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Reply to: Hypothetical model ignores many important pathophysiologic mechanisms in fibromyalgia

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We read with great interest the comments by Clauw et al. (Clauw, D. J. et al. Hypothetical model ignores many important pathophysiologic mechanisms in fibromyalgia. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-023-00951-3 (2023))[1] on our Perspective article presenting the Fibromyalgia: Imbalance of Threat and Soothing Systems (FITSS) model (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]. The issues raised are familiar to us, in part because they were reiterated in similar terms during the long and detailed revision process. This process contributed to ensuring the published article deliberately rejects the reduction of fibromyalgia to any one simple causal mechanism. We acknowledge the heterogeneity of fibromyalgia, the multifactorial nature of the myriad of mechanisms involved, and that peripheral nociceptive, autonomic and brain processes play interlocking roles as triggers, modulators and consequences of fibromyalgia (for example, in the section Multidirectionality and the causality conundrum on p. 53)[2].

Thus, we are surprised with Clauw et al.'s statement that we claim that "psychological stress is the sole cause of fibromyalgia" or that "adverse childhood events … are key drivers in the development of fibromyalgia"[1]. Such statements, and the unidirectional causality they imply, are absent in our paper. We acknowledge that there are "very few, if any, prospective longitudinal studies that conclusively demonstrate that psychological stress causes fibromyalgia"[1]. Absence of evidence is not evidence of absence; neither are there studies that conclusively exclude psychological distress as a potential cause or driver of fibromyalgia. Longitudinal studies addressing any risk factors of fibromyalgia are rare. Clauw et al. mention a few risk factors for fibromyalgia that are putatively stronger than psychological distress. All of these factors have a strong relationship with stress and persistent negative emotion, raising questions about their unique causal contributions. The observation that "psychological factors often improve dramatically when pain improves"[1] is not surprising to us and is consistent with our statements: "The aetiological interactions among stress, sleep disturbances and pain are multidirectional," and "Stress and depression can also be initiated or aggravated by chronic pain"[2].

We also agree that precision-medicine approaches that personalize treatment are crucial. However, measures of nociceptive, autonomic and brain pathophysiology are not yet sufficient to enable effective precision treatment. While we wait for 'precision' studies to "align treatments with the underlying mechanisms that are operative in each individual patient", we note that currently available pharmacological treatments are far from personalized. Furthermore, they share psychotropic effects aligned with the concept of diminishing threat and augmenting soothing perceptions. The FITSS model is consistent with personalized medicine and will hopefully inspire such research. In fact, most (if not all) 'precision' observations made so far in fibromyalgia highlight changes in central nervous system structures and dynamics that are associated with both pain and emotion[3–6]: it seems unlikely that they might be related solely to pain and not to emotion.

In sum, we do not disagree with the substantive points in the correspondence from Clauw et al.[1], but we do disagree with how our paper[2] is summarized. We primarily aimed for a balanced paper and so invited the critical contribution of many authors with potentially different views. Consensus is often difficult to achieve, but we believe that engaging different views can both establish common ground and reveal areas where more scientific evidence is needed to resolve ambiguity. We are grateful that the paper, and this correspondence, enables us to further that goal.

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Competing interests

The authors declare no competing interests.