CHAPTER 14

Conditional Analgesia, Negative Feedback, and Error Correction

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Error correction has played an important role in the development of theories of Pavlovian conditioning, and it continues to be a central force driving research on the processes underlying learning and memory. This chapter highlights some of the key aspects of error correction—from the original groundwork that helped formulate the way we think about error correction to recent work looking at some of the physiological mechanisms that comprise error correction. In particular, we focus on the perceptual-defensive-recuperative and negative-feedback models for Pavlovian conditioning, as well as the role of conditional analgesia, attention, and dopamine in error-correction-based processes. We discuss specific applications of error-correction principles in conditioning, but we also try to stress a comprehensive role for error correction, particularly in the selection of appropriate brain circuits for specific functions.

INTRODUCTION

The idea that we correct for the errors we make is as fundamental to behavior as the idea that we learn at all. As animals, it is in our nature to adapt, and integral to this is our ability to respond to our environment. All mammals must be able to continuously update the information they have stored and adjust their behaviors accordingly. This might be as simple as a squirrel learning to correct for the errors it makes jumping from branch to branch or as complicated as a man buying his wife flowers to correct for forgetting the last time. Of great interest—though perhaps not what comes to mind when one intuitively thinks about error and correction—is the idea that the brain physiologically corrects for errors at the mechanistic or structural level. Research aimed at uncovering the processes involved in how the brain performs error-correction calculations has begun to push forward our ideas about error correction and establish it as an extremely rich, deep phenomenon that seems to emerge in every corner of behavior.

While recent, exciting discoveries have brought new attention to the field of error correction (e.g., Fiorillo, Tobler, & Schultz, 2003; Tobler, Fiorillo, & Schultz, 2005), these studies are essentially the relaunching of a long-standing issue in learning theory: What processes support and limit what and how we learn? One powerful idea, first formulated by Leon Kamin (1968, 1969), is that learning is driven by the surprisingness of a reinforcer. This notion of surprise has since been incorporated into a number of theories, several of which describe learning as being regulated by a form of error correction. Notably, the concept was captured more formally by Rescorla and Wagner (1972), who characterized changes in conditioning as a function of the difference between an obtained and an expected reinforcer. In this chapter, we will focus on particular components of the error-correction model as well as its development.

We begin with a model of error correction—the perceptual-defensive-recuperative model (Bolles & Fanselow, 1980), which suggests that the notion of surprise could be conceived as error correction through negative feedback. The perceptual-defensive-recuperative model was the first to suggest differential, competing roles for fear and pain, which function and interact in an error-correction-type fashion for the regulation of defensive behavior. In particular, we highlight the role of conditional analgesia as fundamental to the functioning of this model and future error-correction-based models of fear learning. We will focus on the idea that Pavlovian conditioning is regulated by a negative-feedback mechanism that allows for the calculation and correction of errors at the circuit level. Additionally, we touch upon the nature of errors that produce decrements in responding ("negative" errors), the role of attention in error correction, and recent research suggesting that midbrain dopamine neurons perform error-correction-type functions. We will close by suggesting a novel application of error-correction principles in the selection of particular brain circuits appropriate for specific types of learning.

THE PERCEPTUAL-DEFENSIVE-RECUPERATIVE MODEL

All animals respond with a wide variety of behaviors in reaction to a traumatic event. For example, an animal may identify the presence of a predator, defend itself from attack, or perform recuperative behaviors if injured. The more successful an animal is in performing each of these behaviors, respectively, the more likely that animal is to survive. However, an animal's success is largely determined by its ability to perform each of these behaviors at the appropriate point in time. For instance, licking a wound clean may be extremely beneficial, but only if this behavior is performed after any immediate threat has passed. Indeed, while under attack, an animal must instead focus on defending itself rather than on mending its wounds. Therefore, the ability to select a diverse range of behaviors in response to a traumatic event is important, but the ability to select *when* it is appropriate to perform each behavior is crucial.

The perceptual-defensive-recuperative (PDR) model (Bolles & Fanselow, 1980) explains the course of an animal's behavior in a traumatic situation. At the core of this model is the distinction between fear and pain—a distinction that casts the two as opposing and competitive motivational systems, serving entirely different functions. According to the PDR model, fear, the emotion produced by stimuli that signal noxious events, activates defensive mechanisms, such as freezing and flight behaviors. On the other hand, pain, the sensation produced by noxious stimulation, results in recuperative behaviors, such as resting or tending to an injury. According to this model, it is *because* fear and pain represent distinct motivational systems that they can generate completely different classes of behavior. By making this distinction, the PDR model utilized the emerging evidence on the existence of "antipain" mechanisms in the brain to explain the complexity and time course of animal behavior during a traumatic event.

By 1980, the finding that pain-inhibiting peptides exist endogenously in the brain had already opened up an entire area of research on stress-induced analgesia (Cannon, Liebeskind, & Frenk, 1978; Sherman & Liebeskind, 1980). These opioid neuropeptides (e.g. endorphins, enkephalins) were found to act much like morphine in that they produce an analgesic state and effectively inhibit pain. At the time, the idea that *pain* mechanisms are highly adaptive and functionally useful was well established, however, the notion that an *antipain* system could be equally advantageous was quite novel. The potential advantages of these pain-inhibiting endorphins and enkephalins became the subject of much theory and research (Bolles & Fanselow, 1982). The PDR model offered an explanation for the functional purpose of having both a pain and an antipain system.

According to the perceptual-defensive-recuperative model, pain and pain inhibition work hand in hand to produce adaptive behaviors in traumatic and peritraumatic situations. More specifically, the PDR model suggests that pain and pain-related behaviors (i.e., recuperation) are distinct and work in opposition to fear and fear-related behaviors (i.e., defense).

The key to this distinction is that the model classifies pain inhibition as a defensive behavior. That is, not only will an animal freeze, fight, or flee in defense of itself, but that animal will also inhibit any pain that it has incurred from being injured. Pain inhibition as a form of defense is important because it enables an animal to continue to actively defend itself while under attack. By inhibiting pain, an animal can perform defensive behaviors that would be otherwise impossible after a serious injury. Hence, the PDR model gives a functional significance to endorphins: They enhance an animal's ability to defend itself successfully. Thus, pain and pain inhibition are nothing more than the manifestation of pain- and fear-related behaviors.

In its entirety, the PDR model distinguishes three stages of animal behavior in the face of a traumatic event: the perceptual phase, the defensive phase, and the recuperative phase (Fig. 14.1). In the first phase, an animal perceives a threatening stimulus—a cue or environment that has come to predict the occurrence of a traumatic event. In Pavlovian fear-conditioning terms, the perceptual phase is when an animal encounters an initially neutral, conditional stimulus (CS), which it then learns signals the occurrence of an aversive, unconditional stimulus (US). Thus, the perceptual phase establishes the encoding of a CS-US relationship such that after conditioning, perception of the CS results in expectancy of the US. The emphasis on US expectancy is a vital component of the PDR model.

In the second, *defensive* phase, this US expectancy activates the motive state of fear. Once activated, the fear system motivates a host of defensive behaviors. It is important to note that it is not the US itself that activates a state of fear; rather, it is the *expectancy* of the US—elicited upon perception of the CS—that activates the fear state. This contrasts with the view that a state of fear is automatically triggered in direct response to a noxious stimulus. Indeed, the PDR model breaks with this latter notion of fear, instead classifying fear as a motivational state that is triggered by the occurrence of a CS that predicts a US, rather than by the US directly. This break is important because it shifts fear from being an automatic "reflexive" response to being an anticipatory central motive state that is responsible for the orchestration of a host of defensive behaviors.

In addition, by proposing that fear and pain function in opposition, the PDR model contrasts with the previous two-factor theory (Miller, 1948, 1951; Mowrer, 1939, 1951) that viewed fear as the conditioned form of pain. Instead, the PDR model describes fear as having its own, distinct functional importance. More specifically, the PDR model states that fear functions by organizing an animal's species-specific defense reactions (SSDRs), or the unique behaviors all members of a particular species will exhibit in their defense (Bolles, 1970). For example, freezing, the lack of all movement except that necessitated by respiration, is an SSDR rodents perform when afraid. Freezing reduces the likelihood that rodents will be detected and/or attacked by a predator. Importantly, all rodents will freeze despite the fact that the environmental circumstances signaling threat may be extremely

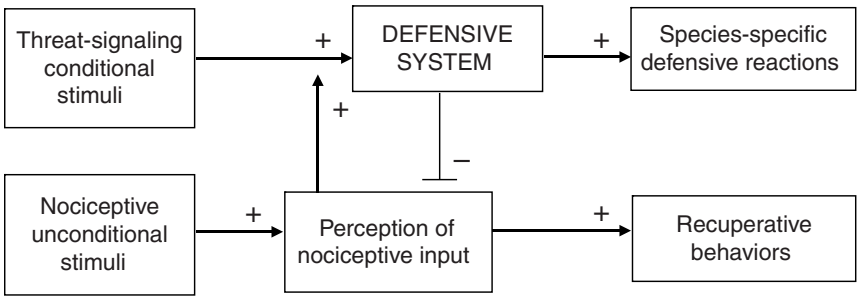

Figure 14.1 Diagram of the PDR model. (Adapted from Fanselow, M. S. (1986). Conditioned fear-induced opiate analgesia: A competing motivational state theory of stress analgesia. *Annals of the New York Academy of Science, 467*, 40–54).

both across rodents and even within a single rodent's experience. The reason why all members of a species uniformly perform a particular defense reaction is that any environment or cue that signals threat is able to activate the motive state of fear, which in turn will be able to generate a fixed SSDR such as freezing. Thus, fear links and organizes environmental input with the appropriate behavioral output.

Importantly, fear also produces an endogenous opioid-mediated state of analgesia, which is key to the inhibition of the perception of nociceptive input. The release of endorphins, much like freezing, is selected to occur through activation of the fear state. Thus, analgesia, like freezing, is simply part of the repertoire of defensive behavior and as such is not an automatic response but rather a conditional response. The idea that endogenous opioids inhibit pain so as to enhance defensive behaviors is supported by experimental work showing that along with defensive behavior, fear produces a loss of integrated pain-elicited responses (Fanselow & Baackes, 1982; Fanselow, Calcagnetti, & Helmstetter, 1989; Fanselow & Helmstetter, 1988). Thus, the second phase of the PDR model is primarily concerned with the central motive state of fear and in particular, the way in which fear organizes defensive behaviors and inhibits pain. This inhibition turns out to serve an important error correction purpose, which we will turn to shortly.

The third, *recuperative* phase focuses on that which was inhibited during the defensive phase: pain. After the perception of threat has passed and fear has subsided, an animal shifts from defending itself to performing recuperative or healing behaviors to any injury it has sustained. An animal that is injured in a conflict will eventually shift from fear-related defensive behaviors to pain-related recuperative behaviors. Because the pain system receives input from noxious stimuli that cause tissue damage, an animal will begin to perform recuperative behaviors, *unless* the pain system is being inhibited by the fear system (i.e., unless the animal's "perception" of pain is altered) (Fanselow & Baackes, 1982). For example, in the presence of more immediate threats to survival, the pain system may be inhibited through conditional analgesic.

A chief role of conditional analgesia is to provide an inhibitory link from the defensive system onto the nociceptive system (Fanselow, 1986) (see Fig. 14.1). More specifically, fear-evoked analgesia serves to inhibit the "detection" of noxious stimuli, offering a clear advantage to an injured animal. This would be an example of defensive behavior taking precedence over recuperative behavior. The idea being that if an animal does not fully "feel" the pain inflicted by a predator, that animal has more of a chance of defending itself in that situation. Thus, our perception of pain is quite distinct from the actual noxious stimulus administered. This gap between what we "feel" and what is actually delivered turns out to be of great importance to error-correction models of traumatic events.

ANALGESIA

Liebeskind and colleagues reported that brain stimulation of the periacqueductal gray (PAG) in rats resulted in a state of analgesia (Mayer, Wolfle, Akil, Carder, & Liebeskind, 1971). This finding was consistent with a similar observation made by Reynolds (1969). Liebeskind and colleagues noted many similarities between opiate and stimulation produced analgesia, notably cross-tolerance, which seemed to suggest that they were stimulating an endogenous opiate-like pathway. This, in part, led to a search for the opioid receptor (Pert & Snyder, 1973a; 1973b) and the natural opiate ligand (Kosterlitz & Hughes, 1975). Additionally, Liebeskind and colleagues discovered the existence of "stress-induced analgesia," which similarly exhibited cross-tolerance with opiates as well as with PAG stimulation (Akil, Mayer, & Liebeskind, 1972b, 1972a, 1976; Mayer et al., 1971). This discovery led to research focused on the functional role of analgesia.

The role of endorphins in eliciting an analgesic state was largely supported by studies looking at shock-induced analgesia. Notably, Lewis and colleagues (Lewis, Cannon, & Liebeskind, 1980; Lewis, Cannon, Stapleton, & Liebeskind, 1980; Lewis, Slater, Hall, Terman, & Liebeskind, 1982; Lewis, Tordoff, Sherman, & Liebeskind, 1982) established the existence of footshock-induced opioid analgesia. Though this endorphin-mediated analgesic response was shown to be

sensitive to training parameters (e.g., shocks had to be discontinuous), these studies helped establish the idea that the brain indeed has a mechanism by which stressful stimuli such as shock could be countered or dampened down by an opposing analgesia. Work by Maier et al. (1980) demonstrated that shock-induced analgesia was eliminated using the opioid antagonist naltrexone and the induction of analgesia was shown to partially depend on the uncontrollability of shock. Again, this work showed that it is not shock per se but a state associated with shock that engages the analgesic response. This research served to solidify the role of endorphins in the mediation of a footshock-triggered analgesic state.

The first suggestion that analgesia might play an important, functional role in fear conditioning came in 1978, when Chance et al. demonstrated that, like stress, conditional fear could also produce a state of analgesia (Chance, White, Krynock, & Rosencrans, 1978). Meanwhile, Fanselow and Bolles (1979b) reported that the opioid antagonist naloxone blocked the preference for signaled shock that rats normally show. Furthermore, Fanselow and Bolles (1979b) demonstrated that animals trained to fear contextual cues showed enhanced levels of fear at test if they had been conditioned in the presence of the opioid antagonist naloxone. In other words, by removing the pain-dampening effect of analgesia, naloxone made the shock a more effective US. This suggests that an analgesia signal, makes shock less aversive, which is consistent with the idea that conditional analgesia is a component of defensive behavior.

Analgesia as a defensive mechanism was further demonstrated by studies looking at the ability of opioid antagonism to restore recuperative behaviors in the presence of fear (Fanselow & Baackes, 1982). Fanselow and Baackes (1982) examined formalin-induced recuperative behavior wherein a rat injected with a dilute formalin solution into its hind paw would subsequently lift and lick the paw (recuperative behavior). This recuperative behavior was suppressed if a fear-eliciting conditional stimulus was simultaneously presented (presumably due to conditional analgesia dampening down nociceptive input). However, if the opioid antagonist naltrexone was administered in addition to the presentation of the CS, formalin-induced recuperative behavior was restored. This finding solidified a role for conditional analgesia in the maintenance of "circa-strike" defensive behavior (Fanselow & Lester, 1988) and the regulation of recuperative behavior. Furthermore, it suggested a valuable theoretical implication for conditional analgesia, namely, that it provides an inhibitory link from the defensive system onto the recuperative system. Importantly, this laid the initial groundwork for a more general model of negative feedback.

NEGATIVE-FEEDBACK REGULATION OF PAVLOVIAN FEAR CONDITIONING

In biology, the notion of negative feedback—that a structure may receive "negative" or opposing information from a source to which it ordinarily sends positive information—is most often used to describe how systems maintain homeostasis. One example of negative feedback can be seen in the role that conditional analgesia plays in fear conditioning.

As described previously, fear conditioning a stimulus (CS) leads to the production of a number of conditional fear responses that may be elicited by that CS. The CS activates the motivational state of fear, which triggers the defensive system and a host of defensive behaviors. For example, a rodent presented with a fearful CS will both freeze and become analgesic. This conditional analgesia causes a reduction in the impact of nociceptive input, therein causing suppression of recuperative behaviors (see Fig. 14.2). A further consequence is the reduction in the ability for that rodent to subsequently condition fear. In other words, because an animal is analgesic, a US that would otherwise be "painful" no longer is.

This reduction in conditioning is revealed by studies which show that conditional fear is enhanced by treatment with the opioid antagonist naloxone (Fanselow, 1981). Similarly, an animal will not condition fear to a CS that is paired with a US if that animal is already analgesic.

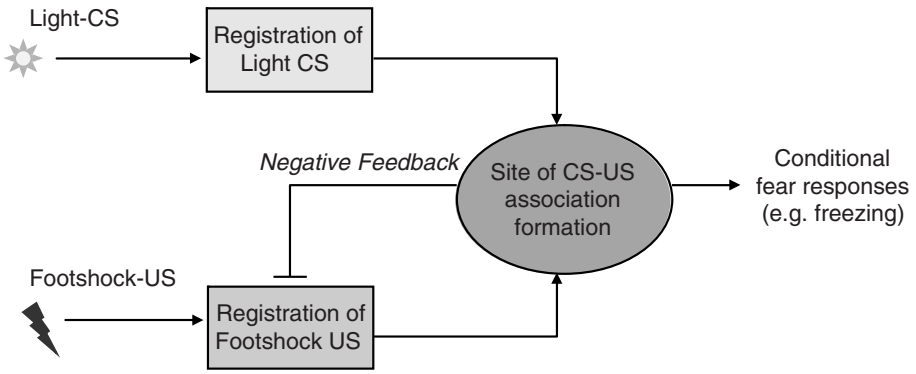

Figure 14.2 The negative-feedback model of fear conditioning. CS, conditioned stimulus; US, unconditioned stimulus.

For this reason, after the first CS-US conditioning trial, any subsequent exposure to that CS (including subsequent CS-US trials) results in the production of conditional analgesia (Fanselow & Bolles, 1979a, 1979b). In turn, this generates a graded reduction in the ability to condition that CS that is proportional to the amount of conditioning that has already accrued to the CS (e.g., Young & Fanselow, 1992). Importantly, the same reduced conditioning would apply to a novel stimulus being paired with the US if an animal is simultaneously exposed to a previously conditioned CS (i.e. "blocking," Fanselow & Bolles, 1979b; McNally, Pigg, & Weidemann, 2004a).

Thus, conditional analgesia reflects the amount of fear conditioning that has accrued to a CS (similar to any other measure of fear-related conditional behavior, e.g., freezing). This information is then fed back to the very structures involved in detecting nociception, which results in an overall dampening of perceived nociceptive input and hence a reduction in subsequent conditioning. In other words, conditional analgesia provides a descending *negative feedback* onto the ascending reinforcing input responsible for the acquisition of fear (Fanselow, 1986, 1998) (see Fig. 14.2).

This negative-feedback model of conditioning provides a physiological mechanism by which Rescorla-Wagner-type calculations can be made. For example, the negative-feedback model physiologically explains US-limited phenomena such as blocking, similar to how the Rescorla-Wagner model handles such phenomenon conceptually. In blocking (Kamin, 1968, 1969), conditioning of a CS, such as a light, is reduced if the light is presented in compound with another, previously conditioned CS, such as a tone. Prior conditioning of the tone blocks subsequent conditioning of the light. Kamin's discovery of the phenomenon of "blocking" established that contiguity, or pairing of a CS and US, was not sufficient to produce conditioning. Kamin concluded that what mattered was not contiguity, but instead the surprising aspect of the US. If the US was surprising, then conditioning of the CS would occur. Thus, the blocked light-CS fails to condition because the US is not surprising.

Rescorla and Wagner took this notion of surprise further by developing a mathematical model of Pavlovian conditioning in which US processing played a central role (Rescorla & Wagner, 1972). This equation ($\Delta V = \alpha\beta(\lambda - \Sigma V)$) simply states that on a given conditioning trial, the change in the associative strength of a particular CS is equivalent to the amount of surprise on that trial—where surprise can be thought of as the difference between what you get (λ) minus what you expected to get (ΣV)—multiplied by the salience of the CS and the US.

For our purposes, the term of interest here is the surprise term or prediction error ($\lambda - \Sigma V$). It is this term for which the negative-feedback model of fear conditioning offers a physiological mechanism. In the model, λ refers to the actual, physical intensity of the US, which gets registered

by the central nervous system (e.g., the dorsal horn of the spinal cord), and ΣV refers to the amount of conditioning that has accrued to all stimuli present. We emphasize this pathway because it is the best documented and most thoroughly implicated (Basbaum & Fields, 1984). However, any conditioning-dependent response that mitigates the impact of the US would operate in this manner. Since there is already evidence for the conditioning of analgesia and subsequent reduction in the amount of nociception detected, conditional analgesia perfectly fits as the physiological correlate to the ΣV term in the Rescorla-Wagner model. Thus, the magnitude of conditional analgesia (ΣV), which gets subtracted from the nociceptive value of an aversive US (λ) in the Rescorla-Wager model is in line with analgesia's physiological role of providing negative feedback onto the area registering nociceptive input.

Rescorla-Wagner's λ – ΣV term stands for surprise, but it is also an error term. Surprise is nothing more than the prediction error made when you get something you did not expect to get. In the negative-feedback model, analgesia is the mechanism regulating such errors. For this reason, saying that an aversive US is fully expected is to simply say that the CS is fully conditioned, and the amount of conditional analgesia is sufficient to cancel out the impact of the US. When analgesia is not sufficient to cancel out US impact (i.e., $\lambda > \Sigma V$), there is error. This resulting error serves as the reinforcing signal. Thus, the greater the analgesic feedback, the smaller the error.

The model can be tested by blocking endogenous opioids with antagonists (e.g. naloxone or naltrexone). Without endogenous opioid-mediated conditional analgesia, the model predicts that $\Delta V = \alpha\beta(\lambda - \Sigma V)$ becomes $\Delta V = \alpha\beta(\lambda)$. There is extensive evidence for this prediction. For instance, a number of findings demonstrate that opioid antagonists such as naloxone attenuate blocking if they are administered in the second phase of a blocking experiment (Fanselow & Bolles, 1979a, 1979b; Galli et al., 2009; McNally et al., 2004a) (see Fig. 14.3). In addition, Young and Fanselow (1992) showed that administration of naloxone prior to conditioning results in increased conditioning asymptotes, thereby concluding that naloxone may function to lift the limits on the US's ability to condition in a manner analogous to increasing the intensity of the actual shock itself.

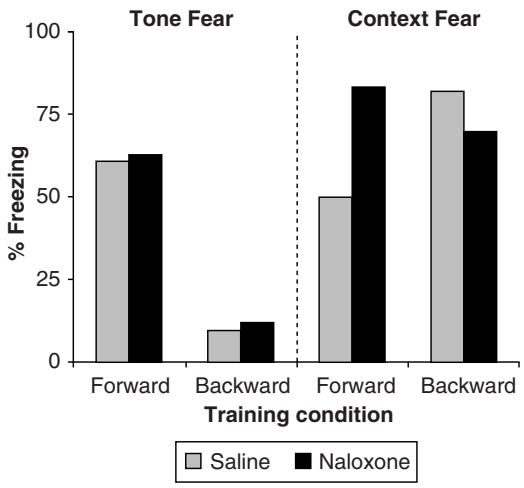

Figure 14.3 Naloxone causes unblocking in a one-trial context-blocking experiment. During Phase 1, rats received either 15 forward or 15 backward pairings of a 30-sec tone and shock. In Phase 2, the rats were given an injection of saline or naloxone and placed in a novel context. There they received a single presentation of the tone followed by shock. The left panel (Tone Fear) shows that there was more conditioning to the forward- than backward-paired tone and naloxone did not alter the expression of this fear. The right panel (Context Fear) shows fear conditioning to the context by the single shock. In saline-treated rats, the reduced context conditioning of the forward-trained group relative to the backward-trained group indicates blocking. Naloxone prevented this blocking effect. (Adapted from Fanselow, M. S., & Bolles, R. C. (1979b). Triggering of the endorphin analgesic reaction by a cue previously associated with shock - reversal by naloxone. *Bulletin of the Psychonomic Society, 14*(2), 88–90).

More recently, we have shown that the opioid antagonist naltrexone attenuates overshadowing—another Pavlovian phenomenon thought to occur due to limitations on the US's ability to support conditioning (Zelikowsky & Fanselow, 2010). In overshadowing, a highly salient CS reduces conditioning to a concurrently presented low-salience CS (Pavlov, 1927),

again suggesting that the US is limited in the amount of conditioning it can support. However, if naltrexone is administered to an animal prior to training, overshadowing of the less salient CS is significantly attenuated (Zelikowsky & Fanselow, 2010). The fact that naltrexone allows for the conditioning of the low-salience CSs gives further evidence that naltrexone may work to lift the limits off of the US's ability to condition. According to the negative-feedback model, overshadowing, like blocking, occurs because conditional analgesia is elicited. The more salient CS will have a faster rate of acquisition, and hence rapidly generates a conditional analgesia that blocks conditioning to the less salient, slow to condition, CS.

DECREMENTAL ERROR CORRECTION

Initial tests of the negative-feedback model specifically addressed error correction when the expectation is less than the received reinforcer (e.g., acquisition). In this case, the error term signals increments in associative strength. Another type of error correction is when the expectation is greater than the reinforcer—an error signal that leads to decrements in responding (e.g., extinction). A programmatic series of studies by McNally and colleagues (McNally, Pigg, & Weidemann, 2004b; McNally et al., 2004a) has shown that opioid antagonists also block this latter type of error correction.

McNally and colleagues (2004a, 2004b) found that there are situations in which conditional analgesia exceeds the amount needed to fully cancel the reinforcing aspects of the US (i.e., when the prediction error, $(\lambda - \Sigma V)$, is negative). In these cases, administration of an opioid antagonist blocks these "inhibitory" forms of learning such as extinction (McNally & Westbrook, 2003) and Pavlovian overexpectation (McNally et al., 2004a). In overexpectation, two CSs that have each been independently trained with a US are presented together and reinforced with the same size US such that what is expected is "double" what is actually received and hence $\lambda - \Sigma V$ is negative. Similarly, in extinction, the CS is repeatedly presented in the absence of the US and hence what is expected is greater than what is received.

These data fit nicely with the negative-feedback model, if one assumes that there is some baseline level of activity (resting firing rate of neurons) in ascending pain pathways under unstimulated conditions. The resting firing rate would not produce changes in conditioning alone (i.e., would not support reinforcement). On the other hand, unpredicted painful events would increase firing rate and support fear acquisition. However, if activity in the descending (analgesic) arm of the circuit was greater than needed to reduce painful input, the firing rate in the pathway should drop below the resting rate (see Fig. 14.2). Such a condition would be met, for example, when a CS is presented without a US, as is the case in extinction. Instances in which the firing rate slips below baseline would promote decreases in associative strength. Consequently, opioid antagonists that prevent analgesia would hinder such decrements in associative strength. This model is physiologically plausible because morphine not only suppresses pain-induced activity of dorsal horn neurons but also suppresses the spontaneous firing rate of these neurons (Einspahr & Piercey, 1980). The application to fear conditioning is supported by the finding that naloxone—at least under some circumstances—can prevent extinction (McNally & Westbrook, 2003).

The idea of a negative-feedback model of conditioning is extremely powerful in that it offers a physiological mechanism by which perception of the US changes as conditioning progresses in a manner analogous to that described so elegantly by the Rescorla-Wagner model. This model is further emboldened by the existence of anatomically independent negative-feedback loops in other forms of Pavlovian conditioning (e.g., eyeblink conditioning; Kim, Krupa, & Thompson, 1998).

ERROR CORRECTION AND ATTENTION

While we have focused on error correction as conceived by US-processing models of conditioning, it should also be noted that there is a

large body of literature focused on the role of CS associability in conditioning (Mackintosh, 1975b; Pearce & Hall, 1980). While US processing models suggest that the error-correction signal is a reinforcement signal, CS processing models (e.g., Mackintosh and Pearce-Hall) suggest that error-correction signals adjust "associability," which in turn has an effect on a constant reinforcement signal.

In particular, CS-processing views of conditioning lay the success or failure of conditioning on the amount of attention the CS is or is not able to garner. Most often, the more attention paid to a CS, the more it can successfully be conditioned. Although attentional theories are not necessarily in agreement regarding the factor most likely to generate an attention-grabbing CS (i.e., the CS is a good predictor of a US, a novel predictor, or simply innately salient), they agree that conditioning depends on whether attention is paid to the CS. Thus, these theories explain phenomena such as overshadowing not in terms of US limitations, but in terms of properties of the CS.

One notable advantage of associability models is that they are able to explain latent inhibition. In latent inhibition, a stimulus that has been preexposed is subsequently retarded in its ability to be conditioned (Lubow, 1973, 1989). This slower rate of acquisition can be accounted for using an associability model, which focuses on the CS and its salience, where CS pre-exposure serves to reduce the salience of a CS and hence the rate of acquisition. However, because latent inhibition occurs in the absence of a reinforcer, explaining it in terms of the negative-feedback model is problematic. Indeed, Young and Fanselow (1992) failed to block latent inhibition with an opioid antagonist (see Fig. 14.4).

However, there are phenomena—one-trial blocking—that cannot be explained by associability models but can be accounted for by US-processing models. In one-trial blocking (Cole & McNally, 2007; Mackintosh, 1975a) one conditioning trial with a single stimulus is followed by a conditioning trial with a compound stimulus. The stimulus introduced in the compound is blocked. Since blocking consists of earlier training experience (the pre-compound conditioning phase), a US-processing model, such as Rescorla-Wagner, can easily account for one-trial blocking. Indeed, one-trial blocking is prevented by the administration of an opioid antagonist (Cole & McNally, 2007; Fanselow & Bolles, 1979a). However, associability models, which depend on previous experience with the CS, cannot explain one-trial blocking.

Thus, it is likely that changes in both US processing and changes in CS associability contribute to Pavlovian conditioning. For example, the slow rate of learning that follows after a CS has

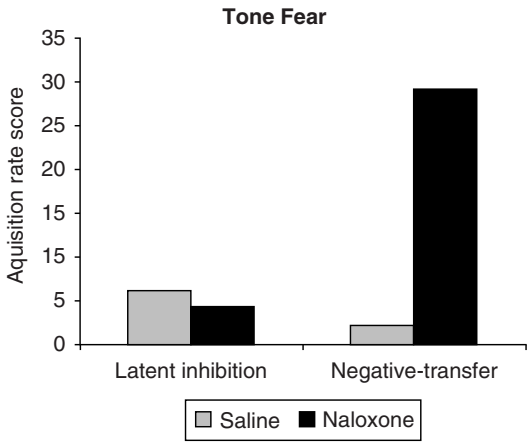

Figure 14.4 Naloxone blocks Hall-Pearce negative transfer, but not latent inhibition. During Phase 1, rats received either one exposure to a 64-sec tone only (latent inhibition groups) or one pairing of a 64-sec tone followed by a 1-sec low-intensity footshock (negative-transfer groups) per day over 10 days. In Phase 2, rats were given an injection of saline or naloxone and received a single tone presentation followed by a high-intensity footshock per day over 2 days. The graph displays difference scores for freezing to the tone on the first versus second day of Phase 2. Low scores indicate the slow acquisition expected of latent inhibition and Hall-Pearce negative transfer. Saline groups showed latent inhibition and negative-transfer effects. However, naloxone prevented negative transfer but left latent inhibition intact. (Adapted from Young, S. L., & Fanselow, M. S. (1992). Associative regulation of Pavlovian fear conditioning: Unconditional stimulus intensity, incentive shifts, and latent inhibition. *Journal of Experimental Psychology: Animal Behavior Processes, 18*(4), 400–413).

been previously conditioned with a weak US (negative-transfer; Hall & Pearce, 1979) *is* blocked by naloxone (Young & Fanselow, 1992). These findings are summarized in Figure 14.4. Thus, by integrating CS-associability and US-processing views of conditioning, a wide breath of Pavlovian phenomena can be accounted for.

Lastly, it should be noted that one-trial overshadowing cannot be accounted for by any of these models. One-trial overshadowing (Mackintosh, 1971) is a variant of the basic overshadowing effect; however the effect is achieved with a single conditioning trial of a compound CS. The occurrence of one-trial overshadowing is problematic for US-processing models such as the negative-feedback model because negative feedback is only generated after the first conditioning trial. Similarly, associability models also require prior experience to drive interaction between stimuli. This suggests that initial competition between stimuli may be driven from a purely perceptual or attentional level. Thus, in addition to US-processing and CS-associability factors, raw attentional factors may also play an important role in Pavlovian conditioning.

A number of studies have provided evidence for the role of dopamine in the regulation of attentional factors in Pavlovian phenomenon. In most of these studies, administration of a dopamine (DA) agonist often attenuates the Pavlovian phenomenon of interest. For example, amphetamine (which releases DA) has been shown to disrupt blocking (Crider, Solomon, & McMahon, 1982; Ohad, Lubow, Weiner, & Feldon, 1987) as well as overshadowing (O'Tuathaigh & Moran, 2002). Further studies have narrowed this effect down to the role of the DA D_1 receptor in attentional processes, as the selective D_1 agonist SKF 38393 attenuates overshadowing (O'Tuathaigh & Moran, 2002; Zelikowsky & Fanselow, 2010). Importantly, the indirect dopamine (DA) agonist D-amphetamine sulphate was shown to disrupt both blocking and overshadowing within a single study (O'Tuathaigh et al., 2003). In a separate task sensitive to attentional factors, Granon et al. (2000) showed that injecting SKF 38393 directly into the medial prefrontal cortex (mPFC) enhanced attentional performance in this task, suggesting that dopamine in the mPFC may play a role in the regulation of attentional processing in Pavlovian conditioning.

An account of Pavlovian processes that attributes conditioning on the first trial to attentional factors, subsequent trials to a negative-feedback mechanism, and previous CS exposure to an associability model, would have a good chance of encompassing many of the phenomenon that occur in Pavlovian conditioning. The fact that both the opioid antagonist naltrexone and the dopamine D_1 agonist SKF 38393 attenuate Pavlovian overshadowing (albeit differently), suggests that multiple mechanisms may indeed contribute to the same Pavlovian phenomena (Zelikowsky & Fanselow, 2010). These multiple mechanisms may work hand in hand in a temporal fashion and/or may even mutually compensate for each other.

RECENT ADVANCES IN ERROR CORRECTION: DOPAMINE NEURONS

While error correction–calculating circuits have been described for fear and eyeblink conditioning (Fanselow, 1998; Kim et al., 1998), recent work has suggested that in positive reinforcement learning, certain groups of neurons respond as though they detect mismatches between earned and expected rewards.

More specifically, a number of studies from Schultz and collaborators have suggested that firing of midbrain dopamine neurons operate according to error-correction-type rules in the regulation of reward learning (Fiorillo et al., 2003; Hollerman & Schultz, 1998; Schultz, 1997, 1998; Schultz, Dayan, & Montague, 1997; Tobler, Dickinson, & Schultz, 2003; Tobler et al., 2005; Waelti, Dickinson, & Schultz, 2001). These studies find that burst activity of midbrain dopamine neurons—that is, the "phasic" dopamine response—can be seen following food or liquid rewards. However, if a reward is already predicted by a cue (i.e., a stimulus has been well conditioned to predict a food US), this burst activity does not occur, and if an expected reward is omitted, activity in these neurons is depressed (see Schultz, 2007 for a review).

Schultz and colleagues interpret the behavior of these neurons as demonstrative of encoding the discrepancy between a predicted reward and the reward actually received. Thus, the output of these midbrain dopamine neurons seem to behave much like an error signal—with positive errors correlated to increased activity in these neurons and negative errors with depressed activity. In Rescorla-Wagner terminology, the response of these dopamine neurons is meant to represent the surprise term ($\lambda - \Sigma V$). Thus, Schultz and colleagues suggest that these dopamine neurons represent unexpected reinforcers and therefore act as a signal for reinforcement. This role is consistent with the long-standing view that dopamine acts as the brain's reward system. It also implicates dopamine in the regulation of both prediction error and attention in Pavlovian conditioning.

However, there are critical outstanding issues surrounding this view. First, unlike the more fully understood fear and motor learning systems, we do not know how these neurons actually calculate error. A second issue is that after conditioning, midbrain dopamine neurons will also react to a predictive CS with a phasic response. Thus, these neurons seem to both generate an expectancy type signal (Rescorla-Wagner's V term) as well as an error signal (Rescorla-Wagner's $\lambda - V$ term). However, an expectancy signal drives your response based on what you have learned (V), whereas an error signal drives your learning based on how you have responded ($\lambda - V$). These are very different actions and require different computations. How are the neurons that receive these signals to discriminate between these two different meanings?

A third issue, noted by Redgrave and Gurney (2006), lies in the fact that the occurrence of the phasic dopamine response has a very short latency (70–100 ms) from stimulus onset (Schultz, 1998). So short in fact, that it occurs during an animal's "preattentive" processing phase—in other words, before the animal could actually identify a reward and/or its value. Thus, it becomes less clear what exactly these neurons contribute.

In an alternative account, Redgrave and Gurney (2006) suggest that instead of signaling an unpredicted reward, the phasic dopamine response signals an animal to "reselect" an action that was immediately followed by an unpredicted biologically significant event. According to this "reselection hypothesis," the phasic dopamine response plays much more of a causal role. It allows an agent to recognize that a particular action it performed in a particular contextual backdrop preceded an unexpected biologically salient event and hence may be a probable cause. According to this hypothesis, an animal uses the phasic dopamine signal to differentiate between events for which it is responsible from events for which it is not, regardless of any immediate reward value (Redgrave & Gurney, 2006; Redgrave, Gurney, & Reynolds, 2008).

This account is further supported by experiments from Winterbauer and Balleine (2007), showing that amphetamine enhances performance on a response (lever pressing) that was followed by the delivery of a simple visual stimulus. This solidifies a role for dopamine in the reselection of a response, despite the absence of any reward contingency. Taken together, these reselection studies suggest that instead of signaling reward values, dopamine neurons may signal events that should be attended to, which dovetails nicely with our earlier discussion of the role of dopamine in selective attention. Certainly stimuli that you have learned about (V) and stimuli that signal surprise ($\lambda - V$) should be attended to. Thus, the actual profile of responding of these neurons is more in line with an attentional view.

CIRCUIT SELECTION AND ERROR CORRECTION

Thus far, we have described the manner by which particular circuits in the brain operate to calculate and correct for errors. We have also discussed the behavioral implications of error correction, namely that error-correction-type rules can be used to explain a wide range of Pavlovian phenomenon (e.g., overshadowing and blocking). We covered evidence consistent with a role for US limitations and negative-feedback circuits as well as the role of attention

and dopamine in the regulation of these phenomena. However, we would like to take the notion of error correction one step farther. We propose that the very same error-correction rules that govern "stimulus selection" may also regulate how the brain selects circuits. The case of contextual fear memory is a particular poignant example of how such "circuit selection" may be occurring in the brain.

In contextual fear conditioning, an animal learns to fear an environment in which it has received an aversive US (e.g., footshock). The memory of the context is initially stored in the hippocampus for a period of time, as lesions of the hippocampus immediately following contextual fear conditioning result in a complete loss of memory (Anagnostaras, Maren, & Fanselow, 1999; Kim & Fanselow, 1992). However, it has been shown that if damage to the hippocampus is sustained *prior* to training, animals are able to condition fear to a context (Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998; Maren, Aharonov, & Fanselow, 1997; Wiltgen, Sanders, Anagnostaras, Sage, & Fanselow, 2006). Such data suggest that hippocampal damage produces retrograde amnesia but does not necessarily produce anterograde amnesia. It appears that although an animal may "normally" use its hippocampus to learn and store a representation of a place, in the absence of the hippocampus animals can compensate and form a representation of that place.

Thus, when the primary, hippocampus-based circuit is compromised, an alternate circuit may be "selected" by the brain (Fanselow, 2010). However, this alternate circuit does not learn if the hippocampus is already engaged in learning. The interesting question remains as to the source and nature of this compensation. Retrograde amnesia studies tell us that the hippocampus—and not the alternate circuit—will normally form a configural representation of a place (see Fanselow, 2000). On the other hand, anterograde studies tell us that the alternate circuit may be utilized when the hippocampus is compromised.

Just as the hippocampus has been shown to be important for context learning and memory, the basolateral amygdala (BLA) has been found to be vital for fear learning and memory (e.g., see Fanselow & LeDoux, 1999; Gale et al., 2004). Similar to the case with the hippocampus, a rodent with lesions or inactivation of the BLA may compensate and demonstrate fear learning and memory, provided that a strong regimen is used for training (Maren, 1999; Ponnusamy, Poulos, & Fanselow, 2007; Poulos et al., 2010). The same pattern holds for fear learning by subnuclei within the BLA complex (Angladda-Figueroa & Quirk, 2005). Thus, fear learning and memory, like context learning and memory, seem to follow a similar pattern: A particular structure and circuit are normally used, but if they are damaged *prior* to—but not *subsequent* to—learning, then an alternate pathway may compensate.

A remaining question is why the alternate circuit does not learn when the primary circuit is learning. One solution is that perhaps circuits, just like regular discrete cues, behave according to associative learning rules such as those that govern Pavlovian overshadowing. According to this idea, "salient" circuits would be selected for conditioning, while others would be overshadowed in a manner similar to discrete cues (see Fanselow, 2010). And, as is the case with an overshadowed discrete *cue*, an overshadowed *circuit* may be given the chance to learn if the limits on the amount of learning normally supported (i.e., λ) are removed or lifted. Thus, because an opioid antagonist such as naltrexone attenuates the overshadowing of a cue, by presumably lifting the limits on a US's ability to condition (Zelikowsky & Fanselow, 2010), the same effect should be translatable to the selection of an "overshadowed" circuit.

Taking the rules of associative learning and competition and applying them more broadly to circuit selection has powerful implications. Notably, it suggests that circuits, like discrete stimuli, can be learned about, despite being weaker or less salient, provided the amount of learning that is supported can be increased. This has important practical repercussions regarding patients suffering from some form of brain damage in which a primary pathway for learning and memory is compromised. It also has theoretical implications in that it suggests the depth and

breadth of error-correction is quite wide. Error correction is not simply a mechanism for enabling fine motor movements or predicting a reward; it forms the very basis and framework for how of our brains select appropriate circuits for specific types of learning.

CONCLUSIONS

In this chapter, we have tried to present a picture of how error-correction processes can drive and mold the way we learn and behave. From the idea that a key component of defense is the successful inhibition of recuperation (PDR model), to more mechanistic notions of negative feedback and dopamine signaling, it seems that conditioning is driven incrementally by discrepancies between what actually happens in our environment and what we expect to happen. Whether this discrepancy is more sensitive to factors such as attention, environmental limitations on what can be learned, or what direction an error occurs (i.e., incremental vs. decremental), the basic idea remains the same: Our behavior is a result of what we expect about our environment compared to what we do not. In this chapter, we have emphasized particular mechanisms by which such errors may be calculated (e.g., analgesia-mediated negative feedback or dopamine signaling and reward). Additionally, we suggest that error correction may in fact comprise a much more global mechanism. Namely, that the rules that underlie error correction are ubiquitous in the brain; they are used by specific brain circuits to perform particular functions, and they are also used by the brain overall to select circuits for more complex and integrated functions.

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