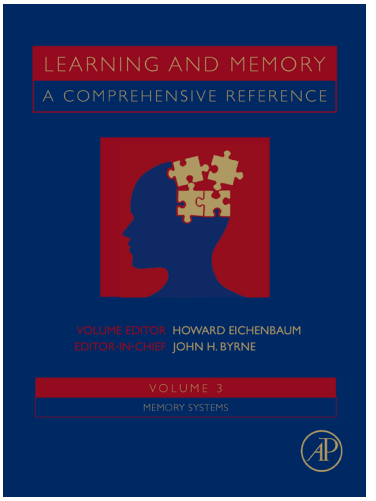

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3.24 Emotional Learning: Animals

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3.24.1 Introduction

The capacity to learn and retain information, whether it is the sequence and rhythm of muscle movements required for a motor skill or the details of a traumatic emotional experience, imbues organisms with an enormous advantage for coping with an ever-changing world. How the brain forges memory from experience has been a question of considerable interest to psychologists and neuroscientists for decades. What has become clear in the last several decades is that memory representations are not monolithic and are therefore not wrought by a singular core of specialized brain tissue. Rather, multiple brain systems and regions participate in the encoding and storage of many different types of memories for skills, emotions, facts, and episodes, and so on.

The parsing of memory into different domains is probably best illustrated by the dissociation in memory systems apparent after brain lesions in people. In the 1960s, Milner described the most instructive and well-studied case of dissociable brain systems for memory in a man known by his initials as H.M. (Milner, 1962). Patient H.M. came to Milner's attention when he presented with severe amnesia, both for past events and newly experienced events, after he received a bilateral medial temporal lobe resection for intractable epilepsy. Despite his profound amnesia for episodes in his daily life, he exhibited apparently normal learning and memory for a variety of motor tasks, including mirror-tracing and rotary pursuit. The critical observation made by Milner was that H.M.'s memory deficit was selective for certain types of information. She necessarily concluded that there must be multiple memory systems in the brain. In particular, the medial temporal lobe the hippocampus, which was the major site of brain damage in H.M., was clearly critical for episodic memory, but not motor memory. Years of research have now confirmed this view and revealed dissociable neural systems underlying memory for emotional events, pleasurable rewards, skeletal motor responses, sensory percepts, and facts and episodes, to name but a few.

This implies that any single experience is always a hybrid of memorable events traced in different neural circuits in the brain. Consider the memory of a traumatic experience, such as an armed robbery by a masked man in a convenience store. The victim of

such a crime is likely to vividly recollect the time and place of the crime, as well as the events leading up to and following the event. In addition, there may be visceral emotional responses, such as a racing heart and sweating palms, that are evoked by aspects of the robbery – such as the sight of a man in a ski mask on a snowy day years after the crime. The victim might also form the opinion that convenience stores are dangerous places after the experience. Hence, the armed robbery filters through several memory systems, leaving its trace in memories about where and when the episode occurred, the emotional consequences of the event, and factual knowledge about the event, among others.

The memory system that is the focus of this chapter is that concerned with emotional information. Emotions, of course, come in several varieties – fear, love, anger, joy, and so on. However, the most productive neurobiological analysis of emotional learning has been in the context of aversive emotions such as fear. There has been considerable work in both human and animals on the anatomy and physiology of the memory system for fear. This focus on fear memory has been driven by many factors, including the isomorphism of fear responses in humans and animals, the rapid acquisition and long-term stability of fear memory, and the primacy of fear memory in the context of behavioral systems adapted to defense and self-preservation. Moreover, from a clinical perspective, dysfunction in emotional memory systems is at the heart of the most prevalent psychiatric disorders in humans. Specifically, anxiety disorders including posttraumatic stress disorder, panic disorder, and specific phobias are rooted in pathological fear memories. The aim of this chapter is to explore the emotional memory system, focusing on the contribution of experimental studies in animals to fostering our understanding of the nature and properties of emotional learning and memory, particularly for aversive events, in humans. The approach that is followed in this chapter is to use studies of brain function and anatomy to inform the properties of emotional memory and, similarly, to leverage psychological theory and animal behavior to inform the nature of the brain systems underlying emotional learning and memory. This behavioral neuroscience perspective on the emotional learning and memory systems in animals has had great influence on modern thinking about the neurobiology of memory, in a general sense. This chapter will not consider the extensive literature on the cellular, genetic, and molecular mechanisms underlying learning, which are the focus of other chapters in this volume.

3.24.2 Behavioral Models for Exploring the Neural Substrates of Emotional Learning

Before considering in depth the neural systems underlying emotional learning and memory, it is important to understand the paradigms and methods used to investigate aversively motivated learning and memory in the laboratory. The experimental investigation of emotional learning has its roots in Watson and Rayner's classic demonstration of fear learning in the human infant, Little Albert (Watson and Rayner, 1920). In this case study of human fear learning, Watson presented Albert with a live, white rat and subsequently hammered an iron rod to produce a loud, startling sound that sent Albert into tears. After several conditioning trials, Albert came to fear the rat and burst into tears and attempted to avoid the rat when presented with the animal, even in the absence of the loud noise. Watson and Rayner (1920) argued that emotional responses could be conditioned in much the same way as discrete motor or salivary responses, as described by Pavlov. This provided an important demonstration of the use of Pavlovian procedures to study emotional learning and laid the groundwork for subsequent studies in both humans and animals of the nature and properties of aversively motivated learning.

Although Watson and Rayner's examination of Little Albert was a noteworthy proof of concept that fear could be established through conditioning procedures, the successful analysis of emotional learning and memory systems required the development of behavioral tasks that could be adapted to laboratory animal subjects and brought under rigorous experimental and parametric control. In most cases, these tasks were developed in efforts to understand the psychological properties of learning and memory systems (rather than brain substrates *per se*), whether in the context of motor skill acquisition, appetitive learning, or aversively motivated learning, for example. Indeed, the work that emerged from psychological laboratories in the early to mid-twentieth century proved to be crucial for understanding the process and content of learning. These advances in psychological learning theories were essential to adapting behavioral tasks to the analysis of learning and memory systems in the brain.

3.24.2.1 Instrumental Conditioning Paradigms

The types of learning tasks used in analyzing the psychological and neural substrates underlying emotional learning can be classified in general terms according to their associative contingencies. Broadly speaking, one class of task requires that the animal learn that the delivery of an aversive stimulus is a consequence of its behavior. These tasks therefore involve an instrumental contingency and are variously referred to as instrumental conditioning or operant conditioning tasks. In the context of aversive learning, animals are often instrumentally trained to avoid a noxious stimulus, such as the delivery of footshock on an electrified grid floor. Hence, one might arrange that a conditioned stimulus (CS) will signal the occurrence of a footshock unconditioned stimulus (US). In some tasks, such as a shuttle-box avoidance task in rats, the animal can avoid the aversive US if it learns to move from one side of the box to the other when the CS is initiated. In this case the animal learns an active response to avoid shock. Active avoidance tasks may take several forms, from one-way active avoidance (in which the animal always shuttles in one direction from a consistently dangerous compartment to a consistently safe compartment) to two-way or shuttle avoidance (in which either compartment might be associated with shock and the animal learns to shuttle, in either direction, on alternate trials). Other active avoidance tasks might take advantage of entirely different response requirements, such as wheel-running avoidance, in which rabbits step in a running wheel to avoid shock, or conditioned taste avoidance, in which animals learn to avoid a novel taste that is followed by gastrointestinal malaise induced with an emetic such as lithium chloride.

In other instrumental avoidance tasks, such as inhibitory avoidance conditioning, the animal learns that making a response, such as walking from an illuminated compartment to a darkened compartment of a chamber, will result in shock delivery. In this case, the animal learns to avoid footshock by inhibiting its tendency to move to the dark side of the apparatus when it is returned to the illuminated chamber. Thus, the animal learns a passive avoidance response in this situation. There are many variants of passive avoidance tasks, including step-through passive avoidance of the sort just described, or step-down avoidance, in which movement from a small, elevated platform to a larger arena is punished with footshock. Animals that have learned to press a bar for food will suppress that response if it comes to yield footshock. Similarly, thirsty animals will avoid licking a water spout if contacts with the spout lead to a shock. In another variant of passive avoidance training, rats are placed in a chamber that houses an exposed, electrified shock probe. Upon contacting the probe, the animal receives a shock and subsequently avoids the probe. In addition to avoiding contact with the probe, the animal will spray bedding or any other substrate at the probe in an effort to bury it. Defensive burying is an ethologically relevant avoidance behavior observed by animals in response to noxious stimuli in their environments.

In every instrumental task described, the animal learns that its behavior has consequences for the likelihood of experiencing an aversive event. In one case, the animal learns that its behavior causes the aversive event and then learns to withhold that response in the future (i.e., passive avoidance tasks), and in another case the animal learns that its behavior terminates an aversive stimulus, and it can avoid the aversive event by making a behavioral response (i.e., active avoidance tasks). Thus, in passive avoidance tasks, the probability of various approach behaviors is decreased by punishment, yielding passive avoidance. In active avoidance tasks, the probability of an active avoidance response is increased through negative reinforcement (removing an aversive stimulus). In both cases, it is important to appreciate that although the task is orchestrated to reinforce one behavioral response or another, the instrumental association between a stimulus and a response (the so-called stimulus–response or S–R association) is certainly not the only thing learned in the situation. Of course, for successful performance in such tasks, animals must learn associations between stimuli (stimulus–stimulus or S–S associations, such as the CS–US association), associations between behavioral responses and their outcomes (response–outcome or R–O associations), and any other information incidental to task performance that defines the episode in the stream of the animal's experience. So, simple conditioning tasks are often much more complicated than they would appear to be at first glance.

3.24.2.2 Pavlovian Conditioning Paradigms

The other major class of aversive conditioning tasks that has been adapted to study emotional memory systems does not require the instrumental contingency that is at the heart of avoidance conditioning

tasks. In classical or Pavlovian conditioning, just as in instrumental conditioning, animals learn an association between stimuli and their consequences, such as an auditory CS and a footshock US that it predicts. However, in Pavlovian conditioning, the animal's behavior is inconsequential to the delivery of either stimulus; CSs and USs are delivered irrespective of the animal's behavior, and the animal cannot engage in behavior to avert or avoid the US. In this sense, Pavlovian conditioning simplifies the analysis of the underlying brain systems because it eliminates some of the associative processes that operate in the context of instrumental conditioning tasks (namely, instrumental S–R and R–O associations).

Pavlovian conditioning tasks designed to characterize emotional learning and memory, such as learning fear, typically utilize noxious USs such as electric shock applied to the feet or, in some cases, electric current delivered through fine wires implanted in the neck or around the eye. Other aversive USs that are effective for conditioning fear include loud sounds, such as bursts of white noise (Watson actually used a loud sound to condition fear of rats in Little Albert), air puffs, illness induced by emetics such as lithium chloride, and inhalation of carbon dioxide. These aversive USs can be signaled by a variety of CSs including lights, sounds (most typically pure tones or white noises), olfactory stimuli, or even the places or contexts in which the animal encounters the US. What tends to vary across different Pavlovian fear conditioning tasks is the behavioral (or autonomic) response used to index fear. The choice of response system depends on many factors, not the least of which is the animal species used in the experiments. In rats and mice, a variety of response measures have been used. In a naturalistic setting, rodents show a hierarchy of defensive behavior in response to predatory threat. When a predator is near, but not yet in contact with, the prey, a rat or mouse will exhibit freezing behavior, which is characterized by nearly complete immobility, as a means to avoid detection by the predator. In the laboratory, freezing behavior is readily conditioned to places in which aversive USs are delivered (Blanchard and Blanchard, 1969). Interestingly, unlike other notable forms of Pavlovian conditioning, the learned fear response (the conditioned response or CR) does not take the form of the activity burst that is generated by the shock US. Running, jumping, and vocalization characterize the activity burst of a rat to footshock; this collection of responses resembles a rat's circa-strike response to a predatory attack. It is widely believed that the activity burst reflects the sensory properties of the shock US, whereas the freezing response is a function of the affective (fear-engendering) properties of the aversive event. Hence, many studies of fear conditioning in rodents rely on freezing behavior as an index of fear. In addition to freezing, rats exhibit a number of other behavioral and autonomic responses that can be used to index fear. For instance, they show less recuperative behavior to a painful formalin injection into their paw because of fear-induced hypoalgesia. Fear is also associated with increased heart rate and blood pressure and the release of stress hormones such as glucocorticoids.

Another popular measure for indexing fear is the change in the acoustic startle reflex that is observed in the presence of a fear-provoking stimulus (Brown et al., 1951). In the fear-potentiated startle paradigm, rats or mice are exposed to a series of loud noise bursts to index their acoustic startle amplitudes. After this phase they are exposed to Pavlovian fear conditioning procedures in which a visual CS is paired with a footshock US. To assess the fear engendered by the CS, the rats are once again exposed to the acoustic startle stimuli, but now in the presence of the visual CS on some trials. Under these conditions, the acoustic startle response is greatly elevated on trials in which the fearful CS is present relevant to trials without the CS. Fear, then, is indexed indirectly by potentiation of the startle response. Another indirect measure of fear described by Estes and Skinner is the suppression of appetitive responding in the presence of a fearful CS (Estes and Skinner, 1941). In this case, animals were first instrumentally trained to press a bar for a food reward. When the animals were reliably pressing the bar for food, they underwent (typically in another chamber) fear-conditioning procedures. The animals were then once again allowed to respond instrumentally for food. When presented with the fearful CS in this situation, instrumental responding during the CS dropped considerably relative to intervals before or after delivery of the CS. This bar-press suppression by a fearful CS has historically been used to index the conditioned emotional response (CER), which is synonymous with the conditioned fear response.

3.24.2.3 Naturalistic Conditioning Paradigms

In addition to these traditional models for studying emotional learning, there are some less widely used,

yet more naturalistic, paradigms that have been used for studying aversively motivated learning. For example, social defeat by a dominant conspecific appears to yield a conditioned fear state that shares many of the properties of fear motivated by artificial aversive stimuli, such as footshock (Potegal et al., 1993). In this paradigm, typically conducted in Syrian hamsters, a younger, subordinate animal (the intruder) is introduced into the cage of an older, dominant animal (the resident), which arranges a social interaction whereby the resident behaves aggressively toward the intruder, chasing and biting the subordinate animal. Subsequent to this antagonistic interaction, the intruder exhibits submissive behavior around the dominant animal as well as other, nonthreatening conspecifics. Although the pattern of behavior that emerges from social defeat does not include freezing behavior, there are other commonalties with conditioned fear responses such as a reduction in pain sensitivity (hypoalgesia). Clearly, negative social interactions can yield an aversive state that conditions fear to other conspecifics and even the places where defeat occurs (Razzoli et al., 2006).

Of course, one function of fear is not only to motivate defensive behavior but also, at least in the case of overt fear responses, to communicate an individual's emotional state to nearby conspecifics. This might serve to protect genetically related individuals from external threats bearing on one member of the group. Learned fear through social transmission has been demonstrated in both mice and rats. For instance, mice that witness a conspecific being attacked by biting stable flies will subsequently exhibit hypoalgesia and attempt to bury themselves (to avoid being bitten) when exposed to flies whose mouthparts have been removed (to prevent biting) (Kavaliers et al., 2003). Animals that were never exposed to flies did not exhibit these responses. Social transmission of fear may also influence subsequent aversively motivated learning. In a recent study, rats were housed in pairs, and then one member of the pair was removed and subjected to fear conditioning (Knapska et al., 2006a). After the fear-conditioning episode, the conditioned animal was allowed to interact with its naïve cage-mate. During the interaction, the nonshocked cage-mate exhibited behaviors similar to that of the shocked rat and subsequently acquired a conditioned avoidance response faster than rats whose cage-mate left home but did not undergo fear conditioning. Collectively, these studies suggest that fear can be socially transmitted, can be learned, and can influence subsequent behavior to novel aversive events. Fear learning would appear to promote defensive behavior in not only the individual experiencing an aversive stimulus but also others with whom that animal interacts.

3.24.3 Historical Perspective on Brain Mechanisms of Emotional Learning

To appreciate modern work on the neural mechanisms of aversively motivated learning, it is worthwhile to trace the development of work linking emotion to the brain. There is no doubt that our modern appreciation of the brain circuits involved in aversive learning and memory emerged from early observations on the effects of brain damage on emotional behavior in humans and animals. Emotional learning in humans will be covered in depth elsewhere, but it is worthwhile mentioning one human case as a prelude to the discussion of work in animals. Prior to the nineteenth century, there had been an explosion of detailed descriptions of human brain anatomy, but only small gains in appreciating the function of various brain areas in psychological function. Perhaps the most influential one was the discovery of profound emotional changes in a man named Phineas Gage, whose brain was penetrated by an iron spike in a railway construction accident in 1848. Amazingly, Gage survived the injury to his head, but he was not the same person after recovering from the wound. The surgeon that oversaw Gage's case noted that Gage's personality showed marked changes after the injury. Relative to his gentle demeanor prior to the accident, he angered easily, used profanity, and could not maintain interpersonal relationships after his accident. Emotions, it would appear, had their roots in the brain. Gage's case would not inform the question of brain systems involved in emotional learning and memory *per se*, but it did set the groundwork for understanding the brain mechanisms of emotion, which was then actively pursued in experimental studies in animals.

The experimental investigation of emotional changes after brain injury in animals was heralded by Goltz's work in dogs (Goltz, 1892). Goltz surgically removed large portions of the dog cerebral cortex (a decortication) and noted profound changes in emotional reactivity after the animals recovered from the procedure. He found that any disturbance of the animal, however small, provoked an acute rage

that included barking, biting, deflection of the pinnae, and piloerection among other responses. The animals appeared to assume an emotional state that was only provoked in normal animals by highly aversive stimuli. Cannon and Britton later termed this behavioral state 'sham rage,' to distinguish it from the emotional reaction displayed by normal animals. The importance of Goltz's work was to begin a series of more systematic functional neuroanatomical studies that sought to localize emotional centers in the brain.

In parallel with Goltz's work in Germany, Brown and Schäfer, working in London, described profound alterations in emotional reactivity following temporal lobe lesions in monkeys (Brown and Schafer, 1888). Klüver and Bucy subsequently extended this work by making more discrete lesions and recording detailed behavioral observations of their operated animals (Klüver and Bucy, 1937). Both groups found that temporal lobe resections, which damaged both cortical and subcortical tissue, produced marked behavioral changes, including hyperorality, hypersexuality, visual agnosia, and notably, a loss of fear. For example, monkeys with temporal lobe lesions readily consumed novel and normally avoided foods, such as meat, and they would mouth inedible objects including metallic screws. Moreover, monkeys that once cowered in the presence of humans readily approached and contacted their caretakers after surgery. This work heralded the study of the neural substrates of emotion and focused intense interest on the role of the temporal lobes in the mediation of fear.

Papez, and later MacLean, built on the functional studies in animals and proposed what were to become highly influential neuroanatomical models of emotion systems in the brain (Papez, 1937; MacLean, 1949). Papez used anatomical methods to trace axonal connections between brain structures. He found that brain structures involved in generating emotional responses were highly interconnected and circuitous. His anatomical circuit for emotion included a prominent role for the hippocampus (a medial temporal lobe structure), the anterior thalamus and mammillary bodies in the diencephalon, cingulate lobe of the neocortex, and the major fiber tracts connecting these structures (fornix and mammilothalamic tract). MacLean expanded on the Papez circuit to include other brain structures in the emotional circuit, including the septum and amygdala, in what he termed a larger limbic system that he implicated in emotion. Central to MacLean's theory was the triune brain, which he contended described a systematic pattern of brain evolution along three neural axes: primitive, regulatory centers in the brain stem (the reptilian R-complex); emotional centers in the subcortical limbic system; and higher cognitive centers in the neocortex.

Although the Papez circuit and related limbic system had a potent influence on thought concerning the neural basis of emotion, it is now generally understood that there is no singular emotional center in the brain. Even specific emotions, such as fear, appear to involve brain circuitry that is not constrained by the anatomical circuits described by Papez and MacLean. In the context of aversive learning and memory, for example, it has become clear that a critical brain structure is the amygdala, a temporal lobe structure that was omitted from the Papez circuit. The central role of the amygdala in fear emerged from early work focusing on the consequence of temporal lobe damage on emotional reactivity. Specifically, Weiskrantz found that the loss of fear that Klüver and Bucy described in monkeys with temporal lobe lesions was the consequence of damage to the amygdala (Weiskrantz, 1956). Indeed, recent work has shown that a selective loss of amygdala neurons results in a fear reduction similar to that observed by Klüver and Bucy (Zola-Morgan et al., 1991; Meunier et al., 1999; Kalin et al., 2004). Numerous other studies have demonstrated reduced fear (taming) after amygdala damage in several mammalian species, including rats, cats, rabbits, dogs, and humans (Goddard, 1964). Moreover, electrical stimulation of the amygdala in animals and amygdaloid seizures in humans are associated with autonomic and behavioral changes characteristic of fear (Gloor, 1960; Gloor et al., 1982; Iwata et al., 1987; Davis, 1992). Hence, consensus emerged from these studies that the amygdaloid complex has an indispensable role in the regulation of fear.

3.24.4 Neural Mechanisms of Instrumental Avoidance Conditioning

The discovery of the central role for the amygdala in fear heralded an era of systematic examination of the neural substrates of aversively motivated learning and memory tasks in animals (Sarter and Markowitsch, 1985). Moreover, the observation by Watson and Rayner that fearful emotions could be conditioned in humans led to considerable interest in

how acquired states of fear and anxiety might influence normal and pathological behavior (Watson and Rayner, 1920). Hence, the mid-twentieth century witnessed a convergence of neuroanatomical work on emotion centers in the brain with psychological work on the properties of emotional learning that provided the foundation for systematic studies of the neural circuitry and mechanisms involved in learning about fearful experiences. Several investigators set out to further quantify this function by employing learning and memory tasks. The earliest work in this domain used instrumental avoidance conditioning tasks to investigate the neural mechanisms of learned emotions. And although there has been considerable debate concerning the nature of avoidance learning (Bolles, 1972; Fanselow, 1997), active and passive avoidance conditioning tasks have remained an important method for characterizing an animal's propensity to alter its behavior to avoid aversive stimuli.

3.24.4.1 Active Avoidance Conditioning

The earliest studies to examine the neural substrates of fear-motivated learning used instrumental avoidance tasks, in which animals could avoid an aversive stimulus by making the appropriate behavioral response. Not surprisingly, the amygdala was the focus of this early work, given the important role it had been shown to play in emotional behavior. In the first study of its kind, Brady and colleagues trained cats in a footshock-motivated shuttle avoidance task and found that large amygdala aspirations impaired the acquisition, but not the retention, of the avoidance response (Brady et al., 1954). Subsequent studies extended the active avoidance conditioning deficits after amygdala damage to rats. These deficits were reported in two-way active avoidance (McNew and Thompson, 1966; Campenot, 1969; Bush et al., 1973; Yeudall and Walley, 1977; Schutz and Izquierdo, 1979) and wheel-turning avoidance (Robinson, 1963).

Of course, the amygdala is a heterogeneous structure composed of several anatomically distinct nuclei (Krettek and Price, 1974; Krettek and Price, 1978; Pitkanen et al., 1997; McDonald, 1998; Swanson and Petrovich, 1998; Sah et al., 2003). The basolateral complex of the amygdala is the primary cortical interface of the amygdala and consists of the lateral, basolateral, and basomedial nuclei. These nuclei in turn project heavily to the central nucleus of the amygdala, which is the primary interface of the amygdala to hypothalamic and brainstem structures involved in generating various fear responses. Many of the earlier studies, with some exceptions, damaged the amygdala in its entirety without attention to the different contributions individual amygdaloid nuclei make to avoidance learning and memory. However, some of the early studies attempted to examine the contribution of individual nuclei to avoidance learning. For example, discrete electrolytic lesions to the basolateral complex of the amygdala impaired the acquisition and retention of a shuttle-box avoidance in cats (Horvath, 1963), one-way active avoidance in rats (Werka et al., 1978), and two-way avoidance in rats (Coover et al., 1973). The central nucleus of the amygdala was also shown to be critical for the acquisition, but not retention, of one-way (Werka et al., 1978) and two-way (Roozendaal et al., 1993) active avoidance. Importantly, selective neurotoxic lesions of the central nucleus of the amygdala that spare axonal fibers of passage result in active avoidance conditioning deficits (Sanchez Riolobos, 1986). Interestingly, however, cellular markers of neuronal activity in the amygdala indicate that avoidance training engages primarily the lateral and basolateral nuclei of the amygdala, with little evidence for central nucleus activation (Savonenko et al., 1999; Radwanska et al., 2002; Knapska et al., 2006b). This pattern of activity is consistent with recent work that indicates that the basolateral, but not central nucleus, of the amygdala is particularly involved with instrumental avoidance under some conditions (Killcross et al., 1997; Amorapanth et al., 2000).

In contrast to the amygdala, damage to the hippocampus, the fornix (the major subcortical projection tract of the hippocampus), or the entorhinal cortex (the major cortical interface of the hippocampus) typically produces a facilitation of active avoidance learning (Myhrer, 1975; Weiner et al., 1998; Pouzet et al., 1999; Guillazo-Blanch et al., 2002). As will be discussed next, the enhancement in active avoidance conditioning might be the result of two factors. First, hippocampal lesions increase locomotor activity in a variety of test situations (Douglas, 1967; Blanchard et al., 1977; Maren and Fanselow, 1997). Increases in locomotor activity are likely to foster the emission of escape responses in response to shock during avoidance training and are thus permissive to the acquisition of avoidance responses. Second, hippocampal lesions produce impairments in the acquisition of contextual fear, while having minimal effects on fear to discrete CSs (e.g., Phillips and LeDoux, 1994). Contextual fear tends to retard acquisition of two-way active avoidance insofar as it generates freezing behavior (which

competes with escape and avoidance responding), and it encourages passive avoidance of the compartment of the apparatus that was associated with shock on each subsequent trial. Hence, hippocampal rats unencumbered by contextual fear, accruing CS fear normally, and primed to emit active avoidance responses, outperform normal rats in active avoidance tasks. The hippocampal system does not appear to play a direct role in supporting avoidance learning but, rather, modulates performance in a way that is constrained by the contextual demands of the task.

Gabriel and colleagues have conducted one of the most systematic neural analyses of instrumental avoidance learning in rabbits performing wheel-running responses in a discriminative avoidance task (Gabriel, 1993). In this task, one auditory conditional stimulus (CS+) signals the onset of footshock, whereas a different auditory conditional stimulus (CS−) does not. Rabbits come to respond discriminatively to the two cues, only making stepping responses in a running wheel to avoid footshock in response to the CS+. Consistent with work in rats and cats in other avoidance conditioning tasks, lesions or pharmacological inactivation of the amygdala impair the acquisition of discriminative avoidance conditioning in rabbits (Poremba and Gabriel, 1997a, 1999, 2001). Damage to the lateral and central nuclei of the amygdala appears to be particularly predictive of avoidance deficits in rats with amygdala lesions (Poremba and Gabriel, 1997a). Indeed, discrete lesions of the central nucleus severely impair acquisition of discriminative avoidance learning without affecting instrumental responding for an appetitive reward (Smith et al., 2001). And as noted in earlier reports, the amygdala appears to be particularly important during the acquisition of instrumental avoidance behavior, insofar as reversible inactivation of amygdala neurons with muscimol, a $GABA_A$ receptor agonist, in well-trained rabbits does not impair avoidance responding (Poremba and Gabriel, 1999).

Electrophysiological recordings in a number of interconnected structures reveal that there is a systematic engagement of neuronal populations in encoding the conditioning contingencies and mediating the performance of well-learned behavior (Gabriel, 1993). Earliest to engage during avoidance conditioning are the basolateral amygdala, mediodorsal nucleus of the thalamus, and anterior cingulate cortex; later avoidance performance in well-trained animals is correlated with discriminative neuronal activity in the anterior thalamic nuclei and the posterior cingulate cortex (Gabriel et al., 1991; Maren et al., 1991). Both thalamic structures are critically involved in acquisition and maintenance of avoidance behavior (Gabriel et al., 1989; Steinmetz et al., 1991). Auditory information that drives neuronal firing to the CSs during avoidance training reaches the amygdala, thalamus, and cingulate cortex by way of the auditory thalamus (Poremba and Gabriel, 1997b). Amygdala lesions or inactivation, in addition to impairing acquisition of avoidance responses, impair electrophysiological correlates of avoidance conditioning that develop in the auditory thalamus, particularly the medial division of the medial geniculate nucleus, the anterior and mediodorsal thalamic nuclei, and the anterior and posterior cingulate cortices (Poremba and Gabriel, 1997a; Poremba and Gabriel, 1999; Poremba and Gabriel, 2001; Smith et al., 2001). Electrophysiological correlates of avoidance conditioning have also been observed in the central and basolateral nuclei of rats during both active (Rorick-Kehn and Steinmetz, 2005) and passive (Chang et al., 2005) avoidance.

As in other active avoidance conditioning tasks, damage to the hippocampal formation improves the acquisition of instrumental avoidance conditioning in rabbits (Gabriel and Sparenborg, 1986; Gabriel et al., 1987). Interestingly, hippocampal areas, particularly the subiculum, appear to have an inhibitory influence on anterior thalamic neuronal activity; accordingly, subicular lesions facilitate both CS-elicited spike firing in the thalamus and behavioral performance (Gabriel and Sparenborg, 1986; Gabriel et al., 1987). As suggested earlier, the hippocampus appears to be particularly germane to encoding contextual representations during conditioning. Indeed, hippocampal neurons exhibit highly context-dependent spike firing when auditory CSs acquire multiple meanings (Freeman et al., 1996). Lesions placed in the entorhinal cortex, which is the primary cortical interface of the hippocampus, impairs context-dependent behavioral performance and CS-elicited neuronal activity (Freeman et al., 1997).

Collectively, the results from instrumental avoidance conditioning tasks suggest that the central and basolateral nucleus of the amygdala are involved in acquiring active avoidance responses but are not required for their retention. It has been argued that two processes contribute to the acquisition of avoidance responses (Mowrer, 1947). First, animals acquire Pavlovian fear of the CS and subsequently learn to terminate the CS by making an instrumental avoidance response (see Bolles, 1972, for an alternative interpretation). According to this view, avoidance responses are reinforced by fear reduction when the CS is terminated. Once learned, performance

is maintained by the instrumental contingency, and conditional fear to the CS plays a relatively minor role in supporting performance (Mineka and Gino, 1980). Hence, one explanation for the differential role of the amygdaloid nuclei in the acquisition and retention of instrumental avoidance is that lesions made before training disrupt acquisition because they interfere with Pavlovian fear conditioning, whereas lesions made after training have little effect because Pavlovian fear is not required to sustain performance at that point in training (Maren, 1998).

3.24.4.2 Passive Avoidance Conditioning

Unlike active avoidance tasks, the instrumental contingency in a passive avoidance task is arranged to punish active behavioral response and encourage shock avoidance through inhibition of responding. Similar to active avoidance learning, several studies have indicated a critical role for the amygdala in the acquisition and retention of this form of learning. Large, bilateral amygdala lesions impair the acquisition of a variety of passive avoidance responses in rats (McNew and Thompson, 1966; McIntyre and Stein, 1973; Bresnahan et al., 1976; Nagel and Kemble, 1976; Russo et al., 1976; Liang et al., 1982; Jellestad and Bakke, 1985), mice (Slotnick, 1973), and cats (Horvath, 1963; Ursin, 1965). Smaller electrolytic lesions centered on the basolateral nucleus (Coover et al., 1973; Grossman et al., 1975; Werka et al., 1978) or central nucleus (Grossman et al., 1975; Werka et al., 1978) of the amygdala reproduce these passive avoidance deficits. In contrast, only excitotoxic lesions of the central or lateral nuclei, but not the basolateral nucleus, have been reported to impair step-through inhibitory avoidance (Tomaz et al., 1992); this is an interesting contrast to other studies that find that basolateral, but not central, lesions influence active avoidance responses (Killcross et al., 1997; Amorapanth et al., 2000). In addition to acquisition deficits, impairments in the retention of a passive avoidance response after amygdala lesions have also been reported (Nagel and Kemble, 1976; Liang et al., 1982; Parent et al., 1994, 1995), and reversible inactivation of the amygdala with lidocaine, a voltage-gated sodium channel blocker (Parent and McGaugh, 1994), or muscimol (Holahan and White, 2004a,b) impairs the retention of inhibitory avoidance.

Given the importance of the amygdala, particularly the lateral and central nuclei, in passive avoidance, it is reasonable to consider the possibility that the memory for some aspect of passive avoidance training resides within the amygdala. Passive avoidance conditioning depends on both Pavlovian associations between context and shock and instrumental associations between approach behavior and its aversive outcome (Randall and Riccio, 1969). Unlike active avoidance conditioning, it is likely that Pavlovian associations play a key role in maintaining passive avoidance behavior (most passive avoidance tasks involve only a single training trial) (Randall and Riccio, 1969). As discussed earlier, considerable evidence shows that the central and lateral nuclei of the amygdala are involved in encoding and storing Pavlovian fear memories (e.g., Maren and Quirk, 2004). Therefore, disruption of these structures would be expected to impair the acquisition and expression of passive avoidance behavior. Spared passive avoidance performance that is observed after damage to the basolateral nucleus may be maintained by conditioned fear, which can survive these lesions under some conditions (Nader et al., 2001; Anglada-Figueroa and Quirk, 2005). Nonetheless, basolateral nucleus lesions do impair the acquisition of fear conditioning in other studies (Goosens and Maren, 2001), and these lesions disrupt the expression of conditioned fear when made after conditioning (Anglada-Figueroa and Quirk, 2005). Thus, the contribution of individual amygdaloid nuclei to both the acquisition and retention of passive avoidance warrants further attention, particularly in relation to the effects of these manipulations on Pavlovian fear conditioning.

In addition to the amygdala, the hippocampus plays an important role in the acquisition and retention of passive avoidance conditioning. Hippocampal lesions or electrical stimulation disrupt the acquisition and consolidation of passive avoidance memory (Blanchard and Fial, 1968; Winocur and Bindra, 1976; Munoz and Grossman, 1981; Kesner and Hardy, 1983). Moreover, reversible inactivation of the hippocampus with tetrototoxin, a voltage-gated sodium channel blocker, impairs the acquisition, consolidation, and retrieval of passive avoidance memories (Lorenzini et al., 1996; Ambrogi Lorenzini et al., 1997). The important role of the hippocampus in passive avoidance conditioning is likely due to the prominent role contextual conditioning plays in standard passive avoidance paradigms. That is, step-through and step-down versions of the task, which

are the most commonly used passive avoidance paradigms, essentially consist of an animal-initiated context-shock conditioning trial. The Pavlovian association between context and shock is an important component to passive avoidance performance, insofar as forced extinction of the shock context after avoidance conditioning degrades conditional responding (Randall and Riccio, 1969). Of course, the instrumental approach-shock contingency is also important in shaping passive avoidance, and delay of shock after animals enter the dangerous context (which degrades the response-outcome contingency) reduces passive avoidance performance (Randall and Riccio, 1969). Indeed, the hippocampal contribution to encoding contexts (which is discussed later), as opposed to processing the aversive shock event, appears to play a critical role in the influences of hippocampal manipulations on passive avoidance memory (Malin and McGaugh, 2006). Recent work shows that the representation of contexts by the hippocampus depends, in part, on activity in the amygdala (Roozendaal and McGaugh, 1997; Huff and Rudy, 2004; Huff et al., 2006; Malin and McGaugh, 2006).

Because passive avoidance conditioning can be acquired in a single trial, it has been become one of the most extensively used tasks to explore the pharmacology of emotional learning and memory. Indeed, a variety of pharmacological manipulations within the amygdala can bidirectionally influence (either enhancing or impairing) the retention of passive avoidance memory (Gallagher et al., 1977; McGaugh, 2000, 2004). In this regard, there is substantial evidence that the amygdala is also involved in consolidating memories for aversive experiences outside the amygdaloid circuitry (Cahill and McGaugh, 1998), and the majority of work indicates that the basolateral nucleus of the amygdala in particular is instrumental in this function (Roozendaal and McGaugh, 1997; Roozendaal et al., 1998). It has been argued that the amygdala may not be involved in the local storage of memories for aversive events but, rather, is preferentially concerned with modulating aversive memory in other brain structures (Cahill et al., 2001). However, the roles for the amygdala in Pavlovian association formation and memory consolidation are dissociable. For example, posttraining inactivation of the amygdala with muscimol produces deficits in the retention of inhibitory avoidance conditioning, but not Pavlovian fear conditioning (Wilensky et al., 2000). Therefore, the nature of the amygdala's involvement in aversive learning, whether it is local memory storage or remote memory consolidation, depends importantly on the associative structure of the conditioning situation and the behavioral measures used to index memory (Kapp et al., 1978; Maren, 2003b).

3.24.4.3 Defensive Burying and Shock-Probe Avoidance

Similar to traditional passive avoidance tasks, large lesions of the hippocampus or amygdala lesions impair avoidance of an electrified probe once the probe has been contacted (Treit and Menard, 1997). Neither lesion, however, affects how much time animals spend burying the probe after they have received shock. Small lesions of the amygdala centered on the central nucleus do not affect probe avoidance but do affect immobility that occurs after contact with the electrified probe (Roozendaal et al., 1991). Interestingly, lesions or inactivation of the amygdala, despite reducing probe avoidance during the conditioning session, do not affect subsequent avoidance of the probe during retention testing (Lehmann et al., 2000, 2003). Although this has been interpreted to indicate that the amygdala is not necessary to form probe-shock associations, another possibility is that instrumental contingencies related to the training procedure maintain avoidance in the absence of associative fear of the probe (Maren, 2003b).

3.24.5 Neural Mechanisms of Pavlovian Fear Conditioning

In addition to instrumental avoidance conditioning tasks, Pavlovian fear conditioning has been used extensively to examine the brain substrates of emotional learning and memory (LeDoux, 2000; Maren, 2001; Fanselow and Poulos, 2005; Davis, 2006). Studies of the neural mechanisms of Pavlovian fear conditioning have focused on the contribution and interaction of several interconnected structures, including the amygdala, hippocampus, and prefrontal cortex (McIntosh and Gonzalez-Lima, 1994, 1998). Sensory information reaches each of these structures via both thalamic and cortical routes. To understand the neural basis of fear conditioning, we will consider the contribution of each of these brain areas to various fear conditioning paradigms. This review will focus on the anatomy and physiology of these forms of learning, insofar as the synaptic and cellular basis

of fear conditioning is considered in detail elsewhere (*See* Chapter 4.11). The majority of the work described was conducted in rats, and work in other species will be identified where appropriate.

3.24.5.1 Conditioned Freezing

It has long been appreciated that aversive stimuli evoke freezing behavior in several animal species, particularly rodents. Robert and Caroline Blanchard pioneered the use of freezing behavior as an index of conditioned fear (Blanchard and Blanchard, 1969). Not surprisingly, they were also the first to systematically examine the neural systems involved in the acquisition and retention of conditioned freezing. In early work, they demonstrated a role for the amygdala in the acquisition of conditioned freezing (Blanchard and Blanchard, 1972a). In this case, they used a contextual fear conditioning procedure in which footshocks were delivered in a specific environmental context, and freezing behavior in that context served as the measure of conditional fear. They found that large, bilateral amygdala lesions completely eliminated shock-elicited freezing behavior, as well as unconditional freezing to a cat (Blanchard and Blanchard, 1972a). Interestingly, they also found in related studies that damage to the hippocampal formation produced a similar loss in contextual fear conditioning (Blanchard et al., 1970, 1977; Blanchard and Blanchard, 1972b), but such lesions also elevated motor activity in a number of test situations. Nonetheless, as will be discussed shortly, the hippocampus proves to have a special role in learning about contextual stimuli, and this role comes to influence the acquisition of contextual fear. The use of freezing behavior as an index of learned fear has become the most widely used paradigm for studying the neural mechanisms of emotional learning and memory. This is due in large part to the ease of measuring freezing behavior and the simplicity of the training regimen (appetitive training to establish an operant baseline is not required). For this reason, the most published literature is on this paradigm, and this will be reflected in the extensive coverage of conditioned freezing in this section.

Building on the Blanchards' original work, several laboratories in nearly countless studies have confirmed the critical role for the amygdala in both the acquisition and expression of conditioned freezing behavior using selective lesions of individual amygdaloid nuclei. For example, selective lesions of the basolateral complex, particularly the lateral nucleus, produce severe deficits in both the acquisition and expression of conditioned freezing to discrete CSs (whether auditory, visual, or olfactory) and contexts (LeDoux et al., 1990; Ambrogi Lorenzini et al., 1991; Maren et al., 1996a; Cousens and Otto, 1998; Maren, 1998, 1999b; Amorapanth et al., 2000; Antoniadis and McDonald, 2000; Cahill et al., 2000; Goosens and Maren, 2001; Nader et al., 2001; Blair et al., 2005). It is noteworthy that lesions of the basolateral amygdala made long after conditioning (from a month to over a year) produce a complete retrograde amnesia for conditioned fear manifested as a loss of conditioned freezing (Maren et al., 1996a; Gale et al., 2004). Reversible pharmacological inactivation of the basolateral amygdala with agents such as muscimol (a $GABA_A$ receptor agonist) or lidocaine (a voltage-gated sodium channel blocker) also eliminates the acquisition and expression of conditioned freezing (Helmstetter, 1992a; Helmstetter and Bellgowan, 1994; Muller et al., 1997; Wilensky et al., 1999; Wilensky et al., 2000; Maren et al., 2001; Goosens and Maren, 2003; Blair et al., 2005). Furthermore, the amygdala plays a prominent role in the ontogeny of fear conditioning in rats (Moriceau and Sullivan, 2005, 2006; Moriceau et al., 2006).

An important observation is that deficits in conditioned freezing after basolateral complex lesions can be overcome with extensive training so long as overtraining occurs in a brain-damaged animal; basolateral lesions made after extensive overtraining still yield complete deficits in conditioned freezing (Maren, 1998, 1999b). This argues that although the basolateral complex of the amygdala, including the lateral nucleus of the amygdala, is critical for the acquisition of conditioned freezing, another brain region can compensate for loss of the basolateral complex under some conditions. One possibility is that the central nucleus of the amygdala, which receives a major projection from the basolateral complex (Krettek and Price, 1978; Paré et al., 1995; Savander et al., 1995), has a critical role in the acquisition and expression of conditioned freezing (Paré et al., 2004). This possibility has been supported in preliminary work (Zimmerman et al., 2005).

The possibility that the central nucleus has a critical role in fear conditioning is not novel. Indeed, it has long been appreciated that the central nucleus of the amygdala has a critical role in fear behavior. For example, electrical stimulation of the

central nucleus produces behavioral responses similar to those evoked by stimuli paired with shock (Applegate et al., 1983; Iwata et al., 1987; Kapp et al., 1992). Lesions of the central nucleus of the amygdala, like those of the basolateral complex, prevent the acquisition and expression of conditioned freezing in rats (Amorapanth et al., 2000; Goosens and Maren, 2001; Nader et al., 2001), although there is some evidence of spared fear conditioning with pharmacological manipulations of the central nucleus during conditioning (Goosens et al., 2003; Goosens and Maren, 2003). As mentioned earlier, lesions placed in central amygdala efferents produce selective deficits in certain fear responses such as conditioned freezing in the case of the periaqueductal gray (LeDoux et al., 1988; Kim et al., 1993a; De Oca et al., 1998; Amorapanth et al., 1999) or arterial pressure in the case of the lateral hypothalamus (Iwata et al., 1986b; LeDoux et al., 1988). Because lesions in the central nucleus of the amygdala impair all these fear responses (LeDoux et al., 1988), the evidence suggests that the central nucleus is the final common pathway for the generation of learned fear responses.

There is extensive sensory convergence in both the basolateral complex and central nucleus in the amygdala (Krettek and Price, 1974, 1978; Pitkanen et al., 1997; McDonald, 1998; Swanson and Petrovich, 1998; Sah et al., 2003). In the past, the possibility that associations between sensory inputs occurred exclusively in the basolateral complex, particularly the lateral nucleus, rather than the central nucleus had been emphasized (LeDoux, 1993a,b, 1994, 1995, 2000; Maren, 1996, 1999a,b, 2001, 2003a; Fanselow and LeDoux, 1999; Fendt and Fanselow, 1999). However, it has recently been appreciated, given both anatomical considerations and spared learning in rats with basolateral complex lesions, that the central nucleus has a more important role in fear conditioning than previously thought (Paré et al., 2004). A recent series of experiments indicates that many of the molecular processes believed to operate in the service of long-term memory storage are required in the central nucleus to acquire conditional fear (Wilensky et al., 2006). The important role for the central nucleus in the acquisition of conditioned affective states has also been emphasized in appetitive conditioning paradigms and in conditioned suppression (Cardinal et al., 2002; Balleine and Killcross, 2006). As a result, there is mounting evidence that the central nucleus and basolateral complex might perform different functions in aversive conditioning, at least under some conditions.

Sensory inputs to the amygdala arise from a number of areas, including the medial thalamus (LeDoux et al., 1984; Doron and LeDoux, 2000a,b), hippocampal formation (Ottersen, 1982; Aggleton, 1986; Canteras and Swanson, 1992; Maren and Fanselow, 1995), rhinal cortices (Aggleton, 1986; McDonald and Mascagni, 1997; Shi and Cassell, 1999), and spinal cord (Ma and Peschanski, 1988; Cliffer et al., 1991; Burstein and Potrebic, 1993; Newman et al., 1996). Consistent with this anatomy, single neurons in the basolateral complex and central nucleus of the amygdala respond to auditory, visual, and somatic (shock) stimuli (Applegate et al., 1982; Pascoe and Kapp, 1985a,b; Kapp et al., 1992; Romanski et al., 1993), which indicates that the amygdala is a locus of convergence for information about CSs and USs. Thus, the amygdala is anatomically situated to integrate information from a variety of sensory domains. Extensive pharmacological evidence indicates that synaptic plasticity in the amygdala contributes to both the acquisition and extinction of conditioned freezing (Maren et al., 1996b, 2003; Lee and Kim, 1998; Rosen et al., 1998; Bailey et al., 1999; Weisskopf et al., 1999; Goosens et al., 2000; Nader et al., 2000; Schafe et al., 2000, 2005; Fendt, 2001; Lee et al., 2001, 2006; Malkani and Rosen, 2001; Bauer et al., 2002; Lamprecht et al., 2002; Moita et al., 2002; Rodrigues et al., 2002, 2004; Goosens and Maren, 2003, 2004; Apergis-Schoute et al., 2005; Maren, 2005b; Rumpel et al., 2005; Merino and Maren, 2006; Wilensky et al., 2006).

As mentioned earlier, it is well documented that amygdala damage disrupts not only learned fear but also innate fear under some conditions. For example, rats with amygdala lesions do not exhibit freezing or analgesia in the presence of a cat (Blanchard and Blanchard, 1972a; Fox and Sorenson, 1994); they do show attenuated unconditional analgesia and heart rate responses to loud noises (Bellgowan and Helmstetter, 1996; Young and Leaton, 1996), and they exhibit reduced taste neophobia (Nachman and Ashe, 1974). Amygdala damage does not disrupt all unconditional fear responses, however. Amygdala lesions do not affect open arm avoidance in an elevated plus maze (Treit et al., 1993; Treit and Menard, 1997), unconditional analgesia (Watkins et al., 1993), or unconditioned freezing to a predator odor (Wallace and Rosen, 2001), or after ejaculation (Choi and Brown, 2003). Thus, although amygdala damage may reduce unlearned fear responses under some conditions, it does not appear that a general loss of fear accounts for the memory impairments

observed after lesions or inactivation of the amygdala, as has been suggested by some (Cahill et al., 2001, 1999).

Electrophysiological recordings of amygdaloid neuronal activity support a role for the amygdala in representing conditional fear memories (Maren and Quirk, 2004). Auditory fear conditioning induces short-latency plasticity in amygdala neurons (Quirk et al., 1995, 1997; Armony et al., 1998; Collins and Paré, 2000; Maren, 2000a; Pelletier et al., 2005). This plasticity takes the form of enhanced spike firing elicited by acoustic CSs. Fear conditioning also increases the amplitude of synaptic potentials in lateral amygdala neurons recorded either intracellularly (Rosenkranz and Grace, 2002) or extracellularly (McKernan and Shinnick-Gallagher, 1997; Rogan et al., 1997). The short latency of learning-related changes in spike firing is consistent with plasticity in thalamo-amygdala projections, specifically, projections from the medial division of the medial geniculate nucleus. Amygdala neurons exhibit plasticity earlier in training than auditory cortical neurons, further suggesting that direct thalamo-amygdala projections, rather than cortico-amygdala projections, mediate neuronal plasticity in the lateral amygdala (Quirk et al., 1997). Although spike-firing changes with conditioning are only correlative, it is difficult to determine if they represent fear memories or are consequent to changes in fear and arousal engendered by auditory CSs. A recent study, however, indicates that learning-related changes in the amygdala are independent of conditioned freezing behavior, suggesting that they reflect the associative properties of CSs paired with shock (Goosens et al., 2003). Electrophysiological plasticity also develops in both the auditory thalamus (Weinberger et al., 1972; Supple and Kapp, 1989; Edeline and Weinberger, 1991a,b; McEchron et al., 1996), and the auditory cortex (Edeline et al., 1993; Edeline and Weinberger, 1993; Weinberger, 1995) after auditory fear conditioning. The latency of CS-elicited plasticity in the lateral amygdala is not consistent with transmission of plasticity from the cortex (Quirk et al., 1997; Maren, 2000a); however, transmission of plasticity from the auditory thalamus cannot be ruled out (Weinberger and Bakin, 1998; Cahill et al., 1999). Although thalamic plasticity might modulate the memory formation in the amygdala during fear conditioning (Apergis-Schoute et al., 2005; Parsons et al., 2006), evidence suggests that cellular activity in the amygdala is necessary for both fear conditioning and auditory thalamus plasticity (Maren et al., 2001).

As mentioned earlier, the hippocampus is also involved in conditioned freezing under some conditions. In particular, there is extensive evidence that the hippocampus is involved with encoding the contexts in which aversive stimuli occur (Maren et al., 1998; Anagnostaras et al., 2001; O'Reilly and Rudy, 2001; Sanders et al., 2003). Several investigators have found that lesions of the hippocampus produce rather selective deficits for the acquisition of fear to contextual stimuli, as opposed to discrete CS (Sutherland and McDonald, 1990; Selden et al., 1991; Phillips and LeDoux, 1992, 1994, 1995; Kim et al., 1993a). However, others have not found deficits in the acquisition of contextual fear conditioning after hippocampal damage (Maren et al., 1997; Cho et al., 1999). This has led to the suggestion that contextual fear can be mediated by discrete stimuli within the conditioning chamber (such as the smell of the chamber) (Maren et al., 1997; Rudy and O'Reilly, 1999; Rudy et al., 2002). Interestingly, the amount of training appears to be critical for obtaining deficits in the acquisition of contextual fear insofar as deficits are obtained with limited, but not more extensive, training (Wiltgen et al., 2006). Hippocampal lesions also impair the consolidation of contextual fear memory when made within a month of fear conditioning (Kim and Fanselow, 1992; Maren et al., 1997; Anagnostaras et al., 1999). Although dorsal hippocampal lesions tend to spare auditory fear conditioning, neurotoxic lesions that include the subiculum or ventral hippocampus produce deficits in auditory fear conditioning in many cases (Maren, 1999c; Maren et al., 1997; Richmond et al., 1999; Maren and Holt, 2004). Nonetheless, considerable evidence indicates that contextual and auditory fear conditioning is mediated, at least in part, by dissociable neural systems (Rudy et al., 1999; Venton et al., 2006).

In addition to its role in encoding contextual representations, the hippocampus is involved in contextual memory retrieval (Holt and Maren, 1999; Maren and Holt, 2000; Maren, 2005a). Although the hippocampus is not necessary to retrieve context memories *per se* (e.g., Kim and Fanselow, 1992), it is necessary for using contextual information to retrieve the meaning of an ambiguous CS. For instance, in two related paradigms, latent inhibition and extinction, animals are exposed to a phase of CS-alone presentations either before (in the case of latent inhibition) or after (in the case of extinction) fear conditioning. With these procedures, the CS acquires two different meanings: it predicts a fearful US in the

conditioning phase but does not predict the US during the latent inhibition or extinction phase of training. Importantly, considerable work indicates that both latent inhibition and extinction are context dependent, and contexts are used to inform the animal what a CS means in a particular context (Bouton, 1993). Lesion or reversible inactivation of the dorsal or ventral hippocampus disrupt the context dependence of latent inhibition and extinction and also disrupt the context dependence of lateral amygdala spike firing after extinction (Holt and Maren, 1999; Corcoran and Maren, 2001, 2004; Corcoran et al., 2005; Ji and Maren, 2005; Bouton et al., 2006; Hobin et al., 2006; Maren and Chang, 2006). Based on this work, it appears that the amygdala is involved in associating CSs and USs, and the hippocampus encodes contextual representations and uses those representations to tag CS–US associations to enable their retrieval under conditions in which the CS memory has become ambiguous.

In addition to the hippocampus, considerable attention has been directed at the role of the prefrontal cortex in the extinction of fear conditioning (Quirk et al., 2006). It has been reported that lesions or pharmacological manipulations in the prefrontal cortex impede the recall of extinction without effecting extinction *per se* (Morgan et al., 1993; Quirk et al., 2000; Hugues et al., 2006; Sierra-Mercado et al., 2006). Moreover, prefrontal neurons increase their activity to CSs that have undergone extinction (Milad and Quirk, 2002), an effect that may be regulated by the amygdala (Garcia et al., 1999). Despite the explosion of interest in prefrontal cortical contributions to fear extinction, not all investigators report that prefrontal cortical lesions influence the extinction of conditional fear (Gewirtz et al., 1998; Garcia et al., 2006). Additional work is required to fully understand the contribution of the hippocampus, prefrontal cortex, and amygdala to fear extinction.

3.24.5.2 Conditioned Suppression of Appetitive Responding

As noted earlier, the amygdala has a critical role in the acquisition and expression of Pavlovian fear conditioning as indexed by conditioned freezing. Insofar as it has been argued that conditioned fear contributes to conditioned suppression of appetitive responding (Estes and Skinner, 1941), one would expect a similarly important role for the amygdala in this form of responding. Consistent with this possibility, Kellicutt and Schwartzbaum demonstrated a critical role for the amygdala in the acquisition of a conditioned emotional response, which they assessed by measuring bar-press suppression to an auditory CS previously paired with shock (Kellicutt and Schwartzbaum, 1963). This study used large lesions of the amygdala that were not specific to particular nuclei, but nonetheless it was the first to establish that fear learning requires the amygdala. More recent studies have also found that large lesions of the amygdala or electrical stimulation of the amygdala disrupts conditioned bar-press suppression (Lidsky et al., 1970; Spevack et al., 1975; Kopchia et al., 1992; Mintz and Wang-Ninio, 2001). Importantly, fiber-sparing excitotoxic lesions of amygdaloid nuclei also disrupt the acquisition of conditioned suppression to auditory CSs, such as lick suppression (Selden et al., 1991).

Subtotal lesions of the amygdala, focused on either the basolateral complex or the central nucleus of the amygdala, have also been reported to produce deficits in the acquisition of bar-press suppression (Killcross et al., 1997). In an unconventional paradigm, rats initiated delivery of two different CSs on each of two bars (one bar yielded a CS+ that signaled footshock, and the other bar yielded a CS− that did not signal shock). The paradigm was designed to yield measures of both instrumental avoidance (preferential pressing on CS− bar) and conditioned suppression (reduction in appetitive responding on trials in which the animal delivered a CS+). In this paradigm, both types of lesion impaired conditioned suppression early in training, but ultimately animals with basolateral complex lesions acquired the response. In contrast, animals with basolateral lesions were unable to acquire instrumental avoidance, whereas rats with central nucleus lesions were unimpaired on this measure of aversive conditioning. Based on these results, it has been argued that there is a functional dissociation between the central nucleus and basolateral complex of the amygdala, with the central nucleus mediating Pavlovian conditioned aversive states required for appetitive suppression and the basolateral complex mediating specific sensory representations of biologically relevant outcomes required for instrumental choice (Blundell et al., 2001; Cardinal et al., 2002; Balleine et al., 2003; Balleine and Killcross, 2006).

However, as we have seen, there are considerable data supporting a role for both the central and basolateral nuclei in the acquisition and expression of

Pavlovian conditioned freezing. These data argue that a serial circuit in the amygdala underlies fear memory. A critical factor in revealing dissociations between the central nucleus and the basolateral complex in aversive conditioning may be the extent of training. For instance, deficits in conditioned suppression are equally robust early in training in rats with central or basolateral complex lesions but recover with additional training in some cases (Killcross et al., 1997; Lee et al., 2005). Moreover, as mentioned earlier, deficits in conditioned freezing in rats with basolateral complex lesions, but not central nucleus lesions, recover with additional training (Zimmerman et al., 2005). Hence, these amygdaloid nuclei may operate cooperatively and in a serial manner early in fear conditioning, but functionally dissociate after more extensive training. It remains to be determined how central or basolateral complex lesions affect the expression of conditioned suppression when made after extensive training.

The potent influence of amygdala lesions on the acquisition of conditioned suppression is not a general effect of damage to limbic system structures. For example, electrolytic or excitotoxic lesions of the hippocampus do not impair the acquisition of conditioned bar-press suppression (Wilson et al., 1995; Frohardt et al., 2000; Talk et al., 2002) or lick suppression (Selden et al., 1991) to auditory CSs. Lesions of the septo-hippocampal cholinergic system do not themselves affect the acquisition of conditioned suppression but may alter the competition between discrete CSs and contextual cues in gaining control of behavior (McAlonan et al., 1995; Calandreau et al., 2006). Interestingly, damage to the dorsal noradrenergic bundle, which is one of the major forebrain sources of the catecholaminergic neurotransmitter, norepinephrine, impairs the acquisition of conditioned suppression (Cole and Robbins, 1987). An important issue is whether deficits in bar-press suppression with any neural intervention are secondary to disruptions in conditioned freezing behavior, for example. That is, rats may suppress appetitive responding in the presence of a fear CS because that CS elicits freezing behavior, which competes with licking for water or pressing for food. However, there is evidence that bar-press suppression can occur in rats that otherwise do not show conditioned freezing behavior. Rats with lesions of the midbrain periaqueductal gray, which completely eliminate the expression of conditioned freezing responses (De Oca et al., 1998), while sparing other indices of conditional fear, such as increases in arterial pressure (LeDoux et al., 1988), do not effect bar-press suppression (Amorapanth et al., 1999). This suggests that fear-induced suppression of appetitive responding is not dependent on conditioned freezing in all circumstances.

Relatively little work has been done on the neurophysiological correlates of conditioned suppression. However, a recent study in rats has revealed that auditory CSs paired with footshock produced changes in CS-elicited firing in the dorsal portion of the lateral amygdala (Repa et al., 2001). Interestingly, in some lateral nucleus neurons, these changes occurred before the appearance of conditioned suppression, suggesting that neuronal changes in the amygdala precede appearance of the behavioral CR. In ventral regions of the lateral nucleus, another population of cells was slower to exhibit learning-related changes but showed persistent learning-related activity, even after the behavioral fear response had been extinguished. The development of learning-related changes in amygdala spike firing during the acquisition of conditioned lick suppression has also been shown in monkeys (Rolls, 2000; Paton et al., 2006).

3.24.5.3 Conditioned Hypoalgesia

In addition to conditioned freezing, considerable work has examined the consequences of emotional learning and memory for pain sensitivity. As first described by Bolles and Fanselow (Bolles and Fanselow, 1982), fear has an important role in modulating endogenous opiate levels, thereby influencing pain sensitivity. Hypoalgesia after fear conditioning has been demonstrated in numerous studies (Fanselow and Bolles, 1979), and several investigators have explored the neural mechanisms underlying this effect. As with conditioned freezing, amygdala lesions or pharmacological manipulations prevent the acquisition and expression of conditioned hypoalgesia to contexts that have been paired with footshock (Helmstetter, 1992b; Helmstetter, 1993; Helmstetter and Bellgowan, 1993; Watkins et al., 1993; Good and Westbrook, 1995; Harris and Westbrook, 1995). Also like freezing, the periaqueductal gray is the primary descending target of the amygdala that is required for the expression of conditioned hypoalgesia (Helmstetter and Landeira Fernandez, 1990; Helmstetter and Tershner, 1994; Harris and Westbrook, 1995; Bellgowan and

Helmstetter, 1998; Helmstetter et al., 1998; Tershner and Helmstetter, 2000).

3.24.5.4 Fear-Potentiated Acoustic Startle

Another important model system for analyzing the neural mechanisms of Pavlovian fear conditioning is the fear-potentiated acoustic startle paradigm (Davis, 1992, 2006; Davis and Whalen, 2001). Similar to conditioned freezing, lesions placed in the amygdala, including excitotoxic lesions in the basolateral complex or central nucleus, produce severe impairments in the acquisition and expression of fear-potentiated startle to a visual CS in rats (Hitchcock and Davis, 1986; Sananes and Davis, 1992; Kim and Davis, 1993; Campeau and Davis, 1995b; Lee et al., 1996). Similarly, pharmacological inactivation of either the central nucleus or basolateral complex of the amygdala prevents the acquisition and expression of fear-potentiated startle (Kim et al., 1993b; Walker and Davis, 1997a; Walker et al., 2005). Both thalamic and cortical afferents of the amygdala transmit sensory information to the amygdala for the acquisition and expression of potentiated startle (Rosen et al., 1992; Campeau and Davis, 1995a; Shi and Davis, 1999, 2001). Extensive pharmacological evidence indicates that synaptic plasticity in the amygdala contributes to both the acquisition and extinction of fear-potentiated startle (Miserendino et al., 1990; Falls et al., 1992; Gewirtz and Davis, 1997; Walker and Davis, 2000; Lu et al., 2001; Josselyn et al., 2001; Lin et al., 2001, 2003a,b; Walker et al., 2002; Chhatwal et al., 2006).

In addition to learning-induced potentiation of acoustic startle, ambient illumination (bright light) can lead to nonassociative increases in acoustic startle (Davis, 1998). Unconditioned increases in potentiated startle also involve the amygdala, but interestingly there is a double dissociation in the circuitry for conditioned and unconditioned potentiated startle. Inactivation of the central nucleus of the amygdala affects conditioned increases in startle without influencing unconditioned increases in startle, whereas inactivation of the bed nucleus of the stria terminalis (which receives input from the amygdala) produces the converse pattern of results (Walker and Davis, 1997a). Inactivation of the basolateral complex of the amygdala influences both conditioned and unconditioned potentiated startle.

Although fear-potentiated startle is a widely used measure of fear conditioning, it displays some properties that differentiate it from other indices of conditioned fear. Unlike many of the other measures of conditioned fear, the magnitude of fear-potentiated startle decreases with increases in US magnitude. This decrease in the amplitude of the acoustic startle response is not predicted by formal models of learning and appears to be due to competition with freezing behavior. That is, lesions of the periaqueductal gray that eliminate freezing behavior permit the expression of potentiated acoustic startle by CSs trained with high US intensities (Walker et al., 1997; Walker and Davis, 1997b). Another factor that differentiates the acoustic startle response from other measures of fear is the timing of the conditioned response relative to the CS. Whereas freezing or hypoalgesic responses are tonic and expressed for minutes after the delivery of a brief CS, acoustic startle is only potentiated within a narrow time window that envelopes the expected time of US delivery (Davis et al., 1989; Burman and Gewirtz, 2004). These factors prove valuable for the analysis of temporal relationships that modulate fear expression but also suggest that the neural network involved in the expression of fear-potentiated startle is quite different from that involved in the expression of other fear responses.

3.24.5.5 Cardiovascular Conditioned Responses

In addition to somatic responses, learned fear is associated with the expression of many autonomic and hormonal responses. The most extensively studied autonomic correlates of fear conditioning are changes in heart rate and blood pressure to fearful CSs. Kapp was one of the first to systematically examine the neural basis of heart rate CRs in rabbits during Pavlovian fear conditioning. He found that the central nucleus was critical for the acquisition and expression of heart rate CRs (bradycardia in this case), but not unconditioned responses to either the auditory CS or periorbital shock US (Kapp et al., 1979). Considerable electrophysiological work has revealed that single neurons in the central nucleus exhibit plasticity during the acquisition of heart rate conditioning (Applegate et al., 1982; Pascoe and Kapp, 1985a,b). Subsequent work has shown that cell-specific lesion of the central nucleus, and the auditory afferent areas in the thalamus, also disrupt the acquisition and expression of heart rate conditioning in rabbits (Gentile et al., 1986; Jarrell et al., 1986a,b; McCabe et al., 1992, 1993). Foreshadowing recent work implicating the prefrontal cortex in fear

CRs, there is considerable evidence suggesting a role for prefrontal and cingulate cortices in the acquisition of conditioned bradycardia in rabbits (Buchanan and Powell, 1982; Powell, 1992; Powell et al., 1994).

Another brain structure that has been implicated in cardiovascular conditioning in rabbits is the cerebellar vermis, including the medial cerebellar cortex (Supple and Leaton, 1990a,b; Supple and Kapp, 1994). This finding is somewhat surprising because although the cerebellum has an established role in Pavlovian conditioning of discrete motor responses (Christian and Thompson, 2003), it has typically not been implicated in emotional CRs (Lavond et al., 1984; Lee and Kim, 2004). Most of these studies, however, have focused on the lateral cerebellar cortex and its projections to the interpositus nucleus. Moreover, previous studies in rats had indicated a role for the cerebellar vermis in unconditioned fear reactions but found little evidence of the vermis in conditioned fear (Supple et al., 1987, 1988). However, recent work suggests the vermis may have a role in conditioned freezing in rats (Sacchetti et al., 2002, 2005). This raises the possibility that the vermis has a role not only in the cardiovascular components of learned fear responses but also in other somatic fear CRs.

An important role for the auditory thalamus and amygdala has also been observed for heart rate and arterial pressure CRs in rats (LeDoux et al., 1984, 1986; Iwata et al., 1986a; Sananes and Campbell, 1989). In this case, both the lateral and central nuclei of the amygdala are critical for hear rate conditioning (LeDoux et al., 1990; Romanski and LeDoux, 1992). The projections from the amygdala that are involved in the expression of heart rate CRs are distinct from those involved in the other fear CRs that have been discussed. The expression of cardiovascular CRs involves both the lateral and peri-fornical regions of the hypothalamus (Iwata et al., 1986b; LeDoux et al., 1988; Furlong and Carrive, 2007).

3.24.5.6 Social Defeat and Social Transmission of Fear

Laboratory studies of fear conditioning using artificial stimuli under rigid parametric control are highly useful for analyzing the neural substrates of emotional learning and memory. Fear conditioning, of course, is a form of learning with relevance to an animal's niche and is the product of interactions with members of other species (e.g., predators) and even members of the same species (e.g., aggressive conspecifics). For example, in Syrian hamsters social defeat by a resident, dominant conspecific has been shown to yield later submissive behavior in the defeated individual that has some similarities with conditioned fear (Potegal et al., 1993). Interestingly, pharmacological inactivation of the amygdala in the subordinate animal during the aggressive encounter impairs the development of fear-related submissive behavior (Jasnow and Huhman, 2001; Jasnow et al., 2004a,b). In addition, augmenting molecular pathways that foster amygdala plasticity facilitate the development of submissive behavior that follows social defeat (Jasnow et al., 2005). Although the neurobiological analysis of this form of social fear conditioning is relatively young, it is interesting that it too requires the amygdala.

Conditioned fear is not only the product of certain social interactions but is also the source itself for generating fear in conspecific animals that have not themselves experienced aversive stimuli. There are multiple routes by which fear in one individual might be communicated to another. In rodents, olfactory stimuli and ultrasonic vocalizations are potent in this regard (Blanchard and Blanchard, 1989). Lesions of the amygdala, but not hippocampus, prevent the acquisition of fear-conditioned ultrasonic vocalizations (Koo et al., 2004; Lee and Kim, 2004). Moreover, both conditioned and unconditioned vocalization after discharges are sensitive to central amygdala damage (Borszcz and Leaton, 2003). The fact that conditional fear-induced vocalizations depend on the amygdala is not surprising insofar as all the Pavlovian fear CRs we have discussed depend on the amygdala.

However, an interesting new discovery is that the amygdala of a naïve observer appears to be engaged by the fearful behavior of a conspecific that has undergone an aversive fear-conditioning procedure (Knapska et al., 2006a). In this case, molecular markers of cellular activity (c-fos expression) were upregulated in several amygdaloid nuclei of rats merely exposed to a cage-mate that had undergone fear conditioning, even though the observers themselves never experienced the aversive conditioning procedure. This is similar to the activation of the human amygdala that has been observed by verbal warnings of potential fear experiences without actual presentations of an aversive stimulus (Phelps et al., 2001). Interestingly, subsequent emotional learning and memory in the observer rats, which was assessed in a shock-motivated shuttle avoidance task, was facilitated. This suggests that a brief social interaction

with a cage-mate that undergoes an aversive learning experience promotes aversive learning in an otherwise naïve animal. Apparently, fear conditioning has an important role in promoting adaptive defensive behavior in both the individual experiencing an aversive event, as well as others that are in proximity to the affected individual. In both cases, amygdala activity appears essential.

3.24.6 Conclusions

Animal models have proved incredibly informative for understanding the neural basis of emotional learning and memory. In fact, animal work has provided the groundwork for understanding the neural systems underlying emotional memory in humans. Consistent with the results that have emerged from animal studies, several investigators have now revealed an important role for the human amygdala in fear conditioning (Davidson and Irwin, 1999). Patients with amygdala pathology do not exhibit Pavlovian fear conditioning to either visual or auditory cues paired with loud noise (Bechara et al., 1995; LaBar et al., 1995), and patients with amygdala damage fail to recognize fear in facial expressions (Adolphs et al., 1995, 1999; Young et al., 1995). Functional neuroimaging has extended these lesion studies by revealing amygdala activation to visual or vocal expressions of fear (Morris et al., 1996; Phillips et al., 1997; Whalen et al., 1998; Whalen et al., 2004) and during Pavlovian fear conditioning (Buchel et al., 1998; LaBar et al., 1998; Morris et al., 1998; Morris and Dolan, 2004). Thus, the neural mechanisms of fear conditioning appear to exhibit homology across several mammalian species.

Of course, it is also important to stress that the amygdala does not encode every aspect of an aversive learning experience. For example, humans with amygdala damage exhibit intact declarative memory for a fear-conditioning experience, despite failing to exhibit conditional fear responses to stimuli paired with loud noise (Bechara et al., 1995). Similarly, rats with amygdala lesions avoid a compartment in which they have received footshock, despite failing to exhibit conditional freezing to the contextual cues associated with shock (Vazdarjanova and McGaugh, 1998). These results indicate that multiple memory systems are engaged during relatively simple learning and memory tasks. Thus, the amygdala operates to encode certain aspects of an emotional event, whereas other brain structures including the hippocampus and prefrontal cortex encode other aspects of the event that together integrate a robust representation of the emotional experience.

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