

# Expectancies and Beliefs: Insights from Cognitive Neuroscience

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## Abstract

Expectations influence clinical outcomes and ongoing experience across nearly all psychological domains. They color our perceptions, drive learning and memory, and shape the generation of emotional responses. Despite their profound influence, researchers have only recently begun to focus on the mechanisms by which expectancies actually modulate subjective experience. This chapter describes a cognitive neuroscience approach to the study of expectations, focusing on expectancy effects on affective experience. First a brief history is provided of the development of expectation as a construct with explanatory power in psychology, and several distinct types of expectancy are discussed. Next, the chapter describes the role of expectations in affective processes, both during anticipation and during the experience of hedonic outcomes. The chapter ends with a discussion on the brain mechanisms currently thought to underlie expectations and their effects, first focusing on expectancies across domains, and then specifically on pain, an area that has proven to be a particularly tractable and informative model system.

**Key Words:** expectancy, beliefs, placebo, anticipation, emotion, cognitive neuroscience, conditioning, pain, learning

*High expectations are the key to everything.*

—Sam Walton, founder of Wal-Mart

*I find my life is a lot easier the lower I keep my expectations.*

—Calvin, from “Calvin and Hobbes,” by Bill Watterson

*Expect nothing, live frugally on surprise.*

—Alice Walker

Expectations shape the world we perceive, for better and for worse. Students tend to score lower on IQ tests when teachers expect them to perform poorly (Raudenbush, 1984; Rosenthal, 1994). Experimenters' expectations influence experimental outcomes (Rosenthal & Rubin, 1978), even in simple observational studies of animal behavior: Rats are slower when they are tested by experimenters

who believe the rats were specifically bred to perform poorly in mazes, in contrast to experimenters who believe the rats come from a brighter breed (Rosenthal & Fode, 1963). Expectations can also be profoundly beneficial. Expectations that a medical treatment will be beneficial can elicit placebo effects that influence pain (Price, Craggs, Verne, Perlstein, & Robinson, 2007), depression (Kirsch & Sapirstein,

1998), symptoms of Parkinson's disease (de la Fuente-Fernandez et al., 2001), and other physiological outcomes (Meissner, Distel, & Mitzdorf, 2007). Although outcomes are shaped toward expectations in all of these examples, expectations can also bias perception in the opposite direction. Individuals often complain when peers rave about a popular new film, for fear of experiencing disappointment if the film fails to live up to expectations. In sum, expectancies color all areas of affective experience. They fill us with dread or excitement. They affect how we experience events themselves. They bias our memories of significant occasions, sometimes outweighing the influence of our feelings during the event. Thus, it is not surprising to see disagreement over whether it is better to expect the best, expect the worst, or attempt to live life without expectations.

The study of expectations is a very broad one indeed, as expectations play a critical role in virtually every area of psychology and neuroscience. Their effects operate across multiple levels of analysis, from social behavior to low-level neurobiological responses. They are critical in perception, learning (from simple conditioning to complex problem solving), memory, attention, judgment and decision-making, social behavior, and disorders of the mind and brain. Their study is embedded within each field of psychology and is encapsulated by none. Despite the pervasive influence of expectancy, researchers have only recently begun to examine the precise brain mechanisms by which expectancies modulate perception, emotion, and judgment.

Here, we describe a cognitive neuroscience approach to the study of expectations, focusing on the effects of expectations on brain processes and behavior, and on the cognitive and brain mechanisms that underlie them. Rather than comprehensively reviewing expectancy effects across all areas of psychology, we will focus on expectancy effects in affective processes, including the experience of pain and other responses to events with high relevance for physical and social well-being. Among all the domains of affective and clinical outcomes influenced by expectations, pain is the most well studied, with strong evidence for causal effects of expectations on the experience of both clinical and experimental pain (Benedetti, Carlino, & Pollo, 2011; Vase, Petersen, Riley, & Price, 2009; Vase, Riley, & Price, 2002).

### A Brief History: Conditioning vs. Expectancy

Expectancies have been defined in many ways, but a basic commonality across definitions is that

expectations involve a belief that something will happen in the future (Kirsch, Lynn, Vigorito, & Miller, 2004). Expectancy theory dates back to the middle of the twentieth century, when behaviorism dominated the field. Woodworth (1947) and Tolman (1949) 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 (1972), who argued 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 ( $S^*$ ); thus a hungry animal will be more likely to exhibit responses than a sated one because of a difference in  $S^*$ . Finally, Rescorla and Wagner (1972) formalized a model of classical conditioning to explain phenomena such as blocking and conditioned inhibition, which suggest that learning does not depend on simple contiguity between conditioned and unconditioned stimuli. Instead, conditioned responses are elicited on the basis of the information value of conditioned cues, not simply as reflexive responses to the cues themselves (Rescorla, 1988). Thus, according to this perspective, expectancies underlie most forms of learning (Reiss, 1980). Notably, these accounts also suggest that expectancies can be studied in basic animal models.

The definition of expectancy evolved with the cognitive revolution. Researchers focused on a more cognitive interpretation of the notion of expectancy, requiring that expectancies involve explicit, verbalizable awareness of contingencies. This gave rise to important distinctions between conditioning and expectancy. Conditioning in humans can produce explicit awareness of stimulus contingencies and thus lead to conscious expectancies (Brewer, 1974; Kirsch, 1985). Expectancies of this type can be distinguished from other types of conditioned learning that are unconscious, in several ways (Benedetti et al., 2003; Kirsch et al., 2004). First, insofar as conditioning can occur without conscious awareness (Clark, Manns, & Squire, 2002; Lovibond & Shanks, 2002), it is distinct from expectancy. Second, conscious expectancies can be elicited by verbal information or social observation, without

any previous experience with a given stimulus or situation. Third, if conditioned effects are impervious to changes in expectations, they are likely distinct from expectancy.

Interest in the relationship between conditioning and expectancy grew when the medical community began to acknowledge the power of expectancy. 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” (Beecher, 1955), which included an early meta-analysis of 15 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. In the half-century 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 (Benson & Friedman, 1996; Brown, 1998; Chaput de Saintonge & Herxheimer, 1994; Stefano, Fricchione, Slingsby, & Benson, 2001). As part of this effort, a heated debate focused on whether placebo effects depend on expectancy or conditioning.

Conditioning accounts explained placebo effects as arising from a lifetime of associations between pills, white coats, and hospital settings and treatment-induced positive outcomes. Those who held this perspective argued that when these contextual factors are presented in the absence of drug treatment, they elicit healing as a conditioned response (Voudouris, Peck, & Coleman, 1985, 1989, 1990; Wickramasekera, 1980). Indeed, conditioned drug effects are prevalent in rats as well as humans (Herrnstein, 1962), though rats may develop some forms of expectations as well (Schoenbaum, Takahashi, Liu, & Mcdannald, 2011). Others argued that placebo effects depend on explicit beliefs, rather than conditioning (De Jong, van Baast, Arntz, & Merckelbach, 1996; Kirsch, 1985; Montgomery & Kirsch, 1997). From this perspective, placebos should only affect clinical outcomes insofar as patients believe in the treatment and expect relief.

A number of studies attempted to directly isolate the effects of conscious expectancies from other conditioned learning (Amanzio & Benedetti, 1999; Benedetti et al., 2003; De Jong et al., 1996;

Montgomery & Kirsch, 1997; Voudouris et al., 1985, 1989, 1990; for a thorough review, see Stewart-Williams & Podd, 2004). One influential experiment (Benedetti et al., 2003) tested the basis of placebo effects on consciously accessible outcomes (pain in healthy controls and motor performance in patients with Parkinson’s disease) and physiological outcomes that are not accessible to direct conscious experience (cortisol and growth hormone secretion). The critical groups went through conditioning phases (pretreatment with the analgesic ketorolac for pain conditioning, subthalamic nucleus stimulation for Parkinson’s patients, and treatment with sumatriptan for cortisol and growth hormone secretion) 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 biophysical and hormonal responses depend on conditioning (i.e., they did not reverse with instructions), whereas effects on physical responses (pain and motor performance) depend on conscious belief.

Understanding the contributions of conscious and nonconscious processes continues to be a critical issue for the field of expectancy research. However, the vast majority of studies of expectancy effects combine both verbal information and conditioning in order to maximize expectancy effects on outcome measures, as illustrated in the typical paradigms described below. Thus, unless otherwise noted, we include both conscious beliefs and nonconscious anticipatory processes in our consideration of expectancy effects.

### Types of Expectancies

There are two broad classes of expectancy: *stimulus expectancies* and *response expectancies*. The former focuses on beliefs about stimuli in the external world, while the latter focuses on beliefs about one’s own responses to the external world.

Stimulus expectancies can be divided into beliefs about the *timing* of an event, and beliefs about *stimulus characteristics*; in the stress literature, these have been referred to as “contingency predictability” and “what-kind-of-event predictability,” respectively

(Miller, 1981). To study stimulus expectancies, researchers often pair arbitrary cues with verbal information and/or conditioning, so that cues acquire predictive value and induce expectations. Very large bodies of literature on “fear conditioning” in the aversive domain (Delgado, Olsson, & Phelps, 2006; Rogan, Stäubli, & LeDoux, 1997) and conditioned reinforcement in the appetitive domain (Balleine & Killcross, 2006; Dayan & Balleine, 2002) focus on the effects of the cues themselves on brain and behavior, but there are also effects of cues with learned information value on perceptions of and responses to subsequent outcomes. To study these effects, researchers test whether behavioral and brain responses to a single subsequent stimulus are affected by cue-based expectancies, as illustrated in Figure 23.1. For example, to examine the effects of expectations about stimulus characteristics, colored shapes might be paired with two intensities of aversive electric shocks: a mild stimulus and a highly aversive stimulus. During a later test phase, each shape might be paired with a moderately aversive stimulus, and researchers can assess whether cue-based expectancies influence how the stimulus is perceived. Using this approach, researchers have examined whether perception is affected by expectations about stimulus intensity (Arntz, van den Hout, van den Berg, & Meijboom, 1991; Brown, Seymour, Boyle, Elderedy, & Jones, 2008; Keltner et al., 2006; Lorenz et al., 2005; Ploghaus et al., 2000; Wallace, 1985), location (Coull &

Nobre, 1998; Downing, 1988; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999), and category (Bollinger, Rubens, Zanto, & Gazzaley, 2010; Zellner, Strickhouser, & Tornow, 2004). Results from these paradigms are summarized in Figure 23.1A. As described later in this review, the dominant finding is that perceived outcomes are assimilated toward expected values.

A similar approach can be used to study expectations about timing, as illustrated in Figure 23.1B. One cue (e.g., an arbitrary shape) might be consistently followed 5 seconds later by an aversive shock stimulus, whereas another might be unrelated to the time of shock onset, inducing uncertainty. If researchers are interested in studying anticipation or dread, researchers can examine responses to the cue itself. To study the effects of predictability or uncertainty, analyses can focus on responses to the shock as a function of the antecedent cue. Using this approach, researchers have studied behavioral and neural effects of predictability (Alink, Schwiedrzik, Kohler, Singer, & Muckli, 2010; Berns, McClure, Pagnoni, & Montague, 2001; Carlsson et al., 2006; Crombez, Baeyens, & Eelen, 1994), anticipation (Carlsson, Petrovic, Skare, Petersson, & Ingvar, 2000; Hsieh, Stone-Elander, & Ingvar, 1999; Jensen et al., 2003; Kahnt, Heinze, Park, & Haynes, 2010; Knutson, Adams, Fong, & Hommer, 2001; Koyama, Tanaka, & Mikami, 1998; Ploghaus et al., 1999; Porro et al., 2002; van Boxtel & Böcker, 2004), and dread or anticipatory anxiety (Berns

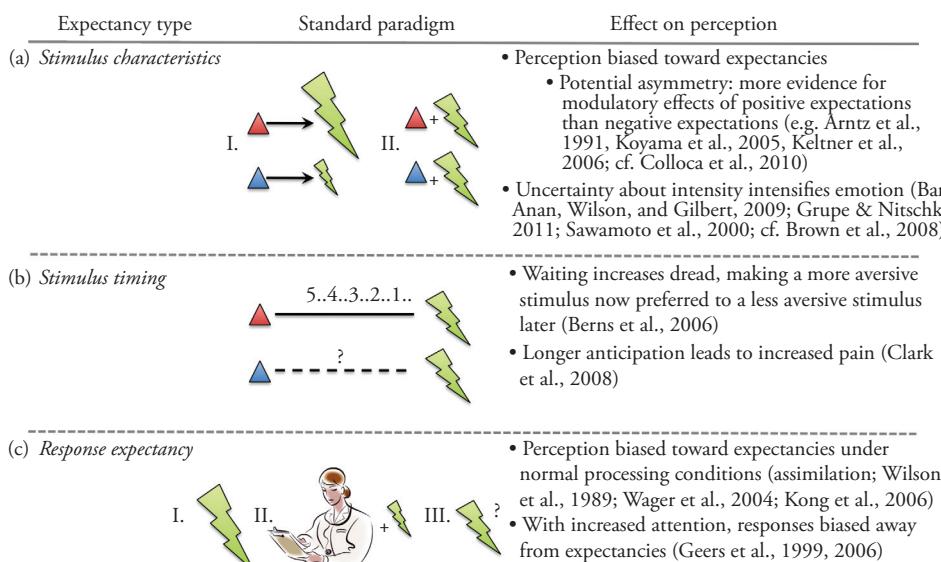


Figure 23.1 Types of expectancies. A. Stimulus characteristics. B. Stimulus timing. C. Response expectancy.

et al., 2006; Mobbs et al., 2007, 2009; Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006; Simmons, Matthews, Stein, & Paulus, 2004). As summarized in Figure 23.1, and as discussed in more detail below, expectations about stimulus timing also influence perception, affecting both brain and behavioral responses. For example, shock after a long delay is perceived as more unpleasant than shock after a short delay, and individuals who report the highest sensation of dread show greater activation in pain-related regions during this delay period (Berns et al., 2006).

A second class of expectancies is concerned primarily with one's internal response to the outside world, rather than the state of the outside world per se. When beliefs concern one's own *nonvolitional responses* (e.g., emotional reactions, physiological responses, pain), they are referred to as *response expectancies* (Kirsch, 1985). Examples of response expectancies include the placebo response (expectations for healing that accompany otherwise inert treatments; Kirsch, 1985, 1999, 2004) and affective forecasting (beliefs about one's future state; Wilson & Gilbert, 2003). To study response expectancies, researchers generally manipulate the context surrounding an experience. This is most often accomplished through placebo manipulations, which combine conditioning and verbal information to induce expectations about a treatment that, unbeknownst to subjects, is actually pharmacologically inert (see Figure 23.1C). During a later test phase, the placebo treatment is administered, and researchers test whether participants' experience is affected.

These different types of expectations often occur in tandem in natural situations. For example, a host might inform a dinner party guest that his or her ex-partner was also invited and will arrive any second. Chances are that this guest will feel a sense of dread (expectation about timing), anticipating an unpleasant conversation (expectation about stimulus characteristics) and expecting to feel uncomfortable (response expectancy). As these expectancies are therefore often linked, they are regularly discussed interchangeably in the expectancy literature, particularly in the case of pain-related stimulus expectancies and response expectancies. However, each can be effectively isolated and brought under experimental control, using the experimental approaches described above. One important outstanding question is whether these expectancies are supported by distinct or overlapping mechanisms.

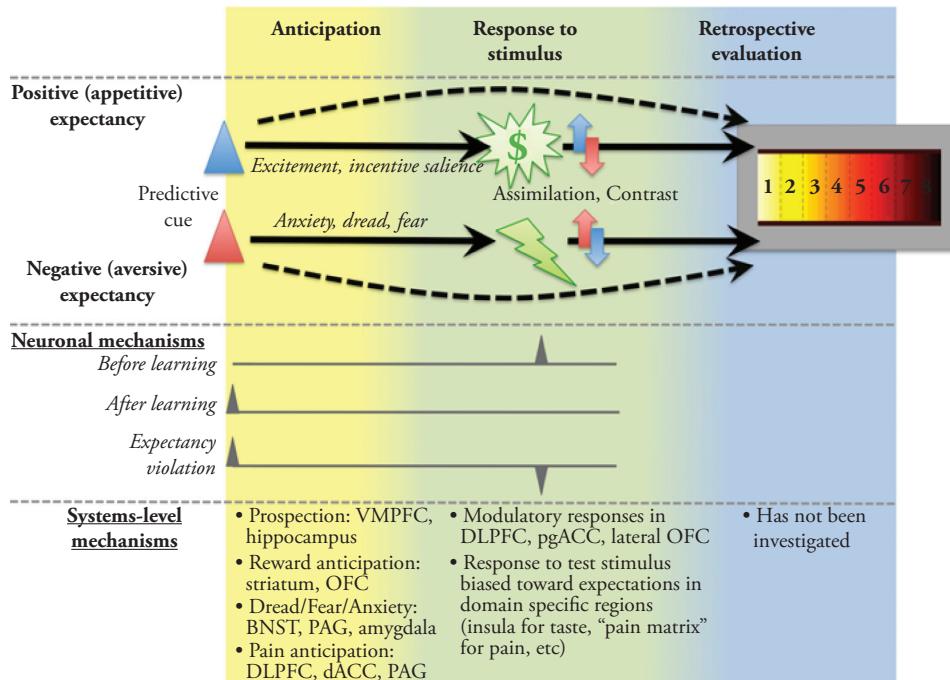
## The Role of Expectancy in Affective Processing

Expectancies are particularly powerful in affective domains. Expectations influence responses to pleasant and unpleasant tastes (Berns et al., 2001; Nitschke, Dixon, et al., 2006; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Sarinopoulos, Dixon, Short, Davidson, & Nitschke, 2006), monetary reward and punishment (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Christakou, Brammer, Giampietro, & Rubia, 2009; Elliott, Friston, & Dolan, 2000; Rolls, McCabe, & Redoute, 2007; Spicer et al., 2007), positive and negative emotional images (Bermpohl et al., 2006; Petrovic et al., 2005), and other affect-eliciting material such as humorous cartoons and films (Geers & Lassiter, 1999, 2002; Wilson, Lisle, Kraft, & Wetzel, 1989). A great number of studies have demonstrated that expectancies modify pain perception; we review this work in detail in the final section of this review. In each of these domains, expectations influence each stage of affective processing: before, during, and after emotional experience (see Figure 23.2). We review expectancy effects on each of these stages in detail in the following sections.

### *Anticipatory Expectancy Effects*

The period immediately preceding the appearance of an expected stimulus or event has garnered a great deal of attention in emotion and learning research. While anticipatory emotions and learning mechanisms are highly related, they are also dissociable, as described below. Anticipation is characterized by approach and avoidance behaviors and emotions, illustrated in the top panel of Figure 23.2. When a positive stimulus is expected, this results in approach behavior and a subjective sense of excitement or reward anticipation. This anticipatory state can be characterized as a kind of "wanting" (Berridge & Robinson, 1998), depending on the motivational state of the organism, and is likely to be mediated by phasic dopamine release in the nucleus accumbens and other forebrain areas from the ventral tegmental area (Schott et al., 2008; Tsai et al., 2009). An expected aversive stimulus elicits avoidance behavior and may cause subjective sensations of fear, dread, or anxiety, depending on the level of certainty (*anxiety* is the state of aversive anticipation without a specific object, whereas *fear* involves expectations about specific events).

While a detailed discussion of the literature on these emotions is outside the scope of this review, a substantial number of neuroimaging studies have focused on identifying neural mechanisms



**Figure 23.2** Expectancy effects on stages of affective processing. BNST, ; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; PAG, periaqueductal gray; pgACC, pregenual anterior cingulate cortex; VMPFC, ventromedial prefrontal cortex.

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underlying the generation of each of these affective responses (Bernset al., 2006; Knutson, Adams, et al., 2001; Knutson, Fong, Adams, Varner, & Hommer, 2001; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Mobbs et al., 2007, 2009; Phelps et al., 2001). Some current claims about the brain substrates underlying different types of affective responses related to expectancy are summarized at the bottom of Figure 23.2. A number of individual studies imply that varieties of anticipatory affect are associated with distinct neural signatures, but the sensitivity and specificity of brain activity in these areas for particular types of affective states has not been established in humans. Meta-analyses indicate that claims of one-to-one mappings between affective states and gross anatomical brain regions are not likely to be warranted (Barrett & Wager, 2006; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Wager, Phan, Liberzon, & Taylor, 2003; cf. Phan, Wager, Taylor, & Liberzon, 2002).

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In addition, the rather straightforward view that “positive” and “negative” affective responses are natural categories respected by the brain, and that positive and negative affect are de facto triggered by appetitive and aversive cues, is likely to require substantial revision. A major contribution

of appraisal and psychological construction-based theories of emotion (Barrett & Wager, 2006; Ellsworth & Scherer, 2003; Scherer, 1999) is to illustrate the powerful influences of complex social and situational information on the types of affective responses that might be elicited by predictive cues. Cues that predict desired rewards, for example, could trigger arousal, eagerness, and approach behavior if rewards are accessible, but frustration and aggression if they are not. Cues that predict aversive outcomes can elicit avoidance behavior if escape strategies are available, anxiety if the cues are ambiguous with respect to the timing and nature of outcomes, fear if outcomes are aversive and impeding, or aggression if the perceived cause of threat is another individual.

As illustrated in cartoon form in the middle panel of Figure 23.2 (adapted from Schultz, 2007), the anticipation period is also critical in the context of computational and neural models of reinforcement learning. These models, discussed in detail later in this review (see section below, “How Do Expectancies Emerge?”), suggest that when an organism has learned that a cue predicts a subsequent reward, dopaminergic midbrain neurons fire in response to the cue (Schultz, 2007; Schultz,

Dayan, & Montague, 1997; Schultz & Dickenson, 2000). Similar patterns have been observed in primate amygdala for both appetitive and aversive outcomes (Belova, Paton, Morrison, & Salzman, 2007). The neuronal and neurochemical levels of analysis are not incompatible with the specific anticipatory emotions discussed above, and current perspectives generally attempt to integrate across these levels, but this is a challenging endeavor. For example, whereas the amygdala was once thought of as one of the main “seats of emotion” and many have posited a specific role for it in signaling fear, current theories focus on amygdala involvement in processes that are related, but not specific, to fear, such as cue value (Salzman, Paton, Belova, & Morrison, 2007) and vigilance or stimulus salience (Whalen et al., 2009).

### **Expectancy Effects on Affective Experience**

Expectations affect not only anticipatory responses but also responses to emotional stimuli themselves. For example, cue-based expectancies influence whether tastes are perceived as pleasant or unpleasant (Nitschke et al., 2006; Sarinopoulos et al., 2006). Information about the price of a wine influences how much it is enjoyed (Plassmann, O’Doherty, Shiv, & Rangel, 2008). Beliefs about anxiolytic treatments reduce the unpleasantness of aversive images (Petrovic et al., 2005). Expectancy effects on subjective experience also extend to social influences. Knowing that other people enjoyed a cartoon causes people to find it more humorous (Wilson et al., 1989). Appraisal theories of emotion suggest that emotion generation depends critically on an individual’s evaluation of his or her context, which is influenced by current, remembered, and imagined future circumstances (Ellsworth & Scherer, 2003; Scherer, 1999). Thus, as with expectancy effects on anticipatory processes, affective responses to outcomes can potentially be influenced by complex appraisals.

In 1989, Timothy Wilson and co-authors formalized the Affective Expectancy Model (AEM; Wilson et al., 1989), which posits that subjective emotional responses depend as much on expectations as they do on emotional stimuli themselves. According to the AEM, affective experiences stem from an interaction between affective expectations (expectations about what one will feel) and stimulus characteristics. When emotional responses are biased in the direction of expectancies, this is referred to as *assimilation*. The AEM suggests that assimilation conserves processing resources by allowing faster, shallower processing of stimuli when a priori

expectations about emotional meaning are strong. Thus, emotional responses will assimilate to expectancies when (1) affective expectations are congruent with a stimulus (e.g., when individuals expect to like a *New Yorker* cartoon that is indeed funny), or (2) ~~or~~ when affective expectancies are incongruent with a stimulus but processing is minimal (e.g., when individuals expect to like a boring *New Yorker* cartoon and therefore turn the page quickly after a chuckle). In both of these cases, attentional resources are conserved during stimulus processing and introspection, as demonstrated by speeded response times during stimulus viewing and during reaction probes (Wilson et al., 1989); thus, the discrepancy between the stimulus and expectancies is not noticed in the incongruent case because of superficial attention. Laboratory investigations find evidence of assimilation across a host of domains, including pain (Atlas, Bolger, Lindquist, & Wager, 2010; Keltner et al., 2006; Kong et al., 2006, 2008; Koyama, McHaffie, Laurienti, & Coghill, 2005; Wager et al., 2004; Wager, Scott, & Zubieta, 2007), taste (Nitschke, Dixon, et al., 2006; Plassmann et al., 2008; Sarinopoulos et al., 2006), emotion (Klaaren, Hodges, & Wilson, 1994; Wilson et al., 1989), and person perception (Hamilton & Sherman, 1996; Rosenthal, 1987, 1994; Rosenthal & Rubin, 1978).

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While experimentally manipulated expectancies generally lead to assimilation, common belief suggests that having positive expectations can actually lead to negative outcomes. The statement “I didn’t want to get my hopes up” belies the notion that expecting something positive will only lead to disappointment. Individuals often avoid seeing a film that has received rave reviews from friends and critics, for fear that the experience will not “live up to expectations” and will instead be less enjoyable than if the film had been seen without prior information. *Contrast* describes the phenomenon whereby subjective experience is biased away from expectancies. Echoing earlier theories from work in priming and categorization (Herr, 1986; Herr, Sherman, & Fazio, 1983; Lombardi, Higgins, & Bargh, 1987), Wilson hypothesized that contrast occurs when affective expectations are incongruent with stimulus valence and individuals notice this discrepancy. In this case, stimulus processing and the formation of affective responses will take longer.

While Wilson failed to find evidence of contrast effects on perception in his original studies, subsequent work did find evidence of contrast effects. One experiment (Geers & Lassiter, 1999) tested

Wilson's predictions about level of encoding using a unitization paradigm, in which subjects segment films on the basis of meaningful actions. One group was instructed to segment a film that was not funny into the *largest* meaningful actions (gross-level attention), while a second group was instructed to segment behavior based on the *smallest* meaningful actions (fine-grained attention). This attention manipulation was crossed with an expectancy manipulation (positive expectation vs. no expectation about the film). Results confirmed the predictions of the AEM: within the gross-level attention group, participants with positive expectations enjoyed the film more than those with no expectations (assimilation), but within the fine-grained attention group, participants with positive expectations enjoyed the film *less* than those without expectations (contrast).

Contrast also occurs when individuals have prior exposure to an expectation-inconsistent stimulus (Geers, Helfer, Kosbab, Weiland, & Landry, 2005). Geers and colleagues crossed an expectancy manipulation (positive expectation vs. no expectation) with prior exposure to a relatively humorless film. Half the group saw the film and returned several weeks later to participate in a supposedly unrelated experiment that happened to show the same film. Those in the positive expectation group who had seen the film rated it as less funny than those who had seen the film but had no expectations in the subsequent session, and those who had positive expectations without prior exposure to the film.

Contrast is also observed when expectations are accompanied by uncertainty (Zellner et al., 2004): When unfamiliar food products are paired with congruent or incongruent expectations, incongruent expectations lead to contrast, rather than uncertainty.

Finally, individual differences can influence whether contrast or assimilation will occur. Assimilation is more likely for optimists (Geers & Lassiter, 2002) and for individuals low in need for cognition (Geers & Lassiter, 2003), whereas pessimists and those high in need for cognition take longer to process stimuli and hence notice discrepancies and show contrast effects.

Thus, in each of these examples, attention seems to moderate the relationship between expectations and affective experience. Prior exposure, uncertainty, pessimism, and need for cognition all increase fine-grained attention and lead to contrast, whereas assimilation is dominant with broad attention. Notably, neuroimaging studies of expectancy

have focused on identifying the mechanisms underlying effects that assimilate with expectations. Understanding the mechanisms underlying contrast effects, the conditions under which they arise, and the relationship between contrast and feelings of disappointment or surprise are important directions for future work.

### **Retrospective Expectancy Effects**

Affective expectations can directly influence retrospective evaluations of affective experiences, independent of responses to the event. For example, in one study that took place at the end of a fall semester (Klaaren et al., 1994), students predicted how much they expected to enjoy their upcoming winter vacation. Several weeks after students returned from break, Klaaren and colleagues collected ratings of overall vacation enjoyment, as well as ratings of specific experiences during the vacation. Retrospective ratings of overall enjoyment were predicted by not only experiences while on the vacation but also pre-vacation expectancies. (In this case, expectancies did *not* influence the enjoyableness of vacation experiences themselves.) In a follow-up study, the authors experimentally manipulated expectations and found similar results. Participants who were invited to take part in an "enjoyable" study enjoyed watching a film at the lab more than a separate group that was given no information about the study, but also reported greater willingness to return and more overall enjoyment several weeks later, independent of their experience during the film. Similar results have been found in studies of placebo analgesia, which have sometimes been found to be larger in retrospective reports than immediate ratings of pain (De Pascalis, Chiaradia, & Carotenuto, 2002; Price, Milling, Kirsch, & Duff, 1999).

Taken together, these findings suggest that pre-experience expectancies may directly influence retrospective evaluations, represented by the dashed line in Figure 23.2. Expectancy effects on retrospective reports may result from biased memories of pretreatment (baseline) experiences (Feine, Lavigne, Dao, Morin, & Lund, 1998) or biased memories of affective experiences relative to concurrent ratings of those experiences (De Pascalis et al., 2002; Price et al., 1999). In addition, different factors may influence online vs. retrospective ratings: Retrospective ratings of colonoscopies depend on peak pain and pain at the end of the procedure, rather than integrating across the entire duration of real-time ratings (Redelmeier & Kahneman, 1996; Redelmeier, Katz, & Kahneman, 2003). Finally, expectancy effects on

retrospective reports may reflect self-consistency biases (Wells & Sweeney, 1986), whereby individuals report experiences consistent with expectations simply to maintain self-esteem and avoid psychological uncertainty. As discussed in more detail later, the question of whether expectations affect retrospective evaluations without affecting stimulus processing has caused a heated debate in the field of placebo research, and is one of the critical reasons to test whether expectations affect more objective outcome measures, such as pain-related brain responses.

### Mechanisms of Expectancy

It is clear that expectancies strongly modify affective experience. We now turn to the psychological processes and neural mechanisms hypothesized to support these effects. We focus here on the processes that give rise to expectancies, those likely to be involved in maintaining expectancies, and those thought to play a modulatory role in affecting perception.

### How do Expectancies Emerge?

There are two main routes to expectancy formation: experience-dependent expectancies (e.g., those elicited by conditioning), and expectancies formed without direct exposure (e.g., those elicited by verbal instructions). While both routes might lead to similar mechanisms of expectancy maintenance and downstream modulation, the pathways involved in the development of these two types of expectancies are likely to be quite distinct.

First, expectations can be based on one's own experiences or previous reactions to a stimulus. This can occur for both simple classical conditioning-based expectancies and more complex response expectancies. One important line of work in the field of reinforcement learning provides a mechanistic account of how experience-based expectations are developed in the simple case of stimulus expectancies that arise through classical conditioning. A cartoon depicting this chain of events (adapted from Schultz, 2007) is presented in the middle panel of Figure 23.2. In brief, in response to an unpredicted rewarding event, dopaminergic midbrain neurons increase their firing rates, signaling a prediction error (Schultz et al., 1997; Schultz & Dickinson, 2000). Over time, as an animal learns that rewards are predicted by an antecedent cue, the same neuron will respond to the cue, now signaling predictive value. Hence, this value signal represents an expectation about the reward that will be

delivered. After learning, if the cue is presented but a reward is not delivered, the firing rate in the same neurons will decrease relative to baseline at the time when the reward was expected. This decrease in firing rate signals a negative prediction error (reward expected, but not delivered), which will update expected value on the following trial. These patterns of neural responses can be described by computational models (Rescorla & Wagner, 1972; Sutton & Barto, 1981), and neuroimaging studies have shown that the same models predict brain responses in humans during reward learning (O'Doherty, 2004; O'Doherty et al., 2003) as well as during aversive learning (Delgado, Li, Schiller, & Phelps, 2008; Ploghaus et al., 2000; Seymour et al., 2004, 2005) and even in purely cognitive domains (Aron et al., 2004; Rodriguez, Aron, & Poldrack, 2006). Medial and lateral orbitofrontal cortex, which contains neurons that flexibly encode both aversive and rewarding outcomes (Morrison & Salzman, 2009), appears to represent the expected values of specific cues and outcomes (McDannald, Lucantonio, Burke, Niv, & Schoenbaum, 2011; Murray, O'Doherty, & Schoenbaum, 2007; Schoenbaum & Roesch, 2005; Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009; Schoenbaum, Saddoris, & Stalnaker, 2007). Prediction errors are encoded primarily by the ventral striatum (Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008; McDannald et al., 2011; O'Doherty et al., 2004; Rutledge, Dean, Caplin, & Glimcher, 2010; Schoenbaum & Setlow, 2003) and basolateral amygdala (Belova, Paton, & Salzman, 2008; Roesch, Calu, Esber, & Schoenbaum, 2010; Schoenbaum, Chiba, & Gallagher, 1998; Schoenbaum, Setlow, Saddoris, & Gallagher, 2003). The dynamic effects of expected value and prediction errors on responses in these systems illustrate how expectancies emerge, how expectancy violations affect neural responses, and how experiences update expectations over time in the case of simple conditioning-based learning.

Response expectancies that involve predictions about more complex scenarios are unlikely to be fully explained by these simple computational models. Research on affective forecasting focuses on understanding how individuals predict future emotional responses to hypothetical situations, and why these predictions are generally incorrect (Gilbert & Wilson, 2009). A dominant hypothesis is that previous experiences influence future expectations through mental simulation, or *prospection*. Individuals may use memories of prior experiences to imagine themselves in a future situation, and use their feelings about the imaginary situation to

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in the middle panel of Figure 23.2. In brief, in response to an unpredicted rewarding event, dopaminergic midbrain neurons increase their firing rates, signaling a prediction error (Schultz et al., 1997; Schultz & Dickinson, 2000). Over time, as an animal learns that rewards are predicted by an antecedent cue, the same neuron will respond to the cue, now signaling predictive value. Hence, this value signal represents an expectation about the reward that will be

generate predictions about future emotions and affective events (Gilbert & Wilson, 2007, 2009; Schacter, Addis, & Buckner, 2007).

Explicit prospection is thought to depend on interactions between self-related processing and episodic memory, both of which converge in the ventromedial prefrontal cortex (VMPFC). Self-related processing is a placeholder term for the representation of information relevant for the status and well-being of the social and physical self. Such representations appear to involve the VMPFC in connection with (a) dorsomedial prefrontal and lateral temporal systems important in social cognition and (b) subcortical regions involved in valuation and affect. Episodic memory involves VMPFC in connection with a circuit that includes the hippocampus and surrounding medial temporal regions and the posterior cingulate (Addis, Pan, Vu, Laiser, & Schacter, 2009; Buckner & Carroll, 2007; Fellows & Farah, 2005; Schacter et al., 2007; Wheeler, Stuss, & Tulving, 1997). In addition, mental simulation might elicit hedonic reactions that would in turn affect domain-specific mechanisms associated with the imagined experience (Gilbert & Wilson, 2007). Consistent with this hypothesis, humans and primates show increased activation of brain regions involved in nociception when anticipating pain (Koyama et al., 1998; Porro et al., 2002), and similarly, when anticipating reward, individuals activate brain regions that are also activated in response to rewarding events (Bray, Rangel, Shimojo, Balleine, & O'Doherty, 2008; Knutson, Adams, et al., 2001; Knutson, Fong, et al., 2001). It is important to note that it may be impossible to dissociate anticipatory affect associated with prospection from computations of expected value. Value and anticipatory affect go hand in hand and might very well involve the same underlying processes.

People also form affective expectancies in the absence of direct experience with a stimulus or situation. An individual might expect to like a film on the basis of friends' impressions and critics' reviews. Expectations might also stem from knowledge of how one is supposed to behave in a certain situation; for example, one might never have spoken in public, but might know that giving a talk is generally anxiety provoking. A number of studies have investigated the neural systems underlying learning in these contexts. Observational learning has been studied with vicarious conditioning paradigms (Colloca & Benedetti, 2009; Hygge & Ohman, 1978; Mineka & Cook, 1993; Olsson & Phelps, 2004). Rule-based learning can be tested by

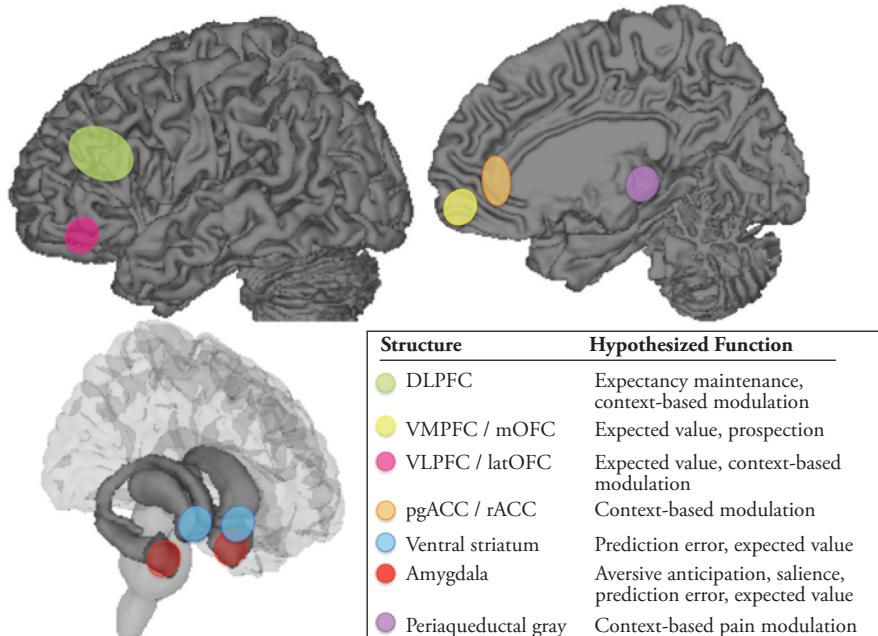
delivering verbal information about contingencies and testing responses without actual reinforcement (Amanzio & Benedetti, 1999; Colloca & Benedetti, 2006; Colloca, Sigaudo, & Benedetti, 2008; Colloca, Tinazzi, et al., 2008; Funayama, Grillon, Davis, & Phelps, 2001; Grillon, Ameli, Woods, Merikangas, & Davis, 1991; Phelps et al., 2001). These studies suggest that these different routes to learning elicit similar effects as experience-dependent learning, including physiological responses (e.g., differential skin conductance responses; Hygge & Ohman, 1978; Mineka & Cook, 1993) and placebo and nocebo effects (Colloca & Benedetti, 2009), though placebo effects based on verbal information without conditioning are smaller than those based on experience or social observation (Amanzio & Benedetti, 1999; Colloca & Benedetti, 2009). Both routes are associated with amygdala activation during fear learning, similar to standard fear conditioning (Phelps, 2006). Vicarious learning or its autonomic expression, however, might depend critically on the left amygdala, as patients with left temporal lobe lesions fail to show potentiated startle responses as a function of verbal information (Funayama et al., 2001).

### **How Are Expectancies Maintained?**

Expectancy involves maintenance of a belief, particularly in the case of conscious, verbalizable expectancies. Two regions have been consistently observed in studies of expectancy effects in various domains that are likely to support expectancy maintenance: the dorsolateral prefrontal cortex (DLPFC), and the ventrolateral prefrontal cortex (VLPFC)/lateral orbitofrontal cortex (OFC) (Atlas, Wager, D'Esposito, & Smith, 2009; Wager, 2005b; see Figure 21.11). Studies of executive working memory consistently activate the DLPFC (Wager & Smith, 2003), and it is activated during anticipation and experience in a number of experimental investigations of expectancy effects on pain (Atlas et al., 2010; Craggs, Price, Perlstein, Verne, & Robinson, 2008; Wager, Atlas, Leotti, & Rilling, 2011; Wager et al., 2004; Watson et al., 2009), taste (Sarinopoulos et al., 2006), and emotion (Petrovic et al., 2005). Direct stimulation of the DLPFC also appears to block placebo-based expectancy effects on pain (Krummenacher, Candia, Folkers, Schedlowski, & Schönbaechler, 2009). Interestingly, the DLPFC is not only critical for working memory, but it also plays a key role in cognitive control (Kim, Johnson, Cilles, & Gold, 2011; Miller, 2000; Miller & Cohen, 2001; Taren, Venkatraman, & Huettel, 2011). Thus, this region

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**Figure 23.3** General brain mechanisms of expectancy. See Figure 23.2 and text for abbreviations.

has been thought to be key in maintaining expectancies and in modulating perception in accordance with expectancies, as described in more detail below (Lorenz, Minoshima, & Casey, 2003). The VLPFC/lateral OFC has also been activated in a number of placebo studies (Lieberman et al., 2004; Petrovic et al., 2005; Wager et al., 2004, 2011) and is generally thought to support affective value, expectancy maintenance, and regulation of emotion (Kringelbach, 2005; Lieberman et al., 2004; Petrovic et al., 2010; Wager, 2005b).

When expectancies concern affective stimuli or outcomes, they involve predictions about affective value. As mentioned above, learning studies suggest that the OFC tracks—and is necessary for representing—the expected value of anticipated outcomes (Hare et al., 2008; Mcdannald et al., 2011; Murray et al., 2007; Schoenbaum & Roesch, 2005; Schoenbaum et al., 2007, 2009). Recent evidence suggests that it is less important for tracking the overall expected value of cues, and rather is necessary for representing specific outcomes associated with specific cues (Schoenbaum, Takahashi, Liu, & Mcdannald, 2011). It also may be most important for “model-based” expectancies (Daw, Niv, & Dayan, 2005; Daw, O’Doherty, Dayan, Seymour, & Dolan, 2006), in which expected value is determined by forward-looking conceptualization and prediction of future outcomes. Thus, in

studies of stimulus expectancies like those depicted in Figure 23.1, lateral OFC may become activated in anticipation of pain—that is, in response to pain-predictive cues—in order to represent the value of the upcoming pain associated with that cue. Similarly, it may be active in placebo conditions, because the expected value is heavily determined by conceptual processes, placing metabolic demands on expectancy formation in lateral OFC. Lateral OFC is one of the most consistently activated areas in placebo studies (Wager & Fields, *in press*) and by this view, lateral OFC may also be essential for placebo effects.

### **How Do Expectancies Modulate Affective Responses?**

Whether they lead to assimilation or contrast, expectancies are likely to affect perception through specific mediating psychological mechanisms (Wager, 2005a). Here, we consider both the psychological processes likely to give rise to these effects and the neural mechanisms that may support expectancy-based changes in downstream processes that in turn affect perception.

Three specific regions have emerged as central in expectancy-based modulation across domains. These are the DLPFC, particularly in the left hemisphere, the lateral OFC, and the pregenual/rostral anterior cingulate cortex (rACC). Each of these regions is

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associated with expectancy-based *increases* that are correlated with the magnitude of expectancy effects on subjective experience, and the magnitude of expectancy effects on downstream domain-specific responses (e.g., amygdala activation during emotion processing, insula responses during taste perception, insula and thalamus responses during pain) (Atlas et al., 2010; Bingel, Lorenz, Schoell, Weiller, & Buchel, 2006; Craggs, Price, Verne, & Perlstein, 2007; Kong et al., 2006; Sarinopoulos et al., 2006; Wager et al., 2004, 2011). While these patterns of interactions among brain regions suggest that these regions are involved in expectancy-based modulation, it is unknown whether this modulation comes about through expectancy-related changes in intervening psychological processes.

First, as hypothesized in the AEM (Wilson et al., 1989), expectancies may induce changes in attention. As a result of expectations, individuals may engage in more superficial encoding or might attend selectively to congruent information. This hypothesis is supported by research suggesting that expectancies that are congruent with stimulus properties lead to faster processing and decision-making than incongruent expectancies (Wilson et al., 1989). Individuals adjust somatic attention in response to expectations for high pain (Johnston, Atlas, & Wager, 2012) and during placebo treatment (Geers, Helfer, Weiland, & Kosab, 2006). Interestingly, in one recent study (Johnston, Atlas, & Wager, 2012), cue-based expectations for high pain increased focus on the body, and focus on the body actually *reduced* expectancy effects on pain reports. Thus expectancy-based changes in attention produced effects opposite in sign from those of expectancies, suggesting that robust expectancy effects on pain experience must be supported at least in part by mechanisms other than changes in attention. Similarly, other recent work suggests that at least some types of expectancy effects, particularly those elicited by placebo treatments, are not reducible to changes in attention. Buhle and Wager (Buhle, Stevens, Friedman, & Wager, 2012) found that both placebo and a difficult, attention-demanding working memory task reduced pain, but that these effects were essentially completely additive. The fact that the placebo treatment and the difficult cognitive task neither interfered with nor potentiated one another suggests that their mechanisms and processing resources may be independent.

Second, in the case of response expectancies or expectations about negative or positive stimuli, affective expectancies might increase or decrease

stress and anxiety (Aslaksen & Flaten, 2008; Wager, 2005a). This hypothesis is supported by research demonstrating that individuals with low state anxiety show larger placebo responses (McGlashan, Evans, & Orne, 1969; Vase, Robinson, Verne, & Price, 2005), that individual differences in placebo analgesia are correlated with changes in subjective stress (Aslaksen & Flaten, 2008), and that nocebo effects, or effects of expectations that a treatment will *increase* pain, are abolished by benzodiazepines, a class of anxiolytics (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006). Expectancy-induced changes in anxiety, stress, and general affective state are likely to cause nonspecific effects that would be additive with stimulus effects.

A third possibility, mentioned above, is that expectancies might modulate evaluations and decision-making without changing stimulus processing (Wager, 2005a). This hypothesis is supported by sensory decision theory (SDT) studies that suggest that placebo treatments change response criteria, but not discriminability of pain processing (Clark, 1969; Feather, Chapman, & Fisher, 1972), and that expectancies influence retrospective pain ratings by biasing memories of pretreatment pain (Price et al., 1999). In addition, in many cases placebo effects on reported pain are substantially larger than corresponding effects on brain markers of pain-processing (Wager, Matre, & Casey, 2006).

Finally, expectancy-based modulation might involve unique mechanisms unexplained by these proposed mediating psychological factors. One specific line of research has focused on the endogenous opioid system and its role in placebo analgesia. Placebo effects are abolished by the opioid antagonist naloxone (Eippert, Bingel et al., 2009; Levine, Gordon, & Fields, 1978), and PET imaging studies indicate that placebo responses are accompanied by increased  $\mu$ -opioid receptor (MOR) binding in limbic regions (Scott et al., 2007, 2008; Wager, Scott, & Zubieta, 2007; Zubieta et al., 2005). Consistent with the idea that opioids are critical for expectancy-based modulation, placebo analgesia is also associated with increases in activation in the MOR-rich rACC and the periaqueductal gray (PAG) (Bingel et al., 2006; Petrovic, Kalso, Petersson, & Ingvar, 2002; Wager et al., 2004), as well as increased connectivity between these regions (Bingel et al., 2006; Wager et al., 2007) that is abolished with naloxone (Eippert, Bingel et al., 2009). The PAG produces analgesia when stimulated in humans (Baskin et al., 1986; Boivie & Meyerson, 1982) and has inhibitory connections with primary afferent nociceptors

in the spinal cord's dorsal horn (Basbaum & Fields, 1984; Fields, 2004). Several studies have demonstrated that placebo analgesia can reduce responses to noxious events in the spinal cord, consistent with descending modulation (Eippert, Finsterbusch, Bingel, & Buchel, 2009; Goffaux, de Souza, Potvin, & Marchand, 2009; Goffaux, Redmond, Rainville, & Marchand, 2007). While this literature supports the idea that placebo treatments can engage “gate control” mechanisms that can block nociceptive afferents at the spinal level (Melzack & Wall, 1965), the scope and importance for overall analgesia of these potential spinal effects are unknown. In addition, it is unknown whether opioids underlie stimulus expectancy effects, or whether opioid-based modulation or other specific mechanisms could mediate expectancy effects in non-nociceptive affective domains.

### Expectancy Effects on Affective Experience

While research on conditioning and learning models has provided a strong picture of the neural mechanisms that give rise to expectations about reward and punishments, we know far less about how expectations affect *perception* of affective events. As mentioned in the previous sections, a critical question has been whether expectancies modulate affective processing, or whether they modulate decision-making and subjective reports independent of actual experience. Early studies used sensory decision theory to separate changes in stimulus discriminability from changes in report criterion and found that placebo analgesia was associated with changes in decision criteria but not sensitivity (Clark, 1969; Feather et al., 1972), suggesting that expectancies affect decision-making but not sensory processing. However, later studies have used neuroimaging and electrophysiological approaches to demonstrate that expectancies modulate responses within brain regions relevant for processing pain (Atlas et al., 2010; Brown, Seymour, Boyle et al., 2008; Brown, Seymour, El-Deredy, & Jones, 2008; Koyama et al., 2005; Price et al., 2007; Wager et al., 2004, 2006; Watson et al., 2009), taste (Nitschke, Dixon, et al., 2006; Sarinopoulos et al., 2006), and emotion (Petrovic et al., 2005; Sharot, De Martino, & Dolan, 2009). This suggests that affective expectancies do indeed modulate brain responses.

However, expectancies can affect brain responses in a domain-relevant region without that region driving subjective experience. There are many examples of stimulus effects on domain-relevant brain responses that do not contribute to conscious

perception, such as amygdala activation to unperceived laser stimulation (Bornhovd et al., 2002) and masked emotional faces (Whalen et al., 1998, 2004). Further, many of the regions involved in affective processing have multiple roles. For example, expectancy effects have been observed on insula responses to noxious stimulation (Koyama et al., 2005; Price et al., 2007; Wager et al., 2004) as well as to pleasant and aversive tastes (Nitschke, Dixon, et al., 2006; Sarinopoulos et al., 2006). While the insula is reliably activated by noxious and gustatory stimuli, it is also affected by interoception (Craig, 2002, 2009), general task set (Dosenbach et al., 2006), negative affect (Shackman et al., 2011), and a variety of emotions (Lindquist et al., 2012). Each of these processes might be affected by changes in expectancy. Thus, expectancy-induced changes in the insula or other affective regions might reflect changes in attention, anxiety, or other processes that are affected by expectancy, rather than changes in basic stimulus processing. This account would be consistent with Wilson’s idea that an experience that fails to meet expectations is processed the same, but also involves disappointment (Wilson et al., 1989). It might be this disappointment (or relief, in the case of positive experiences like analgesia) that contributes to subjective experience. Thus, while expectancies might modulate activation in domain-relevant regions, subjective reports may still be driven by regions involved in decision-making and evaluation independent of activation within primary regions. In order to isolate the mechanisms whereby expectancies affect subjective experience, expectancy effects on the brain need to be related to expectancy effects on behavioral outcomes.

This has been accomplished through individual differences analyses, which suggest that the magnitude of expectancy effects on perception is correlated with the magnitude of expectancy effects on the brain. For example, individuals who report larger placebo effects on pain also show larger placebo effects on rACC and DLPFC responses (Wager et al., 2004, 2011), and those who report larger nocebo effects show larger increases in dACC (Kong et al., 2008). While this suggests that there is indeed a relationship between subjective experience and the magnitude of expectancy effects on brain activation, individual differences analyses cannot show that these factors are causally related. A number of personality variables are related to placebo-based expectancy effects on pain responses, including optimism (Geers et al., 2005; Morton, Watson, El-Deredy, & Jones, 2009), suggestibility

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(De Pascalis et al., 2002), and reward responsiveness (Scott et al., 2007). Thus, these factors may independently influence expectancy effects on behavior as well as expectancy effects on the brain.

To identify the pathways whereby expectancies modulate *ongoing* affective experience, expectancy effects on brain and behavior must be measured and related within subjects and over time. One can thus isolate whether manipulated expectations affect activation within domain-specific regions and whether those changes in turn affect responses, or whether responses reflect decision-making biases independent of activation within sensory regions. In a recent fMRI study (Atlas et al., 2010), we used an approach called multilevel mediation analysis to identify the brain regions that support the dynamic relationships between cue-based stimulus expectancies and expectancy effects on affective experience. We focused on expectancy effects on pain, as pain provides an ideal model system of affective processing. We found that expectancy effects on dynamic pain were mediated by three classes of brain regions: those thought to support changes in value (e.g., OFC, striatum), those implicated in cognitive control and downstream modulation (e.g., DLPFC, pgACC), and those that were also specifically activated by painful stimulation, which are described in more detail below. In the following section, we review the brain mechanisms that underlie pain processing and review findings from our lab and others

isolating the paths by which expectations modulate pain perception.

### Expectancy Effects on Pain

The hedonic domain of pain processing provides an ideal platform by which to study the transfer from external stimulus to subjective perception and to test where along this pathway expectancies affect perception. First, noxious stimuli are objectively quantifiable. In thermal pain models, temperature is a characteristic of the external stimulus, and it is possible to measure the effects of small changes in the noxious stimulus; the direct effects of objective changes in noxious input are referred to as *nociception*.

Second, nociception is well studied in both human and animal models, and the brain regions that are affected by changes in noxious stimuli, often referred to as the “pain matrix,” are highly conserved across species. This has led to a well-characterized understanding of the ascending pathways that transfer a noxious input (e.g., a small pinprick, or a hot flame) from peripheral nociceptors to the spinal cord to the central nervous system, depicted in Figure 23.4 (lower right). In brief, noxious input is registered by A $\delta$ , A $\beta$ , and C-fiber primary afferent nociceptors (PANs) in the periphery, which synapse at in the spinal cord’s dorsal horn. Many PANs project via the *lateral spinothalamic tract* to contralateral thalamus (ventral posterior lateral and ventral posterior inferior nuclei), which in

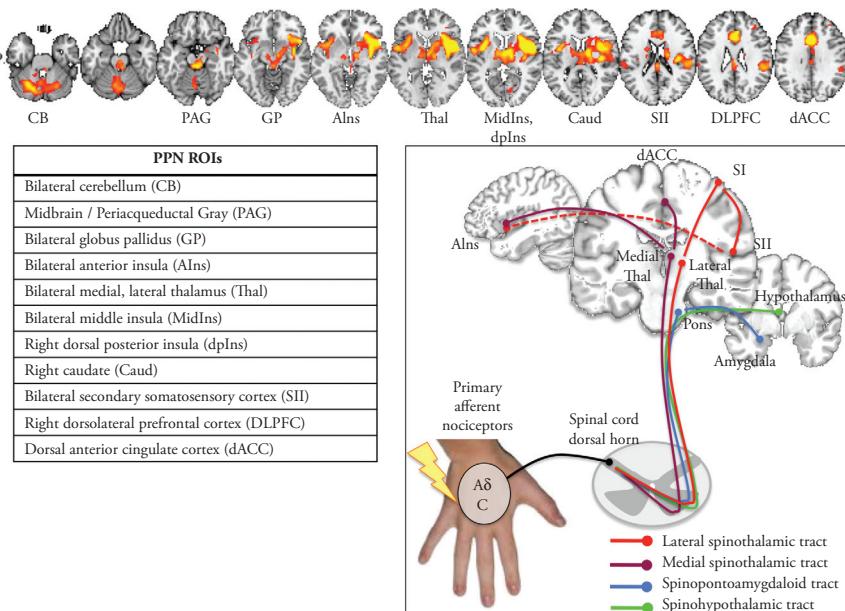


Figure 23.4 The pain processing network (PPN). ROIs, regions of interest.

turn project to primary and secondary somatosensory cortex (SI and SII). Other PANs project via the *medial spinothalamic tract* to medial thalamus (ventral medial posterior and central lateral nuclei) followed by dorsal anterior cingulate and anterior insula. In addition to these spinothalamic pathways, there are also direct projections to the hypothalamus (spinohypothalamic tract; Giesler, Katter, & Dado, 1994); to the amygdala by way of pontine nuclei (spinopontoamygdaloid tract); to midbrain structures including the periaqueductal gray (spino mesencephalic tract); and to the caudal medulla and reticular formation (spinoreticular tract). (For more detailed reviews, see Almeida, Roizenblatt, & Tufik, 2004; Price, 2000; Treede, Kenshalo, Gracely, & Jones, 1999; Willis & Westlund, 1997.) The central nervous system regions that receive input from these various pathways are reliably activated by noxious input, as shown in the top row of Figure 23.4. In an analysis that tested the effects of noxious stimulus intensity across five different studies of thermal heat pain ( $n = 114$ ) (Atlas et al., 2010, 2012), we observed heat-related activation (high- vs. low-intensity stimulation) of all of the targets of these afferent pathways, with the exception of S1 (see note in Figure 23.4). For the remainder of this review, these regions are defined as the pain-processing network, or PPN.

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Third, the concept of pain actually refers to a subjective percept that is distinct from nociception. Pain involves both sensory and affective components (Loeser & Treede, 2008); in other words, the subjective percept has location and intensity information, but also involves unpleasantness and a motivation to escape the noxious stimulus. This dissociation makes pain unique from other perceptual domains and allows it to serve as a model of affective processing. Interestingly, the precise central nervous system mechanisms that give rise to subjective pain have not been fully distinguished from those that are associated with nociception. Researchers have focused more directly on dissociating sensory and affective components of subjective pain; a general consensus is that lateral spinothalamic targets are associated with pain's sensory components, while targets of the medial spinothalamic tract are relevant for the motivational and affective components of pain (Price, 2000; Rainville, 2002). It is important to note that this distinction is primarily supported by a series of studies that used hypnosis to modify pain unpleasantness. When participants focused on decreasing pain unpleasantness, dACC activation decreased, but noxious stimulus-evoked responses

in S1 and insula were unaffected (Rainville, Carrier, Hofbauer, Bushnell, & Duncan, 1999; Rainville, Duncan, Price, Carrie, & Bushnell, 1997). Another study showed that ratings of pain unpleasantness were correlated with pain-related regional cerebral blood flow (rCBF) responses in dACC, while intensity ratings were correlated with posterior cingulate responses. However, studies that have attempted to dissociate "bottom-up," stimulus-driven brain responses from those that predict pain reports have not been consistent (Apkarian, Darbar, Krauss, Gelnar, & Szeverenyi, 1999; Craig, Chen, Bandy, & Reiman, 2000), and thus the roles of specific individual brain structures in creating the subjective experience of pain are still not entirely clear. It is likely that pain emerges from integrated activity across regions (Coghill, Sang, Maisog, & Iadarola, 1999) and that one cannot point to some regions as evidence for "sensory" modulation and others as evidence for "affective" modulation.

Finally, pain is highly modifiable by expectations. Unpredictable noxious stimuli and those preceded by longer anticipation are perceived as more painful than predictable stimuli (Carlsson et al., 2006; Hauck et al., 2007; Miller, 1981; cf. Crombez et al., 1994). Cue-based expectations about the intensity of a noxious stimulus bias perception of the stimulus in the direction of expectations (Atlas et al., 2010; Keltner et al., 2006; Lorenz et al., 2005; Ploghaus et al., 2001), although several studies have found an asymmetry whereby cue-based expectations for low pain decrease pain ratings (similar to the placebo effect), but cue-based expectations for high pain do not increase pain (Arntz, 1996; Koyama et al., 2008).

Interestingly, when expectations about stimulus timing and intensity are combined there is an interaction whereby certain expectations for high-intensity stimuli lead to increased dread (Berns et al., 2006) and higher pain reports than uncertain expectations (Brennan, Seymour, Boyle, et al., 2008; Lorenz et al., 2005). Pain perception is also highly affected by response expectancies, or expectations about one's internal affective experiences and responses. This is most obvious in the case of placebo analgesia, whereby individuals experience less pain in response to an inert treatment when conditioning and/or instructions lead them to believe the treatment will reduce pain (for reviews, see Atlas et al., 2009; Benedetti, 2007; Benedetti et al., 2011; Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005; Bingel, Schoell, & Buchel, 2007; Cavanna, Strigaro, & Monaco, 2007; Colloca, Benedetti, & Porro, 2008;

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Faria, Fredrikson, & Furmark, 2008; Hoffman, Harrington, & Fields, 2005; Kapchuk, 2002; Price, Finniss, & Benedetti, 2007; Wager, 2005c). Placebo responses are highest in pain (Hróbjartsson & Gøtzsche, 2001, 2004; Vase et al., 2009), for chronic pain, a debilitating condition that costs the United States an estimated \$635 billion annually in medical treatment and lost productivity (Committee on Advancing Pain Research, 2011), cognitive interventions that involve changes in beliefs about pain ~~have been shown to be highly effective~~ (Keefe, Dunsmore, & Burnett, 1992; Morley, Eccleston, & Williams, 1999; Nicholas, Wilson, & Goyen, 1992; Vlaeyen & Morley, 2005). Thus, experienced pain is strongly affected by expectations about the self, expectations about the intensity of a stimulus, and expectations about stimulus timing. The question remains whether these effects reflect changes in nociception, changes in processes like anxiety or positive affect that are additive with nociception, or changes in decision-making and pain evaluation mechanisms.

To address this question, we manipulated stimulus expectancies and examined the brain mechanisms that link cue-based expectancies with trial-by-trial changes in subjective pain experience (Atlas et al., 2010). In a task similar to the one depicted in the top row of Figure 23.1, auditory cues elicited expectations for barely painful or highly painful thermal stimulation, and we assessed how cues influenced pain reports and brain responses to a single level of medium heat. We used multilevel mediation analysis to identify brain regions that (1) are modulated by predictive cues, (2) predict trial-to-trial variations in pain reports, and (3) formally mediate the relationship between cues and reported pain. Cues influenced heat-evoked responses in all PPN regions, including both medial and lateral pain pathways. A subset of PPN regions, including anterior cingulate cortex, anterior insula, and thalamus, formally mediated cue effects on pain. Effects on these regions were in turn mediated by cue-evoked anticipatory activity in the medial OFC and ventral striatum, areas not previously directly implicated in nociception but discussed earlier in supporting more general processes such as expected value and prediction. Thus, these findings illustrate that domain-general anticipatory processes in OFC and striatum link to domain-specific expectancy effects (i.e., effects on PPN), which in turn directly predict trial-by-trial expectancy effects on subjective pain. Future research should test whether parallel mechanisms support expectancy effects on other hedonic domains.

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## Conclusions

Expectations and beliefs play a pervasive role in the workings of the brain. Expectations are central to learning, affect and emotion, and the coordination of adaptive behavior. Even in the heyday of behaviorism, some theorists argued that expectations—explicit mental representations of specific future outcomes—played a fundamental role in shaping animal behavior, and research since then has reinforced the notion that mental representations operate alongside simpler forms of neural plasticity to drive learning. We do not simply react to events; we anticipate them, and we respond—often in advance—to pursue opportunities and ward off threats. In a world where second chances were hard to come by, our ancestors could not afford not to anticipate the future and respond proactively, and we have inherited this legacy. Because of the fundamental importance of expectations in physical and social well-being, they are also of fundamental importance in driving emotion, and they color our experiences in many ways. They can elicit basic affective responses and full-blown emotions in their own right, and they can influence how we perceive expected events, including those that are clinically and medically relevant. Thus, the emerging study of the brain mechanisms that underlie expectancy belongs to many fields—the study of affect and emotion, learning, and the clinical sciences—and has something to contribute to all of them.

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