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Review

# Does Active Inference Provide a Comprehensive Theory of Placebo Analgesia?

Christopher Milde, Laura S. Brinskelle, and Julia A. Glombiewski

## ABSTRACT

Placebo interventions generate mismatches between expected pain and sensory signals from which pain states are inferred. Because we lack direct access to bodily states, we can only infer whether nociceptive activity indicates tissue damage or results from noise in sensory channels. Predictive processing models propose to make optimal inferences using prior knowledge given noisy sensory data. However, these models do not provide a satisfactory explanation of how pain relief expectations are translated into physiological manifestations of placebo responses. Furthermore, they do not account for individual differences in the ability to endogenously regulate nociceptive activity in predicting placebo analgesia.

The brain not only passively integrates prior pain expectations with nociceptive activity to infer pain states (perceptual inference) but also initiates various types of actions to ensure that sensory data are consistent with prior pain expectations (active inference). We argue that depending on whether the brain interprets conflicting sensory data (prediction errors) as a signal to learn from or noise to be attenuated, the brain initiates opposing types of action to facilitate learning from sensory data or, conversely, to enhance the biasing influence of prior pain expectations on pain perception. Furthermore, we discuss the role of stress, anxiety, and unpredictability of pain in influencing the weighting of prior pain expectations and sensory data and how they relate to the individual ability to regulate nociceptive activity (endogenous pain modulation). Finally, we provide suggestions for future studies to test the implications of the active inference model of placebo analgesia.

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*… we still did not understand the processes whereby a person's belief in a sham treatment could send a message to his or her pituitary gland to release its own endogenous pharmaceutics.* — Anne Harrington (1)

## BACKGROUND

Placebo effects are the psychological or physiological effects that can be directly attributed to receiving a substance or undergoing a procedure but that are not due to the inherent powers of that substance or procedure (2). Placebo responses are more general than placebo effects because placebo responses also include nonspecific effects such as regression to the mean, spontaneous remission, and normal disease fluctuations, known and unknown cointerventions, baseline misclassification, and other artifacts (3). Therefore, to separate placebo effects from placebo responses, carefully designed paradigms should include no-treatment control participants, that is, participants who are not exposed to experimental manipulations (4,5). Placebo effects are also found in active treatments (e.g., when receiving the pharmacologically active drug) (6). Specifically, in chronic pain (3,7–9) and depression (10,11), pronounced placebo effects are observed with medium to large effects. Placebo analgesia can be as strong as the response to a pharmacological treatment, as seen in chronic pain (12).

The most common placebo manipulations are classical conditioning and verbal suggestions (6). In classical conditioning, placebo effects are conceptualized as conditioned responses (13–15). The active treatment (e.g., analgesic drug) serves as an unconditioned stimulus, and administration methods (e.g., the color, shape, and taste of the drug) serve as conditioned stimuli. Individuals are assumed to implicitly learn associations between the unconditioned stimulus and the conditioned stimuli. Similarly, symbols and rituals of the medical context (e.g., familiar sight of the health care provider, disinfection procedures) also become associated with the beneficial or detrimental effects of the active treatment (16). When the active treatment is replaced by an inactive treatment (e.g., a placebo pill), the administration method may trigger placebo effects (4). Other conditioning paradigms implicitly manipulate nociceptive activity by surreptitiously decreasing noxious stimulation intensities in the presence of placebo cues (14,17–19). Placebo effects can also be induced by verbal suggestions. In a typical verbal suggestion paradigm, the placebo group receives treatment efficacy information ("This is a fast and potent analgesic."), whereas the control group does not receive treatment-related information. Subsequently, both groups receive an inactive treatment to control for any influences of the inactive treatment, thus allowing for the measurement of the specific effects of the expectation manipulation on therapeutic outcomes (20).

 
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Various contextual and individual factors influence susceptibility to placebo and nocebo effects (6). Furthermore, imaging studies (21–23) and pharmacological studies (4,24,25) have identified neural correlates and opioid and non-opioid pathways that are involved in placebo analgesia. Placebo analgesia has been formulated as a Bayesian problem of integrating prior expectations of pain states with sensory data that deviate from those pain states (26). For example, placebo paradigms generate expectations of pain relief, which are not accompanied by corresponding reductions in nociceptive activity. Prior expectations of pain states are integrated with sensory data, and both are weighted by their respective precision to form a percept (26–28).

However, current predictive processing models of placebo analgesia do not provide a comprehensive framework of the actions that the brain can use to integrate and react to expectations of pain states that are not matched by corresponding sensory data indicating those pain states. Therefore, an overarching theoretical framework is lacking, which explains how attentional shifts or endogenous regulation of nociceptive activity are used in the processes of integrating pain relief expectations with nociceptive signals to mediate placebo analgesia (1,16,29). Answering these questions could help explain the large interindividual variability in placebo responsiveness, which reflects limitations in our understanding of placebo mechanisms (22,30). Current models only emphasize the passive integration of pain relief expectations and nociceptive signals (i.e., perceptual inference) (26,31) or the role of somatic attention in placebo analgesia (27). Furthermore, these models are often based on the premise that the ability to perceive nociceptive signals accurately reduces placebo analgesia (28,32,33).

We provide a comprehensive overview of the brain's ability to infer pain states in common placebo paradigms when presented with pain expectations that conflict with sensory data. More specifically, we define the conditions under which active inference should promote or mitigate placebo analgesia. We argue that the active inference approach makes more differentiated assertions regarding placebo responsiveness in different placebo paradigms, such as classical conditioning or verbal suggestion paradigms.

## PREDICTIVE PROCESSING MODELS OF PLACEBO ANALGESIA

Predictive processing models assert that the brain does not simply receive and interpret bottom-up signals from the periphery but rather generates top-down predictions about the expected causes of sensory signals (34). This inferential process is necessary because the true causes of sensory signals remain hidden and are not directly accessible to the brain. Therefore, the brain uses expectations to improve and accelerate the deduction of the causes of often noisy and ambiguous sensory signals (35). According to the predictive coding perspective, perceptual contents are primarily driven by top-down predictive signals that emerge from hierarchically organized generative models of the causes of sensory signals (36,37). Mismatches between prior expectations and sensory data are encoded as prediction errors (PEs) that provide corrective feedback for subsequent predictions of expected sensory signals (Figure 1) (36).

Placebo manipulations generate mismatches (i.e., PEs) between expected pain states and sensory data that are indicative of those pain states (26). For example, verbal suggestions can generate expectations of pain relief which are not supported by reductions in nociceptive activity because the inactive treatment does not influence nociceptive activity.

Because prior expectations and the sensory data given those prior expectations (likelihood) are associated with varying degrees of uncertainty, refinement of generative models is not simply linearly driven by PEs. These uncertainties in prior expectations and sensory data are conceptualized in their precision (corresponding to the inverse variance of the prior and likelihood, respectively) (Figure 1A). Psychologically, precisions correspond to the confidence that an individual assigns to prior expectations versus the relevance that the individual attributes to sensory data (27). Therefore, placebo analgesia depends on both: PE (difference between expected pain relief and the pain relief indicated by the sensory data) and the assumed precisions (confidences) that are assigned to the expected pain relief and the sensory data (26,27) (Figure 1A).

High precision of the prior (small width of the prior distribution) reduces belief updates, whereas high precision of the sensory data (small width of the likelihood distribution) increases belief updates (38). However, a hyperprecise prior can cause cognitive immunization, resulting in a dissociation of prior expectations from corrective sensory feedback so that expectations are maintained despite conflicting sensory data (39–41). According to an influential predictive processing model of medically unexplained symptoms (MUSs) (42), which are defined as symptom perceptions that are not consistent with (patho)physiology (42), MUSs arise from hyperprecise (but biased) prior expectations. Because of the learning history of individuals with MUSs, there is an increased propensity to perceive harmless sensory signals as symptoms because prior expectations of symptoms overly bias the perception of sensory data (39,42,43). Therefore, symptoms are perceived even when sensory data does not indicate pathophysiology; thus, MUSs can be aptly described as "somatovisceral illusions" (42). The same rationale could be applied to placebo effects, in which placebo manipulations may promote precise but biased expectations of pain relief, which are not supported by sensory data (indicating ongoing pain) (26).

## LEARNING FROM SENSORY DATA OR STICKING WITH PRIOR EXPECTATIONS?

According to predictive processing models, prior expectations should bias pain perception even when sensory data contradict those expectations (Figure 1) (44,45). However, prior expectations can deviate significantly from sensory data, indicating that expectations are misleading and should be corrected. Hird *et al.* (46) found measurable boundaries to the biasing influence of prior expectations on pain perception. Large mismatches between cued pain intensities and noxious stimulation intensities nullified the influence of cued pain intensities on pain perception in a deception-free cue-conditioning paradigm. It is noteworthy that the boundaries at which cued pain intensities no longer biased pain perception varied greatly from person to person.

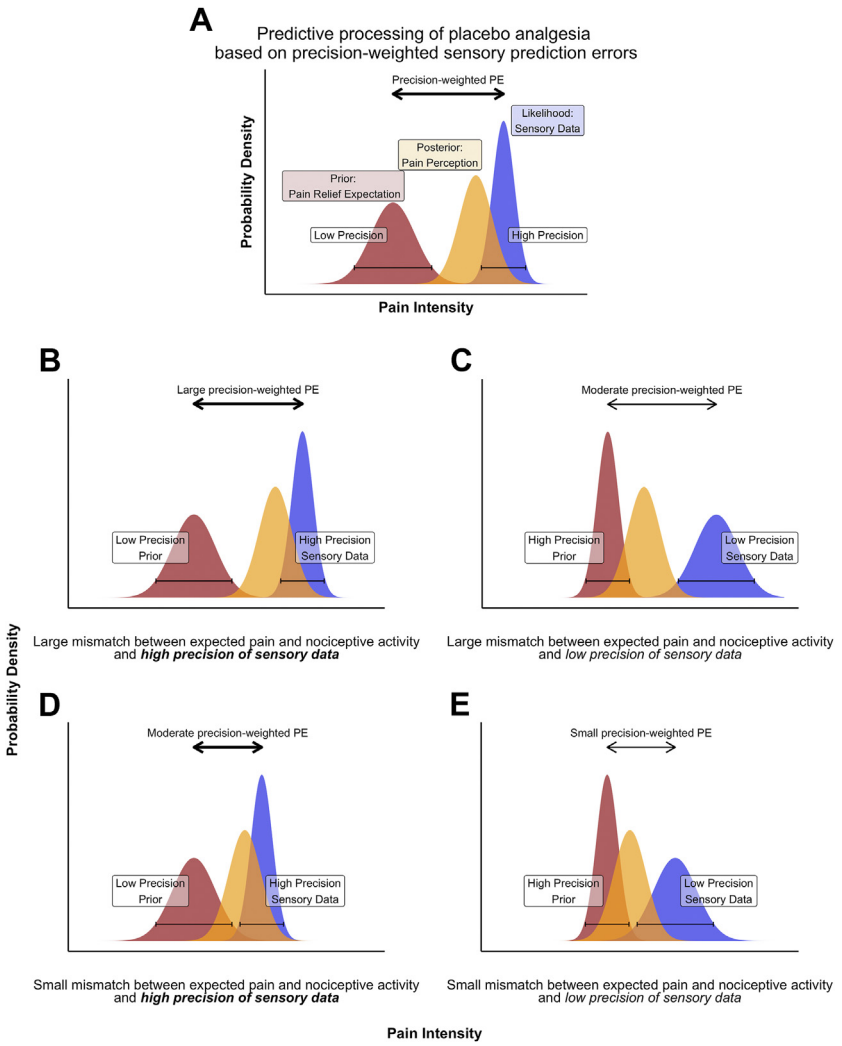


**Figure 1.** Predictive processing model of placebo analgesia. **(A)** Predictive processing models posit that placebo analgesia (posterior pain perception: yellow distribution) results from Bayes-optimal integration of prior expectations of pain relief (prior: red distribution) with sensory data (likelihood: blue distribution). Suggestions of pain relief generate conflicts between expected pain relief and sensory data, indicating ongoing pain. According to predictive processing, placebo analgesia depends on both prediction errors (PEs) (difference in central tendency between expected pain relief and sensory data) and the assumed precisions (confidences) that are assigned to the anticipated pain relief and the sensory data (precision ratio, corresponding to the respective widths of the prior and likelihood distributions). Therefore, depending on the respective precisions of prior expectations and sensory data, equal distances in central tendency between prior expectations and sensory data can result in different precision-weighted PEs. Thus, the precision weighting of sensory PEs is indicated by the linewidth, with larger linewidths indicating larger precision weighting of sensory data vs. prior expectations of pain relief. **(B)** Large precision-weighted PEs are expected when the sensory data strongly deviate from the expected pain (large difference in central tendency between expected pain relief and sensory data) and when the assumed precision of the sensory data is high (large linewidth of PEs). In this case, prior expectations can easily be updated by the sensory data. **(C, D)** Moderate precision-weighted PEs are expected when **(C)** the mismatch between expected pain and sensory data is large but the assumed reliability (precision) of the sensory data is low (small linewidth of PEs) or **(D)** the mismatch between the expected pain and sensory data is small but the assumed reliability of the sensory data is high. **(E)** Small precision-weighted PEs are expected when the mismatch between expected pain and sensory data is small and the precision of the sensory data is low. In this case, prior pain expectations can dominate the pain perception.

What factors determine these boundaries? According to the opposing process model of perception (47), perceptual systems are always confronted with a tradeoff between what we expect is more likely but also less informative. Therefore, perceptual systems could bias perceptions that are based on prior expectations (more likely) or, conversely, reduce the influence of expectations on perception by accentuating sensory data that contradict prior expectations (more informative).

Biasing perception based on expectations carries the risk of missing meaningful changes in the environment or within the body, such as potential tissue damage. Conversely, minimizing the influence of expectations on perception also comes at a cost because sensory signals are inherently noisy and ambiguous (37,38), and detailed sensory processing is time consuming (48,49). Therefore, biasing perception based on prior expectations is adaptive when sensory data are assumed to be noisy (44,50) or when rapid perceptual categorization is preferred over detailed sensory analysis (e.g., when rapid action is required in anticipation of a threat) (43,51). For example, it is adaptive to bias visual perception based on prior expectations of familiar objects when navigating through one's own kitchen in the dark. Conversely, accentuating unexpected sensory information would improve perception when sensory data are deemed to be precise (informative). For example, when picking up an object of unknown density and size, the influence of proprioceptive expectations should be reduced, and muscular effort should be adjusted primarily based on unexpected proprioceptive sensory information.

Two important conclusions can be drawn when these concepts are applied to the boundary effects of the influence of cued intensities on perceived pain intensities (46). First, boundary effects are found when cued intensities (prior expectations) and noxious stimulation intensities (sensory data) show large mismatches, which should facilitate learning from sensory data that contradict prior expectations. Conversely, small mismatches between cued intensities and stimulation intensities should enhance the influence of prior expectations on biasing pain perception. Second, large interindividual

differences in boundary effects may be explained by interindividual differences in weighting PEs. Therefore, the confidences (precisions) that individuals assign to cued intensities versus their ability to veridically infer pain intensities from sensory data vary from person to person. Thus, the brain should declare sensory data as meaningful signals to learn from when mismatches (i.e., PEs) between expected pain and nociceptive activity are large and the precision of the sensory data is assumed to be high (resulting in large precision-weighted PEs) (Figure 1B). Conversely, the influence of prior expectations on biasing pain perception should be increased when PEs between expected pain and nociceptive activity are small and the precision of the sensory data is assumed to be low (resulting in small precision-weighted PEs) (Figure 1E). If PEs are large but the precision of the sensory data is low (Figure 1C), or conversely, if PEs are small but the precision of the sensory data is high (Figure 1D), then pain perception should be moderately biased by expectations.

## ACTIVE INFERENCE THEORY OF PLACEBO ANALGESIA

How can the brain increase the influence of prior expectations on biasing pain perception when precision-weighted PEs are small or, conversely, facilitate learning from sensory data when precision-weighted PEs are large?

Bayes-optimal integration of prior expectations and sensory data is aimed at minimizing future PEs (34). However, minimization of future PEs cannot only be achieved by passively updating generative models by sensory data contradicting those expectations (perceptual inference) (Figure 1). The brain can also initiate various actions which ensure that sensory data are consistent with prior expectations (active inference) (Figure 2). Active inference provides a rich set of options to minimize future PEs using the combined effects of action and perception (34). What actions can the brain perform to adjust sensory data to expectations of pain relief (or increase)—that is, to make sensory data consistent with those expectations?

First, the brain can initiate regulatory actions that adjust nociceptive activity to prior expectations of pain states. For example, in anticipation of pain relief, the brain can facilitate descending pain inhibition by releasing endogenous opioids (4,52). Second, the brain can increase or decrease attention to sensory data that is either consistent or that conflict with prior pain expectations (27). Selectively allocating attention to sensory data that support prior expectations of pain relief (or increase) is defined as selective sampling (53,54). For example, the brain might preferentially allocate attention to sensory data

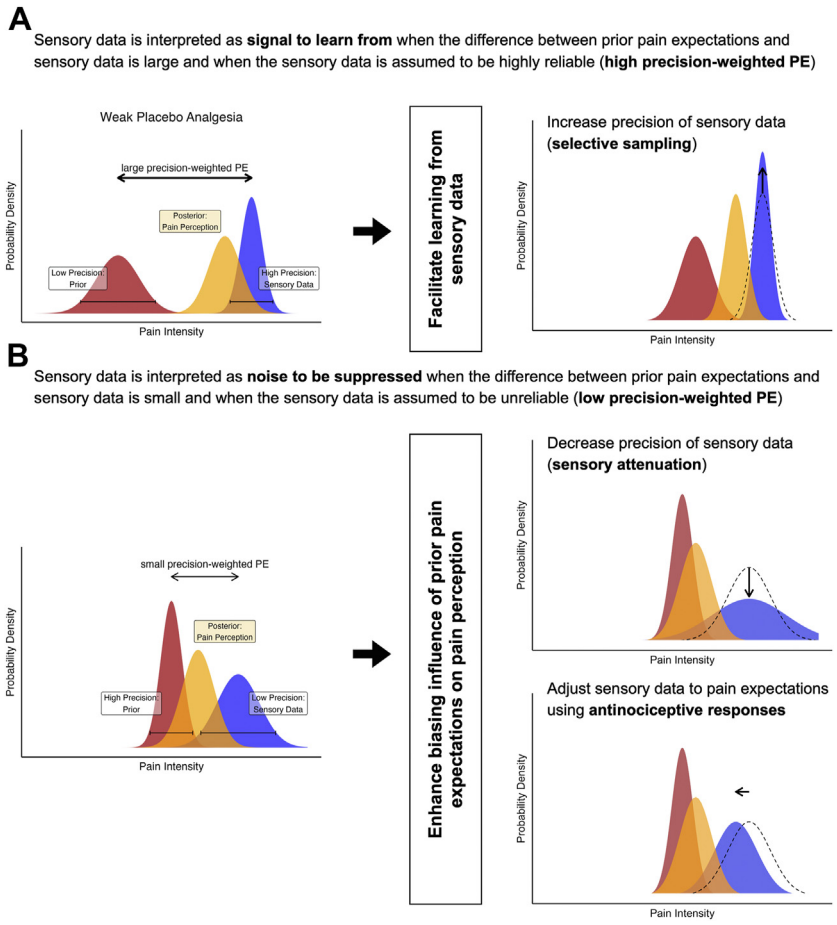


**Figure 2.** Active inference strategies to **(A)** facilitate learning from large precision-weighted prediction errors (PEs) or **(B)** enhance the influence of prior expectations of pain states on biasing pain perception. The widths of the red and blue distributions indicate the assumed precisions of pain expectations (prior) and sensory data (likelihood). The distance between the prior (red distribution) and the likelihood (blue distribution) indicates PE. The linewidth of PEs indicates the relative weighting of prior expectations vs. sensory data, with larger linewidths of precision-weighted PEs indicating stronger weighting of sensory data vs. prior pain expectations. **(A)** Large precision-weighted PEs are assumed when the difference between expected pain and sensory data is large and the precision of the sensory data is high (i.e., high confidence in the sensory data). In this case, learning from sensory data that conflicts with prior expectations is facilitated by increasing somatic attention to sensory signals or initiating (pro- or antinociceptive) actions to improve learning from sensory data. **(B)** Conversely, small precision-weighted PEs are assumed to enhance the influence of pain expectations on biasing pain perception. This could be achieved by sensory attenuation of sensory data conflicting with prior expectations or by pro- or antinociceptive responses that fulfill the prior expectation of an increase or decrease in pain.

that indicate pain relief when anticipating pain relief (27). Accordingly, individuals who were instructed to closely monitor the bodily effects of the active drug (which was a placebo) reported more placebo symptoms than those who received no instructions (55). Furthermore, there is often a high degree of correspondence between reported placebo or nocebo effects and therapeutic or side effects described in the therapeutic information (11,46). This finding can be explained by passive perceptual inference, in which high-precision prior expectations of placebo or nocebo effects make the reporting of those effects more likely. However, according to the active inference model, information about therapeutic effects and side effects should also selectively decrease attention to sensory data that conflict with anticipated bodily effects (sensory attenuation) and increase attention to sensory data that confirm anticipated bodily effects (selective sampling) (53).

## ACTIVE INFERENCE IN CLASSICAL CONDITIONING AND VERBAL SUGGESTION PARADIGMS

Placebo paradigms generate conflicts between expected pain states (prior) and sensory data for those pain states (likelihood) (26,56). However, placebo analgesia is differentially realized in classical conditioning and verbal suggestion paradigms (Figure 3). While verbal suggestion paradigms manipulate prior expectations of pain states, classical conditioning paradigms manipulate sensory data for those pain states by surreptitiously increasing or decreasing nociceptive activity during conditioning (17).

In classical conditioning paradigms, high-precision PEs should facilitate placebo analgesia because implicit expectations of pain relief can only be generated when sensory data reliably indicate analgesia in the presence of placebo cues. Therefore, active inference strategies that facilitate learning from PEs should increase placebo analgesia in conditioning paradigms (Figure 3A). In contrast, verbal pain relief suggestions can only induce placebo analgesia when pain relief expectations are not challenged by high-precision PEs. Thus, active inference strategies that enhance the influence of prior expectations on biasing pain perception should increase placebo analgesia in verbal suggestion paradigms (Figure 3C). Current predictive processing models fail to distinguish between the different involvement of predictive processing in verbal suggestion and classical conditioning paradigms.

## SMALL PRECISION-WEIGHTED PEs INCREASE PLACEBO ANALGESIA IN VERBAL SUGGESTION PARADIGMS

In verbal suggestion paradigms, small precision-weighted PEs are expected to increase placebo analgesia because sensory

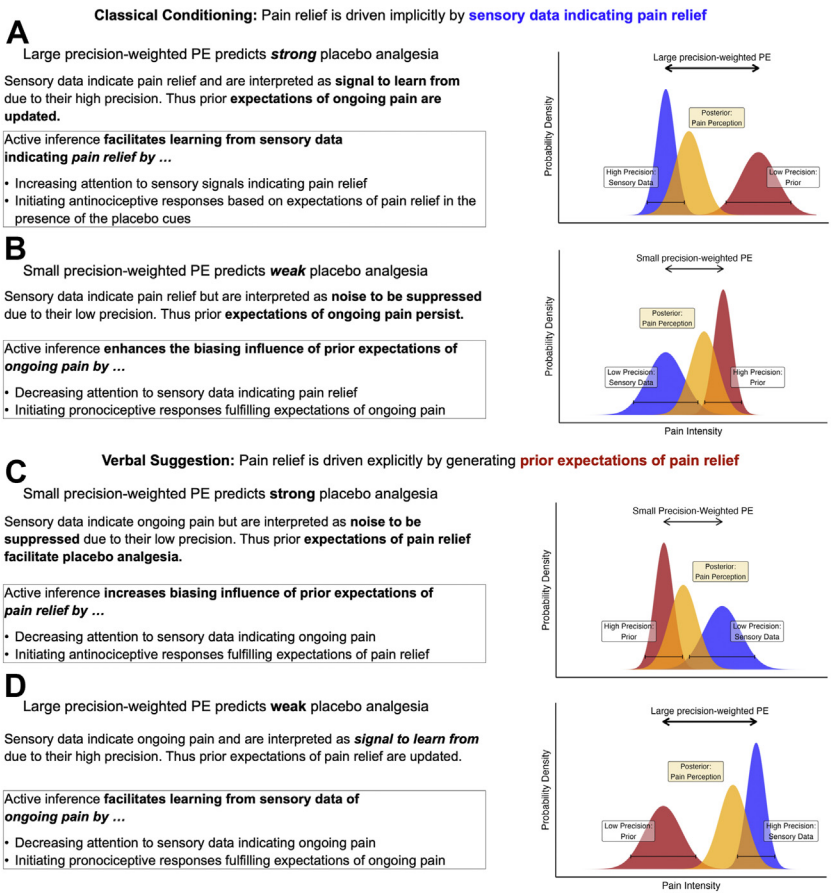


**Figure 3.** Susceptibility to placebo analgesia in classical conditioning vs. verbal suggestion paradigms. Active inference theory implies opposite assumptions about placebo responsiveness in classical conditioning (top) and verbal suggestion paradigms (bottom). **(A)** Large precision-weighted prediction errors (PEs) are assumed to increase placebo responsiveness in classical conditioning because placebo cues can only predict reliable pain relief if the reduction in sensory activity caused by the unconditioned stimulus is recognized as a reliable signal of pain relief. Active inference can increase learning from sensory data by increasing attention to sensory signals (selective sampling) that indicate pain relief or by initiating antinociceptive regulatory responses. **(B)** Small precision-weighted PEs are assumed to reduce placebo analgesia in classical conditioning because placebo cues do not reliably indicate pain relief. **(C)** Small precision-weighted PEs are assumed to enhance the biasing influence of prior expectations of pain relief suggestions because sensory signals of ongoing pain are declared as insignificant noise to be attenuated. The biasing influence of prior expectations of pain relief can be enhanced by selective attention to sensory signals that confirm pain relief (selective sampling) or antinociceptive physiological responses. **(D)** Large precision-weighted PEs are assumed to decrease placebo analgesia in verbal suggestion paradigms because sensory signals that conflict with prior expectations of pain relief are assumed to revise prior expectations of pain relief.

data that contradict prior expectations are declared as noise to be attenuated (Figure 3C). Therefore, pain relief suggestions can bias pain perception more easily. In contrast, large precision-weighted PEs should reduce placebo analgesia in verbal suggestion paradigms because anticipated pain relief is easily revised by sensory data that indicate ongoing pain (Figure 3D).

Consistently, individuals with chronic pain who show higher variability in daily pain ratings preferentially respond to placebo (57,58). Moreover, individuals who rate noxious stimulation intensities more reliably are less responsive to pain relief suggestions (32,33). It is noteworthy that individuals with diabetic neuropathic pain who improved significantly during pain reporting accuracy training also showed less placebo analgesia in a pregabalin-placebo trial, indicating that placebo analgesia is hampered when the ability to accurately perceive nociceptive activity is improved (33). These findings suggest that individuals with higher accuracy in perceiving nociceptive signals show a stronger tendency to revise suggestions of pain relief by assigning more precision to sensory data indicating ongoing pain. The brain can enhance the biasing influence of prior expectations of pain relief by initiating antinociceptive responses that adjust the nociceptive activity to the anticipated pain relief (Figure 2B). Descending pain inhibition can not only be facilitated by stimulating the release of endogenous opioids (4,59) but also by non-opioid mechanisms (60,61). Furthermore, the brain can reduce the precision of PEs using sensory attenuation, which increases the width of the likelihood distribution (27,62) (Figure 2B). Consequently, Bayesian updating of expected pain relief is hampered because PEs have less impact on refuting pain relief expectations.

To date, only a few studies have investigated the mediating influence of somatic attention on placebo analgesia or pain perception (27,63,64). In one study, it was suggested to participants that they receive a drug (which was a placebo in all groups), a drug or placebo, or a placebo (55). Half of the participants in each group were instructed to closely monitor bodily sensations after receiving the drug or placebo, while the other half did not receive attention instructions. The somatic attention instruction predicted the reporting of more placebo symptoms in the drug group, while the somatic attention instruction had no effect on symptom reporting in the drug or placebo group or the placebo group. These findings indicate that selective attention to the body can increase placebo effects when the precision (confidence) of receiving a drug is sufficiently high. Conversely, participants who were experiencing less pain during a working memory task showed larger nocebo hyperalgesia, indicating that distraction from pain may facilitate nocebo responses (63). These findings suggest that placebo analgesia and nocebo hyperalgesia can be modified by increasing or decreasing (e.g., distraction) attention to sensory data that are consistent with the placebo or nocebo suggestion. However, modulations of somatic attention may affect placebo responsiveness only when the precision that is assigned to prior expectations is sufficiently high (27,55).

## LARGE PRECISION-WEIGHTED PEs INCREASE PLACEBO ANALGESIA IN CLASSICAL CONDITIONING PARADIGMS

In classical conditioning paradigms, large precision-weighted PEs are assumed to increase placebo analgesia because placebo cues can only indicate pain relief if the reduction in nociceptive activity caused by the active treatment is recognized as a reliable signal of pain relief (Figure 3A). Therefore, if the analgesic does not reliably reduce nociceptive activity or if the individual has only limited ability to perceive the reduction in nociceptive activity accurately, the placebo cues cannot indicate reliable analgesia because the precision-weighted PEs are too small to indicate pain relief (Figure 3B). Accordingly, experimentally reducing the accuracy of sensory data in a placebo conditioning paradigm predicted less placebo analgesia (31). This study compared 2 groups experiencing the same mean reduction in noxious stimulation intensity during conditioning. While stimulation intensity was reduced by a constant amount in one group (large precision-weighted PEs), stimulation intensity varied greatly in the other group (small precision-weighted PEs). Consistent with the assumption that large precision-weighted PEs during conditioning should increase placebo analgesia, reliable reductions in stimulation intensity predicted larger placebo analgesia than variable reductions in stimulation intensity (31). These findings suggest that higher accuracy (or confidence) in perceiving nociceptive activity predicts larger placebo analgesia in conditioning paradigms because more precision is assigned to sensory data that indicate pain relief (28,33). If the placebo cues were indicative of reliable analgesia during conditioning, prior expectations of pain relief (in the presence of placebo cues) should have yielded high precision after conditioning. Thus, the placebo cues can elicit potent placebo analgesia when the active treatment is replaced by the inactive treatment. Potent placebo analgesia in the presence of placebo cues could be facilitated by initiating antinociceptive responses (e.g., release of endogenous opioids) or sensory attenuation of sensory signals indicating ongoing pain (Figure 2B).

Persistent placebo analgesia has commonly been found in classical conditioning paradigms (65). However, these persistent placebo effects cannot be sufficiently explained by passive integration of prior expectations of pain states and sensory data for those pain states (i.e., perceptual inference). For example, consider a patient with ongoing pain who is participating in a conditioning paradigm with an opioid drug. The brain must infer pain from prior expectations of ongoing pain, which are not matched by corresponding nociceptive activity during the conditioning phase (because the opioid reduced nociceptive activity) (Figure 3A). According to perceptual inference, the brain could update beliefs about pain states by learning from PEs, indicating pain relief. However, such pain relief expectations are volatile and should be quickly corrected by sensory data in the testing phase when nociceptive activity returns to baseline after the opioid has been replaced by the inactive treatment. In addition, referring to active inference, the conditioning with the opioid-induced physiological (antinociceptive responses) and attentional changes (e.g., selective sampling of sensory data indicating pain relief, attenuation of sensory data indicating pain increase) could explain persistent placebo analgesia.

## EVOLUTIONARY FUNCTION OF ACTIVE INFERENCE IN PLACEBO ANALGESIA AND PAIN PERCEPTION

Active inference is a more promising approach to explaining the physiological manifestations of placebo analgesia than

perceptual inference (66) because it relates placebo analgesia to homeostatic principles (53,67,68). Pronociceptive and antinociceptive responses are understood as regulatory actions that minimize discrepancies between expected and actual nociceptive inputs (53). From this perspective, active inference in nocebo hyperalgesia is analogous to the allostatic (preparatory) and homeostatic (reactive) responses that occur when anticipating or dealing with physical or social stressors (53,69). Pronociceptive responses stimulate defensive behaviors that improve coping with physical threats (70–72), e.g., by increasing arousal (73–75). Conversely, antinociceptive responses reduce the allostatic load that is associated with prolonged pain-related stress responses, thereby helping to conserve resources for other tasks such as foraging or reproduction (38,69,73,76).

Because threats to bodily integrity remain uncertain, regulation of nociceptive activity should depend on the tradeoff between the cost of defensive responses and the cost of not expressing defensive responses when physical threats actually exist (71,72,77). Defensive responses to protect the body are assumed to be inexpensive, while the cost of missing defensive (e.g., pronociceptive) responses in the event of physical threats is high (71). In chronic pain, the brain might have learned a "better safe than sorry" strategy (43), e.g., being overly protective so as to not miss any signals of bodily threat and being overly prone to showing pronociceptive responses. Therefore, high precisions (confidences) are assigned to prior expectations of pain aggravation and sensory data indicating pain aggravation. In this sense, deficient endogenous pain modulation in chronic pain (78,79) may be understood as an active inference strategy that facilitates defensive behavior in various biopsychosocial contexts rather than as an antinociceptive dysfunction (73). This may explain why a recent meta-analysis failed to provide evidence for the involvement of endogenous opiates in facilitating placebo analgesia in chronic pain (30). Emphasizing the tradeoff between the cost of missing potential threats to bodily integrity versus the allostatic load associated with maintaining defensive pain behaviors underscores the fact that the precision that is assigned to sensory data does not simply depend on accuracy in perceiving nociceptive signals (28,32,33) but rather on the affective-motivational nature of the pain.

## THE ROLE OF ACTIVE INFERENCE IN PLACEBO ANALGESIA: MEASURING CHANGES IN ENDOGENOUS PAIN MODULATION

Endogenous pain modulation can be measured using various paradigms, such as temporal summation of pain or conditioned pain modulation (CPM) (80,81). In CPM, noxious stimulation at one body site serves as a conditioning stimulus that reduces pain evoked by a test stimulus applied at a distant site (80). Larger CPM responses indicate better descending pain inhibition (82). It has been proposed that placebo analgesia and CPM rely on similar neurocognitive mechanisms of endogenous pain modulation (82–84). Accordingly, psychological factors that predict placebo effects also predict CPM responses (85,86). While studies using trait questionnaires often fail to find associations between anxiety or stress-related variables and CPM responses (87), experimentally inducing stress often reduces CPM responses (88–90). Moreover, verbally suggesting that the conditioning stimulus in the CPM increases (nocebo) or decreases pain (placebo) predicted increased (nocebo) or decreased (placebo) CPM responses, respectively (85). However, changes in CPM responses were only found in individuals who showed increased or decreased stress levels during the nocebo or placebo intervention. These findings are consistent with the evolutionary perspective that antinociceptive responses are too expensive when a perceived threat to bodily integrity is high.

Conversely, when the context is perceived as safe and the brain infers that it has sufficient resources to cope with physical threats, the brain should reduce pain-related stress responses by dampening nociceptive activity, thereby saving metabolic and cognitive resources for other tasks (71). This perspective may explain why chronic pain populations (in which pain is often perceived as unpredictable and uncontrollable) show deficient endogenous pain modulation (78,79), while athletes (who voluntarily engage in sports competitions that are known to elicit pain) exhibit more efficient endogenous pain modulation than nonathletes (91). Consistent with the assumption that maintaining compensatory dampening of nociceptive activity is too expensive when coping with unpredictable threats, inducing stress blocks descending pain inhibition in healthy participants (88,89). Interestingly, athletes lose their advantage in endogenously inhibiting pain over nonathletes when under acute stress (90). Therefore, perceived threat should be taken into account when estimating how much precision is assigned to prior expectations of pain versus sensory data (43,92).

The dorsolateral prefrontal cortex and the periaqueductal gray (PAG) are pivotal nodes of the descending pain inhibition system (93). A recent functional magnetic resonance imaging study with healthy participants found evidence for differential involvement of the descending pain inhibition system depending on whether high-intensity noxious stimuli were received unexpectedly or could be anticipated (92). Using drift-diffusion modeling in combination with a probabilistic cueing paradigm, the authors could distinguish between the influence of expectations on biasing pain decision making (prior to sensory processing) versus the influence of expectations on changing sensory processing (e.g., via descending pain inhibition). The study found that dorsolateral prefrontal cortex activity preceded PAG activation during stimulation only when the expected high-pain stimulus was actually received. Conversely, the PAG was not activated during stimulation when the high-intensity stimulus was received unexpectedly (cueing low pain, receiving high pain). Moreover, unexpectedly receiving high pain was associated with increased drift rates in the drift-diffusion model, indicating facilitated learning from the sensory data. Notably, these drift rates were correlated with both amygdala activity and connectivity between the amygdala and PAG.

These findings suggest that healthy participants dampen nociceptive activity (using descending pain inhibition) only when noxious stimulation occurs within predictable contexts. Conversely, unexpectedly receiving high-intensity stimulation may block descending pain inhibition and facilitate threat-related processing (e.g., increased amygdala-PAG connectivity). Whether these findings generalize to chronic pain populations, in which pain is often uncontrollable and unpredictable, has yet to be evaluated.

## SUGGESTIONS FOR FUTURE STUDIES

Several implications can be derived from the active inference model of placebo analgesia that could be tested in future studies.

Although it has been proposed that higher accuracy in perceiving nociceptive activity decreases placebo analgesia (28), we argue that perceiving nociceptive activity accurately may increase placebo analgesia in conditioning paradigms. Placebo cues can only indicate analgesia when the surreptitious reduction in nociceptive activity was reliably perceived during conditioning. Most studies have used combinations of suggestions and conditioning, and the combination often leads to stronger placebo analgesia (94,95). Therefore, we propose further investigating how accuracy in perceiving nociceptive activity influences placebo analgesia when combining conditioning and suggestions. In most placebo studies, suggestions precede conditioning. However, the order of conditioning and verbal suggestions influences placebo analgesia (95). It could be speculated that assigning more precision to sensory data than to prior expectations leads to stronger placebo analgesia when conditioning precedes verbal suggestions because assigning more precision to sensory data, which indicates pain relief during conditioning, is assumed to facilitate learning from sensory data using active inference strategies. Therefore, individuals who show larger precision-weighted PEs should be more easily persuaded by pain relief suggestions when the brain has previously adjusted sensory data to pain relief expectations during the conditioning phase (e.g., via antinociceptive responses) (Figure 3).

Studies have shown that prior expectations bias pain perception only when the noxious stimulation intensity does not deviate much from the expected pain (46,92). However, these studies have neither measured the influence of the individual's ability to perceive nociceptive activity accurately nor investigated the influence of the perceived threat that is induced by the mismatches between cued pain intensities and noxious stimulation intensities. Therefore, we propose investigating whether individual boundaries regarding the influence of prior expectations on biasing pain perception (96) can be predicted by 1) the accuracy in perceiving nociceptive activity, 2) the confidence in perceiving nociceptive activity accurately, and 3) the perceived threat induced by incongruences between cued intensities and noxious stimulation intensities.

Novel computation paradigms allow quantification of the relative contributions of expectations versus sensory data in predicting pain perception (92,97,98). These paradigms allow for better explanations of endogenous control phenomena by accounting for the dynamic integration of prior expectations and sensory data in pain perception, which cannot be captured in conventional paradigms such as CPM or temporal summation of pain (97). For example, in the nociceptive predictive processing task (97), the association strength between a cue and a slightly suprathreshold nociceptive stimulus is gradually reduced after conditioning (by increasing the number of trials during which cues are followed by subthreshold stimuli). A computational model is used to estimate the gradual curves of learning (conditioning phase) and unlearning (test phase) the cue-stimulus association, making it possible to quantify the relative contributions of prior expectations and sensory data on pain perception.

Quantifying the contributions of prior expectations versus sensory data in different affective contexts may provide clinically relevant predictors of placebo analgesia and nocebo hyperalgesia. Based on our model, larger weighting of prior expectations should predict placebo analgesia in verbal suggestion paradigms, while prioritizing sensory data should predict placebo analgesia in conditioning paradigms.

Moreover, we propose studying differences in the weighting of prior expectations versus sensory data in populations that show either deficient (e.g., chronic pain) or superior (e.g., professional athletes) endogenous pain modulation. To further investigate the role of perceived threat in assigning precisions to prior expectations versus sensory data, these novel computational paradigms can be used to measure the impact of acute stress on the relative contributions of prior expectations and sensory data to pain perception. Because chronic pain is characterized by uncontrollable pain and systematic perceptual aberrations (99–101), we speculate that chronic pain populations show larger weighting of prior expectations of pain aggravation, which leads to highly precise but biased perceptions of pain (101).

## CONCLUSIONS

Placebo manipulations generate conflicts between expected pain states and sensory data for those pain states. Models of placebo analgesia often refer only to factors that influence expectations of pain without further considering the expectation-supporting or expectation-violating function of processing and regulating nociceptive activity.

Referring to the question raised in the title, the active inference model of placebo analgesia advances our understanding of the way that Bayesian inference could explain changes in the psychophysiological manifestations of placebo analgesia due to placebo or sham manipulations one step further. It makes specific predictions about how the brain can use precision-weighted PEs to endogenously modulate nociceptive activity or shift attention to nociceptive activity to either increase the biasing influence of prior expectations (small precision-weighted PEs) or increase learning from sensory data (large precision-weighted PEs). However, future studies must answer the question of whether the active inference model of placebo analgesia provides a comprehensive model of placebo analgesia.

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## ARTICLE INFORMATION

From the Department of Psychology, Rheinland-Pfälzische Technische Universität Kaiserslautern-Landau, Landau, Germany.

Address correspondence to Christopher Milde, Ph.D., at christopher.milde@rptu.de.

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