

# THE NEUROSCIENCE OF MAMMALIAN ASSOCIATIVE LEARNING

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■ **Abstract** Mammalian associative learning is organized into separate anatomically defined functional systems. We illustrate the organization of two of these systems, Pavlovian fear conditioning and Pavlovian eyeblink conditioning, by describing studies using mutant mice, brain stimulation and recording, brain lesions and direct pharmacological manipulations of specific brain regions. The amygdala serves as the neuroanatomical hub of the former, whereas the cerebellum is the hub of the latter. Pathways that carry information about signals for biologically important events arrive at these hubs by circuitry that depends on stimulus modality and complexity. Within the amygdala and cerebellum, neural plasticity occurs because of convergence of these stimuli and the biologically important information they predict. This neural plasticity is the physical basis of associative memory formation, and although the intracellular mechanisms of plasticity within these structures share some similarities, they differ significantly. The last *Annual Review of Psychology* article to specifically tackle the question of mammalian associative learning (Lavond et al. 1993) persuasively argued that identifiable “essential” circuits encode memories formed during associative learning. The next dozen years saw breathtaking progress not only in detailing those essential circuits but also in identifying the essential processes occurring at the synapses (e.g., Bi & Poo 2001, Martinez & Derrick 1996) and within the neurons (e.g., Malinow & Malenka 2002, Murthy & De Camilli 2003) that make up those circuits. In this chapter, we describe the orientation that the neuroscience of learning has taken and review some of the progress made within that orientation.

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## CORE QUESTIONS

Three core questions dominate the neuroscience of associative learning. At the systems level we ask, what are the brain circuits that mediate between environmental stimuli and acquired behavior? Then, within those circuits, what synapses must undergo modification for learning to occur? The third question is decidedly more molecular: What intracellular events occur at those sites of critical plasticity to confer the necessary changes in the synaptic efficacy that underlies the formation of a new memory? The preponderance of research on these issues has used Pavlovian conditioning preparations, where dependent relationships between two stimuli result in altered reactions to those stimuli. The behavioral change of interest is to a stimulus that provokes new behavior because receiving a biologically significant stimulus is conditional upon its presence. The stimulus that provokes new behavior is the conditional stimulus (CS) because the reaction to it is conditional upon experiencing a relationship with the biologically significant stimulus. Because behavior is evoked by the biologically relevant stimulus independent of a conditional relationship with another stimulus, it is called an unconditional stimulus (US). A fundamental truth, recognized by neuroscientists of learning for some time, is that the US and the type of reaction it causes determine what neural circuits and what sites of plasticity mediate particular changes in behavior. One implication of this is that there is not a single mechanism for associative learning. Rather, there are many separate systems of associative learning, and although these systems may share some characteristics, they are just as likely to be different from one another. It also means that for analytic purposes it is critical to focus on specific model systems to understand the neural basis of learning.

We have chosen two model systems, Pavlovian conditioning of the eyeblink response and Pavlovian conditional fear, as the model systems for the subject of this review. In eyeblink conditioning, a relatively neutral stimulus such as a tone becomes a CS because it is paired with a US such as an air puff or mild shock delivered near the eye to produce an eyeblink. In fear conditioning, a tone CS also may be used, but it is paired with a more threatening US such as foot shock. These are the appropriate models to focus on for several reasons. For both of these systems, staggering progress has been made on each of the three questions raised above. Additionally, the two employ almost completely nonoverlapping circuits. Finally, the behavioral phenomenology of these systems is very different. Fear conditioning is rapidly learned and fear responses are relatively diffuse in timing and topography. Eyeblink is slowly learned, but is characterized by precise timing of a very exact behavioral topography. Additionally, in eyeblink conditioning, the conditional response (CR) to the CS is a near-replica of the unconditional response (UR) to the US; both CR and UR are an eyeblink. In fear conditioning, the CR has

little topographical relationship to the UR, except that it is defensive. For example, a rat or a mouse will show a vigorous burst of activity in response to the shock, but the CR used in most neuroscientific studies of fear is a complete suppression of activity called freezing (Fanselow 1980).

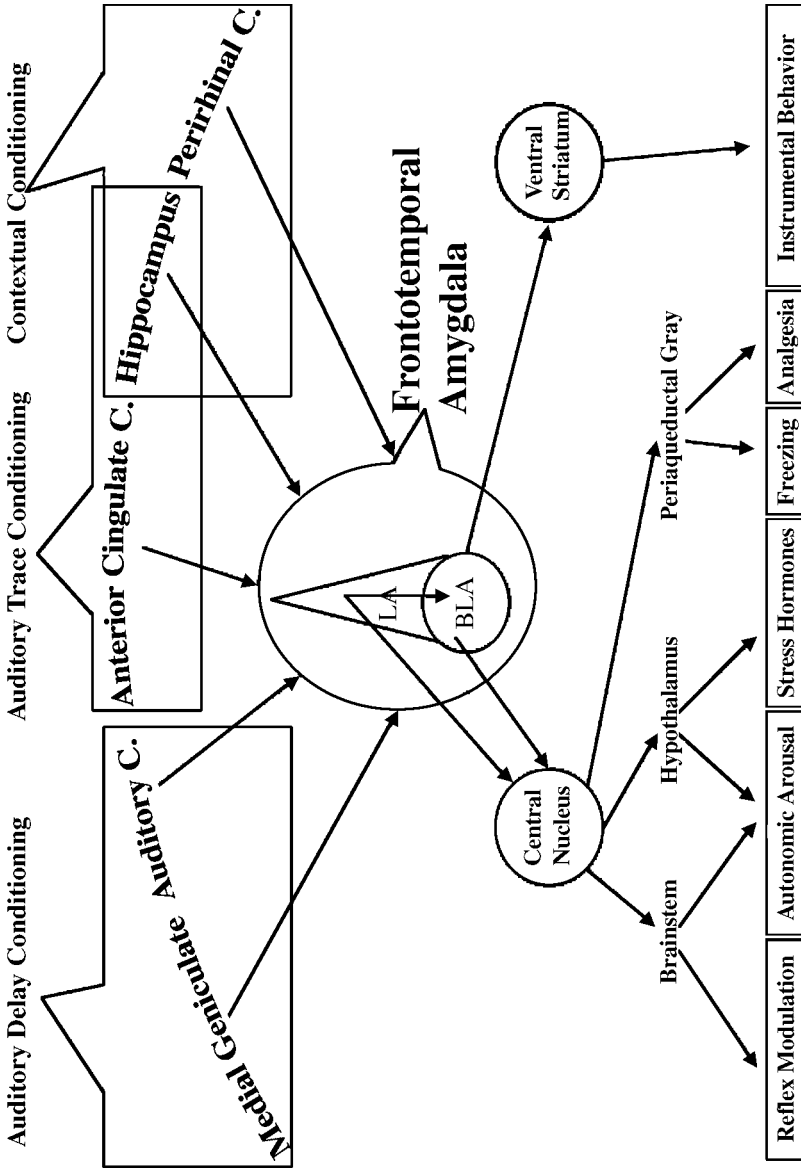
## TECHNIQUES

The use of genetically engineered mice has taken on an increased role in the arsenal of techniques used to understand the neural basis of learning. These molecular genetic techniques are unique in their ability to target specific proteins and eliminate, overexpress, or alter their composition. These tools have become increasingly sophisticated, such that tissue selectivity and temporal control of the mutations are becoming available. However, traditional techniques such as lesions, pharmacological manipulations, and electrophysiological stimulation and recording remain important contributors to our understanding. It needs to be recognized that there is no one superior technique; rather, the greatest analytical power derives from combining various approaches. We try to represent that in this review.

## MODEL SYSTEMS

### Fear Conditioning

**NEURAL CIRCUITRY OF FEAR CONDITIONING** The neural hub for fear conditioning is the amygdala, which is composed of several nuclei in the anterior portion of the medial temporal lobe. Sensory stimuli corresponding to potential CSs arrive at what Swanson & Petrovich (1998) refer to as the frontotemporal amygdala (FTA) because it interconnects frontal and temporal cortices. This region corresponds to the almond-shaped region for which the amygdala originally derived its name, and often is referred to as the basolateral complex because it contains the lateral and basal nuclei. CS information from the thalamus, hippocampus, and several cortical regions reaches the FTA via glutamatergic projections (i.e., neurons releasing the excitatory neurotransmitter glutamate; see Figure 1). The most straightforward and best-characterized CS pathway is a direct projection from the medial geniculate nucleus of the thalamus to the dorsal portion of the lateral nucleus of the amygdala (LeDoux et al. 1991). This pathway carries auditory information to the amygdala and is sufficient for delay conditioning to simple auditory CSs, where tone onset occurs briefly before US onset and CS termination is coincident with either US onset or termination (Romanski & LeDoux 1992). When the CS requires greater processing, polysynaptic routes to the FTA become necessary and the amygdala receives CS information from cortex. For example, the apparatus or context cues present at the time of shock reach the basolateral amygdala via the ventral angular bundle after processing by the hippocampus and entorhinal cortex (Anagnostaras et al. 1999, Maren & Fanselow 1995) and also reach the lateral amygdala from the perirhinal and postrhinal cortex (Amaral et al. 1992). Although damage to the



**Figure 1** The basic circuit for contextual fear conditioning organized according to various types of conditional stimuli at the *top* and conditional fear responses at the *bottom*. LA refers to the lateral nucleus of the amygdala and BLA refers to the basolateral nucleus of the amygdala. The BLA and the LA are parts of the frontotemporal amygdala and comprise the neuroanatomical hub for learned fear.

ventral angular bundle, perirhinal cortex, and postrhinal cortex produces deficits in context conditioning, it has little effect on delay conditioning to a simple auditory cue (Bucci et al. 2000, Burwell et al. 2004, Maren & Fanselow 1995). Interestingly, when the auditory stimulus is similar to the ultrasonic distress call of a rat, perirhinal lesions will attenuate conditioning (Lindquist et al. 2004), again indicating that stimulus complexity determines whether the monosynaptic projections from the thalamus will be sufficient to inform the FTA about the presence of the CS.

One can increase the complexity of the fear conditioning procedure to an auditory cue simply by having CS termination occur briefly before US onset. Pavlov called this procedure trace conditioning because he believed a trace of the CS must remain in the nervous systems to bridge the gap between the CS and US. Like context conditioning, trace fear conditioning requires the hippocampus (McEchron et al. 1998, Quinn et al. 2002). However, lesions of the anterior cingulate cortex reduce trace conditioning but do not affect context conditioning (Han et al. 2003). Additionally, using gene expression as a marker for cellular activity, trace conditioning caused greater activation of the anterior cingulate cortex than delay conditioning with the same stimuli. Thus, the anterior cingulate may play the bridging role to which Pavlov referred. Figure 1 groups various types of CS information with the regions that contribute to processing this information. Each of these regions contains monosynaptic projections to the FTA (Amaral et al. 1992).

Information about the reinforcing US arrives at the amygdala from a number of routes, all of which appear to be sufficient, but none appear to be necessary. Pain information arrives at the FTA directly from the posterior thalamus as well as via the insular cortex (Brunzell & Kim 2001, Jasmin et al. 2004, Lanuza et al. 2004, Shi & Davis 1999). However, although combined lesions of both of these forebrain routes attenuate conditioning to a tone, context conditioning proceeds normally (Brunzell & Kim 2001). Pain information from subcortical structures such as the parabrachial nucleus, nucleus of the solitary tract, and even the dorsal horn of the spine reach the central nucleus of the amygdala (Benarroch 2001, Burstein & Potrebic 1993, Gauriau & Bernard 2002). However, there do not seem to be any major monosynaptic projections from the central nucleus to the FTA, at least in the rat (DeOlmos et al. 1985).

The primary output of the FTA for the generation of conditional fear responses is the central nucleus of the amygdala, which projects to a wide range of regions responsible for emotional responses (see Figure 1). Autonomic reactions are triggered by direct projections to regions of the brainstem and hypothalamus responsible for controlling autonomic function (Kapp et al. 1979, LeDoux et al. 1988). Central nucleus projections to the brainstem modulate several simple reflexes, including the auditory startle response (Canli & Brown 1996, Rosen & Davis 1990, Rosen et al. 1991). Projections to the hypothalamus lead to an elevation of activity in the pituitary-adrenal axis (Feldman & Weidenfeld 1998). Defensive responses are triggered by projections to the periaqueductal gray, which also trigger an endogenous opioid-mediated analgesic state (Fanselow 1991). This analgesia is of particular importance because it provides a negative feedback regulation of the

ascending painful information that supports fear conditioning (Fanselow 1998). This regulation serves to keep the level of fear appropriate to the level of threat and directs fear toward the best predictors of aversive outcomes.

Not all conditional fear-relevant behaviors are controlled via the central nucleus because termination of a fear CS still serves as a reinforcer in rats with central nucleus lesions (Amorapanth et al. 2000, Killcross et al. 1997). It is possible that fear modulates instrumental behavior via projections from the basolateral nucleus to the ventral striatum (French & Totterdell 2003). Some anxiety-related responses are mediated by projections from the FTA to the bed nucleus of the stria terminalis, but it is not clear if these projections play a role in normal fear conditioning (Walker et al. 2003).

Fear not only produces behavior, it affects cognitive activity as well. The FTA has extensive projections to the frontal and temporal lobes; for example, all the cortical-FTA projections in Figure 1 are reciprocal (Amaral et al. 1992). The influence of the central nucleus is certainly not entirely descending, either. It can generate cortical arousal through its control of the ascending cholinergic projections from the basal forebrain (Jolkkonen et al. 2002). Together, this array of ascending and descending projections generates the diffuse set of behavioral manifestations referred to as a fear state.

**SITES OF CRITICAL PLASTICITY** An assumption of neuroscientific theories of associative learning is that convergence of CS and US information onto particular cells leads to changes in synaptic strength at the synapses mediating the CS input to those commonly activated cells. This synaptic plasticity is the mechanism that underlies association formation. Learning is the induction of these synaptic changes and the presence of memory depends on the stability of these changes. Long-term potentiation (LTP) induced by activation of the N-methyl-D-aspartate (NMDA) type of glutamate receptor is the most heavily emphasized form of plasticity for fear conditioning. This long-lasting form of synaptic strengthening was first discovered in the hippocampus and can be induced when glutamate activity at initially “weak” synapses is paired with stimulation that causes the cell to spike (Bliss & Gardner-Medwin 1973, Bliss & Lomo 1973). Such a dual pattern is necessary for NMDA receptor activation and the ensuing calcium influx at the ion channel of this receptor leads to strengthening at those NMDA receptor-containing synapses (Collingridge et al. 1983, Malinow & Miller 1986). This is an attractive model for Pavlovian conditioning because a CS-generated glutamatergic input that at first weakly activates a synapse will be potentiated if the US causes the cell to fire within a temporally limited window. Thus, the cells that participate in this plasticity must receive both CS and US inputs.

It is clear that individual cells within the lateral nucleus respond to tones that can serve as an auditory CS and shocks that can serve as a US (Romanski et al. 1993). Furthermore, electrical stimulation of auditory input to the FTA (medial geniculate to lateral nucleus) supports long-term plasticity (Clugnet & LeDoux 1990). Indeed, LTP induction in this pathway produced by electrical stimulation

increases the FTA's response to a tone (Rogan et al. 1997). Following fear conditioning, cells within the amygdala show increased firing to the CS, suggesting that the CS input has been potentiated following conditioning (Quirk et al. 1997). Finally, McKernan & Shinnick-Galagher (1997) compared brain slices containing the auditory pathway from the auditory thalamus to the lateral nucleus taken from fear-conditioned and control animals. Stimulation of this projection caused greater activation of the amygdala in trained animals, suggesting that fear conditioning induces potentiation of this pathway. Thus, there is a very convincing case that auditory fear conditioning normally supports long-term potentiation of the pathway carrying simple tone information from the medial geniculate nucleus to the lateral amygdala. There is also good evidence that the pathways described above carrying information from the cortex to the FTA and from the hippocampus to the FTA are capable of long-term potentiation (Chapman et al. 1990, Maren & Fanselow 1995, Yaniv et al. 2000). Because administration of NMDA antagonists to the amygdala prevents the acquisition of fear conditioning, it is highly likely that LTP in the FTA supports changes necessary for fear conditioning (Fanselow & Kim 1994, Miserendino et al. 1990).

If LTP is a mechanism of memory formation and LTP in the FTA is normally critical for fear conditioning, then the FTA is presumably encoding some important aspect of the fear-conditioning experience. This must be a general aspect of the experience because the FTA is equally important for fear of simple and complex conditional stimuli (Gale et al. 2004). Because the level of fear is highly dependent on the emotional significance of the US, the memory for emotional significance is one possible candidate for the information that the amygdala has encoded. One method that has proven successful in probing the content of associative memory, particularly for the memory of a US, is the reinforcer revaluation technique. For example, Rescorla (1974) gave rats pairings of tone and weak shock such that the tone alone would provoke a low level of fear. In one group of rats, Rescorla changed how the rats valued the memory of shock by giving them a series of strong shocks without the tone. These rats then behaved as if the tone had been paired with a strong shock. Since the tone-shock association should not be strengthened because of receiving shock by itself, the changes in behavior must be related to changes in the memory for shock. Variants of this procedure have been used to probe the content of associations in a range of situations (Dayan & Balleine 2002). If the FTA is encoding the emotional significance of the US, amygdala activity should be important during memory revaluation, and this appears to be the case. If the amygdala is inactivated only during the memory-inflating strong shocks, rats respond to the tone at levels appropriate to the weak shock with which it was paired while amygdala activity was normal and not at the inflated level (Fanselow & Gale 2003). That is, inactivation of the amygdala during memory revaluation prevents revaluation. FTA lesions made after training eliminate conditional responding even if the memory is allowed to consolidate for a period that approaches the adult life span of the rat (17 months), which suggests that the amygdala permanently encodes the emotional significance of the shock reinforcer (Gale et al. 2004).

Of course, for conditioning you must have not only a representation of emotional significance but also a representation of the stimuli that are associated with that emotional significance. During the course of conditioning to a tone, changes in the medial geniculate cells code the auditory signal (Edeline & Weinberger 1992). Individual cells respond differentially to tones of different frequencies, and during conditioning, many of these cells retune so that the frequency specificity shifts in the direction of the tone paired with shock. These changes in the representation of the tone appear to depend on the amygdala because inactivation of the amygdala prevents the plasticity in the medial geniculate (Maren et al. 2001, Poremba & Gabriel 2001). Individual cells in the auditory cortex also show shifts in their preferred tuning toward the frequency of reinforced CS (Edeline et al. 1993).

NMDA-dependent activity plays a role in the learning about the contextual CS associated with shock as NMDA antagonists injected into the hippocampus or genetic deletion of NMDA receptors from the CA1 region of the hippocampus interfere with contextual fear conditioning (Shimizu et al. 2000, Young et al. 1994). Indeed, genetic manipulations that enhance NMDA receptor function can enhance contextual fear learning (Tang et al. 1999). This learning seems to be specifically about contexts because blocking NMDA antagonists only during a time where the animal is exploring a context eliminates the benefits of that exploration (Stote & Fanselow 2004). Inactivating the amygdala at the time of exploration also prevents the benefits of exploration (Huff & Rudy 2004), similar to the effect of amygdala inactivation on retuning of auditory-responsive neurons in the thalamus. This is somewhat surprising, given that there is no emotion-provoking shock during the exploration period; however, this may reflect emotional arousal due to novelty or handling by the experimenter. During fear conditioning, theta rhythm activity generated by a tone paired with shock synchronizes in hippocampus and amygdala (Seidenbecher et al. 2003). Additionally, hippocampal neurons will differentially respond to tones that were paired, as opposed to not paired, with shock, but only in their place fields (Moita et al. 2003). Thus, it is clear that fear conditioning represents a rich interplay between the structures that encode the emotional, signaling, and contextual aspects of the learning.

Questions about plasticity for Pavlovian conditioning typically focus on those related to sensory inputs as opposed to response outputs. This is no doubt because Pavlovian conditioning is thought of as learning about stimulus relationships, which results in preprogrammed responses to new stimuli. However, there is no a priori reason to assume that synaptic strengthening cannot play a role at the other relays in the circuit mediating between environment and behavior. A suggestion that there is also significant plasticity within the response-generation pathways comes from analyses of development of fear systems. The ability to condition fear to different CS appears at different ages, as does the ability to express fear in different responses (Hunt & Campbell 1997). Fear-induced freezing occurs at an earlier age than fear-induced potentiation of the startle reflex (Hunt 1999). Fan & Richardson (2002) used odor-shock pairings to train rats at an age when they were old enough to express fear in terms of odor avoidance, but too young to express fear

in terms of potentiation of the startle response. The intriguing result is that if the rats were not tested until they were old enough to express potentiated startle, they showed avoidance but not enhanced startle. The finding that animals only express behaviors available at the time of training suggests that some component of the plasticity occurs within the response-generation machinery. Thus, it seems that in fear conditioning, important plasticity occurs in the pathways corresponding to CS, US, and CR. All of this plasticity must be rapidly induced because significant fear conditioning occurs with a single pairing of CS and US.

**INTRACELLULAR MEDIATORS OF PLASTICITY** If CS and US convergence in the FTA causes potentiation of the glutamatergic synapses activated by the CS, changes must be occurring within the presynaptic neuron, the postsynaptic neuron, or both. The majority of what we know about the intracellular events that support synaptic strengthening comes from studies of long-term potentiation in rodent hippocampal neurons or from studies of gill and siphon withdrawal reflexes of the marine mollusk *Aplysia* (Pittenger & Kandel 2003). There has been considerable debate within each of these two domains as to whether presynaptic or postsynaptic changes are of primary importance, although the hippocampal work has tended to emphasize postsynaptic processes and the *Aplysia* work has emphasized presynaptic processes (Antonov et al. 2003, Lisman 2003, Roberts & Glanzman 2003). Presynaptic changes could take the form of greater neurotransmitter release per action potential arriving at the relevant synaptic terminals. Postsynaptic changes typically take the form of changes that make the postsynaptic cell more responsive to a fixed amount of neurotransmitter release. This could happen through restructuring the postsynaptic region to be more responsive to glutamate, such as the insertion of more of the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors that mediate the majority of excitatory glutamatergic transmission (Isaac et al. 1995, Liao et al. 1995). Obviously, such changes are not logically exclusive. Rather, coordinated changes in both pre- and postsynaptic regions would be synergistic, and there is some evidence that postsynaptic activity may trigger retrograde messengers that affect their presynaptic contacts (Boehring & Snyder 2003). Finally, some forms of plasticity result in increased synaptic contacts through the growth of new dendritic spines (Muller et al. 2002, Trachtenberg et al. 2002). Thus, we have a rich field of candidates for learning-related cellular changes in the FTA.

Determination of which changes contribute to learning requires indirect methods because it is not feasible at this time to identify, *in vivo*, whether or not neurotransmitter release or receptor density has changed at the individual synapses responsible for learning. The first suggestion that increased transmitter release may be critical to fear-related plasticity in the FTA was made by Maren & Fanselow (1995). They used an *in vivo* LTP preparation that stimulated the ventral angular bundle, which carries information from the hippocampus and entorhinal cortex to the basolateral nucleus. High-frequency stimulation of this pathway induced a form of long-term potentiation that reduced paired-pulse facilitation. Paired-pulse

facilitation is an enhanced postsynaptic response to the second of two closely spaced electrical stimulations of the presynaptic neuron. This observation of an interaction between paired-pulse facilitation and FTA-LTP is critical because paired-pulse facilitation results from increased neurotransmitter release by the presynaptic terminal. The idea is that if neurotransmitter release is already optimized by LTP, then additional manipulations designed to enhance neurotransmitter release, such as paired-pulse facilitation, should produce little effect. Like acquisition of fear conditioning, induction of the LTP was prevented by application of an NMDA antagonist (Maren & Fanselow 1995). These researchers went on to confirm that either severing the ventral angular bundle with electrolytic lesions or killing the cells in the region of the FTA that received these projections with a neurotoxin prevented contextual fear conditioning, providing evidence that this pathway participates in contextual fear conditioning. The pattern of results suggests that the acquisition of fear depends on postsynaptic activation of NMDA receptors, which in turn sets in motion processes that lead to increased neurotransmitter release by the presynaptic neuron.

Subsequently, Huang & Kandel (1998) replicated the interaction of FTA LTP and paired-pulse facilitation using an *in vitro* slice preparation where stimulation of the external capsule caused LTP in the lateral nucleus. The external capsule contains projections from the auditory cortex to the lateral amygdala, which suggests that in this pathway, too, expression of potentiation involves increased neurotransmitter release by the presynaptic neuron. Again consistent with the earlier report, NMDA receptors were critical for induction of LTP. Additionally, because injecting a calcium chelator into the postsynaptic neuron blocked LTP, calcium influx through the NMDA receptor appears to be critical for the postsynaptic contribution to the LTP. Paired-pulse facilitation and LTP were attenuated by blocking protein kinase A (PKA) activity in both the presynaptic and postsynaptic cells. However, blocking PKA in the postsynaptic cell alone did not affect LTP. Thus, the increased transmitter release caused by LTP depends on presynaptic activation of PKA (Huang & Kandel 1998). Brain slices containing the auditory pathway from either the thalamus (McKernan & Shinnick-Gallagher 1997) or cortex (Tsvetkov et al. 2002) to the lateral amygdala taken from fear-conditioned animals show enhanced neurotransmission accompanied by an increased probability of neurotransmitter release, which suggests that presynaptic changes are generally involved in the formation of fear memories. The finding that infusion of PKA inhibitors into the amygdala blocks acquisition of long- but not short-term memory for conditional fear is consistent with the hypothesis that PKA-regulated presynaptic changes mediate fear learning (Goosens et al. 2000, Schafe & LeDoux 2000).

Induction of the presynaptic changes mediating learning requires NMDA-receptor activation of the postsynaptic neuron. At this point, there is reasonable detail about the postsynaptic cascade within the FTA that contributes to the formation of memory, and these events are roughly parallel to the postsynaptic events that contribute to plasticity in the CA1 region of the hippocampus (see, e.g., Lynch 2004, Pittenger & Kandel 2003). The influx of calcium ions through the NMDA

receptor results in persistent activation of calcium-calmodulin-dependent protein kinases (CaMK). Genetically induced deletions of one type of CaMK (CaMKII) impair several forms of learning in mice, although much of the work has focused on hippocampus-dependent learning (e.g., Silva 2003). Mayford et al. (1996) targeted a mutation to a specific amino acid within the CaMKII molecule that interfered with its normal activation. Mice bearing this mutation in a manner restricted to amygdala and striatal neurons had a deficit in fear conditioning. Similarly, genetic deletion of CaMKIV appears to produce selective deficits in fear learning and FTA-LTP (Wei et al. 2002). Both auditory fear conditioning and LTP-inducing electrical stimulation of the medial geniculate-amygdala pathway cause activation and movement of CaMKII into dendritic spines of lateral nucleus neurons (Rodrigues et al. 2004). Electron and light microscopy confirmed that this activated CaMKII is associated with postsynaptic NMDA receptors located in spines that synapse with the terminals of neurons that originate in the medial geniculate. Rodrigues et al. also found that infusions of pharmacological inhibitors of CaMKII into the FTA blocked both fear conditioning and LTP.

Activation of CamK is known to activate cyclic-AMP response element-binding protein (CREB), which is a regulator of gene expression and memory (Impey et al. 1998, Kida et al. 2002, Tully 1997). Along with a loss of fear conditioning, mice with a genetic deletion of CaMKIV show reduced CREB activation in the FTA (Wei et al. 2002). Increasing CREB expression in the FTA by introducing additional copies of the CREB gene carried by a virus enhances long-term memory for fear (Josselyn et al. 2001). Gene expression is further implicated because mRNA for the immediate early gene *Zif268* is expressed specifically in the lateral amygdala following fear conditioning (Rosen et al. 1998). Blockade of the transcription of DNA to RNA within the amygdala prevents the acquisition of fear memories (Bailey et al. 1999), as does translation of RNA into protein (Schafe & LeDoux 2000).

Some important issues have not been resolved. It is not known what these new proteins are or how they function to produce enduring changes in synaptic efficacy in the FTA. Protein synthesis in the postsynaptic cell seems necessary for the induction of the essential plasticity, but the critical changes in the expression of this plasticity appear to be presynaptic. Some combination of postsynaptic calcium influx, activation and movement of CamK into postsynaptic spines, and/or gene expression-mediated protein synthesis in the nucleus of the postsynaptic neuron initiates PKA-dependent presynaptic changes confined to the synapses that participated in the learning. Of course, this is such a fast-evolving field that these questions may well be answered by the time this review appears in print.

As pointed out in the section above, fear conditioning involves plasticity at a number of sites. Here we have chosen to focus on the FTA because it is the site most relevant to the formation of new associations between the CS and US, and the presently available data make the strongest link between intracellular events and specific learned behaviors in vertebrate animals. In addition, with the exception of the hippocampus, little is known about the intracellular events mediating

plasticity in these other regions. Certainly, the knowledge of the intracellular events mediating plasticity for the CA1 field of the hippocampus is more detailed than it is for the amygdala. Although much of the postsynaptic cascade is similar in the two, a critical mediator of hippocampal plasticity is the insertion of new AMPA-type glutamate receptors into the postsynaptic region (Isaac et al. 1995, Liao et al. 1995, Pickard et al. 2001). However, the current state of knowledge does not preclude such postsynaptic changes in the FTA, and there is certainly evidence for a presynaptic influence on hippocampal LTP (Lisman 2003). Indeed, one can be reasonably confident that the plasticity underlying learning in these structures will turn out to be a result of an active dialogue between the pre- and postsynaptic neurons.

*Generalization to humans* Although it is impossible to perform equivalently detailed analysis in humans, to the extent that such work has been done the specifics are remarkably consistent. Bechara et al. (1995) examined a patient with Urbach-Wiethe disease, a condition that results in bilateral calcification and atrophy of the amygdala with little damage to any other medial temporal lobe structures. The patient had pronounced loss in delay fear conditioning assessed by autonomic arousal despite the fact that her memory for the details (declarative memory) of the conditioning session was completely intact. Consistent with the lesion data, functional magnetic resonance imaging (fMRI) shows enhanced blood flow to the amygdala during delay fear conditioning (LaBar et al. 1998), and this amygdala activation is highly correlated with the conditional fear response (Cheng et al. 2003). However, hippocampal activity is correlated more with the cognitive appreciation of the situation than with the emotional response (Cheng et al. 2003). Similarly, humans with hippocampal damage and an intact amygdala show normal fear conditioning with a loss of declarative memory for the conditioning situation (Bechara et al. 1995). Contextual fear conditioning has not been studied in humans. Knight et al. (2004) found that trace and delay CS produced similar activation of the human anterior cingulate; this contrasts with the differential activation found in mice. It is not clear if this is because the animal studies examined cellular markers of activity that were more precise (Han et al. 2003) or because the human studies trained trace, delay, and unpaired stimuli in the same subjects (Knight et al. 2004).

## Eyeblink Conditioning

**NEURAL CIRCUITRY OF EYEBLINK CONDITIONING** The core neural component for eyeblink conditioning is the cerebellum, a brain structure located just caudal to the cerebral hemispheres and overlying the dorsal surface of the brainstem. The neuronal cell bodies of the cerebellum form a thick cortical layer that covers the underlying white matter (axons) and deep cerebellar nuclei. These nuclei, organized in medial-lateral orientation, consist of the fastigial, interpositus, and dentate nuclei. The relays of cerebellum are organized in highly regular manner, with well-defined sensory input and motor output pathways.



1992, Thompson & Krupa 1994, Yeo et al. 1985). Substitution of peripheral CSs with direct electrical stimulation of either the pontine nucleus or IPN serves as a very powerful CS, producing conditioning that is more rapidly acquired than to light or tone (Poulos & Thompson 2004, Steinmetz et al. 1986, Tracy et al. 1998).

Somatosensory information corresponding to an air-puff or mild eye-shock US arrives at the cerebellum primarily by climbing fibers from the inferior olive (see Figure 2). This essential US pathway includes the trigeminal nucleus, which in turn innervates the inferior olive, which sends axonal processes to the cerebellum via climbing fibers. The climbing fibers and their collaterals synapse on Purkinje cells and IPN neurons of the cerebellum and utilize glutamate and CRH as primary neurotransmitters (Ito 2002). Prior to training, lesions of the inferior olive prevent eyeblink conditioning, whereas similar lesions following conditioning result in extinction with continued paired training (McCormick et al. 1985). Conversely, electrical stimulation of the inferior olive that elicits behavioral responses when used as a US produces conditioning at a rate, magnitude, and topography similar to peripheral USs (Mauk et al. 1986).

The IPN is not only a primary site of CS-US convergence, but also a primary cerebellar motor output responsible for the generation of the conditional eyeblink response. The IPN, like the motor cortex, contains a somatotopic representation of the entire body (Schultz et al. 1979). For example, in the rabbit, direct electrical stimulation of the medial aspects of IPN elicits movements in the lower trunk and hind limb areas, whereas stimulation of lateral portions of IPN evokes movements in the head area that include eyelid closure (McCormick et al. 1983). This eyelid region of the IPN sends heavy projections to the contralateral magnocellular red nucleus. From the red nucleus, projections to a set of motor nuclei trigger the expression of the conditional eyeblink response. The same motor nuclei also receive direct and indirect projections from the trigeminal nucleus, responsible for producing the unconditional eyeblink reflex.

Under simple delay conditioning procedures, the cerebellum and its associated brainstem regions are necessary and sufficient for the acquisition and expression of conditional eyeblink responses (Figure 2). However, damage to the medial septum, a primary source of cholinergic projections to the hippocampus, retards the rate of delay conditioning (Berry & Thompson 1979). Conversely, intraseptal injections of scopolamine, an acetylcholine receptor antagonist that suppresses hippocampal functioning, also slow eyeblink conditioning (Salvatierra & Berry 1989, Solomon & Gottfried 1981). However, if the hippocampus is lesioned first, scopolamine no longer impairs learning (Solomon et al. 1983). Thus, for delay eyeblink conditioning, a functionally compromised hippocampus is more detrimental to learning than is the absence of the hippocampus. As similarly described in fear conditioning, the introduction of a stimulus-free period between the CS and US requires the hippocampus. Lesions of the hippocampus, which produce no discernable effects on delay conditioning, markedly impair trace eyeblink conditioning (Beylin

et al. 2001, Solomon et al. 1986). In trace conditioning, lesions made one month following training do not impair performance of trace CRs (Kim et al. 1995) in a manner that parallels hippocampus-dependent consolidation of context fear (Kim & Fanselow 1992). Anatomical evidence suggests that interactions between the cerebellum and hippocampus occur indirectly, with the hippocampus modulating CS and US input by interacting with the pontine nucleus and inferior olive (Lee & Kim 2004).

**SITES OF CRITICAL PLASTICITY** In eyeblink conditioning, it is quite clear that both neurons of IPN and Purkinje cells of the cerebellar cortex receive CS and US inputs. Therefore, it is conceivable that plasticity at one or both sites mediates the formation and storage of eyeblink memory traces. Furthermore, anatomical evidence reveals that both cerebellar regions send and receive reciprocal connections among each other (see Figure 2). For this reason, determining the relative contributions of IPN and cerebellar cortex has been difficult. Initial findings by McCormick et al. (1981) demonstrated that electrolytic lesions of the dentate-IPN region and large aspirations of cerebellar cortex completely abolished all expression of conditional eyeblink responses without affecting the UR. Later studies revealed that lesions of the anterior lateral IPN as small as 1 mm<sup>3</sup> are sufficient to completely abolish CRs (Lavond et al. 1984). Further, temporary inactivation methods demonstrate that inactivation of the IPN during training completely prevents learning, as evidenced by the lack of CRs following inactivation (Clark et al. 1992; Krupa & Thompson 1995, 1997). In contrast, learning is not prevented by inactivation of an efferent pathway or its target, the red nucleus, which completely abolishes CR expression (Clark & Lavond 1993, Krupa & Thompson 1995, Krupa et al. 1993). These results suggest that the essential plasticity cannot occur efferent to the IPN and that essential memory trace (or traces) is established and maintained in the cerebellum. Single- and multiple-unit recordings in the IPN show learning-related unit activity, also found in the cerebellar cortex, that precedes and predicts occurrence of the behavioral CR (Berthier & Moore 1986, 1990; Gould & Steinmetz 1994; King et al. 2001; McCormick & Thompson 1984; Rogers et al. 2001). Moreover, lesions or temporary inactivation of the IPN (Thompson & Krupa 1994) abolish neuronal recording of conditioning-related unit activity in many regions of the essential eyeblink circuitry (see Figure 2). Removal of cerebellar cortical tissue has been reported to result in varying effects in eyeblink conditioning. Although it has been reported that lesions of cerebellar cortex prevent the acquisition of conditional eyeblink responses (Garcia et al. 1999), all other studies to date report either no effect or impairments in acquisition, retention, and/or CR timing (Lavond & Steinmetz 1989, Logan et al. 1994, McCormick & Thompson 1983, Perrett et al. 1993). Perhaps the clearest interpretation of these lesion studies is provided by Purkinje cell degeneration (PCD) mice. Several weeks after birth of these mice, Purkinje cells, the sole output of the cerebellar cortex, completely degenerate. PCD mice acquire eyeblink

conditioning at a slower rate and lower level than wild-type mice, but they do learn (Chen et al. 1996). Further, CRs expressed tended to have shorter peak latencies.

Recent work by Bao et al. (2002) suggests that CR expression and timing may be completely dissociable and that memory traces for eyeblink CRs may be encoded in a functionally distinct manner in both the cerebellar cortex and IPN. In their study, rabbits displaying well-timed CRs were given sequential IPN application of the gamma-aminobutyric acid (GABA<sub>A</sub>) agonist muscimol and the GABA<sub>A</sub> antagonist picrotoxin, which resulted in the expression of reduced onset and peak CR latencies poorly timed to the US. Such results are consistent with studies by Mauk and associates using high concentrations of picrotoxin (Garcia & Mauk 1998, Medina et al. 2001). This disruption of CR timing following blockade of cortical outputs suggests that the memory traces for learned timing and for basic associative eyeblink memory may be expressed within two distinct sites of plasticity, the cerebellar cortex and IPN, respectively.

Early cerebellar learning theories proposed plasticity within the cerebellar cortex, specifically at the parallel fiber-Purkinje cell (PF-PC) synapses, as a general mechanism of motor learning (Albus 1971, Marr 1969). Albus (1971) further hypothesized that the high tonic-firing rate of Purkinje cells resulting in sustained GABAergic inhibition of the IPN could be released by a decrease in PF-PC synaptic strength. Empirical evidence for this theory came with the discovery that long-term depression (LTD) resulting from simultaneous low-frequency stimulation of parallel fibers and climbing fibers could result in persistent decreases in PF-PC synaptic efficacy (Ito & Kano 1982). However, under such parameters of simultaneous CS and US presentation, eyeblink conditioning does not develop. Further work by Chen & Thompson (1995) demonstrated that under specific *in vitro* conditions that did not block GABA receptors, LTD could be induced by repeated parallel fiber and climbing fiber stimulation separated by 250 msec, matching the optimal eyeblink conditioning interstimulus intervals. In contrast, simultaneous stimulation of parallel and climbing fibers can elicit LTD in the presence of the GABA antagonist bicuculline. Indeed, in the intact animal, direct electrical stimulation of parallel fibers as a CS and climbing fibers as a US produces appropriately timed eyeblink conditioning (Shinkman et al. 1996).

Recent investigations both *in vivo* and *in vitro* have begun to examine plasticity specific to the IPN and its synapses. One attractive mechanism of memory formation in eyeblink conditioning is long-term plasticity of the mossy fiber-IPN synapse. Racine (1986) previously reported that tetanic electrical stimulation of mossy fibers induces LTP of the mossy fiber-IPN synapse. Perhaps the most compelling evidence of conditioning-specific synaptic plasticity comes from recent findings by Kleim and colleagues (2002) using unbiased stereological synapse quantification methods. In this study, rats trained in delay eyeblink conditioning exhibited an increased number of excitatory IPN synapses compared to unpaired and untrained controls. Moreover, because the expression of CRs is driven solely by the CS, increases in excitatory IPN synapses are likely to occur along the CS

pathway, specifically at mossy fiber-IPN synapses. There was no increase in inhibitory synapses in the IPN (presumably from Purkinje axons). A form of non-synaptic plasticity also has been implicated in cerebellar learning. Aizenman & Linden (2000) showed that direct high-frequency stimulation of deep nuclear neurons of the cerebellum under reduced levels of inhibition resulted in persistent increases in maximum firing rate. Interestingly, IPN electrical stimulation to eyeblink thresholds are markedly reduced following eyeblink conditioning, suggesting possible conditioning-related increases in IPN excitability (Poulos et al. 2002). Conversely, infusion of NMDA antagonist APV, in the IPN, which in vitro blocks the induction of intrinsic excitability (Aizenman & Linden 2000), selectively impairs conditioning but not expression of eyeblink CRs (Chen & Steinmetz 2000a).

**INTRACELLULAR MEDIATORS OF PLASTICITY** In eyeblink conditioning the combination of evidence from several levels of analysis strongly suggests that the development and maintenance of the adaptive (well-timed) associative memory (CRs) are mediated by plasticity occurring in at least two cerebellar regions, the cortex and IPN. Moreover, the forms of plasticity that contribute to learning have yet to be directly identified in vivo; therefore, it is imperative to employ molecular and genetic methods to isolate key components of plasticity and learning. At the level of the IPN, if an increase in synaptic strength is a mechanism of the primary CS-US memory, then alterations of intracellular mediators of LTP or synaptogenesis should compromise conditioning. Further, if depression of synaptic function in the cortex mediates the appropriate timing of the associative memory, utilizing methods to manipulate expression of key molecular components of cerebellar cortical LTD should affect conditional responding and timing.

The demonstration that eyeblink conditioning is associated with an increase in the number of IPN excitatory synapses prompts important questions as to possible mechanisms of synapse formation in the adult central nervous system that may mediate memory formation. Almost certainly any physical or chemical changes in neurons involve alterations in gene expression and/or protein structure. Gomi et al. (1999) demonstrated that inhibition of RNA synthesis in the IPN profoundly impairs learning but not the expression of eyeblink CRs. Conversely, inhibition of protein synthesis similarly reduces the rate of conditioning (Bracha et al. 1998). Gomi et al. (1999) further identified a kinase whose expression increased in the IPN with eyeblink conditioning. Isolation of cDNA and sequence analysis revealed that the expressed gene was KKIAMRE kinase, a member of the CDC2-related and mitogen-activated protein (MAP) family. Both inhibitors of protein kinases and specific MAP kinase p38 markedly impair learning but not CR expression (Chen & Steinmetz 2000b, Zhen et al. 2001). Evidence of synaptogenesis, or gene transcription and translation, does not preclude a role for mossy fiber-IPN LTP as a mechanism of learning, such that LTP may be an antecedent or act in concert with synaptogenesis to promote memory formation. Like amygdala-dependent fear conditioning and hippocampal-dependent maze learning, application of an NMDA receptor antagonist, which prevents learning and amygdala and

hippocampal LTP, markedly impairs eyeblink conditioning (Chen & Steinmetz 2000a).

A reduction in PF-PC synaptic strength at multiple and spatially distinct synapses is an attractive model that could promote the appropriate temporal release of IPN inhibition and hence expression of appropriately timed conditional eyeblink responses. Indeed, single-unit recordings of Purkinje cells reveal decreases and increases in firing rates that immediately precede the expression of well-timed CRs (King et al. 2001). The requirements for eyeblink conditioning, like those of PF-PC LTD, are typically associative. Both can be induced by parallel fiber and Purkinje cell stimulation. To date, molecular mechanisms of cerebellar LTD are more clearly understood. The induction of cerebellar LTD is initially triggered by activation of mGluR1 metabotropic and AMPA receptors. Mutant mice deficient in mGluR1 and impaired in the induction of LTD are also impaired in eyeblink conditioning (Aiba et al. 1994). Further, blockade of cerebellar cortical AMPA receptors, which block the induction of LTD (Wang & Linden 2000), also has been reported to impair the acquisition and expression of CRs (Attwell et al. 1999, 2001). Following activation of glutamate receptors, transient activation of protein kinase C (PKC) is essential. Transgenic mice with Purkinje cell-specific inhibition of PKC, which prevents the induction of LTD, show impairments in eyeblink conditioning (Goossens et al. 2001, Koekkoek et al. 2003). Conversely, eyeblink conditioning results in an increase in membrane-bound PKC specific to cerebellar cortical tissue (Freeman et al. 1998). Further, inhibition of nitric oxide, which blocks the induction of LTD (Shibuki & Okada 1991), results in attenuated eyeblink acquisition and learning-related neural activity in the IPN (Allen & Steinmetz 1996). Expression of PF-PC LTD is expressed postsynaptically, possibly as a reduction in the number of functional AMPA receptors produced by endocytosis. Interestingly, quantitative autoradiography reveals eyeblink conditioning-related decreases in ( $^3\text{H}$ ) AMPA binding to synaptic subpopulations of cerebellar cortical AMPA receptors (Hauge et al. 1998). Additional support for the LTD hypothesis comes from mice deficient in glial fibrillary acidic protein; these mice show normal excitatory synaptic transmission and have no observable motor deficits, but are markedly deficient in PF-PC LTD and have impaired eyeblink conditioning (Shibuki et al. 1996).

It is likely that the eyeblink conditioning results in plasticity at a number of sites. Here we have chosen to focus primarily on two critical sites of plasticity, the IPN and cerebellar cortex. It should be noted that within each of these regions, synaptic plasticity at sites other than PF-PC and mossy fiber-IPN synapses has been identified and discussion of such sites and mediators of plasticity and their potential contributions to eyeblink conditioning has been reviewed by Hansel et al. (2001). However, these potential mechanisms have yet to be tested in eyeblink conditioning. As pointed out above, much of the research in cerebellar synaptic plasticity has focused on PF-PC LTD. However, because most of the evidence suggests that eyeblink conditioning can occur independent of the cerebellar cortex, it seems likely that elucidating the molecular mechanisms of IPN plasticity (LTP

and/or synaptogenesis) may yield for the first time a cellular substrate of cerebellar memory.

**Generalization to humans** The results obtained in animal studies of eyeblink conditioning correspond closely to the evidence available in human eyeblink conditioning. The combination of lesion, neuroimaging, and observation in amnesic patients confirms that the cerebellum plays a critical role in eyeblink conditioning in humans as well. Positron emission tomography in humans reveals changes in glucose metabolism in the cerebellum correlated with eyeblink conditioning (Blaxton et al. 1996, Logan & Grafton 1995, Molchan et al. 1994, Schreurs et al. 1997). Moreover, fMRI shows increases in cerebellar cortex and deep nuclear activity over the course of eyeblink conditioning (Lemieux & Woodruff-Pak 2000). In addition, both positron emission tomography and fMRI reveal activation of the medial temporal lobe, which includes the hippocampus (Lemieux & Woodruff-Pak 2000, McIntosh & Schreurs 2000). In amnesic patients suffering from bilateral medial temporal lobe damage, trace conditioning under a long trace interval is markedly impaired, whereas delay eyeblink conditioning is normal (Clark & Squire 1998, McGlinchey-Berroth et al. 1997, McGlinchey-Berroth 2000). However, patients with bilateral as well as with unilateral cerebellar lesions ipsilateral to the trained eye are severely impaired in delay and trace eyeblink conditioning (Daum et al. 1993, Lye et al. 1988, Solomon et al. 1989, Topka et al. 1993). In sum, across a wide spectrum of mammals including humans the cerebellum is critically for the acquisition, retention, and expression of conditional eyeblink responses.

## CONCLUSIONS

Different types of learning and memory must be analyzed as separate systems that evolved to solve specific functions. Emotional memory, examined through Pavlovian fear conditioning, and specific motor responses, examined through Pavlovian eyeblink conditioning, arise from largely different neural circuits. Even the specific mechanisms that produce memory at the cellular level are different.

We also need to recognize that there are a few important similarities. At the circuit level, both systems require input from similar cortical structures when conditioning becomes more complex. The hippocampal contribution to trace conditioning is the clearest example. Additionally, a negative feedback circuit regulates learning in both systems, although the specific circuit is very different (Fanselow 1998). In terms of plasticity, there is considerable overlap in the specific molecules that regulate synaptic plasticity, although these molecules may play different roles in the different forms of learning. Two emerging findings are critical. The first finding is that the mechanisms of learning involve a coordinated interplay between pre- and postsynaptic regions, and the second is that learning and gene expression are so intimately related that the old nature-nurture distinction is of little value.

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