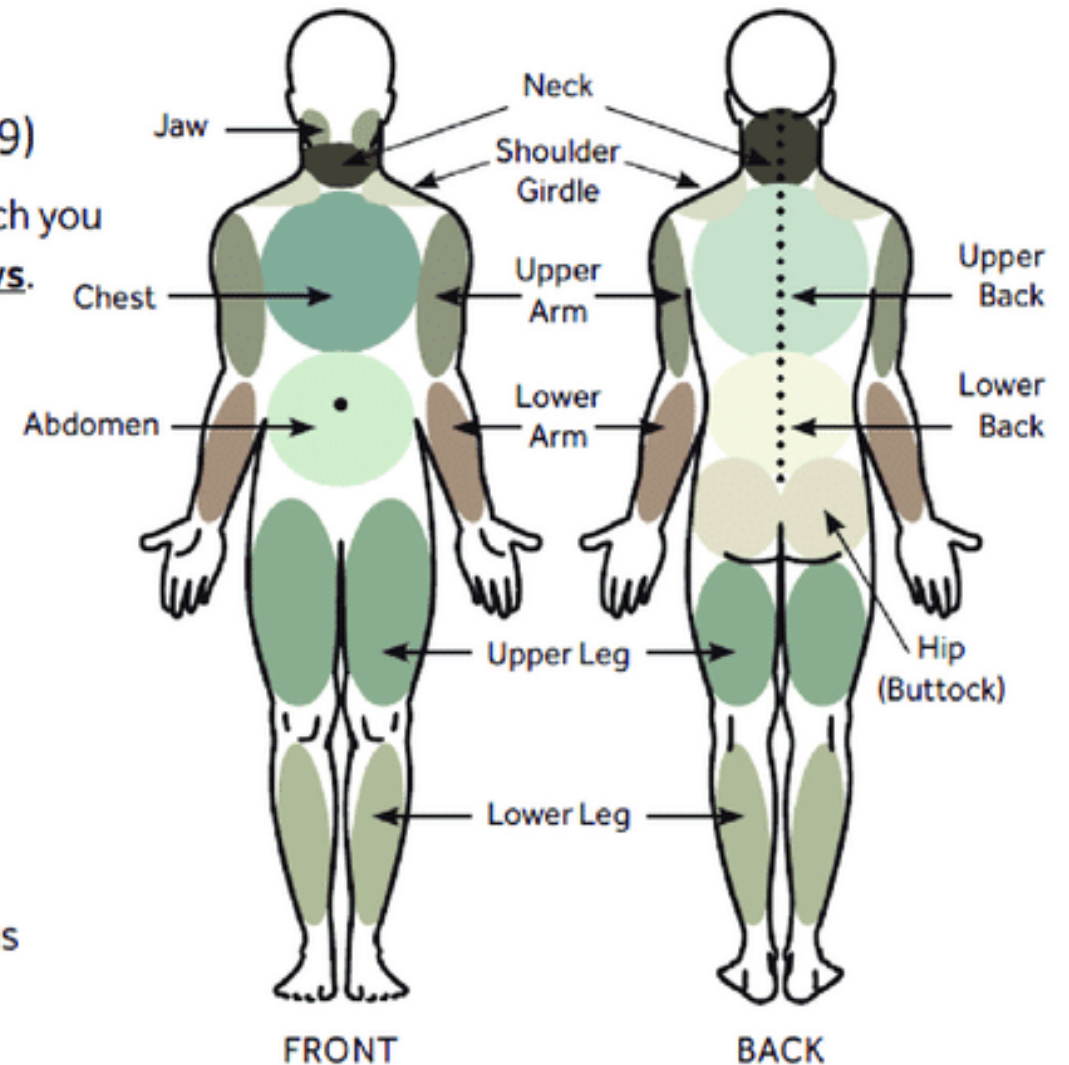
Widespread Pain Index (WPI)

(1 point per check box; score range: 1–19)

Please check the boxes below for each area in which you have had pain or tenderness during the past 7 days.

- | | |
|---|--|
| <input type="checkbox"/> Shoulder girdle, left | <input type="checkbox"/> Lower leg left |
| <input type="checkbox"/> Shoulder girdle, right | <input type="checkbox"/> Lower leg right |
| <input type="checkbox"/> Upper arm, left | <input type="checkbox"/> Jaw left |
| <input type="checkbox"/> Upper arm, right | <input type="checkbox"/> Jaw right |
| <input type="checkbox"/> Lower arm, left | <input type="checkbox"/> Chest |
| <input type="checkbox"/> Lower arm, right | <input type="checkbox"/> Abdomen |
| <input type="checkbox"/> Hip (buttock) left | <input type="checkbox"/> Neck |
| <input type="checkbox"/> Hip (buttock) right | <input type="checkbox"/> Upper back |
| <input type="checkbox"/> Upper leg left | <input type="checkbox"/> Lower back |
| <input type="checkbox"/> Upper leg right | <input type="checkbox"/> None of these areas |

WPI score: _____



Symptoms Severity Score SSS



6/9

F. Wolfe, D. J. Clauw, M. Fitzcharles, D. L. Goldenberg, R. S. Katz, P. Mease, A. S. Russell, I. J. Russell, J. B. Winfield, M. B. Yunus, The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. *Arthritis Care & Research* **62**, 600–610 (2010).

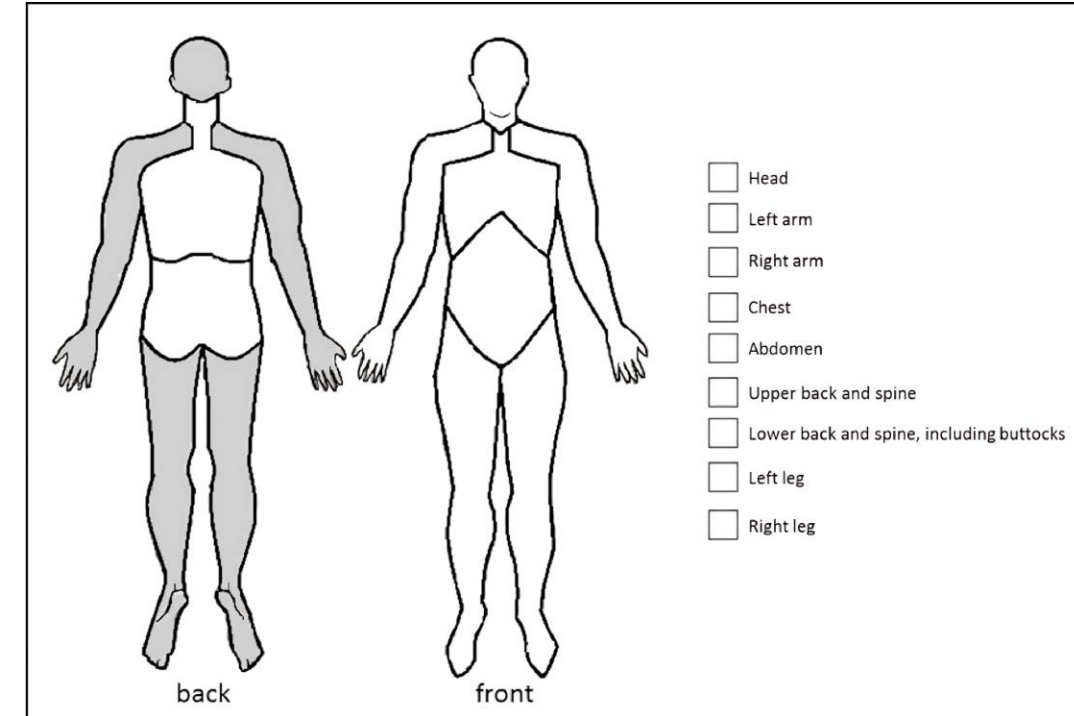
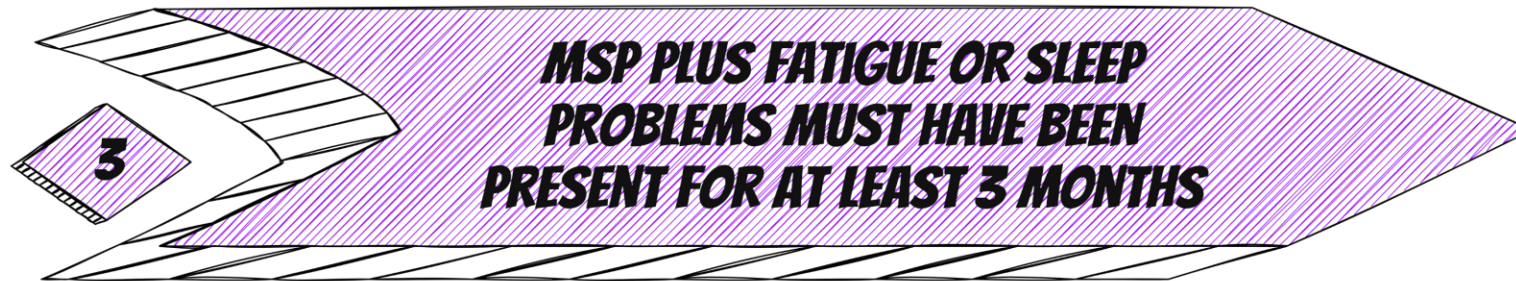
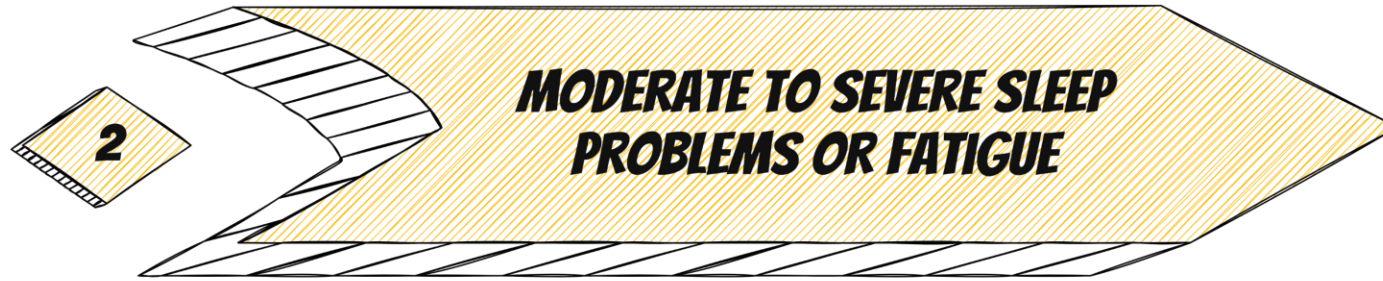
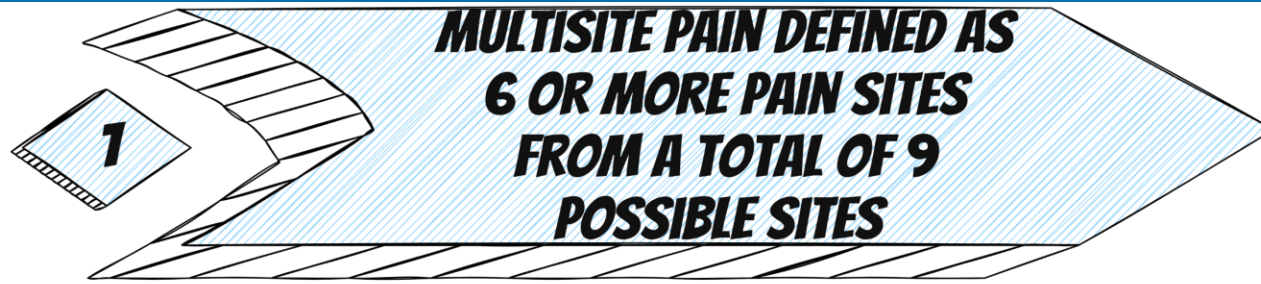
Symptoms Severity Score SSS

0 MUSCLE PAIN 0 NERVOUSNESS 0 LOSS/CHANGE IN TASTE
0 IRRITABLE BOWEL SYNDROME 0 CHEST PAIN 0 SEIZURES
0 FATIGUE/TIREDNESS 0 BLURRED VISION 0 DRY EYES
0 THINKING OR REMEMBERING PROBLEM 0 FEVER 0 SHORTNESS OF
BREATH
0 MUSCLE WEAKNESS 0 DIARRHEA 0 LOSS OF APPETITE
0 HEADACHE 0 DRY MOUTH 0 RASH
0 PAIN/CRAMPS IN ABDOMEN 0 ITCHING 0 SUN SENSITIVITY
0 NUMBNESS/TINGLING 0 WHEEZING 0 HEARING DIFFICULTIES
0 DIZZINESS 0 RAYNAULD'S 0 EASY BRUISING
0 INSOMNIA 0 HIVES/WELTS 0 HAIR LOSS
0 DEPRESSION 0 RINGING IN EARS 0 FREQUENT URINATION
0 CONSTIPATION 0 VOMITING 0 PAINFUL URINATION
0 PAIN IN UPPER ABDOMEN 0 HEARTBURN 0 BLADDER SPASMS
0 NAUSEA 0 ORAL ULCERS

0 symptoms Give yourself a score of 0
1 to 10 Give yourself a score of 1
11 to 24 Give yourself a score of 2
25 or more Give yourself a score of 3

AAPT-APS

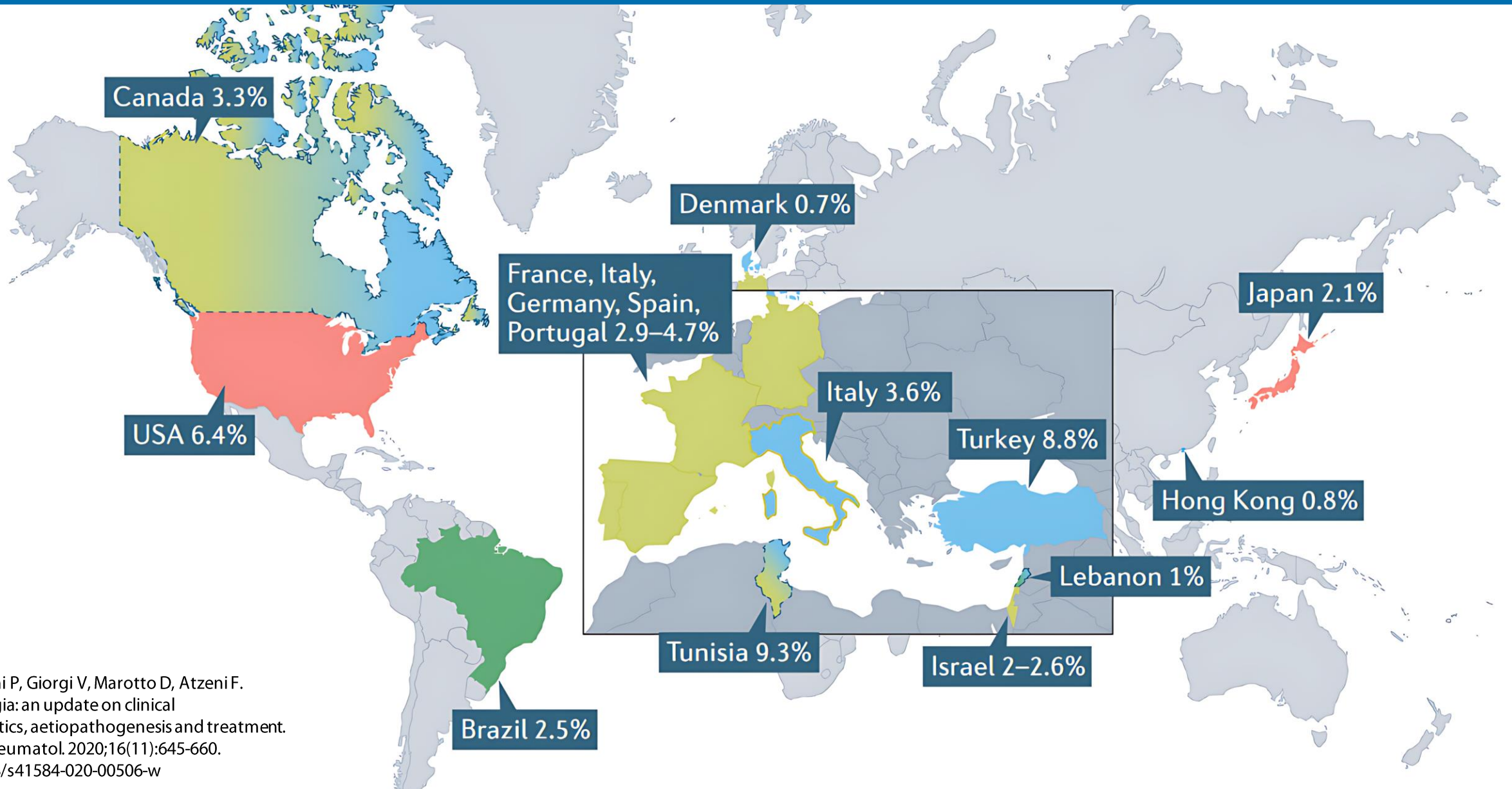
Diagnostic Criteria for Fibromyalgia



The presence of another pain disorder or related symptoms does not rule out a diagnosis of FM. However, a clinical assessment is recommended to evaluate for any condition that could fully account for the patient's symptoms or contribute to the severity of the symptoms.

L. M. Arnold, R. M. Bennett, L. J. Crofford, L. E. Dean, D. J. Clauw, D. L. Goldenberg, M.-A. Fitzcharles, E. S. Paiva, R. Staud, P. Sarzi-Puttini, D. Buskila, G. J. Macfarlane, AAPT Diagnostic Criteria for Fibromyalgia. The Journal of Pain 20, 611–628 (2019).

Prevalence and burden of disease



Prevalence and burden of disease

Criteria and/or questionnaire	Country or region	Study	Total prevalence (%)
1990 ACR	Hong Kong	Scudds et al. (2006) ¹³	0.8
	Denmark	Prescott et al. (1993) ¹⁵	0.7
	Italy	Salaffi et al. (2005) ¹⁶	3.6
	Turkey	Turhanoglu et al. (2008) ⁸	8.8
The 2010 ACR criteria	Japan	Nakamura et al. (2014) ⁷	2.1
	USA	Vincent et al. (2013) ¹²	6.4
LFESSQ	Israel	Ablin et al. (2012) ¹⁴	LFESSQ-4: 2.6 LFESSQ-6: 2.0
	France, Italy, Germany, Spain and Portugal	Branco et al. (2009) ⁵	LFESSQ-4: 4.7 LFESSQ-6: 2.9
COPCORD	Brazil	Rodrigues Senna et al. (2004) ¹⁰	2.5
LFESSQ and the 1990 ACR criteria	Canada	White et al. (1999) ¹¹	3.3
	Tunisia*	Guermazi et al. (2008) ⁹	9.3
COPCORD and the 1990 ACR criteria	Lebanon	Chaaya et al. (2011) ⁶	1
	World	Queiroz (2013) ¹	2.7

Quality of life

TABLE 1 Descriptive statistics of questionnaires of quality of life (QoL) (SF-36 subscales and global mean score), and Fibromyalgia severity (FSQ), as well as of the different variables considered as factors of influence on QoL.

QoL/FM severity	Mean (SD)	Variables affecting QoL	Mean (SD)
SF-36 (n = 129)		FM symptoms	
Physical Role	28.34 (20.36)	Pain (NRS) (n = 126)	7.29 (1.88)
Physical Function	42.36 (19.92)	Anxiety and depression (HADS) (n = 130)	21.22 (7.28)
Body Pain	22.36 (15.92)	Sleep quality (PSQI) (n = 127)	13.09 (4.37)
General Health	29.82 (16.71)	Lifestyle	Percentage (yes-no)
Vitality	25.27 (13.55)	Balanced Diet (n = 129)	74.4%–25.6%
Social Function	39.92 (24.01)	Regular Exercise (n = 131)	69.5%–30.5%
Mental Health	40.09 (14.87)	Overweight (n = 130)	58.5%–41.5%
Emotional Role	54.26 (28.30)	Smoke (n = 129)	22.5%–77.5%
Mean Score	35.29 (13.62)	Multi-medication (n = 131)	38.2%–61.8%
FSQ (n = 131)	21.01 (4.96)		

BMI, Body Mass Index; FSQ, Fibromyalgia Survey Questionnaire; NRS, Numeric Rating Scale; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; HADS, hospital anxiety and depression scale.

The cost of Fibromyalgia

- Estimates of the standardized average annual costs per patient per year ranged from **\$ 1750** to **\$ 35,920** in the USA considering only health care costs, and from \$ 6208 to \$ 9505 according to the articles that considered overall total direct costs.
- In Europe, the mean annual direct health care costs per patient ranged between **\$ 1250** and **\$ 8504** per patient, while Canadian studies showed how health care annual direct costs varied from **\$ 4085** to **\$ 5264** per patient.
- With regard to Asian countries, health care costs have been estimated around \$ 2373 per patient in Israel, \$ 5879 in Iran [74], \$ 813 in Korea and \$ 19,802 in Japan.

Genetic predisposition

- **CATECHOLAMINE-O-METHYLTRANSFERASE (COMT)**
- **MONOAMINE OXIDASE (MAOA)**
- **SEROTONIN TRANSPORTER (SLC6A4) AND RECEPTORS (HTR2A, HTR3A, HTR3B)**
- **μ 1 OPIOID RECEPTOR (OPRM1)**
- **BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF)**
- **GLUTAMATE IONOTROPIC RECEPTOR AMPA TYPE SUBUNIT 4**
- **CANNABINOID RECEPTOR 1**

- **TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL SUBFAMILY V MEMBER (TRPV3)**
- **TACHYKININ RECEPTOR 1**
- **SODIUM VOLTAGE-GATED CHANNEL ALPHA SUBUNIT 9 (SCN9A)**
- **DOPAMINE RECEPTOR D3**
- **ADRENOCEPTOR BETA 2**
- **ANDROGEN RECEPTOR GENE (ADRB2 AND ADRA1A)**



FM and personality

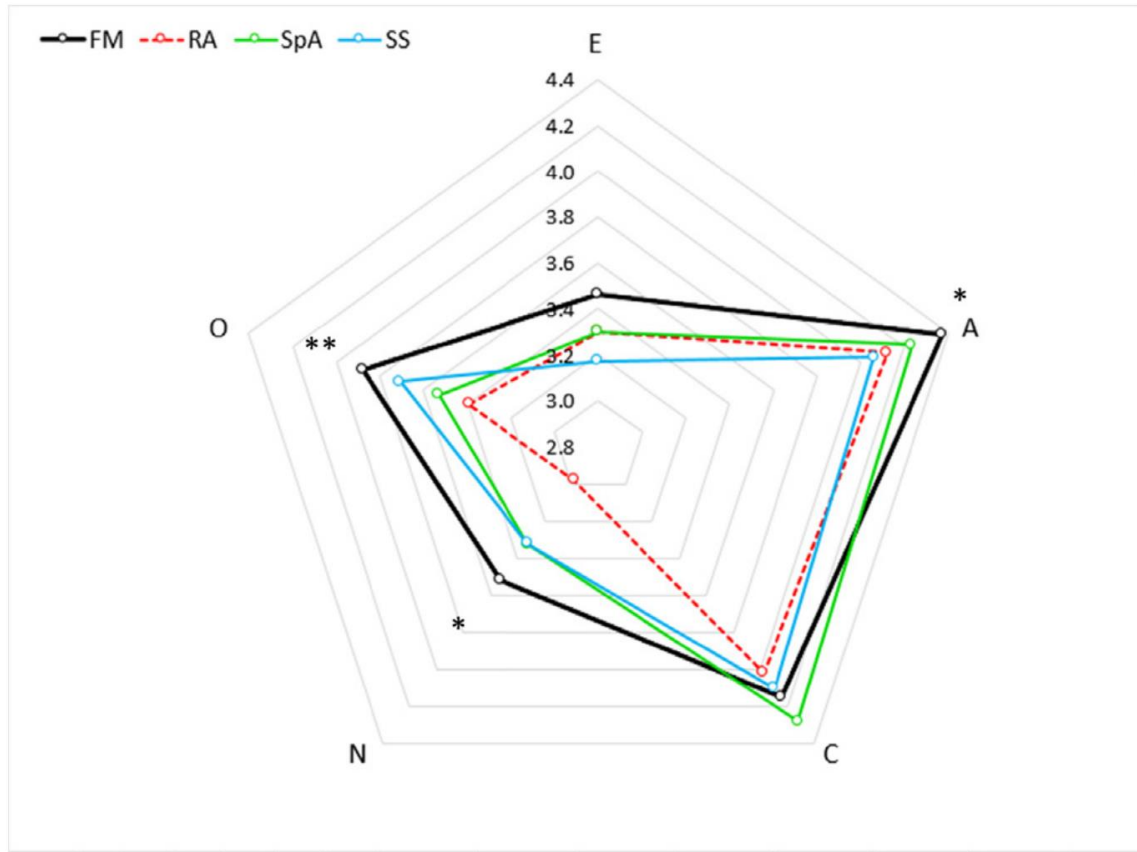
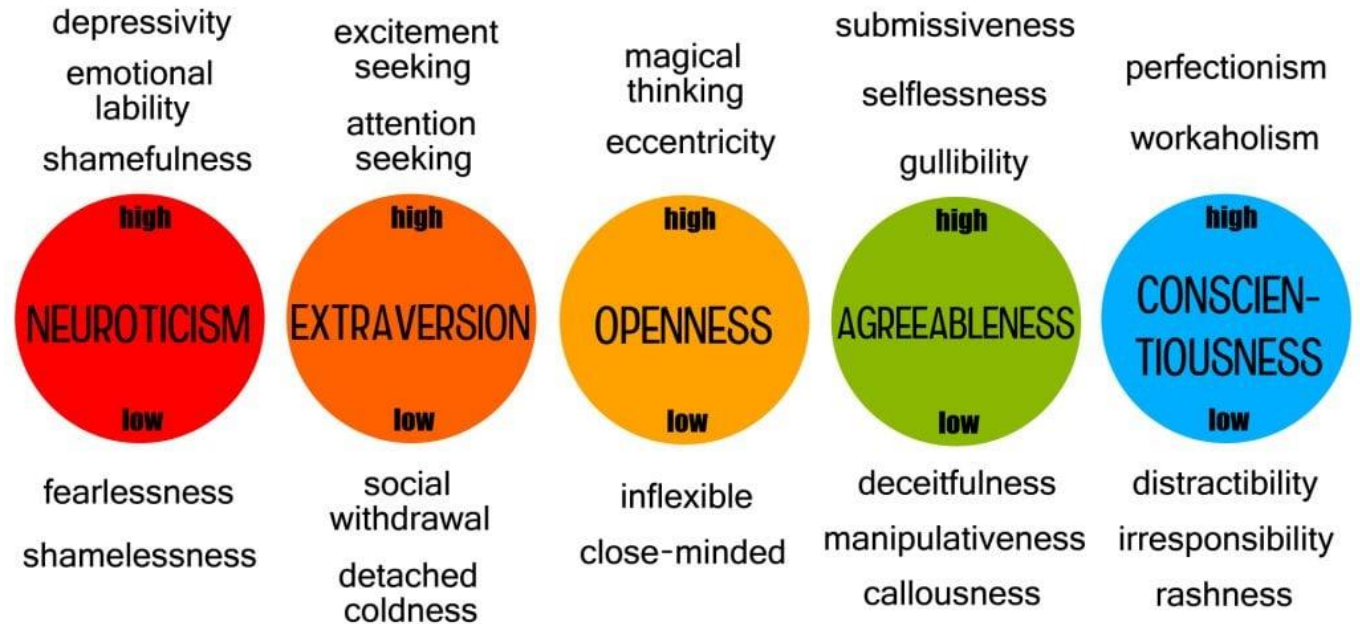


Fig. 1. Comparison of the personality dimensions in rheumatic diseases. FM: fibromyalgia, RA: rheumatoid arthritis, SpA: spondyloarthritis, SS: Sjögren's syndrome. * $P < 0.05$; ** $P < 0.01$.

FM patients had higher scores on ***agreeableness, neuroticism and openness*** than those with other rheumatic diseases taken as a whole

The big 5 model

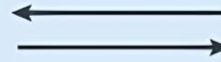


Pathophysiology

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



Top
down

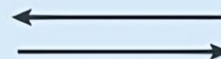
Bottom
up



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

Peripheral sensitization
(↓ nociceptive threshold)

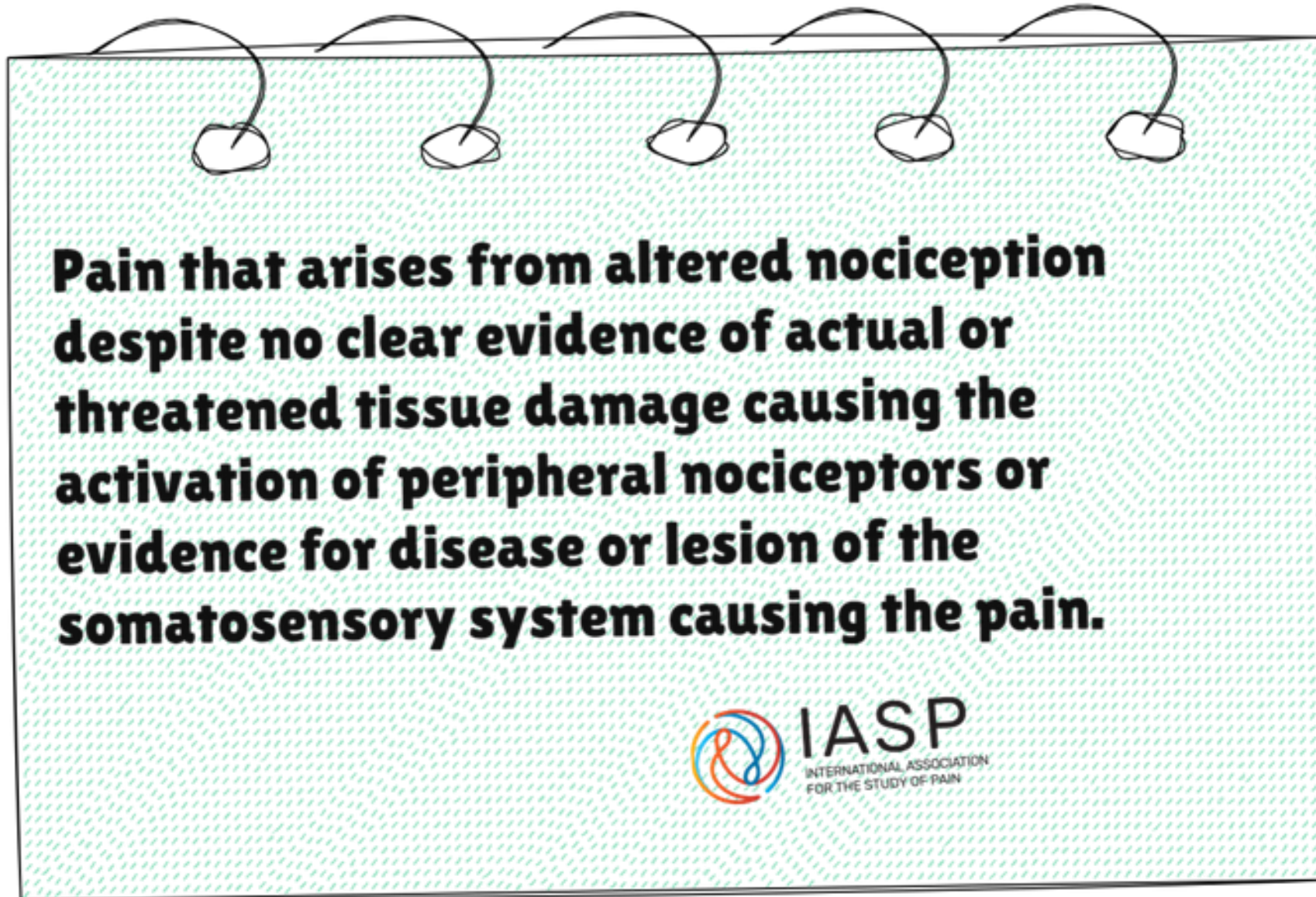
- Neuroinflammation
- Small fibre neuropathy
- Peripheral nociceptive stimuli or any chronic painful disease
- Genetic factors



■ Nociplastic alterations

■ Pathogenic mechanisms

Nociplastic pain: the third way



Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. PAIN. 2020;161(9).

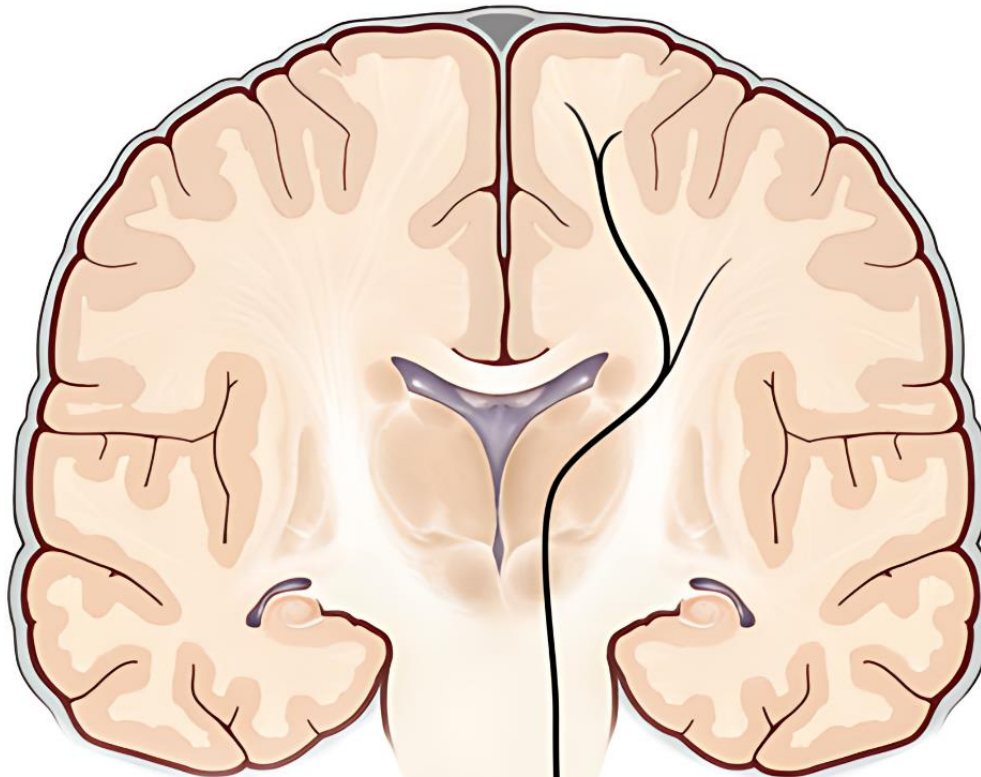
https://journals.lww.com/pain/Fulltext/2020/09000/The_revised_International_Association_for_the.6.aspx
Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain states? Pain. 2016;157(7):1382-1386.

doi:10.1097/j.pain.0000000000000507

Nociplastic pain

Features of nociplastic pain conditions

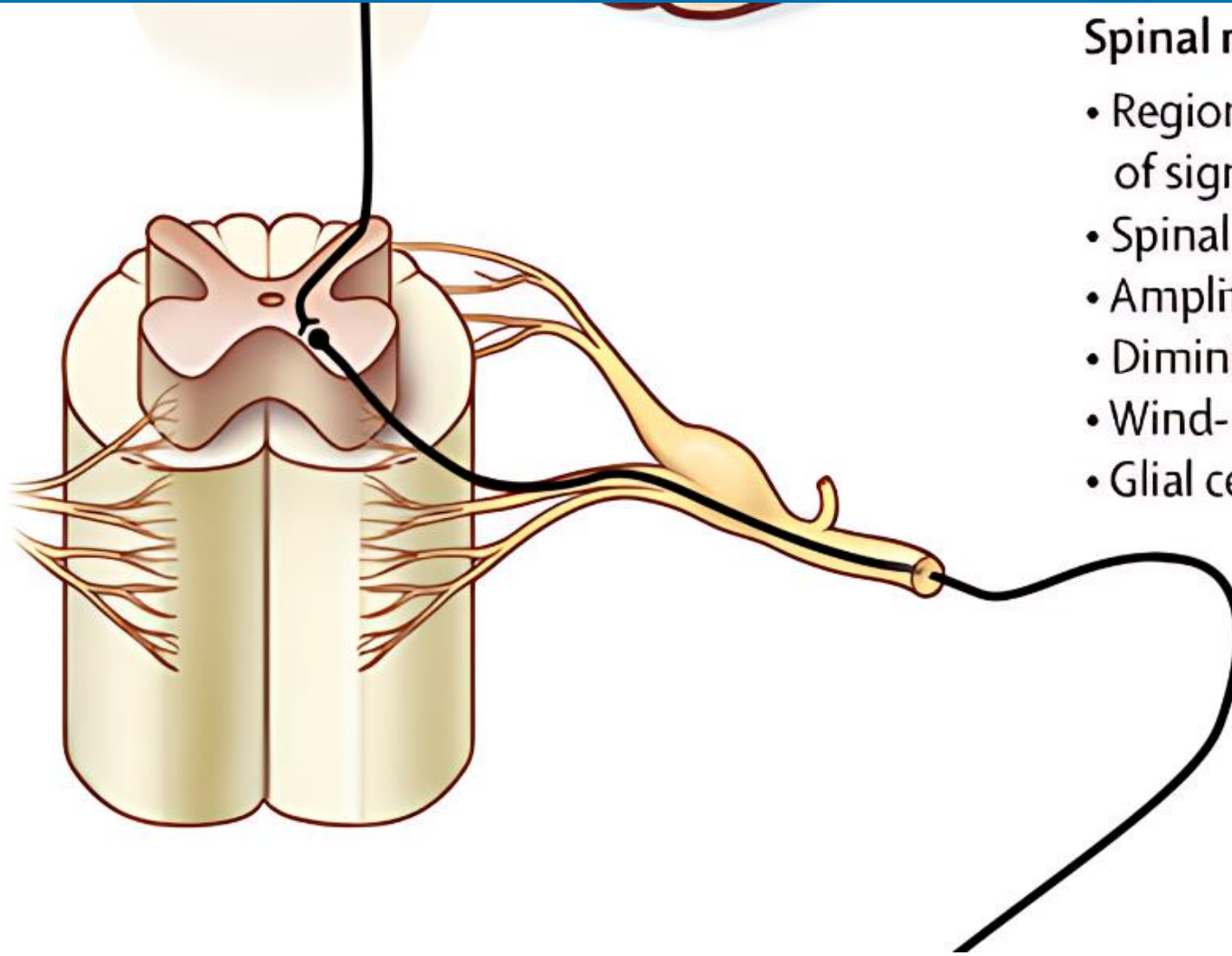
- Combined peripheral and central pain sensitisation
- Hyper-responsiveness to painful and non-painful sensory stimuli
- Associated features
 - Fatigue
 - Sleep disturbance
 - Cognitive disturbances
 - Hypersensitivity to environmental stimuli
 - Anxiety and depressed mood



Supraspinal mechanisms

- Hyper-responsiveness to pain stimuli
- Hyperactivity and connectivity in and between brain regions involved in pain
- Decreased activity of brain regions involved in pain inhibition (ie, descending inhibitory pathways)
- Elevated cerebrospinal fluid substance P and glutamate concentrations, decreased GABAergic transmission
- Changes in the size and shape of grey and white matter regions involved in pain processing
- Glial cell activation

Nociplastic pain



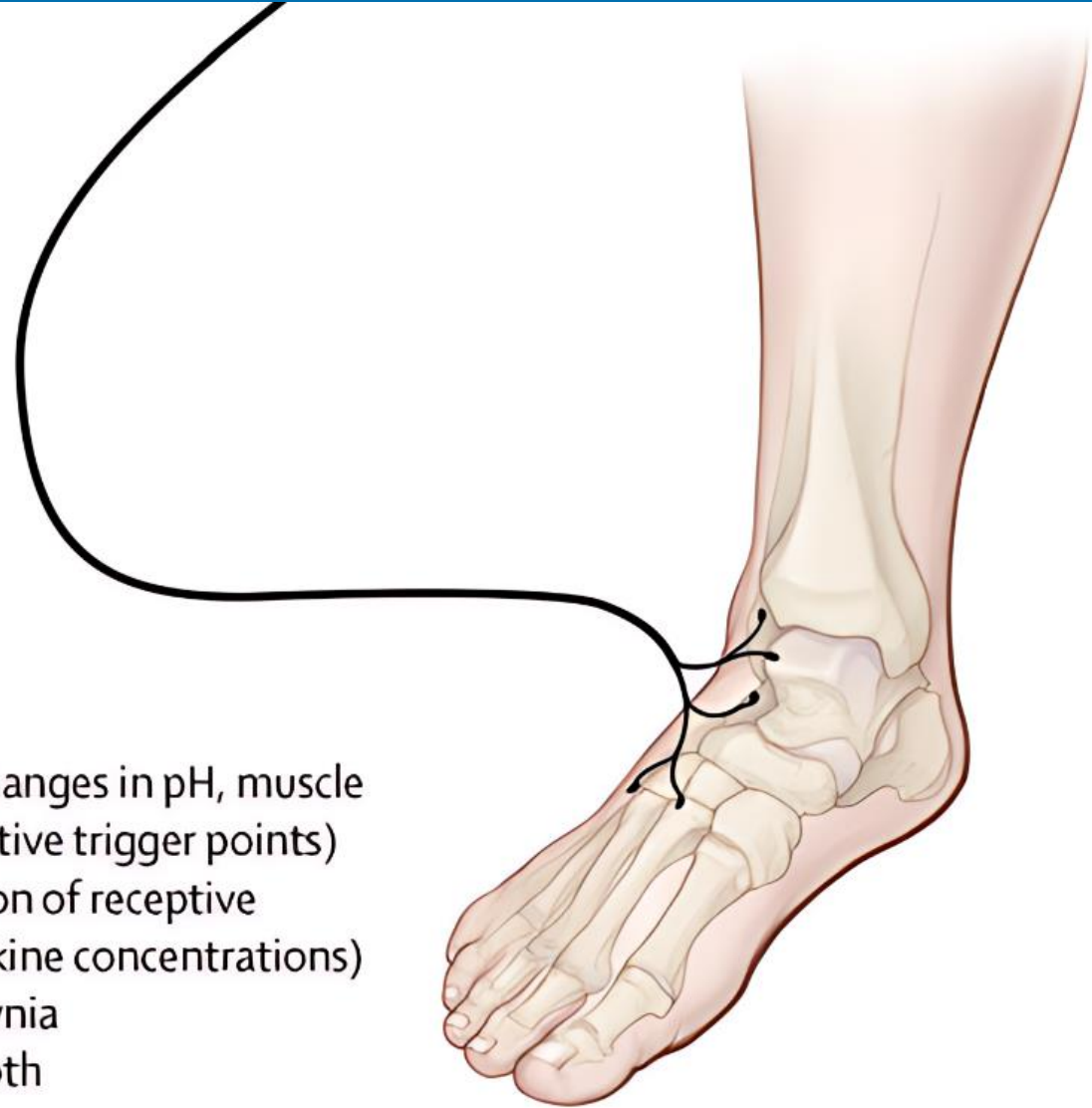
Spinal mechanisms

- Regional clustering and convergence of signals from different pain loci
- Spinal cord reorganisation
- Amplified spinal reflex transmission
- Diminished spinal inhibition
- Wind-up and temporal summation
- Glial cell activation

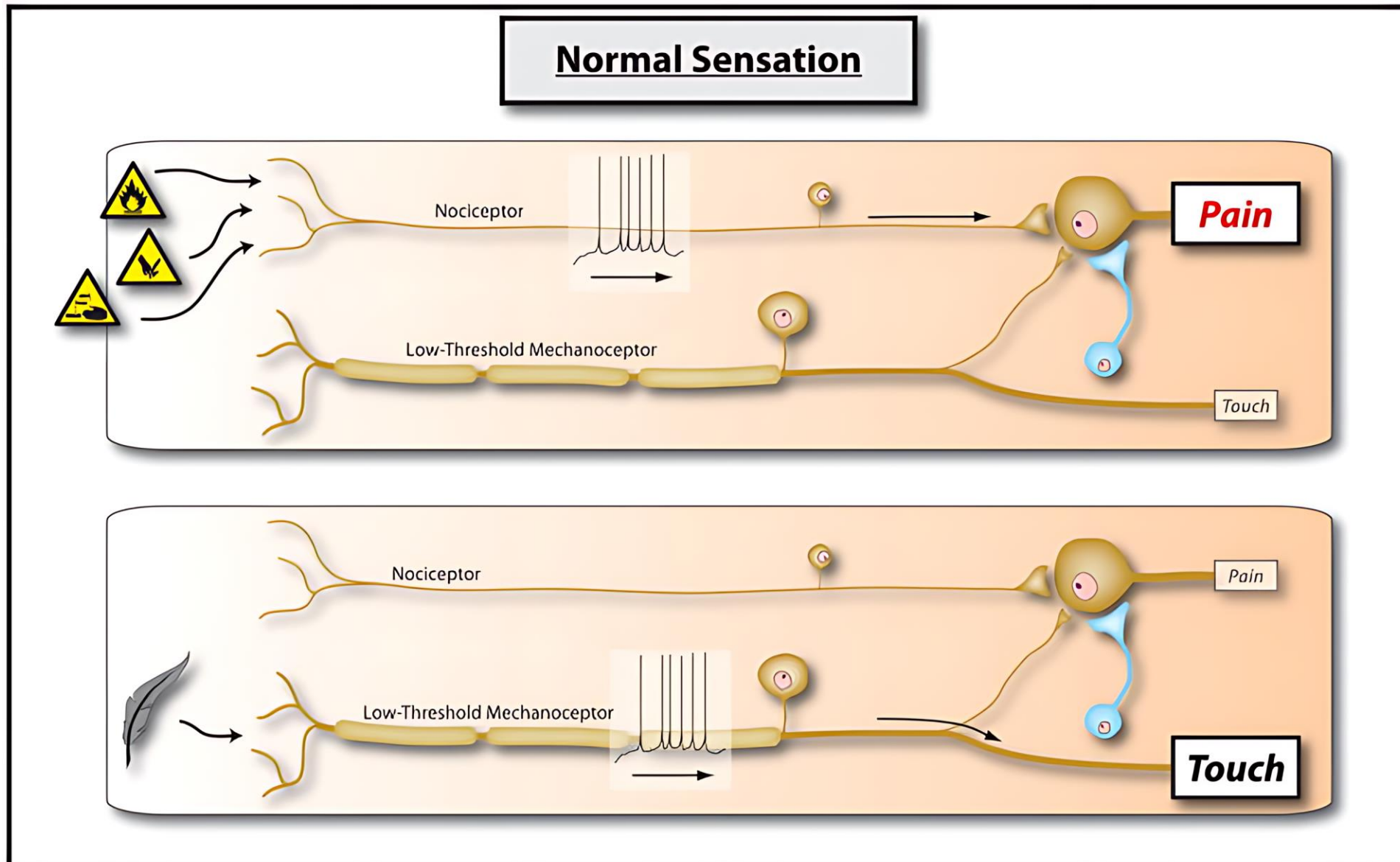
Nociplastic pain

Peripheral features

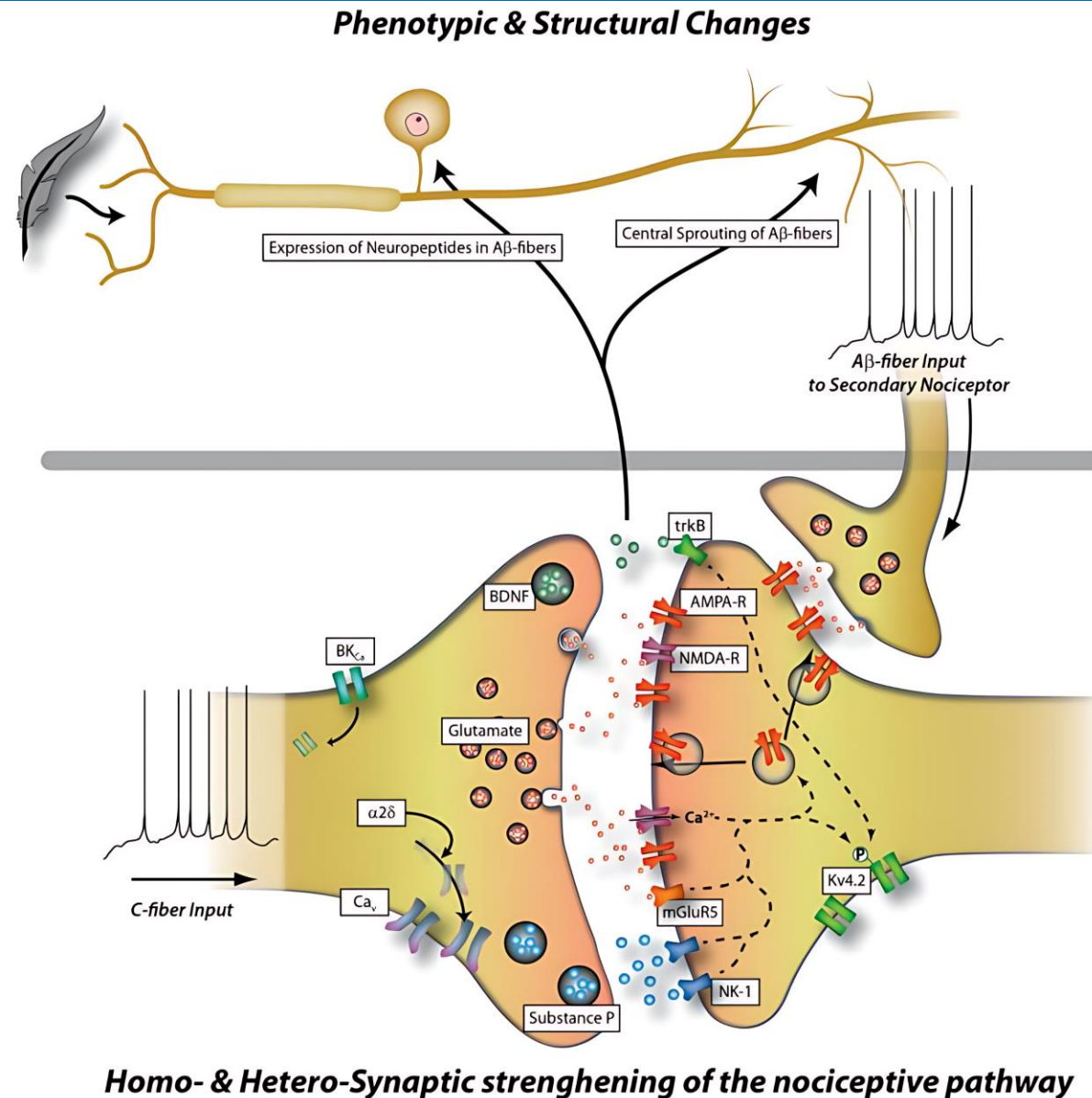
- Minor local muscle pathology (eg, changes in pH, muscle fibre composition, and latent and active trigger points)
- Peripheral sensitisation (eg, expansion of receptive fields, elevated cytokine and chemokine concentrations)
- Hyperalgesia, dysesthesia, and allodynia
- Localised or diffuse tenderness, or both



Central sensitization

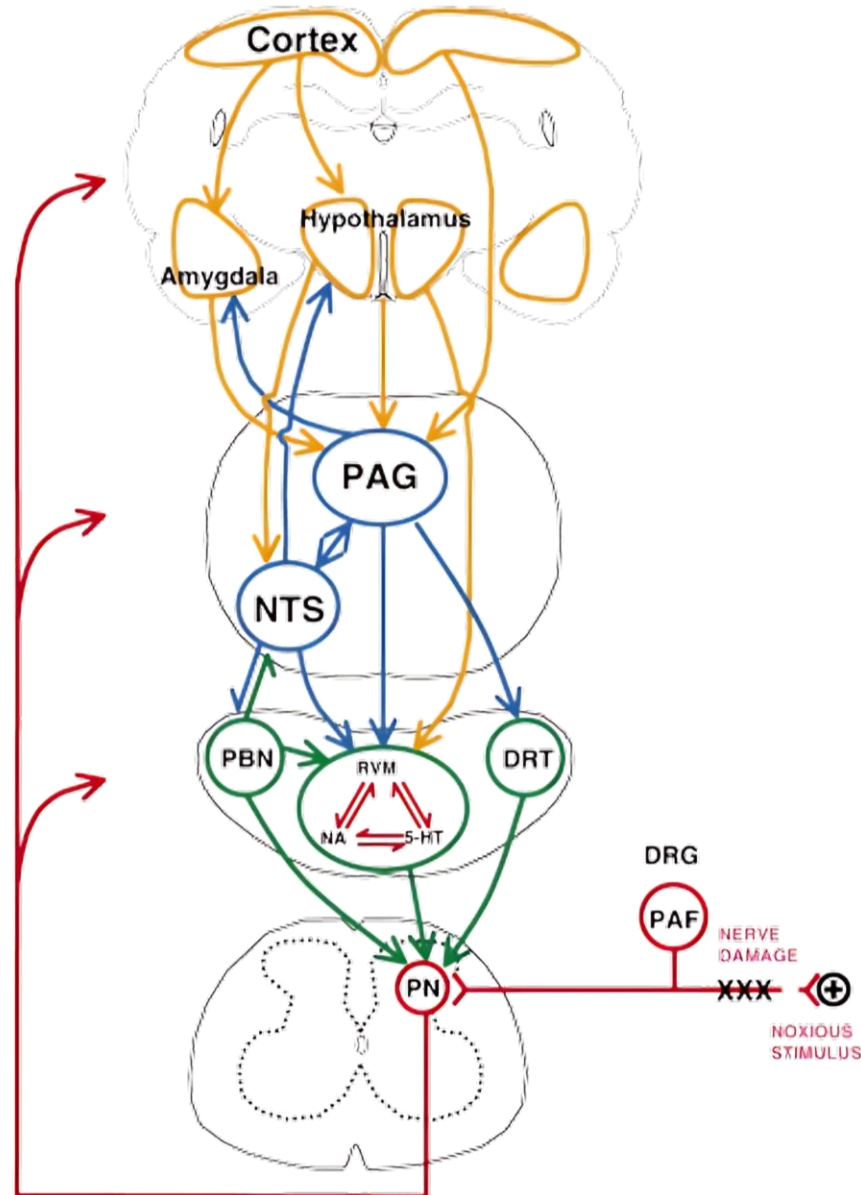


Central sensitization

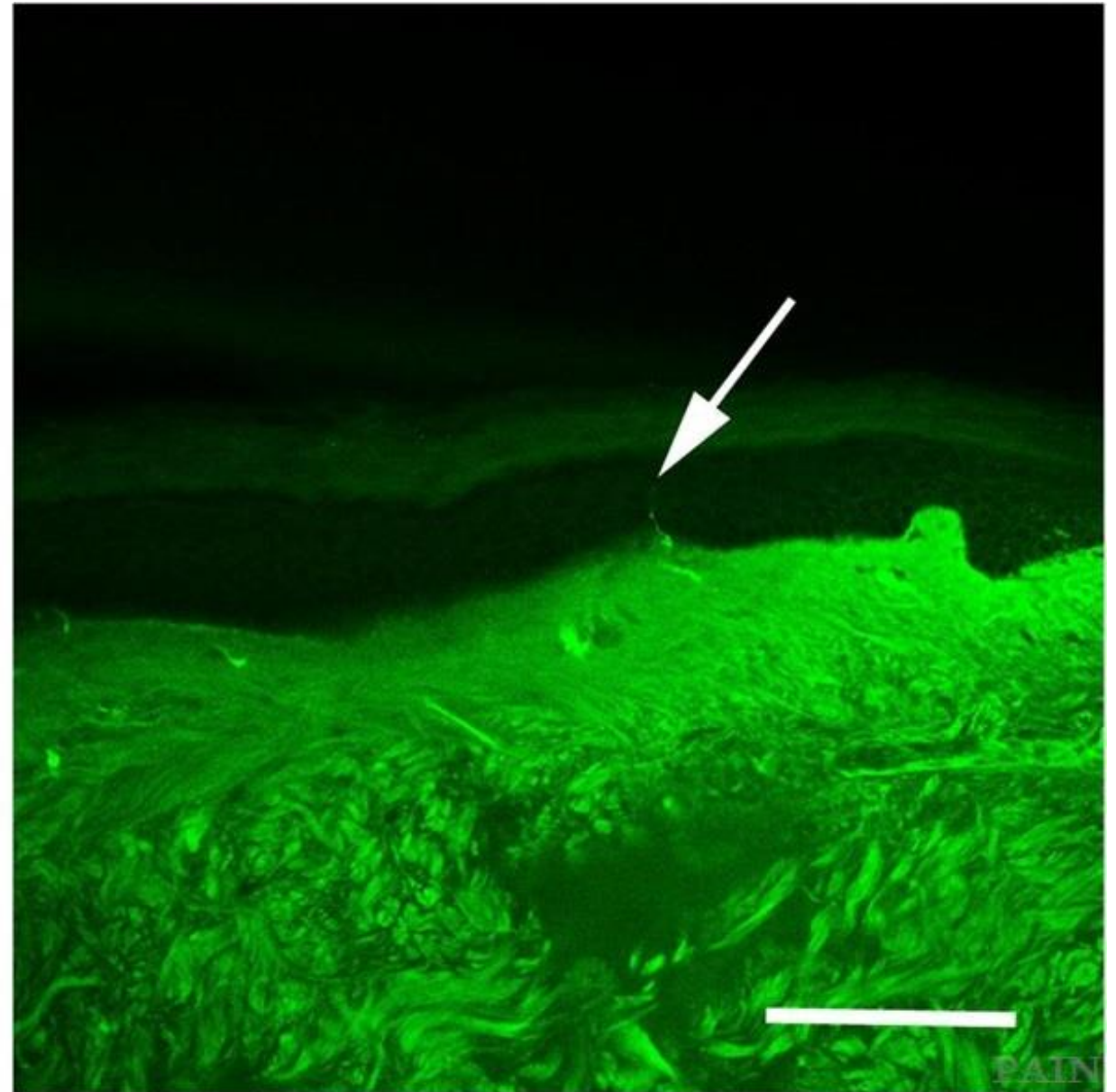
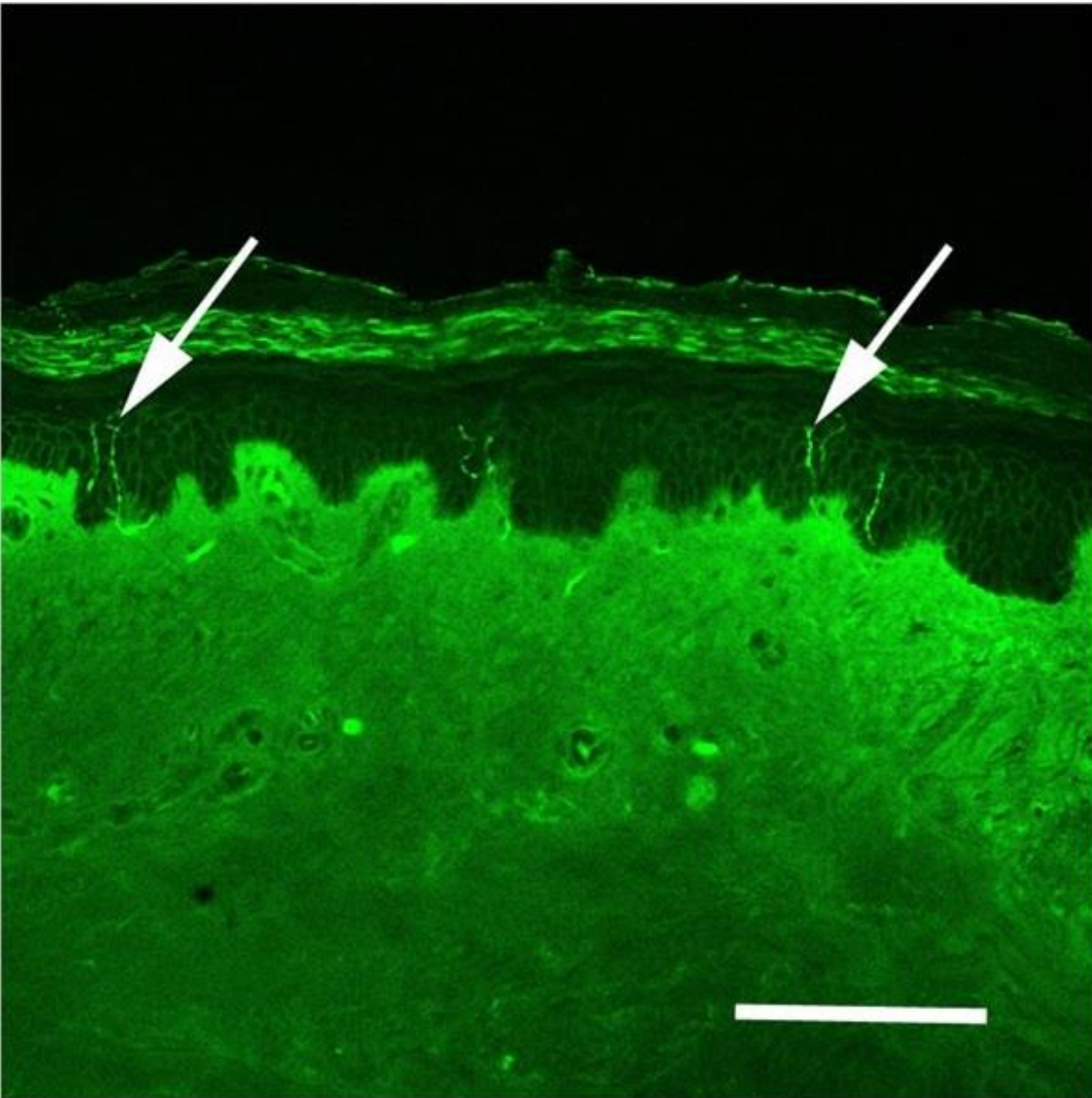


von Hehn CA, Baron R, Woolf CJ.
Deconstructing the Neuropathic
Pain Phenotype to Reveal Neural
Mechanisms. *Neuron*
2012;73:638–52.
<https://doi.org/10.1016/j.neuron.2012.02.008>.

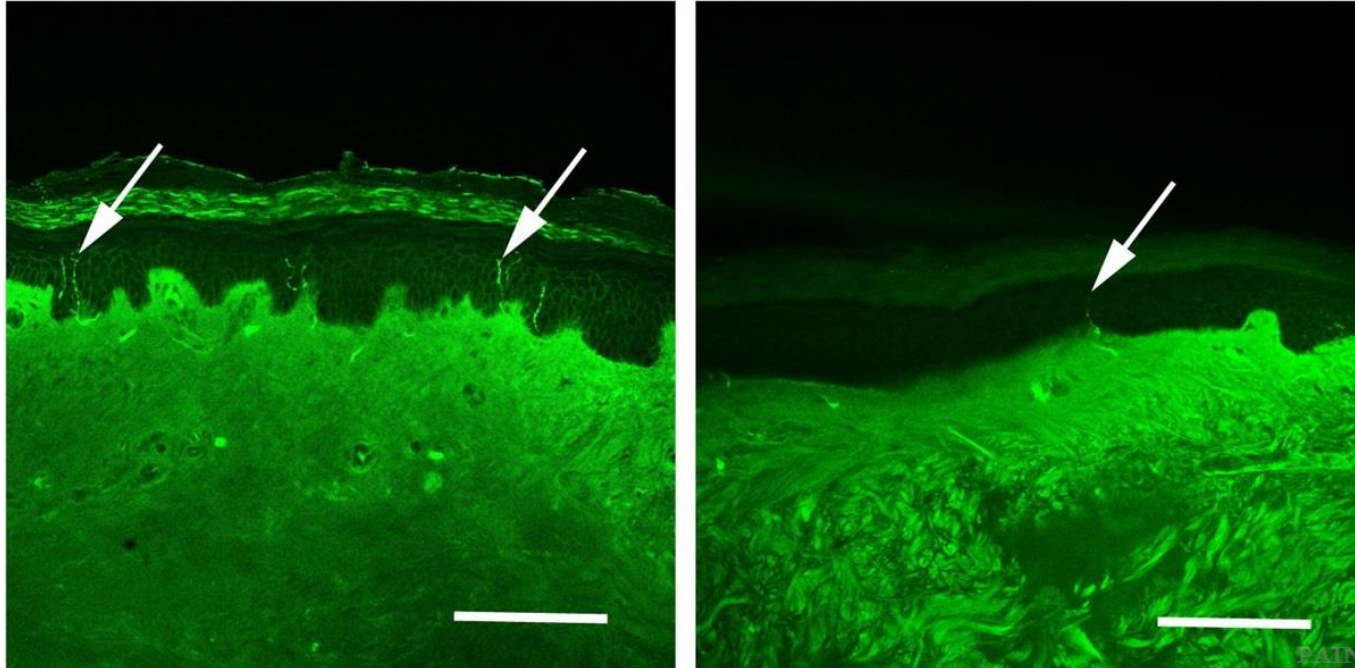
Descending pathways



Small-fiber neuropathy



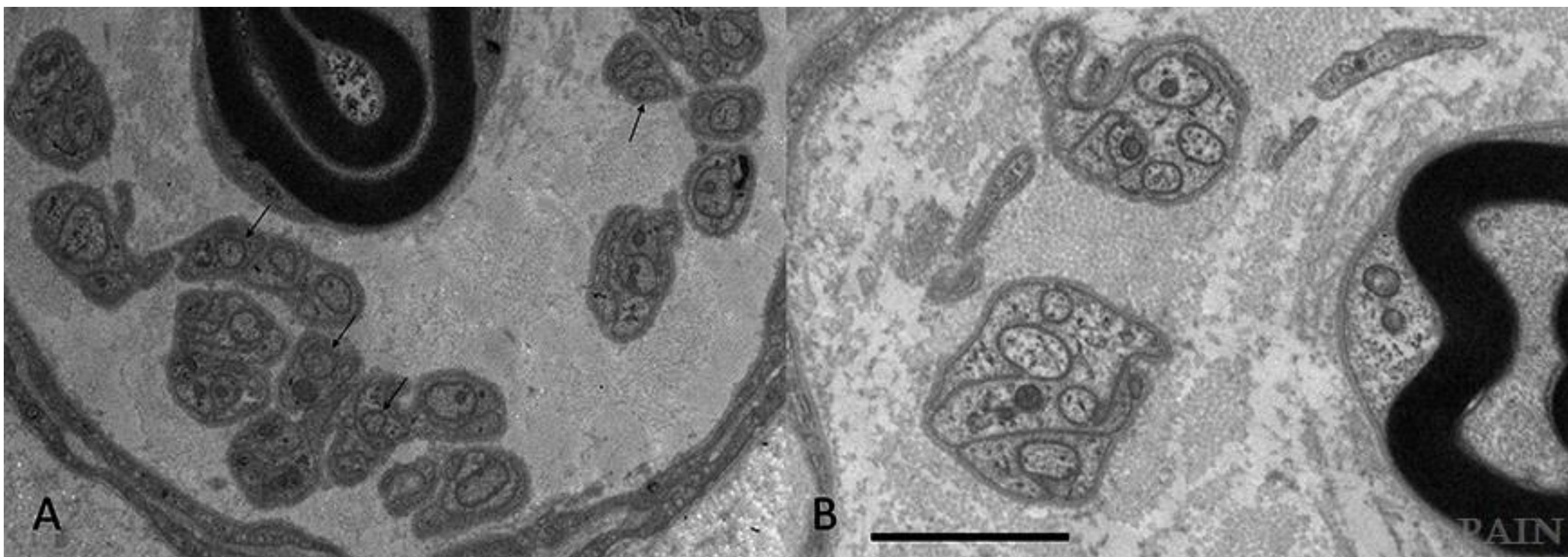
Small-fiber neuropathy



Immunohistochemical visualization of sensory nerve endings in distal-leg skin biopsy by anti-PGP9.5-immunoreactivity. Arrows depict labeled axons.

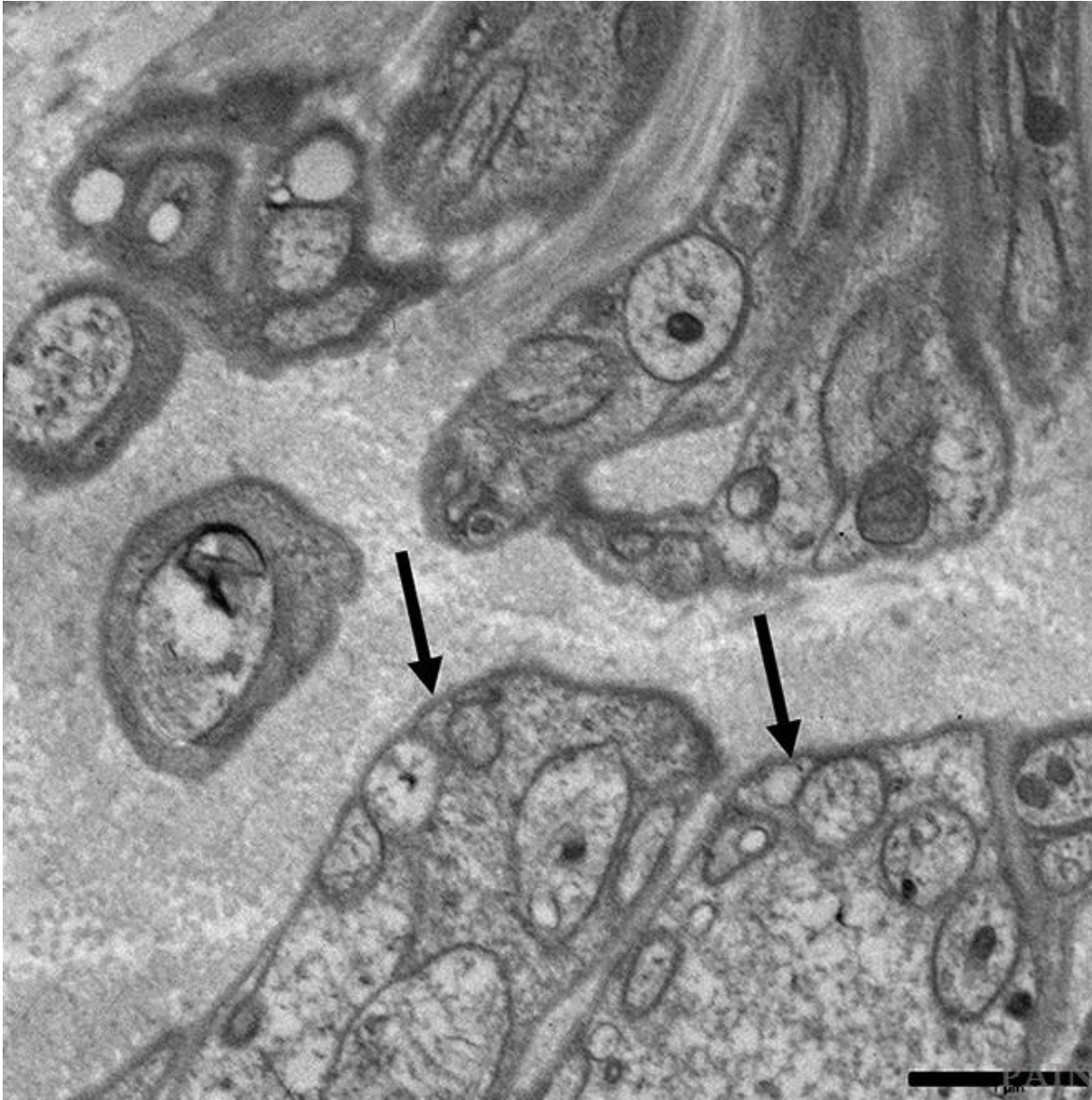
- (A) Biopsy from 44-year-old Caucasian female, control subject with normal density of epidermal innervation (337 neurites/mm² skin surface area; at the 76th centile of predicted value).
- (B) Biopsy from 47-year-old Caucasian female, fibromyalgia subject with reduced density of epidermal innervation diagnostic for small-fiber polyneuropathy (135 neurites/mm² skin surface area; at the 3rd centile of predicted value). Bars represent 50 μ m.

Small-fiber neuropathy



Example of axons with reduced diameters in patients with FMS. Electron micrograph of a Remak bundle ($\times 2704$). Numerous unmyelinated fibers of small diameter (arrows) are found in a patient with FMS (A), but not in a normal control (B). Bar = 2 μm . FMS, fibromyalgia syndrome.

Small-fiber neuropathy



Example of ballooned Schwann cells in patients with FMS. Electron micrograph of a Remak bundle. Example of ballooned Schwann cells (arrows), which were found in a minority of patients with FMS. Bar = 1 μm . FMS, fibromyalgia syndrome.

K. Doppler, H. L. Rittner, M. Deckart, C. Sommer, Reduced dermal nerve fiber diameter in skin biopsies of patients with fibromyalgia. *Pain* 156,2319–2325 (2015).

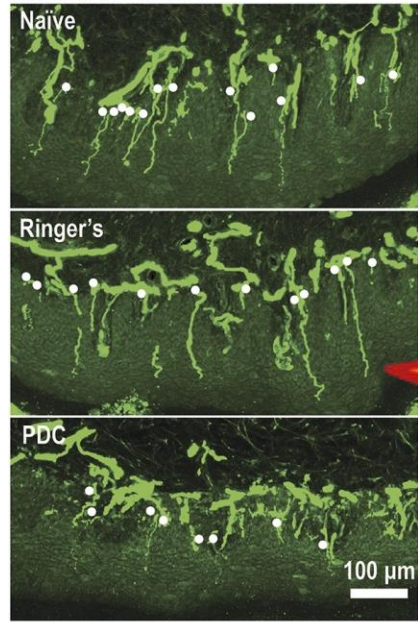
Who came first?



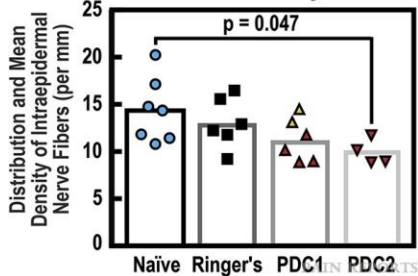
The bidirectional relationship

Bilateral insular glutamate transport inhibitor l-trans-Pyrrolidine-2,4-dicarboxylic acid (PDC) administration produced a persistent increase in multimodal pain behaviors and a decrease in peripheral nerve fibers in rat.

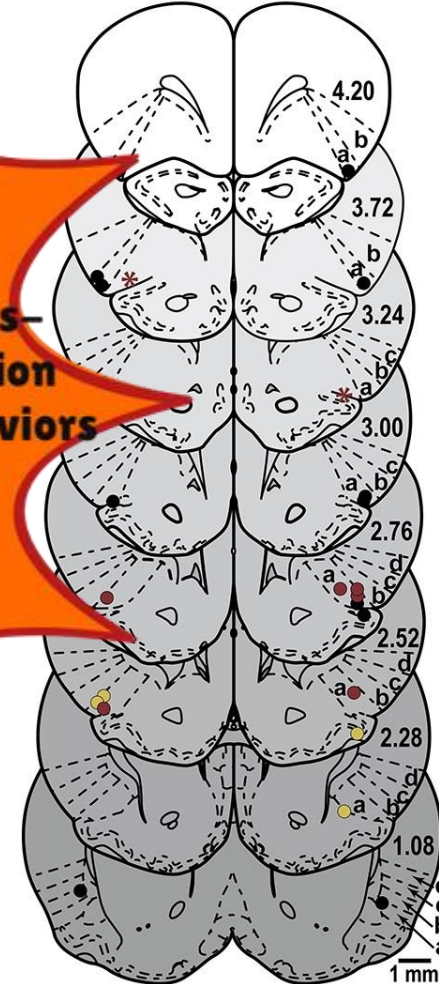
A Representative Intraepidermal Nerve Fiber Counts



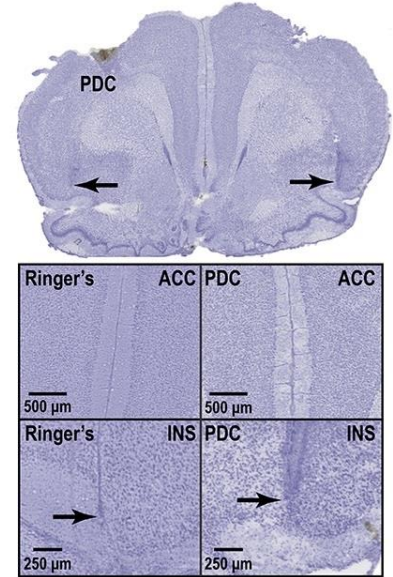
B Uni- and Bi-Lateral Delivery of PDC



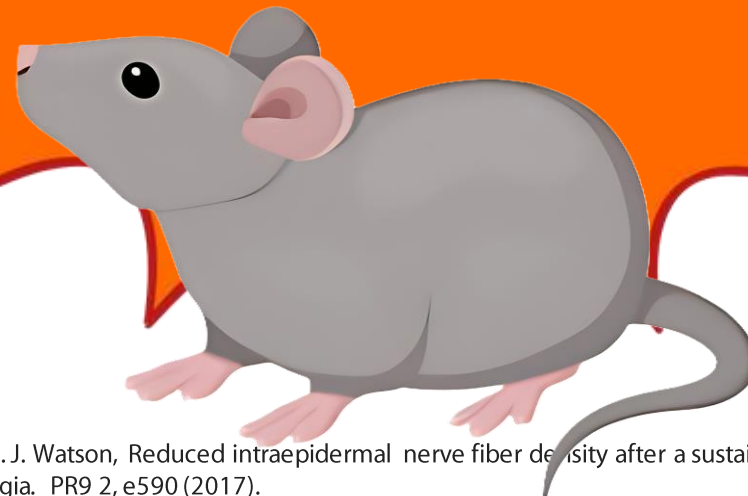
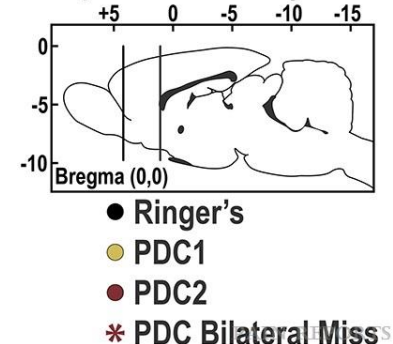
A Histological Location of Each Microinjection Site



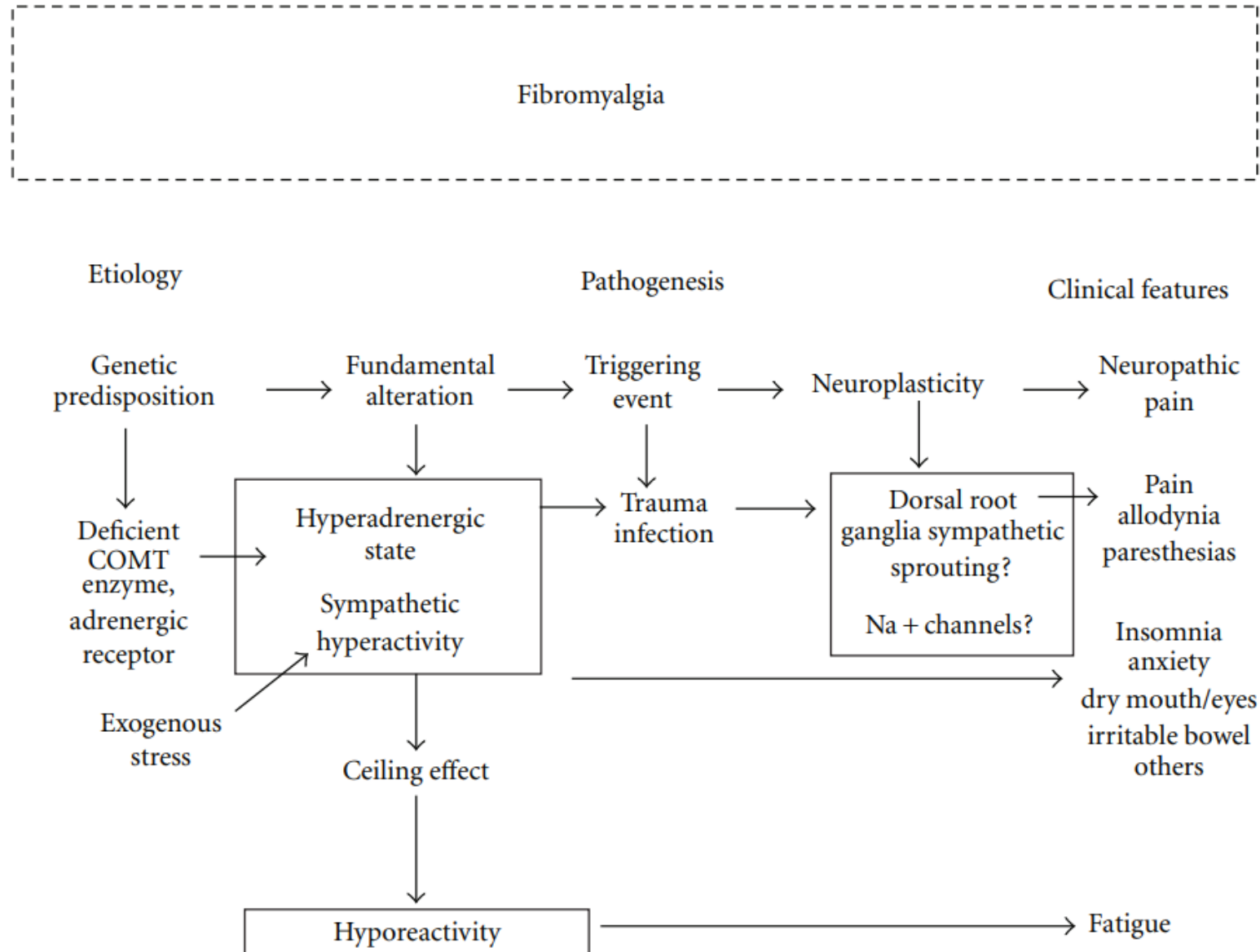
B Representative Cresyl Violet Stained Sections



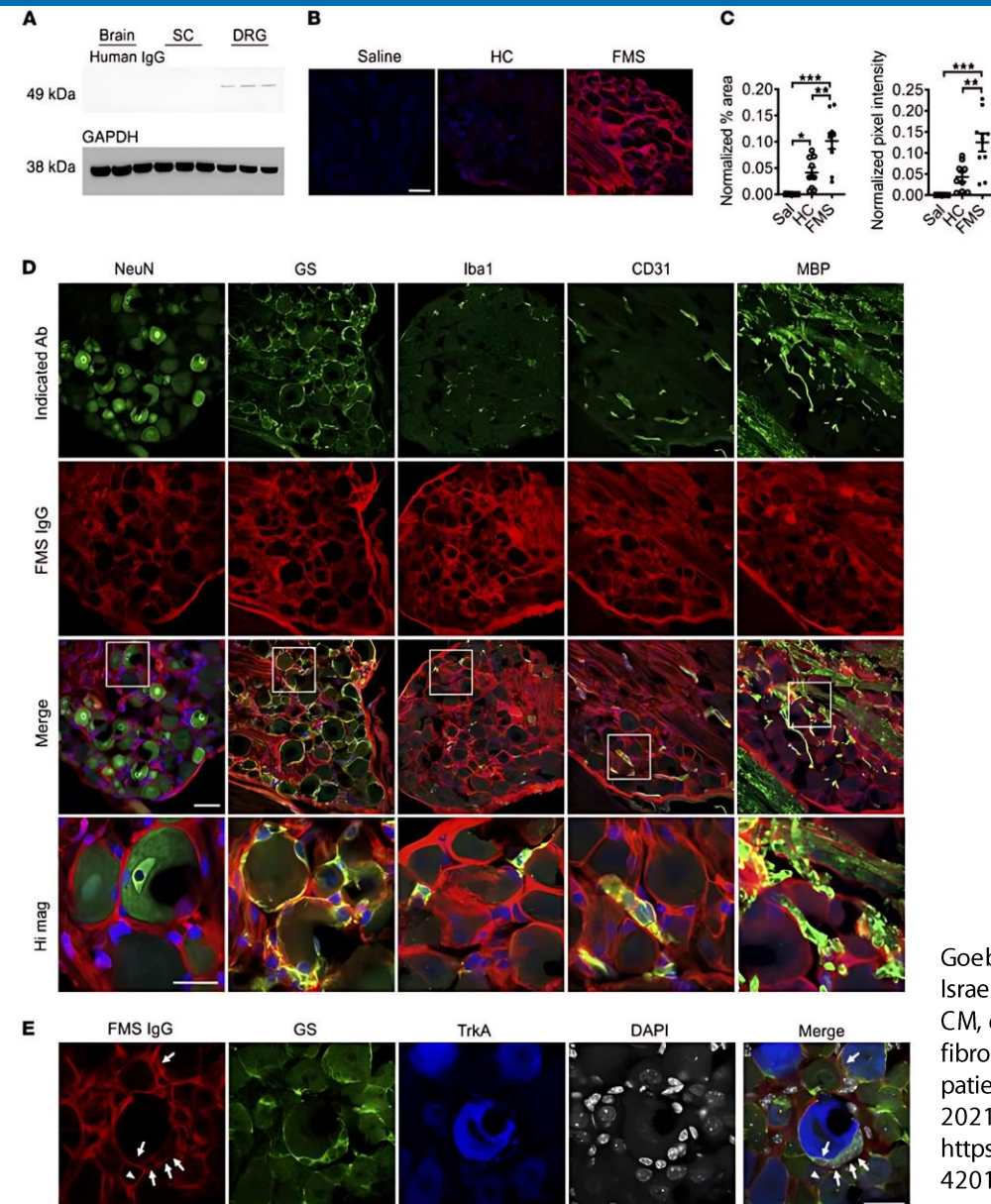
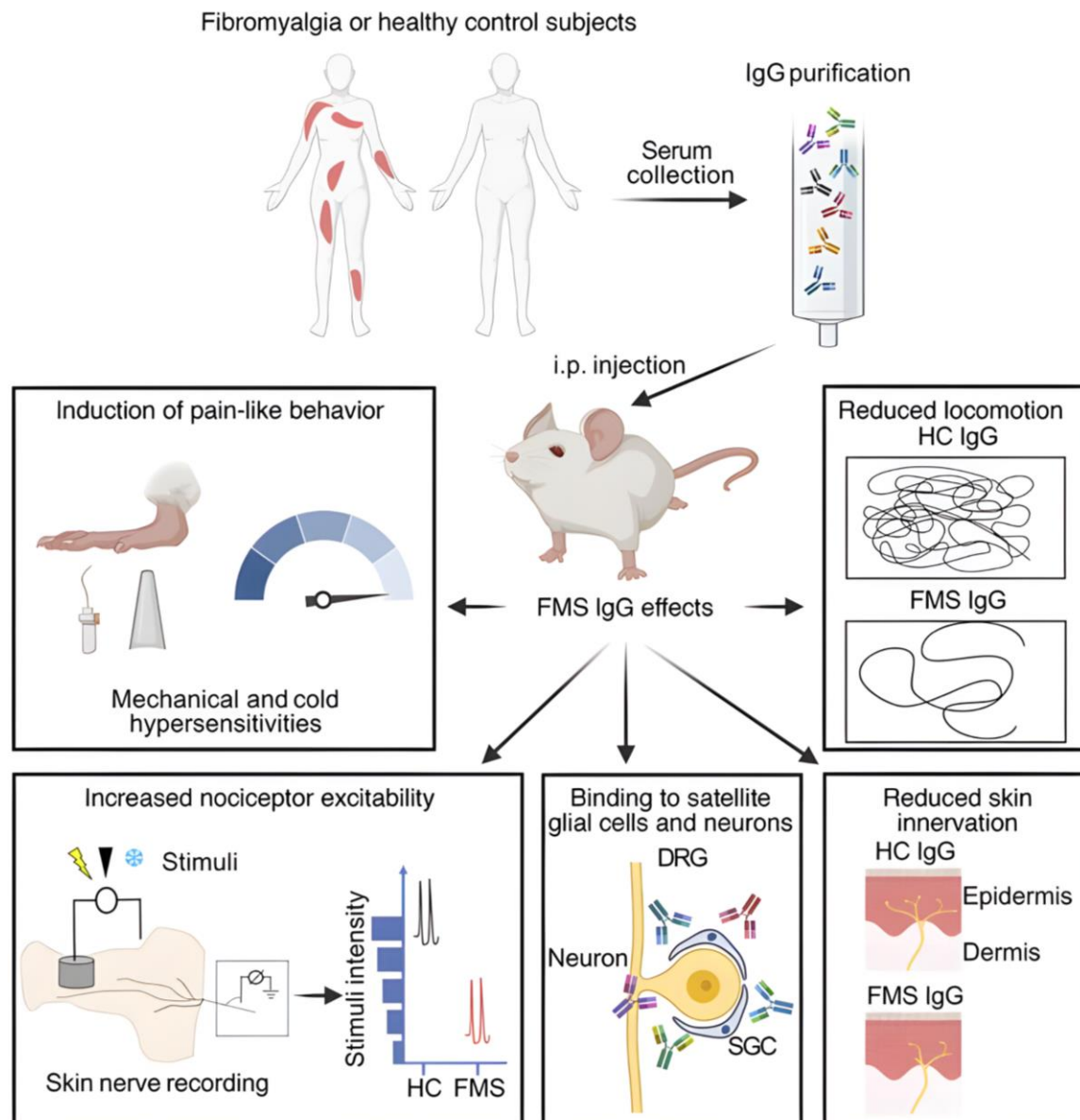
C Sagittal Schematic Showing the AP Span of the Microinjections



The «Stress-related dysautonomia» model

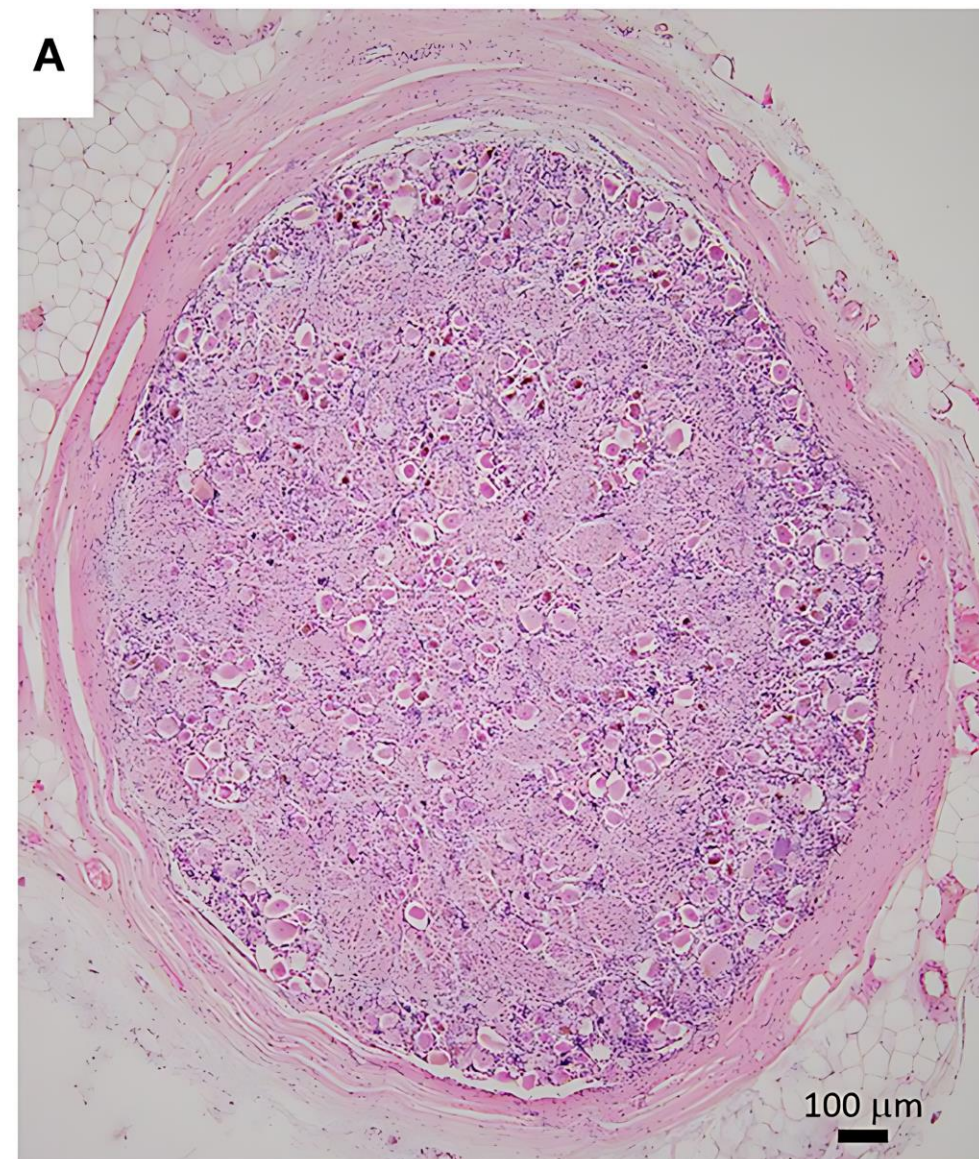
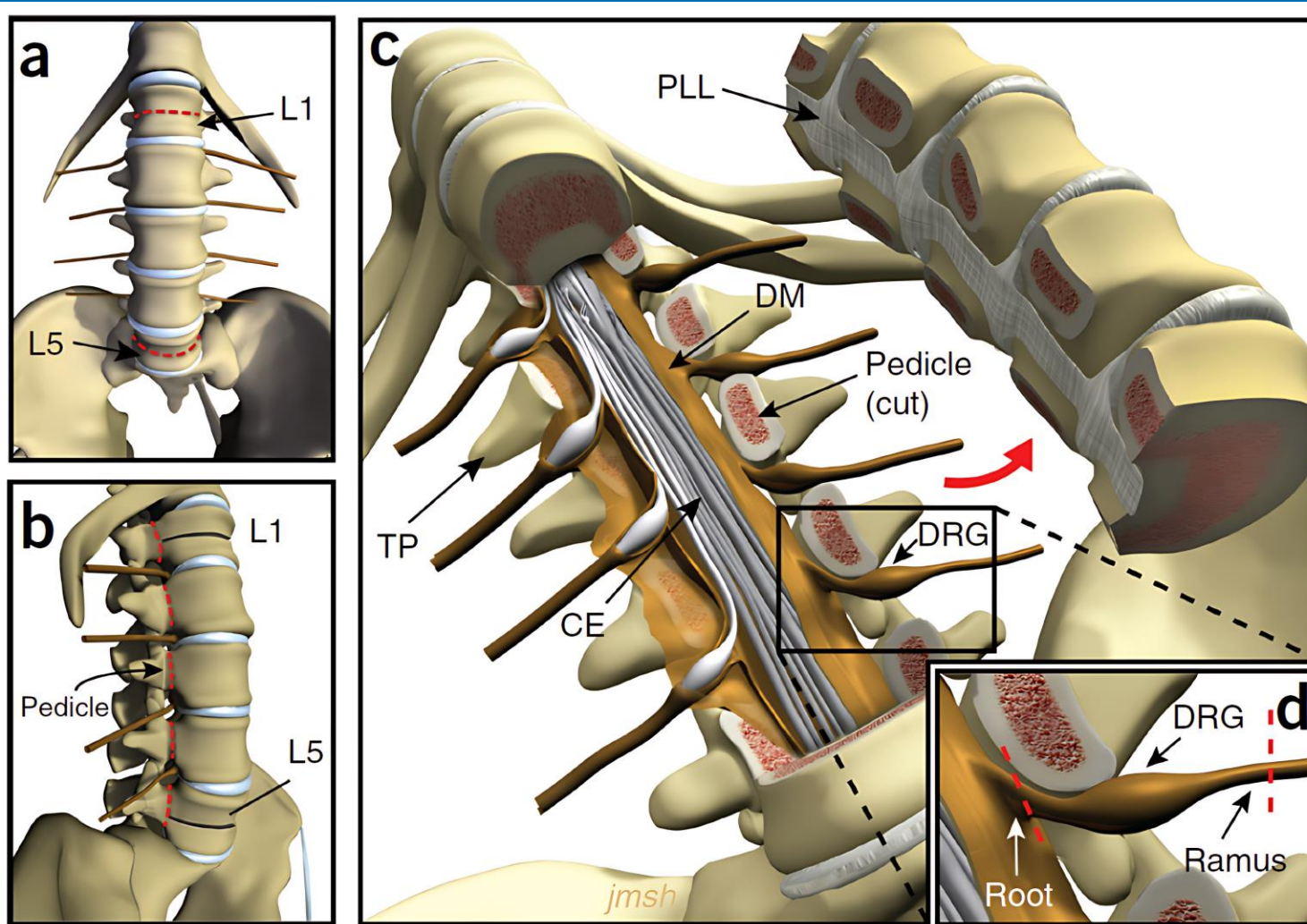


A communicable disease?



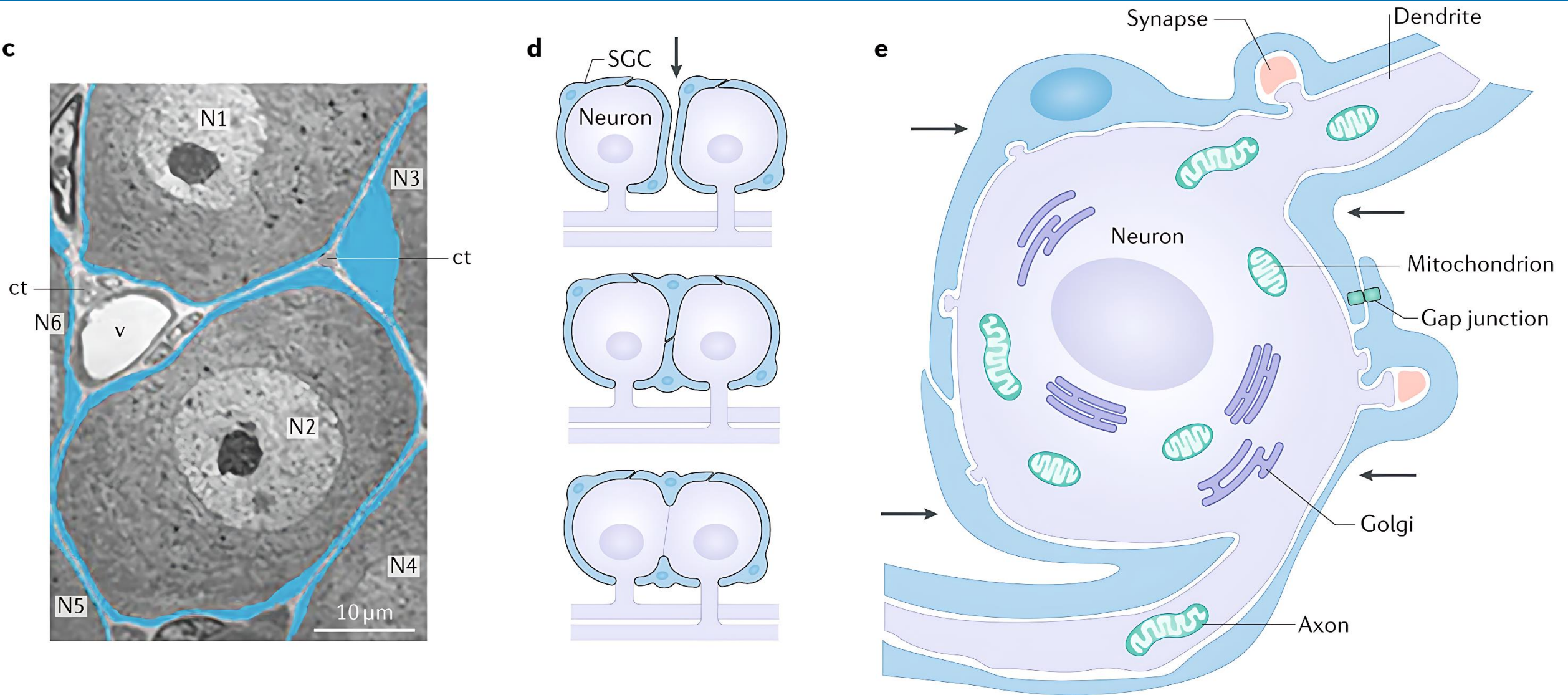
Goebel A, Krock E, Gentry C, Israel MR, Jurczak A, Urbina CM, et al. Passive transfer of fibromyalgia symptoms from patients to mice. *J Clin Invest* 2021;131. <https://doi.org/10.1172/JCI144201>.

A communicable disease?



M. V. Valtcheva, B. A. Copits, S. Davidson, T. D. Sheahan, M. Y. Pullen, J. G. McCall, K. Dikranian, R. W. Gereau, Surgical extraction of human dorsal root ganglia from organ donors and preparation of primary sensory neuron cultures. *Nat Protoc* 11, 1877–1888 (2016).
R. V. Haberberger, C. Barry, N. Dominguez, D. Matusica, Human Dorsal Root Ganglia. *Frontiers in Cellular Neuroscience* 13 (2019).

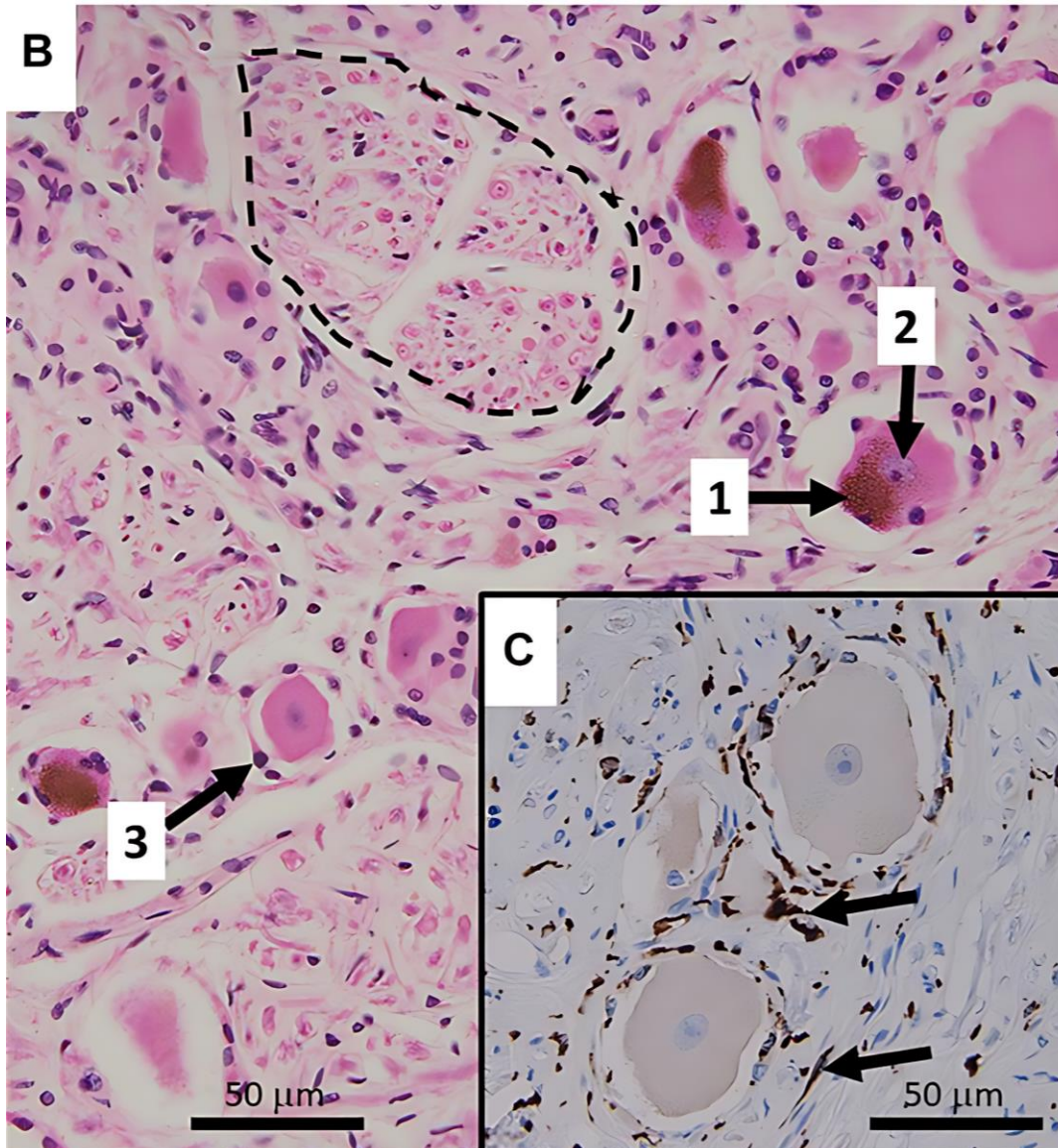
A communicable disease?



M. Hanani, D. C. Spray, Emerging importance of satellite glia in nervous system function and dysfunction. *Nat Rev Neurosci* 21, 485–498 (2020).

R. V. Haberberger, C. Barry, N. Dominguez, D. Matusica, Human Dorsal Root Ganglia. *Frontiers in Cellular Neuroscience* 13 (2019).

A communicable disease?



Cell bodies of sensory neurons containing lipofuscin (1) and a nucleus with a prominent nucleolus (2), surrounded by satellite cells (3). Bundles of nerve fibers (dashed line) are predominantly present in the center of the ganglion. The HE staining method results in shrinkage of the cell bodies which disconnects them from the layer of satellite cells. (C) Immunohistochemistry micrograph for CD163 with counterstaining for hematoxylin shows the presence and distribution of macrophages (arrows) in DRG.

A communicable disease?

HUMAN SENSORY GLIA CELLS (SGCS) AND NEURONAL FUNCTION

01

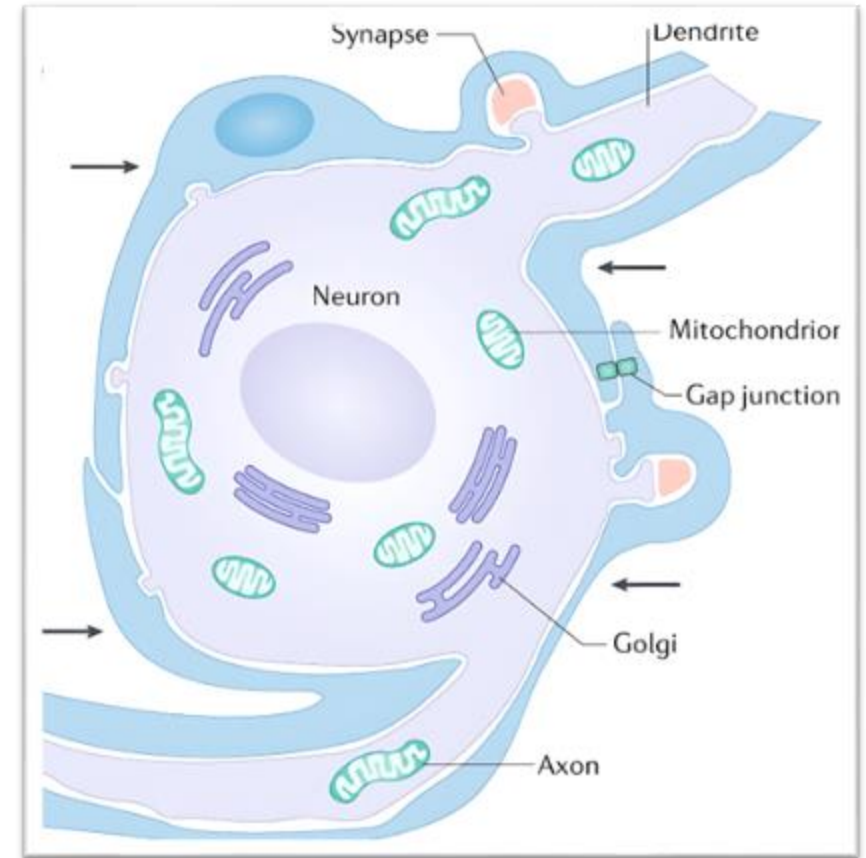
SGCs, a group of DRG and TG-specific glia cells, surround the initial segment and build an envelope around nerve cell somata. Human SGCs exhibit characteristic immunoreactivities for S100 beta protein and glutamine synthetase.

SGCs show the presence of the metabotropic glutamate receptor 2/3, ATP-sensitive inward rectifying potassium channel 1.4, and the excitatory amino acid transporter 1. SGCs also show inter-SGC connections and the presence of connexin 43, a major component of gap-junctions.

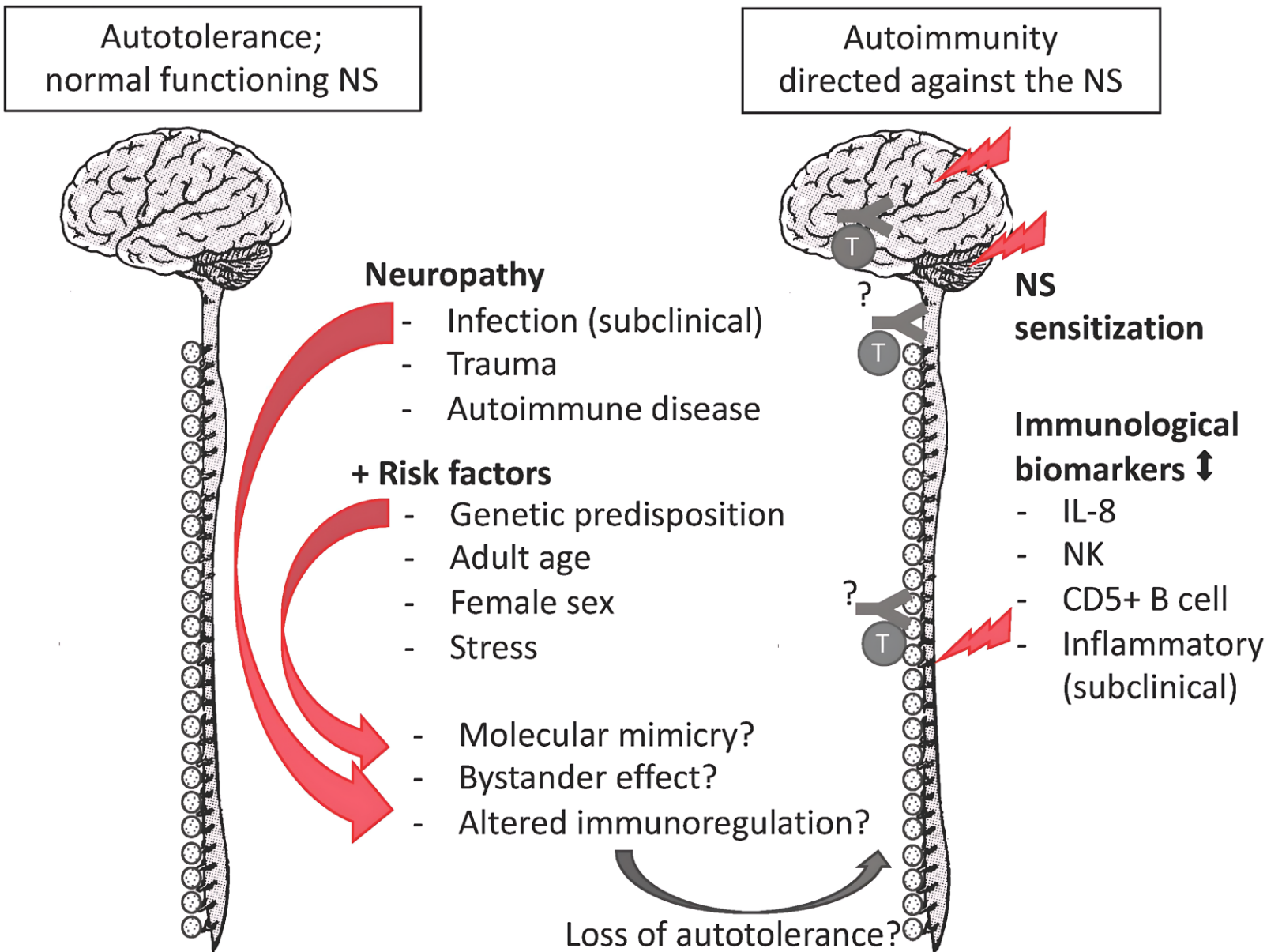
02

03

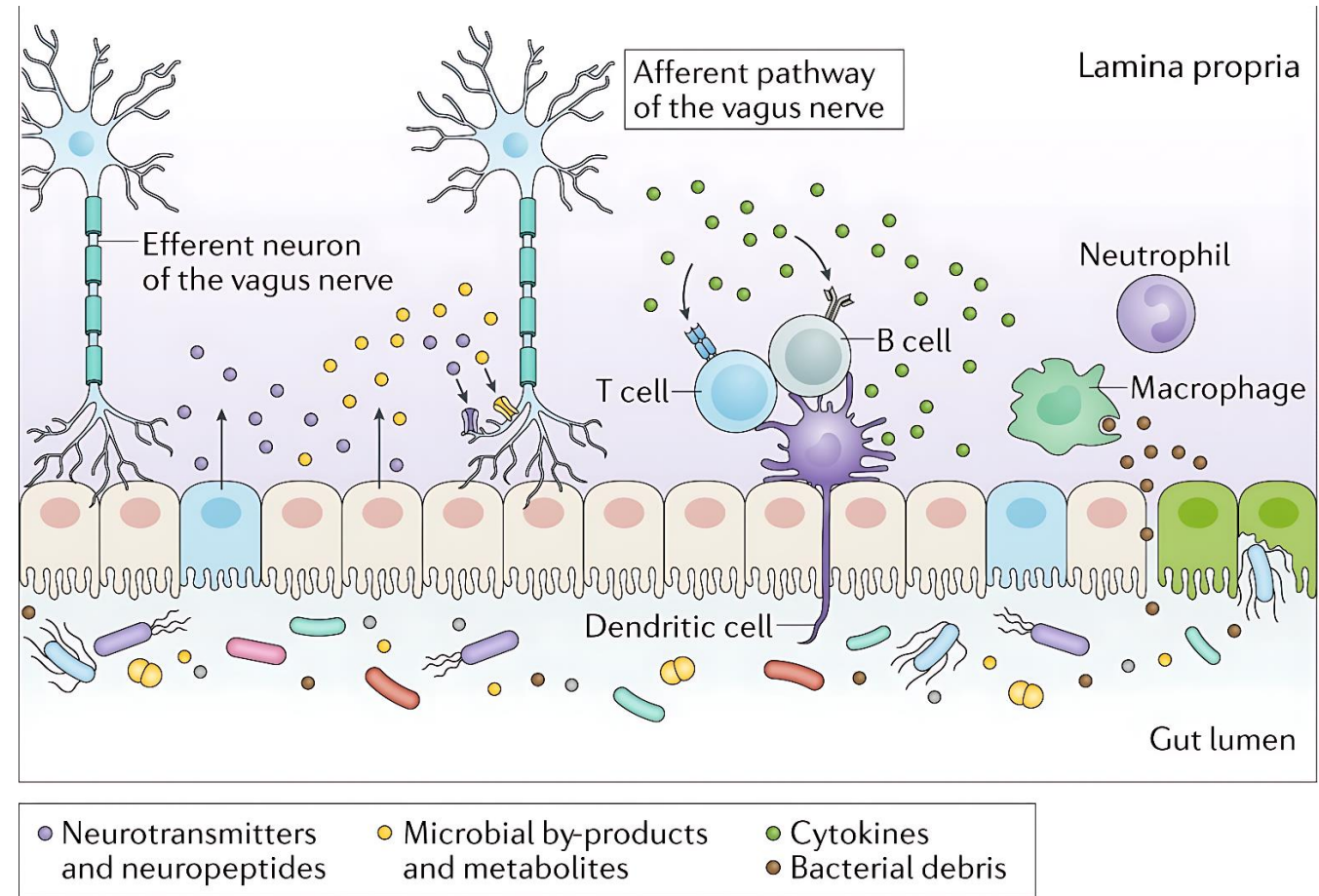
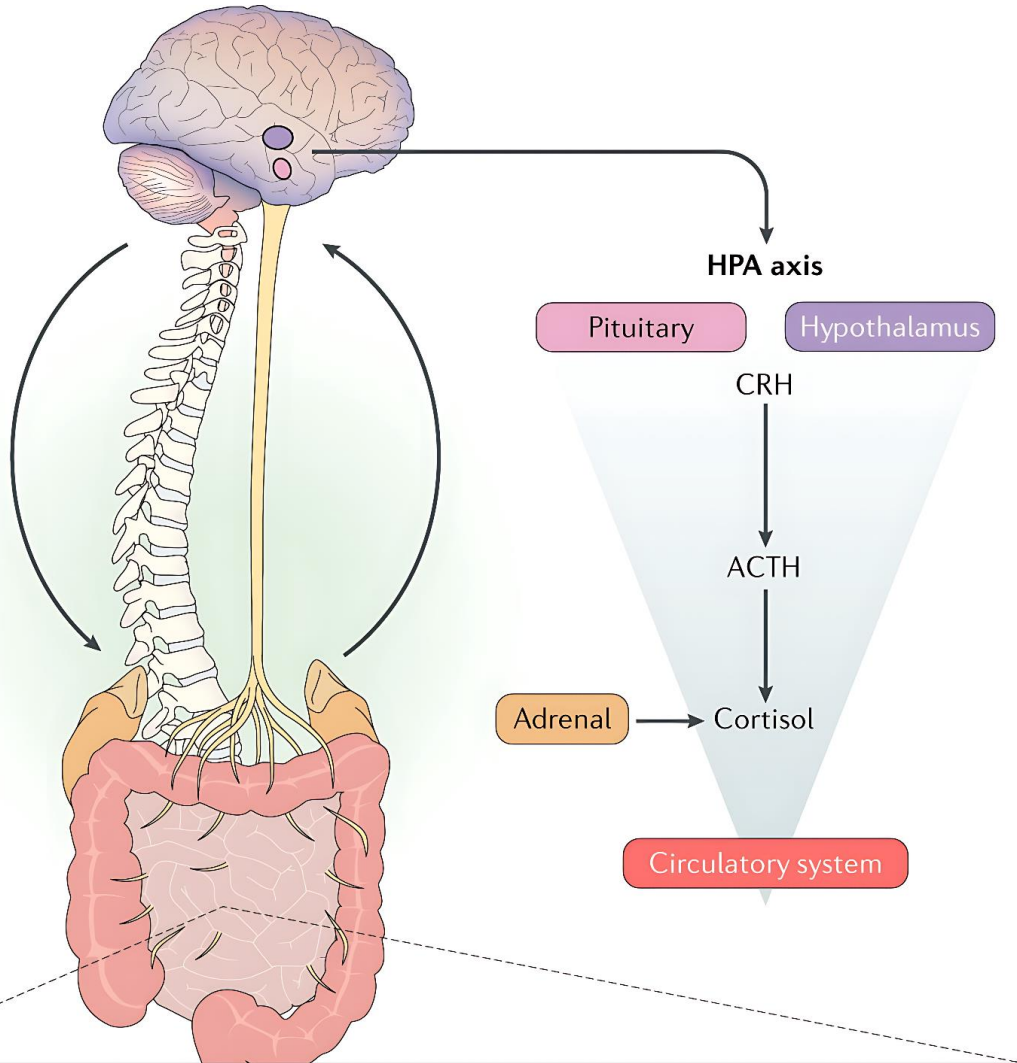
Immunoreactivity for NaV1.7 in GFAP-positive putative SGCs within DRG removed from patients with cancer-related neuropathic pain suggests SGC involvement in cells-to-cell communication. SGCs in human DRG express class I and II Major Histocompatibility Complex and a class of pathogen- and damage-associated pattern recognition receptors, the Toll-like receptors.



«Autoimmune» model



The gut-brain axis



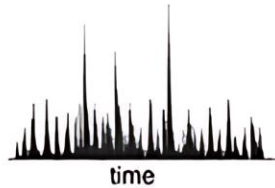
Dysbiosis and metabolomics

Untargeted Metabolomics

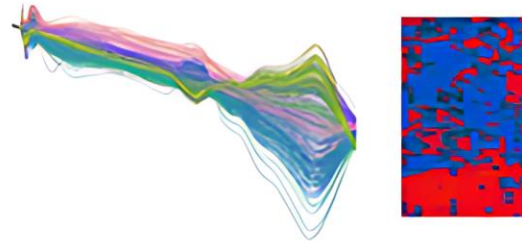
LC/MS of Metabolite Extract



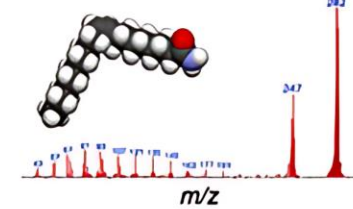
Overlaid
Extracted Ion Chromatograms (EIC)



Alignment and Data Analysis



Tandem MS Database

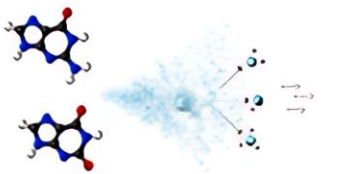


Output

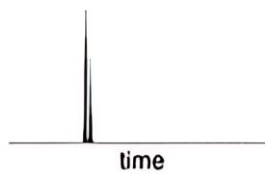


Targeted Metabolomics

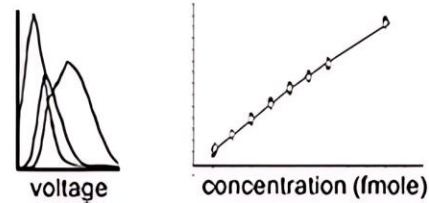
LC/MS of Standards



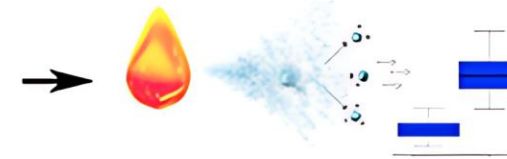
Selected Reaction Monitoring (SRM)



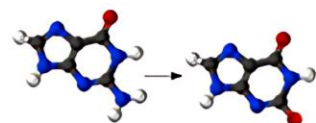
Optimization and Quantification



LC/MS of Metabolite Extract



Output



Dysbiosis and metabolomics

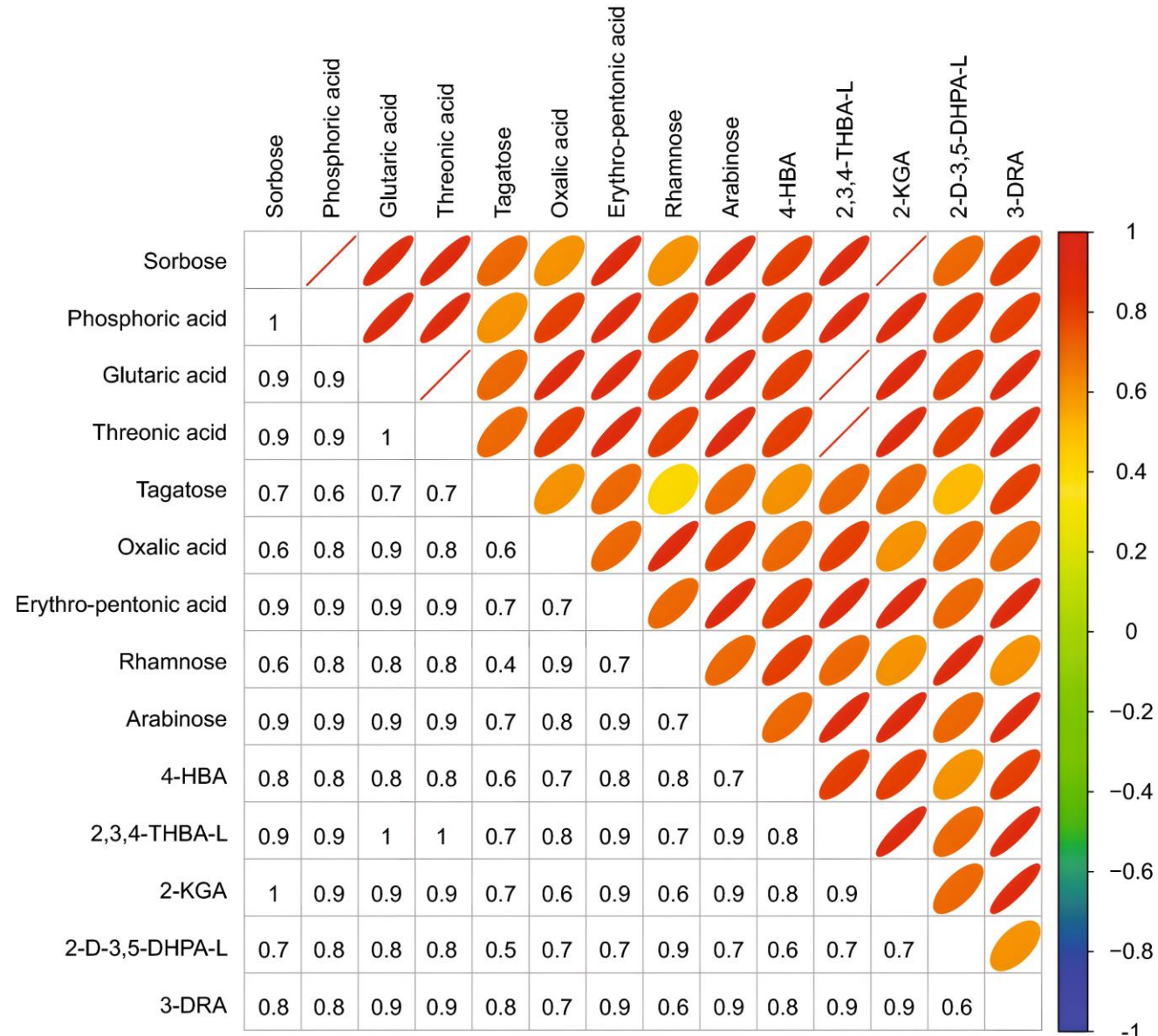
Table 1 Important metabolites in FMS patients relative to CO controls

#	Metabolite	VIP	M–W	B–F	ES	FC	FMS		CO		CF		CN	
		> 2.0	< 0.05	5%	> 0.5	> 10	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	Sorbose	27.9	< 0.00001	0.00026	0.82	> 550	549	438	0	n/a	0	n/a	0.01	0.05
2	Phosphoric acid	11.2	0.00011	0.00028	0.82	59	147	111	2.47	2.39	0.05	0.09	5.42	6.95
3	Glutaric acid	10.6	0.00011	0.00028	0.82	144	77	60	0.53	0.59	0.39	0.33	0.76	0.77
4	Threonic acid	8.7	< 0.00001	0.00027	0.82	298	39	28	0.13	0.40	0.04	0.09	1.78	5.69
5	Tagatose	7.3	0.00024	0.00031	0.67	> 550	103	154	0	n/a	0	n/a	0.01	0.05
6	Oxalic acid (CO&CF)	7.2	0.00011	0.00027	0.82	21	46	24	2.11	2.69	6.79	5.32	12.13	6.56
7	Erythropentonic acid	6.9	< 0.00001	0.00027	0.82	526	28	22	0.05	0.12	0.21	0.51	0.24	0.41
8	Rhamnose	4.7	0.00011	0.00027	0.82	81	15	9	0.19	0.17	0	n/a	0.01	0.05
9	Arabinose	3.9	0.000017	0.00028	0.80	44	19	17	0.44	0.64	0.56	0.51	0.27	0.46
10	4-HBA (CO&CN)	3.6	0.00109	0.00185	0.59	57	36	36	0.62	1.15	0.09	0.13	0.15	0.62
11	2,3,4-Trihydroxybutyl-L	3.3	0.000021	0.00029	0.79	24	13	10	0.54	1.41	0.51	0.70	0.60	0.47
12	2-Keto-1-gluconic acid	2.8	< 0.00001	0.00026	0.82	> 550	19	15	0	n/a	0	n/a	0	n/a
13	2-D-3,5-DHPL	2.8	0.0000199	0.00031	0.68	17	28	25	1.67	2.27	1.30	2.41	3.26	4.80
14	3-D-Ribohexonic acid	2.6	0.0000089	0.00029	0.72	> 550	31	30	0	n/a	0	n/a	0	n/a

Means and standard deviations (SD) for the metabolites listed are shown for the FMS patients and three control groups (CO, CF and CN). Twelve metabolites were important and common for all three control groups relative to FMS, while two (#6 & 10) were common to only two groups, as indicated in brackets

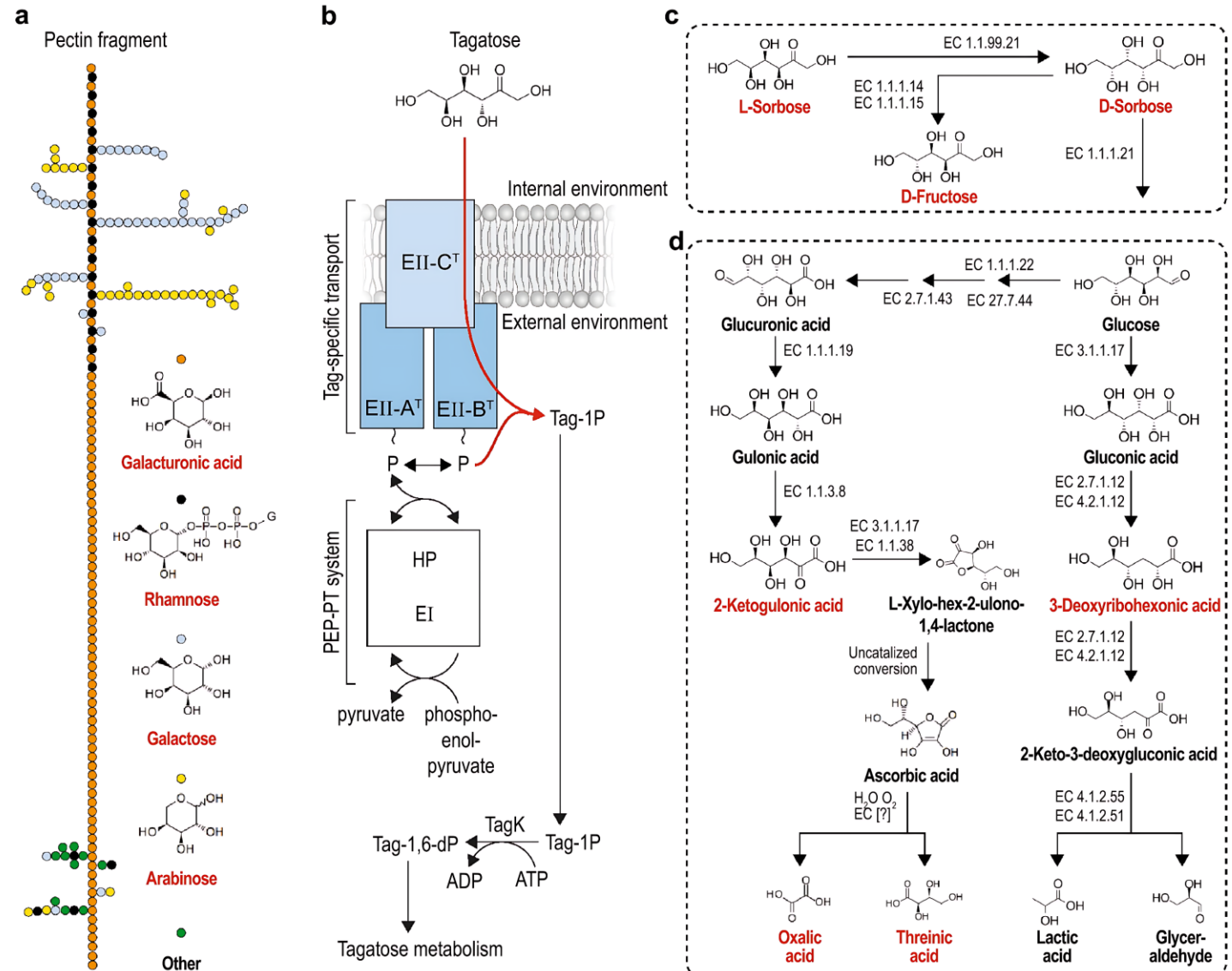
VIP variables important in projection, *M–W* Mann–Whitney *p* values, *B–F* Bonferroni–Holm test, *ES* effect size, *FC* fold change, *4-HBA* 4-hydroxybutyric acid, *2,3,4-trihydroxy-butyl-L* 2,3,4-trihydroxybutyl-lactone, *2-D-3,5-DHPL* 2-deoxy-3,5-dihydroxypentanoic-lactone

Dysbiosis and metabolomics



Malatji BG, Mason S, Mienie LJ, Wevers RA, Meyer H, Van Reenen M, et al. The GC-MS metabolomics signature in patients with fibromyalgia syndrome directs to dysbiosis as an aspect contributing factor of FMS pathophysiology. *Metabolomics* 2019;15:54. <https://doi.org/10.1007/s11306-019-1513-6>.

Dysbiosis and metabolomics



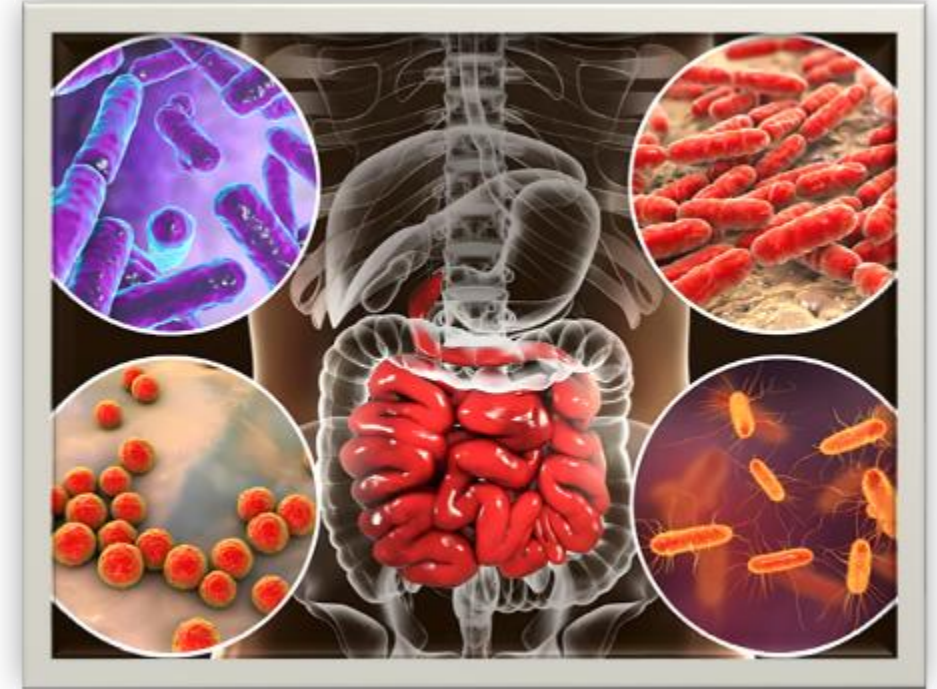
Malatji BG, Mason S, Mienie LJ, Wevers RA, Meyer H, Van Reenen M, et al. The GC-MS metabolomics signature in patients with fibromyalgia syndrome directs to dysbiosis as an aspect contributing factor of FMS pathophysiology. *Metabolomics* 2019;15:54. <https://doi.org/10.1007/s11306-019-1513-6>.

Dysbiosis in Fibromyalgia

The human genome encodes enzymes for digesting complex carbohydrates from plants, which are broken down by the gut microbiome into monosaccharides like arabinose, rhamnose, xylose, and galactose.

Dysbiosis, an imbalance in the gut microbiome, can lead to an abnormal urinary monosaccharide profile, such as increased arabinose levels observed in patients with fibromyalgia syndrome (FMS).

Dysbiosis is suggested to be part of the pathophysiology of FMS, with evidence of a disturbed composition of gut microbiota in affected patients.



Malatji BG, Mason S, Mienie LJ, Wevers RA, Meyer H, Van Reenen M, et al. The GC-MS metabolomics signature in patients with fibromyalgia syndrome directs to dysbiosis as an aspect contributing factor of FMS pathophysiology. *Metabolomics* 2019;15:54. <https://doi.org/10.1007/s11306-019-1513-6>.

Dysbiosis in Fibromyalgia

The phosphoenolpyruvate:carbohydrate phosphotransferase system (PTS) in bacteria plays a key role in regulating transport, phosphorylation, and metabolism of monosaccharides, with mutants of PTS losing the capacity to utilize monosaccharides for growth.

Malatji BG, Mason S, Mienie LJ, Wevers RA, Meyer H, Van Reenen M, et al. The GC-MS metabolomics signature in patients with fibromyalgia syndrome directs to dysbiosis as an aspect contributing factor of FMS pathophysiology. *Metabolomics* 2019;15:54. <https://doi.org/10.1007/s11306-019-1513-6>.

Metabolites in urine, not typically found in normal urine, can be used for metagenomic investigations of the gut microbiota to understand dysbiosis in patients with FMS

Various metabolites in urine, such as 4-hydroxybutyric acid and sorbose, are linked to microbial metabolism, host metabolism, and microbiome-host co-metabolism, providing insights into the systemic metabolism hypothesis of FMS pathophysiology.

M. H. Saier, The Bacterial Phosphotransferase System: New frontiers 50 years after its discovery. *J Mol Microbiol Biotechnol* **25**, 73–78 (2015).

Primary Metabolic Functions

Catalysis of:

- Sugar transport
- Sugar phosphorylation
- Sugar chemoreception

Secondary Regulatory Functions

Control of the activities of:

- PTS permeases
- Non-PTS permeases
- Catabolic enzymes
- Adenylate cyclase
- Transcription factors (many)

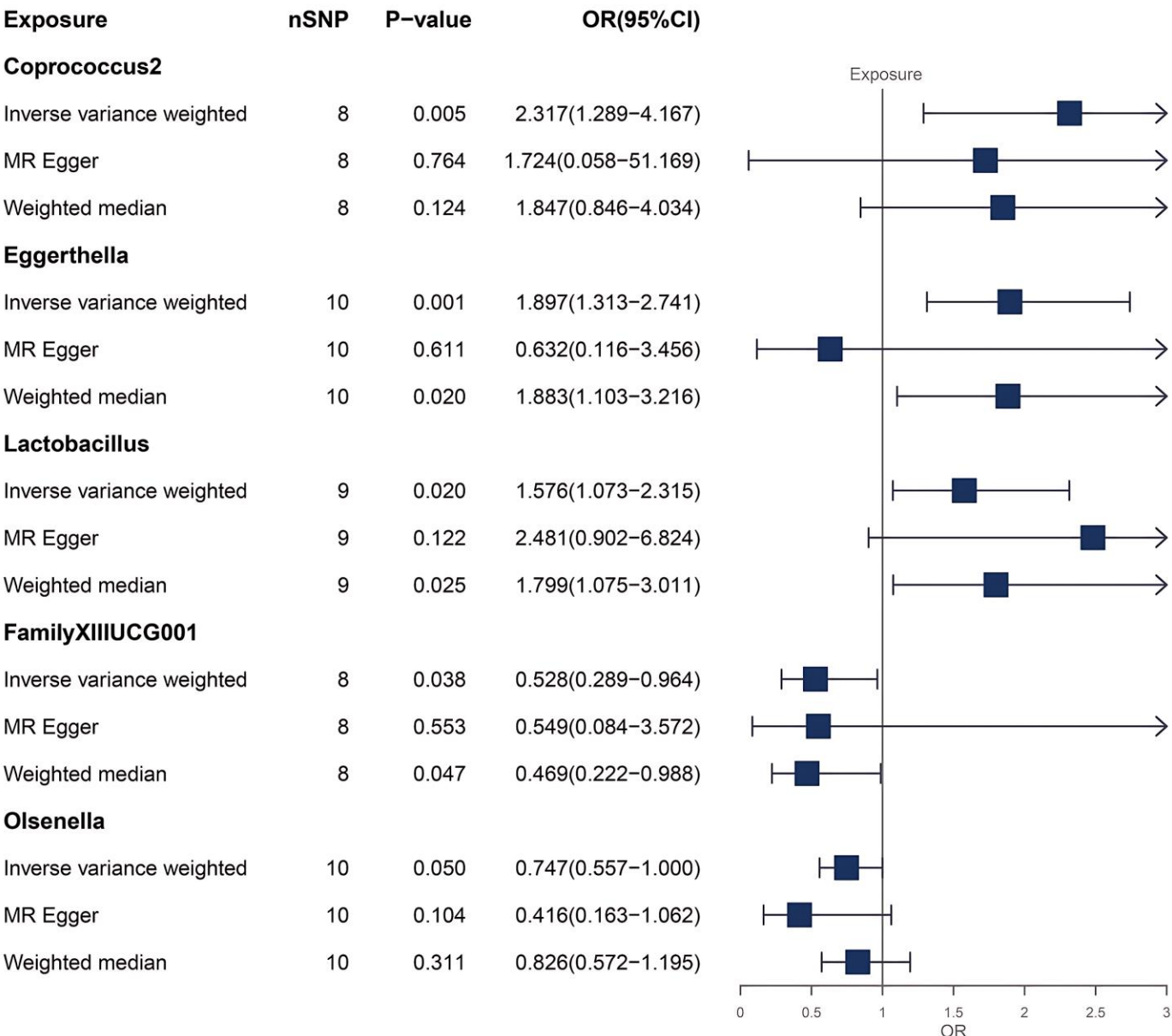
Control of physiological processes including:

- Ionic homeostasis (potassium transport)
- Glycogen accumulation
- Polyhydroxybutyrate storage
- Nitrogen utilization
- Phosphorous metabolism
- Biofilm formation
- Virulence
- Transposon-mediated directed mutation

Dysbiosis and metabolomics

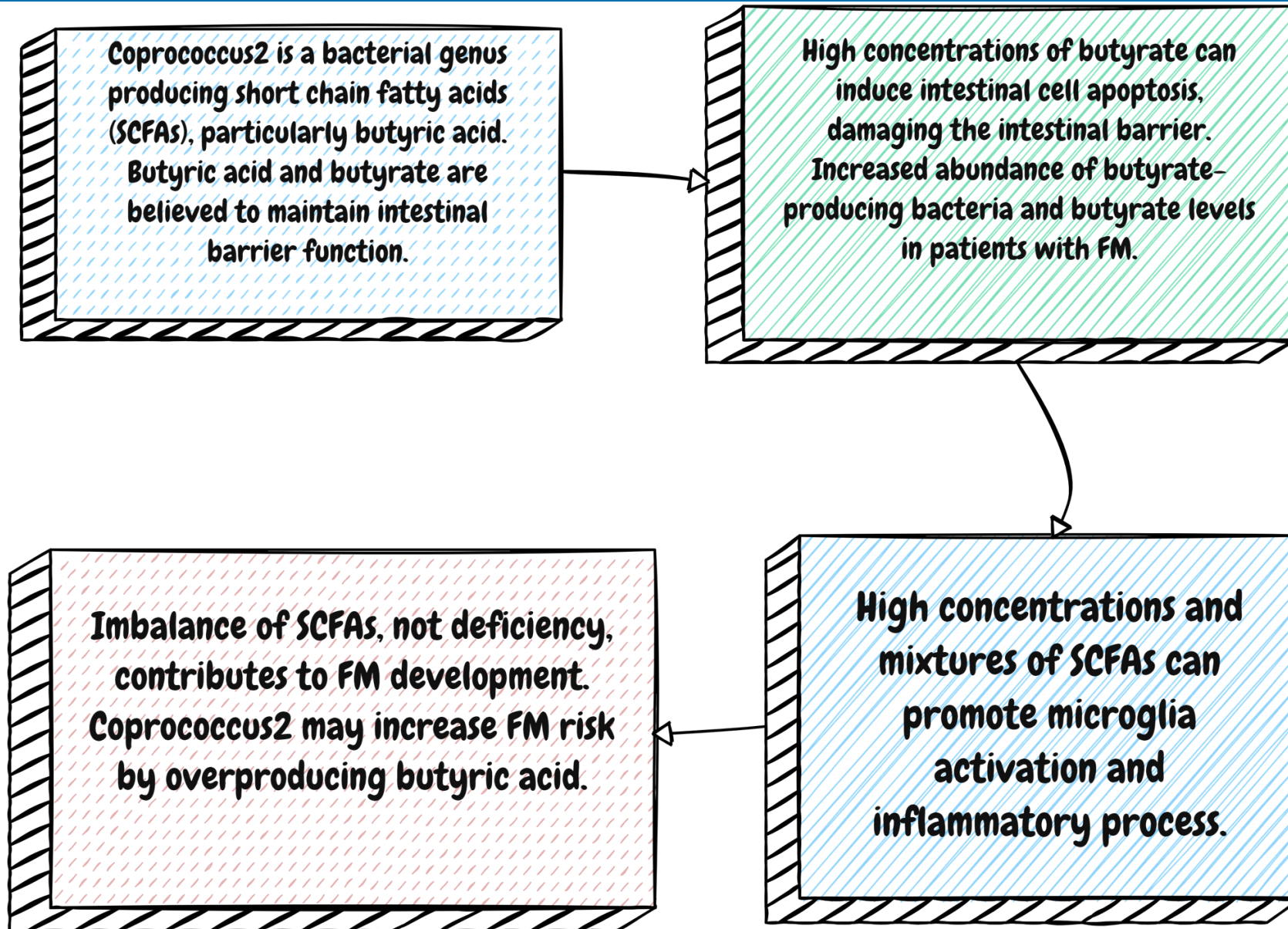
Here, the overall urinary metabolite profile observed in the FMS patients suggests that (1) energy utilization is a central aspect of this pain disorder, and (2) dysbiosis seems to prevail in FMS patients, supporting the model that microbiota may alter brain function through the gut-brain axis (Mayer et al. 2015), with the gut being a gateway to generalized pain

Gut microbiome and Fibromyalgia

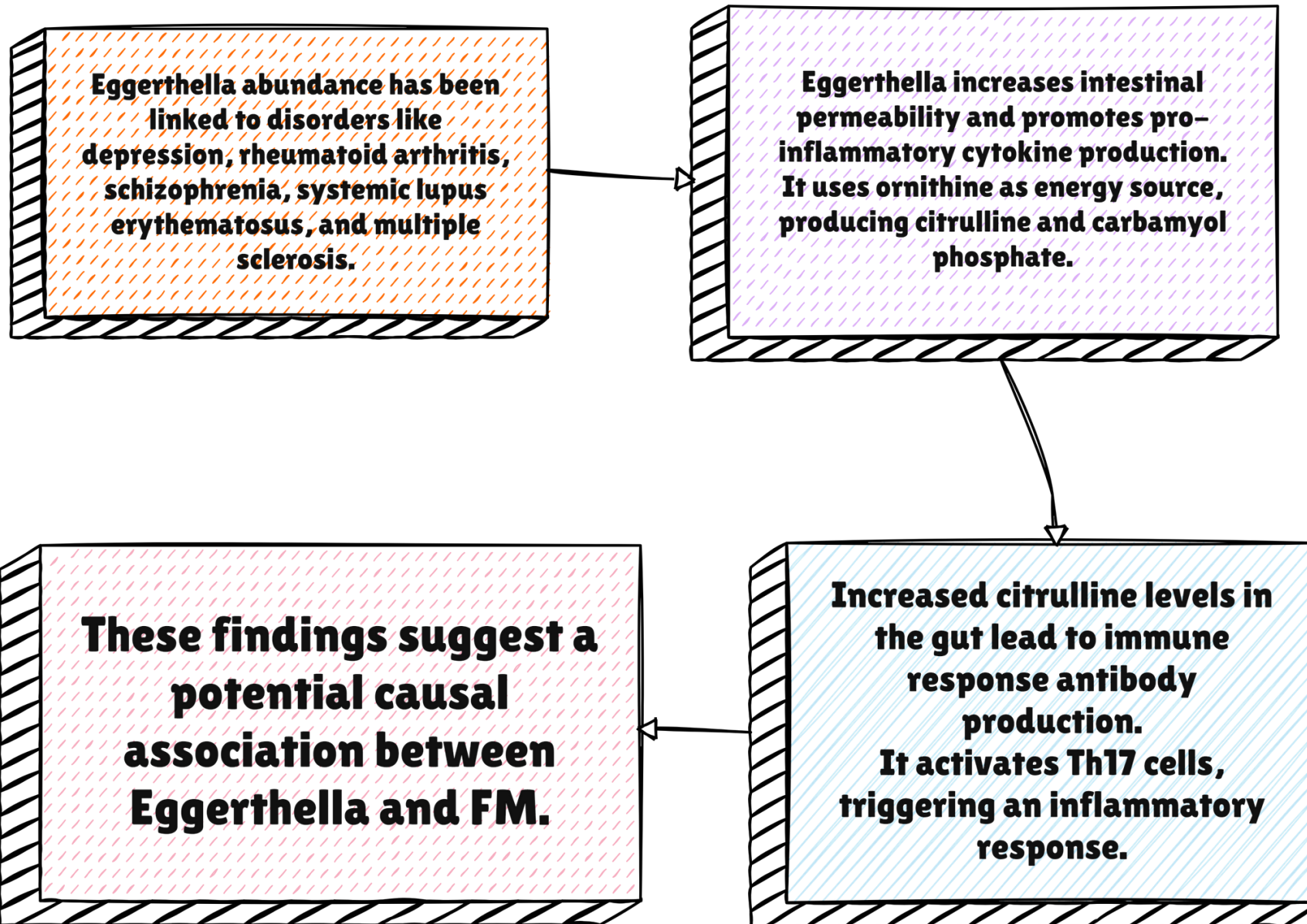


Z. Wang, D. Jiang, M. Zhang, Y. Teng, Y. Huang, Causal association between gut microbiota and fibromyalgia: a Mendelian randomization study. Front. Microbiol. 14, 1305361 (2024).

Coprococcus



Eggerthella



Lactobacillus

LACTOBACILLUS, A PROBIOTIC, HAS BEEN LINKED TO INCREASED RISK OF FIBROMYALGIA (FM). LACTOBACILLUS PLANTARUM IS-10506 CAN UPREGULATE SEROTONIN LEVELS, WHILE LACTOBACILLUS ACIDOPHILUS AND LACTOBACILLUS RHAMNOSUS CAN DOWNREGULATE 5-HT LEVELS. SEROTONERGIC DYSFUNCTION IS A MAJOR HYPOTHESIS OF FIBROMYALGIA, SUPPORTED BY DRUGS ALTERING SEROTONIN METABOLISM.

LACTOBACILLUS RUMINIS CAN STIMULATE THE PRODUCTION OF TUMOR NECROSIS FACTOR (TNF), WHICH CAN CROSS THE BLOOD-BRAIN BARRIER AND INCREASE ITS PERMEABILITY.

LACK OF GENETIC VARIANT STATISTICS IS LIMITED TO THE OVERALL EFFECT OF LACTOBACILLUS IN THIS STUDY.

LACTOBACILLUS RUMINIS MAY CONTRIBUTE TO MEMBRANE DYSFUNCTION TRIGGERED BY MICROGLIA THROUGH ELEVATED TNF LEVELS, CONTRIBUTING TO FM DEVELOPMENT.

Brain networks

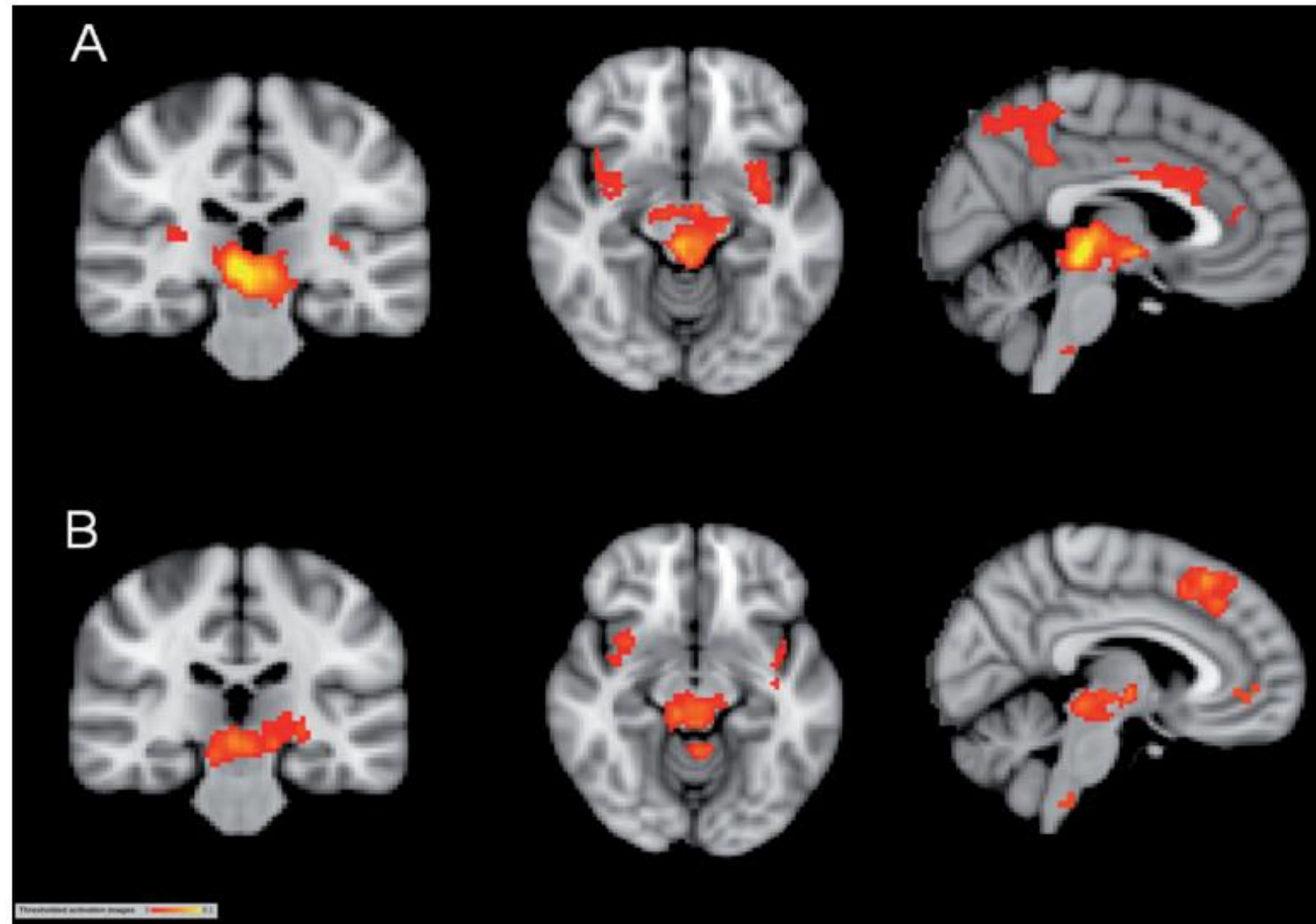
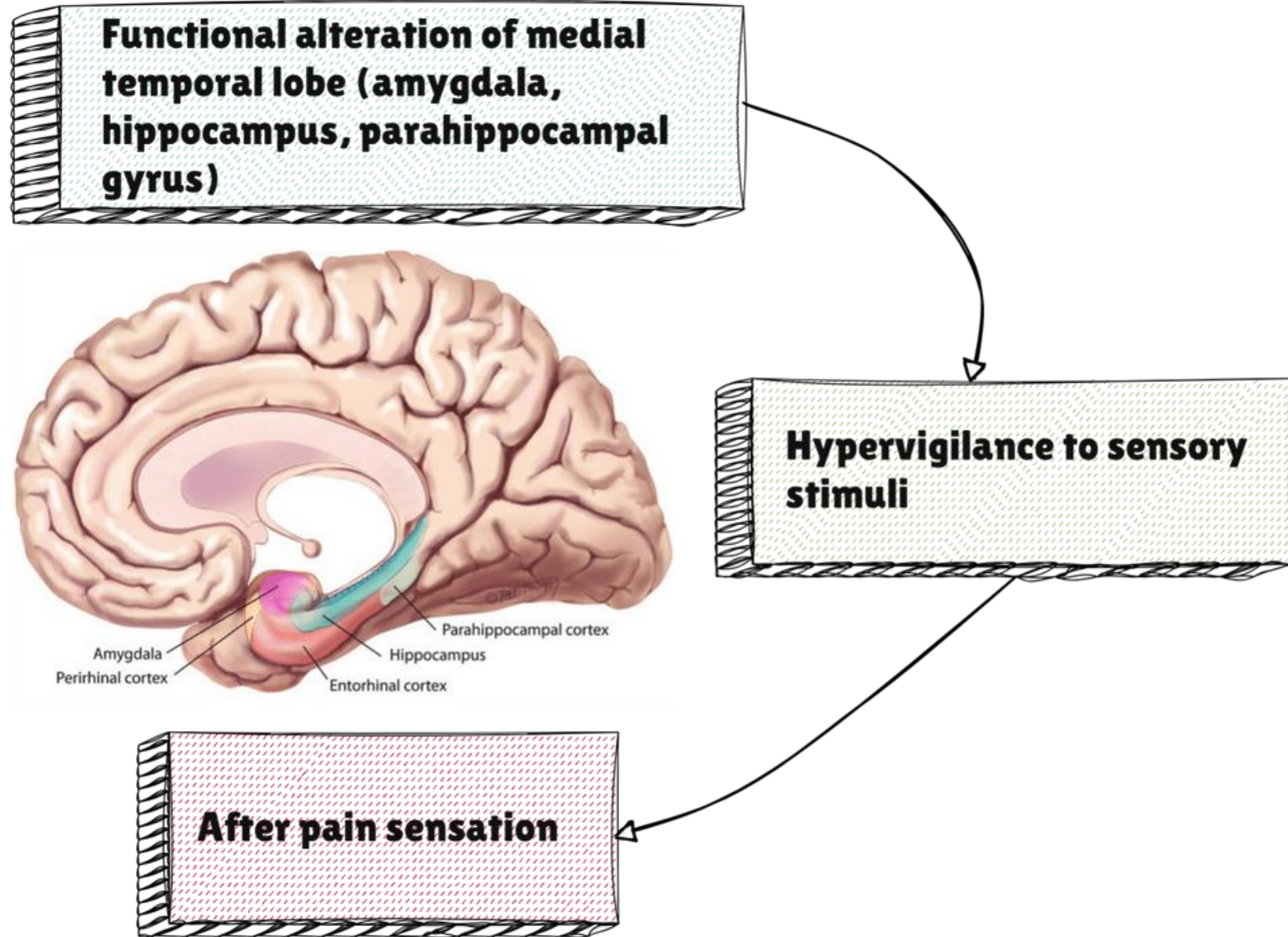


Fig. 1. Statistical maps of positive functional resting state connectivity with the PAG in (A) 20 fibromyalgia patients and in (B) 15 age and gender matched healthy controls. Statistical threshold corresponded to $Z > 3$ and a correct cluster significance of $p < 0.05$.

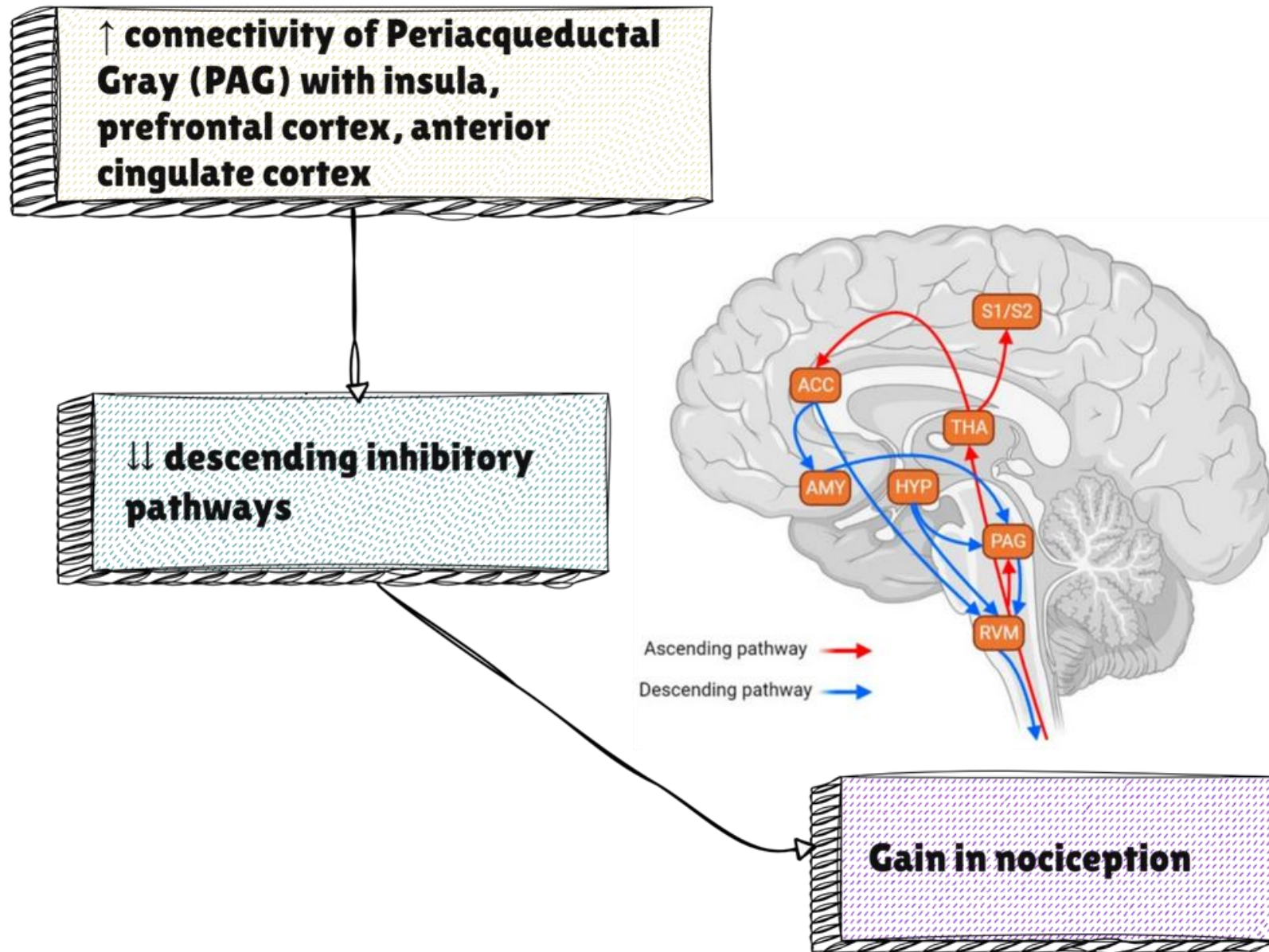
A. Truini, E. Tinelli, M. C. Gerardi, V. Calistri, C. Iannuccelli, S. La Cesa, L. Tarsitani, C. Mainero, P. Sarzi-Puttini, G. Cruccu, F. Caramia, M. Di Franco, Abnormal resting state functional connectivity of the periaqueductal grey in patients with fibromyalgia. *Clin Exp Rheumatol* **34**, S129-133 (2016).

Brain networks



de Tommaso M, Vecchio E, Nolano M. The puzzle of fibromyalgia between central sensitization syndrome and small fiber neuropathy: a narrative review on neurophysiological and morphological evidence. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol.* 2022;43(3):1667-1684. doi:10.1007/s10072-021-05806-x

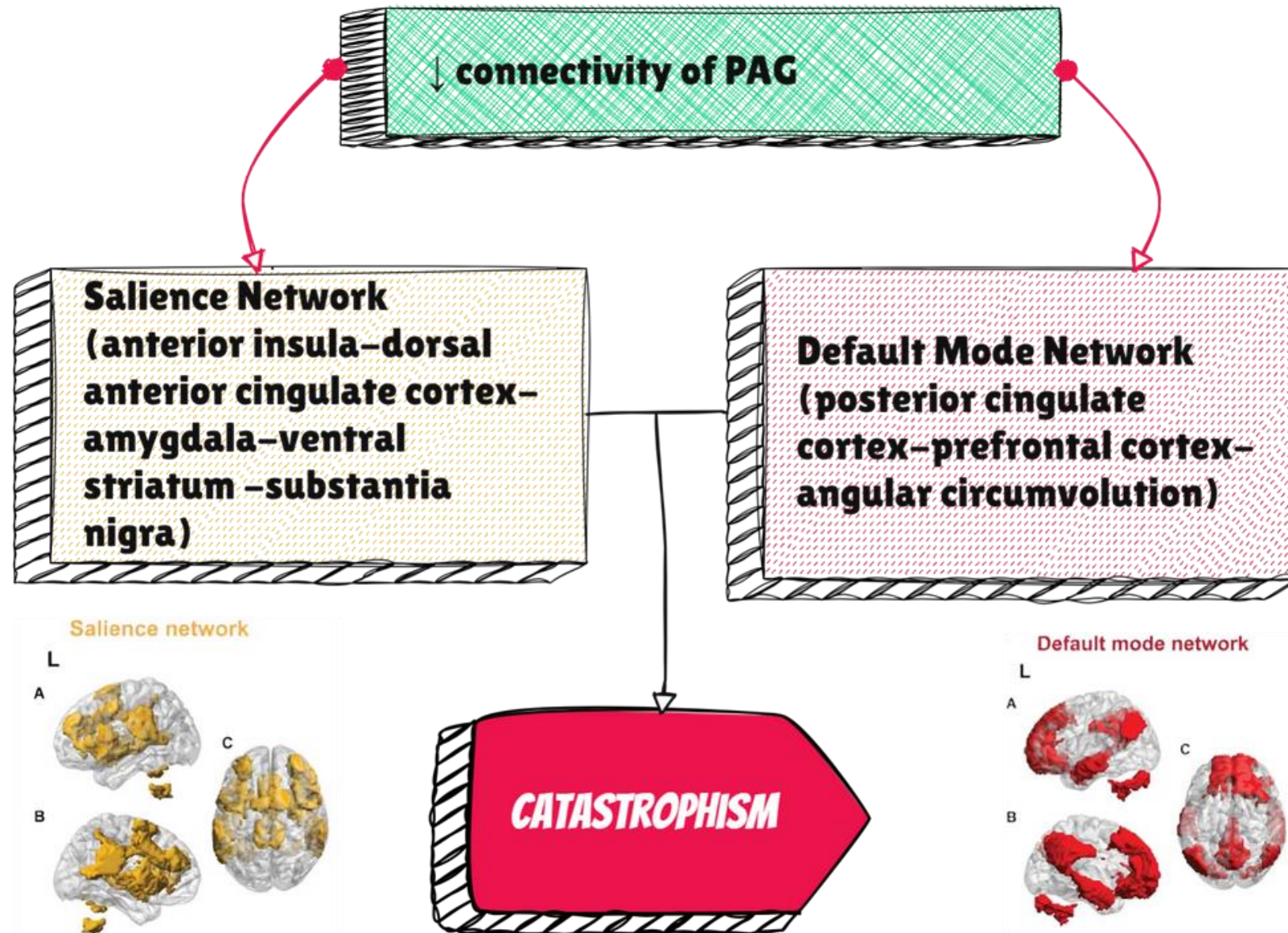
Brain networks



de Tommaso M, Vecchio E, Nolano M. The puzzle of fibromyalgia between central sensitization syndrome and small fiber neuropathy: a narrative review on neurophysiological and morphological evidence. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol.* 2022;43(3):1667-1684. doi:10.1007/s10072-021-05806-x

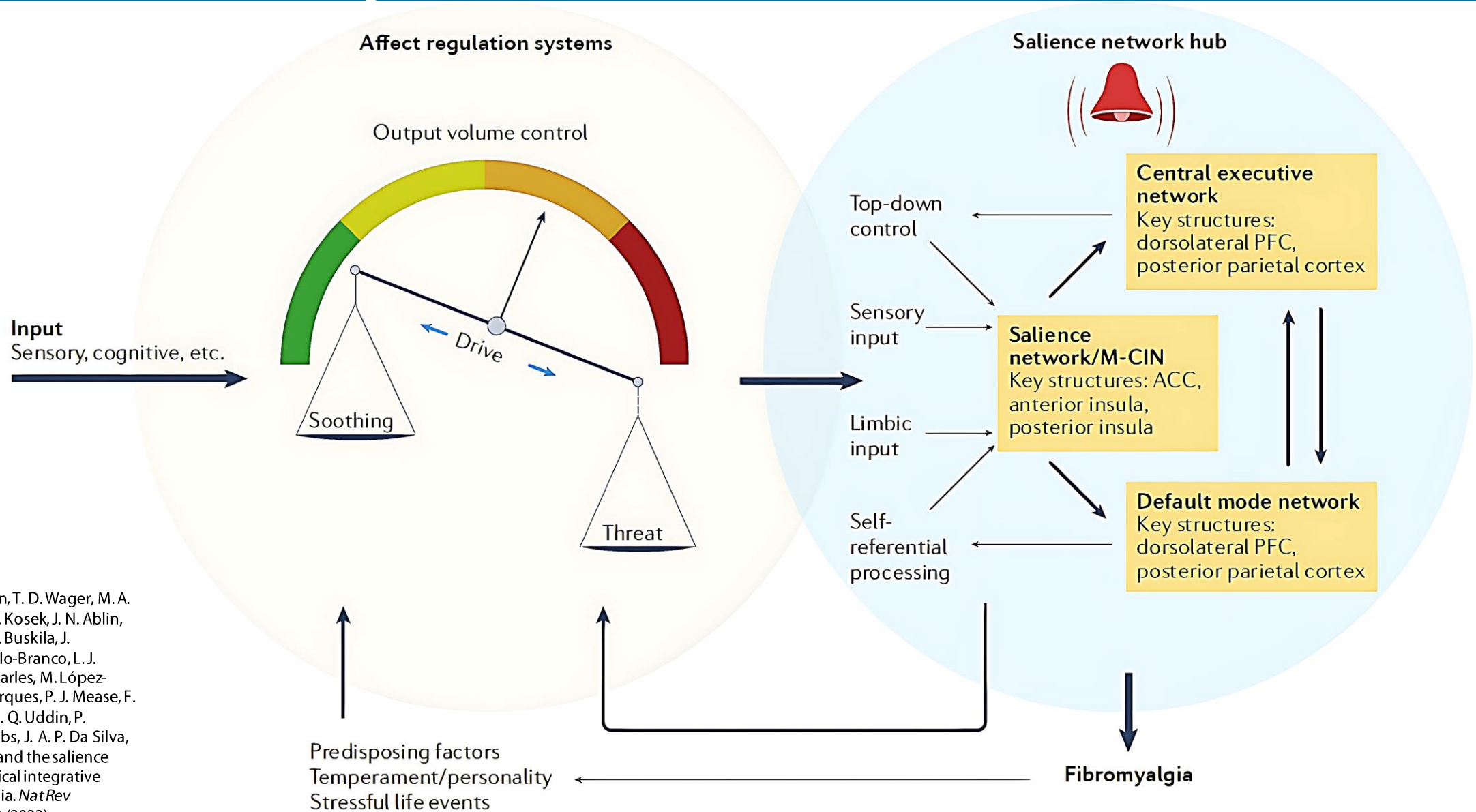
M. Pagliusi, F. V. Gomes, The Role of The Rostral Ventromedial Medulla in Stress Responses. *Brain Sciences* 13, 776 (2023).

Brain networks



de Tommaso M, Vecchio E, Nolano M.
The puzzle of fibromyalgia between
central sensitization syndrome and
small fiber neuropathy: a narrative
review on neurophysiological and
morphological evidence. *Neurol Sci*
Off J Ital Neurol Soc Ital Soc Clin
Neurophysiol. 2022;43(3):1667-1684.
doi:10.1007/s10072-021-05806-x
J. Schimmelpfennig, J. Topczewski,
W. Zajkowski, K. Jankowiak-Siuda,
The role of the salience network in
cognitive and affective deficits.
Frontiers in Human Neuroscience 17
(2023).

“Fibromyalgia: Imbalance of Threat and Soothing Systems (FITSS)” model



A. M. Pinto, R. Geenen, T. D. Wager, M. A. Lumley, W. Häuser, E. Kosek, J. N. Ablin, K. Amris, J. Branco, D. Buskila, J. Castelhana, M. Castelo-Branco, L. J. Crofford, M.-A. Fitzcharles, M. López-Solà, M. Luís, T. R. Marques, P. J. Mease, F. Palavra, J. L. Rhudy, L. Q. Uddin, P. Castilho, J. W. G. Jacobs, J. A. P. Da Silva, Emotion regulation and the salience network: a hypothetical integrative model of fibromyalgia. *Nat Rev Rheumatol* **19**, 44–60 (2023).

More than just neurophysiology and pain...

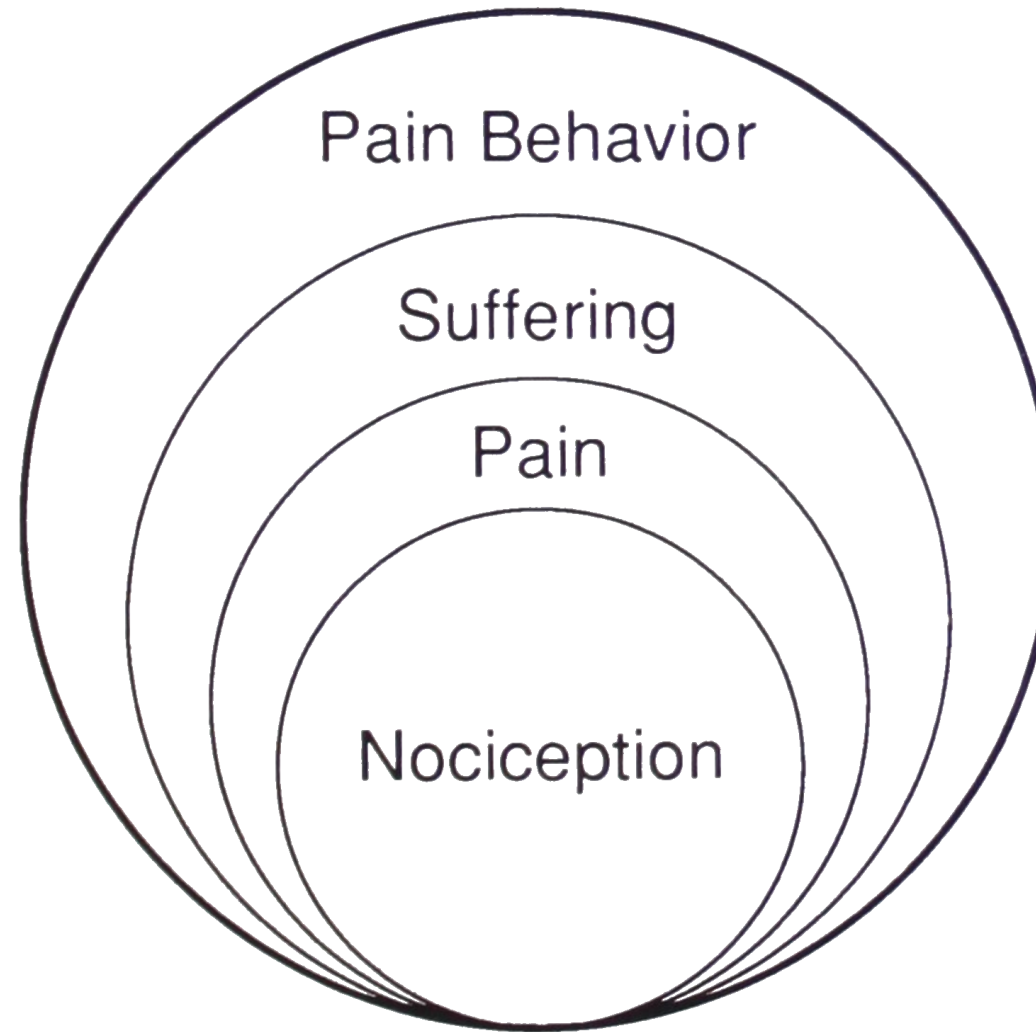


FIG. 1. Depiction of the universe of pain via nested circles that identify four components of pain

Clinical management

JAMA Internal Medicine | [Original Investigation](#)

Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia A Systematic Review and Meta-analysis

Rodrigo Oliveira Mascarenhas, MSc; Mateus Bastos Souza, BAppSc; Murilo Xavier Oliveira, PhD; Ana Cristina Lacerda, PhD; Vanessa Amaral Mendonça, PhD; Nicholas Henschke, PhD; Vinícius Cunha Oliveira, PhD

R. O. Mascarenhas, M. B. Souza, M. X. Oliveira, A. C. Lacerda, V. A. Mendonça, N. Henschke, V. C. Oliveira, Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia: A Systematic Review and Meta-analysis. JAMA Intern Med 181, 104 (2021).

Clinical management

MAIN OUTCOMES AND MEASURES Pain intensity measured by the visual analog scale, numerical rating scales, and other valid instruments and QOL measured by the Fibromyalgia Impact Questionnaire.

RESULTS A total of 224 trials including 29 962 participants were included. High-quality evidence was found in favor of cognitive behavioral therapy (weighted mean difference [WMD], -0.9; 95% CI, -1.4 to -0.3) for pain in the short term and was found in favor of central nervous system depressants (WMD, -1.2 [95% CI, -1.6 to -0.8]) and antidepressants (WMD, -0.5 [95% CI, -0.7 to -0.4]) for pain in the medium term. There was also high-quality evidence in favor of antidepressants (WMD, -6.8 [95% CI, -8.5 to -5.2]) for QOL in the short term and in favor of central nervous system depressants (WMD, -8.7 [95% CI, -11.3 to -6.0]) and antidepressants (WMD, -3.5 [95% CI, -4.5 to -2.5]) in the medium term. However, these associations were small and did not exceed the minimum clinically important change (2 points on an 11-point scale for pain and 14 points on a 101-point scale for QOL). Evidence for long-term outcomes of interventions was lacking.

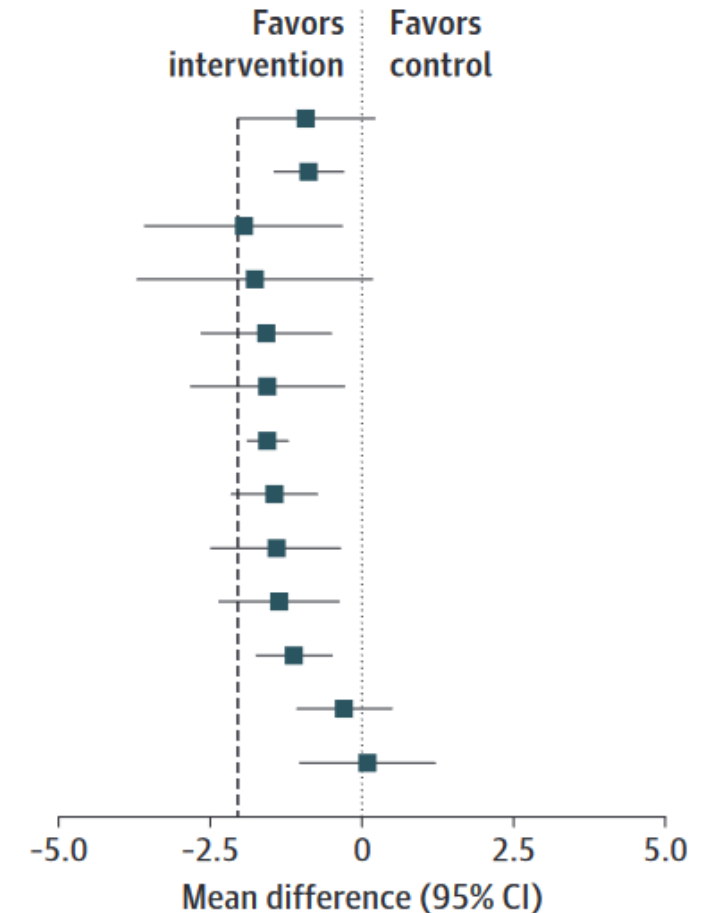
CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis suggests that most of the currently available therapies for the management of fibromyalgia are not supported by high-quality evidence. Some therapies may reduce pain and improve QOL in the short to medium term, although the effect size of the associations might not be clinically important to patients.

Clinical management

Figure 2. Summary of High- and Moderate-Quality Evidence Meta-analysis on Treatment of Pain in Fibromyalgia

A Short-term outcomes

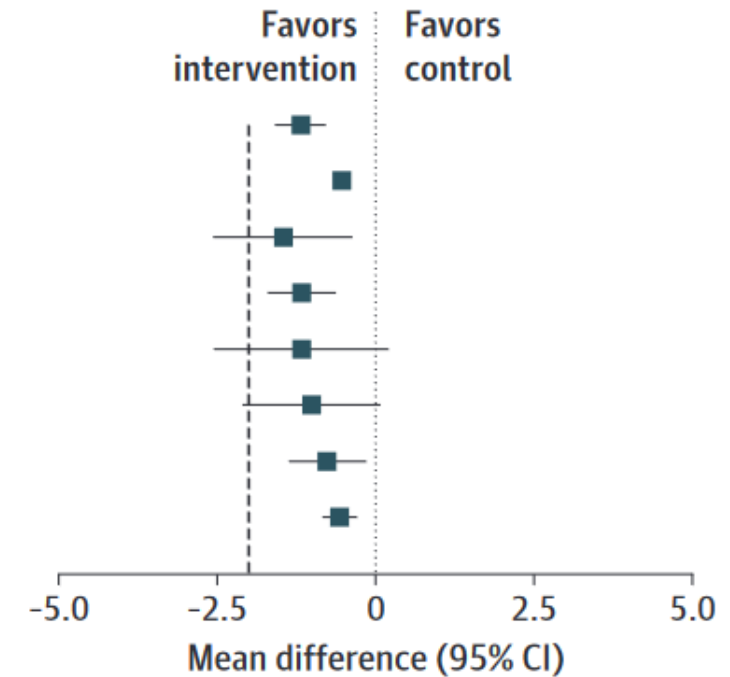
Intervention	Trials, No.	Participants, No.	I^2	Mean difference (95% CI)	GRADE
Antiemetics	2	456	0	-0.9 (-2.0 to 0.2)	High
CBT	14	905	0	-0.9 (-1.4 to -0.3)	High
TENS	2	238	0	-1.9 (-3.5 to -0.3)	Moderate ^a
Hyperbaric oxygen therapy	2	83	0	-1.8 (-3.7 to 0.2)	Moderate ^a
Magnetic field therapy	5	260	1	-1.6 (-2.6 to -0.5)	Moderate ^a
Acupuncture	5	400	0	-1.5 (-2.8 to -0.3)	Moderate ^b
Exercises	13	624	0	-1.5 (-1.9 to -1.2)	Moderate ^c
tDCS	7	284	0	-1.4 (-2.1 to -0.8)	Moderate ^a
Manual therapy	2	138	0	-1.4 (-2.4 to -0.4)	Moderate ^a
TMS	12	437	0	-1.4 (-2.3 to -0.4)	Moderate ^d
Nutritional supplements	7	338	0	-1.1 (-1.7 to -0.5)	Moderate ^a
Analgesics	2	141	0	-0.3 (-1.0 to 0.5)	Moderate ^a
EEG neurofeedback	2	90	0	0.1 (-1.0 to 1.2)	Moderate ^a



Clinical management

B Medium-term outcomes

Intervention	Trials, No.	Participants, No.	I^2	Mean difference (95% CI)	GRADE
CNS depressants	2	1121	0	-1.2 (-1.6 to -0.8)	High
Antidepressants	12	7424	0	-0.5 (-0.7 to -0.4)	High
Massage or myofascial release therapy	2	102	0	-1.5 (-2.5 to -0.4)	Moderate ^a
Exercises	13	963	0	-1.2 (-1.7 to -0.6)	Moderate ^c
Nutritional supplements	2	58	0	-1.2 (-2.5 to 0.2)	Moderate ^a
Magnetic field therapy	2	105	0	-1.0 (-2.1 to 0.1)	Moderate ^a
CBT	2	159	0	-0.8 (-1.4 to -0.2)	Moderate ^a
Anticonvulsants	4	2726	0	-0.6 (-0.8 to -0.3)	Moderate ^c

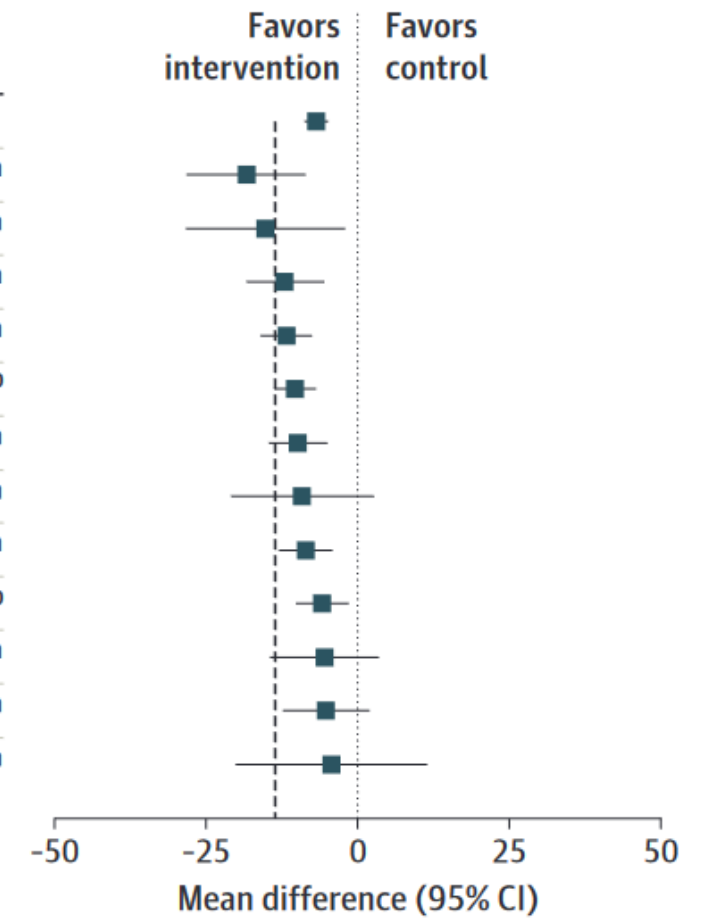


Clinical management

Figure 3. Summary of High- and Moderate-Quality Evidence Meta-analysis on Quality of Life in Fibromyalgia

A Short-term outcomes

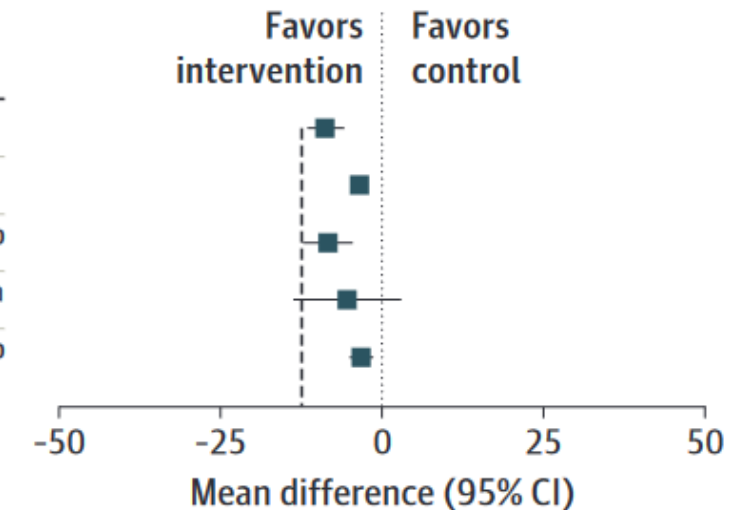
Intervention	Trials, No.	Participants, No.	<i>I</i> ²	Mean difference (95% CI)	GRADE
Antidepressants	12	2478	0	-6.8 (-8.5 to -5.2)	High
Acupuncture	3	284	0	-18.3 (-27.9 to -8.6)	Moderate ^a
Magnetic field therapy	3	171	4.4	-15.2 (-28.1 to -2.3)	Moderate ^a
tDCS	4	197	1.5	-11.9 (-18.1 to -5.6)	Moderate ^a
Balneotherapy	4	216	0	-11.7 (-15.7 to -7.7)	Moderate ^a
Exercises	16	723	2.5	-10.3 (-13.4 to -7.2)	Moderate ^b
Manual therapy	2	138	0	-9.8 (-14.5 to -5.2)	Moderate ^a
Exercises and whole-body vibration	2	62	0	-9.1 (-20.6 to 2.4)	Moderate ^a
TMS	8	220	0	-8.5 (-12.7 to -4.3)	Moderate ^a
CBT	17	1231	0	-5.8 (-9.9 to -1.6)	Moderate ^b
Analgesics	2	141	0	-5.4 (-14.2 to 3.3)	Moderate ^a
Vibratory stimulation therapy	2	123	0	-5.2 (-12.2 to 1.7)	Moderate ^a
CBT and exercises	2	175	0	-4.3 (-19.8 to 11.3)	Moderate ^a



Clinical management

B Medium-term outcomes

Intervention	Trials, No.	Participants, No.	I^2	Mean difference (95% CI)	GRADE
CNS depressants	3	1135	0	-8.7 (-11.3 to -6.0)	High
Antidepressants	11	8171	0	-3.5 (-4.5 to -2.5)	High
Exercises	15	943	1.5	-10.3 (-13.9 to -6.8)	Moderate ^b
Growth hormone	2	170	0	-5.3 (-13.5 to 2.8)	Moderate ^a
Anticonvulsants	4	2723	0	-3.1 (-4.6 to -1.6)	Moderate ^b



Antidepressants: duloxetine

**THE THERAPEUTIC ACTION OF THESE DRUGS
INVOLVES TWO DISTINCT MECHANISMS**

An acute, central mechanism that requires

- **descending noradrenergic inhibitory controls**
 - α 2A adrenoceptors
 - mu opioid receptors MOR
 - delta opioid receptors DOR

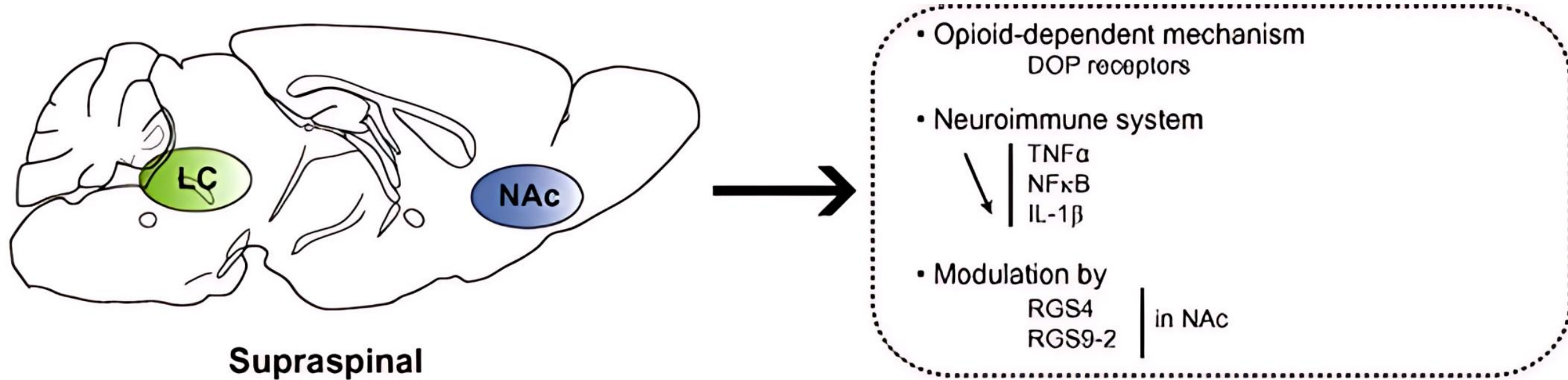
A delayed, peripheral mechanism that requires

- **noradrenaline from peripheral sympathetic endings**
 - β 2 adrenoceptors
 - delta opioid receptors DOR
- **Inhibition of neuroimmune mechanisms / downregulation of the TNF- α -NF- κ B signaling pathway**

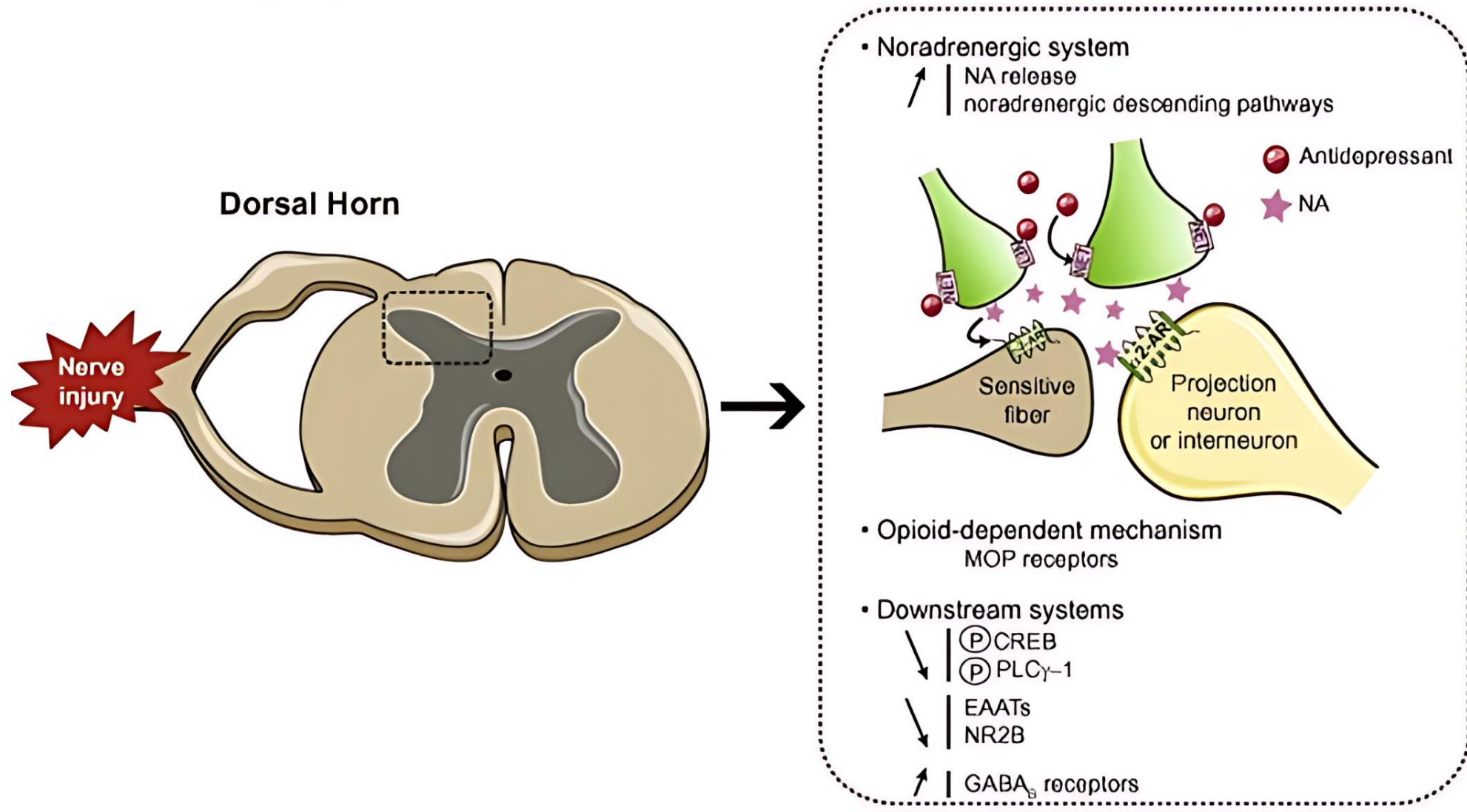
Kremer M, Yalcin I, Goumon Y, et al. A Dual Noradrenergic Mechanism for the Relief of Neuropathic Allodynia by the Antidepressant Drugs Duloxetine and Amitriptyline. J Neurosci Off J Soc Neurosci. 2018;38(46):9934-9954. doi:10.1523/JNEUROSCI.1004-18.2018

Kremer M, Salvat E, Muller A, Yalcin I, Barrot M. Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights. Neuroscience. 2016;338:183-206. doi:10.1016/j.neuroscience.2016.06.05

Antidepressants



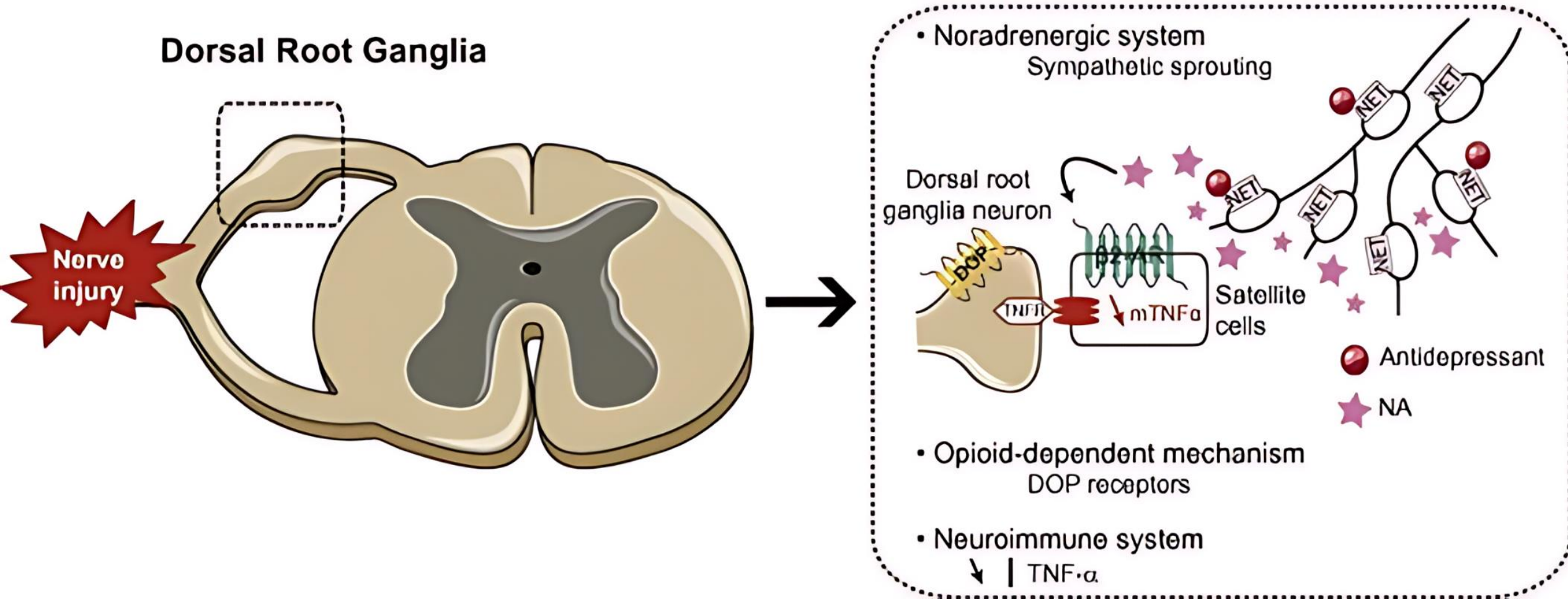
Antidepressants



Kremer M, Yalcin I, Goumon Y, et al. A Dual Noradrenergic Mechanism for the Relief of Neuropathic Allodynia by the Antidepressant Drugs Duloxetine and Amitriptyline. J Neurosci Off J Soc Neurosci. 2018;38(46):9934-9954. doi:10.1523/JNEUROSCI.1004-18.2018

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Antidepressants

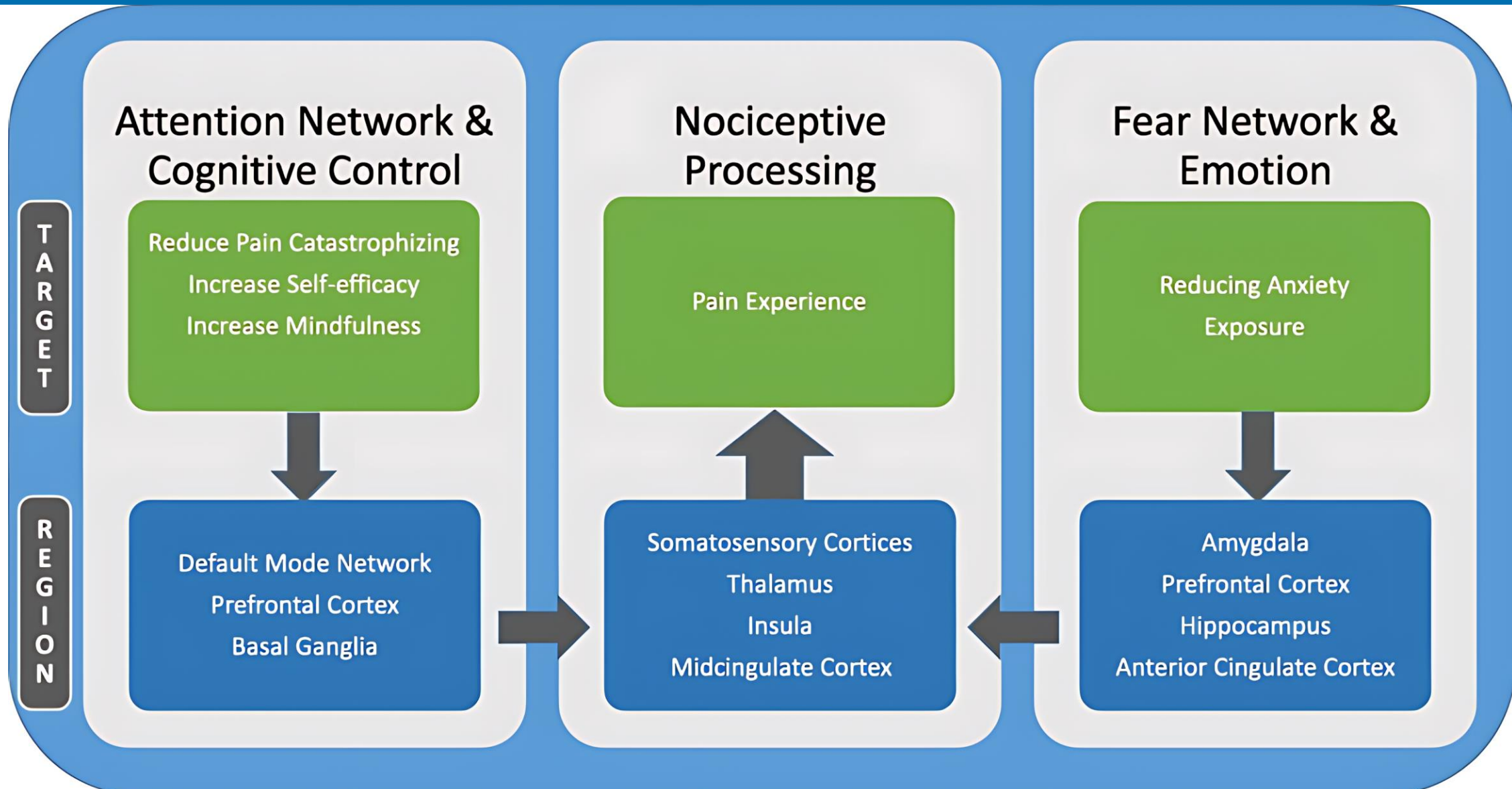


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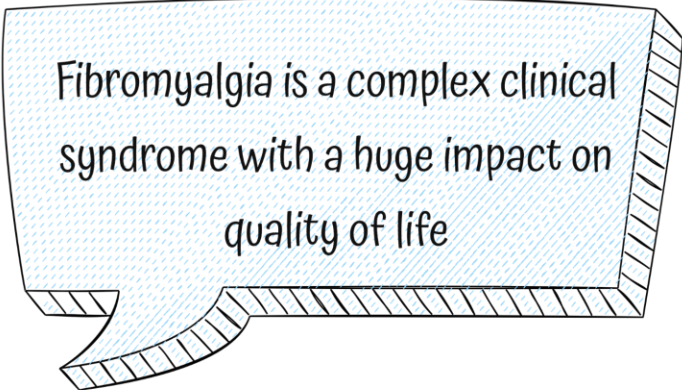
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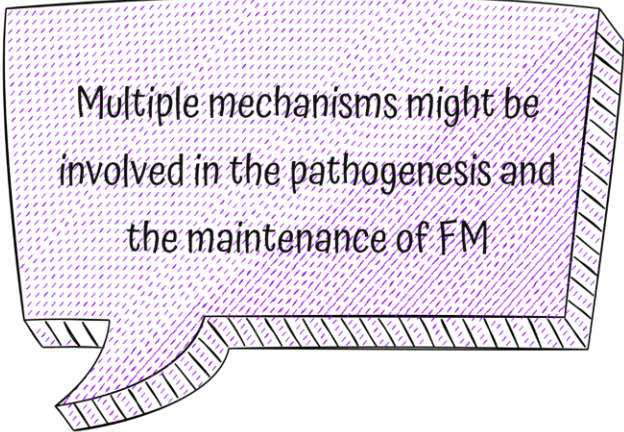
Nonpharmacological treatments



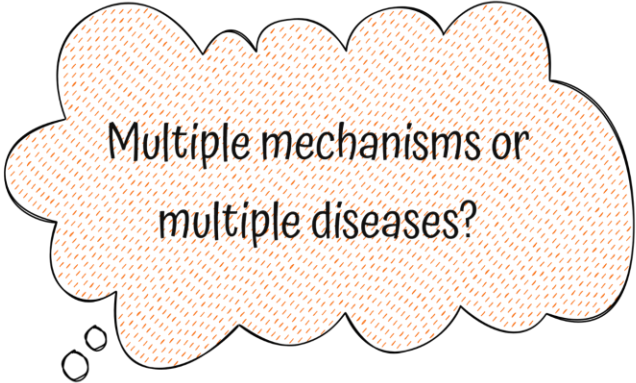
Take home messages




Fibromyalgia is a complex clinical syndrome with a huge impact on quality of life



Multiple mechanisms might be involved in the pathogenesis and the maintenance of FM



Multiple mechanisms or multiple diseases?



New insights = new therapies?