https://doi.org/10.1038/s41584-023-00949-x

Imbalance of threat and soothing systems in fibromyalgia: rephrasing an established mechanistic model?

In their Perspective article, Pinto et al. propose that fibromyalgia results from an imbalance in emotion regulation, reflected by an overactive 'threat' system and an underactive 'soothing' system, that keeps the brain 'salience network' (also known as the midcingulo-insular network) in continuous alert mode (Pinto, A. M. et al. Emotion regulation and the salience network: a hypothetical integrative model of fibromyalgia. *Nat. Rev. Rheumatol.* **19**, 44–60 (2023))[1]. This proposal is similar to the established model that suggests fibromyalgia is a stress-evoked sympathetically maintained neuropathic pain syndrome[2]. Some information overlooked in the Pinto et al.[1] article might serve to better explain the intricate pathophysiology of fibromyalgia.

Investigations using different methods including analysis of heart rate variability have shown that patients with fibromyalgia and similar maladies have an overactive sympathetic (threat response) system and an underactive parasympathetic (soothing) system[3,4]. This autonomic dysfunction provides a coherent explanation for the multisystem symptoms of fibromyalgia. A new suggestion by Pinto et al.[1] is the proposal of salience network hyperactivity in fibromyalgia. However, there is a tight anatomical and functional overlap between the central autonomic nervous system and the salience network[5]. Salience network hyperactivity in fibromyalgia reveals a state of high alert of the threat response system, but it does not mean that this network is the primary source of pain.

The hypothesis of Pinto et al.[1] was formulated after "extensive review of the current pathophysiological perspectives on fibromyalgia"[1]. They embrace the orthodox theory that proposes fibromyalgia as a centralized pain syndrome. Surprisingly, they mention only in passing, and dismiss, the clear relationship between fibromyalgia and small nerve fibre pathology[6]. Furthermore, they do not acknowledge accumulating evidence proposing dorsal root ganglia as the key neural hubs where different physical, psychological, infectious and/or autoimmune stressors could be converted into neuropathic pain. Dorsal root ganglia house the small nerve fibre nuclei; each nucleus is tightly enveloped by immunocompetent glial cells[7]. Severe fibromyalgia is associated with a certain dorsal root ganglion sodium channel genetic variant[8]. IgG from patients with fibromyalgia injected into mice provokes pain behaviour and peripheral denervation; in such instances, IgG is exclusively deposited in the dorsal root ganglia[9]. The animal model of neuropathic pain is clear: different stressors, including psychological distress, induce hyperalgesia in mice as well as phenotypic modifications in dorsal root ganglia that establish abnormal connections between the sympathetic nervous system and the nociceptive system[7].

Pinto et al.[1] allude to a study by Hung et al.[10] as an argument that favours central sensitization in fibromyalgia. In fact, the experiments by Hung et al.[10] suggest that mice exposed to repeated sound stress develop chronic non-inflammatory hyperalgesia secondary to overexpression of pro-nociceptive mediators at the dorsal root ganglia.

In conclusion, the proposed 'Fibromyalgia: Imbalance of Threat and Soothing Systems' model is not different from the previously described hypothesis that suggests that fibromyalgia is a stress-evoked sympathetically maintained neuropathic pain syndrome. However, there is an alternative explanation to the predominant view of fibromyalgia as a centralized pain syndrome. Dorsal root ganglia may be the key fibromyalgia neural hubs where different stressors, including psychological distress, could be converted into neuropathic pain.

There is a reply to this letter by Pinto, A. M. et al. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-023-00950-4 (2023).

Manuel Martínez-Lavín ✉
Rheumatology Department, National Institute of Cardiology, Mexico City, Mexico.
✉e-mail: drmartinezlavin@gmail.com

Published online: 23 March 2023

References

1. Pinto, A. M. et al. Emotion regulation and the salience network: a hypothetical integrative model of fibromyalgia. *Nat. Rev. Rheumatol.* **19**, 44–60 (2023).
2. Martinez-Lavin, M. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. *Arthritis Res. Ther.* **9**, 216 (2007).
3. Martínez-Lavín, M., Hermosillo, A. G., Rosas, M. & Soto, M. E. Circadian studies of autonomic nervous balance in patients with fibromyalgia: a heart rate variability analysis. *Arthritis Rheum.* **41**, 1966–1971 (1998).
4. Martínez-Martínez, L. A., Mora, T., Vargas, A., Fuentes-Iniestra, M. & Martínez-Lavín, M. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. *J. Clin. Rheumatol.* **20**, 146–150 (2014).
5. Ferraro, S. et al. The central autonomic system revisited — convergent evidence for a regulatory role of the insular and midcingulate cortex from neuroimaging meta-analyses. *Neurosci. Biobehav. Rev.* **142**, 104915 (2022).
6. Grayston, R. et al. A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: implications for a new paradigm in fibromyalgia etiopathogenesis. *Semin. Arthritis Rheum.* **48**, 933–940 (2019).
7. Martínez-Lavín, M. Dorsal root ganglia: fibromyalgia pain factory? *Clin. Rheumatol.* **40**, 783–787 (2021).
8. Vargas-Alarcon, G. et al. A SCN9A gene-encoded dorsal root ganglia sodium channel polymorphism associated with severe fibromyalgia. *BMC Musculoskelet. Disord.* **13**, 23 (2012).
9. Goebel, A. et al. Passive transfer of fibromyalgia symptoms from patients to mice. *J. Clin. Invest.* **131**, e144201 (2021).
10. Hung, C. H. et al. Activation of acid-sensing ion channel 3 by lysophosphatidylcholine 16:0 mediates psychological stress-induced fibromyalgia-like pain. *Ann. Rheum. Dis.* **79**, 1644–1656 (2020).

Competing interests

The author declares no conflict of interest.