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

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We read with interest the correspondence by Manuel Martínez-Lavín on our Perspective article (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], which argues that our proposed 'Fibromyalgia: Imbalance of Threat and Soothing Systems (FITTS)' model echoes the existing view of fibromyalgia as a stress-evoked sympathetically maintained neuropathic pain syndrome (Martínez-Lavín, M. Imbalance of threat and soothing systems in fibromyalgia: rephrasing an established mechanistic model? *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-023-00949-x (2023))[2]. Specifically, Martínez-Lavín[2] proposes that various stressors (for example, physical, psychosocial, infectious and autoimmune) lead to dorsal root ganglion neuroplasticity, which is 'the' primary driver of pain[3].

In our view, a core challenge in the pathophysiology of fibromyalgia is the reconciliation of the many potential mechanisms involved, their relative importance and their roles as causes or consequences of fibromyalgia. We dedicated our paper to this aim, but this probably cannot be fully accomplished. The pathophysiology of fibromyalgia is too complex for a unidimensional view, which Martínez-Lavín seems to recognize when stating elsewhere[4] that fibromyalgia "cannot be explained by the prevailing linear-reductionist medical paradigm". There may be several potential origins, but once the vicious circle is established, it is almost impossible — and probably irrelevant — to separate the egg from the chicken.

We acknowledge the importance of the autonomic nervous system (ANS) in the pathophysiology of fibromyalgia, although there is no formal evidence of causation. The same holds true for peripheral small fibre pathology, which may be a primary driver of nociceptive input, but may also result from top-down mechanisms[5]. Moreover, small fibre pathology is present in only around 50% of people with fibromyalgia[6] and often presents as phenotypically different from small fibre neuropathy[7]. It is likely that both central and peripheral mechanisms contribute to fibromyalgia in varying degrees in individual patients.

We note that, elsewhere, Martínez-Lavín[8] has written that "fibromyalgia is clearly a stress-related disorder", which supports our view of the importance of psychological and social factors, such as trauma and distress. We acknowledge that the connections between emotions and the ANS are likely to be bidirectional: emotions can cause changes in the ANS, but conversely, changes in the ANS can influence affective processes and contribute to distorted perceptions of threat and soothing in the central nervous system. Distinguishing cause and effect is very challenging.

Our FITTS model expands the hypothesis of Martínez-Lavín[2] by embracing a broader concept of threat as the general perception of unsafety rather than the mere presence of a stressor[9]. Drawing from previous literature, we have broadened the original focus on sympathetic activity and its dysfunction to accommodate the concept of soothing, as well as linking sympathetic and parasympathetic tone to threat and safeness, respectively[1]. The potential role of safeness and soothing has been, with a few exceptions[10], rarely addressed in the literature on ANS and fibromyalgia.

The importance of psychosocial factors in fibromyalgia justifies their relevance in the FITSS model but should not be seen as the only, or even major, driving factor. We contend that the originality and strength of our proposal is the integration of the many previously proposed mechanisms and models in a unified framework. We believe that fibromyalgia can be viewed as resulting from vicious circles or 'hanging mobile' dynamics, in which each mechanism could simultaneously be cause and consequence.

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Competing interests

The authors declare no competing interests.