Neuron, Vol. 36, 567–584, November 14, 2002, Copyright ©2002 by Cell Press

Behavioral and Neural Analysis of Extinction

Review

Karyn M. Myers[1,3] and Michael Davis[1,2,3,4]
[1]Department of Psychology
[2]Department of Psychiatry and Behavioral Sciences
[3]Center for Behavioral Neuroscience
Emory University
Atlanta, Georgia 30322

The neural mechanisms by which fear is inhibited are poorly understood at the present time. Behaviorally, a conditioned fear response may be reduced in intensity through a number of means. Among the simplest of these is extinction, a form of learning characterized by a decrease in the amplitude and frequency of a conditioned response when the conditioned stimulus that elicits it is repeatedly nonreinforced. Because clinical interventions for patients suffering from fear dysregulation seek to inhibit abnormal, presumably learned fear responses, an understanding of fear extinction is likely to inform and increase the efficacy of these forms of treatment. This review considers the behavioral, cellular, and molecular literatures on extinction and presents the most recent advances in our understanding while identifying issues that require considerable further research.

Introduction

The substantial psychiatric and societal problems associated with fear-related disorders and the need for effective clinical interventions for their treatment are receiving increasing attention in light of the terrorist attacks on September 11, 2001. Until quite recently, however, relatively little guidance has been forthcoming from laboratory investigations of the mechanisms of fear inhibition. The reasons for this oversight are numerous, but interest in the question has been growing and will almost certainly continue to do so, given the impetus of these unsettling events.

The behavioral and neural mechanisms of fear acquisition are already well understood, thanks in large part to studies of simple forms of aversive conditioning in animals. The most extensively studied of these is Pavlovian fear conditioning, a form of learning in which an animal (typically a rat) is exposed to pairings of a neutral conditioned stimulus (CS), such as a light or tone, with a fear-inducing unconditioned stimulus (US), such as a mild footshock, and comes to exhibit a conditioned fear response (CR) to the CS. Behavioral techniques for the inhibition or suppression of this acquired fear have been known for some time. Among the simplest of these is extinction, a form of learning characterized by a decrease in the amplitude and frequency of a CR when the contingent relationship between the CS and US is compromised, as most commonly occurs when the CS is repeatedly presented in the absence of the US. This basic protocol is very similar to those employed by clinicians specializing in the treatment of fear disorders in humans, which commonly involve exposure to the feared object in the absence of any overt danger. Extinction of fear conditioning in animals is thus an excellent model system for the study of fear inhibition, and one whose implications for exposure-based psychotherapies are particularly straightforward.

Behavioral studies of extinction have been ongoing since the late 19th century, whereas a neural analysis of extinction and inhibition is still in its infancy. The study of the neural basis of extinction has been facilitated by the fact that extinction can be measured in the same Pavlovian conditioning paradigms used to study the mechanisms of CR acquisition and expression. At the same time, however, this endeavor has been hampered by misconceptions as to the nature and significance of extinction, which is sometimes characterized as a process of "forgetting" or "unlearning" (implying that the loss of a CR may simply reflect the reversal of the plasticity associated with acquisition) rather than a new learning process accompanied by additional plasticity (e.g., Kitazawa, 2002). Because these misconceptions continue to linger even as the literature on the cellular basis of extinction grows, we believe a review of the broader extinction literature and its implications is needed. We will begin with a brief discussion of the behavioral and theoretical work on extinction and will then turn to studies of its neural and cellular bases.

Behavioral Features and Theories of Extinction

The study of extinction began with Pavlov (1927), who discovered that the conditioned salivary response of his dogs to a food-signaling cue diminished and finally disappeared when the cue was repeatedly presented in the absence of food. This decrease in the amplitude and frequency of a CR as a function of nonreinforced CS presentations is ubiquitous across paradigms (appetitive and aversive) and species (*C. elegans* to humans), and is referred to as *extinction*. Extinction is not due to forgetting of the original CS-US association, as CRs are quite resistant to loss with the simple passage of time (G.D. Gale et al., 1999, Soc. Neurosci., abstract; McAllister et al., 1986). Rather, extinction is an active learning process that is distinct from acquisition and requires additional training to develop (Figure 1A). It should be noted that there is evidence for a nonassociative component of extinction as well (e.g., Frey and Butler, 1977), which has been incorporated into certain psychological (Rescorla and Heth, 1975; Robbins, 1990) and cellular theories (Hawkins and Kandel, 1984); however, we will focus upon the associative component in this review.

Some psychological theories have described extinction as an "unlearning" process dependent on a violation of the CS-US contingency established in acquisition (Rescorla and Wagner, 1972; Wagner and Rescorla, 1972). In the associative language of these theories, it is argued that the CS-US association mediating CR performance is weakened and ultimately lost over the course of extinction training, such that the CS loses its ability to produce a CR. Although this is perhaps the

[4]Correspondence: mdavis4@emory.edu

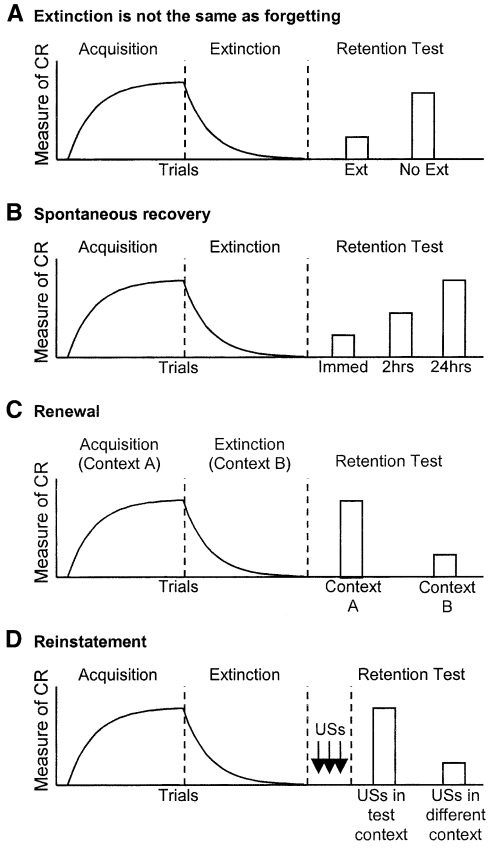

Figure 1. Extinction Is a Form of New Learning that Is Characterized by Several Salient Behavioral Features

(A) Extinction is not the same as forgetting because the acquired fear response (CR) does not disappear unless the CS is nonreinforced in the interval between acquisition and test. (B) At relatively extended intervals following extinction, the extinguished CR reappears. The magnitude of this "spontaneous recovery" increases with the length of the extinction-to-test interval. (C) Extinction is context specific. Following acquisition in context A and extinction in context B, a retention test in context B reveals extinction-appropriate behavior (i.e., little or no CR) whereas a similar test in context A reveals acquisition-appropriate behavior (i.e., the extinguished CR is "renewed"). (D) An extinguished CR reappears (is "reinstated") when unsignaled presentations of the US are interposed between the completion of extinction training and a subsequent retention test, but only if the USs are presented within the context of the retention test.

most parsimonious account of extinction, considerable evidence has emerged to challenge the unlearning view. For example, it has long been established that the expression of extinction dissipates over time, a phenomenon known as spontaneous recovery (for a review, see Robbins, 1990) (Figure 1B). The magnitude of the recovered CR is commonly seen to increase with the length of the rest interval, such that a negatively accelerated curve of CR return as a function of time since extinction training is obtained (M.R. Milad et al., 2001, Soc. Neurosci., abstract; Robbins, 1990). A related phenomenon, known as renewal, presents a similar challenge. Renewal refers to the reappearance of an extinguished CR when an animal (Bouton and Bolles, 1979a) or human (Rodriguez et al., 1999) is tested in a context different from that in which extinction training took place (Figure 1C). Both spontaneous recovery and renewal indicate that a CS retains its ability to drive a CR following extinction, and must therefore retain at least some of the strength it acquired upon being paired with the US.

In response to findings such as these, an alternative class of theories was developed that proposes that extinction is a form of new learning that counteracts the expression of the CR (Bouton, 1993; Konorski, 1948; Pavlov, 1927; Wagner, 1981). In colloquial terms, these "inhibitory" theories suggest that extinction is characterized by the development of a new connection between the CS and US representations that effectively says "now, in this place, the CS no longer predicts shock." In associative terms, this process is described as the generation and strengthening of a second, inhibitory association between the CS and US representations, which acts in parallel with the excitatory association and directly opposes the tendency of the excitatory association to activate the US representation. Inhibitory theories are able to explain many of the basic behavioral features of extinction when certain additional assumptions are made. The most popular of these has been to propose that inhibitory associations are generally more "labile," or subject to disruption, than are excitatory associations, and hence are lost with the passage of time (spontaneous recovery) or a shift of context (renewal) (Bouton, 1993; Konorski, 1948; Pavlov, 1927).

Regardless of the particulars of the approach taken, the idea that a single CS can control both excitatory and inhibitory tendencies is supported by a wealth of empirical evidence (Barnet and Miller, 1996; Delamater, 1996; Droungas and LoLordo, 1994; Konorski, 1948; Matzel et al., 1988; Rescorla, 1979, 1982, 1993; Tait and Saladin, 1986; Williams and Overmier, 1988; Williams et al., 1992). A particularly direct and impressive demonstration was presented by Tait and Saladin (1986), who trained rabbits with a tone CS and periorbital shock US and examined two different response measures, eyeblink conditioning and lick suppression. The CS and US were presented in a backward conditioning arrangement (i.e., the US temporally preceded the CS), which has been reported by some authors to produce excitatory conditioning to the CS (such that the CS produces a weak CR), and by others to produce inhibitory conditioning to the CS (such that the CS is retarded in its acquisition of a CR when it is subsequently paired with the US in a forward conditioning arrangement) (e.g., Cole and Miller, 1999). The rabbits exhibited more pronounced lick suppression to the tone than did a variety of control groups, suggesting that the tone was excitatory. However, the same rabbits were retarded in their acquisition of a conditioned eyeblink response when they were subsequently exposed to standard forward pairings of the tone and the US, suggesting that the tone was also inhibitory. A single-association model clearly cannot account for the simultaneous display of excitation and inhibition by a single CS; hence, this finding strongly implicates the coexistence of excitatory and inhibitory CS-US associations (for an elegant theoretical account of these data, see Wagner and Brandon, 1989).

Additional support for inhibitory theories of extinction comes from findings that extinguished CSs may act similarly to conditioned inhibitors, or CSs that have es-

tablished a purely inhibitory association with the US. Conditioned inhibitors are most commonly produced by training one CS, A, as a conditioned excitor (i.e., A-US trials), and then presenting the to-be-inhibitory CS, X, in compound with A and omitting the US (i.e., AX-no US trials). The conditioned inhibitor acquires the ability to reduce the magnitude of a CR produced by an excitor (a standard summation test of inhibition), even though the excitor continues to produce the CR when presented by itself (Rescorla, 1969). The conditioned inhibitor is also slowed in its acquisition of a CR if it is subsequently paired with the US (a retardation test of inhibition), as in the study of Tait and Saladin (1986) described above (Rescorla, 1969).

Calton et al. (1996) reported that considerable "overtraining" of extinction (i.e., continuation of extinction training well beyond the point at which the CR has disappeared) produces a CS that acts like a conditioned inhibitor by passing summation and retardation tests (but see Aguado et al., 1998; see also Schachtman et al., 2000). Moreover, the expression of conditioned inhibition may under some circumstances be enhanced by "extinction" (that is, repeated nonreinforced presentations) of the inhibitory CS (Devito and Fowler, 1987; Williams and Overmier, 1988), and inhibitory CSs may behave like extinguished stimuli in exhibiting spontaneous recovery (Hendersen, 1978; Schachtman et al., 2000; Thomas, 1979) and renewal (Bouton and Nelson, 1994; Bouton et al., 1993; Fiori et al., 1994). These parallels between conditioned inhibitors and extinguished CSs are among the strongest evidence to date that extinction may be understood in terms of the development and strengthening of an inhibitory association, which is apparently synonymous with that which develops under more traditional procedures for generating conditioned inhibition (see also Falls and Davis, 1995).

Neural Analysis of Extinction

If the above-described theoretical work on extinction is to be useful in guiding neural studies, then it must be articulated in cellular as opposed to associative terms. Any of a number of possibilities exist for doing so; for example, the "excitatory" and "inhibitory" responses to a CS may be orchestrated by different brain structures (e.g., amygdala versus prefrontal cortex), different populations of cells within a structure (e.g., glutamatergic versus GABAergic neurons), or different types of molecules within individual cells (e.g., kinases versus phosphatases; activators versus repressors of transcription). Of these possibilities, the first two have received the most attention. Attempts to identify an inhibitory brain structure that is sensitive to nonreinforcement and modulates structures essential for CR production have been ongoing for some time, and have variously focused on the hippocampus, lateral septum, sensory cortex, and prefrontal cortex. More recently, investigators have turned their attention to the physiological, pharmacological, and molecular mechanisms of the development and expression of extinction. In what follows, we consider each of these literatures in turn, after first discussing some of the methodological considerations that must be taken into account when evaluating the studies therein.

Definitions and Methodological Considerations

It is important to point out that the term extinction is used in several different ways. Extinction may refer to (1) the experimental procedure used to produce a decrement in the amplitude and frequency of the CR; (2) the decremental effect of this procedure on the CR, which can be measured both at the time the CS is presented in the absence of the US and at a later time; or (3) the hypothesized associative or cellular process responsible for that effect. For the purposes of this review, we will define the experimental procedure as *extinction training*, the decrement in the CR measured during extinction training as *within-session extinction*, and the decrement measured at some interval after extinction training as *extinction retention*. The term *extinction* will be reserved for the process underlying the loss of the CR.

Because extinction may be defined and measured in different ways by different investigators, there are a number of apparent inconsistencies in the cellular literature that may not be as troubling as they appear at first glance. For example, much of the work has evaluated the effect of some treatment on either within-session extinction or extinction retention, and conclusions as to the contribution of the structure or mechanism of interest to a generalized "extinction" process have been drawn accordingly. However, this approach overlooks the fact that a single treatment may produce different or even opposite effects on within-session extinction and extinction retention, which presumably correspond to short-term and long-term extinction memory phases. Likewise, the treatment may have quite different effects on extinction retention at varying post-extinction training intervals. It is extremely important, therefore, to keep this in mind when evaluating extinction research, and to apply the same methodological standards as one would when studying the encoding, consolidation, and expression of acquisition.

A related consideration concerns the time at which a manipulation is applied with respect to the extinction training episode. Studies using lesions induced prior to acquisition, extinction training, or a subsequent retention test have often produced very different results, some of which may be attributable to relatively trivial factors. For example, lesions given prior to Pavlovian excitatory conditioning (pre-acquisition lesions) have been used quite frequently, despite the potential confounding of the effect of the lesion on acquisition with its effect on extinction. Indeed, because "resistance to extinction" is often a sensitive measure of the strength of acquisition (Annau and Kamin, 1961), the possibility of a difference between lesioned and control groups in the rate or asymptote of acquisition—even if this is not readily apparent in the data—complicates the interpretation of any difference between these groups in extinction. Thus in our opinion, it is preferable to first expose animals to CS-US pairings and then perform the manipulation either prior to extinction training (if within-session extinction is the measure of interest) or at various intervals following the completion of training (if extinction retention is to be assessed). Ideally, one would examine both of these phases of extinction learning and memory in separate groups of animals.

Are There Inhibitory Structures in the Brain?

Many of the earliest studies of the neural basis of extinction sought to identify a brain structure serving as the source of the inhibition postulated by psychological theories. An extensive literature exists on the contribution of the hippocampus to extinction and inhibition more generally (for a review, see Schmajuk, 1984), although no consensus was ever reached as to the precise role, if any, played by this structure. The lateral septum has also been the source of interest in this regard (Thomas, 1988), but again a variety of conflicting findings dampened enthusiasm for the hypothesis that the septum may act to inhibit conditioned emotional responses controlled by other brain regions. Nevertheless, this general strategy continues to be pursued today, with contemporary studies focusing on the cerebral cortex—specifically, the sensory and prefrontal cortices—and the extinction of conditioned fear responses.

Sensory Cortex. It is well known that plasticity may be induced in sensory cortices in Pavlovian conditioning situations (for a review, see Weinberger, 1998a). Although the changes associated with exposure to CS-US pairings are by far the best characterized, there is a small literature documenting cortical plasticity during extinction training (for a review, see Falls and Davis, 1995). Some authors have found that acquisition-related cortical plasticity is reversed with nonreinforced CS exposure (Diamond and Weinberger, 1986; Gassanov et al., 1985) while others have reported little or no change (Brons and Woody, 1980; Quirk et al., 1997).

Quirk et al. (1997; see also Armony et al., 1998), for example, hypothesized that the auditory cortex and its projections to the lateral amygdala may be a site of long-term retention of fear memory, given their findings that the cortex exhibits extinction-resistant plasticity over the course of multiple nonreinforced CS trials whereas the lateral amygdala generally does not (but see Repa et al., 2001). Moreover, they suggested that an interplay between the two structures is necessary for the development of extinction, such that the cortex directs the reshaping of amygdalar plasticity during nonreinforced CS trials while the amygdala maintains the extinction-resistant plasticity of the cortex.

Two studies (LeDoux et al., 1989; Teich et al., 1989) provided provisional support for this notion by demonstrating that sensory cortical lesions retard extinction (Table 1). A limitation of both studies, however, lies in the fact that the lesions were induced prior to acquisition and the role of the cortex in within-session extinction and extinction retention was not dissociated. A study conducted in our laboratory (Falls and Davis, 1993) using both pre- and post-acquisition lesions failed to observe any effect of complete lesions of visual cortex on either within-session extinction or extinction retention to a visual CS (Table 1). Although there are many procedural differences between the two sets of studies, the findings clearly indicate that extinction can proceed normally in the absence of sensory cortex under some circumstances.

Prefrontal Cortex. In their discussion of the putative role of sensory cortex in extinction, Quirk et al. (1997; see also LeDoux et al., 1989) emphasized that the sensory cortex likely feeds extinction-related information forward to higher order cortical areas, such as the cingulate, subiculum, and/or prefrontal cortex, for additional processing and more finely tuned behavioral control. By this account, lesions of these higher order areas should interfere with extinction.

The prefrontal cortex has been the subject of much investigation with respect to extinction and response perseveration; however, an understanding of its role remains elusive. One complication has stemmed from the fact that lesions of different subregions of the prefrontal cortex have led to widely differing effects on extinction as well as initial acquisition (Morgan and LeDoux, 1995, 1999; Quirk et al., 2000). Moreover, some of the lesion effects have not been replicated despite the use of nominally identical experimental protocols (Table 1). For example, Morgan et al. (1993) reported that medial prefrontal cortical lesions had no effect on initial acquisition of fear conditioning but retarded subsequent extinction to a tone (but not a contextual CS), while very similar studies conducted by Gewirtz et al. (1997) and Quirk et al. (2000) found no difference between lesioned and control groups in the rate or asymptote of within-session extinction (see also Vouimba et al., 2000). Gewirtz et al. (1997) also found no difference between groups in extinction retention, whereas Quirk et al. (2000) reported increased spontaneous recovery (i.e., impaired extinction retention) in lesioned animals (see also K. Lebron and G.J. Quirk, 2001, Soc. Neurosci., abstract). Finally, Morrow et al. (1999) reported that dopamine depletion within the prefrontal cortex impaired extinction when a high, but not a low, shock intensity had been used in acquisition.

Despite these inconsistencies in the lesion literature, the prefrontal cortex continues to attract a great deal of attention as a putative locus of extinction-related plasticity, perhaps because studies employing other methodologies, such as imaging and single unit recording, have tended to provide more unilateral support for this notion (e.g, C.J. Cannistraci et al., 2001, Soc. Neurosci., abstract; Herry and Garcia, 2002). For example, Milad and Quirk (2002) recorded single unit activity in the rat infralimbic cortex during habituation, acquisition, extinction training, and retention test phases of a Pavlovian fear conditioning task, and found that cells in this area (but not in the prelimbic or medial orbital cortex) were responsive to the tone CS during the retention test, but not other phases of conditioning. Moreover, the degree to which the cells were tone responsive was inversely correlated with spontaneous recovery of freezing, such that unit responses to the tone tended to be more robust in rats exhibiting less freezing in test (i.e., better retention of extinction). Additional experiments attempted to establish a causal, rather than a correlational, role for the infralimbic cortex in extinction by electrically stimulating the cortex during extinction training. Rats receiving stimulation during nonreinforced tone presentations showed less freezing in the extinction training session and in a subsequent retention test than did rats for which tone presentations and stimulation were unpaired or rats receiving tone presentations in the absence of stimulation, suggesting that activity in this area does indeed contribute to CR suppression in extinction.

Studies such as this one clearly indicate that additional work is needed to clarify the role of the prefrontal cortex and its various subregions in the development

Table 1. Effect of Sensory Cortex and Prefrontal Cortex Lesions on Extinction

	Species	Type of Conditioning	Lesion			Effect		Reference
			Type	Structure	Time	Within-Session Ext	Ext Retention	
Sensory Cortex	Rat	CER	Aspiration	Visual ctx	pre-acq	Impaired		LeDoux et al. (1989)
	Rabbit	HR conditioning	Electrolytic	Auditory ctx	pre-acq	Impaired[a]		Teich et al. (1989)
	Rat	Pavlovian FC	Aspiration	Visual ctx	pre-acq	No effect	No effect	Falls and Davis (1993)
					post-ext		No effect	
Prefrontal Cortex	Rat	Pavlovian FC	Electrolytic	dmPFC	pre-acq	No effect[a,b]		Morgan and LeDoux (1995)
	Rat	Pavlovian FC	Electrolytic	vlPFC	pre-acq	No effect[a]		Morgan and LeDoux (1999)
	Rat	Pavlovian FC	Electrolytic	vmPFC	pre-acq	Impaired (tone)[a] No effect (context)[a]		Morgan et al. (1993)
	Rat	Pavlovian FC	Electrolytic	rvmPFC	pre-acq	No effect	No effect	Quirk et al. (2000)
				vmPFC	pre-acq	No effect	Impaired	
	Rat	Pavlovian FC	Electrolytic	mPFC	pre-acq	No effect	No effect	Gewirtz et al. (1997)
					pre-ext	No effect	No effect	
	Mouse	Pavlovian FC	Electrolytic	dmPFC	pre-ext	No effect[a]		Vouimba et al. (2000)
	Rat	Pavlovian FC	6-OHDA	mPFC	pre-acq	Impaired (0.8 mA)		Morrow et al. (1999)
					pre-acq	No effect (0.4 mA)		
					pre-ext	Impaired (0.8 mA)		

[a] Indicates that within-session extinction and extinction retention were not dissociated, as in a study employing days to criterion as a measure of extinction.

[b] In this study, the lesion was associated with a general increase in fear in the acquisition and extinction phases of the experiment. Thus, while the lesioned animals did require a greater number of days of extinction training to reach an extinction criterion, they also required fewer days of acquisition training to acquire the CR.

Abbreviations: acq, acquisition; CER, conditioned emotional response; CTA, conditioned taste aversion; ctx, cortex; d, dorsal; ext, extinction; FC, fear conditioning; HR, heart rate; l, lateral; m, medial; PFC, prefrontal cortex; r, rostral; v, ventral.

Table 2. Contribution of Neurotransmitter and Second Messenger Systems to Extinction

			Drug Administration						
							Effect		
	Species	Type of Conditioning	Target	Drug	Site	Time	Within-Session Ext	Ext Retention	Reference
Glutamate	Rat	Pavlovian FC	NMDA receptors	AP5	Amygdala	pre-ext		Impaired	Falls et al. (1992)
			AMPA receptors	CNQX	Amygdala	pre-ext		No effect	
	Rat	Pavlovian FC		DCS	Systemic	pre-ext		Facilitated	Walker et al. (2002)
					Amygdala	pre-ext		Facilitated	
				DCS + (±)HA966	Systemic	pre-ext		No effect	
	Rat	Pavlovian FC	NMDA receptors	CPP	Systemic	pre-ext	No effect	Impaired (24 hr test)	Santini et al. (2001)
						pre-ext	No effect	No effect (48 hr test)	
						24 hr post-ext		No effect (48 hr test)	
						pre-ext and 24 hr post-ext	No effect	Impaired (48 hr test)	
	Mouse	Pavlovian FC	LVGCCs	Nifedipine, nimodipine	Systemic	pre-ext	Impaired	Impaired	Cain et al. (2002)
						pre-test		No effect	
						pre-ext and pre-test	Impaired	Impaired	
	Rat	CTA	NMDA receptors	AP5	Insular ctx	pre-ext		No effect[a]	Berman and Dudai (2001)
GABA	Mouse	Avoidance	$GABA_A$ receptors	Picrotoxin	Systemic	immed post-ext		Facilitated	McGaugh et al. (1990)
						2 hr post-ext		No effect	
	Rat	Avoidance	GABA/BZD rec complex	Diazepam	Systemic	pre-ext	No effect	Impaired	Pereira et al. (1989)
	Rat	Pavlovian FC	GABA/BZD rec complex	FG7142	Systemic	pre-ext	Impaired	Impaired	Harris and Westbrook (1998)
						pre-ext and pre-test	Impaired	Impaired	
						pre-test (ext context)		Impaired	
						pre-test (novel context)		No effect	
β-*Adrenergic Transmission*	Rat	Pavlovian FC	β-adrenoreceptors	Propranolol	Systemic	pre-ext		Impaired	Cain and Barad (2001)
						pre-ext and pre-test		Impaired	
			α2 autoreceptors	Yohimbine	Systemic	pre-ext		Facilitated	
	Rat	CTA	β-adrenoreceptors	Propranolol	Insular ctx	pre-ext		Impaired[a]	Berman and Dudai (2001)
Dopamine	Rat	Pavlovian FC	DA reuptake	Cocaine	Systemic	pre-ext	No effect	Impaired	Willick and Kokkinidis (1995)
						pre-ext and pre-test	No effect	Impaired	
	Rat	Pavlovian FC	DA vesicular transporter	Amphetamine	Systemic	pre-ext		Impaired	Borowski and Kokkinidis (1998)
			D1 receptors	SKF 38393	Systemic	pre-ext		Impaired	
					Systemic	pre-test		Impaired	
			DA reuptake	Cocaine	Systemic	pre-test		Impaired	
	Rat	Pavlovian FC	D2 receptors	Quinpirole	Systemic	pre-ext		Impaired	Nader and LeDoux (1999)
Acetylcholine	Rat	Avoidance	Muscarinic receptors	Scopolamine	Systemic	pre-test		Impaired	Prado-Alcala et al. (1994)
	Rat	CTA	Muscarinic receptors	Scopolamine	Insular ctx	pre-ext		No effect[a]	Berman and Dudai (2001)
Endogenous Cannabinoids	Mouse	Pavlovian FC	Cannabinoid rec 1 (CB1)	SR141716A	Systemic	pre-acq	No effect	No effect	Marsicano et al. (2002)
						pre-ext	Impaired	Impaired	
						pre-test		No effect	

(*continued*)

Table 2. Continued

	Species	Type of Conditioning	Drug Administration: Target	Drug	Site	Time	Effect: Within-Session Ext	Effect: Ext Retention	Reference
Intracellular Signaling	Rat	Pavlovian FC	MAPK	PD98059	Amygdala	pre-ext		Impaired	Lu et al. (2001)
					Hippocampus	pre-ext		No effect	
	Rat	Avoidance	MAPK	PD98059	Hippocampus	pre-ext		Impaired	Szapiro et al. (2002)
			CaMKII	KN-62	Hippocampus	pre-ext		Impaired	
			PKA	Rp-cAMPs	Hippocampus	pre-ext		Impaired	
	Rat	CTA	MAPK	PD98059	Insular ctx	pre-ext	No effect[a]		Berman and Dudai (2001)
Protein Synthesis	Rat	CTA	Translation	Anisomycin	Insular ctx	pre-ext	Impaired[a]		Berman and Dudai (2001)
	Rat	CTA	Translation	Anisomycin	Amygdala	pre-ext	No effect[a]		Berman et al. (2001)
	Mouse	Avoidance	Translation	Anisomycin	Systemic	pre-ext		Impaired	Flood et al. (1977)
						post-ext		Impaired	
	Rat	Avoidance	Translation	Anisomycin	Hippocampus	pre-ext		Impaired	Vianna et al. (2001)
	Mouse	Pavlovian FC	Translation	Anisomycin	Systemic	pre-ext	No effect	No effect	Lattal and Abel (2001)
		Water maze	Translation	Anisomycin	Systemic	pre-ext	No effect	No effect	

[a]Indicates that within-session extinction and extinction retention were not dissociated, as in a study employing days to criterion as a measure of extinction.

Abbreviations: acq, acquisition; CTA, conditioned taste aversion; ctx, cortex; DA, dopamine; ext, extinction; FC, fear conditioning; hr, hours; immed, immediately; rec, receptor.

and retention of extinction within different behavioral paradigms. Because the prefrontal cortex is so poorly represented in rodents (Preuss, 1995), it may be preferable to use nonhuman primates in analyzing its role.

On the whole, the search for an inhibitory brain structure has not been very fruitful, as no one structure has emerged whose putative role in extinction has not been met with substantial empirical challenges. It is, perhaps, overly simplistic to assume that a brain structure might serve such a generalized role as behavioral inhibition, even with respect to a well-defined form of learning whose underlying circuitry is relatively circumscribed (but see Medina et al., 2001). Perhaps because of this, neuroscientists have increasingly turned their attention to a cellular and molecular analysis of extinction.

What Is the Nature of the Plasticity Underlying Extinction?

Cellular and molecular analyses hold considerable promise for elucidating the mechanisms of extinction, just as they have for acquisition, but present their own methodological difficulties. In the absence of a defined anatomical locus of extinction, many investigators have resorted to the use of systemic manipulations whose insights into the essential mechanisms involved are relatively limited. Nevertheless, some investigators have capitalized on well-characterized paradigms, such as fear conditioning, and have found that targeted (e.g., intra-amygdalar) treatments that affect acquisition often affect extinction as well. In what follows, we consider the evidence for the involvement of a variety of neurotransmitter and second messenger systems in extinction, which has emerged primarily from studies of fear conditioning and conditioned taste aversion.

Glutamate. A large body of literature suggests that glutamate, acting at ionotropic (AMPA, NMDA) and metabotropic (mGluRs) receptors, is critically involved in learning and memory (for a review, see Walker and Davis, 2002) and in forms of synaptic plasticity believed to underlie these processes (e.g., long-term potentiation) (Kullmann et al., 2000; Watkins and Collingridge, 1989). For example, Miserendino and colleagues (1990) reported that pre-training, intra-amygdala infusions of the NMDA receptor antagonists AP5 and AP7 blocked excitatory fear conditioning to a visual CS as assessed with fear-potentiated startle. This primary finding has since been replicated using auditory (Campeau and Davis, 1992) and olfactory cues (G.Y. Paschall et al., 2001, Soc. Neurosci., abstract) as conditioned fear stimuli, second-order reinforcers as the aversive US (Gewirtz and Davis, 1997), conditioned freezing as an alternative measure of fear (Fanselow and Kim, 1994), and most recently using ifenprodil—a compound that interferes specifically with the NMDA receptor's 2B subunit—to disrupt NMDA receptor function (Rodrigues et al., 2001).

In light of the evidence that extinction is a form of new learning, Falls et al. (1992) investigated the possibility that fear extinction might also recruit amygdalar NMDA receptors. Rats were first exposed to a standard fear conditioning protocol (10 pairings of a light CS and footshock US on each of two days). Several days later, separate groups of rats received intra-amygdalar infusions of different concentrations of AP5 immediately prior to extinction training, which took place on each of two days and consisted of 30 presentations of the light in the absence of shock. Extinction retention was then

tested the following day. AP5 produced a dose-dependent blockade of extinction (Table 2) that could not be attributed to antagonism of NMDA receptors outside of the amygdala, damage to the amygdalar complex, or an impairment of sensory transmission during extinction training. Interestingly, pre-extinction training infusions of the AMPA receptor antagonist CNQX were without effect. A similar blockade of extinction of contextual fear conditioning, inhibitory avoidance, and eyeblink conditioning has since been reported with administration of AP5 and MK-801 (Kehoe et al., 1996; Lee and Kim, 1998; Szapiro et al., 2002), and additional studies have confirmed that these effects cannot be explained by state dependency (Baker and Azorlosa, 1996; Cox and Westbrook, 1994).

An implication of this work is that extinction might actually be facilitated if it were possible to enhance the functioning of the NMDA receptor. Although competitive NMDA receptor agonists are associated with neurotoxicity due to unregulated calcium entry, other drugs that influence NMDA receptor function have a more favorable profile. One such compound is D-cycloserine (DCS), a partial agonist at the strychnine-insensitive glycine binding site on the NMDA receptor complex. In a study that was similarly designed to that of Falls et al. (1992), we (Walker et al., 2002) found that DCS facilitated extinction in a dose-dependent manner following either systemic administration or direct infusion into the amygdala, but had no effect in animals that did not receive extinction training (Table 2). The effect of DCS was completely blocked by co-administration of the glycine binding site antagonist (±)HA966 at a dose that by itself did not block extinction (although higher doses of this antagonist did block extinction). In a similar vein, Tang et al. (1999) have demonstrated that transgenic mice overexpressing the NMDAR2B subunit exhibit facilitated acquisition and extinction of conditioned freezing.

It has been suggested that the involvement of NMDA receptors in fear extinction is time dependent and restricted to the formation of long-term as opposed to short-term extinction memory. Santini et al. (2001) reported relatively little impairment in the expression of freezing or conditioned suppression of bar pressing in rats administered the NMDA receptor antagonist CPP prior to extinction training, and little difference between CPP- and vehicle-treated groups in either the rate or extent of within-session extinction (Table 2). By contrast, extinction retention as assessed 24 hr later was severely impaired, consistent with the findings of previous studies. Interestingly, the deficit was no longer evident when the retention test was conducted 48 hr post-extinction training. Santini et al. (2001) interpreted this finding in terms of a delayed, NMDA receptor-dependent consolidation process that permitted the impaired extinction memory of CPP-treated rats to be reconstructed. Indeed, when CPP was administered both prior to and 24 hr after extinction training, and extinction retention was assessed 48 hr post-extinction training, the CPP-treated rats were again impaired.

A shift from NMDA receptor-independent short-term memory formation to NMDA receptor-dependent consolidation processes has been reported in other learning paradigms as well (Kentros et al., 1998; Shimizu et al., 2000), although the molecular mechanisms whereby the short-term plasticity is orchestrated in these cases remain poorly understood. In fear extinction, there is some evidence that L type voltage-gated calcium channels (LVGCCs), which have been implicated in an NMDA receptor-independent form of amygdalar LTP (Weisskopf et al., 1999), may be selectively involved in within-session extinction. Cain et al. (2002) examined the effect of the LVGCC blockers nifedipine and nimodepine on the acquisition and extinction of fear conditioning, and found that both within-session extinction and extinction retention were dose-dependently impaired by pre-extinction training, systemic administration of either drug (Table 2), whereas acquisition was unaffected by similar drug administrations prior to CS-US pairings (but see Bauer et al., 2002). Extinction retention was not affected when either drug was administered prior to test and extinction training had been conducted drug-free, and additional controls indicated that the impairment associated with pre-extinction training drug administration could not be explained by state dependency. Thus, it is possible that extinction initially recruits LVGCCs but later requires additional, NMDA receptor-dependent processes for the consolidation and/or maintenance of extinction memory.

Despite this substantial body of evidence for the involvement of NMDA receptors in fear extinction, there is evidence that NMDA receptor dependence is not characteristic of extinction within all learning paradigms. Berman and Dudai (2001) reported that infusion of AP5 into the insular cortex did not block extinction of a conditioned taste aversion (CTA), despite the fact that similar intra-insular cortex infusions of AP5 prior to saccharin-$LiCl^-$ pairings do impair CTA acquisition (Rosenblum et al., 1997).

GABA. Because extinction reflects the operation of an active inhibitory process, it is possible that GABA, the major inhibitory neurotransmitter in the mammalian brain, serves as the source of that inhibition via its actions at ionotropic ($GABA_A$) and metabotropic ($GABA_B$) receptors. It has been argued for some time that GABA is involved in the consolidation of excitatory learning, as GABA agonists disrupt (e.g, Castellano et al., 1989) and GABA antagonists facilitate (e.g., Yonkov and Georgiev, 1985) the acquisition of inhibitory avoidance. More recently, these findings have been extended to inhibitory fear learning as well. For example, McGaugh et al. (1990) reported that systemic administration of the GABA antagonist picrotoxin prior to extinction training in an active avoidance paradigm enhanced extinction retention in a test conducted 24 hr later (Table 2). The facilitatory effect of picrotoxin was specific to animals receiving extinction training, as there was no difference in test performance between nonextingushed, vehicle-treated and nonextinguished, drug-treated groups. In a similarly designed study, Pereira et al. (1989) found that systemic, pre-extinction training administration of diazepam, a benzodiazepine that acts at the GABA receptor complex to increase Cl^- flux, had no effect on performance within an extinction session but was associated with impaired retention in a test conducted 24 hr later. It has been suggested that the apparent effects of GABAergic compounds on extinction retention actually reflect state dependency (Bouton et al., 1990); however, others have

challenged this conclusion (Castellano and McGaugh, 1989, 1990).

In addition to its putative role in the consolidation of inhibitory fear learning, GABA has also been implicated in the expression of extinction. Harris and Westbrook (1998) demonstrated that systemic administration of FG7142, an inverse agonist of the $GABA_A$ receptor, dose-dependently impaired within-session extinction of freezing and, when administered prior to test, blocked extinction retention in the context in which extinction training had been given but had no effect on performance in a novel context (Table 2). That is, vehicle-treated but not FG7142-treated animals exhibited extinction retention when tested in the extinction training context, but both groups showed a similar renewal of the CR when tested in a novel context. This is significant in that it indicates that FG7142 did not nonspecifically increase activity levels or the frequency of the CR, but rather "selectively reversed the component of extinction linked to the environmental context where extinction training had occurred" (Harris and Westbrook, 1998, pp.113). Separate experiments indicated that the disruption of extinction by FG7142 was not due to state dependency. Thus, it appears that GABA-mediated inhibition is indeed involved in the expression of extinction, and furthermore that CS-induced GABA release is itself modulated by other systems that are responsive to factors such as contextual cues.

When taken together with the findings of McGaugh et al. (1990) and Pereira et al. (1989), these results suggest that manipulations of GABA transmission may have different effects when applied prior to extinction training versus the extinction retention test. One possible explanation for this set of observations is that the development of the plasticity associated with extinction depends not on GABA but on some other neurotransmitter(s), such as glutamate. It seems likely that extinction is associated with a strengthening of connections between sensory pathways transmitting CS-related information and a population of GABAergic cells mediating extinction performance. If so, then GABA release during extinction training would be expected to hinder extinction since the development of neural plasticity requires significant excitation of target cells (i.e., membrane depolarization, activation of NMDA receptors or LVGCCs, calcium entry, etc.), which GABA release would counteract. Thus it follows that GABA agonists will retard, and GABA antagonists will facilitate, extinction if they are present during the critical period of plasticity. By contrast, when extinction has already consolidated and retention is assessed, GABA release would inhibit the firing of other, presumably glutamatergic neurons, which are themselves responsible for the generation of a CR. Thus, pre-test administrations of GABA agonists should facilitate, and GABA antagonists should impair, extinction retention. This scenario has a certain amount of intuitive appeal and accounts for much of the data; however, it should be noted that the finding of Harris and Westbrook (1998) that the $GABA_A$ inverse agonist FG7142 was associated with an impairment of within-session extinction is a significant exception.

β-Adrenergic Transmission. It is well established that the strength of a memory may be modulated by any of a number of pharmacological agents, among the most extensively studied of which are compounds affecting β-adrenergic transmission (for reviews, see Cahill and McGaugh, 1996; McGaugh, 2000). Generally, adrenergic agonists administered either systemically or directly into the amygdala facilitate memory for fear conditioning and other learning paradigms, whereas adrenergic antagonists block this facilitatory effect. These effects are evident when injections are given prior to or immediately following training, but not with extended training-to-injection intervals, suggesting that these compounds act on memory consolidation as opposed to encoding or retrieval.

Consistent with the idea that inhibitory learning involves a similar consolidation process, there is some evidence that extinction memory may be modulated in a comparable manner by the same agents (Table 2). C.K. Cain and M.G. Barad (2001, Soc. Neurosci., abstract), for example, demonstrated that extinction of contextual fear conditioning is facilitated by yohimbine (an α2 autoreceptor antagonist) and impaired by propranolol (a β-adrenoreceptor antagonist) given immediately prior to extinction training, as assessed in tests conducted 24 and 48 hr later in the absence and presence of the drug, respectively. Similarly, Berman and Dudai (2001) found that extinction of conditioned taste aversion, like acquisition, was blocked by pre-extinction training, intra-insular cortex infusions of propranolol.

Dopamine. While less extensive than the literature on β-adrenergic transmission, there is evidence to suggest that dopamine, particularly within the prefrontal cortex, also modulates memory processes (Williams and Goldman-Rakic, 1995). Dopaminergic transmission has also been implicated in fear conditioning, such that D1 or D2 receptor antagonists administered either systemically (Greba and Kokkinidis, 2000) or directly into the amygdala (Greba et al., 2001; Greba and Kokkinidis, 2000; Guarraci et al., 2000, 1999), or lesions of midbrain dopamine systems (Borowski and Kokkinidis, 1996), impair the acquisition and expression of fear. Similarly, dopamine agonists (Borowski and Kokkinidis, 1994) or electrical stimulation of the ventral tegmental area (Borowski and Kokkinidis, 1996) facilitate these processes.

Several studies have implicated dopaminergic transmission in fear extinction. Willick and Kokkinidis (1995) reported that systemic injections of cocaine (which blocks dopamine reuptake) had no effect on within-session extinction but impaired extinction retention in a Pavlovian fear conditioning paradigm, an effect that could not be explained by state dependency. A subsequent study extended this finding to amphetamine (which increases dopamine release through its interaction with synaptic vesicles) and the specific D1 agonist SKF38393, and further indicated that cocaine and SKF38393 impair extinction retention when administered prior to test (Borowski and Kokkinidis, 1998). Similarly, Nader and LeDoux (1999) reported that systemic, pre-extinction training administrations of the D2 agonist quinpirole produced an impairment of extinction as tested drug-free 24 hr later, although possible state-dependent effects cannot be ruled out in this study. Finally, El-Ghundi et al. (2001) found that D1 receptor knockout mice were impaired in extinction retention in an inhibitory avoidance paradigm, as assessed at several time points post-extinction training.

As previously described, 6-OHDA lesions of monoaminergic (primarily dopaminergic) fibers of the medial prefrontal cortex impair within-session extinction of fear conditioned with strong shocks (Morrow et al., 1999). These data might at first sight appear to be inconsistent with the blockade of extinction seen after systemic administration of dopamine agonists; however, the two sets of studies differ in that the effect of the lesion was evaluated in within-session extinction whereas the systemic drug effects were observed in extinction retention. Thus, it may be possible that short- and long-term extinction involve different receptor mechanisms (cf. Santini et al., 2001). Furthermore, depletion of dopamine in medial prefrontal cortex may enhance responses of subcortical dopamine neurons. Although Morrow et al. (1999) found no effect of the lesions on dopamine metabolism in the nucleus accumbens during extinction, it is possible that the lesions still elevated dopamine release in other structures, such as the basolateral complex of the amygdala (Deutch et al., 1990; King et al., 1997). Thus, treatments that increase dopamine transmission in the amygdala either directly (e.g., systemic administration of dopamine agonists) or indirectly (e.g., depletion of prefrontal dopamine) may appear to block extinction via an increase in conditioned fear.

Acetylcholine. There is a very large literature on the involvement of cholinergic systems in learning, memory, and the cognitive impairments associated with aging and Alzheimer's disease (e.g., Gallagher and Colombo, 1995). A number of studies have examined the effects of manipulations of cholinergic transmission on performance in Pavlovian conditioning tasks and on physiological correlates of learning, and generally have reported that administration of muscarinic antagonists or lesions of cholinergic nuclei produce pronounced deficits in CR acquisition and expression (e.g., Han et al., 1999), whereas administration of acetylcholinesterase inhibitors or stimulation of the nucleus basalis facilitate these processes (e.g., Weinberger, 1998b).

There is a small, somewhat dated literature on the involvement of acetylcholine in extinction in instrumental conditioning tasks, which we will not consider further (for a review, see Mason, 1983). More recent studies have examined the effect of the muscarinic antagonist scopolamine on extinction of fear conditioning and conditioned taste aversion. Prado-Alcalá et al. (1994) found that systemic, pre-test administration of scopolamine impaired extinction retention in a passive avoidance paradigm following extensive extinction training, an effect that subsequently was found to vary in magnitude with the dose of scopolamine and the length of the extinction training to retention test interval (Roldan et al., 2001). The selective impairment of extinction in these studies is significant in that it indicates that manipulations of cholinergic systems may spare avoidance retention under some circumstances (cf. Duran-Arevalo et al., 1990).

By contrast, Berman and Dudai (2001) reported that pre-extinction training infusions of scopolamine into the insular cortex had no effect on extinction of conditioned taste aversion, despite the involvement of cholinergic transmission in CR acquisition in this paradigm (Naor and Dudai, 1996).

Endogenous Cannabinoids. Among the most recent additions to the extinction literature is a study by Marsicano et al. (2002) examining the contribution of endogenous cannabinoid ("endocannabinoid") release and CB1 cannabinoid receptor activation to fear extinction. Because cannabinoid receptors are located within areas of the brain involved in learning and memory, such as the amygdala, and endocannabinoids have been implicated in modulation of neurotransmitter release (Di Marzo et al., 1998) and memory formation (Hampson and Deadwyler, 1998; Reibaud et al., 1999), Marsicano et al. examined the involvement of this system in the acquisition, retention, and extinction of Pavlovian fear conditioning in mice.

CB1 receptor knockout mice were normal in the acquisition and retention of fear to a tone that was paired with footshock, but were impaired in extinction when the tone was repeatedly nonreinforced over several test sessions. Fine-grained analysis of freezing across the duration of the tone presentations revealed that the knockouts did not differ from wild-type littermate controls in spontaneous recovery, suggesting that the CB1 receptor is preferentially involved in within-session extinction. Likewise, animals receiving systemic injections of the CB1 receptor antagonist SR141716A prior to acquisition or an extinction retention test were not different from vehicle-treated controls, whereas animals treated with the antagonist prior to extinction training were impaired in both within-session extinction and extinction retention (Table 2).

The involvement of the CB1 receptor in extinction suggests that endocannabinoid release is upregulated during or shortly following extinction training. Marsicano et al. (2002) quantified endocannabinoid levels in punches of the basolateral amygdala complex and prefrontal cortex in mice that had received either paired presentations of a tone and footshock (paired-extinguished group) or unpaired presentations of these stimuli (unpaired-extinguished group) and were sacrificed immediately following extinction training. Additional animals received paired tone-shock presentations but were not re-exposed to the tone (paired-nonextinguished group). The concentrations of two major endocannabinoids, anandamide (AEA) and 2-arachidonylglycerol (2-DG), were significantly higher in the basolateral amygdala of the paired-extinguished group than the other two groups, whereas concentrations did not differ among the groups in the prefrontal cortex.

In vitro electrophysiological analysis of the basolateral amygdala complex revealed few differences in input resistance, resting membrane potential, or long-term potentiation (LTP) between knockout or SR171416A-treated animals and wild-type or vehicle-treated controls. However, slices from knockout or antagonist-treated mice did exhibit an impairment in long-term depression of $GABA_A$-mediated IPSCs (LTD_i) following low-frequency stimulation of the lateral amygdala close to the external capsule. Marsicano et al. (2002) interpreted this finding to indicate that CB1-mediated inhibition of GABAergic networks in the amygdala leads to a potentiation of responding in glutamatergic principal neurons, thereby contributing to suppression of the behavioral response. However, it is not clear at the present time how to reconcile this hypothesis with findings from other studies implicating GABAergic transmission in the development

and expression of fear extinction (Harris and Westbrook, 1998; McGaugh et al., 1990; Pereira et al., 1989).

ACTH and Vasopressin. Work by DeWied, Van Wiersima, Izquierdo, Richardson, and their co-workers indicates that administration of various peptides such as adrenocorticotropic hormone (ACTH) or vasopressin either before of after extinction training attenuates subsequent extinction performance. Because most of these experiments involve active avoidance, these very interesting observations will not be reviewed here (for a review, see Falls and Davis, 1995).

Intracellular Signaling. The involvement of NMDA receptors and LVGCCs in fear extinction suggests that second messenger systems activated by increases in intracellular calcium concentrations may be critical to the plasticity underlying this form of learning. Among the many calcium-responsive molecules are the kinases CaMKII, PKA, and MAPK, each of which is thought to play a key role in LTP and memory formation (for reviews, see Dudai, 2002; Schafe et al., 2001).

Evidence for the involvement of CaMKII, PKA, and MAPK in fear extinction is provided by two recent studies examining fear-potentiated startle and inhibitory avoidance, respectively (Table 2). Lu et al. (2001) reported that pre-extinction training, intra-amygdala infusions of the MAPK inhibitor PD98059 blocked extinction of fear-potentiated startle as assessed in a retention test conducted 24 hr later. The effect was site specific (i.e., not seen with localized infusions into the hippocampus) and not attributable to amygdalar damage or state-dependent learning. Szapiro et al. (2002) also reported an impairment of extinction of inhibitory avoidance with pre- or post-extinction training, intra-hippocampal infusions of PD98059, as well as (in separate groups) the CaMKII inhibitor KN-62 and the PKA inhibitor Rp-cAMPs. In this study, rats were given a single acquisition trial and then, beginning 24 hr later, were subjected to a single extinction trial on each of four successive days. Drug infusions were restricted to the first extinction session and yet the impairment of extinction was evident throughout testing.

The MAPK cascade has also been implicated in the formation of long-term, but not short-term, memory for conditioned taste aversion (Berman et al., 1998). MAPK does not seem to be importantly involved in extinction in this paradigm, however, as pre-extinction training, intra-insular cortex infusions of PD98059 are without effect (Berman and Dudai, 2001). This dissociation is perhaps not surprising, as it will be recalled that NMDA receptors similarly have been implicated in the acquisition but not extinction of a conditioned taste aversion (Berman and Dudai, 2001).

Protein Synthesis. Because extinction is a form of new learning, it might be expected to be protein synthesis dependent (Davis and Squire, 1984). Indeed, the fact that fear extinction is dependent on PKA, MAPK, and CaMKII, each of which participates in second messenger cascades culminating in gene transcription, would seem to add support to this hypothesis. Nevertheless, the few studies that have examined the effects of protein synthesis inhibitors on extinction have produced widely varying results.

Berman and Dudai (2001), for example, reported that pre-extinction training, intra-insular cortex infusions of the protein synthesis inhibitor anisomycin impaired extinction of conditioned taste aversion. By contrast, pre-extinction training infusions of anisomycin into the central nucleus of the amygdala were without effect (D.E. Berman et al., 2001, Soc. Neurosci., abstract). This latter finding is particularly surprising since anisomycin impairs retention of conditioned taste aversion acquisition when infused into either site (Rosenblum et al., 1993). Thus, the protein synthesis dependence of CTA extinction appears to vary by region.

The extinction of both active and inhibitory avoidance, by contrast, seems to be clearly dependent on protein synthesis. Flood et al. (1977), for example, reported a disruption of extinction retention within an active avoidance paradigm when anisomycin was administered either prior to or shortly following extinction training. Likewise, Vianna et al. (2001) found that pre-extinction training infusions of anisomycin into CA1 were associated with an impairment of extinction retention in an inhibitory avoidance paradigm in each of several test sessions conducted at 24 hr intervals, drug-free (Table 2).

In still other learning paradigms, there is evidence that protein synthesis is necessary for neither within-session extinction nor extinction retention. Lattal and Abel (2001) examined the effect of pre- and post-extinction training systemic anisomycin administration within contextual fear conditioning and Morris water maze paradigms. In neither task did anisomycin have an effect on within-session extinction or performance in a subsequent retention test (Table 2). By contrast, pre-training administration of anisomycin severely disrupted the acquisition of both tasks.

The diversity of these findings is quite surprising and may indicate that the molecular mechanisms of extinction differ among behavioral paradigms and, in some instances, diverge from those underlying acquisition. However, an additional complication within this literature has arisen quite recently with the report of Nader et al. (2000) that a "reactivated" fear memory is sensitive to intra-amygdalar, post-reactivation infusions of anisomycin. In this study, the reactivation procedure involved exposure to a tone in the absence of shock (i.e., an extinction trial) 24 hr after an initial tone-shock pairing. Rats infused with anisomycin immediately after, but not 6 hr after, the nonreinforced tone presentation showed little freezing to the tone in a test session conducted 24 hr later. This is quite the contrary of the finding of other investigators, such as Vianna et al. (2001), that retention of acquisition is *facilitated* in rats treated with anisomycin immediately following nonreinforced CS or context exposure (Figure 2). Whereas Nader et al. (2000) framed their findings in terms of a "reconsolidation" process initiated by reactivation of the initial memory, during which time the memory is sensitive to disruption by amnestic agents, Vianna et al. (2001) came to the very different conclusion that anisomycin blocked the consolidation of extinction without affecting the already consolidated acquisition memory.

It is not at all clear why such apparently similar experimental protocols as those employed in the Nader et al. (2000) and Vianna et al. (2001) studies should produce such opposite results. Although it could be argued that the difference in the nature of the learning involved (Pav-

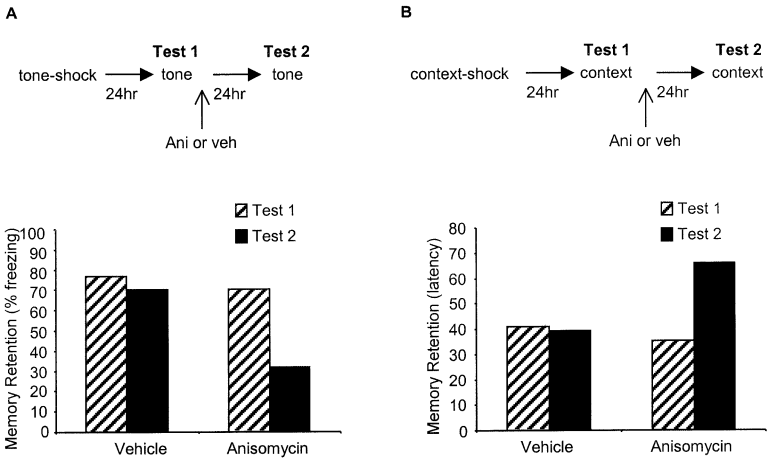

Figure 2. Investigators Examining the Mechanisms of "Reconsolidation" of Acquisition Memory Have Come to Very Different Conclusions than Have Those Examining the Mechanisms of Extinction, Despite the Use of Similar Experimental Protocols

(A) Nader et al. (2000) reported that a Pavlovian fear memory is disrupted by intra-amygdalar infusions of the protein synthesis inhibitor anisomycin immediately following exposure to a tone in the absence of shock, 24 hr after an initial tone-shock pairing. Thus, rats showed normal freezing to the tone prior to the aniosomycin infusion (Test 1) but little freezing to the tone in a test session conducted 24 hr later (Test 2). (B) Vianna et al. (2001), by contrast, found that retention of acquisition was facilitated in rats subjected to intra-hippocampal infusions of anisomycin immediately following nonreinforced context exposure in an inhibitory avoidance paradigm. Thus, anisomycin-treated rats were indistinguishable from controls in an initial test conducted in the absence of drug (Test 1), but showed significantly longer latencies (i.e., facilitated retention) in a test conducted 24 hr later (Test 2). Data redrawn from Nader et al. (2000) and Vianna et al. (2001), respectively.

lovian versus instrumental) or the site of anisomycin infusion (amygdala versus hippocampus) may have been significant, other studies examining reconsolidation of reactivated memories have made use of instrumental, hippocampal-dependent paradigms and have reported amnesia for initial learning following memory reactivation and administration of any of a variety of amnestic treatments—findings very similar to those of Nader et al. (2000).

This puzzling pattern of data merits considerable further attention. Perhaps it will be possible to tease apart findings of impaired extinction versus disrupted reconsolidation on the basis of some procedural variable, however unlikely this seems at the present time. For example, it could be that there are two separate processes at work following a reactivation/extinction episode, one being reconsolidation of the reactivated memory and the other being a new learning process initiated by omission of the US (i.e., extinction). The outcome of any given study might depend on whichever of these two processes—one tending to strengthen the original memory and the other tending to weaken its expression—is affected to a greater extent by the manipulation. In the absence of additional data, however, it is not possible to draw any definitive conclusions at this time as to the protein synthesis dependence of extinction.

Contextual Modulation of Extinction

A third line of investigation within the extinction literature is concerned with the mechanism(s) by which the expression of extinction is controlled by other cues. Earlier we introduced the phenomenon of *renewal*, which refers to the observation that extinction retention is evident in the context of extinction training but not in another context (Bouton and Bolles, 1979a). There is another, similar phenomenon known as *reinstatement*, in which unsignaled presentations of the US following extinction training also disrupt the expression of extinction (Rescorla and Heth, 1975), assuming those US exposures occur in the context of the extinction retention test (Bouton and Bolles, 1979b) (Figure 1D). Both renewal and reinstatement indicate that an extinguished CS maintains some of the strength it acquired upon being paired with the US; however, the uncovering of this latent strength with a context shift (renewal) or unsignaled US presentations (reinstatement) seems to be due to different associative mechanisms. Renewal is believed to reflect the acquisition of a modulatory influence over the expression of the CR by the context of extinction training, whereas reinstatement appears to be due to the development of an excitatory context-US association whose value sums with that of the CS-US association to produce a suprathreshold CR. Whatever the mechanism, however, the implication of contextual cues in both phenomena has led several investigators to examine the role of the hippocampus, a structure that is widely believed to be critical for the formation of multimodal, contextual/spatial representations (e.g., Fanselow, 1999), in the expression of extinction.

It should be pointed out that this literature evolved separately from the older literature on the involvement of the hippocampus in extinction, which we mentioned in passing in an earlier section of this paper. The distinction between these two lines of research lies in the focus of the contemporary literature on the hippocampus as a modulator of extinction-related information stored elsewhere in the brain, whereas the older literature proposed that the hippocampus may itself be the locus of extinction plasticity (see, e.g., Douglas, 1967).

Studies of the involvement of the hippocampus in reinstatement and renewal have generally involved permanent or temporary inactivations of the hippocampus or fimbria-fornix, which in all but one case were induced prior to acquisition (Table 3). Wilson et al. (1995) and Frohardt et al. (2000), for example, examined the effect of pre-acquisition lesions of the hippocampus and fimbria-fornix, respectively, on the reinstatement of an extinguished conditioned emotional response (CER) by unsignaled footshocks. Both groups reported that neither acquisition nor within-session extinction was affected by the lesion, but reinstatement was abolished (i.e., extinction retention was superior in lesioned rats than in sham-lesioned controls). In a similar study using an appetitive conditioning paradigm and pre-acquisition hippocampal lesions, however, Fox and Holland (1998)

Table 3. Effect of Hippocampal Lesions on the Contextual Control of Extinction

	Species	Type of Conditioning	Lesion			Effect		Reference
			Type	Structure	Time	Within-Session Ext	Ext Retention	
Reinstatement	Rat	CER	Radiofrequency	Fimbria-fornix	pre-acq	No effect	Facilitated	Wilson et al. (1995)
	Rat	CER	Neurotoxic	Hippocampus	pre-acq	No effect	Facilitated	Frohardt et al. (2000)
	Rat	Magazine entry	Neurotoxic	Hippocampus	pre-acq	No effect	No effect	Fox and Holland (1998)
Renewal	Rat	CER	Radiofrequency	Fimbria-fornix	pre-acq	No effect	No effect	Wilson et al. (1995)
	Rat	CER	Neurotoxic	Hippocampus	pre-acq	No effect	No effect	Frohardt et al. (2000)
	Rat	Pavlovian FC	Muscimol	Hippocampus	pre-test		Facilitated	Corcoran and Maren (2001)

Abbreviations: acq, acquisition; CER, conditioned emotional response; ext, extinction; FC, fear conditioning.

reported no effect of the lesion on reinstatement. This inconsistency cannot be attributed to the nature or locus of the lesion, as Fox and Holland (1998) used neurotoxic hippocampal lesions similar to those of Frohardt et al. (2000). It has been suggested that the choice of an appetitive versus an aversive conditioning situation may be significant (Frohardt et al., 2000), although it is not clear why these paradigms should be differentially sensitive to the same manipulation.

The involvement of the hippocampus in the renewal effect is similarly controversial (Table 3). Pre-acquisition lesions of the hippocampus (Frohardt et al., 2000) or fimbria-fornix (Wilson et al., 1995) have no apparent effect, but pre-test hippocampal inactivation using local infusion of the GABA agonist muscimol impairs renewal (i.e., facilitates extinction retention within the test context) (Corcoran and Maren, 2001). This latter finding is particularly informative because the use of post-extinction inactivation precludes the possibility of recovery of function mediated by recruitment of other brain regions. Thus, it appears that contextual modulation can be acquired in the absence of a functional hippocampus, but that under normal circumstances the hippocampus is critically involved. It is interesting to note that renewal is detectable not only at a behavioral level of analysis, but also in the firing patterns of individual neurons within the lateral amygdala in a fear conditioning situation (J.A. Hobin and S. Maren, 2001, Soc. Neurosci., abstract).

How Is Nonreinforcement Detected?

The research discussed thus far has been explicitly concerned with the mechanisms of extinction. There is another literature, however, which is relevant to an understanding of extinction but is not addressed to this problem per se. This literature is concerned with the changes in the effectiveness of a US over the course of conditioning, and as such provides clues as to how the non-occurrence of an expected US, a critical feature of extinction training protocols, may be detected.

Both theoretical (Rescorla and Wagner, 1972) and neural (e.g., Kim and Thompson, 1997) models of learning generally assume that the efficacy of the US in producing associative change gradually decreases as it comes to be reliably predicted by the CS. This mechanism accounts for the negatively accelerated learning curve as well as phenomena such as blocking (Kamin, 1969; Kim et al., 1998). Neural theories propose that the CS comes to inhibit brain areas normally activated by the US, thus reducing its effective impact. When learning is asymptotic, CS-induced inhibition perfectly counteracts US-induced excitation. Thus, when the US is withheld, CS-induced inhibition occurs in the absence of any counteractive US-induced excitation, an event that somehow initiates the process of extinction.

For example, in rabbit eyeblink conditioning, the US activates cells in the inferior olive, which sends US information to cerebellar structures that undergo plasticity. The inferior olive, in turn, is subject to inhibition by the interpositus nucleus, which is indirectly activated by the CS. Over the course of conditioning, US-related unit activity in the inferior olive is increasingly inhibited (but only when the US is preceded by the CS) and the development of plasticity within the cerebellum is slowed (Kim et al., 1998; Sears and Steinmetz, 1991). Eventually, late in acquisition, the inferior olive is inhibited to such

an extent that the US produces no net activation and no further plasticity occurs. When the US is then omitted, the CS-induced inhibition of the inferior olive is not countered by US-evoked excitation, and the firing rate of the inferior olive is depressed well below baseline. Somehow, this serves as a signal to initiate extinction (see Mauk and Donegan, 1997). Consistent with these ideas, Medina et al. (2002) demonstrated that intra-olivary infusions of the GABA antagonist picrotoxin (which prevents CS-induced inhibition) block extinction of eyeblink CRs.

Apparently similar changes in US efficacy over the course of conditioning are reflected in the firing patterns of dopaminergic neurons in primates exposed to a CS paired with juice or food (for a review, see Schultz, 1998). Early in training, dopaminergic neurons of the ventral tegmental area respond vigorously to the US, but with increasing numbers of CS-US pairings, the firing patterns of these same neurons shift such that the US-driven firing is suppressed (but only on those trials in which the US is preceded by a CS) while a response to the CS gradually develops. On trials in which the CS is presented but the US is withheld, the cells exhibit a biphasic activation-depression response in which their firing rate increases in the presence of the CS but decreases below baseline at the expected time of US delivery. Note that the US-related firing of the dopaminergic neurons is quite analogous to the firing patterns of the inferior olive, which is activated by an unpredicted US, not affected by a predicted US, and inhibited by the absence of a predicted US (see also Waelti et al., 2001). Unlike the inferior olive, however, the dopaminergic neurons are also responsive to the CS and code for its value as a predictor of the US. Although, once again, it is not clear how such changes might lead to extinction, these data provide further evidence that omission of a well-predicted US is associated with changes in cellular activity that could be involved in extinction.

Concluding Remarks

Clearly, extinction is the subject of an exciting and burgeoning area of research with significant implications for an understanding of the mechanisms of learning. Not only is extinction, as an inhibitory form of learning, distinct from the excitatory learning most commonly employed in cellular studies, but it is sufficiently simple to be subjected to cellular and molecular analysis within the same model systems. Significantly, the study of extinction is also likely to shed light on questions surrounding the consolidation and reconsolidation of memory, which have thus far proven to be difficult to resolve.

Perhaps the largest and most important issue facing extinction researchers at the present time is the identification and characterization of those features of extinction that are shared with acquisition as well as those that seem to be unique to the development of inhibition. This is particularly evident at the cellular level, where there seem to be very different degrees of overlap in the mechanisms of acquisition and extinction within different learning paradigms. It is possible, therefore, that in contrast to acquisition, extinction may be supported by fundamentally different neural mechanisms in different learning paradigms, perhaps as a function of the brain region engaged, the nature of the US (i.e., appetitive or aversive), the nature of the CR (i.e., emotional or skeletal), or any of a number of other factors. This point is particularly evident when comparing extinction of fear conditioning and conditioned taste aversion, as each seems to recruit its own constellation of cellular and molecular mechanisms.

In fear conditioning, for example, extinction is characterized by many of the same neural mechanisms as is acquisition. Activation of amygdalar NMDA receptors by glutamate is essential (Falls et al., 1992), although perhaps only at some delay after extinction training, during the consolidation period (Santini et al., 2001). L type VGCCs also contribute to extinction plasticity, including that underlying within-session extinction (Cain et al., 2002). Long-term extinction memory can be modulated by manipulations of a number of transmitter systems, including GABA (e.g., McGaugh et al., 1990), norepinephrine (C.K. Cain and M.G. Barad, 2001, Soc. Neurosci., abstract), dopamine (e.g., Willick and Kokkinidis, 1995), and acetylcholine (Prado-Alcalá et al., 1994; Roldan et al., 2001), and the directionality of this modulation is the same as it is for acquisition. Fear extinction also recruits many of the same intracellular signaling pathways, such as the PKA, MAPK, and CaMKII cascades (Lu et al., 2001; Szapiro et al., 2002), and may thereby initiate gene transcription and protein synthesis (e.g., Vianna et al., 2001).

The most significant cellular difference between fear acquisition and extinction is the neurotransmitter responsible for the expression of learning. Extinction expression seems to be mediated by GABA (Harris and Westbrook, 1998) whereas CR expression likely reflects the release of excitatory neurotransmitters such as glutamate (cf. Walker and Davis, 2002). Just as it is routinely assumed that the acquisition of a CR is due to the strengthening of connections between pathways transmitting CS-related information and populations of principal neurons whose output ultimately mediates CR execution (e.g., Blair et al., 2001), it seems likely that extinction involves a strengthening of connections between those same sensory pathways and a separate, GABAergic population of neurons that acts to inhibit the CR. The many similarities between the neural mechanisms of fear acquisition and extinction may reflect this presumably shared characteristic of synaptic strengthening. It is interesting to speculate that the differences are due to the identity (i.e., glutamatergic versus GABAergic) of the cells being contacted.

In striking contrast to this scenario, extinction of conditioned taste aversion shares very few features with acquisition. Whereas acquisition is dependent on intra-insular cortex NMDA receptors, β-adrenergic and cholinergic transmission, the MAPK cascade, and protein synthesis, extinction is unaffected by manipulations of any of these except β-adrenergic transmission and protein synthesis (Berman and Dudai, 2001). It has been argued that CTA extinction, as a process of learning something new about a taste and its relationship to illness, is more akin to the acquisition of an aversion to a familiar (i.e., pre-exposed) taste rather than to a novel taste (Berman and Dudai, 2001). In support of this idea, it has been found that the acquisition of an aversion to a familiar taste, like extinction, can develop independently of cholinergic transmission and the MAPK cas-

cade (Berman and Dudai, 2001). In conditioned taste aversion, therefore, it may be that the distinction between "learning anew" and "learning the new" (Berman and Dudai, 2001) is more significant, mechanistically speaking, than is the distinction between acquisition and extinction.

We have focused on the cellular and molecular literatures because these have been the most informative to date in elucidating the mechanisms of extinction. However, the other literatures we have described pose a number of important and as-yet unresolved issues that are likely to contribute significantly to our understanding as well. For example, work on the cerebellum and midbrain dopaminergic systems has revealed that individual neurons sense the lack of an expected US; however, the mechanisms whereby they do so, and the means by which they presumably induce extinction-related plasticity in downstream circuits, remain unknown. Likewise, the extensive behavioral work on contextual modulation of extinction (Bouton, 1993) begs the question as to how this might be orchestrated by the brain, an issue that is poorly understood at the present time. Finally, the putative involvement in fear extinction of structures such as the sensory and prefrontal cortices is a question that continues to arouse considerable interest, and one which will likely continue to be the source of controversy until the conflicting findings are resolved or integrated into a single theory.

Acknowledgments

This work was supported by National Institute of Mental Health Grants MH 47840, MH 57250, MH 52384, and MH 59906, the Woodruff Foundation, and the STC Program, the Center for Behavioral Neuroscience, of the National Science Foundation under Agreement No. IBN-9876754. We are indebted to David Walker, Donna Toufexis, Nathan Schulteiss, and Eric Kandel for their valuable comments on an earlier draft of the manuscript.

References

Aguado, L., Hall, G., Harrington, N., and Symonds, M. (1998). Illness-induced context aversion learning in rats with lesions of the dorsal hippocampus. Behav. Neurosci. *112*, 1142–1151.

Annau, Z., and Kamin, L.J. (1961). The conditioned emotional response as a function of US intensity. J. Comp. Physiol. Psychol. *54*, 428–432.

Armony, J.L., Quirk, G.J., and LeDoux, J.E. (1998). Differential effects of amygdala lesions on early and late plastic components of auditory cortex spike trains during fear conditioning. J. Neurosci. *18*, 2592–2601.

Baker, J.D., and Azorlosa, J.L. (1996). The NMDA antagonist MK-801 blocks the extinction of Pavlovian fear conditioning. Behav. Neurosci. *110*, 618–620.

Barnet, R.C., and Miller, R.R. (1996). Second-order excitation mediated by a backward conditioned inhibitor. J. Exp. Psychol. Anim. Behav. Process. *22*, 279–296.

Bauer, E.P., Schafe, G.E., and LeDoux, J.E. (2002). NMDA receptors and L-type voltage-gated calcium channels contribute to long-term potentiation and different components of fear memory formation in the lateral amygdala. J. Neurosci. *22*, 5239–5249.

Berman, D.E., and Dudai, Y. (2001). Memory extinction, learning anew, and learning the new: dissociations in the molecular machinery of learning in cortex. Science *291*, 2417–2419.

Berman, D.E., Hazvi, S., Rosenblum, K., Seger, R., and Dudai, Y. (1998). Specific and differential activation of mitogen-activated protein kinase cascades by unfamiliar taste in the insular cortex of the behaving rat. J. Neurosci. *18*, 10037–10044.

Blair, H.T., Schafe, G.E., Bauer, E.P., Rodrigues, S.M., and LeDoux, J.E. (2001). Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. Learn. Mem. *8*, 229–242.

Borowski, T.B., and Kokkinidis, L. (1994). Cocaine preexposure sensitizes conditioned fear in a potentiated acoustic startle paradigm. Pharmacol. Biochem. Behav. *49*, 935–942.

Borowski, T.B., and Kokkinidis, L. (1996). Contribution of ventral tegmental area dopamine neurons to expression of conditioned fear: effects of electrical stimulation, excitotoxin lesions, and quinpirole infusion on potentiated startle in rats. Behav. Neurosci. *110*, 1349–1364.

Borowski, T.B., and Kokkinidis, L. (1998). The effects of cocaine, amphetamine, and the dopamine D1 receptor agonist SKF 38393 on fear extinction as measured with potentiated startle: Implications for psychomotor stimulant psychosis. Behav. Neurosci. *112*, 952–965.

Bouton, M.E. (1993). Context, time and memory retrieval in the interference paradigms of Pavlovian conditioning. Psychol. Bull. *114*, 80–99.

Bouton, M.E., and Bolles, R.C. (1979a). Contextual control of the extinction of conditioned fear. Learn. Motiv. *10*, 455–466.

Bouton, M.E., and Bolles, R.C. (1979b). Role of contextual stimuli in reinstatement of extinguished fear. J. Exp. Psychol. Anim. Behav. Process. *5*, 368–378.

Bouton, M.E., and Nelson, J.B. (1994). Context specificity of target versus feature inhibition in a feature-negative discrimination. J. Exp. Psychol. Anim. Behav. Process. *20*, 51–65.

Bouton, M.E., Kenney, F.A., and Rosengard, C. (1990). State-dependent fear extinction with two benzodiazepine tranquilizers. Behav. Neurosci. *104*, 44–55.

Bouton, M.E., Rosengard, C., Achenbach, G.G., Peck, C.A., and Brooks, D.C. (1993). Effects of contextual conditioning and unconditioned stimulus presentation on performance in appetitive conditioning. Q. J. Exp. Psychol. B *46B*, 63–95.

Brons, J.F., and Woody, C.D. (1980). Long-term changes in excitability of cortical neurons after Pavlovian conditioning and extinction. J. Neurosci. Physiol. *44*, 605–615.

Cahill, L., and McGaugh, J.L. (1996). Modulation of memory storage. Curr. Opin. Neurobiol. *6*, 237–242.

Cain, C., Blouin, A., and Barad, M.G. (2002). L-type voltage-gated calcium channels are required for extinction, but not for acquisition or expression, of conditional fear in mice. J. Neurosci. *22*, 9113–9121.

Calton, J.L., Mitchell, K.G., and Schachtman, T.R. (1996). Conditioned inhibition produced by extinction of a conditioned stimulus. Learn. Motiv. *27*, 335–361.

Campeau, S., and Davis, M. (1992). Fear potentiation of the acoustic startle reflex using noises of various spectral frequencies as conditioned stimuli. Anim. Learn. Behav. *20*, 177–186.

Castellano, C., and McGaugh, J.L. (1989). Retention enhancement with post-training picrotoxin: lack of state dependency. Behav. Neural Biol. *51*, 165–170.

Castellano, C., and McGaugh, J.L. (1990). Effects of post-training bicuculline and muscimol on retention: lack of state dependency. Behav. Neural Biol. *54*, 156–164.

Castellano, C., Brioni, J.D., Nagahara, A.H., and McGaugh, J.L. (1989). Posttraining systemic and intra-amygdala administration of the GABA-B agonist baclofen impairs retention. Behav. Neural Biol. *52*, 170–179.

Cole, R.P., and Miller, R.R. (1999). Conditioned excitation and conditioned inhibition acquired through backward conditioning. Learn. Mem. *30*, 129–156.

Corcoran, K.A., and Maren, S. (2001). Hippocampal inactivation disrupts contextual retrieval of fear memory after extinction. J. Neurosci. *21*, 1720–1726.

Cox, J., and Westbrook, R.F. (1994). The NMDA receptor antagonist

MK-801 blocks acquisition and extinction of conditioned hypoalgesia responses in the rat. Q. J. Exp. Psychol. *47B*, 187–210.

Davis, H.P., and Squire, L.R. (1984). Protein synthesis and memory: a review. Psychol. Bull. *96*, 518–559.

Delamater, A.R. (1996). Effects of several extinction treatments upon the integrity of Pavlovian stimulus-outcome associations. Anim. Learn. Behav. *24*, 437–449.

Deutch, A.Y., Clark, W.A., and Roth, R.H. (1990). Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. Brain Res. *521*, 311–315.

Devito, P.L., and Fowler, H. (1987). Enhancement of conditioned inhibition via an extinction treatment. Anim. Learn. Behav. *15*, 448–454.

Diamond, D.M., and Weinberger, N.M. (1986). Classical conditioning rapidly induces specific changes in frequency receptive fields of single neurons in secondary and ventral ectosylvian auditory cortical fields. Brain Res. *372*, 357–360.

Di Marzo, V., Melck, D., Bisogno, T., and De Petrocellis, L. (1998). Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. Trends Neurosci. *21*, 521–528.

Douglas, R.J. (1967). The hippocampus and behavior. Psychol. Bull. *67*, 414–442.

Droungas, A., and LoLordo, V.M. (1994). Evidence for simultaneous excitatory and inhibitory associations in the explicitly unpaired procedure. Learn. Motiv. *25*, 1–25.

Dudai, Y. (2002). Molecular bases of long-term memories: a question of persistence. Curr. Opin. Neurobiol. *12*, 211–216.

Duran-Arevalo, M., Cruz-Morales, S.E., and Prado-Alcalá, R.A. (1990). Is acetylcholine involved in memory consolidation of over-reinforced learning? Brain Res. Bull. *24*, 725–727.

El-Ghundi, M., O'Dowd, B.F., and George, S.R. (2001). Prolonged fear responses in mice lacking dopamine D1 receptor. Brain Res. *892*, 86–93.

Falls, W.A., and Davis, M. (1993). Visual cortex ablations do not prevent extinction of fear-potentiated startle using a visual conditioned stimulus. Behav. Neural Biol. *60*, 259–270.

Falls, W.A., and Davis, M. (1995). Behavioral and physiological analysis of fear inhibition. In Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD, M.J. Friedman, D.S. Charney, and A.Y. Deutch, eds. (Philadelphia: Lippincott-Raven Publishers), pp. 177–202.

Falls, W.A., Miserendino, M.J.D., and Davis, M. (1992). Extinction of fear-potentiated startle: blockade by infusion of an NMDA antagonist into the amygdala. J. Neurosci. *12*, 854–863.

Fanselow, M.S. (1999). Learning theory and neuropsychology: configuring their disparate elements in the hippocampus. J. Exp. Psychol. Anim. Behav. Process. *25*, 275–283.

Fanselow, M.S., and Kim, J.J. (1994). Acquisition of contextual Pavlovian fear conditioning is blocked by application of an NMDA receptor antagonist D,L-2-amino-5-phosphonovaleric acid to the basolateral amygdala. Behav. Neurosci. *108*, 210–212.

Fiori, L.M., Barnet, R.C., and Miller, R.R. (1994). Renewal of Pavlovian conditioned inhibition. Anim. Learn. Behav. *22*, 47–52.

Flood, J.F., Jarvik, M.E., Bennett, E.L., Orme, A.E., and Rosenzweig, M.R. (1977). Protein synthesis inhibition and memory for pole jump active avoidance and extinction. Pharmacol. Biochem. Behav. *7*, 71–77.

Fox, G.D., and Holland, P.C. (1998). Neurotoxic hippocampal lesions fail to impair reinstatement of an appetitively conditioned response. Behav. Neurosci. *112*, 255–260.

Frey, P.W., and Butler, C.S. (1977). Extinction after aversive conditioning: an associative or nonassociative process? Learn. Motiv. *8*, 1–17.

Frohardt, R., Guarraci, F.A., and Bouton, M.E. (2000). The effects of neurotoxic hippocampal lesions on two effects of context following fear extinction. Behav. Neurosci. *114*, 227–240.

Gallagher, M., and Colombo, P.J. (1995). Aging and the cholinergic hypothesis of cognitive decline. Curr. Opin. Neurobiol. *5*, 161–168.

Gassanov, U.G., Merzhanova, G.K., and Galashina, A.G. (1985). Interneuronal relations within and between cortical areas during conditioning in cats. Behav. Brain Res. *15*, 137–146.

Gewirtz, J., and Davis, M. (1997). Second order fear conditioning prevented by blocking NMDA receptors in the amygdala. Nature *388*, 471–474.

Gewirtz, J.C., Falls, W.A., and Davis, M. (1997). Normal conditioned inhibition and extinction of freezing and fear potentiated startle following electrolytic lesions of medial prefrontal cortex. Behav. Neurosci. *111*, 712–726.

Greba, Q., and Kokkinidis, L. (2000). Peripheral and intraamygdalar administration of the dopamine D1 receptor antagonist SCH 23390 blocks fear-potentiated startle but not shock reactivity or the shock sensitization of acoustic startle. Behav. Neurosci. *114*, 262–272.

Greba, Q., Gifkins, A., and Kokkinidis, L. (2001). Inhibition of amygdaloid dopamine D2 receptors impairs emotional learning measured with fear-potentiated startle. Brain Res. *899*, 218–226.

Guarraci, F.A., Frohardt, R.J., and Kapp, B.S. (1999). Amygdaloid D1 dopamine receptor involvement in Pavlovian fear conditioning. Brain Res. *827*, 28–40.

Guarraci, F.A., Frohardt, R.J., Falls, W.A., and Kapp, B.S. (2000). The effects of intra-amygdalois infusions of a D2 dopamine receptor antagonist on fear conditioning. Behav. Neurosci. *114*, 647–651.

Hampson, R.E., and Deadwyler, S.A. (1998). Role of cannabinoid receptors in memory storage. Neurobiol. Dis. *5*, 474–482.

Han, J.S., Holland, P.C., and Gallagher, M. (1999). Disconnection of the amygdala central nucleus and substantia innominata/nucleus basalis disrupts increments in conditioned stimulus processing in rats. Behav. Neurosci. *113*, 143–151.

Harris, J.A., and Westbrook, R.F. (1998). Evidence that GABA transmission mediates context-specific extinction of learned fear. Psychopharmacology (Berl.) *140*, 105–115.

Hawkins, R.D., and Kandel, E.R. (1984). Is there a cell-biological alphabet for simple forms of learning? Psychol. Rev. *91*, 375–391.

Hendersen, R.W. (1978). Forgetting of conditioned fear inhibition. Learn. Motiv. *9*, 16–30.

Herry, C., and Garcia, R. (2002). Prefrontal cortical long-term potentiation, but not long-term depression, is associated with the maintenance of extinction of learned fear in mice. J. Neurosci. *22*, 577–583.

Kamin, L. (1969). Predictability, surprise, attention and conditioning. In Punishment and Aversive Behavior, B. Campbell and R. Church, eds. (New York: Appleton-Century-Crofts), pp. 279–296.

Kehoe, E.J., Macrae, M., and Hutchinson, C.L. (1996). MK-801 protects conditioned response from extinction in the rabbit nictitating membrane preparation. Psychobiology *24*, 127–135.

Kentros, C., Hargreaves, E., Hawkins, R.D., Kandel, E.R., Shapiro, M., and Muller, R.V. (1998). Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. Science *280*, 2121–2126.

Kim, J.J., and Thompson, R.F. (1997). Cerebellar circuits and synaptic mechanisms involved in classical eyeblink conditioning. Trends Neurosci. *20*, 177–181.

Kim, J.J., Krupa, D.J., and Thompson, R.F. (1998). Inhibitory cerebello-olivary projections and blocking effect in classical conditioning. Science *279*, 570–573.

King, D., Zigmond, M.J., and Finlay, J.M. (1997). Effects of dopamine depletion in the medial prefrontal cortex on the stress-induced increase in extracellular dopamine in the nucleus accumbens core and shell. Neuroscience *77*, 141–153.

Kitazawa, S. (2002). Ready to unlearn. Nature *416*, 270–273.

Konorski, J. (1948). Conditioned Reflexes and Neuronal Organization (London: Cambridge University Press).

Kullmann, D.M., Asztely, F., and Walker, M.C. (2000). The role of mammalian ionotropic receptors in synaptic plasticity: LTP, LTD, and epilepsy. Cell. Mol. Life Sci. *57*, 1551–1561.

Lattal, K.M., and Abel, T. (2001). Different requirements for protein synthesis in acquisition and extinction of spatial preferences and context-evoked fear. J. Neurosci. *21*, 5773–5780.

LeDoux, J.E., Romanski, L., and Xagoraris, A. (1989). Indelibility of subcortical memories. J. Cogn. Neurosci. *1*, 238–243.

Lee, H., and Kim, J. (1998). Amygdalar NMDA receptors are critical for new fear learning in previously fear-conditioned rats. J. Neurosci. *18*, 8444–8454.

Lu, K.-T., Walker, D.L., and Davis, M. (2001). Mitogen-activated protein kinase cascade in the basolateral nucleus of the amygdala is involved in extinction of fear-potentiated startle. J. Neurosci. *21*, RC162.

Marsicano, G., Wotjak, C.T., Azad, S.C., Bisogno, T., Rammes, G., Grazia Cascio, M., Hermann, H., Tang, J., Hofmann, C., Zieglgänsberger, W., et al. (2002). The endogenous cannabinoid system controls extinction of aversive memories. Nature *418*, 530–534.

Mason, S.T. (1983). The neurochemistry and pharmacology of extinction behavior. Neurosci. Biobehav. Rev. *7*, 325–347.

Matzel, L.D., Gladstein, L., and Miller, R.R. (1988). Conditioned excitation and conditioned inhibition are not mutually exclusive. Learn. Motiv. *19*, 99–121.

Mauk, M.D., and Donegan, N.H. (1997). A model of Pavlovian eyelid conditioning based on the synaptic organization of the cerebellum. Learn. Mem. *3*, 130–158.

McAllister, W.R., McAllister, D.E., Scoles, M.T., and Hampton, S.R. (1986). Persistence of fear-reducing behavior: Relevance for the conditioning theory of neurosis. J. Abnorm. Psychol. *95*, 365–372.

McGaugh, J.L. (2000). Memory: a century of consolidation. Science *287*, 248–251.

McGaugh, J.L., Castellano, C., and Brioni, J. (1990). Picrotoxin enhances latent extinction of conditioned fear. Behav. Neurosci. *104*, 264–267.

Medina, J.F., Garcia, K.S., and Mauk, M.D. (2001). A mechanism for savings in the cerebellum. J. Neurosci. *21*, 4081–4089.

Medina, J.F., Repa, J.C., Mauk, M.D., and LeDoux, J.E. (2002). Parallels between cerebellum- and amygdala-dependent conditioning. Nat. Rev. Neurosci. *3*, 122–131.

Milad, M.R., and Quirk, G.J. (2002). Infralimbic cortex neurons signal memory for extinction of conditioned fear. Nature, in press.

Miserendino, M.J.D., Sananes, C.B., Melia, K.R., and Davis, M. (1990). Blocking of acquisition but not expression of conditioned fear-potentiated startle by NMDA antagonists in the amygdala. Nature *345*, 716–718.

Morgan, M.A., and LeDoux, J.E. (1995). Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. Behav. Neurosci. *109*, 681–688.

Morgan, M.A., and LeDoux, J.E. (1999). Contribution of ventrolateral prefrontal cortex to the acquistion and extinction of conditioned fear in rats. Neurobiol. Learn. Mem. *72*, 244–251.

Morgan, M.A., Romanski, L.M., and LeDoux, J.E. (1993). Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci. Lett. *163*, 109–113.

Morrow, B.A., Elsworth, J.D., Rasmusson, A.M., and Roth, R.H. (1999). The role of mesoprefrontal dopamine neurons in the acquisition and expression of conditioned fear in the rat. Neuroscience *92*, 553–564.

Nader, K., and LeDoux, J. (1999). The dopaminergic modulation of fear: Quinpirole impairs the recall of emotional memories in rats. Behav. Neurosci. *113*, 152–165.

Nader, K., Schafe, G.E., and LeDoux, J.E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature *406*, 722–726.

Naor, C., and Dudai, Y. (1996). Transient impairment of cholinergic function in the rat insular cortex disrupts the encoding of taste in conditioned taste aversion. Behav. Brain Res. *79*, 61–67.

Pavlov, I.P. (1927). Conditioned Reflexes (London: Oxford University Press).

Pereira, M.E., Rosat, R., Huang, C.H., Godoy, M.G.C., and Izquierdo, I. (1989). Inhibition by diazepam of the effect of additional training and of extinction on the retention of shuttle avoidance behavior in rats. Behav. Neurosci. *103*, 202–205.

Prado-Alcalá, R.A., Haiek, M., Rivas, S., Roldan-Roldan, G., and Quirarte, G.L. (1994). Reversal of extinction by scopolamine. Physiol. Behav. *56*, 27–30.

Preuss, T.M. (1995). Do rats have prefrontal cortex? The Rose-Woolsey-Akert program reconsidered. J. Cogn. Neurosci. *7*, 1–24.

Quirk, G.J., Armony, J.L., and LeDoux, J.E. (1997). Fear conditioning enhances different temporal components of tone-evoked spike trains in auditory cortex and lateral amygdala. Neuron *19*, 613–624.

Quirk, G.J., Russo, G.K., Barron, J.L., and Lebron, K. (2000). The role of ventromedial prefrontal cortex in the recovery of extinguished fear. J. Neurosci. *20*, 6225–6231.

Reibaud, M., Obinu, M.C., Ledent, C., Parmentier, M., Böhme, G.A., and Imperato, A. (1999). Enhancement of memory in cannabinoid CB1 receptor knock-out mice. Eur. J. Pharmacol. *379*, R1–R2.

Repa, J.C., Muller, J., Apergis, J., Desrochers, T.M., Zhou, Y., and LeDoux, J.E. (2001). Two different lateral amygdala cell populations contribute to the initiation and storage of memory. Nat. Neurosci. *4*, 724–731.

Rescorla, R.A. (1969). Pavlovian conditioned inhibition. Psychol. Bull. *72*, 77–94.

Rescorla, R.A. (1979). Conditioned inhibition and extinction. In Mechanisms of Learning and Motivation: A Memorial Volume to Jerzy Konorski, A. Dickinson and R.A. Boakes, eds. (Hillsdale, NJ: Earlbaum), pp. 83–110.

Rescorla, R.A. (1982). Some consequences of associations between the excitor and the inhibitor in a conditioned inhibition paradigm. J. Exp. Psychol. Anim. Behav. Process. *8*, 288–298.

Rescorla, R.A. (1993). Inhibitory associations between S and R in extinction. Anim. Learn. Behav. *21*, 327–336.

Rescorla, R.A., and Heth, C.D. (1975). Reinstatement of fear to an extinguished conditioned stimulus. J. Exp. Psychol. Anim. Behav. Process *1*, 88–96.

Rescorla, R.A., and Wagner, A.R. (1972). A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. In Classical Conditioning II: Current Research and Theory, A. Black and W.F. Prokasy, eds. (New York: Appleton-Century-Crofts), pp. 64–99.

Robbins, S.J. (1990). Mechanisms underlying spontaneous recovery in autoshaping. J. Exp. Psychol. Anim. Behav. Process. *16*, 235–249.

Rodrigues, S.M., Schafe, G.E., and LeDoux, J.E. (2001). Intra-amygdala blockade of the NR2B subunit of the NMDA receptor disrupts the acquisition but not the expression of fear conditioning. J. Neurosci. *21*, 6889–6896.

Rodriguez, B.I., Craske, M.G., Mineka, S., and Hladek, D. (1999). Context-specificity of relapse: effects of therapist and environmental context on return of fear. Behav. Res. Ther. *37*, 845–862.

Roldan, G., Cobos-Zapiain, G., Quirarte, G.L., and Prado-Alcalá, R.A. (2001). Dose- and time-dependent scopolamine-induced recovery of an inhibitory avoidance response after its extinction in rats. Behav. Brain Res. *121*, 173–179.

Rosenblum, K., Meiri, N., and Dudai, Y. (1993). Taste memory: The role of protein synthesis in gustatory cortex. Behav. Neural Biol. *59*, 49–56.

Rosenblum, K., Berman, D.E., Hazvi, S., Lamprecht, R., and Dudai, Y. (1997). NMDA receptor and the tyrosine phosphorylation of its 2B subunit in taste learning in the rat insular cortex. J. Neurosci. *17*, 5129–5135.

Santini, E., Muller, R.U., and Quirk, G.J. (2001). Consolidation of extinction learning involves transfer from NMDA-independent to NMDA-dependent memory. J. Neurosci. *21*, 9009–9017.

Schachtman, T.R., Threlkeld, R., and Meyer, K. (2000). Retention of conditioned inhibition produced by extinction. Learn. Motiv. *31*, 283–300.

Schafe, G.E., Nader, K., Blair, H.T., and LeDoux, J.E. (2001). Memory consolidation of Pavlovian fear conditioning: a cellular and molecular perspective. Trends Neurosci. *24*, 540–546.

Schmajuk, N.A. (1984). Psychological theories of hippocampal function. Physiol. Psychol. *12*, 166–183.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. J. Neurophysiol. *80*, 1–27.

Sears, L.L., and Steinmetz, J.E. (1991). Dorsal accessory inferior olive activity diminishes during acquisition of the rabbit classically conditioned eyelid response. Brain Res. *545*, 114–122.

Shimizu, E., Tang, Y.P., Rampon, C., and Tsien, J.Z. (2000). NMDA receptor-dependent synaptic reinforcement as a crucial process for memory consolidation. Science *290*, 1170–1174.

Szapiro, G., Vianna, M.R.M., McGaugh, J.L., Medina, J.H., and Izquierdo, I. (2002). The role of NMDA glutamate receptors, PKA, MAPK and CaMKII in the hippocampus in extinction of conditioned fear. Hippocampus, in press.

Tait, R.W., and Saladin, M.E. (1986). Concurrent development of excitatory and inhibitory associations during backward conditioning. Anim. Learn. Behav. *14*, 133–137.

Tang, Y.P., Shimizu, E., Dube, G.R., Rampon, C., Kerchner, G.A., Zhuo, M., Liu, G., and Tsien, J.Z. (1999). Genetic enhancement of learning and memory in mice. Nature *401*, 63–69.

Teich, A.H., McCabe, P.M., Gentile, C.C., Schneiderman, L.S., Winter, R.W., Liskowsky, D.R., and Schneiderman, N. (1989). Auditory cortex lesions prevent the extinction of heart rate conditioning to tonal stimuli in rabbits. Brain Res. *480*, 210–218.

Thomas, D.A. (1979). Retention of conditioned inhibition in a barpress suppression paradigm. Learn. Motiv. *10*, 161–177.

Thomas, E. (1988). Forebrain mechanisms in the relief of fear: the role of the lateral septum. Psychobiology *16*, 36–44.

Vianna, M.R., Szapiro, G., McGaugh, J.L., Medina, J.H., and Izquierdo, I. (2001). Retrieval of memory for fear-motivated training initiates extinction requiring protein synthesis in the rat hippocampus. Proc. Natl. Acad. Sci. USA *98*, 12251–12254.

Vouimba, R.-M., Garcia, R., Baudry, M., and Thompson, R.F. (2000). Potentiation of conditioned freezing following dorsomedial prefrontal cortex lesions does not interfere with fear reduction in mice. Behav. Neurosci. *114*, 720–724.

Waelti, P., Dickinson, A., and Schultz, W. (2001). Dopamine responses comply with basic assumptions of formal learning theory. Nature *415*, 43–48.

Wagner, A.R. (1981). SOP: a model of automatic memory processing in animal behavior. In Information Processing in Animals: Memory Mechanisms, N.E. Spear and R.R. Miller, eds. (Hillsdale, NJ: Lawrence Erlbaum Associates), pp. 5–47.

Wagner, A.R., and Brandon, S.E. (1989). Evolution of a structured connectionist model of Pavlovian conditioning (AESOP). In Contemporary Learning Theories: Pavlovian Conditioning and the Status of Traditional Learning Theory, S.B. Klein and R.R. Mowrer, eds. (Hillsdale, NJ: Erlbaum), pp. 149–189.

Wagner, A.R., and Rescorla, R.A. (1972). Inhibition and learning. In Inhibition in Pavlovian Conditioning, R.A. Boakes and M.S. Halliday, eds. (London: Academic Press).

Walker, D.L., and Davis, M. (2002). The role of glutamate receptors within the amygdala in fear learning, fear-potentiated startle, and extinction. Pharmacol. Biochem. Behav. *71*, 379–392.

Walker, D.L., Ressler, K.J., Lu, K.-T., and Davis, M. (2002). Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J. Neurosci. *22*, 2343–2351.

Watkins, J.C., and Collingridge, G.L. (1989). The NMDA Receptor (New York: Oxford University Press).

Weinberger, N.M. (1998a). Physiological memory in primary auditory cortex: characteristics and mechanisms. Neurobiol. Learn. Mem. *70*, 226–251.

Weinberger, N.M. (1998b). Tuning the brain by learning and by stimulation of the nucleus basalis. Trends Cogn. Sci. *2*, 271–273.

Weisskopf, M., Bauer, E.P., and LeDoux, J.E. (1999). L-type voltage-gated calcium channels mediate NMDA-independent associative long-term potentiation at thalamic input synapses to the amygdala. J. Neurosci. *19*, RC48.

Williams, G.V., and Goldman-Rakic, P.S. (1995). Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. Nature *376*, 572–575.

Williams, D.A., and Overmier, J.B. (1988). Some types of conditioned inhibitors carry collateral excitatory associations. Learn. Motiv. *19*, 345–368.

Williams, D.A., Overmier, J.B., and LoLordo, V.M. (1992). A reevaluation of Rescorla's early dictums about Pavlovian conditioned inhibition. Psychol. Bull. *111*, 275–290.

Willick, M.L., and Kokkinidis, L. (1995). Cocaine enhances the expression of fear-potentiated startle: Evaluation of state-dependent extinction and the shock-sensitization of acoustic startle. Behav. Neurosci. *109*, 929–938.

Wilson, A., Brooks, D., and Bouton, M.E. (1995). The role of the rat hippocampal system in several effects of context extinction. Behav. Neurosci. *109*, 828–836.

Yonkov, D.I., and Georgiev, V.P. (1985). Memory effects of GABAergic antagonists in rats trained with two-way active avoidance tasks. Acta Physiol. Pharmacol. Bulg. *11*, 44–49.