

**Deconstructing the Sensation of Pain:
The Influence of Cognitive Processes on Pain Perception**

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Phenomena such as placebo analgesia or pain relief through distraction highlight the powerful influence cognitive processes and learning mechanisms have on the way we perceive pain. Although contemporary models of pain acknowledge that pain is not a direct readout of nociceptive input, the neuronal processes underlying cognitive modulation are not yet fully understood. Modern concepts of perception, which include computational modelling to quantify the influence of cognitive processes suggest that perception is critically determined by expectations and their modification through learning. Research on pain has just begun to embrace this view. Insights into these processes promise to open up new avenues to pain prevention and treatment by harnessing the power of the mind.

Watching a captivating film while a dentist is fixing your tooth can help you endure the much-dreaded visit with surprisingly little pain. Cognitive processes such as distraction have the potential to change the way we perceive pain – for better or for worse, as I will show below. Based on a rich psychological literature, brain imaging studies in humans have sought to describe and characterize the influence of cognitive factors on the neural processing and perception of pain since the 1980s. I will first give an overview of our current understanding of mechanisms and neural pathways to cognitive pain modulation and highlight the most important recent strands of research in this field with an emphasis on experimental studies in healthy individuals. In the second part, I will outline how these findings may be integrated with modern concepts of perception using computational models to explore the influence of cognition on pain at a more fundamental level.

The search for a ‘signature of pain in the brain’

A modulatory influence of cognitive factors on the perception of pain has been documented for a number of processes including attention, anticipation, catastrophizing, (re-)appraisal and perceived control over pain (1). Undoubtedly the most impressive and most extensively studied example is a placebo analgesic response. Patients with agonizing levels of pain can report complete pain relief after administration of a sugar pill they think is a powerful painkiller. But do such changes in pain reports indeed reflect a change in pain perception and neural pain processing – or just a report bias? Answering this question is notoriously difficult given the highly subjective nature of pain. Attempts to identify an objective read-out of pain

based on brain imaging data are controversially discussed (2). Brain activation induced by noxious input might in fact not be pain-specific but also reflect processes that are (inherently) linked to pain such as the detection of salient events (3). Historically, the network of brain regions involved in pain processing ('pain matrix') has been divided into a sensory-discriminative and a cognitive-affective system. The *sensory-discriminative system* which includes the lateral thalamus, primary and secondary somatosensory cortex (SI, SII) was thought to process nociceptive input including its intensity, localisation and quality. In contrast, the *cognitive-affective system* comprising regions such as the anterior insula and anterior cingulate cortex was implicated in psychological aspects of pain. However, this strict dichotomy turned out to be an oversimplification as sensory-discriminative brain regions, for instance, can also be sensitive to cognitive processes. Moreover, studies using a decoding approach (i.e., the prediction of pain perception based on activation patterns in the brain) demonstrated that the prediction is significantly improved when the different brain regions are considered together. In the so far most rigorous attempt to characterize the 'neurological pain signature' (NPS), Wager and colleagues (4) used a machine-learning algorithm to predict the perceived intensity of experimentally induced heat pain in healthy volunteers. The identified network comprising brain regions such as thalamus, SI, SII, anterior insula and anterior cingulate cortex (ACC) afforded a specificity of about 90% in discriminating physical pain from related phenomena (e.g., 'pain' due to social exclusion). Although these first findings are encouraging, further validation of this 'objective marker' is needed including its translation to clinical pain and generalizability to different types of pain and pain modulation.

The descending pain control system: top-down modulation of pain

Neuroimaging studies have not only been concerned with target regions of cognitive pain modulation but also with modulatory areas that implement the modulation. The so-called descending pain control network comprises regions such as the dorsolateral prefrontal cortex (DLPFC), rostral anterior cingulate cortex and periaqueductal gray (PAG) (5). Activation and functional connectivity between these regions are positively correlated with the level of pain relief reported. The engagement of this modulatory control network has been linked to reduced activation in other pain-related brain regions, albeit with varying consistency. Furthermore, the top-down influence has been shown to alter responses in the spinal dorsal horn which suggests that it can modulate nociceptive processing at an early stage (6). The DLPFC is thought to play a pivotal role in top-down control of pain, because its transient lesioning using transcranial magnetic stimulation (TMS) abolishes the placebo analgesia (7). Most of our knowledge of the pain control system stems from neuroimaging studies on placebo analgesia but this system has also been found to be engaged during other types of cognitive operations leading to pain reduction (e.g., distraction; 8). Descending pain inhibition is largely mediated through endogenous opioids (9). There is, however, evidence for the contribution of other neurotransmitters including cannabinoids (10) and dopamine (11). Taken together, research on the descending pain control system has described a network that is sensitive to cognitive manipulations and can interact with other brain regions involved in pain processing.

The fronto-striatal system: valuation of nociceptive input and higher-order integration of different aspects of pain

Do changes in perception based on cognitive modulation differ from those induced by changes in noxious input? Woo and colleagues (12) directly compared the modulation of pain through different intensity levels of heat and through cognitive self-regulation of pain in the same individuals. While the former was indeed reflected in changes in the NPS, self-regulation had no effect on the NPS but was associated with changes in functional connectivity (i.e., the crosstalk between brain regions) of mesolimbic brain structures including the ventromedial prefrontal cortex (vmPFC) and nucleus accumbens (NAc). This finding is remarkable for two reasons. First, it challenges the concept of the NPS as a universal signature of pain in the brain. If the NPS is to be established as an objective readout of pain, it is expected to reflect changes in pain irrespective of the type of modulation that led to the change in perception. Second, it highlights the contribution of the mesolimbic network that has been implicated in learning and valuation rather than in pain processing as such. It could therefore be speculated that this network translates sensory, cognitive and affective aspects of pain into a 'common currency' to integrate them and give rise to one unified pain experience. In a longitudinal study involving brain imaging (13) functional and structural characteristics of vmPFC and NAc have been shown to predict the development of chronic pain. Based on these findings, it has been postulated that the frontostriatal system is key not only for the conversion of nociception into the perception of pain but also for the transition from acute to chronic pain (14, 15).

Attention and the influence of spontaneous brain activity on pain perception

Changes in pain perception have not only been observed following deliberate cognitive operations but can also occur spontaneously (16). Recent work linked this finding to spontaneous fluctuations in attention to pain that depend on dynamic changes in resting state activity in three distinct brain circuitries (17): (i) the 'salience network' that is involved in the detection of biologically relevant stimuli and events and comprises brain regions such as mid cingulate cortex, anterior insula, temporo-parietal junction and DLPFC (18); (ii) the default mode network (DMN) that shows a reduced signal level during activity compared to a relaxed non-task state and includes regions such as a medial prefrontal cortex, posterior cingulate cortex and precuneus, the lateral posterior lobe and medial temporal lobe (19) and (iii) the descending pain control system described above. Using an experience sampling approach in which participants indicate to which extent they had paid attention to a noxious stimulation pain, activation in the 'salience network' was found when attention spontaneously focused on pain (20). In contrast, the default mode network (DMN) was engaged when attention was focused away from pain (20). Individuals' intrinsic attention to pain (defined by the test-retest reproducibility of an individual's tendency to attend away from pain) was related to their structural and functional connectivity between DMN and the descending pain control system (and the PAG in particular; 18). Importantly, alterations in the interplay between the salience, default mode and descending pain control network have also been related to heightened attention to pain in chronic pain patients (17). Although speculative at this time-point, research into the neural basis of altered spontaneous focussing on

pain might therefore also be relevant for understanding the ‘interruptive function of pain’ (21) on concomitant cognitive processes in clinical pain populations.

The need for a comprehensive unified framework of cognitive pain modulation

The studies portrayed above have provided important insights into the *implementation* of cognitive pain modulation. They leave, however, critical questions regarding its initiation, maintenance and integration unanswered. The processes described in the previous sections need to be carefully orchestrated to integrate momentary demands with long-term goals (22) and thereby ensure survival of the organism. What triggers cognitive pain modulation and what prevents or stops it? Furthermore, the actual interface between cognitive processes and pain as a perceptual experience has only insufficiently been described so far. How are cognitive influences woven into the perceptual process that gives rise to the experience of pain?

The construction of a pain experience: ‘Perception as inference’

Modern concepts of perception outside the pain field have begun to address these questions using computational models. In computational modelling, measurable indices of behavior that results from the inferential process (e.g., categorization of stimuli as painful vs. non-painful, response times) are used to inform a theoretical model, which maps sensory input (e.g., noxious stimulation) onto behavior.

Indicators of this mapping are subsequently used in the analysis of functional neuroimaging data to characterize the inferential process. In the most prominent theoretical framework of this lineage termed ‘predictive coding’, perception is conceptualized as an inferential process in which prior information is used to generate expectations about future perception and to interpret sensory input (23). During the perceptual process, incoming sensory information are compared against a ‘template’ or expectation that reflects prior information. The concept of predictive coding acknowledges that we are more likely to perceive sensory information in accordance with our template than with competing interpretations. Perception is thereby understood as a process that favors expected outcomes and weighs down information that is incongruent with the expectation. Evidence for such biased perception in the context of pain comes from studies using explicit cues to signal the intensity or onset of an upcoming noxious stimulus (24, 25) or, in more complex paradigms, the predictability or controllability of the stimulation (e.g., 26). Moreover, the generation of expectations is a shared feature of most cognitive processes that have been related to pain modulation, despite their many differences (27). Biased perceptual inference has recently been postulated to contribute to various diseases including functional motor and sensory syndromes and psychiatric disorders (28).

Studies in animals and humans have begun to unravel neural mechanisms underlying the inferential process and to characterize the influence of prior information and expectations (29). Collectively, they show that expectations can bias perception by introducing changes not only in sensory brain regions but also in those involved in

interpreting the incoming information. This concept extends the traditional view that a cognitive influence has to be implemented in a top-down fashion (as, for instance, reflected in the concept of the descending pain control system) by emphasizing the relevance of higher-order cortical processes that translate incoming information into perception. In line with this notion we have shown that biased decision-making can explain the influence of prior expectations on the perception of pain (30). In sum, the concept of 'perception as inference' allows for the integration of cognitive factors into the perceptual process itself and highlights the relevance of expectations for perception formation.

Learning and updating of internal models about pain

If the influence of expectations on perception is so profound, why do we not simply foster the most extreme expectations of radical pain relief as part of any pain treatment? Although the influence of expectations is undoubtedly strong, there are clearly limits to the extent expectations can influence the perception of sensory signals (31). Our representations of reality first and foremost enable us to successfully navigate the environment with minimal costs, which renders delusional ideations impractical. A significant deviation of our expectations from reality should therefore lead to course correction – an updating or revision of our expectations. Predictive coding and learning models rooted in this approach assume that when expected and observed sensory information diverge, a 'prediction error message' is generated in the brain that serves as a teaching signal for model updating (Fig. 2). So far, prediction error (PE) signaling has been studied extensively in the context of

reward learning and perceptual decision-making in the visual and auditory system. However, a limited number of studies has explored aversive PE processing using noxious stimuli as an aversive experience during learning in humans (32–35).

But what constitutes a significant enough deviation to challenge our current model and trigger updating? Both premature and delayed model updating can be risky. Premature or overly frequent updating might lead to a highly volatile and unreliable model and also absorb large amounts of attentional resources for constant monitoring. Conversely, delayed model updating might bear the risk that true changes are not considered early enough to prevent costly erroneous decisions. Individuals can optimally integrate newly available information into their existing model when short-lasting noxious stimuli are applied under controlled experimental conditions. There is, however, ample evidence that information integration and learning is sub-optimal in patients suffering from chronic pain (36), leading to change-resistant mental representations of pain and delayed updating.

Premature updating of expectations, on the other hand, might be particularly detrimental when the maintenance of positive expectations could aid treatment success and their (premature) downward corrections might compromise the outcome. As with placebo analgesia, the experience of insufficient pain relief during treatment might be irreconcilable with the expectation of a successful treatment – and therefore lead to model updating (37). Treatment expectations are – if at all – often only assessed once prior to treatment onset but it seems reasonable to assume that expectations are modified if the treatment effect falls short of pre-treatment expectations. This downwards adjustment may not only cause patients to

drop out of treatment programmes but directly prejudices treatment success because the inferential processes of pain perception and treatment judgment is no longer supported by a positive expectation of pain relief. Critically, negative treatment experiences have a prolonged effect that can also hamper subsequent unrelated treatment (38). In sum, learning models characterize the modification of expectations when new information becomes available and could be applied to explore aberrant learning that is frequently found in the context of chronic pain.

Conclusions and outlook

With the departure from a rather rigid concept of pain as a direct readout of sensory input, neuroimaging of cognitive pain modulation has provided valuable insights into the complex nature of pain and its neural basis. However, further research is needed to integrate the various efforts into a coherent model that addresses all aspects of modulation including its initiation, implementation and monitoring and also includes the existing behavioral and neuroimaging literature (39). The concept of predictive coding could provide the theoretical framework for this endeavor. For example, Büchel and colleagues (37) pointed out that although the descending pain control system is commonly interpreted as a top-down influence, its constituting brain regions have reciprocal connections, which allow for up- and downwards projections of information. They therefore suggest that – in line with the concept of predictive coding - the descending system could be part of a larger recurrent network exchanging PE signals at all levels of the neuraxis. Several findings point at a critical role of the DLPFC in orchestrating this network. As described above, the DLPFC is

part of various networks that are involved in cognitive pain modulation. It plays a key role in evidence accumulation during perceptual decision-making, as described in the context of ‘perception as inference’ (40) and learning. The integration of these different strands of research with respect to DLPFC functioning and its governance of learning networks can be expected to provide the much-needed unifying model of neural mechanisms underlying cognitive pain modulation.

The concept of pain as an actively constructed experience that is determined by expectations and their modification through learning has far-reaching implications for pain treatment and prevention. Treatment success is known to be critically depending on patients’ expectations, not only in the context of placebos but also with active interventions such as analgesic drugs (41). Expectations - in turn – are shaped by the information that is provided by health care practitioners. How could information be designed to optimally guide expectations for maximum treatment outcome? How could aberrant information processing be addressed using the framework of predictive coding? Future research should explore the translation of research on the inferential process underlying the perception of pain into clinical practice to optimally inform pain prevention and treatment strategies.

Patients’ complaints about pain that persists despite numerous treatment attempts are often dismissed as being “all in their head”. Modern pain research has shown that this notion is in fact true for any kind of pain, acute and chronic, easy to treat or resistant to all treatments currently available. We are only beginning to understand that the head (or brain, for that matter) also holds the key to new ways to help patients conquer their pain.

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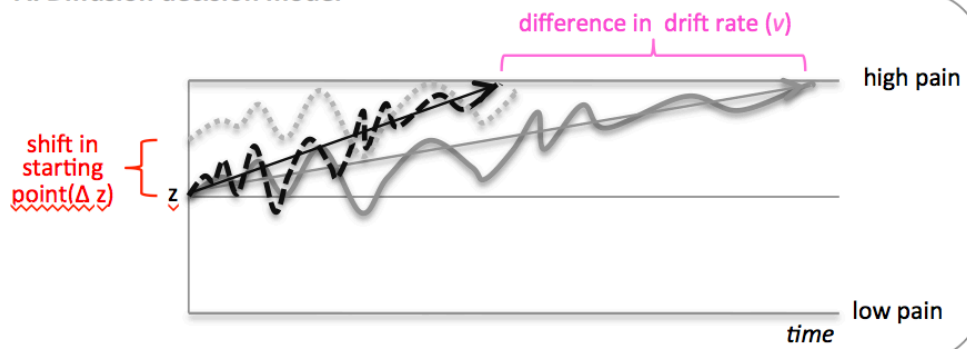
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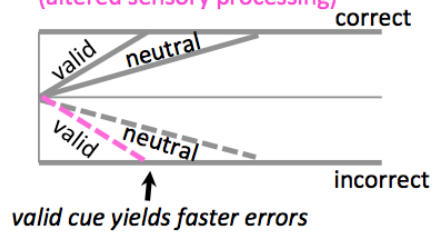
Fig. 1. Influence of expectations on pain: Altered sensory processing or biased perceptual decision-making? (A) Accumulator model within the framework of 'perception as inference' to describe the decision in a binary decision-making task. The decision can be understood as an accumulation of evidence that initiates a response as soon as the decision threshold for one of the options is reached. Without prior information the probability of both alternatives is identical (grey solid line). If high-intensity pain is expected this prior information could lead to altered sensory processing (black dotted line) or a shift in prior towards the high pain boundary (dotted grey line). **(B)** and **(C)**. The two types of bias can be distinguished because they result in different response times for incorrect choices. **(D)** Influence of prior information on perceptual decision-making in the context of pain (30). Participants saw one of three visual cues on each trial which signalled different probabilities for low-intensity and high-intensity pain: (1) 80% high, 20% low; (2) 20% high, 80% low; (3) 50% high, 50% low. Participants had to indicate as quickly as possible whether they received a high or low intensity stimulus. Response time and accuracies were recorded. **(E)** Prior information affected perceptual decision-making. A direct comparison of both types of bias revealed that this influence of prior information was based on a decision-making bias. Expectation shifted the prior towards the expected outcome. This was true for both, the expectation of high-intensity pain (red circle) and of low-intensity pain (orange circle). Only when participants expected a high-pain stimulation but received a low intensity stimulation, there was an increased drift rate (magenta circle).

Fig. 2. Prediction error processing and learning in the context of pain: a schematic overview. Sensory input or pain-related cues trigger a pain-related expectation. Subsequently, nociceptive input is compared to the expectation that reflects prior information. If incoming information is in line with prior assumptions, the expectation is confirmed. If they diverge, a prediction error signal is generated and the expectation is updated through a learning rule. Note that the generation of a prediction error might not necessarily lead to a revision of the expectation; following up on prediction errors might selectively be impaired in a pathological state and contribute to aberrant learning in the context of pain.

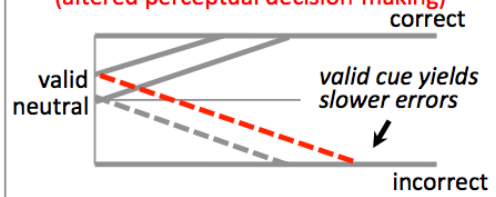
A. Diffusion decision model



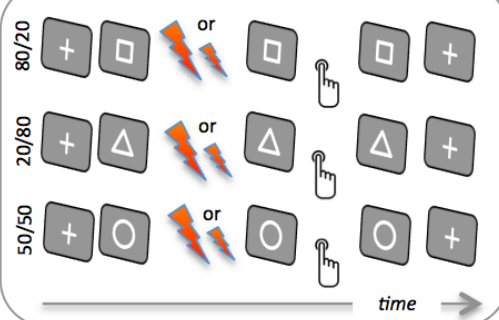
B. Bias in drift rate (altered sensory processing)



C. Bias in starting point (altered perceptual decision-making)



D. Experimental design



E. Results

