Tired of pain or painfully tired?

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#### 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.\textsuperscript{22} elegantly describes 3 pathways within a motivational framework through which chronic pain may affect fatigue. This letter is intended to complement 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,\textsuperscript{13} including 5 prospective studies showing that fatigue developed after pain onset\textsuperscript{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,\textsuperscript{2,19} whereas 2 other studies found no significant associations in longitudinal analyses.\textsuperscript{3,15} Although additional evidence for pain prospectively predicting fatigue in patients with chronic pain has emerged since,\textsuperscript{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 children\textsuperscript{7} and adults,\textsuperscript{8} as well as the development of neck and shoulder pain in younger adults,\textsuperscript{18} and that burnout symptoms, including fatigue, predict musculoskeletal pain onset among employees.\textsuperscript{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.\textsuperscript{22} 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\textsuperscript{11,14,25,27} (which has been ascribed to sensitization of the central nervous system\textsuperscript{30,14,18,21}). Moreover, although exercise usually increases pain thresholds in healthy individuals,\textsuperscript{12,24,26} it has the opposite effect in individuals with chronic fatigue.\textsuperscript{12,24,26} Animal research has also shown that healthy mice demonstrate hyperalgesia after fatigue induction.\textsuperscript{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.\textsuperscript{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.

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#### References


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We agree with the authors that this indicating that the presence of fatigue increases the
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