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REVIEW

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Pain perception as hierarchical Bayesian inference: A test case for the theory of constructed emotion

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Abstract

An intriguing perspective about human emotion, the theory of constructed emotion considers emotions as generative models according to the Bayesian brain hypothesis. This theory brings fresh insight to existing findings, but its complexity renders it challenging to test experimentally. We argue that laboratory studies of pain could support the theory because although some may not consider pain to be a genuine emotion, the theory must at minimum be able to explain pain perception and its dysfunction in pathology. We review emerging evidence that bear on this question. We cover behavioral and neural laboratory findings, computational models, placebo hyperalgesia, and chronic pain. We conclude that there is substantial evidence for a predictive processing account of painful experience, paving the way for a better understanding of neuronal and computational mechanisms of other emotions.

KEYWORDS
Bayesian brain hypothesis, Bayesian inference, emotion, pain, predictive processing

INTRODUCTION

Students of emotion are aware that there is a longstanding debate on how the concept of *emotion* should be defined.[1,2] Textbook definitions of emotion typically refer to a brain state that integrates changes in phenomenology, peripheral physiology, and behavior; but instances that scientists classify as emotion can occur without one or several of these key components,[3] and the definition does not exclude phenomena that are typically not thought to involve emotion (e.g., effort). Currently, much of emotion science progresses vigorously without a consensus of a definition,[4] while debate between competing theories of emotion continues.[5]

A breakthrough in our understanding of emotion occurred when researchers began considering emotion from the lens of predictive processing, where instances of emotion are constructed from domain-general processes, rather than boxed as a special state associated with specialized neural circuits. In this review, we will briefly introduce the predictive processing framework and explain how it applies to emotion. We then argue that this perspective renders pain a useful laboratory model for the study of emotion and review the body of literature that conceives of the pain system, and its potential dysfunction, according to predictive processing and empirical tests of this claim. We conclude by discussing the similarities and differences of pain and emotions in the light of predictive processing.

AN INTRODUCTION TO THE PREDICTIVE PROCESSING FRAMEWORK

The idea that perception by living organisms results from a process of making inferences about the causes of sensations can be traced back to Helmholtz, some 150 years ago. This avant-garde intuition recently led to the formalization of perception and action as processes of hierarchical inference in the brain under the predictive processing framework.[6,7] The explanatory scope of the framework now ranges from learning, planning, and decision-making,[8,9] to interoception,

BOX 1. Glossary

Active Inference: In its initial, simplest formulation, this concept refers to the minimization of prediction errors by acting upon the environment so as to change sensory inputs and confirm an organism's beliefs or predictions (*changing the world*, i.e., action). More recent formulations articulate a process theory explaining diverse cognitive processes from perception to action.

Bayesian brain hypothesis: Initial formulation of how the brain can be thought of as a predictive organ trying to infer the most likely causes of the sensory signals it receives through approximated Bayesian inference.

Bayesian inference: A mathematical description of the optimal way to update one's belief (*prior*) about the world when receiving new information (*likelihood*, e.g., sensory observations), given a generative model of the world (and its associated *model evidence*). The inference is implemented using Bayes' rule to give rise to an updated belief about the world (*posterior*):

$$posterior = \frac{prior \times likelihood}{model\ evidence}$$

Free-energy principle: A normative principle proposing that self-organizing systems are able to temporarily shield themselves from the tendency to disorder prescribed by the second law of thermodynamics (entropy), because they minimize a quantity called *free energy*, an upper-bound on statistical surprise. A corollary of the free-energy principle describing how living organisms engage in free-energy minimization through two complementary inferential processes: perception and action.

Generative model: A statistical model hypothetically used by our brain to generate predictions about the world's hidden states that cause the observations it receives. It is specified by a probability over hidden states (the *prior*) before observing any data, and a *likelihood* function of observing some data given these hidden states. It can also be called an *internal* or *forward* model.

Hierarchical predictive coding: A process theory providing a biologically plausible algorithm for the implementation of approximated Bayesian inference, and, therefore, active inference, in the animal brain. It hypothesizes that brain microcircuits constitute hierarchical architectures that can perform efficient message passing and explain away sensory signals by minimizing (precision-weighted) prediction errors.

Placebo effects: The clinical benefits obtained from a medical intervention where the key active treatment (e.g., a drug or medical device) has been replaced by an inert one without any physiological effects.

Prediction error: The difference between what was predicted and what was actually observed by the brain. According to hierarchical predictive coding, this signal would be transmitted upward in the cortical hierarchy to serve as an updating signal for our generative models.

Predictive processing: An emerging theoretical framework in cognitive neuroscience that aims to explain perception, action, and everything mental. It makes use of conceptual tools from theoretical neurobiology, computational neuroscience, and machine learning, such as the Bayesian brain hypothesis, active inference, or hierarchical predictive coding, which have in common a commitment to Bayesian inference.

emotions, and the sense of self.[10–13] It can be difficult to fully grasp the reach and power of predictive processing to explain the working of our brain because it uses complex and diverse theoretical neuroscience concepts. Therefore, in the following paragraphs, we will offer a basic introduction to this framework (also, see Box 1 for a glossary of terms). We will first present the mathematical concept of Bayesian inference and the resulting Bayesian brain hypothesis, which can be seen as an embryonic version of predictive processing. We then introduce the free-energy principle and the process theory stemming from it: active inference. Together, they explain why and how living systems must engage in Bayesian inference for their survival. Finally, we depict hierarchical predictive coding, a potential algorithmic solution our brain uses to solve this inference problem.

Bayesian inference and the Bayesian brain hypothesis

According to predictive processing theories, our brain constantly strives to infer the world's (hidden) states that cause our sensations through an (internal) generative model of the environment and its interactions with our body. Bayesian inference describes the process by which pre-existing beliefs about the world, encoded by this generative model, are updated every time we gather novel sensory evidence. Pre-existing beliefs are represented in a probability density function called a *prior*, which in the Gaussian case can be completely described by its mean and variance. For example, our brain has a prior that light comes from above because it evolved through millions of years under the sun without artificial lighting.[14] Beliefs about how worldly causes generate observable consequences are represented by a probability density, called the *likelihood*, which expresses the probability of gathering the actual observation depending on the various possible worldly causes. The prior and likelihood densities are then combined according to Bayes' rule, computing an updated belief, called the *posterior*, about the world in the face of new evidence. To extend the example using the *light from above* prior, a darker patch on our path, combined with the knowledge of light coming from above, may result in the posterior that there is a cave in the hillside. This simple example is thought to

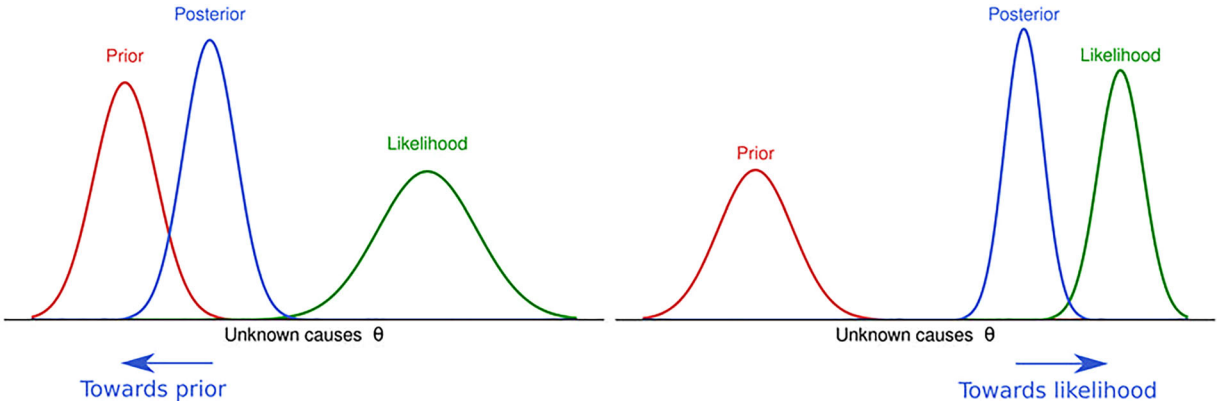

FIGURE 1 The precision of prior (red) and likelihood (green) distributions determines their respective weights during Bayesian inference according to Bayes' rule, and thus the shape of the posterior (blue).

be at the basis of many visual illusions. Predictive processing has also been applied to the acquisition of semantic knowledge and the use of language. Using the same example, a sign pointing hikers to look out for a nearby cave may create a prior that facilitates detection of the cave.[15]

Limited knowledge about the world is represented by a prior distribution with a large variance (low precision), corresponding to a low confidence about prior beliefs. Conversely, if prior knowledge is deemed reliable and trustworthy, this translates into a more precise prior distribution. Similarly, if observations from the world are considered noisy and unreliable, the likelihood distribution would be characterized by a flatter shape (large variance). The precision of prior and likelihood distributions determines their respective weights during Bayesian inference according to Bayes' rule, and thus the shape of the posterior. In other words, the posterior can be more, or less, informed by the prior or the likelihood, depending on their respective precisions (Figure 1).

Initial formulations of this idea, the Bayesian brain hypothesis, proposed that our brain performs approximated Bayesian inference and learning for a number of cerebral functions, from perception to cognition.[16] According to Knill and Pouget, the brain accounts for different sources of uncertainty by encoding information in the form of probability distributions. Based on computational simulations, they claimed that such encoding could be implemented at the level of neuronal populations, although unequivocal empirical proofs of neuronal probabilistic processing are still lacking.[17,18] At the cognitive level, multiple lines of evidence supported the hypothesis that human observers behave in a (near) Bayes-optimal manner; not in the sense that their behavior is perfect or ideal—we all intuitively know that this is not the case—but because it conforms to the integration of prior knowledge and current evidence while accounting for uncertainty.[16]

The free-energy principle and active inference

The free-energy principle, developed by Karl Friston and colleagues, describes the evolutionary advantage of minimizing free energy, an upper bound on statistical surprise.[19,20] Statistical surprise is a measure of the difference between the outcome that was encountered and the outcome predicted given a generative model of the world.[6] To resist entropy (disorder) and remain within physiological bounds, living organisms have to suppress the surprise of their sensory observations over time, and so avoid events that are surprising for their phenotype. For example, being out of water is surprising for a fish but not for a terrestrial animal. The free-energy principle is a normative principle, stating that any self-organizing system must minimize free energy, but not exactly how it does so. Friston and colleagues, therefore, appealed to active inference as a process theory of how this principle is realized in living organisms.

Active inference[21–23] proposes that perception and action are not just two inferential processes with distinct objectives. Instead, they work together for a common goal: to minimize discrepancies between the organism's generative model and the world, a goal that amounts to reducing surprise, or free energy.[23] Perception, or perceptual inference, involves updating a generative model so predictions fit observations, thereby reducing or explaining away the surprise signal coming from sensory states. But encountering a highly surprising event, such as when a fish finds itself out of water, is disastrous; just knowing which events are surprising is not enough to avoid danger. Active inference minimizes surprise by acting upon our body and/or the world to change sensory states and thus fulfill predictions of our generative model instead of updating them.[9,21] The fish jumps back into the water, and now its observations match those predicted by its evolved generative models. Both inferences that update internal models (changing your mind), and inferences giving rise to action that changes the eventual experience (changing the world) work in synergy to reduce free energy.

Imagine reading a book during a stormy night when suddenly the thunderstorm causes a power failure. The sensory signal you have predicted is light on the pages of the book. Rather than update this prediction and now predict darkness, you can achieve your goal by going down to the basement to switch the electricity back on. The darkness means that you cannot rely on precise visual information to move around, but you could use your memory of your house as a good, albeit not fully reliable, prior. You will likely pass into an exploratory mode, actively sampling tactile information while walking

in the dark to confirm or disconfirm the mental map of your house through active inference. Your internal model that predicted light on the page matches observations when you return to the armchair and resume reading.

Hierarchical predictive coding

The free-energy principle and active inference do not specify how free energy minimization is implemented in the brain. For this purpose, we need to appeal to a process theory providing a physiologically grounded and computationally plausible implementation of Bayesian inference. Friston and colleagues elaborated on the predictive coding algorithm from Rao and Ballard,[24] suggesting that descending predictions from higher cortical areas can be intuitively understood as arising from an *internal* generative model of the world.[19,25] For example, following haptic stimulation during your trip to the basement in the example above, primary somatosensory cortices would compare ascending sensory inputs from the thalamus to descending prediction from higher areas, such as secondary somatosensory cortices. Only the residual *prediction errors* are transmitted upward to the next level, where they serve as a new input and are compared to downward predictions from the area above. This efficient message-passing strategy, hierarchical predictive coding, would be repeated time and again along the full cortical hierarchy with various relays depending on the sensory modality. As described originally by Mumford, such reciprocal passing of information is plausible given the hierarchical organization of the cortex and its massive backward connections.[26] Cast in Bayesian terms, prediction errors from level $n-1$ (or sensory inputs at sensory cortices) can be seen as the likelihood of an observation, predictions from level $n+1$ are *empirical* priors over hidden causes of this observation, and their combination as a prediction error would be the *posterior* at level n, becoming the next *likelihood* for the level $n+1$. Within sensory cortices, minimizing prediction errors along the cortical hierarchy amounts to updating generative models through perceptual inference. Under simplifying assumptions, free energy can be seen as the long-term average of prediction errors. This is how perception and eventual perceptual learning takes place.

Simple actions, such as peripheral reflexes, can be seen as instances of hierarchical predictive coding in the motor system, equipped with reflex arcs. In this framework, descending projections from cortical motor areas to spinal cord motor neurons are no longer seen as simple motor commands issued by a central control system, but as proprioceptive predictions about states (position, orientation, forces applied, etc.) of a specific limb.[22,27] The realization of movements would then be guided by the minimization of proprioceptive prediction errors between these predictions and the actual states of our limbs and muscles. Extending your arm to reach the light switch actively minimizes the discrepancy between your current sensations (hand moving) and the expected ones (hand on switch).

Naturally, complex actions also involve long-term goals. Which process is implemented to minimize surprise—a change to the internal generative model (perceptual inference) or action to change the external reality and, therefore, the ensuing experience (active inference)—depends on the precision of the respective predictions about the sensory consequences of action on the one hand and about sensory prediction errors arising from perceptual inference on the other hand.[28]

CAN WE UNDERSTAND EMOTION AS A PREDICTIVE PROCESS?

Emotions as Bayesian inferences

In the same way that brains are thought to build internal models for perceptual objects and for semantic concepts, they may also build models of emotion concepts. Barrett has spearheaded thinking about emotion from the lens of Bayesian inference. We will now describe how predictive processing can apply to human emotion by summarizing and clarifying what we believe are the central tenets of Barrett's theory of constructed emotion. According to this theory, emotion models, like other generative models, are activated in a process akin to pattern completion through their match with exteroception or interoception.[29] To see how this would work, imagine that while feeling your way down to your basement in the dark you hear a loud noise. You may start to wonder whether it was just a thunderbolt or someone breaking in, progressively recruiting a generative model (the *physically intimidated* model) that best infers your current sensory state.

Perhaps more often than other concepts, emotion concepts generate predictions not only about future external sensations, but also about imminent bodily movements that are necessary to handle the emotion-provoking situation. Activating the *physically intimidated* model may instigate several physiological and motor predictions preparing your body to freeze, flee, or fight. According to the free energy principle, we can understand these reactions by considering that the overarching prediction of body integrity caused you to act in order to decrease future prediction errors associated with a dangerous encounter. At the highest level, the desired, and, therefore, predicted, sensory state is of intact body integrity where you are safe from an aggressor. At lower levels, this prediction cascades to predictions about limb movement. At a lower level still, the predicted impact of these movements to allostasis generates predictions about changes to physiological states, for example, increased heart rate and blood pressure. These predictions may be consciously felt as affect and give emotions their intensity.[29] Active inference may also operate at a cognitive level where the activated emotion model constrains the schemas we may entertain to aid us in interpreting the ongoing event.[30] Being in this scenario, the physically intimidated may favor activation of schemas such as *I am in danger* and *I must seek help*, or the less adaptive, *I am completely helpless*, which evoke further active inference processes. New sensory evidence, such as a faint movement in the dark or the return of power, may reinforce or dismiss the model and its predictions, and internal generative models are updated to generate more accurate predictions in the future. Figure 2 (top) illustrates the essence of this idea.

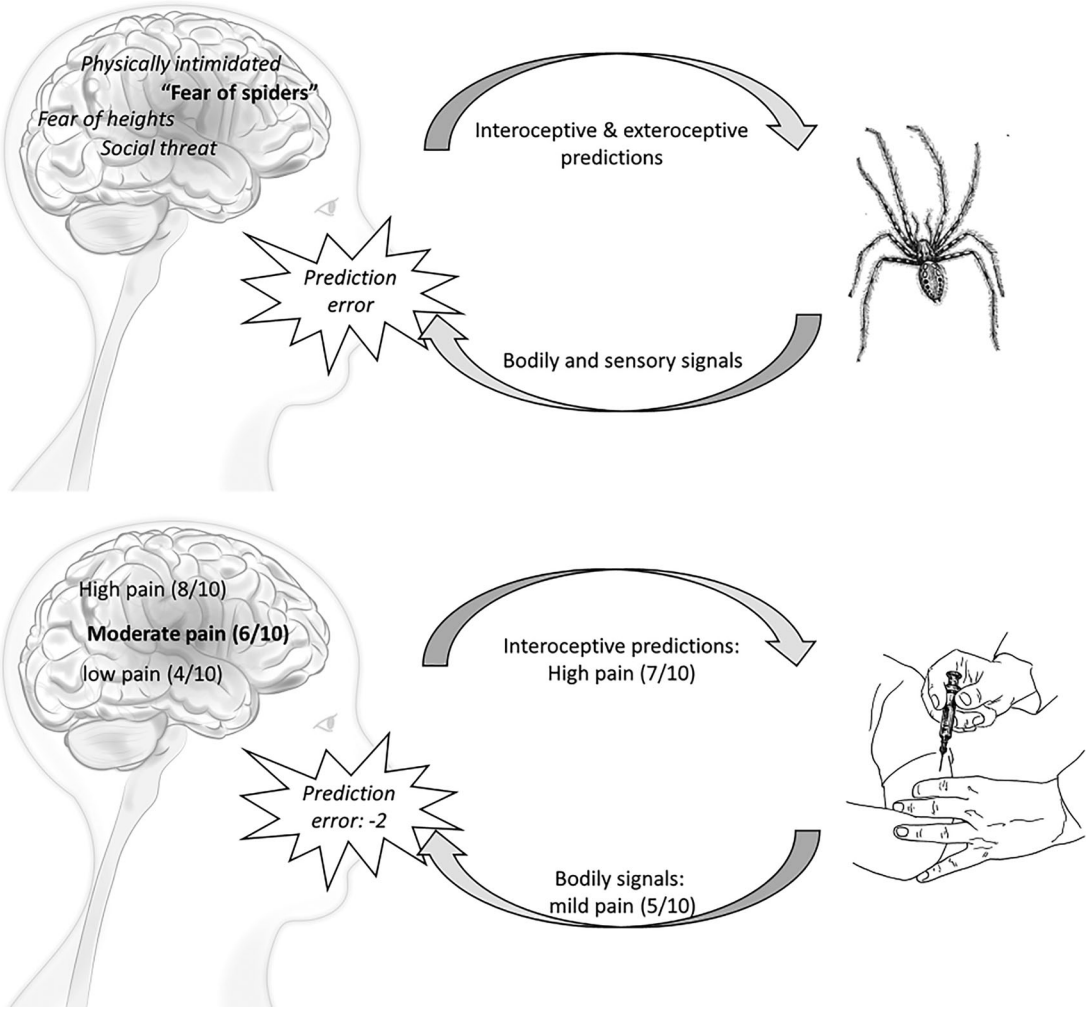

FIGURE 2 *Top*: The sensory signals associated with a surprising encounter with a house spider proves a good match with the generative model "fear of spiders." It matches other generative models (fear of heights, social threat) less well. *Bottom*: A person predicts to suffer high pain from an injection (e.g., at a level they rate "7" on a 0–10 scale, where 0 is no pain and 10 is the worst possible pain). The signal projecting to the brain corresponds to a peripheral stimulation corresponding to "5." The signal is 2 units lower than predicted, resulting in a negative prediction error. The internal model the person now holds about injection pain is updated to "6."

We propose a corrective to the view that the theory of constructed emotion involves "the classification of the experienced appraisal-arousal pattern as an instance of an emotion category."[31] Instead, we believe that according to the theory, either exteroceptive or interoceptive information alone suffices to activate an emotion model such as the *physically intimidated* model. As a function of one's personal past history, the activated model gives rise to specific predictions, which span the somatic, visceral, and cognitive, and which may or may not involve one of the many elements encompassed by the term *arousal*.[32] Barrett emphasizes that internal models such as *physically intimidated*, *social threat*, *fear of heights*, or *fear of spiders* are all different, in the sense that they are matched by different sensory states and generate different predictions, and that one's *physically intimidated* model may be different from another's. Nevertheless, shared cultural understanding means that all may be eventually categorized as instances of the concept *fear*.

Empirical support for the theory of constructed emotion

It is challenging to test predictive processing models,[33] and even more challenging to test these models as they apply to emotion. In this section, we cover some of the key evidence that has been brought up to support the theory. First, in the theory of constructed emotion, internal models of emotions are constructed and updated in the same way as other generative models, such as the model of the direction of light, the possible location of a cave, or the layout of your house. For this reason, the theory is supported by evidence utilizing advanced multivariate techniques to show that emotional stimuli can activate many domain-general brain regions outside those traditionally thought to be dedicated to emotion[34] and that emotions activate distributed patterns across the brain.[35,36] Even emotions consisting of varieties of fear activate a largely nonoverlapping set of brain regions when induced

by videos that evoked either fear of heights, of spiders, or social threats.[37]

The theory is also supported by evidence that no single brain region expresses particular emotions selectively, a finding that aligns better with this theory than its competitors. This conclusion from a meta-analysis of neuroimaging data[38] is corroborated by neuropsychological data where, strikingly, patients with amygdala lesions, even those who have abnormal fear responses,[39] reported feeling fear when deprived of oxygen and exhibited commensurate psychophysiological changes.[40] These results agree with earlier findings that brain lesions that included the amygdala impaired fear learning but not the increased skin conductance response to loud noises,[41] and evidence from animals and human electrophysiology that fear does not reside in the amygdala.[42] Yet, there is some debate on how to interpret the distributed patterns of activations that researchers have found to be associated with emotion manipulations. Barrett and Satpute[3] claim that there is no brain region or pattern that is consistently and specifically activated for each emotion category. While they believe that each study samples particular instances of emotion that have no shared essence, others suggest that some aspects of the distributed pattern may nevertheless be invariant.[43]

The theory of constructed emotion anticipates a lot of variability in how emotion is represented in the brain because it posits that most generative models are acquired through diverse life experiences. Therefore, the theory provides a natural explanation to findings that emotion recognition varies across populations[44] and can be highly context-dependent,[45] but explains less well the high accuracy[46] and cross-cultural similarity[47] in labeling facial expressions of emotion even when under free choice conditions.[48]

Finally, because generative models for emotion resemble other concepts, the theory is also supported by findings that semantic manipulations[49] or brain abnormalities that impair semantic function, such as semantic dementia,[50] alter emotion recognition. Although promising, the interpretation of impaired emotion recognition in semantic dementia is challenged by recent evidence that semantic dementia, a disease primarily associated with damage to the ventral temporal lobe, may also be associated with damage to subcortical regions including the amygdala.[51] Additionally, these experiments targeted semantic knowledge of emotion, not the emotional experience per se.[52] This distinction is important because conceptual knowledge of emotion, evident in the intact ability to generate facial expression of emotions, has been dissociated from the ability to recognize the same expressions.[53]

How we can use pain to study emotion

Despite its appeal, the theoretical claims associated with the application of predictive processing models to emotion are not as specific, and do not lend themselves as easily to empirical tests compared to Bayesian approaches in vision and auditory neuroscience. Vision experimenters can vary the mean and variance of a luminance stimulus and measure reported brightness rather uncontroversially. By contrast, in emotion experiments, an intuitive evaluation by the experimenter or by participants that a particular stimulus is scary or neutral is an inevitable aspect of stimulus validation.[54] Huge inter- and intra-subject variability add to this challenge. Because hearing a creepy noise during a thunderstorm can evoke anything from laughter, to surprise, to fear, depending on individual sensibility and context,[3] it is impossible to ascertain in advance how an individual would respond even when the stimulus set is validated at the group level; in other words, there is no correct emotional response. Individual differences may be smaller when the situation is extreme, but there are obvious ethical dilemmas and practical challenges for triggering intense emotions in the lab. Moreover, the quick habituation of some emotional responses, and the variable speed with which different measures of the emotional response habituate, makes these problems even more difficult to solve.[55,167] Compounding the elicitation problems is the measurement problem: emotion researchers also lack any one-to-one mapping between the evoked emotion and any measurable quantity.[56] None of these challenges are unique to the theory of constructed emotion, but together with the complexity of the theoretical claims, the evidence base that supports the theory of constructed emotion is, for the most part, indirect.

More fundamentally, it is possible that predictive processing theories may not apply to emotion because although there is agreement that emotion, unlike a mood, is about a stimulus, it lacks the perceptual object that characterizes vision and audition.[57] Predictive processing models have successfully accounted for findings in vision and audition, where perception corresponds roughly to a distal pattern of light or sound waves, relayed through a dedicated neurophysiological system in the periphery to the central nervous system. But even within the domain of perception research, their ability to account for other senses has been critiqued. Research on olfaction explains that their critique is due to the fact that "stimulus representation isn't the primary business of olfaction. Rather, its job is solving a problem of valuation, rapidly encoding the biological salience of a stimulus and priming our multisensory representation of it to contextually appropriate action."[58] Clearly, the same argument may be made about the application of predictive processing models of visual and auditory perception to emotion, where the distance between the distal and proximal stimulus is even greater, and which is fundamentally evaluative and goal-directed.[59]

Pain provides an interesting case to illuminate the theoretical debate about the usefulness of Bayesian approaches to human emotion because of its intermediate status between a sensation and a subjective feeling. Traditionally, emotion researchers have considered pain to be a sensation, like hunger, a view which was based on the hypothesis that pain can be mapped directly to nociception. It has also been conceptualized as a *homeostatic* emotion[60] rather than a genuine emotion,[61,62] but the growing realization that pain has important affective and evaluative dimensions[63] has inspired a more nuanced consideration.[64] The International Association for the Study of Pain (IASP) defines nociception as the "activity that occurs in the nervous system in response to a noxious stimulus,"[65] namely, a stimulus that causes objective tissue damage. Nociception is thus the theoretical equivalent of the dedicated systems involved in responding to light and sound waves. By contrast, the IASP defines pain as: "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or

potential tissue damage."[65] This definition builds on the now-accepted distinction between pain and nociception.[66] Like emotion, the IASP definition considers pain to have a (negative) valence, as well as to be *about* something—real or imagined tissue damage, typically in a specific part of the body. The observation that like emotion, pain is associated with diverse neural responses in regions that are not specific to pain, and that are highly variable even within individuals,[67] aligns with its emotion-like status. The IASP also emphasizes that, like emotions in Barret's theory, people learn about pain throughout their life.

Pain shares many of the core characteristics of emotion charted by Anderson and Adolphs.[68] The first characteristic is that we can relate emotions to each other. The IASP definition of pain includes its negative valence, which some attribute to appraisal that avoidance mechanisms have failed to protect body integrity.[66] From a perspective where each emotion has a valence and arousal value, pain clearly belongs in the negatively valenced, arousing quadrant,[69] and, therefore, is more similar to emotions such as disappointment and fear than to happiness and satisfaction. Emotions are often thought to serve as common currency in the service of goal pursuit.[70] From an evolutionary perspective, the unpleasantness of pain is an important motivational signal, inherent to the defensive systems that direct organisms away from a stimulus to maintain the ultimate goal—the maintenance of body integrity.[71] Indeed, as discussed in greater depth below, pain is easily conceived as one among other negative emotions that could act as learning and control signals, exerting a speedy, potent control over our behavior, a core characteristic of emotion in Anderson and Adolph's chart.[68] It is possible, of course, for pain itself to evoke other emotions; for example, dental procedure pain is associated with anxiety.[72]

All in all, in the absence of a consensus definition of emotion, it is not possible to determine whether pain falls short. Whether pain is eventually deemed a genuine emotion or not, we argue that if predictive processing has hopes of accounting for emotion, it must account for pain as well. Figure 2 (bottom), therefore, depicts some possible generative models of pain in response to an imminent injection. Those operate like other generative models of emotion, such as fear of spiders. At a practical level, pain is a useful laboratory model for the study of emotion because noxious stimulation provides a ground truth against which to calibrate our dependent measures. Therefore, by testing the predictive processing account of pain, we may provide indirect evidence for, or against, the predictive processing account of emotion. By using Bayesian inference about pain as a useful analogy to study more complex processes, we follow the approach that was formerly productively employed to study the interpersonal self.[13]

THEORY AND EVIDENCE FOR A PREDICTIVE PROCESSING ACCOUNT OF PAIN

Recent theoretical accounts

A Bayesian brain hypothesis of pain perception as it applies to the placebo effect may have been first discussed by El-Deredy, Jones, and colleagues[13,73] and has become a dominant viewpoint,[74] extended to nocebo effects[75] and pain perception in general.[76] Those converging accounts agree that the brain must maintain models of predicted pain, constructed through previous experiences and reflecting current beliefs. Predictions that arise from these generative models are compared to nociceptive inputs to emit a prediction error signal that, in perceptual inference, lead to model updating. Nociceptive signals sent by afferent nociceptors through numerous ascending pain pathways constitute the likelihood. Priors, reflecting predictions about imminent pain, such as its intensity, location, and quality, are issued at higher levels of the descending pain system, and are combined with the likelihood at different levels of the pain processing hierarchy. The perceptual inference mechanism applies to pain just as it is applied to other sensory modalities (visual, auditory), where Bayesian inference over prior and likelihood, modulated by their respective precision, gives rise to a posterior, which corresponds to the actual pain perception (Figure 1). At the neural level, Büchel et al.[74] proposed that predictive processing mechanisms are implemented in pain-related brain regions, as was done with visual[77,78] and auditory systems.[17,79] In accordance with the hypothesized hierarchical implementation of predictive coding in the brain, they suggested to reformulate the dichotomy between independent pain ascending and descending pathways into a single hierarchical system constituted of connected recurrent networks along the pain processing hierarchy. Embracing the predictive processing account of pain does not entail ignoring the differences between pain and other sensory modalities, such as the absence of a unique pain cortex. Rather, pain reports reflect intricate interactions across the entire processing hierarchy, from representation of ascending signals to high-level psychological constructs,[80] and which extends outside the brain, involving multiple bodily systems.[81]

Perceptual inference about pain—changing how noxious one predicts a stimulus would be—is well explained by the predictive processing framework. Yet, pain is not just an inference; it constitutes a danger signal telling us that we are, or will soon be, out of our physiological bounds (be it in terms of temperature, mechanical constraints, or chemistry), and that action is urgently needed. A particularly comprehensive account of perceptual and active inference in pain was offered by Kiverstein and colleagues.[82] They suggest that bodily responses to pain and their accompanying phenomenology can be explained as an integrative process of prediction error minimization by autonomic, endocrine, and immune systems to maintain homeostasis. In their view, inflammatory responses to an injury, endocrine stress response to mobilize metabolic resources, and autonomic activation preparing the body for fight, flight, or freezing, are all allostatic processes orchestrated by a neural–endocrine–immune ensemble in order to decrease the surprise caused by actual or anticipated threats to body integrity. As described earlier, surprise can be resolved through perceptual inference by changing the predictions of the neural–endocrine–immune ensemble (relaxing after the threat has passed) or through active inference by engaging in pain-modulating actions. Their strongest claim is that our experience of pain is constituted by the continuous reciprocal interaction of the whole neural–body axis, therefore, integrating neural and bodily processes and avoiding the distinction between sensory–discriminative, affective–motivational, and cognitive–evaluative dimensions of pain.

This framework is useful in evaluating the possible mechanisms associated with placebo effects. Placebo effects can be large, sometimes approaching the effect size of real treatments;[83] can mask the beneficial effect of new drugs, thus posing a challenge for the evaluation of novel pharmacological therapies;[84] and can prevail even when participants are informed they are getting a placebo.[85] Placebo effects in treatments for pain are referred to as placebo hypoalgesia.[86] A related effect is the nocebo effect hyperalgesia, where predicting strong pain leads to increased pain (e.g., in response to inert treatment).[87] The active ingredient in placebo effects is a psychosocial one, namely, the participant's predictions. The generative model involved in responding to an inactive drug that is described by the physician as a painkiller is constructed based on past experiences with pain, painkillers, and the medical context.[88] Using the terminology introduced earlier, predicting lower pain due to placebo treatments constitutes a prior on pain. The precision of predictions about future pain may be combined with the noisy processing of nociceptive inputs to bring about hypoalgesia. From the perspective of perceptual inference, stronger placebo effects would be observed when predictions about pain, and the treatment, are not only positive, but also very precise, and when the nociceptive inputs are predicted to be noisy.

One question that this view leaves open is why the prediction errors associated with nociception do not update internal models sufficiently to overcome placebo effects. Büchel and colleagues suggest that the reason is highly precise priors for pain reduction that are only minimally updated.[74] Emerging evidence suggests that a confirmation bias mechanism may also play a role.[89] However, when tissue damage is sufficiently intense, a large prediction error should lead to model updating[71] or to the adoption of a different model that better matches incoming signals.[74] Alternatively, persistent placebo effects could be due to active inference. At the neural level, prediction of low pain or pain relief is mediated by at least one specific neurophysiological pathway: the activation of the opioidergic descending pain control system.[90,91] This pathway inhibits the processing of nociceptive inputs at the lower levels of the nervous system, thereby decreasing the activation of pain-specific brain regions and experienced pain. Evidence that placebo effects are associated with decreased response to nociceptive stimulus at the level of the spinal cord[92] aligns well with an active inference account of the placebo effect. Further research is needed to understand which mechanism best explains placebo effects in specific contexts and how the brain arbitrates between perceptual and active inference.

Pain also serves as a teaching signal to predict and avoid harmful events or situations in the future. The reinforcement learning framework describes how pain signals control behavior from innate pain avoidance responses (reflexes), through conditioned responses to pain-accompanying stimuli (cues) learned through Pavlovian learning, and up to more complex action selection and planning developed by instrumental and cognitive learning systems.[93] Recently, there have been attempts to reconcile predictive processing and reinforcement learning views of pain as distinct computational processes interacting within the brain's hierarchical architecture.[94,95] Active inference offers an alternative account of innate, habitual, and goal-directed behavioral actions,[96] which may address limitations of traditional associative learning theories.[97] Within this framework, adaptive behavior requires the minimization of both interoceptive (homeostatic levels) and exteroceptive (sensory goal) prediction errors.

Behavioral and neural imaging evidence

The modulation of pain by positive or negative predictions (hypoalgesia and hyperalgesia) in clinical settings is a well-known phenomenon.[88] Yet, such predictions are most often about the applied treatment, which have an extended temporal span and can involve numerous cognitive, social, and motivational factors that are difficult to disentangle. To gain more understanding on the cognitive and neuronal mechanisms supporting the effects of predictions on pain perception, researchers have used experimental paradigms designed to set cue-based stimulus predictions. Empirical data can test the predictive processing account of pain. The most basic hypothesis can be traced back to Descartes who considered pain to be a direct transduction of nociceptive stimulations alone. A second hypothesis integrates nociception with prior predictions. To an extent, this hypothesis also characterizes reinforcement learning theories, which broadly postulate that the difference between observed and predicted intensity of pain updates its predicted intensity. The third hypothesis, Bayesian inference, arbitrates the balance between the impact of sensory and prior predictions by their respective precision through Baye's rule. Finally, we depict hierarchical predictive coding, a potential algorithmic solution our brain uses to solve this inference problem.[98]

Behaviorally, many studies have shown that cues that inform participants that they will get high pain increase self-reported pain intensity in response to experimental pain stimuli, and that likewise, cues that inform participants that the stimulation will be low decrease reported pain.[99] Findings that predictions modulate neural correlates in the same direction suggest that these effects may not be fully explained through demand characteristics. Ploghaus et al.[100] offered a first review of the neuroscience correlates of the effect of pain predictions. They suggested that even predictions that vary on a trial-to-trial basis can have a strong influence on participants' ratings of pain, as well as, crucially, on brain activation. They identified the rostral anterior cingulate cortex (rACC) and the insula, as well as the posterior cerebellum, to be activated by precise predictions about impending painful stimuli, regardless of whether a lower or higher pain was predicted. A later review[99] confirmed these results but also emphasized the role of the thalamus in setting these predictions, and that of frontal regions associated with emotional appraisal, such as the dorsolateral prefrontal cortex (dlPFC) and orbitofrontal cortex, which could mediate the anticipatory response to cues. The anterior cingulate cortex (ACC) and insula are not only considered core brain regions of the hypothesized second-order attentional–perceptive matrix of pain,[80] but also respond to emotional salience, emotional arousal, and motivational intensity.[101–103]

Geuter and colleagues[104] tested the hypothesis that the rACC and anterior insula are involved in Bayesian inference by submitting

participants to warm or hot thermal stimuli following cues of varying validity, leading to a combination of stimulus type (warm or hot), expectations (more likely warm, more likely hot, or both equally likely), and prediction errors. They found that skin conductance and pupil size were better explained by a Bayesian inference model, which modeled response as the sum of differently weighted predictions and prediction errors compared to models that roughly correspond to the first two hypotheses described above: a stimulus-only model and a stimulus-plus-expectation model. The activation of the anterior insula and the right amygdala recorded with functional magnetic resonance imaging (fMRI) were also best explained by the Bayesian inference model, whereas the activity in the ACC and the posterior insula was best explained by a stimulus-only model.[104] The involvement of the posterior insula in stimulus encoding was hypothesized as it has been associated with the first-order nociceptive matrix of pain,[80] yet surprisingly, and contrary to previous results,[99,100] the ACC did not reflect expectations in this particular study. Fazeli and Büchel[105] replicated and further expanded these results. They showed again an involvement of the anterior insula in coding stimulus intensity and expectation. By cleverly inducing expectations for an aversive outcome by cues that predicted either pain or aversive pictures, they showed that the activation in the anterior insula could not be explained by the prediction of aversiveness per se. Interestingly, they further characterized the ventral part of the anterior insula as specifically coding prediction errors, but further work that replicated this result suggested that this was possibly due to a correlation between pain prediction errors and another computational quantity, and that pain prediction errors are only represented in the periaqueductal gray (PAG).[106] Another study interestingly demonstrated that not only did pain expectations bias ratings in the hypothesized direction, but that reciprocally, pain experience also influenced participants' forthcoming expectations.[89] In particular, the effect of expectations on pain ratings was mediated by the activation of the neurological pain signature (NPS), a pattern of fMRI activity highly sensitive and specific to physical pain that includes the thalamus, the posterior and anterior insulae, the secondary somatosensory cortex, the ACC, the PAG, and other regions.[107] We should bear in mind that some of the above findings are due to the way that pain expectations were operationalized. Koban and colleagues[108] have recently shown that expectations induced by either predictive cues or by nonpredictive social information both influenced pain reports—an effect mediated by regions of the frontoparietal network for both types of expectations. Nevertheless, the effects of expectations on pain were mediated largely by nonoverlapping regions: frontoparietal and the dorsal attention regions mediated social effects, and the hippocampus and occipital regions mediated the effects of cues.

We described how the behavioral and neural correlates associated with pain predictions seem to agree with a predictive processing view of pain. We now discuss the importance of the precision of predictions by reviewing studies on placebo conditioning. Colloca and colleagues[109,110] found that placebo-induced analgesia was stronger and lasted longer when the effectiveness of the placebo treatment was demonstrated to the participants instead of giving them only verbal suggestions.[110] Similarly, participants who received four conditioning trials showed stronger, longer-lasting placebo-induced hypoalgesia and nocebo-induced hyperalgesia effects than participants who only received one.[109] Colloca et al. concluded that the placebo and nocebo effects rely on establishing reliable contingencies between sensory predictions and stimuli, in agreement with Bayesian inference accounts. Büchel's team empirically tested this hypothesis in a recent study by artificially conditioning participants to experience lower heat pain during a transcutaneous electrical nerve stimulation (TENS) condition.[111] Unbeknown to the participants, TENS was not actually applied, but stimulus intensity was reduced surreptitiously during the TENS-on trials of the conditioning phase to mimic the placebo effect. The precision of predictions about the placebo treatment was manipulated by reducing stimulus intensity during TENS-on trials through two different regimes: by either a constant 30% of pain tolerance (high-precision treatment), or to a varying intensity around 30% (low-precision treatment). The subsequent test phase presented participants with the same medium-level stimulation. TENS-on trials were contrasted to control TENS-off. Although they received the same noxious stimulation, participants rated the pain as less painful during the TENS-on, as per the classical placebo effect. Interestingly, this effect was stronger in the participants in the high-precision condition, supporting the Bayesian inference account.

The placebo conditioning results reviewed above show that the learning and subsequent long-lasting effect of predictions depend on their associated precision or inverse uncertainty. However, most of these experiments did not vary uncertainty about the incoming pain itself. Ploghaus et al. argued that uncertainty about the exact intensity of unavoidable painful stimulation would cause hyperalgesia through anxiety-related mechanisms mediated by the ventro-medial prefrontal cortex and the mid-cingulate cortex.[100] Additionally, they argued that certainty of imminent pain intensity would activate the fear response system, leading to a decrease in pain sensitivity.[112] As emphasized in a recent review,[113] this prediction does not align with the predictive processing account of pain perception. According to the Bayesian inference account, uncertain expectations would have a weaker impact on the posterior rather than exert a directional effect.[113] Empirical work controlling for the mean value of cue-based predictions while changing their variance (inverse precision) initially supported Ploghaus' claim, showing higher pain ratings under high uncertainty conditions irrespective of the direction of the induced predictions.[114] But a replication using a larger sample of participants found that when the certainty of predictions was high, pain ratings were biased toward the expected average,[115] as suggested by other results[116,117] and in agreement with the predictive processing understanding of pain. Yet, as they emphasized that while short-term, cue-based uncertainty may not have an effect in experimental settings, it may aggravate chronic pain conditions.[113] We return to this issue below.

Another source of evidence that uncertainty matters to pain experience in accordance with the Bayesian framework is work on the variability of pain reports.[118] Interestingly, pain variability across time is not random, but follows a fractal pattern.[119] A randomized placebo-controlled trial found that individual variability in clinical pain diaries

and in pain reports to un-cued experimental pain was associated with increased susceptibility to placebo effects,[120] in accordance with Büchel's suggestion that imprecise likelihood density will increase placebo susceptibility. Grahl and colleagues observed just this pattern of results in a laboratory study of placebo effects using acute pain.[111] However, the finding that variability in pain reports across time is not random, but follows a fractal pattern, does not seem to align well with a Bayesian account.

We saw in this section how data pertaining to pain predictions and their precision lend support to the predictive processing account of pain. Another way to test predictions from this newly emerging framework of pain perception is to use computational models implementing the hypothesized Bayesian inference processes. Computational modeling permits simultaneous predictions of what individuals predict and how certain their predictions are, while considering trial- and subject-wise variations. Thus, they offer a more comprehensive approach than classical analyses of trial- and subject-averaged ratings.

Insights from computational modeling studies

There is considerable evidence for the superiority of computational models inspired by predictive processing to explain pain perception in humans. A first article by Anchisi and Zanon showed that a Bayesian decision model could explain their behavioral placebo effects as the integration of nociceptive stimulation and cue-based predictions.[121] We described earlier how Grahl et al. ingenuously modulated the precision of a placebo induction; they also fitted a Bayesian model to their behavioral data that replicated the findings of Anchisi and Zanon and also incorporated the crucial role of the precision of treatment predictions.[111] Hoskin et al. developed the idea further by adding session-wide, cue-independent predictions about pain and their precision to a Bayesian model of pain intensity ratings.[122] The advantage of that model was that it allowed participants to vary not only in how they integrate cue and sensory information, but also in their pre-experimental, trait-like bias toward pain, which increased the translational potential of the modeling approach. Bayesian modeling of pain processes was not limited to behavioral responses from participants but also applied to physiological responses, such as pupil size[123] and skin conductance.[123,124] It was also employed to explain fMRI brain activation[105,111,123] and electroencephalogram (EEG) oscillations in humans,[124,125] as well as electrophysiological recordings in freely moving animals.[126]

One drawback of the preceding studies is that they never directly compared Bayesian models of pain to reinforcement learning ones. Jepma et al.[89] did so by building two models integrating the same theoretical principles (perceptual inference, learning, and a novel confirmation-bias mechanism), which differed only in their algorithmic implementation: the Bayesian model relied on dynamical changes in the precisions of sensory inputs and predictions for inference and learning, whereas the reinforcement learning model makes use of fixed parameters. Formal comparisons of simpler instances of both models provided converging evidence for the effect of predictions on pain modulation and a confirmation bias in learning, while direct model comparison revealed that the reinforcement learning model was superior. More recently, Mancini et al. showed that a Bayesian model that inferred frequencies and volatility of pain states provided the best fit to participants' predictions about pain intensity, compared to a more classic Rescola–Wagner reinforcement learning model, during a statistical learning paradigm.[127] Using concurrent fMRI recording, they observed that the signal representing pain predictions was localized in known sensory pain-processing regions, whereas model update was encoded in a fronto-parietal network, and uncertainty of pain inference in the superior parietal cortex. In a follow-up study of temporal statistical learning, they observed that participants' predictions about the forthcoming stimulation, as well as their confidence in this estimation, were again best modeled by a precision-weighted Bayesian inference model.[128]

Although most of the modeling studies reviewed so far could well explain participants' subjective ratings of pain, some important limitations have to be acknowledged. First, it is not presently known exactly what model parameters represent. For example, in Hoskin et al.'s (2019) model, the estimated precision assigned to cue information in particular individuals could refer to a temporary state that informs how they represent pain cues; a trait of that individual that is stable across time; or perhaps a trait of that individual that exceeds the pain domain and describes the precision with which they represent cue information across modalities. Moreover, existing work does not examine the predictive validity of model parameters, namely, whether they are able to predict performance in tasks other than those they were designed to model. Lastly, the majority of studies to date have only simulated pain intensity judgments, ignoring more affective dimensions (e.g., judgments of pain unpleasantness) and its multidimensional phenomenology, which may actually play the biggest role in pathological conditions.[168] Three of our recent studies tried to overcome these issues.

Delgado-Sanchez et al. obtained evidence for test-retest reliability of the model parameters in an updated version of the three-tiered Bayesian model of Hoskin et al. Their results point out that the respective effects of sensory stimulation, cue-based predictions, and prior bias on pain processing are stable over time in healthy participants, encouraging individualized treatments of chronic pain conditions.[129] Additionally, in an unpublished study, Singh and colleagues[130] found that the parameter that corresponds to the precision of the likelihood function estimated in a task where electric pain stimulation was used was correlated with the same parameter in a separate session that used thermal pain stimulation. In that study, they also observed that this parameter correlated with a measure of variability in response to un-cued pain that was extracted from an independent task, the focused analgesia test.[131]

Poublan-Couzardot et al.[132] examined the applicability of Bayesian models not only to the sensory dimension of pain, but also to the affective one. Using a similar pain-cueing paradigm as Hoskin and colleagues on healthy participants with previous meditation experience, they replicated and extended previous findings to simultaneously explain both intensity and unpleasantness pain ratings. They also observed

interesting correlations between the model's parameters encoding prior biases toward pain and psychological constructs of pain catastrophizing and cognitive defusion gathered through questionnaires. Finally, participants' lifetime meditation experience was strongly associated with lower precision of cue-based predictions, as well as lower prior bias toward the affective pain dimension. This last finding provides further insights on the mechanisms of meditation-based pain regulation.

Although this collection of evidence is only preliminary, it supports the hypothesis that some Bayesian model parameters could represent stable individual traits about pain perception and offer a diagnostic value. Taken together, findings from computational modeling studies of pain suggest that predictive processing could be an appropriate theoretical framework to probe the behavioral, physiological, and neural responses to pain. What still needs to be investigated is whether it could also provide a meaningful model for abnormal pain processing conditions such as chronic pain.

A predictive processing model for chronic pain?

Chronic pain is the transformation of an initial acute pain event or disease into a painful experience persisting after the commonly observed healing phase.[133] Differently from normal acute pain, chronic pain does not seem to have adaptive value.[134] The physiological and brain mechanisms causing and maintaining pain chronicity are still poorly understood and very few effective treatments exist, despite chronic pain being one of the primary causes of long-term disability worldwide.[135] A fruitful line of research came with the advanced study of structural, functional, and connectivity changes in the human brain through fMRI. Chronic pain conditions have been associated with critical changes in core nodes of regions associated with pain processing and modulation, with a notable structural decrease in gray and white matter of the dlPFC, ACC, and insula as well as reduced opioid receptor binding and increased neuroinflammation in these regions.[133,136] Whether these structural and functional alterations of key regions of the endogenous pain-modulatory system are a cause or a consequence of chronic abnormal nociceptive transmission is subject to debate.[137] A recent review further formulated these abnormalities as a more global widespread disruption of the brain networks involved in pain processing, modulation, and learning, with variations depending on the specific pain condition.[138] Interestingly, Barroso et al. build their claim on translational evidence from humans and rodent models, where alteration of brain regions involved in reward and motivation as well as memory and learning have been observed. This hypothesis provides interesting tools to understand the impairments of chronic pain patients in the cognitive and affective modulation, not only of pain, but of emotions in general. As a note of hope, the brain alterations we just described do not seem to be permanent,[139] and noninvasive stimulation of the dlPFC has been shown to reduce acute and chronic pain[140]—rendering this brain region an interesting therapeutic target.

Bayesian accounts of this leading health problem have also been proposed and have emphasized two complementary processes. The first process concerns abnormally high precision of pain predictions, which is wrongly generalized to nonthreatening situations.[141,142] The formation of heightened pain predictions is thought to be caused by associative fear learning[143] and could involve altered opioid signaling in key pain-processing regions.[144] This would explain why harmless sensations can produce pain experience in chronic pain patients, a phenomenon called allodynia.[145] Second, incoming sensations in chronic pain patients may be more noisy and thus assigned less precision during pain inference.[146,147] In this situation, a decrease in noxious stimulation, which otherwise attenuates pain experience, may have no effect in chronic pain patients who may disregard sensory information if it is far less precise than their predictions. At the physiological level, increased sensitivity and unreliable nociceptive inputs could be mediated by peripheral and central sensitization mechanisms.[148] Recently, a Bayesian model of chronic pain has been proposed based on these hypotheses,[149] which adequately simulated the difference in pain inference between healthy and chronic cases.

An important realization that stems from the Bayesian perspective is that the experience of pain does not distinguish between scenarios with and without identified real pathology. This realization already goes a long way to address persistent mishandling of unexplained pain complaints.[71,147] Applying predictive processing to pain could be clinically relevant if they could identify which parameters play a role in pain chronification and support patient stratification to treatments. For example, psychological interventions that target patients' abnormal predictions about pain could be of interest when heightened predictions are at play. Indeed, psychotherapies such as cognitive-behavioral therapy, exposure therapy, or mindfulness-based interventions were shown to be effective at improving the affective and cognitive symptoms of some chronic pain patients, but not for all.[150] A promising new approach targets aberrant inferences at an even higher level. Pain reprocessing therapy transforms patients' understanding of their pain, so that they attribute it to a faulty brain signal rather than to peripheral pathology.[151] By teaching patients this new schema, the technique may have led to cognitive and neural reorganization[152] that accounts for its ability to substantially decrease back pain.[153]

CAN INFERENCE THEORIES ILLUMINATE SIMILARITIES AND DIFFERENCES BETWEEN EMOTION AND PAIN?

The ascendance of predictive processing in cognitive neuroscience all but forces us to consider a close relationship between pain and emotion. Consider Ongaro and Kaptchuk's statement that "we do not necessarily feel pain…because we 'sense' it directly from the peripheral body…we feel pain because we predict that we are in pain, based on an integration of sensory inputs, prior experience, and contextual cues."[71] Now compare it to Lisa Feldman Barret's words: "I did not see a snake and categorize it. I did not feel the urge to run and categorize it. I did not feel my heart pounding and categorize it. I categorized sensations in order to see the snake, to feel my heart pounding, and to run. I correctly predicted these sensations, and in doing so, explained them with an instance of the concept 'fear'. This is how emotions are

made."[154] In this section, we consider whether the predictive processing framework for pain could help advance our understanding of emotion and whether the constructed theory of emotion could help advance our understanding of pain.

First, consider the nature of predictions that descend from internal models in emotion and pain. The most obvious difference between pain and other emotions is the presence of a dedicated nociceptive system for pain, but no dedicated peripheral neural pathways for *fear-ception* or *sad-ception*.[64] Interoceptive sensations of tissue damage are the prototypical cause of pain because they mismatch descending predictions of bodily integrity. In emotion research, the question of whether bodily signals are sufficient for emotion to arise has been debated at least since William James. Schacter and Singer famously contended in their influential two-factor theory (as reviewed in Ref. 31) that physiological arousal is necessary and sufficient for emotion to arise. Further research has clarified that physiological arousal is not *necessary* for emotion. For example, a well-controlled study that compared people with disability who did or did not have spinal cord damage observed similarities rather than differences between the two groups.[155] However, when physiological arousal was induced through pharmacological or behavioral manipulation, it did evoke emotions such as anxiety.[156] From the predictive processing perspective, the evidence that some bodily signal evokes emotion suggests that some emotion models make predictions about bodily signals, such that mismatching signals can cause them to be updated and for the corresponding emotion to arise.

The prototypical causes of emotion are audiovisual sensations; for example, when seeing a spider or hearing a suspicious sound that indicates a potential break-in. The theory of constructed emotion (as in the quote above) speaks of a pattern-completion process that allows some such sensations to mismatch and update emotion models. There is debate as to whether audiovisual sensations evoke real pain. Reports of pain as a consequence of social isolation, and the overlap in fMRI BOLD signal–associated manipulations of physical pain and social isolation have been influential in this regard.[157] Nevertheless, while participants readily report feeling pain when they view others in pain, the neural signature differs in the case of somatic and vicarious pain.[158] From the perspective of the theory of constructed emotion, it is reasonable to posit that there is a variety of generative models that in our culture are categorized as instances of the concept of pain. While some descend from higher-level models associated with bodily integrity, others, which we can call *social pain*, generate audiovisual predictions.

Second, consider the potency of descending signals generated by internal models of pain and emotion. It is clear that thoughts and memories can evoke emotion without incoming signals, but this has been more controversial for pain. While interoceptive sensations of tissue damage are *sufficient* for pain, the IASP definition establishes that they are not *necessary*; pain without obvious tissue damage underlies the high prevalence of persistent pain.[135] We have discussed chronic pain from the perspective of predictive processing as potentially resulting from the precise top–down predictions in the presence of noisy bodily signal.

Third, consider the relationship between emotion and pain. Emotions modulate reported pain and its neural correlates, with moderate negative emotions increasing pain and moderate positive emotion decreasing it.[159] The brain regions associated with emotion and pain partially overlap,[64] possibly due to shared characteristics such as high arousal, non-neutral valence, personal relevance, and salience. These characteristics could also explain why the amygdala is associated with the regulation of both emotion and pain.[160] Although in an experimental context, the NPS[122] expresses acute physical pain, in many experimental settings pain stimulation elicits additional activations linked to the broader contextualization and control of the experience.[80] For example, Hashmi and colleagues used Neurosynth to define probabilistic maps of brain regions associated with pain, emotion, and reward, and examined the overlap of these regions with those activated by chronic back pain in a patient sample. Back pain activated pain-related regions in a sample of patients with acute back pain, who suffered from this condition for less than 2 months. By contrast, in back pain patients who suffered from this condition for many years, back pain activated emotion-related regions.[161] Intriguingly, in a 1-year follow-up of those in the acute sample whose pain persisted, activation in emotion-related regions increased and activation in pain-related regions decreased. This finding may be related to the observation that chronic pain is often comorbid with mood disorders and other mental health difficulties.[162] Kiverstein and colleagues[82] discuss a number of ways in which socioemotional information can interact with pain, ranging from the role of attachment in the initial development of generative models of bodily integrity, to how social support can minimize surprise about infringement to bodily integrity.

Fourth, consider active inference. As discussed above, emotions may feel the way they do because of active inference—those neural, endocrine, and immunological predictions generated by activated internal models that are categorized as emotions. The role of active inference is now an important aspect of research on pain as well. In Seymour's model, pain is a signal for learning and control.[93] It is noteworthy that many aspects of this model may apply to other negative emotions just as well as they apply to pain. For example, like pain, mental effort is also typically rated as unpleasant, and as such, reinforces escape and avoidance. And like pain, if exerting mental effort becomes associated with positive outcomes (e.g., in the context of training for the marathon), both may be experienced as subjectively pleasant and lead to behavioral approach.[64,163,164]

Finally, the Bayesian perspective provides a persuasive account of placebo effects. Is there an equivalent in the emotional domain? In the domain of pain, we spoke of placebo errors to denote the surprisingly limited impact that sensory evidence has on the posterior, given highly precise priors of pain reduction associated with clinical contexts. To take an example of a potentially related phenomenon in the emotion domain, consider how dehumanizing others facilitates violence. Normally, thinking of harming others, or witnessing violent acts, activates internal models associated with repulsion and dread, and those associated with social emotions such as moral concern and compassion. Dehumanizing others provides perpetrators with alternative models and precise predictions that are not updated by witnessing the harm their brutal acts cause to fellow humans.[165] Given that some degree of dehumanization is manifest across everyday social interactions,[166]

the theory of constructed emotion is well placed to explain the flexible engagement and disengagement of emotion models.

The analysis above reveals interesting similarities and differences between pain and emotion. We argue that perceptual and active inference and consideration of a variety of generative models are useful for research on both topics.

CONCLUSION

Predictive processing is an intriguing framework for brain function that has captured the energies and imagination of researchers across the cognitive neurosciences. We reviewed applications of this framework to human pain, ranging from behavioral and neural laboratory findings, through their analysis with computational models, to placebo and to chronic pain. Although there are still many open questions, we believe that the empirical evidence from this vast evidence base substantially supports a predictive processing account of pain.

The review was motivated by the argument that because pain is a lot more like emotion than other sensory perceptions, if predictive processing cannot explain pain perception, it might have little chance of accounting for genuine emotion. The theory of constructed emotion withstood this test. The empirical work we reviewed may serve as a guide for the kind of evidence that would be needed to further support a predictive processing account of emotion.

AUTHOR CONTRIBUTIONS

A.P.-C. and D.T. wrote and edited this manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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