A Computational Framework for Understanding the Impact of Prior Experiences on Pain Perception and Neuropathic Pain

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Abstract

Pain perception is influenced not only by sensory input from afferent neurons but also by cognitive factors such as prior expectations. It has been suggested that overly precise priors may be a key contributing factor to chronic pain states such as neuropathic pain. However, it remains an open question how overly precise priors in favor of pain might arise. Here, we first verify that a Bayesian approach can describe how statistical integration of prior expectations and sensory input results in pain phenomena such as placebo hypoalgesia, nocebo hyperalgesia, chronic pain, and spontaneous neuropathic pain. Our results indicate that the value of the prior, which is determined by generative model parameters, may be a key contributor to these phenomena. Next, we apply a hierarchical Bayesian approach to update the parameters of the generative model based on the difference between the predicted and the perceived pain, to reflect that people integrate prior experiences in their future expectations. In contrast with simpler approaches, this hierarchical model structure is able to show for placebo hypoalgesia and nocebo hyperalgesia how these phenomena can arise from prior experiences in the form of a classical conditioning procedure. We also demonstrate the phenomenon of offset analgesia, in which a disproportionally large pain decrease is obtained following a minor reduction in noxious stimulus intensity. Finally, we turn to simulations of neuropathic pain, where our hierarchical model corroborates that persistent non-neuropathic pain is a risk factor for developing neuropathic pain following denervation, and additionally offers an interesting prediction that complete absence of informative painful experiences could be a similar risk factor. Taken together, these results provide insight to how prior experiences may contribute to pain perception, in both experimental and neuropathic pain, which in turn might be informative for improving strategies of pain prevention and relief.

Author summary

To efficiently navigate the world and avoid harmful situations, it is beneficial to learn from prior pain experiences. This learning process typically results in certain contexts being associated with an expected level of pain, which subsequently influences pain perception. While this process of pain anticipation has evolved as a mechanism for avoiding harm, recent research indicates overly precise expectations of pain may in fact contribute to certain chronic pain conditions, in which pain persists even after tissue damage has healed, or even arises without any initiating injury. However, it remains an open question *how* prior experiences contribute to such overly precise expectations of pain. Here, we mathematically model the pain-learning-process. Our model successfully describes several counterintuitive but well-documented pain phenomena. We also make predictions of how prior experiences may contribute the perception of pain and how the same learning process could be leveraged to improve strategies of pain prevention and relief.

Introduction

Pain is beneficial for survival as it can motivate an organism to withdraw from harmful situations and avoid such harmful situations in the future. Despite its clear importance for survival the underlying mechanisms of pain are an active area of research. This limitation in knowledge, along with a wide variability in the pain

experience, render many pain conditions difficult to treat. Chronic pain is one of the leading global burdens of health [1] as well as an enormous personal and economic burden, affecting more than 30% of people worldwide [2]. A first step toward understanding any complex phenomenon is formulating a precise definition. The International Association for the Study of Pain (IASP) have defined pain as [3]:

> *"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"*

As a mechanism of protection from harm, pain should typically only arise when there is actual or potential tissue damage present, and the level of pain experienced should be proportional to the level of that tissue damage. However, pain can sometimes persist after the noxious stimulus has been removed or the tissue damage has healed. In fact, in some cases pain may arise even in absence of initiating tissue damage, as is the case with neuropathic pain (pain caused by a lesion or disease of the somatosensory nervous system [3]). Such maladaptive pain does not accurately reflect the level of harm to which the organism is exposed. How and why neuropathic pain may arise and persist in the absence of tissue damage is poorly understood, and consequently is often very difficult to treat.

Mathematical models of neuropathic pain have primarily focused on mechanisms in peripheral afferent neurons [4–6] and spinal cord neural circuits [6–8]. While neurophysiological changes at this level of the nervous system do contribute to neuropathic pain following peripheral nerve lesions, pain perception is also influenced by cognitive factors such as expectations based on previous experiences. It is suggested that this occurs through statistical integration of sensory input and prior information, for example through Bayesian inference [9–12]. Such models have been used to describe placebo hypoalgesia and nocebo hyperalgesia [13–16], and statistical pain learning [17] under experimental pain paradigms. As for chronic pain, Eckert et al., recently applied a Bayesian framework to illustrate how overly precise priors for being in a state of pain, combined with an ambiguous likelihood of perceiving pain from a sensory stimulation, increases the probability of transitioning to a chronic pain state [18]. Bayesian inference seems like a promising framework for modelling neuropathic pain, as damage to the nervous system often results in disrupted sensory input (corresponding to increased ambiguity of the likelihood), yet it remains an open question how overly precise priors in favor of pain might arise.

How the prior distribution is defined plays an important role in Bayesian inference [19]. One common Bayesian approach for tracking a state that may change over time is Kalman filtering [20], in which the prior is produced by a generative model of the world [19,20]. Here, we present a modified Kalman filter model of neuropathic pain, adapted from previously published models on motor adaptation [21,22]. In our model the state (pain) is estimated using the standard Kalman algorithm. A second Kalman filter is used to update the parameters of the generative model in the first Kalman filter, based on the difference between the predicted and the perceived pain. This reflects that people integrate previous experiences of pain in their future expectations. Our model predicts that previous experiences of pain and stochastic fluctuations of the parameters in the generative model, coupled with ambiguity in sensory input following damage to the nervous system, may be key drivers of neuropathic pain.

Results

Single-layer Kalman filter

The level of pain we experience is typically a result of sensory input arising from noxious stimuli but is also modulated by expectations based on previous experiences and the context in which the stimuli is delivered [9]. Such modulation is not unique to pain; integration of sensory input and expectations occur for any kind of perception. This process is often formalized through statistical accounts, such as Bayesian inference, where different sources of information are combined to form an estimate of the world [19]. An optimal estimate is obtained if the contribution of each source is determined by their respective level of uncertainty. Bayesian inference has successfully been applied to describe a range of perceptual and sensorimotor tasks, both qualitatively and quantitatively [21–23]. Just as for other forms of perception, Bayesian models provide a framework for how expectations can modulate pain perception [13,18,24,25].

Pain is dynamic, meaning that the intensity, quality, and characteristics of the experience change over time. One common Bayesian approach for modelling such temporal dynamics is Kalman filtering [20]. In the Kalman filter a state, x, is estimated based on sensory input and a prior estimate, which is produced by a generative model of the world [19,20]. In the context of pain, we suggest that the state x represents the true level of actual or potential tissue damage, and the estimate $\hat{x}$ represents the perceived pain. We assume that the level of actual or potential tissue damage can be influenced by actions u such that $x^{(k)} \propto Bu^{(k)}$. In addition to the influence of such actions, we assume that tissue damage develops over time as $x^{(k)} \propto Ax^{(k-1)}$, where $0 < A < 1$ implies healing. For ease of communication, we use linear concepts in this model, but the ideas we are exploring extend also to nonlinear concepts. The generative model in the Kalman filter thus consists of parameters $\hat{A}$ and $\hat{B}$ as estimates of the real-world parameters A and B. In this first part we will start by showing that, similar to other Bayesian models explored in literature [13,18,24,25], this Kalman filter can successfully model a variety of pain phenomena, including placebo hypoalgesia, nocebo hyperalgesia, and chronic pain and additionally can produce dynamics representative of spontaneous neuropathic pain.

The influence of expectations on pain perception is commonly and perhaps most clearly demonstrated by the phenomenon of placebo hypoalgesia (or the reverse effect, nocebo hyperalgesia), where identical noxious stimuli may be perceived as less (more) painful depending on the expectations associated with the context in which the stimuli is delivered [26]. Using a Kalman filter, we simulate the placebo (nocebo) effect in the context of a brief noxious stimulus by allowing the generative model parameter $\hat{B}$ be lower (higher) than the real-world value of B, see Figure 1. It is also suggested that the effects of expectations can extend beyond acute pain and could contribute to pain persisting even after the noxious stimulus has been removed and tissue damage has healed [9–12]. In our model this disproportionate pain results from a mismatch between the generative model parameter $\hat{A}$ and the real-world value of A. The contribution of the expectation and the sensory input to the final estimate is determined by their respective uncertainty. The uncertainty in sensory

input is denoted by R, where larger values of R indicate more uncertainty. The simulation results presented in Figure 2 demonstrate elevated uncertainty in the sensory input (higher value of R), in combination with the generative model parameter $\hat{A} \geq A$ results in the perceived pain being significantly higher than the true level of tissue damage and persisting even when the tissue damage has healed.

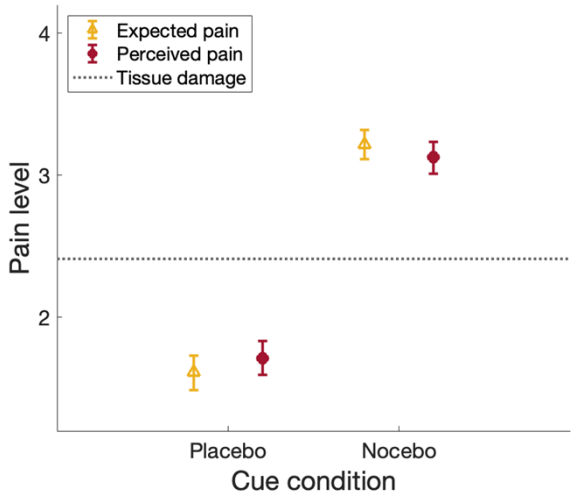

Figure 1 Placebo hypoalgesia (or the reverse effect, nocebo hyperalgesia) is the phenomenon where identical noxious stimuli may be perceived as less (more) painful depending on expectations. In the Kalman filter, the placebo (nocebo) effect corresponds to the generative model parameters being lower (higher) than the real-world values.

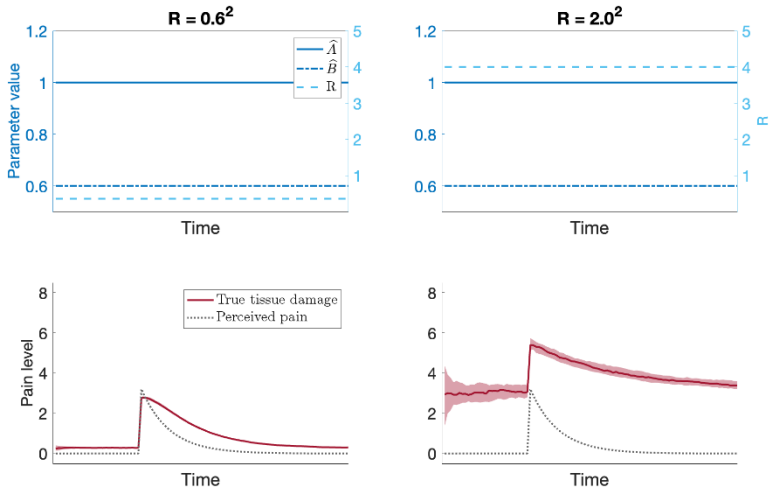

Figure 2 In the Kalman filter model chronic pain corresponds to elevated uncertainty in the sensory input, in combination with the generative model parameter $\hat{A} \approx 1$. Left: when R is low the perceived pain will primarily be influenced by the sensory input and closely correspond to the true level of tissue damage, regardless of the predictions of the generative model (expectations). Right: for a larger value of R, predictions from the generative model influence the perceived level of pain, possibly resulting in a chronically elevated level of pain even after the tissue damage has healed. The shaded areas indicate the interquartile range.

In the context of Bayesian models, elevated uncertainty of sensory input is a requirement for expectations to have a significant enough influence that they cause the level of pain to deviate from what is signaled by the sensory input. We assume that tissue damage itself can cause some disturbance to the sensory receptors that innervate the affected area, resulting in increased uncertainty in sensory input

relating to that region. Sensory input may also be affected by damage directly to peripheral afferent nerves or regions of the central nervous system involved in processing of sensory input. Under these circumstances, pain may arise spontaneously, even without some initiating action or tissue damage. This type of pain is commonly referred to as neuropathic pain. The gradual increase of pain before the onset of tissue damage in the bottom right panel of Figure 2 is one example of how pain can arise spontaneously when the uncertainty in the sensory input is elevated. In Figure 3 we provide additional examples of how, in our model, the expected level of spontaneous neuropathic pain following for example a nerve injury depends on the level of uncertainty in the sensory input (value of R) and the value of the generative model parameter $\hat{A}$.

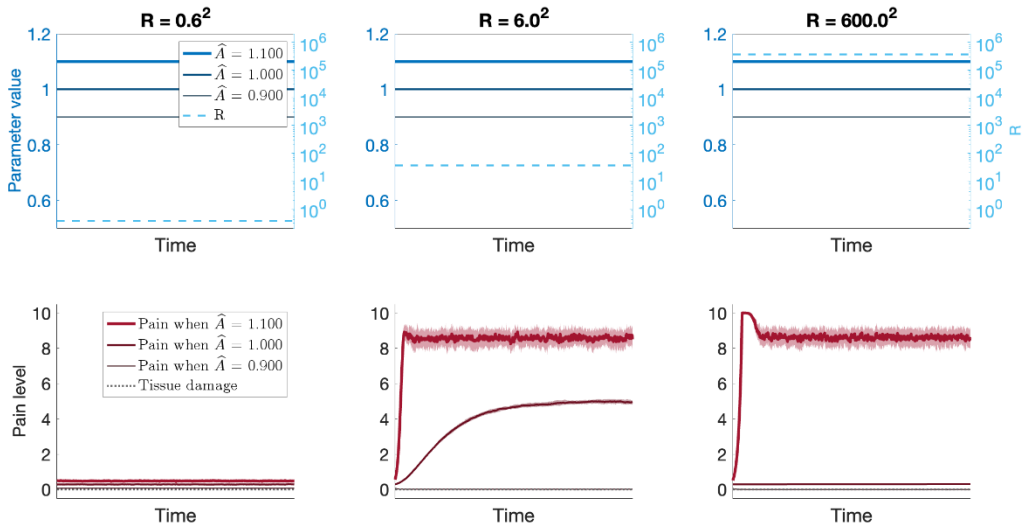

Figure 3 Damage to the sensory nervous system may result in increased uncertainty of sensory input relating to the level of tissue damage. Depending on the level of uncertainty (value of R) and the value of the generative model parameter $\hat{A}$, these changes could result in spontaneous neuropathic pain.

By modeling pain perception as a Kalman filter our results so far have successfully demonstrated pain phenomena such as placebo hypoalgesia, nocebo hyperalgesia, chronic pain, and spontaneous neuropathic pain. We have shown that the level of uncertainty in the sensory input and the values of the generative model parameters may be key contributors to these phenomena. What we have not been able to account for with this model is *how* the values of the parameters in the generative model are determined. The generative model parameters are typically tuned by hand or fit to experimental data (e.g., [13–16]). Although these manually tuned models do give insight to how expectations can influence pain perception, they do not account for how previous experiences shape those expectations. To incorporate how previous experiences contribute to pain expectations we must turn to descriptive models of how the generative model is updated.

The Hierarchical Kalman filter

The traditional Kalman filter gives us a framework for understanding how loss of certainty in sensory input, combined with predictions from a generative model of the world, might contribute to pain phenomena such as placebo hypoalgesia, nocebo

hyperalgesia and spontaneous neuropathic pain. However, in this framework the generative model parameters are manually tuned, and therefore the traditional Kalman filter alone cannot account for how previous experiences influence the generative models and the resulting pain expectations. To address this shortcoming, we turn to recent work on modelling motor adaptation, where a second Kalman filter has been used to update the parameters of the generative model based on the difference between the prediction and the posterior estimate [21,22]. This process reflects that people integrate previous experiences in their future expectations. Here, we adapt the hierarchical Kalman filter to the context of pain and demonstrate with an example of classical conditioning that the model successfully reflects how previous pain experiences influence future expectations.

To verify that the hierarchical model reproduces similar results as the single-layer Kalman filter regarding placebo hypoalgesia and nocebo hyperalgesia, we turn to the concept of classical conditioning. Classical conditioning is a procedure that is often used to induce placebo or nocebo responses in experimental studies [27]. In the conditioning procedure a conditioned stimulus (previously neutral stimulus, e.g., an auditory cue) is repeatedly paired with with an unconditioned stimulus (e.g., a noxious stimulus). Through this process, the conditioned stimulus can come to elicit a response originally associated with the unconditioned stimulus, a so-called conditioned response. In Figure 4 we demonstrate the results of the simulated placebo and nocebo conditioning. First, we show that there is no expectation of pain associated with the conditioned stimulus at baseline. We then assess the expected and perceived pain during the conditioning procedure and note that the expected pain increases for repeated exposure to the unconditioned stimulus. Finally, the effect of the conditioning is tested by pairing each conditioned stimulus with an intermediate-intensity unconditioned stimulus, revealing that the simulated conditioning procedure results in placebo hypoalgesia and nocebo hyperalgesia that qualitatively matches the pattern produced by the single-layer Kalman filter in Figure 1.

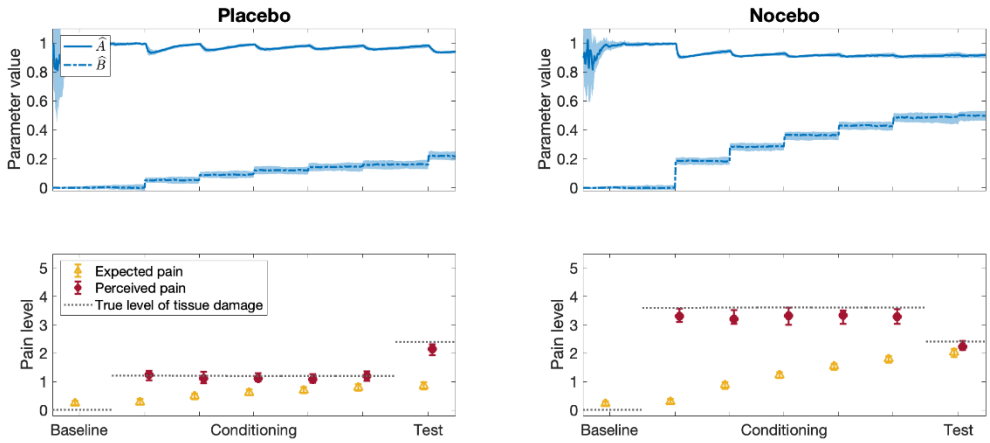

Figure 4 We simulate a placebo (nocebo) conditioning procedure by assessing the expected and perceived pain for a conditioned stimulus paired with repeated low (high)-intensity unconditioned stimulus. The top panels show how the parameters of the generative model are updated over time based on the difference between the expected and perceived pain. At baseline, the conditioned stimulus is not associated with pain. During conditioning the expected pain increases for repeated exposures to the unconditioned stimulus. After conditioning, placebo hypoalgesia (nocebo hyperalgesia) is obtained in response to an

intermediate-intensity test-stimuli (compare to Figure 1). The shaded areas and error bars indicate the interquartile range.

In the single-layer Kalman filter we noted that the value of the generative model parameter $\hat{A}$ and the certainty in the current sensory input, R, influence the level of spontaneous neuropathic pain following nerve injury (*Figure 3*). In the hierarchical Kalman filter model, the value of $\hat{A}$ changes over time, which affects the level of predicted pain. Furthermore, the value of R influences how the generative model updates. These differences result in pain dynamics that differ from what was observed in the single-layer Kalman filter. In particular, the model predicts that the value of $\hat{A}$ at the time of a nerve injury and the level of sensory disruption (i.e., value of R) may play a role in the level and variance of subsequent neuropathic pain, see Figure 5.

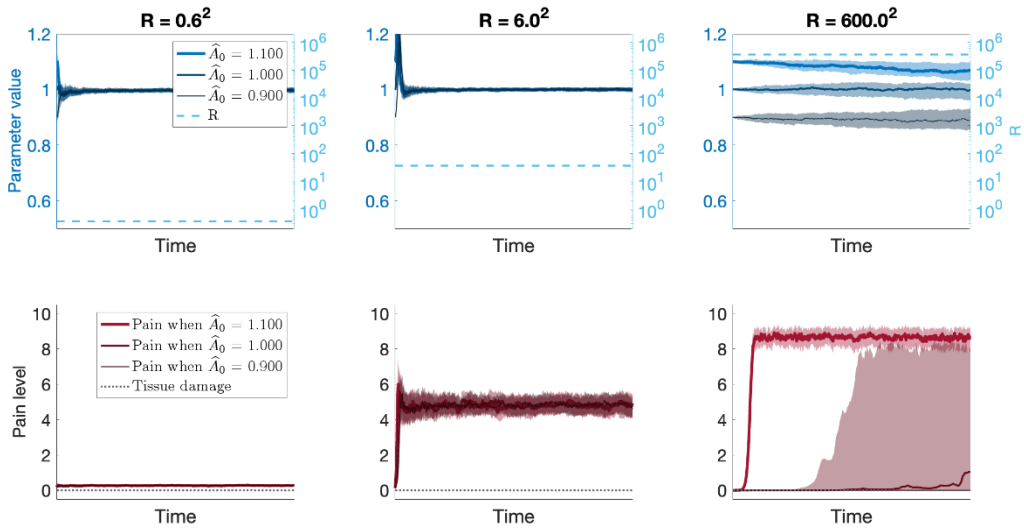

Figure 5 The value of $\hat{A}$ at the time of a nerve injury and the level of sensory disruption (i.e., value of R) may play a role in the characteristics of subsequent neuropathic pain. For $R = 0.6^2$ (left), the perceived pain is strongly influenced by sensory input and remains close to 0. For intermediate valued of R, e.g., $R = 6^2$ (middle), $\hat{A} \approx 1$ regardless of the initial value, and the perceived pain is tonically at an intermediate intensity with little variance. For $R = 600^2$ (right), the value of $\hat{A}$ is no longer at all influenced by sensory input and reduces to a random walk centered at the initial value $\hat{A}_0$ and variance equal to the noise in the generative model. In this scenario, if $\hat{A}_0 > 1$ the pain is likely to stay tonically high, and similarly if $\hat{A}_0 < 1$ the level of pain is likely to drop to stay at 0. If $\hat{A}_0 \approx 1$, the perceived level of pain may vary widely as the value of $\hat{A}$ fluctuates above and below 0.

The classical conditioning example demonstrated how repeated painful experiences allow the generative model to update over time to give more accurate predictions of the real world. Later, we saw that the value of $\hat{A}$ at the time of a nerve injury may determine the existence and level of neuropathic pain. Taken together, the same processes as in classical conditioning could occur also in other contexts, and result in values of the generative model parameters that predispose certain individuals to neuropathic pain. In the hierarchical Kalman filter the value of $\hat{A}$ is determined by previous painful experiences. Intuitively, exposure to persistent pain ($A \approx 1$) typically results in values of $\hat{A}$ close to 1, while exposure to quickly transient pain ($A < 1$) typically gives lower values of $\hat{A}$.

But what happens if there is no exposure to painful experiences? Since there are no periods of decaying pain to inform the generative model, a tonically pain-free state also results in $\hat{A} \approx 1$, regardless of the true value of A. Figure 6 shows how persistent pain (left), quickly transient pain (middle) and complete absence of pain (right) each influence the generative model, and the resulting level of neuropathic pain following a nerve injury (vertical dashed line). Our model corroborates that persistent non-neuropathic pain is a risk factor for developing neuropathic pain following denervation [28–30], and additionally offers an interesting prediction that complete absence of informative painful experiences could be a similar risk factor.

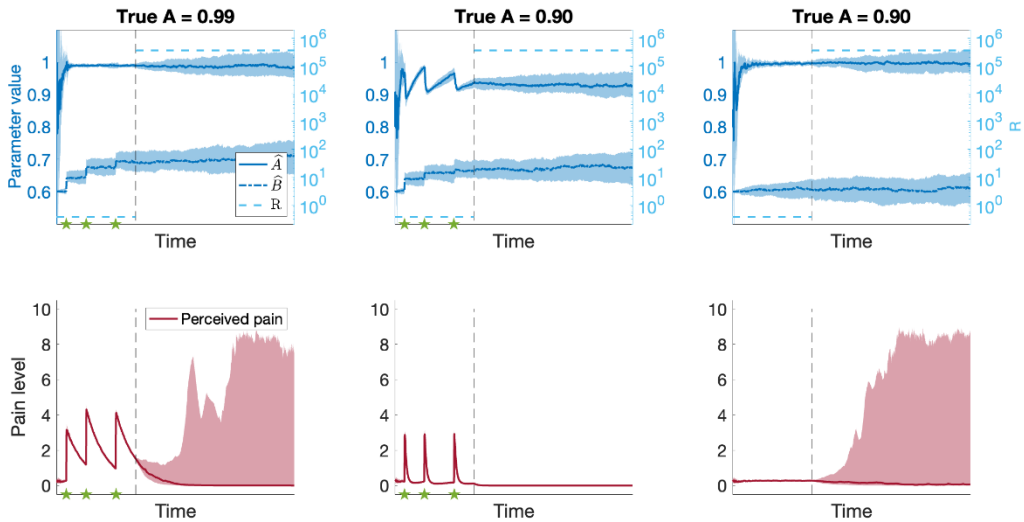

Figure 6 The value of the generative model parameters are determined by previous painful experiences. In the left panels, $A = 0.99$, yielding persistent pain following noxious stimuli (indicated by stars). This value of A results in $\hat{A} \approx 1$, and a high risk of spontaneous neuropathic pain following a nerve injury (vertical dashed line). In the middle panels $A = 0.9$, resulting in quickly transient pain, a lower value of $\hat{A}$ and a lower risk of spontaneous neuropathic pain. In the right panels $A = 0.9$ again, but in this simulation, there are no noxious stimuli. These circumstances result in $\hat{A} \approx 1$ and a higher risk of spontaneous neuropathic pain than in the example in the middle. The shaded areas indicate the interquartile range.

Another phenomenon that relates to the temporal dynamics of pain perception is *offset analgesia*, which is defined as a disproportionally large pain decrease after a minor noxious stimulus intensity reduction [31]. The phenomenon can be elicited by a simple experimental paradigm: noxious thermal stimuli are applied to an area of skin in three consecutive time intervals T1, T2 and T3, where the same temperature is applied during T1 and T3, and the temperature during T2 is slightly higher. This stimulation paradigm typically results in a disproportionate pain reduction in response to the temperature reduction from T2 to T3 as compared to a control condition where a constant temperature is applied throughout all three time intervals. We were curious to see if the adaptive nature of the hierarchical Kalman filter would enable the model to reproduce this phenomenon. As can be seen in Figure 7, the model produces an underdamped response following a reduction in noxious stimuli. This effect is qualitatively similar yet smaller than what is typically observed in experimental studies of offset analgesia. We will elaborate on possible reasons for the magnitude discrepancy in the discussion section.

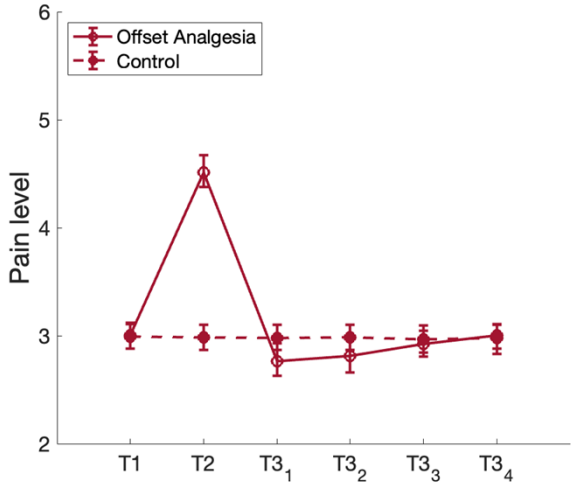

Figure 7 Offset analgesia is defined as a disproportionally large pain decrease after a minor noxious stimulus intensity reduction. This phenomenon is often elicited by applying noxious thermal stimulation of the same temperature in time intervals T1 and T3, separated by time interval T2 with slightly higher temperature. In the control condition a constant temperature is applied throughout all three time intervals. Our simulation results show a qualitatively similar underdamped response to the minor temperature reduction as is observed in experimental studies of offset analgesia.

Discussion

Bayesian inference has been particularly useful in modelling how expectations influence sensory perception [32]. Since the contributions of sensory input and expectations are weighted by their respective certainty, this framework allows for interesting predictions for perception under different levels of certainty in sensory input. In the context of pain, Bayesian models have successfully described several phenomena, including placebo hypoalgesia, nocebo hyperalgesia and chronic pain [13,18,24,25]. However, these models rely on parameters to be tuned by hand or fit to experimental data. While such manually tuned models do give insight to how expectations can influence pain perception, they do not account for how previous experiences shape those expectations, and accordingly cannot explain phenomenon such as classical conditioning, offset analgesia or how certain events might predispose individuals to chronic or neuropathic pain.

Here, we first verified that the Kalman filter, a common Bayesian approach for modelling temporal dynamics, produced results in line with previous, similar Bayesian models, and additionally offered insight to how disruption of sensory input may contribute to spontaneous neuropathic pain. Next, to address how previous experiences contribute to pain expectations we applied a second Kalman filter to update the parameters of the generative model based on the difference between the prediction and the posterior estimate. With this hierarchical model structure, we could again model placebo hypoalgesia and nocebo hyperalgesia that qualitatively matches results from previous Bayesian models, but also show how these phenomena can arise from previous experiences in the form of a classical conditioning procedure. We also showed that, due to the adaptive nature of the hierarchical Kalman filter, the model produced a disproportionally large pain decrease after a minor noxious stimulus intensity reduction, a phenomenon that is commonly referred to as offset analgesia. To our awareness, this phenomenon has not previously been reproduced in mathematical models of pain.

The results on classical conditioning and offset analgesia indicated that the hierarchical Kalman filter model can account for pain phenomena occurring at different time scales. This led us to believe that similar processes might affect pain perception also in the long term. Like simulations with the traditional Kalman filter, the value of the internal model parameter $\hat{A}$ at the time of a nerve injury and the level of sensory disruption (i.e., value of R) played a role in the level and variance of subsequent simulated neuropathic pain. However, with the hierarchical model we could explore how the value of $\hat{A}$ is determined by the pain dynamics before the nerve injury. Our simulations corroborated that persistent non-neuropathic pain is a risk factor for developing neuropathic pain following denervation, which is well established in previous literature [28–30]. The model additionally offered an interesting prediction that complete absence of informative painful experiences could be a similar risk factor. Taken together, these results provide insight to how previous experiences may contribute to pain perception, in both experimental and neuropathic pain, which in turn might be informative for improving strategies of pain prevention and relief.

Neuropathic pain is often resistant to common pharmacological pain treatments [33,34]. Therefore, finding alternative ways of relieving or preventing neuropathic pain is of utmost interest. There exist several mechanisms by which neuropathic pain may arise, such as spontaneous activation of nociceptive afferent sensory fibers, which in our model corresponds to sensory input signaling tissue damage with high certainty. Our model also predicts that spontaneous neuropathic pain will arise if the following two criteria are fulfilled: 1) the generative model predicts pain, and 2) the uncertainty in the sensory input, denoted R, is large. The first of these criteria provides a hint at possible preventative measures, such as avoiding persistent pain before denervation. This is in line with existing literature on risk factors for developing neuropathic pain [28–30]. Another prediction from the model, which might seem controversial, is that exposure to transient pain before denervation might be another strategy for mitigating the risk of developing neuropathic pain. This prediction remains to be established empirically.

When it comes to relieving existing neuropathic pain, we must turn to the second criteria; the uncertainty in the sensory input, R. If R is large, there will be no meaningful input for the generative model to update from, therefore the current model does not offer an avenue for pain relief by addressing the generative model directly. However, if R can be reduced and the sensory input can be controlled such that it signals lower levels of tissue injury, this should lead to lower levels of perceived pain. We intentionally left the definition of *sensory input* somewhat vague in defining the model. Input relating to tissue injury could come in several different sensory modalities, such as nociception, somatosensation and vision. After nerve injury some (or all, e.g., following amputation) of these sensory modalities could be affected, resulting in increased uncertainty of the sensory input. If some of the sensory input could be restored, this could possibly offer an avenue for pain relief. Thus, our model offers a possible explanation for the working mechanism of existing non-pharmacological treatments for neuropathic pain involve some form of sensory restoration [35–38].

In addition to giving clues of possible avenues for pain prevention and relief, our model also offers a prediction for how different levels of sensory disruption may

result in different pain characteristics. Matching sensory symptoms to pain mechanisms is a challenge that researchers and clinicians are grappling with, to better predict treatment responses of individual patients [39,40]. Regarding neuropathic pain, certain sensory characteristics have been found to be particularly common, such as burning pain, numbness, paresthesia (tingling or prickling sensation, “pins and needles”), and pain attacks, sudden bursts of increased pain, or electric shocks [41–44]. The simulation results presented in Figure X indicate that moderately high values or R result in an intermediate level of pain with relatively little variance, which might correspond to a monotonous pain sensation or paresthesia reported by some individuals with neuropathic pain. For higher values of R, more diverse pain dynamics are possible. For example, for $\hat{A} \approx 1$ at the time of the nerve injury, large variance of pain intensity is obtained. Under these conditions pain may vary between high and low intensities, possibly reflecting the pain attacks-descriptor that is often used when screening for neuropathic pain. Thus, our model predicts that monotonous or paresthetic sensations of intermediate intensity might be more common in patients with partial denervation (R intermediate) while pain attacks, monotonously high intensity or complete absence of pain would be expected in patients with complete denervation (R high).

We have focused on modeling pain at the information processing level and have assumed a linear relationship between tissue damage and sensory input arriving to the central nervous system. However, there are a myriad of physical, chemical, and neurobiological processes that modulate sensory afferent signals before they reach the brain. Due to these mechanisms, the mapping from actual or potential tissue damage to sensory input can be quite complex. As an example, thermal discriminative abilities are modified by the temperature to which the skin has been adapted prior to delivering the thermal stimuli, indicating that the relationship between thermal stimulation and sensory input may be non-linear [45]. Omission of this relationship, along with other modulatory mechanisms such as sensitization and habituation, could be an explanation for why our offset analgesia simulations produced an effect that is smaller than typically observed in experiments [46,47]. This limitation also means that our model cannot account for pain phenomenon that may arises because of impairment of pain modulation, such as certain forms of chronic pain.

Predictive coding is a modeling framework that has been suggested to be applicable to pain [48,49]. This framework has a lot in common with the model proposed here, including a hierarchical structure and precision modulated integration of sensory input and predictions. One key difference is the level of abstraction; while our model deals with information processing at the level of cognitive computation, predictive coding is based on processes at the level of neuronal hardware. While a lot remains to be determined regarding the specific function and contributions of various brain regions in pain processing, structures and processes have been identified in which predictive coding may be applicable as a modeling framework [49]. For example, Song et al., successfully modeled local field potentials in ACC and S1 during pain perception in rats using predictive coding [50]. Models targeting different levels of abstraction can generate different predictions related to pain processing. While our model provides predictions regarding pain prevention and treatment through behavioral interventions, models at the implementation level of abstraction, such as

predictive coding, may be able to generate insights regarding neural processes involved in pain perception.

Defining specific sensory modalities is an interesting avenue for future development of the model. Doing so could provide insight to how central processing might contribute to pain conditions such as allodynia, a neuropathic pain phenomenon where pain is elicited by otherwise non-painful stimulation such as cold, warmth or touch. This development of the model might also allow for exploration of the possible mechanism of treatments for neuropathic pain that involve some form of sensory restoration. One example of such a treatment is mirror therapy, which is commonly used for phantom limb pain [36,51]. Phantom limb pain is a particular form of neuropathic pain, where pain is experienced to arise in a missing limb, for example following amputation. In mirror therapy a mirror is used to create a visual illusion that the missing limb is intact, which could be seen as a form of partial sensory restoration. The working mechanism and efficacy of mirror therapy is disputed [52,53], although it seemingly does to provide pain relief to some individuals [51,54,55]. Incorporating several sensory modalities in the model and probing the effect of restoring some of these modalities could shed light on why mirror therapy provides pain relief for some individuals and not in others.

Another limitation of the current model is the lack of actions and decision making. As a mechanism of protection from harm, pain should elicit actions that allow the organism to withdraw from harmful situations that is cause pain and inform decisions on how to avoid such situations in the future. A few different frameworks have been suggested to model this process, commonly involving some variation of reinforcement learning [48,56]. Active inference is another framework that has been suggested to be relevant for the context of pain [57]. This framework has a lot in common with the model presented here, such as updating a generative model of the world, and also includes the possibility of holding the model fixed and altering actions within the world to sample information that better reflects the predictions [58]. Incorporating the feedback between actions and pain perception in our model could provide insights to how behavior might contribute to persistence of pain and what actions might be helpful for pain relief.

Finally, throughout this work we have entirely focused on the *sensory* aspect of pain. According to the definition, pain is a sensory *and emotional* experience, yet pain is often treated as a purely sensory experience both in clinical practice and in research. Meanwhile, chronic pain is commonly comorbid with psychological disorders such as depression and PTSD [59–61], although the linking mechanism between these conditions remains unclear. Ignoring such as significant portion of the pain experience creates a risk of overlooking mechanisms that might contribute to persistence of pain in chronic pain conditions, as well as possible avenues for new and improved pain treatments. For example, neuroimaging studies have found that initially greater functional connectivity within certain motivation–valuation circuitry predicts pain persistence [62] and that spontaneous fluctuations of chronic pain intensity is associated with activity in brain regions that are typically ascribed to emotional processing [63]. Furthermore, there is tentative evidence that incorporating psychological components in pain treatments yields significant improvements in pain relief [64]. We believe that modeling the emotional aspects of

pain is a highly interesting avenue for future research, as it could provide insight to previously underexplored mechanisms contributing to pain persistence and relief.

A framework from psychological and behavioral science that seems to have some relevance to both decision-making and emotion related to pain is *prospect theory*, which has been highly impactful in modeling decision-making under risk [65]. While this framework most commonly is applied to evaluation of financial outcomes, the underlying principles are common to many processes of perception and emotion. Prospect theory relies on a few key cognitive features, including that evaluation is relative to reference point, which is something we have already encountered in the examples of offset analgesia, and loss aversion. *Loss aversion* is the concept where psychological value of loss looms larger than the value of equivalent gain. In the context of pain, loss would typically correspond to an increase in pain, whereas gain corresponds to pain relief. It is not hard to imagine that loss aversion may influence decision-making in pain (in fact there are at least tentative results corroborating this [66]). Furthermore, the psychological value of recent changes in pain intensity may influence the valence of emotional aspects of pain. Taken together, it seems that concepts form prospect theory may offer an avenue for incorporating aspects of the pain experience that have not been captured by this model.

Methods

Computational modeling – Single-layer Kalman filter

In modeling the process of pain perception as a Kalman filter, we suggest that the state x represents the true level of actual or potential tissue damage. For discrete point in time $k = 1,...,n$, we assume that the level of actual or potential tissue damage can be influenced by actions u such that the level of tissue damage follows $x^{(k)} \propto B\ u^{(k)}$, where B is the control gain, determining the change in tissue damage resulting from action u . In addition to the influence of such actions, we assume that tissue damage develops over time as $x^{(k)} \propto Ax^{(k-1)}$, where A is the state transition coefficient. If $0 < A < 1$, the tissue is healing. Thus, we obtain the following expression for tissue damage x

$$x^{(k)} = Ax^{(k-1)} + Bu^{(k)} + \epsilon(0,Q_A) + \epsilon\left(0,|u^{(k)}|Q_B\right),$$

where $\epsilon(0,Q_A)$ is the noise related to the state transition $Ax^{(k-1)}$ and $\epsilon\left(0,|u^{(k)}|Q_B\right)$ is the noise related to the control input $Bu^{(k)}$. Note that the variance of the control input noise is proportional to the magnitude of the control signal $u^{(k)}$, to reflect that the variance of an action (e.g., a movement) is proportional to the magnitude of the action. However, in the examples presented here we only deal with binary set of values for u, namely $u = 0$ or $u = 4$, and thus do not fully explore the implications of this heteroscedasticity.

In Kalman filtering a prior estimate, $\hat{\bar{x}}$, of the state is obtained from a generative model of the world. In the context of pain, we suggest that the prior estimate corresponds to the predicted or expected level of pain. In this model, the generative model consists of parameters $\hat{A}$ and $\hat{B}$, reflecting estimates of the real-world

parameters A and B. Thus, the prior estimate, or expected level of pain, is obtained as

$$\hat{\bar{x}}^{(k)} = \hat{A}^{(k)}\hat{x}^{(k-1)} + \hat{B}^{(k)}u^{(k)}.$$

According to optimal Bayesian integration, the posterior estimate, $\hat{x}$, of the state is a combination of the prior estimate and the sensory input. The sensory input from sensory receptors relating to tissue damage is defined as

$$z^{(k)} = Hx^{(k)} + \epsilon(0,R),$$

where H is the observation matrix mapping from state space (tissue injury) to measurement space (sensory input) and $\epsilon(0,R)$ is the measurement noise, where R denotes the variance in how the sensory input relates to the level tissue damage. In the context of pain, we suggest that the posterior estimate corresponds to the perceived level of pain. In Kalman filtering the posterior estimate is defined as

$$\hat{x}^{(k)} = \hat{\bar{x}}^{(k)} + K^{(k)}\left(z^{(k)} - \hat{\bar{x}}^{(k)}\right),$$

where

$$K^{(k)} = \frac{\bar{P}^{(k)}}{\bar{P}^{(k)} + \mathrm{R}},$$

and $\bar{P}^{(k)} = \hat{A}^{(k)2}P^{(k-1)} + Q_A + |u^{(k)}|Q_B$ is the uncertainty of the prior estimate $\hat{\bar{x}}$. The posterior estimate has covariance $P^{(k)} = \left(1 - K^{(k)}\right)\bar{P}^{(k)}$.

In simulations of the single-layer Kalman filter parameter values are set according to Table 1, unless otherwise specified.

Table 1 Default parameter values for simulations with the single-layer Kalman filter.

Parameter	**Default value**
Variance of sensory noise, R	0.6^2
Variance of state transfer process noise, Q_A	0.05^2
Variance of control input process noise, Q_B	0.1^2
Initial uncertainty in state estimate, $P^{(0)}$	10^6
Real-world state transfer coefficient, A	0.9
Real-world control gain, B	0.8
Estimated state transfer coefficient, $\hat{A}$	0.8
Estimated control gain, $\hat{B}$	0.6

Computational modeling – Hierarchical Kalman filter

This model builds on previous work on motor adaptation [21,22]. Here, pain is estimated using a Kalman filter, and second Kalman filter is used to update the parameters of the generative model, $\hat{\boldsymbol{p}} = [\hat{A},\hat{B}]^T$, based on the difference between the predicted and the perceived pain. This reflects that people integrate previous experiences of pain in their future expectations. The prior estimate of the generative model parameters is given by

$$\hat{\bar{\boldsymbol{p}}}^{(k+1)} = \hat{\boldsymbol{p}}^{(k)} + \epsilon(0,Q_p),$$

where $\epsilon(0,Q_p)$ is noise in the generative model with covariance matrix Q_p. For simplicity we assume that $\hat{A}$ and $\hat{B}$ are independent random variables, and thus the correlation matrix collapses to a diagonal matrix with the variance of the noise of each of the two parameters as the diagonal elements, as follows

$$Q_p = \begin{bmatrix} Q_{pA} & 0 \\ 0 & Q_{pB} \end{bmatrix}.$$

The prior estimate of the generative model parameters has covariance $\overline{P}_p^{(k+1)} = P_p^{(k)} + Q_P$, where $P_p^{(k)}$ is the covariance of the generative model estimate at iteration k.

To form the posterior estimate of the generative model, the prior estimate is combined with the prediction error $\hat{x}^{(k)} - \hat{\bar{x}}^{(k)}$, which has covariance $R_p^{(k)} = P^{(k)} + \overline{P}^{(k)}$. This definition of the prediction error covariance differs somewhat from that used in previous published version of the model. Berniker & Körding used $R_p = R$ and Johnson et al., used $R_p = Q + R$ [21,22]. Our reasoning for updating this definition is simply that we assume that the covariance of the error should be a sum of the covariance of the terms used to compute the error, namely P for $\hat{x}$ and $\overline{P}$ for $\hat{\bar{x}}$. When checking the implications of this update, the model behavior aligns with our expectations. The generative model update takes the form

$$\hat{\boldsymbol{p}}^{(k+1)} = \hat{\boldsymbol{p}}^{(k)} + K_p{}^{(k+1)}\left(\hat{x}^{(k)} - \hat{\bar{x}}^{(k)}\right) + \epsilon(0,Q_p),$$

where K_p is the Kalman gain. Like the traditional Kalman filter, the Kalman gain is defined by the covariance of the terms that are combined to form the posterior estimate,

$$K_p^{(k+1)} = \overline{P}_p^{(k+1)} H_p^{(k)T}\left[H_p^{(k)}\overline{P}_p^{(k+1)} H_p^{(k)^T} + R_p^{(k)}\right]^{-1},$$

where H_p is the mapping from parameter space to state space, defined as

$$H_p^{(k)} = \frac{\partial \hat{x}}{\partial \hat{\boldsymbol{p}}} = \begin{bmatrix} \frac{\partial \hat{x}^{(k)}}{\partial \hat{A}^{(k)}} & \frac{\partial \hat{x}^{(k)}}{\partial \hat{B}^{(k)}} \end{bmatrix} = [H_A \quad H_B] = \left(1 - K^{(k)}\right)\left[\hat{x}^{(k-1)} \quad u^{(k)}\right].$$

Finally, the covariance of the estimated parameters is given by

$$P_p^{(k+1)} = \overline{P}_p^{(k+1)}(I - H_p^{(k)} K^{(k)} K_p^{(k+1)}).$$

This definition of $P_p^{(k+1)}$ also differs somewhat from what has been used in previous published versions of the model. The difference here is the introduction of $K^{(k)}$ as a scaling factor to $H_p^{(k)} K_p^{(k+1)}$. Without the scaling factor K the covariance of the estimated parameters, P_p, will tend to 0 when $R \to \infty$. When there is infinite sensory noise there is no reliable input inform the accuracy of the estimated generative model parameters, and thus P_p should not tend to 0 (since $P_p \approx 0$ indicates high

confidence in the estimated parameters). To address this contradictory behavior, we introduce the scaling factor $K^{(k)}$.

Estimation of the level of pain, $\hat{x}$, is similar to the process outlined for the single-layer Kalman filter. The only difference is in the calculation of the prior state estimate covariance, $\overline{P}$, to which a term $H_p^{(k)2}P_p^{(k)}$ has been added to incorporate the certainty in the generative model estimate in the state estimate. Thus, the prior state estimate covariance is defined as

$$\overline{P}^{(k)} = \hat{A}^{(k)2}P^{(k-1)} + Q_A + |u^{(k)}|Q_B + H_p^{(k)2}P_p^{(k)} \ .$$

In simulations of the hierarchical Kalman filter parameter values are set according to Table 2, unless otherwise specified.

Table 2 Default parameter values for simulations with the hierarchical Kalman filter

Parameter	**Default value**
Variance of sensory noise, R	0.6^2
Variance of state transfer process noise, Q_A	0.05^2
Variance of control input process noise, Q_B	0.1^2
Initial uncertainty in state estimate, $P^{(0)}$	10^6
Real-world state transfer coefficient, A	0.9
Real-world control gain, B	0.8
Variance of generative model parameter $\hat{A}$, Q_{pA}	0.002^2
Variance of generative model parameter $\hat{B}$, Q_{pB}	0.002^2
Initial uncertainty in estimate of $\hat{A}$, $P_{pA}^{(1)}$	10^6
Initial uncertainty in estimate of $\hat{B}$, $P_{pB}^{(1)}$	10^6

Simulations

Since pain commonly is measured on an 11-point scale, where 0=no pain and 10=worst pain imaginable, we let tissue damage x exist on similar 11-point scale of arbitrary units. For simplicity, we let $H = 1$ and dimensionless such that sensory measurements z also exist on an 11-point scale of arbitrary units. In the simulations, $x^{(k)}$ and $z^{(k)}$ are drawn from normal distributions which are truncated at 0 and 10. Truncation is achieved by resampling if the drawn sample falls outside of the permitted range. To account for asymmetry in the resulting distributions due to the truncation, we have chosen to report medians and interquartile ranges, rather than means and standard deviations. These values are computed across 100 simulations, unless otherwise specified.

Matlab code for all simulation results presented in this article are available online at: https://zenodo.org/doi/10.5281/zenodo.10960405.

Figure 1 - Placebo hyperalgesia and nocebo hypoalgesia

In the simulations of placebo hypoalgesia and nocebo hyperalgesia, we let u be the action that precedes or coincides with the noxious stimuli. In experimental paradigms this action typically is in the form of viewing a visual cue or listening to an auditory

cue. It is worth noting that in these experimental settings, it is typically not the action (observing a cue) that causes the noxious stimuli, yet the association is being formed between the action and the perceived level of pain.

The magnitude of u is identical in the placebo and nocebo conditions, what differs between the two is the *expected gain in pain* $\hat{B}$, where we let $\hat{B}_{placebo} \sim N(0.4, 0.2^2)$ and $\hat{B}_{nocebo} \sim (0.8, 0.2^2)$. The values are drawn from normal distributions to reflect inter-individual variations. The expected pain is assessed as the value of $\hat{\bar{x}}$ immediately following the presentation of the cue, while the perceived pain is assessed as the maximum value of $\hat{x}$ in a time window following the noxious stimuli.

Figure 2 – Chronic pain

Default parameter values specified in Table 1 are used in simulations for Figure 2, except for $\hat{A} = 1$, and the value of R which is 0.6^2 in the left panel and 2.0^2 in the right panel. The action resulting in a single brief noxious stimulus is set to $u = 4$.

Figure 3 – Neuropathic pain

In Figure 3, different levels of sensory disruption are simulated by letting the value of R vary, and for each value of R the resulting pain is assessed for different values of $\hat{A}$. To reflect the transition to a state of nerve injury more accurately, all the simulation results shown in the figure are preceded by a simulated period of no sensory disruption ($R = 0.6^2$, default) to allow the estimated state $\hat{x}$ and associated uncertainty P to settle into baseline values.

Figure 4 - Classical conditioning

The classical conditioning simulations follow similar principles as placebo and nocebo simulations. The action u corresponds to the observation of the conditioned stimulus. Initially, $\hat{B} = 0$ to reflect that the conditioned stimulus is not associated with pain before the conditioning procedure. In the placebo conditioning paradigm, the conditioned stimulus is repeatedly paired with a low intensity noxious stimulus. Similarly, in the nocebo conditioning paradigm the conditioned stimulus is paired with a high intensity noxious stimulus. Finally, the effect of conditioning is tested in both cases by pairing the conditioned stimulus with an intermediate level noxious stimulus. The expected pain is assessed as the value of $\hat{\bar{x}}$ immediately following the presentation of the conditioned stimulus, while the perceived pain is assessed as the maximum value of $\hat{x}$ in a time window following the noxious stimuli.

Figure 5 – Spontaneous neuropathic pain

Similar to Figure 3, we simulate different levels of sensory disruption by varying the value of R. A key difference here is that, here, we assess the resulting pain for different *initial values* of $\hat{A}$ at the time of nerve injury. However, due to the adaptive nature of the hierarchical Kalman filter, the value of $\hat{A}$ does not stay constant over time. This also means that we cannot run a baseline period before nerve injury, as in Figure 3, since this would alter the value of $\hat{A}$. Instead, we manually tune the uncertainty of the state and parameter estimations to approximately correspond to the values obtained from other baseline simulations, such that $P = P_{pA} = P_{pB} = 1$ at the time of nerve injury.

Figure 6 – Risk factors for developing neuropathic pain

The first period is simulated using baseline values as specified in Table 2, except for the values of A which are specified in the title of each subplot. In the leftmost and middle subplot actions $u = 6$ (indicated by green stars on the x-axis) result in noxious stimuli, in the rightmost subplot there are no such actions. This period is followed by a simulated nerve injury by increasing the value of R to 600^2.

Figure 7 - Offset analgesia

In experimental paradigms of offset analgesia, the subject typically receives noxious stimuli of varying intensity (temperature) without any associated action. Therefore, throughout all offset analgesia simulations $u = 0$. The level of tissue damage is assumed to be linearly proportionate to the applied temperature. At simulation onset the generative model parameters are set to match the real-world parameters, $\hat{A} = A$ and $\hat{B} = B$. The level of perceived pain is assessed as the median value of $\hat{x}$ in intervals $\{T1, T2, T3_1, T3_2, T3_3, T3_4\}$ as specified in Figure 8**Error! Reference source not found.**. The period immediately following ramp-up or ramp-down of temperature (indicated by Δ in Figure 8) is omitted to account for any delay in change of perceived pain relative to the change in temperature.

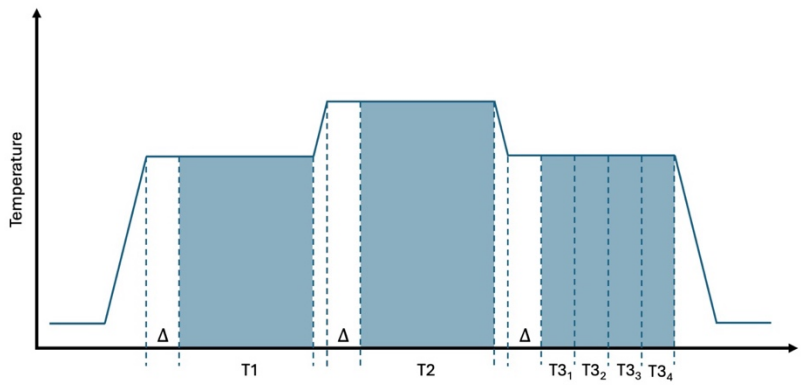

Figure 8 Pain is assessed in the intervals $\{T1, T2, T3_1, T3_2, T3_3, T3_4\}$ in the offset analgesia simulations. The first period following ramp-up or ramp-down of temperature, indicated by Δ in the figure, is omitted to account for any delay in change of perceived pain relative to the change in temperature.

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