SOCIETÀ ITALIANA
G.U.I.D.A.
PER LA GESTIONE UNIFICATA E INTERDISCIPLINARE DEL DOLORE MUSCOLO-SCHELETRICO E DELL'ALGODISTROFIA

V CONGRESSO NAZIONALE

EVERYTHING YOU NEED TO KNOW

BOLOGNA
ROYAL HOTEL CARLTON
27 Febbraio - 1 Marzo 2025

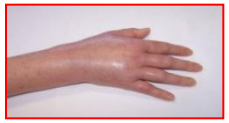
Patogenesi dell'Algodistrofia

Ombretta Di Munno

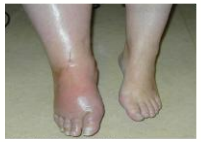
The beginnings of algology

- John Bonica, chair of the Department of Anesthesiology of the Washington University in Seattle,defined the characteristics of the disease in 1953, subdividing it into 3 stages:

- **Stage 1: acute**

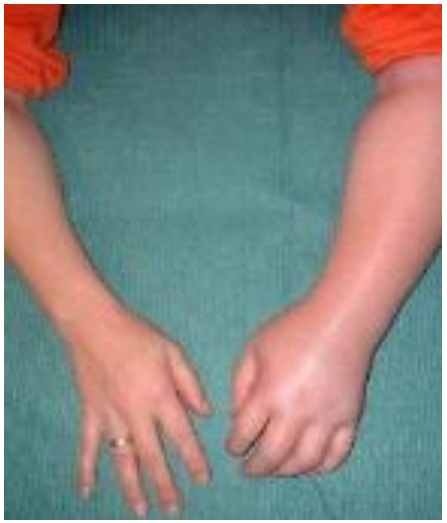


- **Stage 2: dystrophic**



- **Stage 3: atrophic**

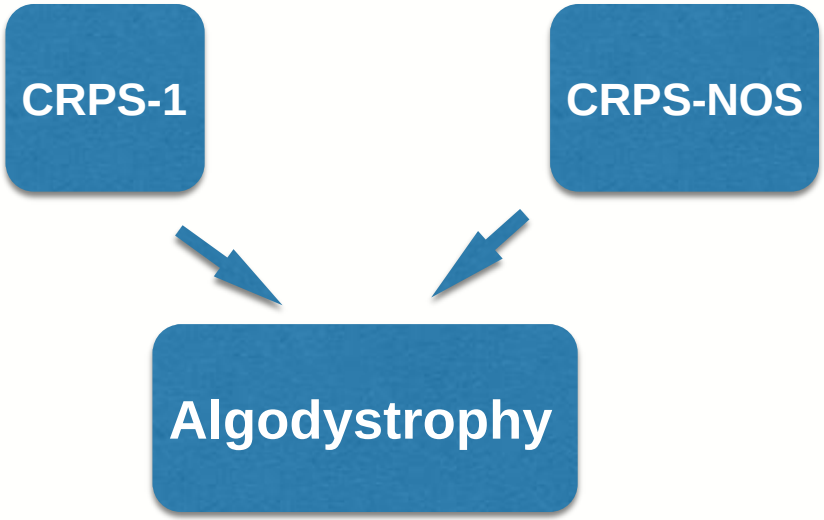
- **Complex regional pain syndrome (CRPS)** is a **consensus-defined** clinically diagnosed pain syndrome with hyperalgesia, allodynia, vasomotor, sudomotor, motor, and trophic symptoms and signs in the affected limb



Committee for Classification of Chronic Pain of the IASP
Schloss Rettershof conference - 1988 and
Orlando conference - 1994

Subtypes of CRPS

- **CRPS 1** = corresponds to the old RSD (without peripheral nerve injury)
- **CRPS 2** = Causalgia (with ascertained peripheral nerve injury)
- **CRPS- NOS (Not Otherwise Specified)** - only partially meets the Budapest criteria and is not attributable to any other pathology

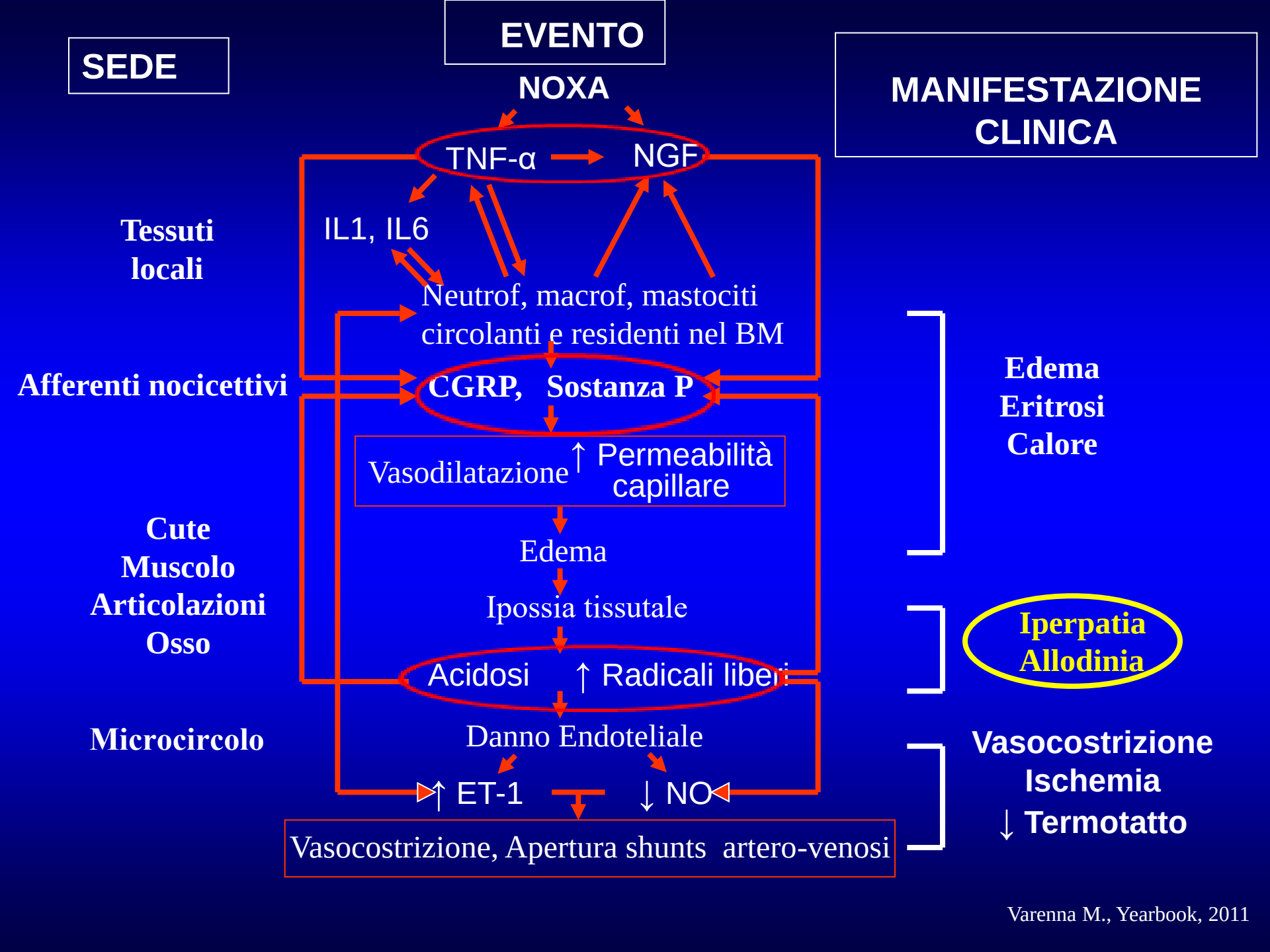


Complex Regional Pain Syndrome: A Comprehensive Review

CRPS Pathophysiology

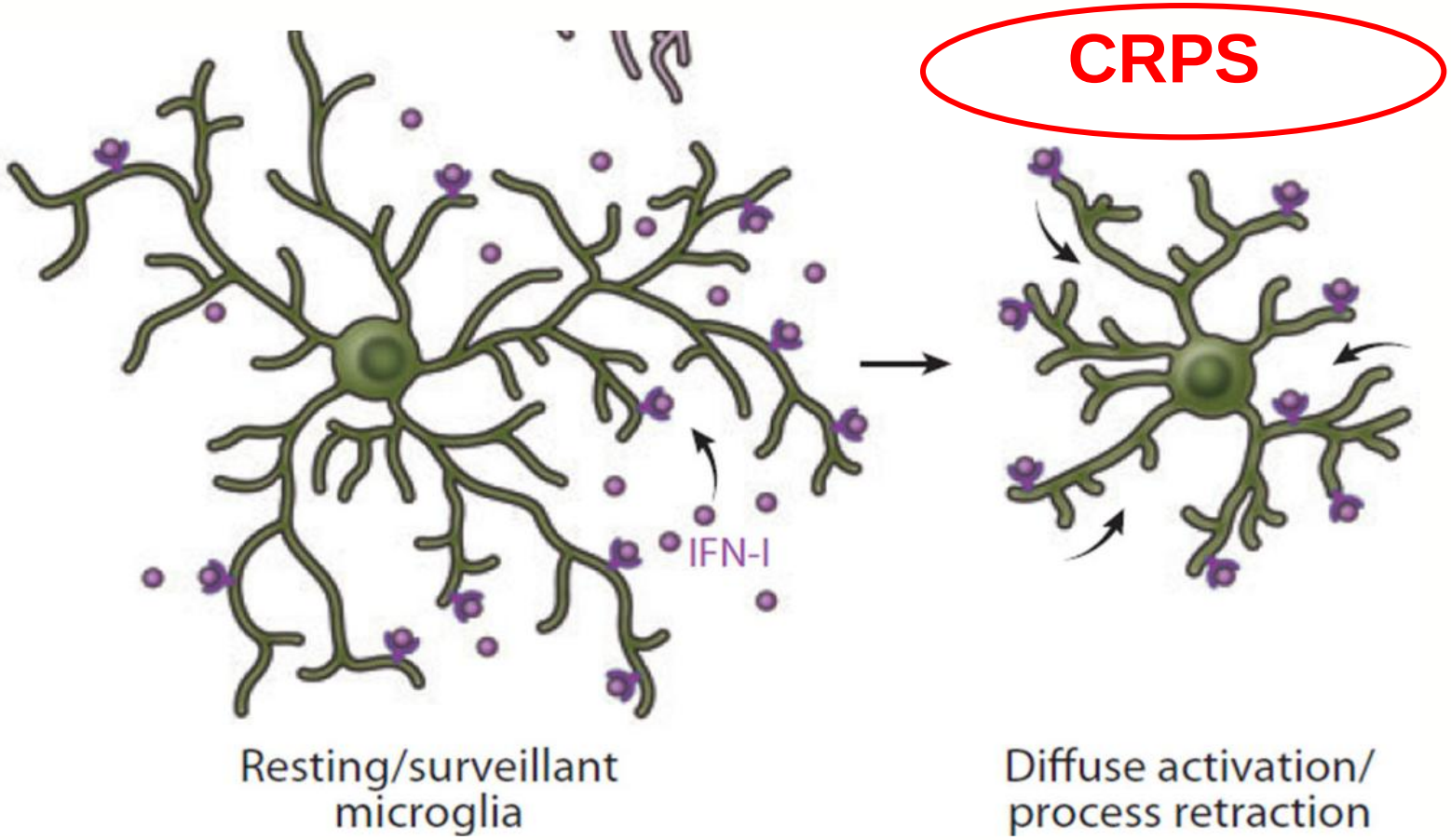
- **Aberrant neuroinflammation in the PNS and CNS**
- **Imbalance in the Autonomic Nervous System**
- **Autoimmunity(innate and more specifically adaptive immune response)**
- *Genetic/Epigenetic Factors(HLA-DQB1 ?)*
- *Psychosocial Factors(post-traumatic stress disorders, elevated levels of anxiety, perception of disability, kinesiophobia, pain-related fear)*
- *A peculiar disturbance of the bone metabolism(osteocyte necrosis)*
- *Alterations to the intestinal microbiota*

Taylor S-S et al, 2021
Varenna M, 2024
Crock LW, 2024
Wen B, 2023



Varenna M., Yearbook, 2011

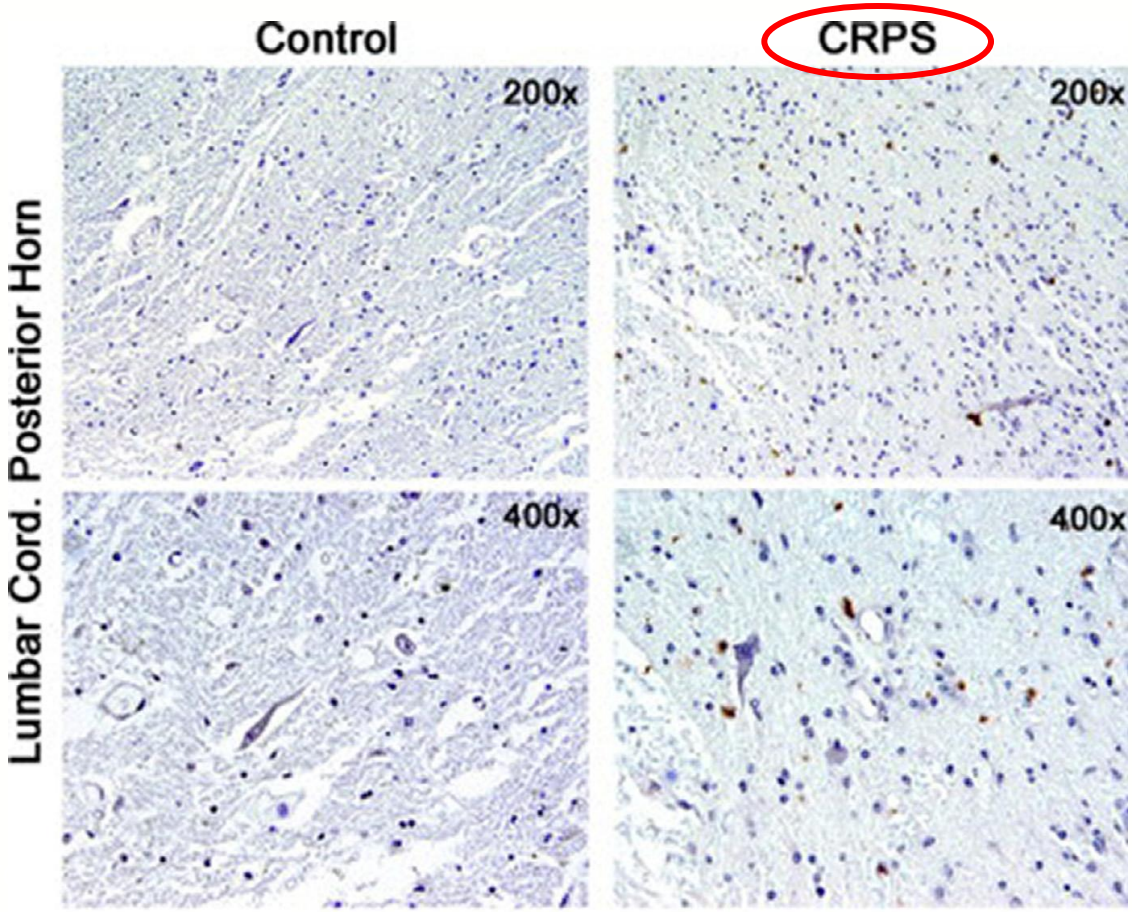
The involvement of microglia in CRPS has been demonstrated in animal studies, thus suggesting a potential link between peripheral neurogenic inflammation and sustained central sensitization through the production of proinflammatory mediators that regulate pain processing



modyf from Nayak D, 2014

Spinal cord histopathological alterations in a patient with longstanding complex regional pain syndrome

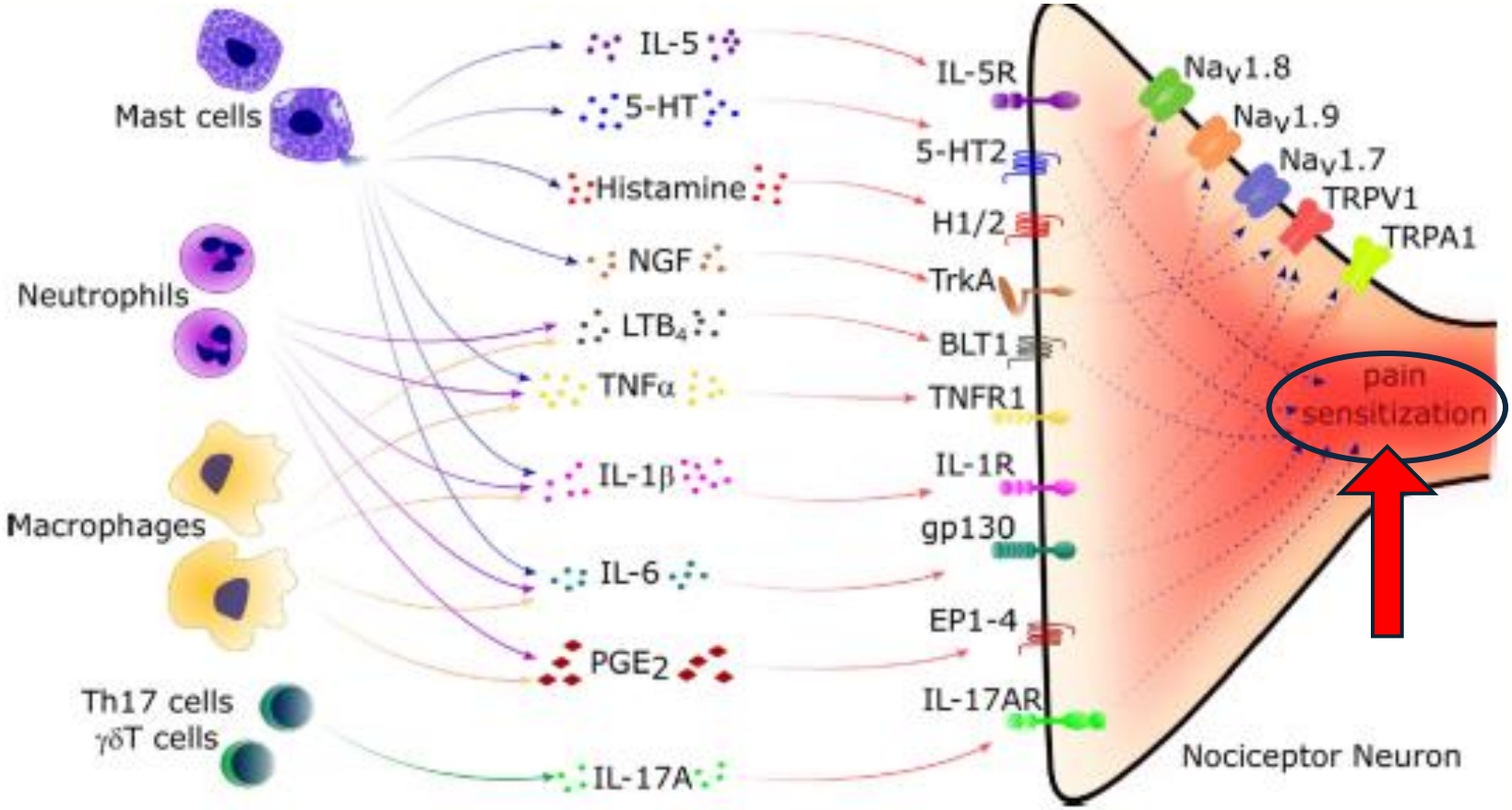
The first documentation of gliosis in CRPS was in a case report of autopsy findings in the spinal cord of a chronic case of CRPS



Del Valle L et al, 2009

Nociceptor Sensory Neuron-Immune Interactions in Pain and Inflammation

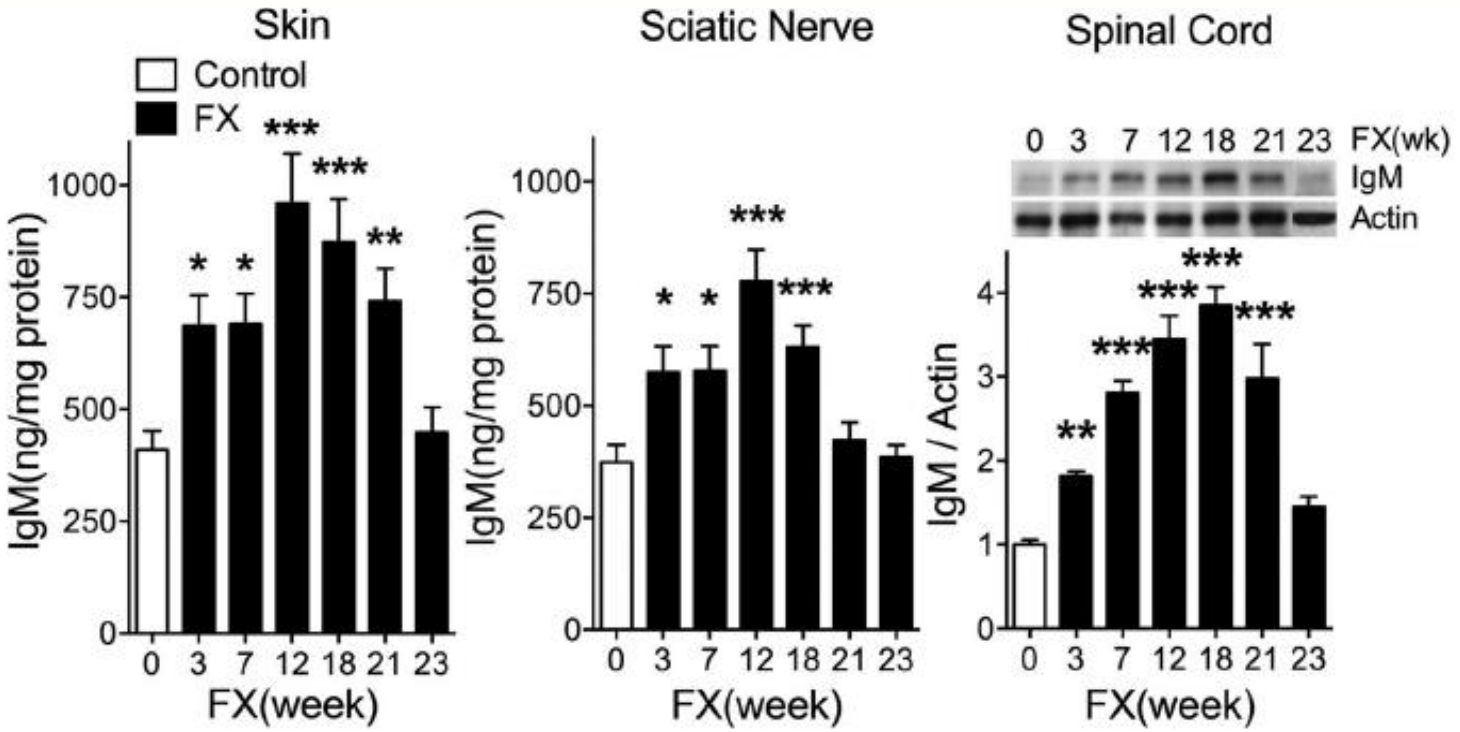
Immune cells at peripheral nerve terminals and within the spinal cord release mediators and autoantibodies which produce peripheral sensitization of nociceptor sensory neurons and pain
In turn, nociceptor neurons release neuropeptides and neurotransmitters from nerve terminals that regulate vascular, innate, and adaptive immune cell responses.



Pinho-Ribeiro FA et al, 2017

Passive transfer autoimmunity in a mouse model of complex regional pain syndrome

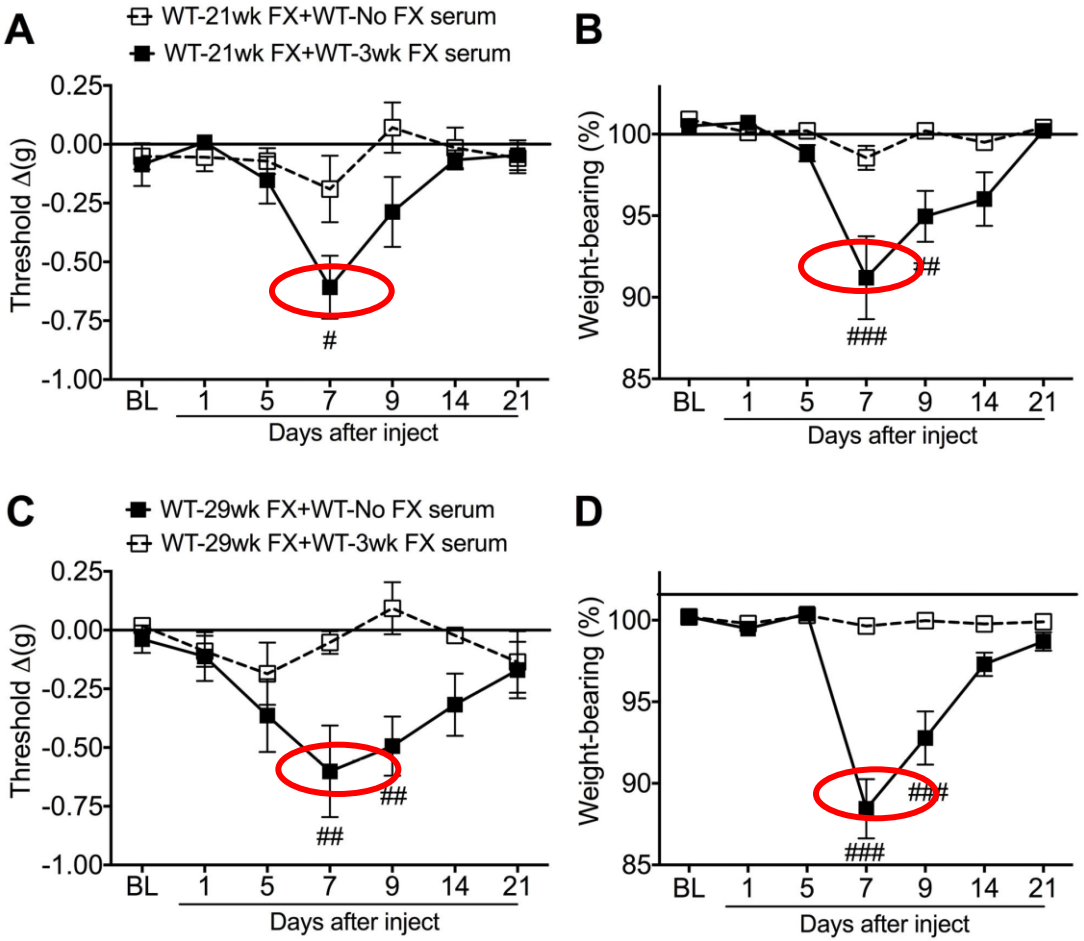
Changes in IgM levels in the ipsilateral hindpaw skin, sciatic nerve, and lumbar spinal cord at 3, 7, 12, 18, **21,** and **23** weeks **after fracture (FX)** in wildtype mice



Guo T, 2018

Passive transfer autoimmunity in a mouse model of complex regional pain syndrome

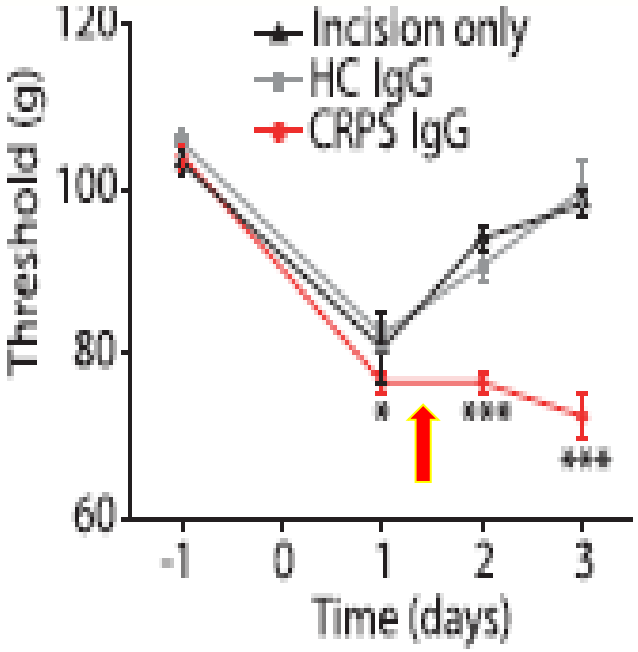
Serum from 3 week post-fracture (FX) wildtype (WT) mice was **pronociceptive in 21** and **29** week post-FX WT mice that had resolved **allodynia** and **unweighting**



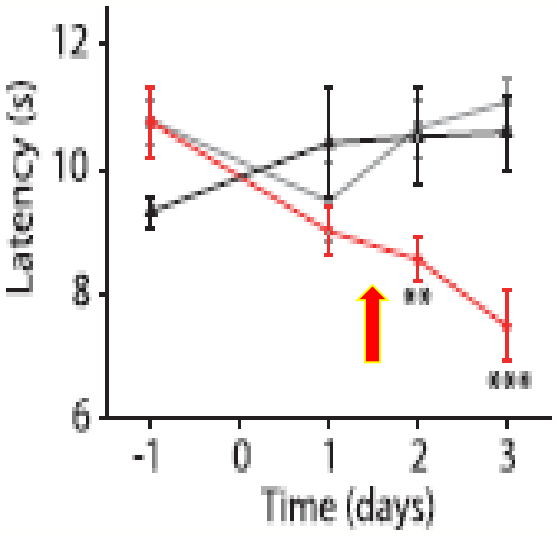
Guo T, 2018

Autoantibodies produce pain in complex regional pain syndrome by sensitizing nociceptors

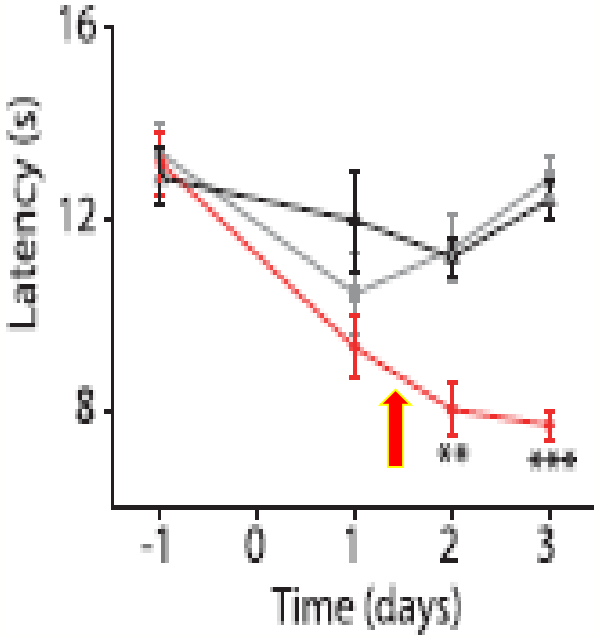
Administration of CRPS patient IgG produces polymodal hypersensitivities in mice



mechanical



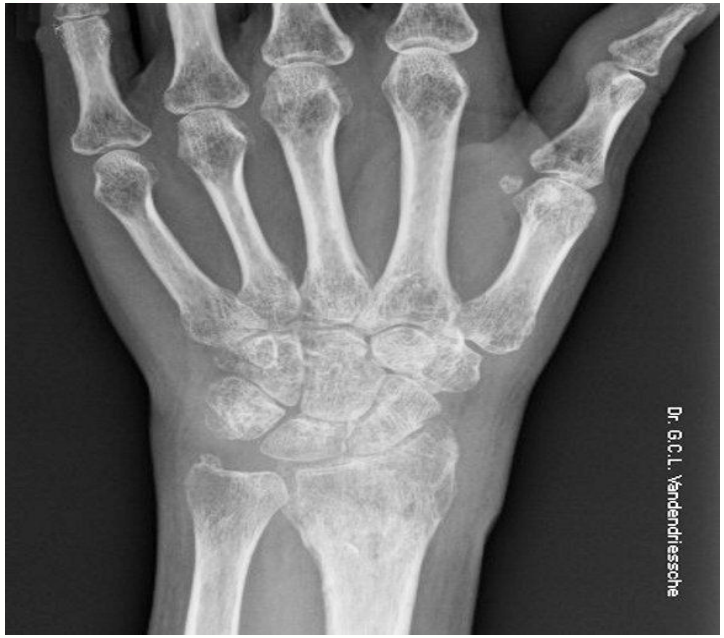
heat

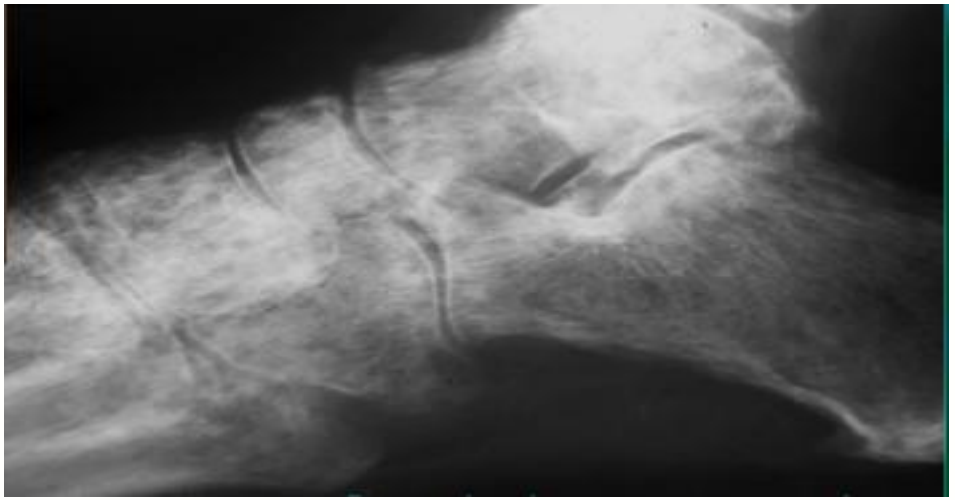


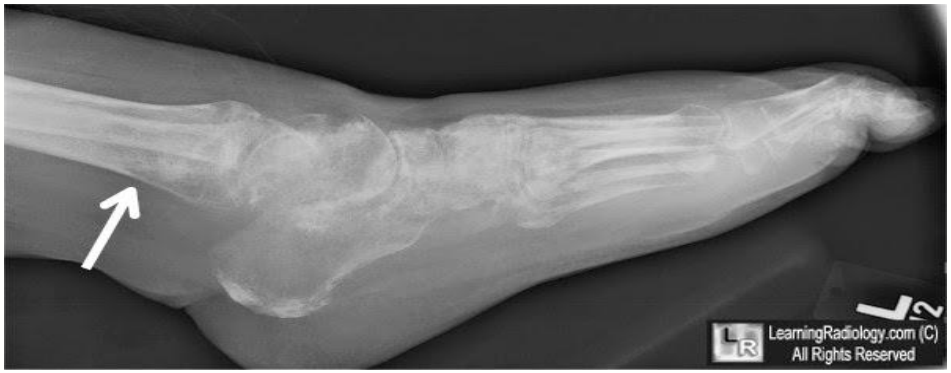
cold

Cuhadara U et al, 2019

Rx Standard


Dr. G.C.L. Vandendriessche

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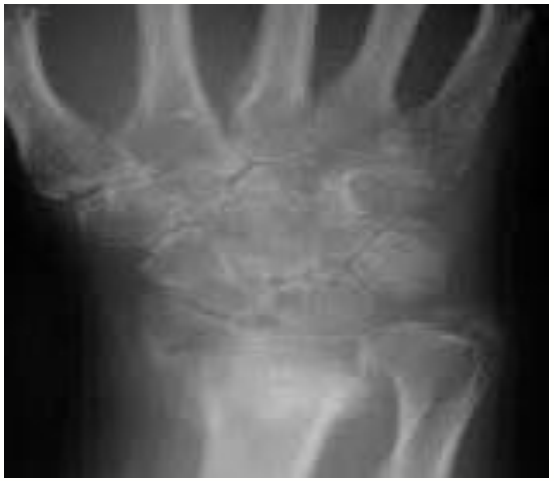
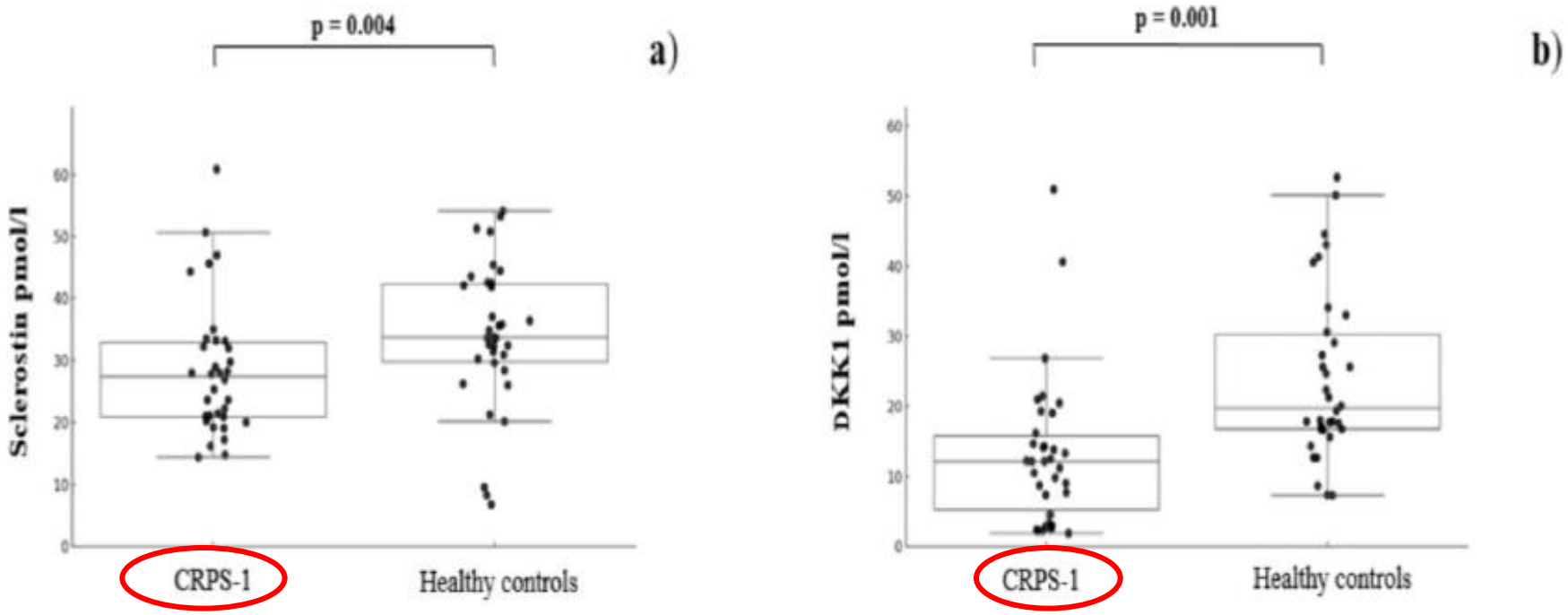


Bone Turnover Markers and Wnt Signaling Modulators in Early Complex Regional Pain Syndrome. A Pre-specified Observational Study

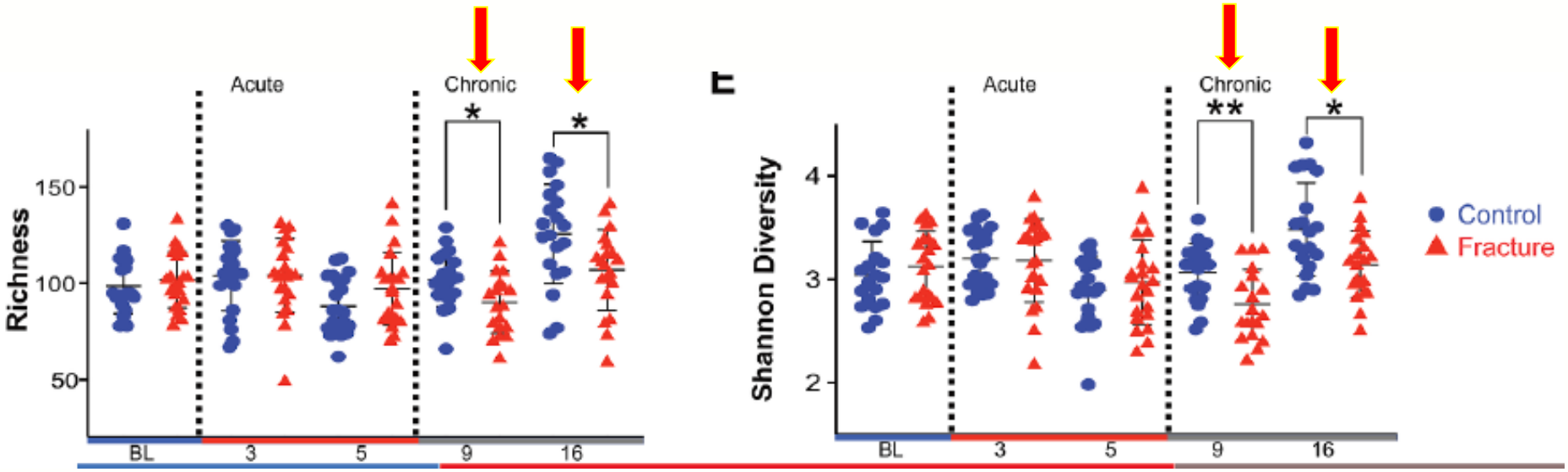
Serum values of Sclerostin a), DKK1 b)



Varenna M et al, 2024

Chronic pain and complex regional pain syndrome are associated with alterations to the intestinal microbiota in both humans and mice. An observational cross-sectional study

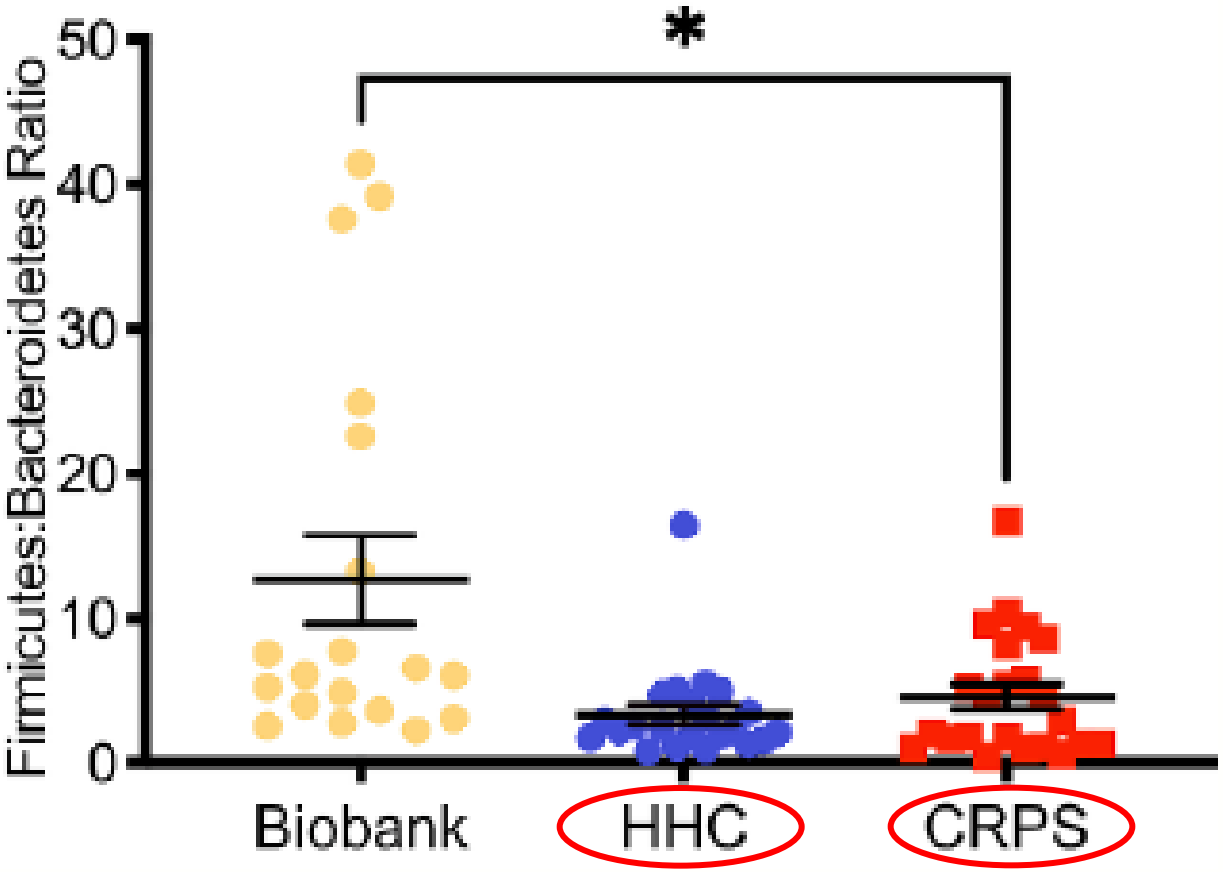
Overall intestinal microbiota composition is altered in a mouse model of CRPS as a function of time: acute (weeks 3-5) and chronic (week 7) mechanical allodynia



Crock LW et al, 2024

Chronic pain and complex regional pain syndrome are associated with alterations to the intestinal microbiota in both humans and mice. An observational cross-sectional study

Specific microbiota taxa and dysbiosis are associated with CRPS

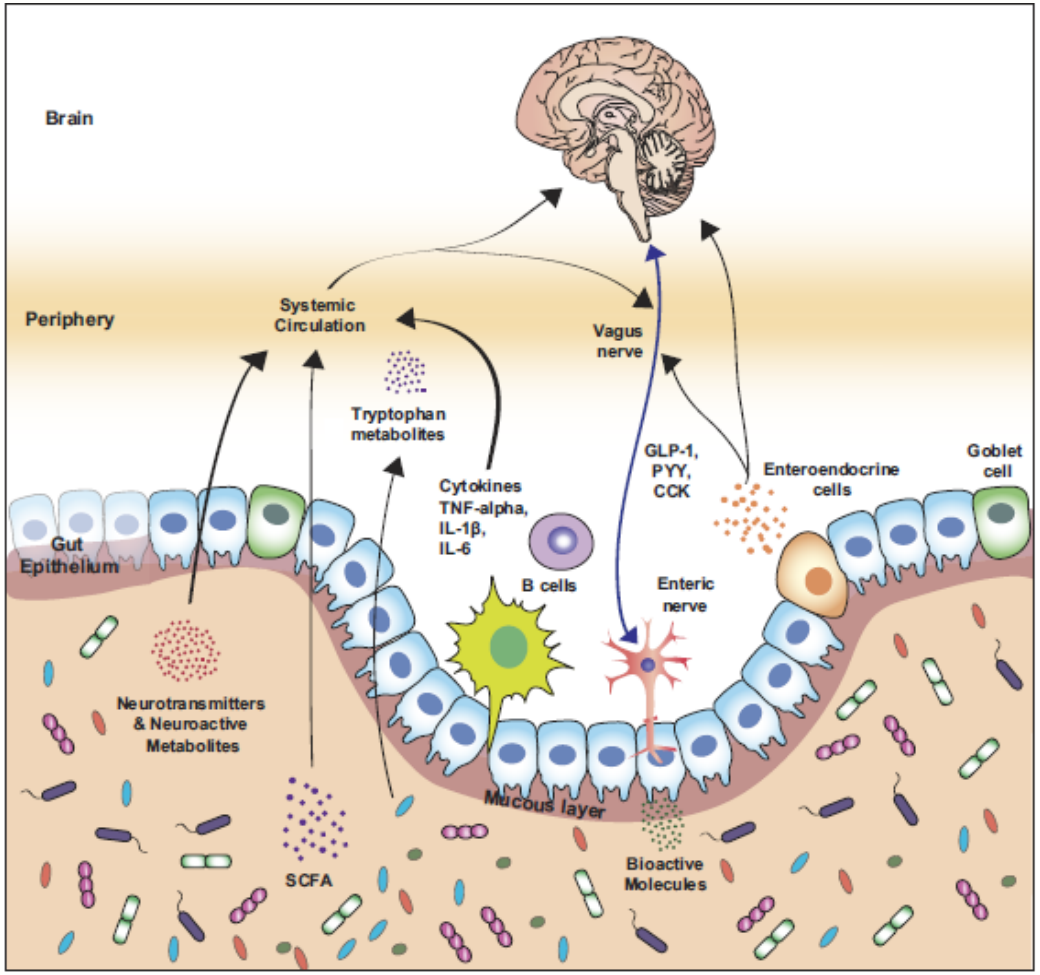


Biobank controls, HHC (household controls) and all CRPS patients (acute and chronic)

Crock LW et al, 2024

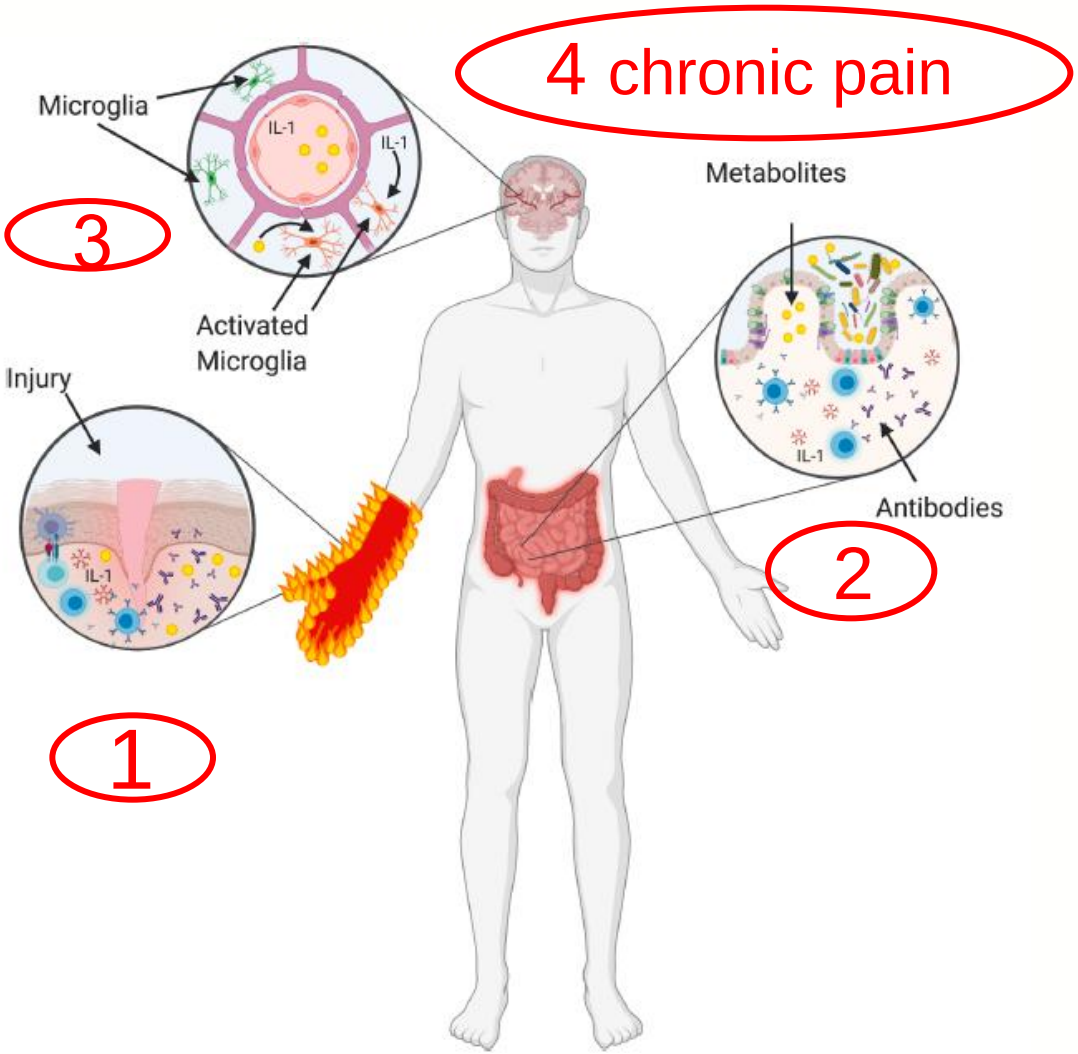
THE MICROBIOTA-GUT-BRAIN AXIS

Schematic outlining the various known bidirectional pathways of communication between the gut-microbiota and the brain, including the immune system, cytokines, the vagus nerve and the enteric nervous system, enteroendocrine and microbial metabolites



CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; IL, interleukin; PYY, peptide YY; TNF, tumor necrosis factor; SCFA, short-chain fatty acid.

A role for the microbiota in complex regional pain syndrome?



Modif from Crock LW et al, 2020

Complex Regional Pain Syndrome

Key Points

The pathophysiology of complex regional pain syndrome(CRPS) has become clearer through research in recent years.

Current evidence suggests that the pathophysiology involves multiple mechanisms through a complex interplay between the inflammation and neuroinflammation, autoimmunity, aberrations in autonomic processing, and both peripheral and central sensitization.

In addition, genetic and psychosocial factors, peculiar disturbances of bone metabolism, and microbiota changes have been postulated as additional factors in the development and persistence of CRPS

It is mandatory to quickly identify this condition and start treatment as soon as possible

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