

Tired of pain or painfully tired?

Citation for published version (APA):

Lenaert, B., Meulders, A., & van Heugten, C. M. (2018). Tired of pain or painfully tired? A reciprocal relationship between chronic pain and fatigue. *Pain*, 159(6), 1178-1179.
<https://doi.org/10.1097/j.pain.0000000000001194>

Document status and date:

Published: 01/06/2018

DOI:

[10.1097/j.pain.0000000000001194](https://doi.org/10.1097/j.pain.0000000000001194)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Eva Kosek^{a,b}
Milton Cohen^c
Ralf Baron^d
Juan-Antonio Mico^e
Andrew S.C. Rice^f

^a*Department of Clinical Neuroscience,
Osher Center, Karolinska Institutet,
Stockholm, Sweden*

^b*Department of Neuroradiology, Karolinska University Hospital,
Stockholm Spine Center,
Stockholm, Sweden*

^c*St Vincent's Clinical School, UNSW Australia,
Sydney, Australia*

^d*Division of Neurological Pain Research and Therapy,
Department of Neurology,
Universitaetsklinikum Schleswig-Holstein, Campus Kiel,
Kiel, Germany*

^e*Department of Neuroscience, CIBER of Mental Health,
CIBERSAM, University of Cadiz,
Cadiz, Spain*

^f*Pain Research, Department of Surgery and Cancer,
Imperial College, Chelsea and Westminster Hospital Campus,
London, United Kingdom*

E-mail address: Eva.Kosek@ki.se (E. Kosek)
<http://dx.doi.org/10.1097/j.pain.0000000000001185>

Tired of pain or painfully tired? A reciprocal relationship between chronic pain and fatigue



Letter to Editor:

The topical review by Van Damme et al.²² elegantly describes 3 pathways within a motivational framework through which chronic pain may affect fatigue. This letter is intended to compliment and complement the authors' contribution by proposing a reciprocal relationship between chronic pain and fatigue.

The unidirectional focus of the proposed approach—from chronic pain to fatigue—is in part justified based on a systematic review on fatigue in chronic pain populations,⁶ including 5 prospective studies showing that fatigue developed after pain onset^{2,3,5,15,19}; suggesting that chronic pain might cause fatigue. However, 2 of these studies did not assess the relationship between pain and fatigue prospectively,^{2,19} whereas 2 other studies found no significant associations in longitudinal analyses.^{3,15} Although additional evidence for pain prospectively predicting fatigue in patients with chronic pain has emerged since,¹³ conclusions on the temporal, let alone causal, relationship between chronic pain and fatigue remain speculative.

Moreover, samples in all studies were selected based on pain presence, limiting the scope of causal inferences. Even if fatigue would be secondary to pain in the presence of chronic pain, this does not rule out the possibility that fatigue may predict (and is causally involved in) chronic pain development. This requires longitudinal designs where subjects are not selected on pain or fatigue presence, or are selected on the absence thereof at baseline. Interestingly, such studies have, for instance, demonstrated that fatigue predicts future onset of abdominal pain in children⁴ and adults,⁸ as well as the development of neck and shoulder pain in younger adults,¹⁶ and that burnout symptoms, including fatigue, predict musculoskeletal pain onset among employees.¹ Such findings support the idea that the relationship between chronic pain and fatigue may be bidirectional. As such, theoretical models would benefit from including this reciprocity. To better understand fatigue in chronic pain, it is important to explain how pain may aggravate fatigue, but also how fatigue may worsen pain.

Central to the motivational framework is the balance between (expected) costs and benefits of ongoing goal-directed behavior. When the costs start to exceed the benefits, this signal is perceived as fatigue, urging goal adjustment. The authors propose that this cost–benefit trade-off is affected by chronic pain. For instance, pain may hinder goal progress, requiring increased top-down effortful control to maintain goal-directed behaviour, which adds to the costs inducing fatigue.²³ Thus, in their model, a sensation that is perceived as painful increases effortful control during goal-pursuit, thereby inducing fatigue. Interestingly, pain perception itself may be influenced by fatigue. Research has shown that individuals suffering from chronic fatigue have lower pain thresholds to pressure and electrical stimulation than healthy controls^{11,14,25,27} (which has been ascribed to sensitization of the central nervous system^{10,14,18,21}). Moreover, although exercise usually increases pain thresholds in healthy individuals,^{9,24,26} it has the opposite effect in individuals with chronic fatigue.^{12,24,26} Animal research has also shown that healthy mice demonstrate hyperalgesia after fatigue induction.^{7,17} These results indicate that, besides pain increasing fatigue during ongoing activity, fatigue during ongoing activity may also exacerbate pain. Therefore, we argue that pain and fatigue may mutually reinforce and perpetuate each other in chronic pain. Future longitudinal and experimental studies should scrutinize this reciprocal relationship.

Finally, the authors seem to equate reduced motivation to fatigue in some instances. We argue that although fatigue may be captured as reduced motivation, not each occurrence of motivational reduction is (or leads to) fatigue. For instance, the authors propose that chronic pain may impair reward processing, which may reduce the weight of the benefits associated with current goal-directed behaviour, thereby inducing fatigue. This conclusion builds on experimental work showing that when the consequences of our actions embody a mixture of reward and (anticipated) pain, this cost–benefit integration leads to attenuated predictive reward signaling in the brain.²⁰ To use a real-life example: If a person goes to the dentist to maintain dental health (reward), the anticipation of pain may reduce the weight of the benefits associated with consulting a dentist. However, referring to this attenuated reward processing as fatigue or fatigue inducing may not be warranted. Indeed, although fatigue may manifest itself as reduced motivation to pursue current goals, certainly not every reduction in motivation for goal-pursuit can be conceptualized as fatigue.

The framework presented by Van Damme et al. opens a new research agenda for fatigue in chronic pain. We propose that expanding their model by integrating reciprocal relationships will allow for a better representation of the complexity of real-life symptom interactions.

Conflict of interest statement

The authors have no conflict of interest to declare.

The contribution of A. Meulders is supported by a Vidi grant from the Netherlands Organization for Scientific Research (NWO), the Netherlands (grant ID 452-17-002). A. Meulders is also a postdoctoral researcher of the Research Foundation Flanders (FWO-Vlaanderen), Belgium, (grant ID: 12E3717N).

References

- [1] Armon G, Melamed S, Shirom A, Shapira I. Elevated burnout predicts the onset of musculoskeletal pain among apparently healthy employees. *J Occup Health Psychol* 2010;15:399–408.

- [2] Bansevicius D, Westgaard RH, Sjaastad OM. Tension-type headache: pain, fatigue, tension, and EMG responses to mental activation. *Headache* 1999;39:417–25.
- [3] Crosby LJ. Factors which contribute to fatigue associated with rheumatoid arthritis. *J Adv Nurs* 1991;16:974–81.
- [4] El-Metwally A, Halder S, Thompson D, Macfarlane GJ, Jones GT. Predictors of abdominal pain in schoolchildren: a 4-year population-based prospective study. *Arch Dis Child* 2007;92:1094–9.
- [5] Feuerstein M, Carter RL, Papciak AS. A prospective analysis of stress and fatigue in recurrent low back pain. *PAIN* 1987;31:333–44.
- [6] Fishbain DA, Cole B, Cutler RB, Lewis J, Rosomoff HL, Fosomoff RS. Is pain fatiguing? A structured evidence-based review. *Pain Med* 2003;4: 51–62.
- [7] Gregory NS, Gibson-Corley K, Frey-Law L, Sluka KA. Fatigue-enhanced hyperalgesia in response to muscle insult: induction and development occur in a sex-dependent manner. *PAIN* 2013;154:2668–76.
- [8] Halder SLS, Mcbeth J, Silman AJ, Thompson G, Macfarlane GJ. Psychosocial risk factors for the onset of abdominal pain. Results from a large prospective population-based study. *Int J Epidemiol* 2002;31: 1219–25.
- [9] Koptyn KF, Arbogast RW. Perception of pain after resistance exercise. *Br J Sports Med* 1998;32:20–4.
- [10] Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol* 2007;26:465–73.
- [11] Meeus M, Nijs J, Huybrechts S, Truijten S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: a case control study. *Clin Rheumatol* 2010;29:393–8.
- [12] Meeus M, Roussel NA, Truijten S, Nijs J. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. *J Rehabil Med* 2010;42: 884–90.
- [13] Nicassio PM, Moxham EG, Schuman CE, Gevirtz RN. The contribution of pain, reported sleep quality, and depressive symptoms to fatigue in fibromyalgia. *PAIN* 2002;100:271–9.
- [14] Nijs J, Meeus M, Van Oosterwijck J, Ickmans K, Moorkens G, Hans G, De Clerck LS. In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. *Eur J Clin Invest* 2012;42: 203–12.
- [15] Schuman C. Pain and depression as predictors of fatigue in fibromyalgia syndrome patients: an investigation with aggregated and disaggregated data. *Diss Abstr Int* 1997;57:7742.
- [16] Siivola SM, Levoska S, Latvala K, Hoskio E, Vanharanta H, Keinänen-Kiukaaniemi S. Predictive factors for neck and shoulder pain: a longitudinal study in young adults. *Spine (Phila Pa 1976)* 2004;29: 1662–9.
- [17] Sluka KA, Rasmussen LA. Fatiguing exercise enhances hyperalgesia to muscle inflammation. *PAIN* 2010;148:188.
- [18] Staud R, Moktech M, Price DD, Robinson ME. Evidence for sensitized fatigue pathways in patients with chronic fatigue syndrome. *PAIN* 2015; 156:750–9.
- [19] Stone AA, Broderick JE, Porter LS, Kaell A. The experience of rheumatoid arthritis pain and fatigue: examining momentary reports and correlates over one week. *Arthritis Care Res* 1997;10:185–93.
- [20] Talmi D, Dayan P, Kiebel SJ, Frith CD, Dolan RJ. How humans integrate the prospects of pain and reward during choice. *J Neurosci* 2009;29:14617–26.
- [21] Ursin H. Brain sensitization to external and internal stimuli. *Psychoneuroendocrinology* 2014;42:134–45.
- [22] Van Damme S, Becker S, van der Linden D. Tired of pain? Toward a better understanding of fatigue in chronic pain. *PAIN* 2018;159:7–10.
- [23] Van der Linden D. The urge to stop: the cognitive and biological nature of acute mental fatigue. In: Ackerman PL, editor. *Cognitive fatigue: multidisciplinary perspectives on current research and future applications*. Washington: American Psychological Association, 2011. p. 149–64.
- [24] Van Oosterwijck J, Nijs J, Meeus M, Lefever I, Huybrechts L, Lambrecht L, Paul L. Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: an experimental study. *J Intern Med* 2010;268:265–78.
- [25] Vecchiet L, Montanari G, Pizzigallo E, Iezzi S, de Bigontina P, Dragani L, Vecchiet J, Giambardino MA. Sensory characterization of somatic parietal tissues in humans with chronic fatigue syndrome. *Neurosci Lett* 1996;208:117–20.
- [26] Whiteside A, Hansen S, Chaudhuri A. Exercise lowers pain threshold in chronic fatigue syndrome. *PAIN* 2004;109:497–9.
- [27] Winger A, Kvarstein G, Wyller VB, Sulheim D, Fagermoen E, Småstuen MC, Helseth S. Pain and pressure pain thresholds in adolescents with chronic fatigue syndrome and healthy controls: a cross-sectional study. *BMJ Open* 2014;4:e005920.

Bert Lenaert^{a,b,c}Ann Meulders^{d,e}Caroline M. van Heugten^{a,b,c}

^aSchool for Mental Health and Neuroscience,
Department of Psychiatry and Neuropsychology,
Faculty of Health, Medicine and Life Sciences,
Maastricht University, Maastricht, the Netherlands

^bDepartment of Neuropsychology and Psychopharmacology,
Faculty of Psychology and Neuroscience,
Maastricht University, Maastricht, the Netherlands

^cLimburg Brain Injury Center, Maastricht, the Netherlands

^dResearch Group Health Psychology,
Faculty of Psychology and Educational Sciences,
KU Leuven, Leuven, Belgium

^eDepartment of Clinical Psychological Science,
Faculty of Psychology and Neuroscience,
Maastricht University,

Maastricht, the Netherlands

E-mail address: bert.lenaert@maastrichtuniversity.nl (B. Lenaert)

<http://dx.doi.org/10.1097/j.pain.0000000000001194>

Reply



Letter to Editor:

In their letter to the editor, Lenaert et al.⁶ commented on our recently proposed motivational framework explaining the frequent occurrence of fatigue in individuals with chronic pain.¹¹ We would like to thank these authors for complimenting and complementing our work and take the opportunity to further discuss some of the issues they raised.

Their main argument concerns the direction of the relationship between chronic pain and fatigue. Our framework was guided by the observation that patients with chronic pain often report heightened fatigue and, as a starting point, we referred to a systematic review suggesting that fatigue may develop as a result of chronic pain.⁴ We agree with the authors that this review does not provide evidence for an exclusive unidirectional causal relationship between chronic pain and fatigue. Yet, it is important to note that it was not our intention to argue for such a relationship. We acknowledge that several studies have suggested that fatigue enhances pain or increases the risk of developing chronic pain disorders. As such, we do not contend the idea that fatigue may influence pain, but we do, however, ask for caution when considering the evidence provided in that direction. For example, heightened pain sensitivity has been demonstrated in patients with chronic fatigue syndrome.⁷ However, for these studies, the same limitation applies as for the studies on fatigue in patients with chronic pain, mentioned by the authors, namely that the samples were selected based on the diagnosis of chronic fatigue syndrome, preventing strong causal claims. The authors also referred to a number of prospective studies,^{1,3,5,8} indicating that the presence of fatigue increases the risk of developing pain complaints. However, in the samples used, fatigue was often only one of a broader set of symptoms indicating burnout, sleeping problems, or general psychological distress. Consequently, it remains unclear whether it was actually fatigue that caused the pain complaints or whether fatigue was an indicator of broader psychological problems playing a role in the development of pain disorders.

Despite the limitations discussed above, we concur that it is likely that pain and fatigue mutually reinforce each other. Such a view is compatible with our proposed theoretical framework. As stated in our theoretical framework, higher-order cognitive processes such as executive control are involved in the