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Review

How expectations shape pain

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ABSTRACT

Pain is highly modifiable by psychological factors, including expectations. However, pain is a complex phenomenon, and expectations may work by influencing any number of processes that underlie the construction of pain. Neuroimaging has begun to provide a window into these brain processes, and how expectations influence them. In this article, we review findings regarding expectancy effects on brain markers of nociception and how expectations lead to changes in subjective pain. We address both expectations about treatments (placebo analgesia and nocebo effects) and expectations about the environment (e.g. expectations about pain itself). The body of work reviewed indicates that expectancies shape pain-intensity processing in the central nervous system, with strong effects on nociceptive portions of insula, cingulate and thalamus. Expectancy effects on subjective experience are driven by responses in these regions as well as regions less reliably activated by changes in noxious input, including the dorsolateral prefrontal cortex and the orbitofrontal cortex. Thus, multiple systems are likely to interact and mediate the pain-modulatory effects of expectancies. Finally, we address open questions regarding the psychological processes likely to play an intervening role in expectancy effects on pain.

Contents

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Expectancy	Effects on pain intensity processing	Relationship to report
A. Placebo analgesia 	•Reductions in dACC, anterior insula, medial thalamus [33, 72, 95] cf. [50] •Spinal modulation [34,39, 40, 61]	•Placebo responders show larger placebo-induced reductions in ACC [95, 99], thalamus, rACC [95] •Responders show larger anticipatory increases in DLPFC and OFC [92, 95] •Correlations in OFC, lateral PFC, parahippocampus, and pons during heat [50]
B. Nocebo hyperalgesia 	•Increases in ACC and anterior insula [48]	•Nocebo responders show increases in insula and primary motor cortex during heat [49] •Inverse correlation with DLPFC and OFC [49]
C. Stimulus expectancies 	•Modulation of bilateral anterior and right posterior insula/SII, medial and lateral thalamus, cerebellum [5] and SI, ACC [51]	•dACC, thalamus, left anterior insula, DLPFC, rACC, OFC, pons, striatum, DMPFC mediate cue effects on trial-by-trial pain reports [5]

Fig. 1. Expectancy effects on pain. Researchers have studied the relationship between expectations and pain processing by studying three types of expectancies (left panel). Studies examine responses to noxious stimulation in pain intensity-related regions (middle panel) and relationship between brain responses and expectancy effects on pain report (right panel). *Top*: Placebo manipulations generally use conditioning and verbal information to induce expectations that an inert treatment will lower pain. *Middle:* Nocebo manipulations induce expectations that treatments will increase pain. *Bottom:* Stimulus expectancy manipulations use pain-predictive cues to induce expectations about the intensity of an upcoming stimulus.

Pain often refers to a sensory experience resulting from actual damage to the body. However, pain is also highly subjective, and can occur even in the absence of physical harm [46]. As such, pain can be influenced by a number of psychological factors, including attention, emotion, and beliefs or expectations. In this review, we ask how expectancies (beliefs and predictions about future events or outcomes) modify pain and pain-related responses in the brain. Numerous studies have shown that pain is influenced by expectations about both treatments and the intensity of painful stimuli, and researchers have employed pharmacological interventions, neuroimaging, and other techniques to isolate the mechanisms that give rise to these effects. However, despite the growth of this field and the rapid progress made in identifying underlying brain mechanisms, a number of critical questions remain unanswered.

In this paper, we attempt to synthesize neuroimaging research across three domains of expectancy and highlight outstanding questions for pain researchers and cognitive/affective neuroscientists. We first assess the extent to which expectations modify nociception and pain-related neurobiological processes. Next, we address the mechanisms that give rise to expectancy effects on subjective pain. We then turn to current theory regarding the modulatory mechanisms that give rise to expectancy effects on pain and nociception as well as the relationships between different types of expectations. Finally, we address outstanding questions regarding the intervening psychological processes that may mediate expectancy effects on pain. Painting a complete picture of the mechanisms underlying expectancy-based pain modulation in turn offers promise for the development of targeted psychological interventions to help individuals deal with chronic pain. In addition, using pain as a model system can elucidate the mechanisms by which beliefs and learning influence affect and hedonic experience more generally.

Throughout this review, we will consider three domains of expectancy: placebo analgesia, nocebo hyperalgesia, and stimulus expectancy effects. First, in the case of *placebo analgesia*, expectations that a treatment will produce pain relief cause pain reduction even when the treatment itself is inert (see Fig. 1, top panel). A recent meta-analysis showed that, relative to a wide range of clinical conditions, placebo treatments are most effective for conditions involving pain [32,33]. Expectations can also exacerbate pain: *nocebo hyperalgesia* refers to the increase in pain that accompanies beliefs that a treatment will cause pain or increase symptoms (see Fig. 1, middle panel). Clinically, cognitive behavioral therapies that involve changes in beliefs about and attitudes toward pain can be very effective [35,54], implying that negative beliefs may support some types of chronic pain. While placebo analgesia and nocebo hyperalgesia both involve beliefs about treatments, recent work suggests that they may be supported by distinct neuromodulatory mechanisms; we address these in detail below. Finally, in addition to being modified by expectations about treatments, pain is also influenced by expectations about noxious stimuli themselves, which may involve distinct mechanisms from placebo. Expectations about stimuli can be elicited by instructions to an individual or arise from spontaneous inferences, or they can develop through basic associative learning processes such as classical conditioning. For example, if different auditory tones predict different levels of heat, then an individual will develop expectations for different pain intensities as a function of the respective tones. If a cue that predicts nonpainful heat is later followed by a moderately painful stimulus, the individual will perceive the noxious stimulus to be less painful than when the painful stimulus is presented alone or preceded by a cue that predicts high pain [5,36,41]. We refer to these predictive cue-based processes as *stimulus expectancies* (see Fig. 1, bottom panel). Researchers have manipulated each of these types of expectancies – placebo, nocebo, and stimulus expectancies – to study their effects on pain in controlled experimental settings. While they are often discussed interchangeably, in this paper we attempt to formally address their inter-relationships and likely shared and divergent mechanisms.

1. Expectancy effects on pain: a rich history

Expectations are fundamental to learning across nearly all sensory and affective domains, including pain. Their study has a rich history dating back to the middle of the twentieth century, when behaviorism dominated the field. Woodworth [90] and Tolman [74] argued that when an animal learns that a tone predicts a shock, the animal is essentially developing an expectation about the timing of

the shock and the relationship between the tone and the stimulus. These ideas were further developed by Bolles [16], who stated that conditioned stimuli do not directly elicit responses; instead, contingent reinforcements cause animals to develop expectancies about outcomes, which in turn elicit responses insofar as the animal is motivated to achieve or avoid that outcome. More formally, animals learn either stimulus-outcome contingencies (S-S*) or response-outcome contingencies (R-S*), and behaviors are exhibited as a function of the value of the expected outcome (S*). For example, a hungry animal will be more likely to exhibit food-approach responses than a satiated animal because of a difference in the value of the expected meal. Finally, Rescorla and Wagner formalized a model of classical conditioning in which learning does not depend on simple contiguity between conditioned and unconditioned stimuli [64]. Instead, conditioning depends on the acquisition of useful information, rather than simple stimulus-response learning [65]. The model explains phenomena that are difficult to explain by considering contingencies alone, such as blocking and conditioned inhibition. In these phenomena, what is learned from a stimulus-outcome pairing depends on the associations between a second conditioned stimulus in ways that suggest it is the predictive (information) value of a conditioned stimulus, rather than contingencies themselves, that is critical for learning. Taken together, this line of work implies that expectancies underlie most forms of learning [63]. This view also suggests that expectancies can be studied in non-human animals.

Interest in expectancy grew when the medical community acknowledged its power. At the same time that Tolman and others were arguing for a new interpretation of classical conditioning, Henry Beecher published an influential article entitled "The Powerful Placebo" [6]. The paper included an early meta-analysis of fifteen studies that administered placebos for conditions as diverse as wound pain, seasickness, anxiety, and the common cold. Beecher reported that placebos were clinically effective for ~35% of the patients in these studies, and reported placebo effects on objective outcomes (both clinically relevant and side effects), such as rashes and pupil diameter. Following his article, researchers focused on identifying the mechanisms underlying the placebo response, motivated at least in part by an effort to harness the body's endogenous healing capabilities to assist modern medicine in providing better patient care. Throughout the course of this research, efforts have focused on two main objectives: (1) isolating the biological mechanisms underlying placebo analgesia; and (2) isolating the traits that determine who will become a "placebo responder."

The first studies to isolate the mechanisms underlying placebo-based pain modulation focused on the endogenous opioid system and its role in placebo analgesia. Levine and colleagues found that placebo analgesia was abolished when patients were given the opioid antagonist naloxone [44], suggesting that endogenous opioid release underlies placebo effects on pain, since the placebo effect was abolished when opioid receptors were blocked. These findings have since been replicated [7,23] and corroborated in other modalities [82,93], expanding our understanding of the role of endogenous opioids in the placebo response. We will return to these findings later in this review (see Section 4).

Interestingly, predicting who would respond to placebo treatment was more difficult. One experiment [45] tested placebo analgesia across three different pain models: labor, postpartum, and experimental pain. If placebo responsiveness were a stable trait, placebo responders would presumably show consistent placebo responses across contexts. However, individuals were not more consistent than would be expected due to chance. Thus Liberman argued that features of the treatment context determine who will respond to placebo (though he also acknowledged the possibility of person × situation interactions). A recent study [87] found similar effects. The same inert treatment was administered across two sessions (test–retest reliability) under two different brand names (context manipulation). Placebo responses were similar across time, within a given context. However, there was no relationship between the placebo response *across* contexts: those who reported strong placebo effects for one brand name were not more likely to report placebo effects for the other brand name. These studies suggest that changing the context changes who will be a placebo responder, implying that placebo responsiveness may not be a stable trait.

In a distinct yet related vein, recent efforts to understand individual differences in placebo responsiveness that focus on placebo response variability *within* a single context have been fruitful. Relative to non-responders, placebo responders report higher optimism and less anxiety [55], have higher levels of putatively "dopamine-related" personality traits such as behavioral activation and optimism [28,55,66], and are more suggestible [22]. Responders also show stronger neural markers of reward responsivity [68], higher levels of dopamine and opioid binding during pain stimulation [67,68,82,93], and larger gray matter density in mesolimbic brain regions (ventral striatum, insula, and prefrontal cortex; [66]). Finally, the magnitude of brain responses during pain anticipation predict who will respond to placebo treatments in experimental tasks [78]. Notably, placebo responses within a domain are moderately reliable across time, with test–retest correlations in the range of 0.6 [55,81]. How can the findings of instability across contexts and reliability within a context be compatible? They can be if both stable person-level factors and person × situation interactions [52] are important for placebo responses. For example, suggestible individuals will tend to believe more strongly (person-level), but different individuals respond differently to different contextual elements (one person may believe that creams are effective but be anxious about injections, while another may believe the opposite). Disentangling these effects is an important, though challenging, goal of future research.

Throughout the history of placebo research, an important debate has focused on whether placebo effects depend on conscious expectancy or conditioning. One difficulty is that conditioning is often defined as non-conscious associative learning, though as we review above, conditioning is actually a process that elicits both expectancies and association-based plasticity. Whatever the mechanism, conditioning accounts of the placebo effect posit that the power of placebos stems from a lifetime of associations between pills, white coats, and hospital settings and treatment-induced positive outcomes. According to this view, when contextual factors are presented in the absence of drug treatment, they elicit healing as a conditioned response [31,75–77,88]. Others have argued that placebo effects depend on explicit beliefs, rather than conditioning [37,53]. From this perspective, placebos should only affect clinical outcomes insofar as patients believe in the treatment and expect relief.

A number of studies have explicitly manipulated verbal instructions to participants in addition to associative pairing in order to tease expectancy and involuntary processes apart; for a thorough review, see [73]. Though this has typically been framed in terms of "expectancy vs. conditioning," in our view, these are not mutually exclusive alternatives. We prefer to describe these studies in terms of (a) whether placebo responses can be elicited by verbal information alone, which does not depend on experience with stimulus-outcome associations; (b) whether placebo responses elicited by experience are *obligatory*, i.e. produced by prior experience irrespective of instructions; and (c) whether placebo responses, once formed, are *involuntary* in the sense that they are impervious to instructions.

On the first point, placebo responses elicited by verbal instructions alone can influence reported pain [19,81], though effects

are weaker than placebo effects induced by observation or conditioning [19] and it is still unclear whether this is partly due to previous experiences with similar cues [18]. On the second point, a seminal experiment by Montgomery and Kirsch [53] demonstrated that experience with S–S* associations alone is not sufficient to produce analgesia if participants do not attribute analgesia to the placebo. In this paradigm, two groups are given a cream (S) and it is paired with reduced noxious stimulus intensity (S*). In one group, participants are told that the stimuli are the same and the cream will reduce their pain. This group shows a placebo response. The other group is told that the stimulus intensity is being reduced. This group does not show a placebo response, demonstrating that the *attribution* (or 'credit assignment') of the experienced contingencies to the placebo is critical. Finally, on the third point, placebo responses formed by a combination of experience with the appropriate attribution may be impervious to changes in expectancy. One elegant experiment [13] tested the basis of placebo effects on consciously accessible outcomes (pain in healthy controls and motor performance in patients with Parkinson's Disease) and unconsciously accessible physiological outcomes (cortisol and growth hormone secretion). The critical groups went through conditioning phases (pre-treatment with the analgesic ketorolac for pain conditioning, subthalamic nucleus stimulation for Parkinson's patients, and treatment with sumatriptan for cortisol and growth hormone section), and then received verbal information that induced expectations that were either consistent or inconsistent with the conditioned response. For instance, one group that was exposed to ketorolac was told that a treatment (really a placebo) would induce hyperalgesia (increased pain, opposing the analgesic effects of ketorolac); if pain increased with placebo during the test phase, that would indicate that placebo effects were due to conscious belief, whereas if they decreased, that would show that placebo effects depend on conditioning. Using this logic, Benedetti et al. showed that placebo effects on pain and motor performance depend on conscious belief (i.e. they reversed with instructions), whereas placebo effects on biophysical and hormonal responses depend on conditioning (i.e. they did not reverse with instructions).

In sum, some emerging principles are that both experience and appropriate credit assignment (expectancy) are critical for producing placebo responses, but some placebo responses once produced do not depend on conscious expectation. These principles need to be tested in further research with both behavioral and brain-based measures. To date, the vast majority of studies of expectancy effects on brain mechanisms combine both verbal information and conditioning in order to maximize expectancy effects on outcome measures. Thus, for the remainder of this review, it should be assumed that researchers combined both approaches to induce expectations, unless otherwise noted.

2. Do expectations influence nociception and pain intensity-related processes? Brain imaging studies weigh in

A critical question throughout this research has been whether expectations cause real neurobiological changes or whether they cause changes in subjective reports without affecting the underlying pain-related physiology. Judgments of all types are influenced by biases and the use of heuristics that need not be related to sensory processes (see [4,79] for brief discussions), and some have argued that placebo analgesia is a product of such biases [32,33]. We address this question by dividing it to two components, with findings summarized in Fig. 1. In this section, we focus on the question of whether expectancy effects on pain go beyond reporting biases and are associated with concomitant changes in nociceptive circuitry and pain intensity-related processes in the brain (see Fig. 1, middle column). In the following section, we address the precise mechanisms that link expectations to subjective pain and decisions about pain experience (see Fig. 1, right column).

To test whether expectancy effects on pain are real, researchers have assessed the extent to which expectancies influence the physiological responses produced by noxious stimuli, both in the periphery and in the central nervous system. Fortunately, the brain regions and pathways involved in nociception are highly conserved across human and animal models and reliably activated by noxious input. This allows researchers to use brain imaging approaches to test whether expectancy effects on pain are associated with concomitant changes in nociceptive circuitry. Current evidence suggests that placebos, nocebos, and stimulus expectancies influence the best currently available brain markers of nociception and pain intensity processing, though this approach has some important limitations, and developing improved biomarkers for pain and its nociceptive components is a critical future direction.

2.1. Placebo effects on pain intensity processing

Researchers use placebo manipulations and experimental pain models to formally examine the mechanisms underlying placebo analgesia. Experimental placebo manipulations combine conditioning and verbal information to induce expectations about a treatment that, unbeknownst to subjects, is actually pharmacologically inert. An experimenter might explain that a treatment is a strong analgesic, and administer the "treatment" while lowering the intensity of a noxious stimulus (see Fig. 1, top panel). During a later test phase, the placebo treatment is administered and compared to a control condition, and researchers test whether behavioral and physiological responses to equivalent noxious stimuli differ as a function of condition (control vs. placebo). In the first study to use functional magnetic resonance imaging (fMRI) to test whether placebo analgesia is associated with placebo effects on so-called "pain matrix" regions, Wager and colleagues administered a placebo cream during imaging while participants received painful shocks and/or contact heat on the forearm [81]. We first identified brain regions that were sensitive to stimulus intensity, and then tested whether any of these 'intensity-coding' regions showed reduced stimulus-evoked responses when participants believed they were receiving a topical treatment, relative to a control condition. Pain-evoked responses in nociceptive portions of insula, thalamus, and anterior cingulate were reduced with placebo treatment. These results suggest that placebo treatments truly affect pain intensity-related processing, arguing against the notion that placebo analgesia simply reflects demand characteristics and report biases. Similar findings were later replicated in patients with irritable bowel syndrome [60]. Phasic nociceptive responses are also modulated by placebo, as measured by noxious laser-evoked potentials using event-related potentials (ERPs) [20,80,86]. Finally, the best evidence that expectancies influence nociceptive signals comes from several recent studies that have demonstrated that placebo analgesia can reduce markers of nociceptive processing in the spinal cord [24,29,30,50]. These studies suggest that nociceptive signals can be blocked before they even reach the level of the brain, supporting a role for descending modulation. One important question is why placebo effects on nociceptive regions are not more widespread, if ascending nociceptive input is truly blocked at the level of the spinal cord. While most studies find effects on medial pain regions [3], one study has reported placebo effects on somatosensory regions [23], using the same paradigm that was later shown to affect spinal responses [24]. We hope that future studies will employ multi-modal techniques or combine spinal and cortical brain imaging to reconcile spinal placebo effects with cortical responses. Finally, while this body of work suggests that placebos induce changes in many markers of pain-related

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responses, not all studies of placebo analgesia have found effects on regions sensitive to noxious stimulus intensity [40].

2.2. Nocebo effects on pain intensity processing

Relative to placebo analgesia, there is much less research on the brain mechanisms underlying nocebo hyperalgesia. One fMRI study examined nocebo effects using an acupuncture model [38]. On the basis of combined verbal information and conditioning, subjects were led to believe that pain would increase with acupuncture to the meridian side of the arm. Sham acupuncture was applied, and responses to noxious heat on nocebo sites were compared to responses on control sites with no expectation. Nocebo treatment induced increases in the medial pain system, including anterior cingulate cortex and bilateral insula. These effects are consistent with placebo effects reviewed above, though, as discussed below, the neuromodulatory mechanisms thought to underlie placebo and nocebo are quite distinct. Future studies should test whether nocebo effects on nociceptive circuitry replicate with other experimental pain models, and test whether similar effects are observed in clinical pain.

2.3. Stimulus expectancy effects on pain intensity processing

Finally, nociceptive brain regions are also modulated by stimulus expectancies. Studies of stimulus expectancy effects on pain reveal that even short-term expectations that vary as a function of cue have strong effects on pain perception and pain-evoked responses [5,41,47]. In one study, we used conditioning and verbal information to induce expectations about noxious heat intensity as a function of auditory tones [5]. Nearly every region that showed differences as a function of temperature also showed differences during heat stimulation when the same temperature was preceded by cues predicting low or high stimulation. These stimulus expectancy effects were arguably more robust than placebo and nocebo effects reviewed above; cue-based expectancies in our task modulated responses in both medial and lateral pain systems, including the dorsal posterior insula, and other studies have found effects on primary somatosensory cortex (SI) [41], whereas placebo and nocebo manipulations are associated primarily with effects on medial pain regions.

The studies reviewed above suggest that expectancy manipulations are associated with real changes in pain-related processing in the brain, ruling out the hypothesis that placebo effects and other types of expectancy effects simply reflect demand characteristics and report biases. Expectations truly influence neurobiological responses to noxious stimuli. However, expectancies might only affect pain-related circuitry because expectancies influence intervening processes such as attention and emotion. Indeed, while the studies reviewed above reveal that expectations modulate responses in regions associated with pain processing, and placebo effects on cingulate, insula, and thalamus are replicable across studies [3,79], other studies found expectancy effects primarily on prefrontal and subcortical regions less clearly associated with nociception, including the lateral prefrontal cortex, orbitofrontal cortex, parahippocampus [40], and caudate [36], among other regions. In fact, the regions that are reliably modulated (insula, cingulate, and thalamus) are actually not specific to pain perception, as they are activated by a number of processes such as interoception, conflict, negative affect, and response inhibition [91]. Thus placebo effects on these regions might be associated with placebo effects on any number of intervening processes. In fact, relatively few placebo studies have found placebo effects on the regions that show the most specificity to pain, such as dorsal posterior insula and secondary somatosensory cortex [42,51]. In summary, studies that test whether expectations influence responses in pain-related brain regions provide strong evidence for the fact that expectancies influence neurobiological processes. However, because the brain regions that are most frequently influenced by expectancy can be shaped by emotion, attention, and other processes that are likely to be affected by expectations, mediating mechanisms must be considered. We return to this issue below (see Section 5).

3. By what mechanisms do expectations influence pain?

While the experiments reviewed above provide evidence that pain-related circuitry is modulated by expectancies, a second critical question is how expectancies actually shape subjective pain. Pain is a complex sensation that involves sensory, motivational, and cognitive components, and affecting any one of these could result in analgesia. Fortunately, brain imaging approaches allow researchers to isolate the pain report-related brain mechanisms that are influenced by placebo treatments and expectancy manipulations. We have summarized these findings in the right panel of Fig. 1. Isolating pain report-related processes – e.g. identifying regions, patterns, or voxels that correlate with pain report within or across individuals – can identify the most proximal predictors of analgesia, whether they are located in pain sensory pathways, other regions, or a combination of these.

3.1. Individual differences in expectancy effects on pain

One approach to testing for placebo effects on report-related processes is to test for correlations between expectancy effects on brain and behavior. For example, Wager et al. [81] found that the individuals who reported the largest placebo effects on pain also showed the largest placebo effects on heat-evoked responses in insula, thalamus, and rostral anterior cingulate cortex (rACC). Notably, typical pain regions were not the *only* regions to predict placebo analgesia. Placebo-related responses in dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC) *prior* to noxious stimulation also predicted individual differences in placebo analgesia, such that the individuals who had the largest placebo effects on pain showed larger placebo-induced *increases* in these regions during pain anticipation. These regions are associated with cognitive control and expected value computation, which might play key roles in shaping subsequent nociceptive responses; we return to this issue below. In fact, a reanalysis of these data using machine learning and pattern analysis techniques showed that responses in canonical pain regions were much *less* predictive of placebo responses than anticipatory responses in networks associated with emotion and affective value [78].

Other studies have also found relationships between individual differences in expectancy effects on pain and the magnitude of neural responses to placebo treatment. Watson et al. [85] found correlations between placebo analgesia and placebo-induced reductions during noxious stimulation in several pain intensity-coding regions (anterior middle cingulate, posterior cingulate, and post-central gyrus). Kong et al. [40] failed to find correlations in pain intensity-coding regions, but observed correlations between prefrontal activation and placebo responses similar to the patterns observed by Wager et al. [81], such that the subjects who reported stronger placebo analgesia in pain showed larger placebo-related increases in bilateral OFC, as well as rACC, lateral prefrontal cortex, cerebellum, parahippocampus, and pons. Finally, Kong et al. [39] found that nocebo-related increases in pain reports were positively correlated with heat-evoked responses in bilateral insula and left primary motor cortex regions, and inversely correlated with responses

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in bilateral DLPFC and OFC. Individual differences in stimulus expectancy effects on pain have not been examined, but, as we describe below, this approach offers a unique opportunity to study the mechanisms that underlie dynamic relationships between brain and behavior that operate within individuals over time.

To test which processes are most predictive of individual differences in placebo effects on pain, we recently employed novel machine-learning techniques to make unbiased predictions of placebo analgesia at the level of individual participants [78]. We used pattern-finding analyses to identify whether individual differences in placebo analgesia were best predicted by patterns of activity within pain networks, emotion networks, or networks involved in executive function and cognitive control. Interestingly, we found that placebo effects on pain were best predicted by responses during both pain anticipation and during noxious stimulation in regions broadly associated with emotional appraisal, including orbitofrontal cortex, insula, amygdala, and other regions identified independently. Many of these regions do not directly respond to increases in noxious stimulus intensity. As discussed below, this may be consistent with research that links placebo effects on pain to general reward processing [66,68], and findings that placebo involves a reduction in anxiety and negative emotion [26,27,55,61].

3.2. Predictors of dynamic expectancy effects on pain

Notably, the brain-behavior correlations reviewed thus far isolate the processes that correlate with *individual differences* in placebo analgesia. To understand the brain mechanisms that dynamically link expectations with subjective pain *within individuals* and across time, expectations must be manipulated on a shorter time scale. To do this, we turn to cue-based manipulations of stimulus expectancies. To understand whether nociceptive systems actually give rise to ongoing expectancy effects on perception, we used formal mediation analysis to identify the regions that link cue effects on pain-evoked responses with cue effects on dynamic subjective pain reports [5]. Cues and pain reports varied on every trial, and we tested whether responses in the brain on a given trial contributed to the link between cue-based expectation for high vs. low pain and concomitant increases and decreases in pain experience. We tested whether heat-evoked responses in nociceptive systems formally mediated cue effects on trial-by-trial pain reports when intensity did not vary. Mediation implies that cue effects on a given brain region explain more variability in pain reports than cues themselves.

While nearly all pain intensity-coding regions were modulated by cue-based stimulus expectancies, a subset of these regions, including insula, cingulate, and thalamus, formally mediated trial-by-trial cue effects on pain. Interestingly, expectancy effects on these regions were in turn mediated by cue-evoked anticipatory responses in ventral striatum and medial OFC. These regions have been widely studied in the context of conditioning and value-based learning in both appetitive and aversive domains across humans and animal models, suggesting a link between these fields and expectancy effects on pain experience. As discussed below, this is consistent with the notion that expectancy effects on experienced pain may be shaped through value-based influences on pain processing. Notably, this finding is also consistent with the fact that anticipatory responses in emotion networks predict expectancy effects across individuals [78]. Finally, nociceptive regions were not the only mediators of cue effects on pain: we also found mediation by left DLPFC, rACC, and pons, among other regions. Thus, the brain regions that link cue-based expectancies to dynamic pain seem to be the same that explain individual differences in placebo analgesia and nocebo hyperalgesia.

4. Modulatory mechanisms

4.1. Neurochemical basis of placebo analgesia

As mentioned above, the first studies to isolate the mechanisms underlying placebo-based pain modulation focused on the endogenous opioid system and its role in placebo analgesia. These studies showed that placebo analgesia was abolished when patients were given the opioid antagonist naloxone [44]. A recent fMRI study showed that naloxone abolishes placebo effects on pain-related brain regions, providing a direct link between neurochemistry and the fMRI findings reviewed above [23]. These findings are complemented by positron emission tomography (PET) studies that visualize μ-opioid receptor (MOR) binding during pain and placebo treatment and show that placebo responses are accompanied by increased MOR binding in limbic regions [69,70,82,93]. Finally, fMRI studies provide further support for the notion that endogenous opioids are critical for expectancy-based pain modulation. Placebo analgesia is associated with increases in activation in the MOR-rich rACC and the periaqueductal gray (PAG) [14,58,81], as well as increased connectivity between these regions [14] that is abolished with naloxone [23]. The PAG produces analgesia when stimulated in humans [15], has inhibitory connections with primary afferent nociceptors in the spinal cord's dorsal horn [25], and, in conjunction with the rostroventral medulla, controls the release of endogenous opioids [25].

Taken together, these studies provide strong evidence that endogenous opioid release plays a key modulatory role in the placebo response. However, multiple neurochemical systems mediate different kinds of analgesic effects, and while opioids are the best-studied system to date, other systems are surely involved. One area in which non-opioid analgesia has been demonstrated is in pharmacologically conditioned placebo effects with non-opioid drugs. In a landmark study, Amanzio and Benedetti [2] conditioned placebo responses by performing repeated injections of analgesic drugs, followed by an injection of saline (placebo) to test whether the injection-related cues alone would produce analgesia. Placebo effects in patients conditioned with morphine were reversed with naloxone, showing evidence for opioid mediation, whereas those in patients conditioned with non-steroidal anti-inflammatory drugs (NSAIDs) were not, implying that another system is primarily responsible. Recently, Benedetti et al. [8] showed that NSAID-conditioned placebo responses were reversed by an antagonist of the CB-1 cannabinoid receptor, implying mediation by endocannabinoid systems.

4.2. Cholecystokinin and nocebo hyperalgesia

Researchers have recently begun to study the neurochemistry underlying nocebo effects on pain. Nocebo effects can be abolished with the cholecystokinin (CCK) antagonist proglumide, suggesting that CCK release underlies nocebo effects on pain [9,11]. Interestingly, proglumide also potentiates placebo [7,10] and opiate analgesia [62]; however, nocebo effects are thought to be unrelated to opioid release, as naloxone does not reverse proglumide-induced nocebo blockade [9]. CCK is implicated in anxiety and panic [1,49], suggesting that nocebo responses may increase anxiety and thus increase pain. Consistent with this, the benzodiazapine diazepam, commonly used as an anti-anxiety treatment, also blocks nocebo hyperalgesia [11], and an fMRI study of nocebo hyperalgesia [38] found nocebo induced increases in the hippocampus, a region implicated in pain-related anxiety [59]. Future research is needed that unpacks the relationships between brain systems, anxiety and stress, and CCK and other neuropeptides in nocebo and placebo responses. Studies that combine neuroimaging with pharmacology and behavioral assessments of emotion seem particularly promising.

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4.3. Neuromodulatory mechanisms underlying stimulus expectancy effects

Endogenous opioids are less likely to underlie stimulus expectancy effects on pain when expectations vary from trial to trial. While the time-course of analgesic effects related to these neurochemical systems has not been studied in detail, any neuromodulatory signals that mediate cue-based expectancy effects on pain must be transient and reversible. Opioid effects are generally believed to be long lasting, as opioid activation can trigger naloxone-insensitive analgesia that extends beyond the original opioid response [83,84]. Similarly, CCK is not a likely neurochemical mediator, as it would likely preclude pain reduction with low pain expectancy. This heterogeneity suggests that multiple different mechanisms may be at work. One possibility is that cue-based expectancies may involve dopamine signaling, which has been linked to computations of prediction error and expected value. This is consistent with formal modeling approaches to aversive learning [71,72], which suggest a critical role for striatal responses. Thus, we hypothesize that phasic dopamine responses are likely to play a key role in cue-based predictions and downstream pain modulation. An important direction will be to use pharmacological approaches to understand the role of neurotransmitter systems in cue-based expectancy effects on pain.

5. Outstanding questions

While the studies reviewed above have begun to paint a picture of the mechanisms by which beliefs influence pain experience, a number of important questions remain unanswered. We have already acknowledged several important questions: first, to what extent do expectancy effects on "pain matrix" regions reflect changes in nociception? What are the relationships between different types of expectations (about stimuli vs. treatments vs. outcomes)? In this section, we address several additional unanswered questions and relevant findings. To what extent are expectancy effects mediated by intervening processes such as attention, anxiety, and positive emotion? Are these psychological processes differentially affected by placebo treatments, nocebo treatments, and/or stimulus expectancies? We hope that these open issues will be resolved through mechanistic investigations as this area of research continues to develop.

5.1. Relationship between expectancy effects and other regulation strategies

Pain is strongly modulated by attention, emotion, and active efforts such as the practice of reappraisal, distancing, imagery, and acceptance strategies, as addressed in other articles in this special issue. Do expectancies work through the same mechanisms as other cognitive interventions? As mentioned above, placebo-related responses in DLPFC *prior* to noxious stimulation also predicted individual differences in placebo effects [81]. In addition, transcranial magnetic stimulation of DLPFC appears to reduce placebo effects [43], and placebo effects on DLPFC are correlated with placebo effects on the PAG [81]. The DLPFC has been associated with a wide range of executive functions, including executive working memory and cognitive control, processes that might be required in order to maintain the placebo context and regulate downstream responses. Thus, one widely held hypothesis is that expectancies are maintained in DLPFC, and that DLPFC has inhibitory connections that modulate downstream pain-related processes [48]. Path modeling approaches support this account, suggesting that DLPFC inhibits dACC during placebo analgesia [21]. Further evidence for this hypothesis comes from the fact that individuals with Alzheimers' Disease, a disorder that involves progressive degeneration of the prefrontal cortex, show reduced placebo effects [12]. This suggests a critical role for DLPFC in regulating pain based on expectations, similar to DLPFC's putative function in emotion regulation [56,57] and other types of cognitive control. Yet as far as we know, endogenous opioids have not been implicated in other types of cognitive control, and descending modulation may be unique to pain-related processing. Are expectancy effects simply a manifestation of cognitive control in the domain of pain, or are they unique?

5.2. Relationship between expectancy effects and attention

A related hypothesis is that placebo effects come about through changes in attention. The Affective Expectancy Model (AEM [89]) suggests that, unless individuals are forced to pay fine-grained attention to affective stimuli, emotional experiences will be biased toward expectations to conserve attention and processing resources. Thus, as a result of feeling safe, individuals may pay less attention to noxious stimulation under placebo treatments, and may bias pain reports toward their expectations.

Several recent studies from our lab have directly tested the role of attention in the context of expectancy effects on pain. Buhle et al. [17] crossed a placebo manipulation with a demanding attention task, and found that the two influenced pain with additive effects, implying separate mechanisms. In a different study, we combined the cue-based expectancy manipulation described above [5] with a trial-by-trial attention manipulation [34]. Consistent with the AEM, we found that expectancy effects were reduced when subjects focused attention toward the painful stimulus. We also found that individuals increased somatic attention when they expected high pain, suggesting that stimulus expectancies may in fact induce changes in attention, and pointing out a potential dissociation with the attention-independent placebo effects studied by Buhle et al. [17]. Finally, threat-induced increases in somatic attention reduced, but did not abolish, expectancy effects on pain, suggesting that at least some of the overall stimulus expectancy effect was mediated through other mechanisms.

5.3. Relationship between expectancy effects and emotion processing

While expectancy effects on pain might be related to traditional "cognitive" factors such as attention and executive function, they might also be related to more "affective" processes such as value learning and mood. Placebo analgesia is associated with reduced anxiety and negative emotion [27,61] and individuals who show larger striatal responses to monetary reward also report higher placebo analgesia and show greater placebo-induced opioid release [68]. Furthermore, as reviewed above, expectancy effects are associated not only with changes in pain-related regions, but also regions associated with affective processing including orbitofrontal cortex, insula, amygdala, and striatum, and these latter systems may be more proximal predictors of placebo responses across individuals [78]. One recent study provides preliminary support for the notion that placebo analgesia affects general emotion processing. Zhang and Luo [92] used a conditioning manipulation (noxious stimulus intensity reduction) to induce expectations for analgesia, and then tested whether placebo administration modulated behavioral and neural responses to aversive images, measured using ERPs. They found that placebo analgesia not only reduced pain reports, but also reduced the unpleasantness of aversive images and modulated ERPs. However, it is important to note that participants in this study were informed that the treatment could also induce changes in negative emotion, though there was no conditioning to enhance this expectation. Thus, these findings may reflect (1) a "transferable" placebo effect that generalizes across domains, (2) a

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general shift in emotion that accompanies placebo analgesia, or (3) placebo effects on anxiety elicited by verbal information, independent of placebo analgesia. Future studies should directly parse out these possibilities, and additionally test whether placebo-induced changes in emotion (e.g. increased positive affect, reduced negative affect) formally contribute to, or mediate, placebo effects on pain.

6. Conclusion

Research on the relationship between expectations and pain experience shows that expectations about treatments and about painful stimuli can profoundly influence brain and behavioral markers of pain perception. In this review, we have integrated research from three different domains: placebo analgesia, nocebo hyperalgesia, and cue-based stimulus expectancy effects on pain. These various types of expectations all influence the best known markers of nociception, though efforts must continue in order to determine the specificity and reliability of these effects. Interestingly, each type of expectation seems to be related to affective processing and value computation in some sense: individual differences in placebo analgesia are best predicted by responses in emotion networks, nocebo hyperalgesia is associated with increased anxiety and draws on anxiety-related neurochemical processes, and cue-based stimulus expectancies influence responses in striatal and orbitofrontal regions that shape nociceptive responses which in turn give rise to subjective pain. Finally, these processes also seem to involve distinct modulatory mechanisms: placebo effects depend on endogenous opioid release, nocebo effects depend on cholecystokinin signaling, and the neurochemical bases of stimulus expectancy effects must rely on phasic mechanisms that can vary from trial to trial.

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