

# How expectations influence pain

Howard L. Fields

## 1. Introduction and discussion: pain from an evolutionary perspective: motivations, predictions, and decisions

The actions of individuals are guided by the motivation to satisfy drives that are homeostatic (hunger, thirst, thermoregulatory, and tissue protection) or species-specific (mating, care of offspring, and social dominance). The satisfaction of these drives through actions provides a benefit in terms of survival and reproductive success. However, actions are associated with variable costs (eg, time, energy, and risk of injury) that reduce their net benefit. Considerations of cost often play a dominant role in decisions, and tissue injury, signaled by nociception and experienced subjectively as pain, can be a significant cost.<sup>53</sup> Consequently, animals act to avoid or terminate pain and their success in achieving this goal is enhanced by learning to respond appropriately to sensory cues that signal an increased probability or intensity of imminent pain (see Seymour and Dolan<sup>48</sup> for a more extensive discussion).

Many behavioral responses occur immediately and predictably after sensory input (eg, reflex withdrawal of a limb after touch of a hot metal surface). Other actions are initiated by internal signals (eg, thirst or hunger) on a slower and less predictable time scale. In addition to these primary homeostatic signals, behavior can be initiated and/or guided by intrinsically neutral cues that come to be associated with salient outcomes (trees with shade, smells with food, and red glow with hot metal surfaces). The biological significance of cues is that they are predictive, allowing individuals to anticipate benefit or harm and to initiate and shape appropriate actions in a timely fashion. Predictions and expectations are guesses about the future. In this chapter, I will use the term “prediction” to refer to a central nervous system process that estimates the probability and value (utility) of future outcomes and the potential costs of actions required to approach or avoid them. I will use the term “expectation” to refer to the subjective correlate of prediction that can only be directly assessed in human subjects.

Pain-predictive cues increase the probability of actions that promote avoidance of pain. Because of the robust benefit of successful responses to pain-predictive cues, the unexpected and/or sudden onset of such cues can have marked effects on behavior. Conversely, contextual cues that signal reduced probability or intensity of pain allow individuals to save the cost

of unnecessary escape/avoidance behaviors and efficiently engage more beneficial actions.

Animals are often faced with pain-related decisions that are in conflict with concurrent motivations for other goals (eg, to approach food or avoid it because of a nearby predator). When conflicts are present, predictions are particularly important because they can promote better outcomes through a decision process. To optimize outcomes, individuals make estimates of anticipated utility and cost for each alternative and then prioritize the optimal behavioral choice.<sup>48</sup> Uncertainty is implicit in making predictions; outcomes can, and often do, either exceed or fall short of what was predicted. Because of uncertainty, prediction errors occur, allowing individuals to update their predictions (ie, to learn from mistakes). When survival is on the line, the biological importance of learning is obvious; consequently, predictions (expectations) are a core feature of nervous system function.

When present, particularly when there is a concurrent conflicting motivation, nociceptive transmission both contributes to and is itself modulated in the course of a decision process. Nociceptive transmission can be either facilitated by the decision to avoid potential injury or inhibited if the decision is to pursue a conflicting goal (eg, feeding<sup>16</sup>). Noxious stimuli, or cues that predict their occurrence, can engage a decision process that works in part by top-down modulation of ascending pain circuits. This prediction process occurs on multiple time scales. It can be rapid and occur without a conscious correlate. Predictions can also occur more slowly and persist for longer periods. Importantly, at slower time scales, the prediction process is more likely to have a subjective correlate in humans, ie, expectation. Because the decision process engages top-down modulatory influences on pain, predictions contribute robustly to the variability in human subjective reports of pain. Such prediction-driven variability has been demonstrated in experimental conditions when the nociceptive stimulus is precisely controlled while pain-predictive cues are systematically manipulated.<sup>4,23,54</sup> I propose that predictions are an inevitable component of all experimental and clinical pains (**Fig. 1**). Understanding the neurobiology of predictions and their influence on pain transmission offers a path for improving clinical outcomes in patients with pain.

## 2. The power of expectation in experimental and clinical settings

Perhaps, the best known and most extensively studied example of the power of expectation on pain is placebo analgesia. Although the concept that belief alone can bestow benefit to bogus treatments was appreciated as early as the 17th century (see Burton, 1628, quoted in Brody<sup>9</sup>), the analgesic effectiveness of placebo administration was firmly established in the 1970s when Jon Levine, Newton Gordon, and I embarked, quite serendipitously, on a set of studies of the treatment of dental

*Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.*

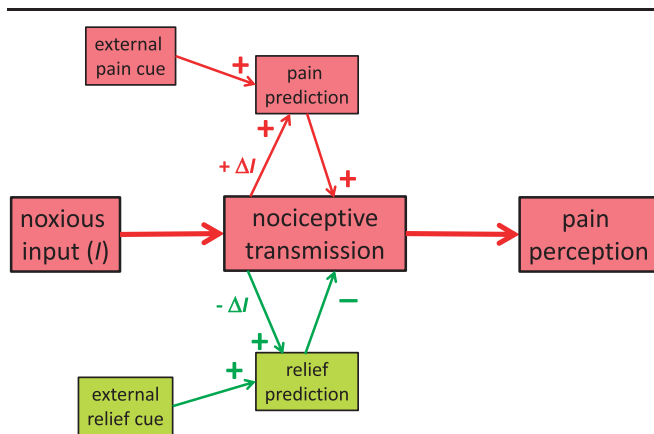
Department of Neurology, University of California, San Francisco, San Francisco, CA, United States

Address: 755 Euclid Ave, Berkeley, CA 94708, United States. Tel.: 510 919 2886. E-mail address: howard.fields@ucsf.edu (H.L. Fields).

PAIN 159 (2018) S3–S10

© 2018 International Association for the Study of Pain

<http://dx.doi.org/10.1097/j.pain.0000000000001272>



**Figure 1.** Predictions modify the intensity of perceived pain. A noxious stimulus of intensity  $I$  activates the nociceptive transmission system. If the noxious stimulus is increasing in intensity ( $+\Delta I$ ), it is predictive of more intense pain than if it is decreasing in intensity ( $-\Delta I$ ). In addition, through learning (or verbal instruction), intrinsically neutral sensory and contextual cues can become predictive of increased or decreased pain. Pain-predictive influences increase pain intensity, whereas pain relief predictive cues inhibit pain intensity; perceived pain intensity is a sum of direct input from the noxious stimulus and the input driven by predictive cues.

postoperative pain. We showed that the opiate antagonist naloxone produced a dose-dependent increase in pain.<sup>32</sup> It turned out that the hyperalgesic effect of naloxone was greater in patients whose pain had dropped when previously given a saline placebo as the first drug in a cross-over design. This observation was later confirmed when the open administration of a saline placebo was compared with its hidden administration.<sup>31</sup> As expected, open administration of a placebo was much more effective than when the subject was unaware that a treatment had been given.

Although expectation of relief is more likely when salient cues associated with possible relief are present, the mere presence of such cues may be ineffective in many subjects; typically, less than half of subjects respond to initial administration of placebo “analgesics.”<sup>28</sup> On the other hand, with conditioning, sensory cues that are contingently paired with reduced pain become increasingly potent in producing analgesia (see Refs. 25 and 42 for review). This is a phenomenon that has been extensively studied; in fact, contextual cues associated with the infusion of active analgesics become analgesic in themselves. For example, after 2 morphine infusions have produced significant analgesia, an infusion of saline with the deceptive information that it is another morphine infusion produces much greater analgesia than saline plus the deceptive information without previous morphine conditioning infusions.<sup>2</sup> Cues associated with a surreptitious lowering of nociceptive input also become effective placebo analgesics.<sup>25,42</sup> Although deception is part of these experiments and is an implicit element of the concept of placebo, expectation effects can be large without explicit deception; conditioning alone can be sufficient. Several studies have compared the effect of cues previously associated with lower pain levels on the subjective pain intensity produced by a more intense nociceptive input. Not surprisingly, cues associated with lower pain levels reduce the pain reported to subsequent, more intense stimuli.<sup>23,25,42</sup> These observations support the view articulated by Kirsch et al.<sup>25</sup> that expectancy is a critical mediating process for the effect of conditioning on perceived pain intensity.

In addition to mediating placebo analgesia, expectations can modify the effectiveness of pharmacologically active analgesic

medications. For example, active analgesics are significantly more effective when given by open infusion than when given by hidden infusion.<sup>3,31</sup> This has been shown for a variety of analgesic drugs and is often referred to as a “placebo” component for their analgesic effect. However, it would be more accurate and less confusing to say that every pain “treatment” has a potential expectation component and some, eg, placebo or hypnosis, have primarily an expectation component.

Beyond its demonstrated immediate power in experimental studies, expectation can affect long-term outcomes for patients with chronic pain, regardless of the treatment protocol.<sup>35</sup> This issue was explicitly studied in a large prospective trial of over 2000 patients with chronic noncancer pain at 3 academic multidisciplinary pain centers in Canada.<sup>10</sup> Patients were assessed before initiating treatment, and treatment programs were highly individualized. Outcomes were assessed at 6 months. The single most robust predictor of clinical improvement (including reduced pain intensity) was the patient’s expectation of improvement at trial entry before any new treatment was initiated.

### 2.1. Expectation effects are bidirectional

In addition to analgesia, verbal instruction and conditioning can elicit expectations of increased pain. In the field of “placebo” research, this phenomenon is known as the nocebo response.<sup>7</sup> In experimental psychophysical studies using controlled thermal noxious stimuli, cues associated with more intense stimuli increase reported pain intensity compared with the same, uncued stimulus.<sup>23</sup> Clinical studies suggest that the analgesic effectiveness of an active drug is reduced by previous administration of a similar appearing ineffective drug.<sup>21,36</sup> Finally, there is accumulating evidence supporting the fear-avoidance model of musculoskeletal pain.<sup>30</sup> In this model, exaggerated expectation of future pain and/or its consequences amplifies nociceptive input and contributes to the development of chronic pain.

### 2.2. Beyond expectation: pain as a pain-predictive cue

Classic psychophysical studies using thermal stimuli demonstrate a clear temperature threshold for pain and a power relationship between noxious stimulus intensity and reported pain intensity.<sup>41</sup> If pain were a purely sensory discriminative experience, such a lawful and predictable relationship would be expected. However, noxious stimuli typically signal tissue damage that is followed by more prolonged and often more intense pain. For example, twisting an ankle produces an immediate pain followed by a prolonged period of pain and tenderness. The important point is that when the subject is awake and the nervous system is intact, pain is virtually never motivationally neutral because it is a signal of actual or potential tissue damage (a cost to be avoided). In addition to signaling potential tissue damage, the onset of pain or an increase in its intensity also signals that a further increase in pain is likely, ie, increasing pain is a pain-predictive cue. Conversely, decreasing pain intensity predicts a decreased threat of tissue damage. It is because of their salience and their power to influence behavioral decisions that change in noxious stimulus intensity, particularly if unexpected, can have a disproportionately large effect on the perceived intensity of subsequent nociceptive stimuli (Fig. 1).

The first dramatic evidence for a significant predictive effect of relatively small changes of noxious stimulus intensity is what has been called “offset analgesia.”<sup>19,57,58</sup> This phenomenon was demonstrated using suprathreshold noxious thermal stimuli. One

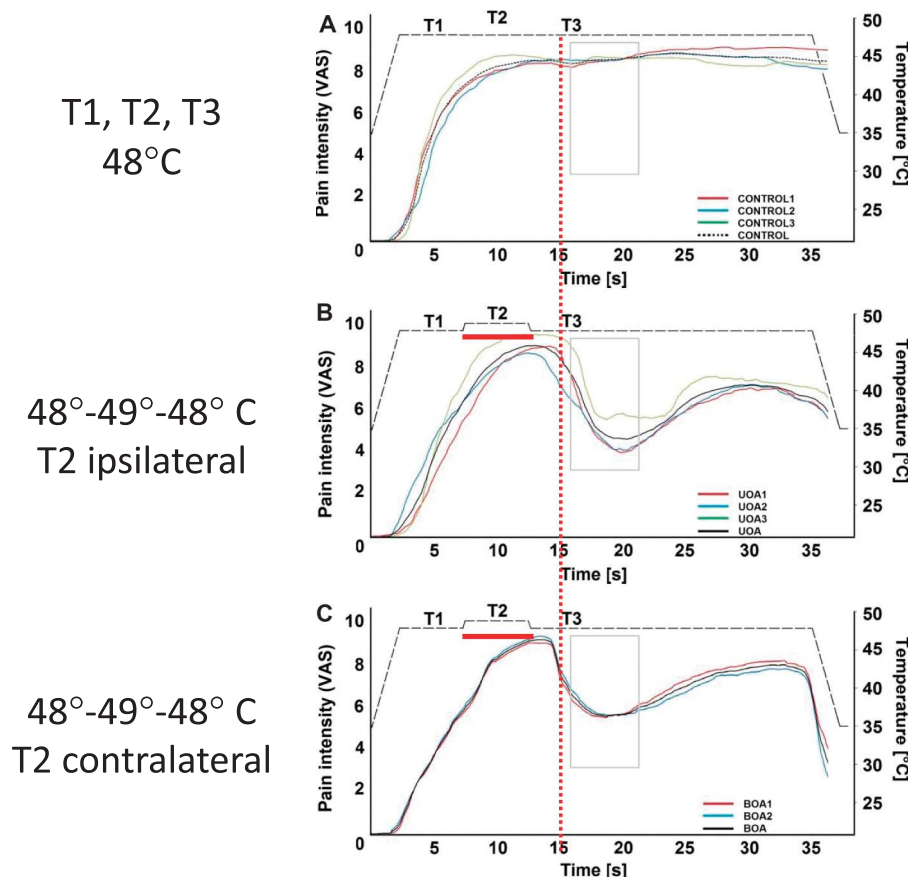
stimulus pattern was a single step from a neutral temperature to an intensity (T1) producing moderate pain. The second pattern had 3 steps: the temperature was initially raised to T1, held for 5 seconds, and then raised again 1°C (T2) for 5 seconds, then lowered back to the original T1 (Fig. 2). Compared with a constant T1 stimulus, the pain rating was significantly lower if it was assessed after a 5-second 1°C increase to T2 and then lowered back to T1. The relatively small decrease in stimulus intensity (return to T1 from T2) produced a very large reduction in perceived pain intensity compared with a steady T1 stimulus. My interpretation of this observation is that the drop in stimulus intensity from T2 back to T1 is a cue predicting pain relief. As with placebo administration, cues that predict decreased pain engage pain inhibitory neurons in a top-down modulatory circuit resulting in a disproportionate drop in perceived pain intensity. This idea is supported by imaging data indicating engagement of periaqueductal gray (PAG) during offset analgesia.<sup>55</sup> We have recently reported a 'mirror' increase (ie, onset hyperalgesia) using a stimulus paradigm that is the inverse of that used by Coghill's group to demonstrate offset analgesia (see Alter et al., abstract 2018, IASP Congress proceedings).

In summary, these findings are consistent with the idea that pain-predictive cues (for either future increases or decreases in pain) are powerful determinants of future perceived pain intensity. Pain-predictive signals (including conditioned cues or simply

increasing pain) will bias decisions toward escape, avoidance, or immobility, and nociceptive transmission circuits will be facilitated to speed initiation of pain avoidance behaviors. Conversely, a small decrease in pain (or a conditioned cue for pain relief) will have the opposite effect. Predictive cues can have effects over the full range of time scales: immediate for transient changes in stimulus intensity, longer lasting for pain-predictive cues in the setting of conflict, and very long lasting when the bias toward pain avoidance becomes habitual (eg, catastrophizing in many patients with chronic pain<sup>43</sup> and decreased motivation [anhedonia] in rodent models of chronic pain<sup>47</sup>). Clearly, understanding of the mechanisms that mediate the effect of predictions on behavioral decisions and perceived pain intensity has the potential to greatly improve clinical pain management.

### 2.3. Top-down inhibition and facilitation of pain: the Motivation-Decision model

At the 2005 IASP meeting in Sydney, Australia, I first proposed the Motivation-Decision model of pain. The key concept of this model is that expectation effects on pain are best understood in the context of decision making. When pain or the threat of pain is present, a concurrent conflicting motivation (eg, a significant reward or greater threat) demands a decision. If the decision is to ignore the pain, top-down modulatory circuits are engaged that



**Figure 2.** Illustrating offset analgesia (image from figure 2, Ligato et al.<sup>34</sup>). Thermal noxious stimuli applied to the volar surface of the forearm in normal subjects. Comparing subjective pain-intensity reports at 48°C under 2 conditions; in one (A), the thermal stimulus is held constant at 48°C during 3 epochs (T1 5", T2 5", and T3 20"); the second (B) is the same except that T2 is a 5" step increase to 49°C and then decrease to T3 20" at 48°C. Note the sharp drop in pain intensity following the offset of the 5" T2 heat pulse (offset analgesia). (C) In these trials, offset analgesia was evoked even when the test step (T2 to 49°C) was applied to the contralateral forearm, although the magnitude of the analgesic effect was less. This shows that offset analgesia has a significant CNS component. CNS, central nervous system; VAS, visual analogue scale.

inhibit nociceptive transmission. In situations where expectation of reward dominates the behavior, top-down pain modulation circuits implement inhibition through serial links that include the release of endogenous opioid peptides.<sup>15</sup> In the case of placebo analgesia, the prediction of reduced pain can be conceptualized as a predicted reward.<sup>48</sup> This proposal was suggested in part by the observation that placebo analgesia can be blocked by the opiate antagonist naloxone.<sup>33</sup> Subsequent work has provided further support for the idea that expectation elicited analgesia involves the top-down pain modulatory circuit described in rodents. Human functional imaging studies have implicated the PAG to rostral ventromedial medulla (RVM) to dorsal horn pain modulatory circuit in placebo analgesia.<sup>12,13</sup> Furthermore, positron emission tomography using the radioligand C<sup>11</sup> carfentanil (a mu-opioid receptor-selective ligand) indicated that placebo analgesia is associated with release of an endogenous opioid acting at the mu-opioid receptor in the PAG.<sup>39</sup> These studies have increased our understanding of the molecular and neural circuit mechanisms of placebo analgesia and support the hypothesis that a top-down circuit engaged by cues predicting pain relief contributes to the implementation of an “ignore pain” decision. It accomplishes this, at least in part, by inhibiting nociceptive transmission at the level of the dorsal horn.

In the Motivation-Decision model, I also proposed that top-down modulation is bidirectional so that if the decision is to respond to the noxious stimulus (and ignore the conflicting motivation), implementation of the response to pain is promoted by descending facilitation of activity in spinal dorsal horn neurons (Fig. 3). In support of this idea, rodent studies show that several nuclei in the top-down modulatory circuit (eg, PAG, nucleus cuneiformis, and RVM) have distinct subsets of neurons that either facilitate (ON cells) or inhibit (OFF cells) dorsal horn responses to noxious stimulation.<sup>15</sup> Although prediction-based facilitation of nociceptive transmission has not been extensively studied in human subjects, we demonstrated using functional magnetic resonance imaging that there is relative activation in the region of nucleus cuneiformis when pain is enhanced by a cue associated with higher stimulus intensity.<sup>23</sup> This same region is activated by other manipulations associated with increased pain.<sup>49,59</sup>

#### 2.4. Midbrain and forebrain decision circuitry

The remarkable human and animal studies reviewed above have given us deep insights into how top-down pain modulatory circuits contribute to implementing the “ignore” or “respond to” pain decisions, but left the upstream circuits involved in the decision process relatively vague. I previously proposed that the decision process involves brain sites originally identified as the core canonical reward circuit. This circuit includes the dopaminergic ventral tegmental area (VTA) and its major sub-cortical forebrain target, the nucleus accumbens (NAc) (see Ref. 55 for a recent review). Rodents will work for direct electrical stimulation of these areas and return to places associated with such stimulation. Involvement of midbrain dopamine neurons is indicated by the demonstration that selective optogenetic stimulation of NAc-projecting VTA dopamine neurons produces positive reinforcement.<sup>50</sup> Consistent with the Motivation-Decision model, opioids or psychostimulants in the VTA or NAc are rewarding and produce analgesia, especially when tonic pain models are used.<sup>1,8,18,22,37</sup>

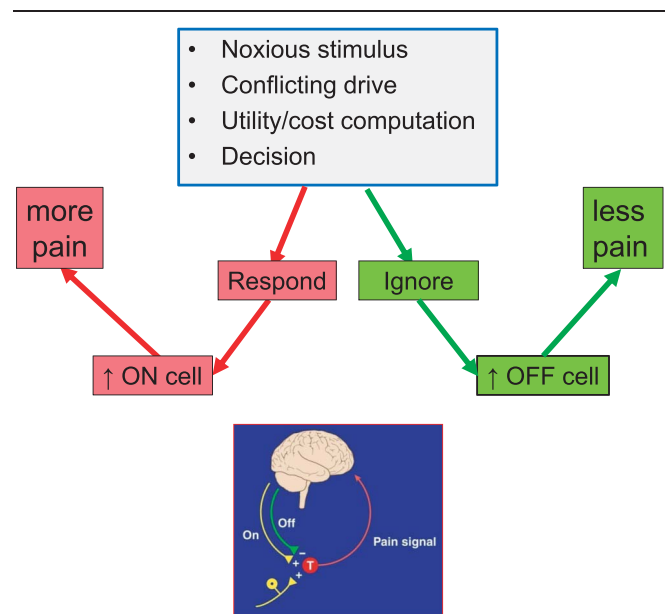
The first inkling that there is more to the VTA to NAc circuitry than reward and approach was the demonstration that although rats will work (push a lever) to initiate electrical stimulation of this

circuit, they will also work to turn it off after the stimulation has been on for several seconds.<sup>38</sup> Furthermore, in opioid-dependent rats, opioid antagonists microinjected into the NAc and VTA produce an aversive output.<sup>51</sup> These studies raise the possibility that parallel circuits in these regions can mediate aversion and reward.

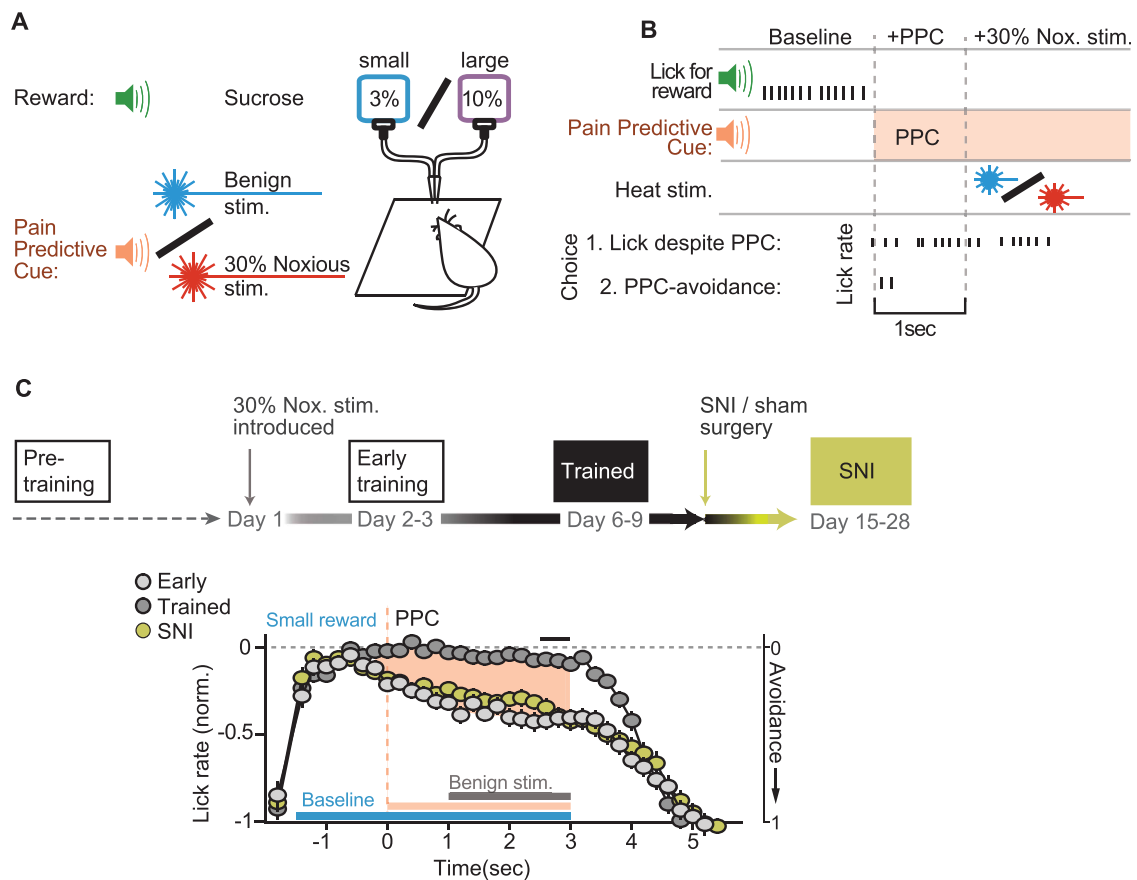
Early evidence for an explicit NAc role in modulating pain responses was provided by human functional imaging studies. Becerra et al.<sup>6</sup> were the first to show that noxious stimuli reliably produce NAc activations. Importantly, these NAc activations occurred before activations of canonical cortical pain areas. Subsequent work has confirmed this discovery and has clearly shown that both pain-associated<sup>17,20</sup> and reward-predictive<sup>26</sup> cues produce strong activations in human NAc. Furthermore, positron emission tomography using C<sup>11</sup>-carfentanil has shown that placebo analgesia is associated with release of endogenous opioids acting at the mu-opioid receptor in the NAc.<sup>39</sup>

Studies in rodents show that different subpopulations of NAc neurons can have opposing responses to reward-predictive cues.<sup>27,52</sup> Most neurons in the NAc are GABAergic medium spiny neurons (MSNs). There are 2 major types of MSNs: those that express the dopamine D1 receptor and those that express the D2 dopamine receptor. Optogenetic activation of D1 NAc MSNs can promote approach and produce reward; conversely, D2 NAc MSNs inhibit approach behavior and produce punishment. Although direct evidence for a role in pain-related behaviors is limited, D2 but not D1 NAc MSNs exhibit an increase in intrinsic excitability and promote allodynia in chronic pain states.<sup>44</sup>

Opioid analgesics work in part through activating pain-inhibiting (OFF) cells in the PAG-RVM-dorsal horn pain modulatory circuit. By contrast, opioid withdrawal produces hyperalgesia by activating pain-facilitating RVM ON cells. Consistent with the idea that D1 MSNs inhibit pain and D2 MSNs facilitate it, the



**Figure 3.** The Motivation-Decision model. When a noxious input occurs in the presence of a conflicting motivation (predator and food), the animal must decide whether to respond or not to the signal of potential tissue damage; this involves a cost/benefit computation and selecting the preferred response. If respond to pain dominates, top-down pain-facilitating circuits (ON cells) are activated, which has the net effect of enhancing nociceptive transmission and speeding the response. Conversely, if the decision is to ignore pain, top-down inhibiting circuits (OFF cells) are activated, which inhibits nociceptive transmission and has an analgesic effect.



**Figure 4.** Experience and chronic pain regulate avoidance elicited by a pain-predictive cue during reward-directed behavior. (A) Schematic of a rat in the testing chamber in which an infrared laser can apply a benign (blue) or noxious (red) heat stimulus to the animal's foreshoulder during consumption of sucrose reward. (B) Task sequence: tone 1 indicates that sucrose is available, a lick in response to tone 1 initiates a trial and delivery of a smaller or larger reward; 1.5 seconds after the first lick and on 85% of the trials, the PPC is presented; 1 second after the onset of the PPC, there is a 30% probability of a noxious heat stimulus. (C) Top: Timeline of the 4 testing sessions. During pretraining, all auditory cues were presented with benign foreshoulder stimulation. Next, as described in (B), the noxious heat stimulus was introduced. Training on the task with the noxious stimulus continued for 6 to 9 days. Next, animals underwent either spared nerve injury (SNI) or sham surgeries; 7 days later, testing resumed. (C) Bottom: Time course and average of normalized lick rates for trials with the small reward during each of the 4 testing sessions. Symbols are mean, vertical lines indicate SEM, and the horizontal dashed line indicates the baseline lick rate. The blue, orange, and black lines at the bottom of each graph indicate sucrose, PPC, and benign foreshoulder stimulation, respectively. Note that the avoidance score is the additive inverse of the normalized lick rate. Changes in avoidance between the 4 sessions show that training reduces avoidance during the PPC, and in the SNI model, PPC-avoidance is reinstated during consumption of the small reward (pretraining,  $n = 11$ , early,  $n = 22$ , trained,  $n = 22$ , and SNI,  $n = 7$ ). Data from Ref. 46. doi: <https://doi.org/10.1016/j.celrep.2017.04.073>. PPC, pain-predictive cue.

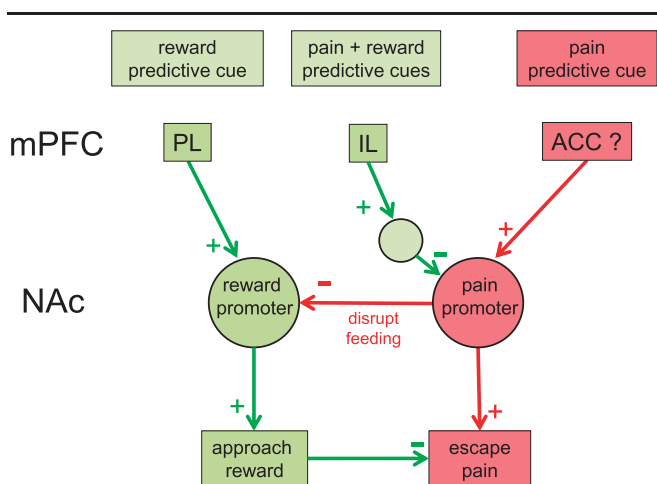
Christie lab used cFos detection to show that D1 MSNs are activated by morphine (like RVM OFF cells), whereas D2 MSNs in NAc are activated during naloxone-precipitated withdrawal in morphine-dependent rats (similar to RVM ON cells).<sup>14</sup> In summary, the weight of current evidence indicates that different groups of NAc neurons can either promote approach or avoidance; and different but interconnected subpopulations of NAc neurons can generate either an appetitive or aversive signal.

### 2.5. Corticostriatal connections influence pain decisions

In addition to dopaminergic input from VTA, the NAc receives excitatory input from the medial prefrontal cortex (mPFC). In rodents, mPFC projections to the NAc are necessary for learned sensory cues to promote both fear-avoidance and reward approach.<sup>40</sup> In humans, Baliki et al.<sup>5</sup> showed that increased correlation of functional magnetic resonance imaging BOLD signals between ventromedial PFC and NAc is a significant predictor of individuals with subacute low back pain who will transition to chronic low back pain. Furthermore, activity in an

NAc-ventral mPFC circuit correlates with cognitive control of pain intensity.<sup>56</sup>

In rodents, an mPFC to NAc circuit can modulate behavioral responses to both acute and chronic noxious stimulation. Wang et al.<sup>29</sup> used the spared nerve injury (SNI) model of chronic neuropathic pain<sup>11,24</sup> to directly study corticostriatal modulation of chronic pain. They first confirmed that rats with SNI have allodynia, anhedonia (decreased sucrose preference), and increased evidence of depression (the forced swim test). In SNI rats, optogenetic activation of neurons in the prelimbic area of the mPFC raised paw withdrawal thresholds to noxious heat and eliminated mechanical allodynia. Furthermore, mPFC activation produced a conditioned place preference, but only in rats with the SNI model of neuropathic pain. This supports the view that SNI produces a tonic aversive state (ie, chronic pain<sup>24</sup>) that is relieved by activation of prelimbic cortex neurons. Importantly, Wang et al.<sup>29</sup> took this work 1 step further by showing that in rats with SNI, optogenetic stimulation of the mPFC terminals in the NAc directly activates NAc neurons, relieves allodynia, and reduces behavioral evidence of depression. These observations are consistent with the hypothesis that mPFC-NAc circuits promote



**Figure 5.** Corticostriatal circuits involved in the decision between reward approach and pain avoidance. Conditioned reward-predictive cues promote approach and consumption through a circuit that involves neurons in the mPFC and a projection to the nucleus accumbens (NAc). Activation of prelimbic (PL) to NAc core axons promotes reward approach, and inhibits allodynia and the aversiveness of tonic pain (see text). Pain-predictive cues interrupt reward consumption, but rats learn to ignore such cues, a process that requires an infralimbic (IL) to NAc shell projection. Note that, in this paradigm, both PL and IL promote reward approach: PL by exciting NAc reward approach neurons (presumably D1 expressing medium spiny neurons) and IL by inhibiting pain-promoting NAc neurons (presumably D2 expressing MSNs). Because corticostriatal projecting neurons are glutamatergic, an inhibitory interneuron is required for inhibition of pain response promoting NAc neurons. ACC, anterior cingulate gyrus; mPFC, medial prefrontal cortex; MSN, medium spiny neuron.

reward approach in part by inhibiting central nervous system and behavioral responses to noxious stimuli.

There is also direct evidence in rodents that an mPFC to NAc connection contributes to action decisions when motivational drives are in conflict. To investigate this issue, we trained rats to enter a receptacle to receive a sucrose reward.<sup>46</sup> On different trials, they received either a low- or a high-concentration sucrose solution. Once they learned this task, an auditory cue was presented 1.5 seconds after the rat began to lick the sucrose (enough time for the rats to assess reward magnitude [ie, taste sweetness]). This cue was followed on 30% of trials by a brief, moderately painful thermal stimulus. The rats rapidly learned that the cue was pain predictive and stopped licking quickly when it was presented to avoid the pain. However, after about 7 training sessions, the rats ignored the cue and continued to lick for sucrose, despite a possible noxious stimulus; ie, they inhibited responses to the pain-predictive cue to maximize sucrose consumption. To determine how tonic pain affects this decision, we induced the SNI model in a group of rats that had learned to ignore the pain-predictive cue. After SNI induction, the rats no longer ignored the pain-predictive cue when the reward was small, but continued to ignore the cue when the reward was large. In other words, the pain-predictive cue recovered its disruptive effect but only for consuming the smaller reward (Fig. 4). Clearly, the rats had “decided” that a big helping of sucrose was worth the risk of a little pain. Similar to its critical role in inhibiting conditioned fear,<sup>40</sup> we showed that the rat’s ability to ignore pain-predictive cues requires the infralimbic (IL) mPFC. Normal rats with reversible chemical inactivation of IL (but not prelimbic or anterior cingulate cortices) lost the ability to ignore the pain-predictive cue. Consistent with this behavioral result, single-unit activity of IL neurons was positively correlated with a rat’s decision to ignore the cue and maintain feeding. It is important to reiterate that this

evidence suggests that increased firing of IL neurons during a pain-predictive cue inhibits pain escape behavior (ie, shifts the decision bias [or preference] from escape to feeding).

A subpopulation of NAc neurons is also activated by the pain-predictive cue. This same population is excited by optogenetic activation of the terminals of IL neurons in the NAc, consistent with the idea that they are driven, in part, by IL inputs. Furthermore, optogenetic activation of IL terminals in the NAc of rats with SNI shifts their decision bias back to feeding over responding to the pain-predictive cue. Clearly, corticostriatal connectivity contributes potently to action decisions when escape from pain is in conflict with reward consumption. In this situation, corticostriatal inhibition of pain escape enables the rat to approach and consume a reward. **Figure 5** is a proposed model for the corticostriatal circuitry involved in deciding between pain escape and approach to a food reward. In this model, mPFC drives NAc D1 MSNs to promote approach to a food reward. Unspecified inputs activate NAc D2 MSNs promoting escape and leading to inhibition of other potentially conflicting actions including food approach. As the rats learn to ignore the pain-predictive cue, mPFC (IL) inputs inhibit the pain-predictive cue-driven circuit that disrupts feeding.

This conclusion is consistent with previous rodent work on conditioned fear, human functional imaging studies implicating mPFC to NAc connectivity in pain/reward interactions and evidence that NAc opioids contribute to placebo analgesia and can both increase consumption of palatable food and inhibit pain.<sup>22,45</sup> This work suggests that mPFC to NAc circuits are candidates to study for understanding decisions when motivations and predictive cues promote conflicting actions. Studies are needed to elucidate the inputs and outputs of the relevant corticostriatal circuits that promote opposing alternatives and to determine how they interact during the critical moments immediately before initiating an action.

### 3. Clinical implications

The robust impact of expectation on perceived pain intensity has important implications, particularly when there is persistent or recurrent nociceptive input (eg, arthritis and chronic headache). Treatment failure early in the course of the disease will contribute to the expectation of future treatment failure. As pointed out above, expectation of pain becomes a self-fulfilling prophecy through top-down amplification of the pain signal. The earlier effective treatment is initiated the sooner expectations for relief and lower pain levels will be achieved and the individual’s own top-down pain inhibition circuits can be engaged. This is a consideration of particular importance when considering the early use of potent analgesics.

Another important clinical issue is direct assessment of patient expectations. Whatever the cause, the patient should be asked whether they expect the proposed treatment plan will be effective. If they do not, this should be addressed as part of the treatment plan; otherwise, a successful outcome will be an uphill battle.

#### 3.1. Summary: motivation, conflict, and decision

The power and ubiquity of expectation effects on perceived pain intensity is a result of the evolutionary imperative to optimize selection of future actions when the risk of tissue damage is significant and there are competing alternatives. The decision process includes corticostriatal connectivity, and the implementation of the decision is through top-down modulatory circuits

that can increase pain intensity if the selected action is to escape pain or decrease it if a competing goal is selected. Under certain conditions, endogenous opioids contribute to implementing the approach reward in part by inhibiting pain transmission. Chronic pain biases the action decision toward pain escape/avoidance, and the implementation of this decision thereby increases the reported pain intensity at any given level of nociceptive input. Innovative strategies, behavioral or pharmacologic, aimed at mitigating these predictive processes have the potential to improve patient outcomes, especially for those with chronic pain.

### Conflict of interest statement

The author has no conflict of interest to declare.

### Acknowledgements

The author would thank Neil Schwartz, Elyssa Margolis, and Ben Alter for edits and suggestions on the manuscript and extensive discussions. Some of the human research work discussed was done by Ben Alter and will be presented at the IASP Congress. The author has served on the Neuroscience Advisory Board for Eli Lilly.

### Article history:

Received 27 March 2018

Received in revised form 28 April 2018

Accepted 1 May 2018

### References

- Altier N, Stewart J. The role of dopamine in the nucleus accumbens in analgesia. *Life Sci* 1999;65:2269–87.
- Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci* 1999;19:484–94.
- Amanzio M, Pollo A, Maggi G, Benedetti F. Response variability to analgesics: a role for non-specific activation of endogenous opioids. *PAIN* 2001;90:205–15.
- Atlas LY, Bolger N, Lindquist MA, Wager TD. Brain mediators of predictive cue effects on perceived pain. *J Neurosci* 2010;30:12964–77.
- Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields H, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci* 2012;15:1117–9.
- Becerra L, Breiter HC, Wise R, Gonzalez RG, Borsook D. Reward circuitry activation by noxious thermal stimuli. *Neuron* 2001;32:927–46.
- Benedetti F, Amanzio M, Vighetti S, Asteggiano G. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *J Neurosci* 2006;26:12014–22.
- Bozarth MA, Wise RA. Intracranial self-administration of morphine into the ventral tegmental area in rats. *Life Sci* 1981;28:551–5.
- Brody H. The lie that heals: the ethics of giving placebos. *Ann Intern Med* 1982;97:112–18.
- Cormier S, Lavigne GL, Choinière M, Rainville P. Expectations predict chronic pain treatment outcomes. *PAIN* 2016;157:329–38.
- Decoster I, Woolf CJ. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. *PAIN* 2000;87:149–58.
- Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, Büchel C. Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron* 2009;63:533–43.
- Eippert F, Finsterbusch J, Bingel U, Büchel C. Direct evidence for spinal cord involvement in placebo analgesia. *Science* 2009;326:404.
- Enoksson T, Bertran-Gonzalez J, Christie MJ. Nucleus accumbens D2- and D1-receptor expressing medium spiny neurons are selectively activated by morphine withdrawal and acute morphine, respectively. *Neuropharmacology* 2012;62:2463–71.
- Fields H. State-dependent opioid control of pain. *Nat Rev Neurosci* 2004;5:565–75.
- Fields HL. A motivation-decision model of pain: the role of opioids. In: Flor H, Kalso E, Dostrovsky J, editors. *Proceedings of the 11th World Congress on Pain*. IASP Press, 2006, Seattle. p. 449–459.
- Forkmann K, Wiech K, Sommer T, Bingel U. Reinstatement of pain-related brain activation during the recognition of neutral images previously paired with nociceptive stimuli. *PAIN* 2015;156:1501–10.
- Franklin KB. Analgesia and abuse potential: an accidental association or a common substrate? *Pharmacol Biochem Behav* 1998;59:993–1002.
- Grill JD, Coghill RC. Transient analgesia evoked by noxious stimulus offset. *J Neurophysiol* 2002;87:2205–8.
- Jensen J, McIntosh AR, Crawley AP, Mikulis DJ, Remington G, Kapur S. Direct activation of the ventral striatum in anticipation of aversive stimuli. *Neuron* 2003;40:1251–7.
- Kantor TG, Sunshine A, Laska E, Meisner M, Hopper M. Oral analgesic studies: pentazocine hydrochloride, codeine, aspirin, and placebo and their influence on response to placebo. *Clin Pharmacol Ther* 1966;7:447–54.
- Kelley AE. Memory and addiction: shared neural circuitry and molecular mechanisms. *Neuron* 2004;44:161–79.
- Keltner JR, Furst A, Fan C, Redfern R, Inglis B, Fields HL. Isolating the modulatory effect of expectation on pain transmission: a functional magnetic resonance imaging study. *J Neurosci* 2006;26:4437–43.
- King T, Vera-Portocarrero L, Gutierrez T, Vanderah TW, Dussor G, Lai J, Fields HL, Porreca F. Unmasking the tonic-aversive state in neuropathic pain. *Nat Neurosci* 2009;12:1364–6.
- Kirsch I, Kong J, Sadler P, Spaeth R, Cook A, Kaptchuk T, Gollub R. Expectancy and conditioning in placebo analgesia: separate or connected processes? *Psychol Conscious (Wash D C)* 2014;1:51–9.
- Knutson B, Wimmer GE, Kuhnen CM, Winkielman P. Nucleus accumbens activation mediates the influence of reward cues on financial risk taking. *Neuroreport* 2008;19:509–13.
- Kravitz AV, Tye LD, Kreitzer AC. Distinct roles for direct and indirect pathway striatal neurons in reinforcement. *Nat Neurosci* 2012;15:816–18.
- Lasagna L, Mosteller F, Von Felsinger JM, Beecher HK. A study of the placebo response. *Am J Med* 1954;16:770–9.
- Lee M, Manders TR, Eberle SE, Su C, D'amour J, Yang R, Lin HY, Deisseroth K, Froemke RC, Wang J. Activation of corticostriatal circuitry relieves chronic neuropathic pain. *J Neurosci* 2015;35:5247–59.
- Leeuw M, Gooossens MEJB, Linton SJ, Crombez G, Boersma K, Vlaeyen JWS. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med* 2007;30:77–94.
- Levine JD, Gordon NC. Influence of the method of drug administration on analgesic response. *Nature* 1984;312:755–6.
- Levine JD, Gordon NC, Fields HL. Naloxone dose dependently produces analgesia and hyperalgesia in postoperative pain. *Nature* 1979;278:740–1.
- Levine JD, Gordon NC, Fields HL. The mechanism of placebo analgesia. *Lancet* 1978;2:654–7.
- Ligato D, Petersen KK, Mørch CD, Arendt-Nielsen L. Offset analgesia: the role of peripheral and central mechanisms. *Eur J Pain* 2018;22:142–9.
- Mondloch MV, Cole DC, Frank JW. Does how you do depend on how you think you'll do? A systematic review of the evidence for a relation between patients' recovery expectations and health outcomes. *CMAJ* 2001;165:174–9.
- Moulin DE, Iezzi A, Amireh R, Sharpe WK, Boyd D, Merskey H. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet* 1996;347:143–7.
- Olds ME. Reinforcing effects of morphine in the nucleus accumbens. *Brain Res* 1982;237:429–40.
- Olds ME, Fobes JL. The central basis of motivation: intracranial self-stimulation studies. *Annu Rev Psychol* 1981;32:523–74.
- Peciña M, Zubieta JK. Molecular mechanisms of placebo responses in humans. *Mol Psychiatry* 2015;20:416–23.
- Peters J, Kalivas PW, Quirk GJ. Extinction circuits for fear and addiction overlap in prefrontal cortex. *Learn Mem* 2009;16:279–88.
- Price DD, Barrell JJ, Gracely RH. A psychophysical analysis of experimental factors that selectively influence the affective dimension of pain. *PAIN* 1980;8:137–49.
- Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol* 2008;59:565–90.
- Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: a critical review. *Expert Rev Neurother* 2009;9:745–58.
- Ren W, Centeno MV, Berger S, Wu Y, Na X, Liu X, Kondapalli J, Apkarian AV, Martina M, Surmeier DJ. The indirect pathway of the nucleus accumbens shell amplifies neuropathic pain. *Nat Neurosci* 2016;19:220–2.
- Schmidt BL, Tambeli CH, Levine JD, Gear RW.  $\mu/\delta$  cooperativity and opposing kappa-opioid effects in nucleus accumbens-mediated antinociception in the rat. *Eur J Neurosci* 2002;15:861–8.

- [46] Schwartz N, Miller C, Fields HL. Cortico-accumbens regulation of approach-avoidance behavior is modified by experience and chronic pain. *Cell Rep* 2017;19:1522–31.
- [47] Schwartz N, Temkin P, Jurado S, Lim BK, Heifets BD, Polepalli JS, Malenka RC. Chronic pain. Decreased motivation during chronic pain requires long-term depression in the nucleus accumbens. *Science* 2014;345:535–42.
- [48] Seymour B, Dolan RJ. Emotion, motivation and pain. In: McMahon S, Koltzenburg M, Tracey I, Turk DC, editors. *Wall and Melzack's textbook of pain*. Philadelphia: Elsevier Saunders, 2013. p. 248–255.
- [49] Sprenger C, Eichler IC, Eichler L, Zöllner C, Büchel C. Altered signaling in the descending pain modulatory system after short-term infusion of the  $\mu$ -opioid agonist remifentanyl. *J Neurosci* 2018;38:2454–70.
- [50] Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. A causal link between prediction errors, dopamine neurons and learning. *Nat Neurosci* 2013;16:966–73.
- [51] Stinus L, Le Moal M, Koob GF. Nucleus accumbens and amygdala are possible substrates for the aversive stimulus effects of opiate withdrawal. *Neuroscience* 1990;37:767–73.
- [52] Taha SA, Fields HL. Encoding of palatability and appetitive behaviors by distinct neuronal populations in the nucleus accumbens. *J Neurosci* 2005;25:1193–202.
- [53] 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.
- [54] Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 2004;303:1162–7.
- [55] Wise RA, McDevitt RA. Drive and reinforcement circuitry in the brain: origins, neurotransmitters, and projection fields. *Neuropsychopharmacology* 2018;43:680–9.
- [56] Woo C-W, Roy M, Buhle JT, Wager TD. Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain. *PLoS Biol* 2015;13:e1002036.
- [57] Yelle MD, Oshiro Y, Kraft RA, Coghill RC. Temporal filtering of nociceptive information by dynamic activation of endogenous pain modulatory systems. *J Neurosci* 2009;29:10264–71.
- [58] Yelle MD, Rogers JM, Coghill RC. Offset analgesia: a temporal contrast mechanism for nociceptive information. *PAIN* 2008;134:174–86.
- [59] Zambrenan L, Wise RG, Brooks JCW, Iannetti GD, Tracey I. A role for the brainstem in central sensitisation in humans. Evidence from functional magnetic resonance imaging. *PAIN* 2005;114:397–407.