

# Tired of pain? Toward a better understanding of fatigue in chronic pain

Stefaan Van Damme<sup>a,\*</sup>, Susanne Becker<sup>b</sup>, Dimitri Van der Linden<sup>c</sup>

## 1. Why we need a better understanding of fatigue in chronic pain

Fatigue is a prevalent complaint in people with chronic pain.<sup>11,46</sup> A study in the general population showed that 64% of the individuals with chronic widespread pain reported co-occurring persistent fatigue.<sup>13</sup> In patients with chronic pain due to spinal cord injury, 70% reported persistent fatigue.<sup>12</sup> Such comorbid fatigue is likely to be an additional source of disability and suffering when left untreated.<sup>1,25,42</sup> Moreover, fatigue might reduce patients' ability and/or willingness to fully engage in treatments aimed at increasing physical activity, such as graded activity or exposure,<sup>58</sup> possibly lowering effectiveness. As such, a good understanding of fatigue in chronic pain patients is crucial. The aim of this review is to discuss the current knowledge on fatigue in chronic pain, to provide conceptual clarification of fatigue, and to develop a theoretical framework explaining fatigue in the context of chronic pain. Based on this framework we discuss a new research agenda and provide recommendations for clinical practice.

## 2. What do we currently know about the interplay between chronic pain and fatigue?

A systematic review<sup>21</sup> investigating fatigue in various chronic pain populations showed that nearly all studies found significant associations between self-reported pain and fatigue and that fatigue was more likely to occur if pain was more intense and present for a longer time. Particularly interesting is that in 5 of the 6 prospective studies included, fatigue developed after pain onset, suggesting that chronic pain might cause fatigue. To date, the influence of (chronic) pain on fatigue has been mainly explained in terms of so-called ego-depletion accounts. For example, it has been hypothesized that the challenges associated with chronic pain lead to depletion of self-regulatory resources, also referred as self-regulatory fatigue.<sup>44</sup> However, depletion accounts have been criticized,<sup>61</sup> and the precise mechanisms and temporal

dynamics of the association between chronic pain and fatigue remain poorly understood.<sup>54</sup>

## 3. The problem of defining fatigue

Fatigue is a complex multifaceted construct with a diverse phenomenology comprising physiological as well as psychological states, and referring to perception as well as performance. This complexity is reflected in the large diversity in available definitions and the lack of a consensus definition. For instance, fatigue has been called not only as an overwhelming sense of tiredness/exhaustion and lack of energy associated with impaired physical and/or cognitive functioning<sup>43</sup> but also as an aversive perception of growing effort needed to sustain a certain task or action.<sup>55</sup>

In this review, we will not focus on physiological aspects, such as muscle tiredness resulting from physical exertion,<sup>20</sup> or sleepiness, which is the mere consequence of an imbalance in sleep-wake mechanisms.<sup>43</sup> We will rather focus on the motivational component of fatigue. Going back to the seminal work of Thorndike,<sup>49</sup> fatigue is considered an adaptive signal urging disengagement from current behavior of decreasing utility. From this old but still valid perspective, fatigue does not necessarily reflect depleted capacity or resources, but rather a motivational state, or "stop-emotion", protecting against inefficient energy expenditure.<sup>26,36,55</sup> In line with this and similar motivational accounts,<sup>7,9,16,32</sup> we propose defining fatigue as an aversive motivational state urging disengagement from effortful behavior of which the costs are currently estimated as exceeding the benefits.

## 4. A motivational framework on fatigue in the context of chronic pain

In designing our theoretical framework, we integrated motivational perspectives on fatigue<sup>7,9,16,26,32,36,55</sup> and chronic pain.<sup>14,18,44,51,52,59,64</sup> Key in our framework (**Fig. 1**) is that the balance between (expected) costs and benefits of current goal pursuit signals whether one should maintain the behaviour or not. When the benefits exceed the costs, this results in motivational drive, promoting goal persistence. When the costs exceed the benefits, the signal is perceived as fatigue, urging goal adjustment. We propose that this costs–benefits trade-off is affected by chronic pain through 3 pathways, namely (1) increased effort to maintain goal-directed behaviour, (2) heightened pain (expectations) during goal pursuit, and (3) impaired reward processing associated with goal-directed behaviour.

The first pathway describes what happens if chronic pain hinders goal progress,<sup>17,39</sup> but one nevertheless wants to uphold goal-directed behaviour at a satisfying level. In that case, the

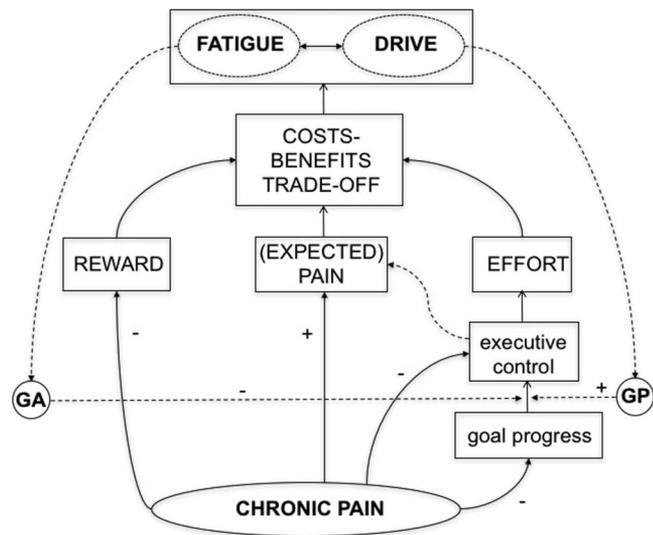
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<sup>a</sup> Department of Experimental-Clinical and Health Psychology, Ghent University, Ghent, Belgium, <sup>b</sup> Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany, <sup>c</sup> Department of Psychology, Education, and Child Studies, Erasmus University, Rotterdam, the Netherlands

\*Corresponding author. Address: Department of Experimental-Clinical and Health Psychology, Ghent University, Henri Dunantlaan 2, 9000 Ghent, Belgium. Tel.: +32-9-264 91 49; fax: +32-9-264 64 89. E-mail address: stefaan.vandamme@ugent.be (S. Van Damme).

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**Figure 1.** Self-regulation perspective on the effects of chronic pain on fatigue. Costs–benefits analysis of current goal-directed behavior determines which motivational signal is generated: fatigue, urging goal adjustment (GA) or drive, promoting goal persistence (GP). The costs–benefits trade-off receives input from 3 sources: (expected) reward, pain, and effort associated with current goal pursuit. Chronic pain affects all 3 components, biasing costs–benefits trade-off towards fatigue. In the right pathway, executive control is recruited to counter the negative effect of chronic pain on goal progress. While this suppresses pain during goal-directed behavior, continuing top–down control is effortful. Moreover, chronic pain is associated with impaired executive functioning. The middle pathway shows heightened pain (expectations) in chronic pain patients. In the left pathway, we propose that chronic pain is associated with impaired reward processing.

automatic tendency to stop or avoid the behaviour should be overruled, and attention should be focused on the goal, which requires recruitment of executive control.<sup>37</sup> There is increasing evidence for the involvement of executive control in suppressing pain and pain-related automatic response tendencies.<sup>30,34</sup> However, such top–down control is increasingly difficult to maintain over time<sup>56</sup> and therefore effortful,<sup>26,62</sup> which adds to the costs inducing fatigue.<sup>55</sup> Ironically, chronic pain is associated with compromised executive functioning,<sup>23,38,41</sup> and lack of attentional control over pain, as argued in affective-motivational models of pain-related attention.<sup>15,33,34,53</sup> What might further worsen the situation is that chronic pain patients often get stuck in largely unsuccessful pain regulation attempts, as pointed out in the misdirected problem solving model.<sup>14,18,51</sup> Ongoing fruitless attempts to control pain demand continuing effort and thus might be crucial in the development of persistent fatigue complaints.

The second pathway indicates that chronic pain is associated with over-predicting the (expected) pain associated with maintaining goal-directed behaviours. Established pain theories on fear-avoidance<sup>58</sup> and catastrophic thinking<sup>45</sup> argue that chronic pain patients appraise pain in an excessively negative way, resulting in heightened pain expectancies. Recently, models of predictive coding and inferential decision-making have been applied to understand why chronic pain patients have heightened pain expectations and how this might shape actual pain perceptions and guide action.<sup>24,40,63</sup> We hypothesize these processes to increase the weight of the costs associated with the behaviour, and thus to induce fatigue. However, cognitive factors, such as self-efficacy beliefs, might counteract the effects of pain on the costs–benefits balance and could be protective factors against the development of fatigue in chronic pain.<sup>29</sup>

In the third pathway, we propose that chronic pain impairs reward processing, which is mirrored, for example, in dysfunctional mesolimbic dopamine systems.<sup>5,48,65</sup> Activation of dopaminergic pathways is also involved in subjective states of energy and motivation, whereas failure to do so is associated with fatigue.<sup>7</sup> Although direct evidence is still lacking, a study in healthy volunteers showed that when receiving a monetary reward was accompanied with anticipation of experimental pain during a task, cortical responses to the reward were attenuated.<sup>47</sup> Impaired processing of rewards is likely to reduce the weight of the benefits associated with current goal-directed behaviour, and to induce fatigue.

## 5. Towards a new research agenda

Our framework generates several possible paths for future research. We describe some examples. First, fundamental studies could systematically examine how pain during task performance may elicit various manifestations of fatigue, including difficulty to initiate or uphold goal-directed behaviour. One hypothesis is that the experience of pain-related task interference initially results in increased effort to uphold task performance, enhanced executive control, and suppression of pain,<sup>8,22</sup> but gradually induces fatigue because of the increased demand of effort. This may yield adaptive strategies, that is, lowering performance standards, resulting in faster decline in performance. This hypothesis is intriguing, as it brings in a temporal aspect, in which fatigue might moderate the effect of pain on performance. Note that simple self-report measures will be insufficient to measure fatigue as described in this review. We recommend a mixed-method approach, adding behavioural paradigms such as the Effort Expenditure for Rewards Task,<sup>50</sup> and psychophysiological measures such as the amplitude of the contingent negative variation or the error-related negativity (Ne/ERN), which are well established in the fatigue literature and have been shown to reflect motivational aspects of fatigue.<sup>6</sup>

Second, the proposed framework might shed new light on commonly observed problems in chronic pain populations such as cognitive dysfunction and attentional bias.<sup>23,38,53</sup> Studies typically look only at mean performance levels, neglecting underlying processes such as shifts in motivation.<sup>6,28</sup> We recommend studying attention dynamics and fluctuations over task course.<sup>31,57</sup> Reduced physical activity in chronic pain patients is often explained by fear-avoidance beliefs.<sup>58</sup> Yet, it has become clear that not all patients have “kinesiophobia”,<sup>14</sup> and that reductions in activity levels are only partially accounted for by fear-induced avoidance.<sup>52</sup> We propose the alternative view that reduced activity might reflect goal disengagement, triggered by fatigue when goal pursuit becomes effortful and unrewarding. This makes an interesting avenue for future research.

Third, our framework suggests ideas for future research about the involvement of neurophysiological mechanisms. Regarding brain circuits, a large processing network is conceivable because the model comprises various aspects (executive functioning, costs–benefits trade-off) known to be processed in many brain regions. One specific region central for executive control is the dorsolateral prefrontal cortex, which exerts top–down influence over information processing and plays a role in downregulation of pain.<sup>35</sup> A brain area highly relevant for rewards–costs trade-offs and decision-making is the anterior cingulate cortex, particularly the dorsal part of this area, or the anterior midcingulate cortex.<sup>60</sup> However, the model comprises complex functions and interactions, rendering it likely that the processes are mediated through altered functional connectivity within an extended

network of brain regions. On a neurochemical level, the dopaminergic system is a likely candidate to be involved in the processes described in the model.<sup>3</sup> Fatigue is associated with failed activation of dopaminergic pathways.<sup>7</sup> Furthermore, dopamine has been shown to mediate the interaction of reward and pain<sup>48</sup> and to bias behaviour either towards pain endurance to consume a reward or towards pain avoidance at the cost of not receiving a reward.<sup>4,5</sup> Other neurotransmitter systems are likely to be involved,<sup>27</sup> but evidence is missing. Further studies are needed to characterize the neurophysiological processes involved. Particularly, the idea that (chronic) pain may change the utility of current goal pursuit, in terms of rewards–costs trade-off, requires further investigation. Specifically, it should be tested whether pain is an additional cost of action, possibly shifting functional connectivity in the related brain circuits. Based on the available literature, we hypothesize this to be mediated by dorsolateral prefrontal cortex and anterior midcingulate cortex.

## 6. Potential treatment implications

Given that the hypothesized interactions between chronic pain and fatigue await further empirical examination, specific recommendations for clinical practice may be premature. However, we speculate about possible pathways toward better care for people with chronic pain. For instance, it is likely that for fatigued chronic pain patients, cognitive-behavioral interventions, such as exposure or graded activity are very effortful, possibly predicting poor treatment response. Pain treatment protocols should consider such barriers,<sup>19</sup> for example, by specifically targeting processes underlying fatigue such as the rewards–costs balance of selected (treatment) goals. To make behavior more rewarding despite the effort required to maintain it when in pain, it is important to help patients selecting valued but feasible goals, for example, using motivational interviewing.<sup>2</sup> Furthermore, techniques aimed at improving self-regulation skills, such as the use of action plans or implementation intentions,<sup>42</sup> may help patients to reduce the effort required to pursue goals. It is only recently that such motivational and self-regulation approaches are explicitly added in pain treatment protocols,<sup>10</sup> and their effect on fatigue remains to be investigated.

## Conflict of interest statement

The authors have no conflict of interest to declare.

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## References

- [1] Affleck G, Tennen H, Zautra A, Urrows S, Abeles M, Karoly P. Women's pursuit of personal goals in daily life with fibromyalgia: a value-expectancy analysis. *J Consult Clin Psychol* 2001;69:587–96.
- [2] Alperstein D, Sharpe L. The efficacy of motivational interviewing in adults with chronic pain: a meta-analysis and systematic review. *J Pain* 2016;17:393–403.
- [3] Ballard IC, Murty VP, Carter RM, MacInnes JJ, Huettel SA, Adcock RA. Dorsolateral prefrontal cortex drives mesolimbic dopaminergic regions to initiate motivated behavior. *J Neurosci* 2011;31:10340–6.
- [4] Becker S, Gandhi W, Elfassy NM, Schweinhardt P. The role of dopamine in the perceptual modulation of nociceptive stimuli by monetary wins or losses. *Eur J Neurosci* 2013;38:3080–8.
- [5] Becker S, Gandhi W, Schweinhardt P. Cerebral interactions of pain and reward and their relevance for chronic pain. *Neurosci Lett* 2012;520:182–7.

- [6] Boksem MA, Meijman TF, Lorist MM. Mental fatigue, motivation and action monitoring. *Biol Psychol* 2006;7:123–32.
- [7] Boksem MA, Tops M. Mental fatigue: costs and benefits. *Brain Res Rev* 2008;59:125–39.
- [8] Buhle J, Wager TD. Performance-dependent inhibition of pain by an executive working memory task. *Pain* 2010;149:19–26.
- [9] Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet* 2004;363:978–88.
- [10] Christiansen S, Oettingen G, Dahme B, Klinger R. A short goal pursuit intervention to improve physical capacity: a randomized clinical trial in chronic back pain patients. *PAIN* 2010;149:444–52.
- [11] Covington EC. Depression and chronic fatigue in the patient with chronic pain. *Prim Care* 1991;18:341–58.
- [12] Craig A, Tran Y, Siddall P, Wijesuriya N, Lovas J, Bartrop R, Middleton J. Developing a model of associations between chronic pain, depressive mood, chronic fatigue, and self-efficacy in people with spinal cord injury. *J Pain* 2013;14:911–20.
- [13] Creavin ST, Dunn KM, Mallen CD, Nijrolder I, van der Windt DA. Co-occurrence and associations of pain and fatigue in a community sample of Dutch adults. *Eur J Pain* 2010;14:327–34.
- [14] Crombez G, Eccleston C, Van Damme S, Vlaeyen JWS, Karoly P. The fear-avoidance model of chronic pain: the next generation. *Clin J Pain* 2012;28:475–83.
- [15] Crombez G, Van Damme S, Eccleston C. Hypervigilance to pain: an experimental and clinical analysis. *PAIN* 2005;116:4–7.
- [16] Eccleston C. *Embodied: The psychology of physical sensation*. Oxford: Oxford University Press, 2016.
- [17] Eccleston C, Crombez G. Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol Bull* 1999;125:356–66.
- [18] Eccleston C, Crombez G. Worry and chronic pain: a misdirected problem solving model. *PAIN* 2007;132:233–6.
- [19] Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. *Am Psychol* 2014;69:153–66.
- [20] Enoka RM, Baudry S, Rudriff T, Farina D, Klass M, Duchateau J. Unraveling the neurophysiology of muscle fatigue. *J Electromyogr Kinesiol* 2011;21:208–19.
- [21] Fishbain DA, Cole B, Cutler RB, Lewis J, Rosomoff HL, Rosomoff RS. Is pain fatiguing? A structured evidence-based review. *Pain Med* 2003;4:51–62.
- [22] Ghandi W, Becker S, Schweinhardt P. Pain increases motivational drive to obtain reward, but does not affect associated hedonic responses: a behavioural study. *Eur J Pain* 2013;17:1093–103.
- [23] Glass JM. Cognitive dysfunction in fibromyalgia syndrome. *J Musculoskel Pain* 2010;18:367–72.
- [24] Hechler T, Endres D, Thorwart A. Why harmless sensations might hurt in individuals with chronic pain: about heightened prediction and perception of pain in the mind. *Front Psychol* 2016;7:1638.
- [25] Henricksson C, Gundmark I, Bengtsson A, Ek A. Living with fibromyalgia: consequences for daily life. *Clin J Pain* 1992;8:138–44.
- [26] Hockey GR. *The psychology of fatigue. Work, effort and control*. Cambridge: Cambridge University Press, 2013.
- [27] Hopstaken JF, van der Linden D, Bakker AB, Kompier MAJ. A multifaceted investigation of the link between mental fatigue and task disengagement. *Psychophysiology* 2015;52:305–15.
- [28] Hopstaken JF, van der Linden D, Bakker AB, Kompier MAJ, Leung YK. Shifts in attention during mental fatigue: evidence from subjective, behavioral, physiological, and eye-tracking data. *J Exp Psychol Hum Percept Perform* 2016;42:878–89.
- [29] Jackson T, Wang Y, Wang Y, Fan H. Self-efficacy and chronic pain outcomes: a meta-analytic review. *J Pain* 2014;15:800–14.
- [30] Karsdorp PA, Geenen R, Vlaeyen JW. Response inhibition predicts painful task duration and performance in healthy individuals performing a cold pressor task in a motivational context. *Eur J Pain* 2014;18:92–100.
- [31] Kucyi A, Salomons TV, Davis KD. Mind wandering away from pain dynamically engages antinociceptive and default mode brain networks. *Proc Natl Acad Sci U S A* 2013;110:18692–7.
- [32] Kurzban R, Duckworth A, Kable J, Myers J. An opportunity cost model of subjective effort and task performance. *Behav Brain Sci* 2013;36:661–79.
- [33] Legrain V, Iannetti GD, Plaghki L, Moraux A. The pain matrix reloaded. A salience detection system for the body. *Prog Neurobiol* 2011;93:111–24.
- [34] Legrain V, Van Damme S, Eccleston C, Davis KD, Seminowicz DA, Crombez G. A neurocognitive model of attention to pain: behavioral and neuroimaging evidence. *PAIN* 2009;144:230–2.
- [35] Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain* 2003;126:1079–91.

- [36] Meijman TF. The theory of the stop-emotion: on the functionality of fatigue. In: Pogorski D, Karwowski W, editors. *Ergonomics and safety for global business quality and productivity*. Warsaw: CIOP, 2000. p. 45–50.
- [37] Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A. The unity and diversity of executive functions and their contributions to complex “frontal lobe” tasks: a latent variable analysis. *Cogn Psychol* 2000;4:49–100.
- [38] Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol* 2011;93:385–404.
- [39] Morley S. Psychology of pain. *Br J Anaesth* 2008;101:25–31.
- [40] Morrison I, Perini I, Dunham J. Facets and mechanisms of adaptive pain behaviour: predictive regulation and action. *Front Hum Neurosci* 2013;7:755.
- [41] Oosterman JM, Dijkerman HC, Kessels RBC, Scherder EJA. A unique association between cognitive inhibition and pain sensitivity in healthy participants. *Eur J Pain* 2010;14:1046–50.
- [42] Schrooten MGS, Vlaeyen JWS, Morley S. Psychological interventions for chronic pain: reviewed within the context of goal pursuit. *Pain Manage* 2012;2:1–10.
- [43] Shen J, Barbera J, Shapiro CM. Distinguishing sleepiness and fatigue: focus on definition and measurement. *Sleep Med Rev* 2006;10:63–76.
- [44] Solberg Nes L, Roach AR, Segerstrom SC. Executive functions, self-regulation, and chronic pain: a review. *Ann Behav Med* 2009;37:173–83.
- [45] Sullivan MJL, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, Lefebvre JC. Theoretical perspectives on the relation between catastrophizing and pain. *Clin J Pain* 2001;17:52–64.
- [46] Tack BB. Self-reported fatigue in rheumatoid arthritis. A pilot study. *Arthritis Care Res* 1990;3:154–7.
- [47] 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.
- [48] Taylor AMW, Becker S, Schweinhardt P, Cahill C. Mesolimbic dopamine signaling in acute and chronic pain. *PAIN* 2016;157:1194–8.
- [49] Thorndike EL. Mental fatigue. *Psychol Rev* 1900;7:466–82.
- [50] Treadway MT, Buckholz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the “EEfRT”? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PLoS One* 2009;4:e6598.
- [51] Van Damme S, Crombez G, Eccleston C. Coping with pain: a motivational perspective. *PAIN* 2008;139:1–4.
- [52] Van Damme S, Kindermans H. A self-regulation perspective on avoidance and persistence behaviour in chronic pain: new theories, new challenges? *Clin J Pain* 2015;31:115–22.
- [53] Van Damme S, Legrain V, Vogt J, Crombez G. Keeping pain in mind: a motivational account of attention to pain. *Neurosci Biobehav Rev* 2010;34:204–13.
- [54] van Dartel SA, Repping-Wuys JW, van Hoogmoed D, Bleijenberg G, van Riel PL, Fransen J. Association between fatigue and pain in rheumatoid arthritis: does pain precede fatigue or does fatigue precede pain? *Arthritis Care Res* 2013;65:862–9.
- [55] 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.
- [56] van der Linden D, Frese M, Meijman TF. Mental fatigue and the control of cognitive processes: effects on perseveration and planning. *Acta Psychol* 2003;113:45–65.
- [57] Van Ryckeghem D, Crombez G. Attentional bias and chronic pain: where to go from here? *PAIN* 2014;155:6–7.
- [58] Vlaeyen JWS, Linton SJ. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *PAIN* 2012;153:1144–7.
- [59] Vlaeyen JWS, Morley S. Active despite pain: the putative role of stop-rules and current mood. *PAIN* 2004;110:512–16.
- [60] Vogt BA. Pain and emotions interact in subregions of the cingulate gyrus. *Nat Rev Neurosci* 2005;6:533–44.
- [61] Vohs KD, Baumeister RF, Schmeichel BJ, Twenge JM, Tice DM, Nelson NM. Making choices impairs subsequent self-control: a limited resource account of decision making, self-regulation, and active initiative. *J Person Soc Psychol* 2008;94:883–98.
- [62] Westbrook A, Braver TS. Cognitive effort: a neuroeconomic approach. *Cogn Effect Behav Neurosci* 2015;15:395–415.
- [63] Wiech K. Deconstructing the sensation of pain: the influence of cognitive processes on pain perception. *Science* 2016;354:584–7.
- [64] Wiech K, Tracey I. Pain, decisions, and actions: a motivational perspective. *Front Neurosci* 2013;7:46.
- [65] Wood PB, Schweinhardt P, Jaeger E, Dagher A, Hakyemez H, Rabiner EA, Bushnell MC, Chizh BA. Fibromyalgia patients show an abnormal dopamine response to pain. *Eur J Neurosci* 2007;25:3576–82.