

- [7] Honig WK, Urucioli PJ. The legacy of Guttman and Kalish (1956): 25 years of research on stimulus generalization. *J Exp Anal Behav* 1981;36:405–45.
- [8] Lethem J, Slade PD, Troup JDG, Bentley G. Outline of a fear-avoidance model of exaggerated pain perception—I. *Behav Res Ther* 1983;21:401–8.
- [9] Linton SJ, Melin L, Götestam KG. Behavioral analysis of chronic pain and its management. In: Hersen M, Eisler RM, Miller PM, editors. *Progress in behavior modification*. Vol. 18: Academic Press, Inc., Orlando, FL. 1984. p. 1–42.
- [10] Main CJ, Keefe FJ, Jensen MP, Vlaeyen JW, Vowles KE. Fordyce's behavioral methods for chronic pain and illness: republished with invited commentaries. Wolters Kluwer Health, Philadelphia, PA. 2015.
- [11] Moseley GL, Vlaeyen JWS. Beyond nociception: the imprecision hypothesis of chronic pain. *PAIN* 2015;156:35–8.
- [12] Wunsch A, Philippot P, Plaghki L. Affective associative learning modifies the sensory perception of nociceptive stimuli without participant's awareness. *PAIN* 2003;102:27–38.

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Reply

Letter To Editor:

We were pleased to see the letter⁸ regarding our recent article on the Imprecision Hypothesis of chronic pain.²² We proposed that generalization of pain as a conditioned response to the non-noxious suite of inputs first associated with noxious input might provide a mechanism by which acute pain transitions into a chronic pain disorder.² The letter highlights the historical and empirical foundations of this idea and the challenges that we face in interrogating it. The letter also reinforces the novelty of this idea and its dependence on a different, albeit firmly established, conceptualization of pain itself.

We wholeheartedly agree that the Imprecision Hypothesis builds on several fundamental and established concepts, and we are mortified to think we would not give due respect to the massive amount of work in pain-related conditioning. However, as Fuchs et al. astutely observe, previous theorists have posited that classical conditioning mechanisms modulate pain through an “indirect” pathway, such as sympathetic arousal, muscle reactivity, and pain-related fear. Indeed, Fuchs et al. have made critical contributions to that body of evidence, and we are among many who have gratefully integrated those concepts into research approaches such as interoceptive⁵ and proprioceptive fear conditioning paradigms¹⁵ and cross-sectional patient–control comparisons.¹⁰ We also have integrated these ideas into our treatments, eg, “addressing the output systems” component of Explaining Pain,¹⁸ and exposure-based treatments for individuals reporting increased pain-related fear.⁴

Fuchs et al. assert “that pain itself as an ‘immediate’ conditioned response is arguable,” also quoting the book chapter by Linton et al.¹³ from 30 years ago—“the conditioned response is not pain, but it can be pain provoking,”—sentiments that Fordyce was proposing even earlier.⁶ Those assertions not only highlight

the novelty of the Imprecision Hypothesis but also point to its integration of a fundamentally different conceptualization of pain: that of a perceptual inference⁷ that motivates protective behavior, rather than serving as a readout of nociceptive input or tissue dysfunction. The idea that previous information about features of a stimulus modulates its perception is clearly a shift from that used in pain-related conditioning studies, but it is not a novel idea in itself.^{7,11} The idea that we are proposing imprecise encoding of the conditioned response, unfortunately, is a misinterpretation of our thesis; we actually propose imprecise encoding of the conditioned stimuli, as per the inverse hypothesis.⁹ This misinterpretation is a common misunderstanding when pain is conceptualized as an input and the brain as a “receipt organ,” rather than conceptualizing pain as an output¹⁷ or perceptual inference. We regret that we did not clearly articulate this, and the letter serves as a reminder to do better.

We agree with Fuchs et al. that a number of challenges must be overcome if we are to comprehensively interrogate the Imprecision Hypothesis. Empirical evidence for the idea that pain can be a conditioned response is still lacking, and the circumstances under which such conditioning may occur are yet to be identified.³ Also, research on stimulus generalization has a long history in both Pavlovian and instrumental conditioning and is currently enjoying an extensive revival. Its application in the area of pain¹⁴ is more recent, however. As Fuchs et al. correctly noted, we need to reveal how complex sensory events are encoded in the first place and what the neurophysiological correlates of imprecise encoding are. Imprecise encoding not only can foster generalization but also alter perceptual memory consolidation and retrieval.¹²

We are making ground amidst these challenges; the examples we provided (for instance, imprecise cortical maps of touch² or proprioception^{1,23} in people with pain [see also Refs. 21,25 for reviews] and expansion of disrupted body parts to spatial zones^{19,20}) have been very useful starting points for our investigations. An exciting avenue is that pain modulation can also be rooted in altered perceptual decision-making.^{16,26} Nonetheless, much needs to be learned, not least being the contributions of emotional, motivational, and cognitive processes.

In summary, we are pleased that Fuchs et al. share our enthusiasm for a new focus of research on learning processes associated with chronic pain and we welcome the opportunity to clarify aspects of the Imprecision Hypothesis. We acknowledge that there is a large body of work that describes an indirect end organ/output system–mediated pathway by which conditioning might exacerbate pain, and we consider that the massive literature on conditioning, on which the Imprecision Hypothesis is grounded, is actually one of the strengths of the hypothesis. We accept that conceptualization of pain as an output or perceptual inference is counter to the dominant conceptual viewpoints in the pain-related conditioning literature, but we also acknowledge that this “new” conceptualization is actually not that new.²⁴ Finally, we contend that the development of new conceptual frameworks can be helpful if they are grounded in established principles and are in line with current theoretical concepts in the field.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

- [1] Bowering KJ, Butler DS, Fulton IJ, Moseley GL. Motor imagery in people with a history of back pain, current back pain, both, or neither. *Clin J Pain* 2014;30:1070–5.

- [2] Catley MJ, O'Connell NE, Berryman C, Ayhan FF, Moseley GL. Is tactile acuity altered in people with chronic pain? A systematic review and meta-analysis. *J Pain* 2014;15:985–1000.
- [3] Crombez G, Baeyens F, Eelen P. Klassieke conditionering en geconditioneerde pijn [Classical conditioning and conditioned pain]. *Gedragstherapie* 1994;27:97–107.
- [4] de Jong JR, Vlaeyen JW, Onghena P, Cuypers C, den Hollander M, Ruijgrok J. Reduction of pain-related fear in complex regional pain syndrome type I: the application of graded exposure in vivo. *PAIN* 2005;116:264–75.
- [5] De Peuter S, Van Diest I, Vansteenwegen D, Van den Bergh O, Vlaeyen JW. Understanding fear of pain in chronic pain: interoceptive fear conditioning as a novel approach. *Europ J Pain* 2011;15:889–94.
- [6] Fordyce WE, Fowler RS Jr, Lehmann JF. Operant conditioning in the treatment of chronic pain. *Arch Phys Med Rehabil* 1973;54:399–408.
- [7] Friston K. Prediction, perception and agency. *Int J Psychophysiol* 2012;83:248–52.
- [8] Fuchs X, Becker S, Kleinböhl D, Diers M, Flor H. Respondent learning in chronic pain: how precise is imprecision? *PAIN* 2015;156:2108–9.
- [9] Guttman N, Kalish HI. Discriminability and stimulus generalization. *J Exp Psychol* 1956;51:79–88.
- [10] Harvie DS, Broecker M, Smith RT, Meulders A, Madden VJ, Moseley GL. Bogus visual feedback alters onset of movement-evoked pain in people with neck pain. *Psychol Sci* 2015;26:385–92.
- [11] Kording KP, Wolpert DM. Bayesian integration in sensorimotor learning. *Nature* 2004;427:244–7.
- [12] Lenaert B, Claes S, Raes F, Boddez Y, Joos E, Vervliet B, Hermans D. Generalization of conditioned responding: effects of autobiographical memory specificity. *J Behav Ther Exp Psychiatry* 2012;43(suppl 1):S60–6.
- [13] Linton SJ, Melin L, Gotestam KG. Behavioral analysis of chronic pain and its management. *Prog Behav Modif* 1984;18:1–42.
- [14] Meulders A, Vandebroek N, Vervliet B, Vlaeyen JW. Generalization gradients in cued and contextual pain-related fear: an experimental study in healthy participants. *Front Hum Neurosci* 2013;7:345.
- [15] Meulders A, Vansteenwegen D, Vlaeyen JW. The acquisition of fear of movement-related pain and associative learning: a novel pain-relevant human fear conditioning paradigm. *PAIN* 2011;152:2460–9.
- [16] Moseley GL, Arntz A. The context of a noxious stimulus affects the pain it evokes. *PAIN* 2007;133:64–71.
- [17] Moseley GL, Butler D. 15 years of explaining pain—the past the present and the future. *J Pain* 2015. doi 10.1016/j.jpain.2015.05.005.
- [18] Moseley GL, Butler D. *The explain pain handbook: protectometer*. Adelaide: Noigroup Publications, 2015. p. 58.
- [19] Moseley GL, Gallace A, Iannetti GD. Neglect-like tactile dysfunction in chronic back pain. *Neurology* 2012;79:327–32.
- [20] Moseley GL, Gallace A, Iannetti GD. Spatially defined modulation of skin temperature and hand ownership of both hands in patients with unilateral complex regional pain syndrome. *Brain* 2012;135:3676–86.
- [21] Moseley GL, Gallace A, Spence C. Bodily illusions in health and disease: physiological and clinical perspectives and the concept of a cortical “body matrix”. *Neurosci Biobeh Rev* 2012;36:34–46.
- [22] Moseley GL, Vlaeyen JW. Beyond nociception: the imprecision hypothesis of chronic pain. *PAIN* 2015;156:35–8.
- [23] Stanton TR, Lin CW, Smeets RJ, Taylor D, Law R, Lorimer Moseley G. Spatially-defined disruption of motor imagery performance in people with osteoarthritis. *Rheumatology* 2012;51:1455–64.
- [24] Wall P. Introduction to the edition after this one. Editorial. In: Wall P, Melzack R, editors. *The textbook of pain*. Edinburgh: Churchill-Livingstone, 1994. p. 1–7.
- [25] Wand BM, Parkitny L, O'Connell NE, Luomajoki H, McAuley JH, Thacker M, Moseley GL. Cortical changes in chronic low back pain: current state of the art and implications for clinical practice. *Man Ther* 2011;16:15–20.
- [26] Wiech K, Vandekerckhove J, Zaman J, Tuerlinckx F, Vlaeyen JW, Tracey I. Influence of prior information on pain involves biased perceptual decision-making. *Curr Biol* 2014;24:R679–81.

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