

# Tired of pain or painfully tired?

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**Eva Kosek<sup>a,b</sup>**  
**Milton Cohen<sup>c</sup>**  
**Ralf Baron<sup>d</sup>**  
**Juan-Antonio Mico<sup>e</sup>**  
**Andrew S.C. Rice<sup>f</sup>**

<sup>a</sup>*Department of Clinical Neuroscience,  
Osher Center, Karolinska Institutet,  
Stockholm, Sweden*

<sup>b</sup>*Department of Neuroradiology, Karolinska University Hospital,  
Stockholm Spine Center,  
Stockholm, Sweden*

<sup>c</sup>*St Vincent's Clinical School, UNSW Australia,  
Sydney, Australia*

<sup>d</sup>*Division of Neurological Pain Research and Therapy,  
Department of Neurology,  
Universitaetsklinikum Schleswig-Holstein, Campus Kiel,  
Kiel, Germany*

<sup>e</sup>*Department of Neuroscience, CIBER of Mental Health,  
CIBERSAM, University of Cadiz,  
Cadiz, Spain*

<sup>f</sup>*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.<sup>22</sup> 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,<sup>6</sup> including 5 prospective studies showing that fatigue developed after pain onset<sup>2,3,5,15,19</sup>; suggesting that chronic pain might cause fatigue. However, 2 of these studies did not assess the relationship between pain and fatigue prospectively,<sup>2,19</sup> whereas 2 other studies found no significant associations in longitudinal analyses.<sup>3,15</sup> Although additional evidence for pain prospectively predicting fatigue in patients with chronic pain has emerged since,<sup>13</sup> 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 children<sup>4</sup> and adults,<sup>8</sup> as well as the development of neck and shoulder pain in younger adults,<sup>16</sup> and that burnout symptoms, including fatigue, predict musculoskeletal pain onset among employees.<sup>1</sup> 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.<sup>23</sup> 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<sup>11,14,25,27</sup> (which has been ascribed to sensitization of the central nervous system<sup>10,14,18,21</sup>). Moreover, although exercise usually increases pain thresholds in healthy individuals,<sup>9,24,26</sup> it has the opposite effect in individuals with chronic fatigue.<sup>12,24,26</sup> Animal research has also shown that healthy mice demonstrate hyperalgesia after fatigue induction.<sup>7,17</sup> 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.<sup>20</sup> 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.

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Bert Lenaert<sup>a,b,c</sup>Ann Meulders<sup>d,e</sup>Caroline M. van Heugten<sup>a,b,c</sup>

<sup>a</sup>School for Mental Health and Neuroscience,  
Department of Psychiatry and Neuropsychology,  
Faculty of Health, Medicine and Life Sciences,  
Maastricht University, Maastricht, the Netherlands

<sup>b</sup>Department of Neuropsychology and Psychopharmacology,  
Faculty of Psychology and Neuroscience,  
Maastricht University, Maastricht, the Netherlands

<sup>c</sup>Limburg Brain Injury Center, Maastricht, the Netherlands

<sup>d</sup>Research Group Health Psychology,  
Faculty of Psychology and Educational Sciences,  
KU Leuven, Leuven, Belgium

<sup>e</sup>Department of Clinical Psychological Science,  
Faculty of Psychology and Neuroscience,  
Maastricht University,

Maastricht, the Netherlands

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

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## Reply



### Letter to Editor:

In their letter to the editor, Lenaert et al.<sup>6</sup> commented on our recently proposed motivational framework explaining the frequent occurrence of fatigue in individuals with chronic pain.<sup>11</sup> 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.<sup>4</sup> 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.<sup>7</sup> 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,<sup>1,3,5,8</sup> 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