Contextual and Temporal Modulation of Extinction: Behavioral and Biological Mechanisms

Mark E. Bouton, R. Frederick Westbrook, Kevin A. Corcoran, and Stephen Maren

Extinction depends, at least partly, on new learning that is specific to the context in which it is learned. Several behavioral phenomena (renewal, reinstatement, spontaneous recovery, and rapid reacquisition) suggest the importance of context in extinction. The present article reviews research on the behavioral and neurobiological mechanisms of contextual influences on extinction learning and retrieval. Contexts appear to select or retrieve the current relationship of the conditional stimulus (CS) with the unconditional stimulus (US), and they are provided by physical background cues, interoceptive drug cues, emotions, recent trials, and the passage of time. The current article pays particular attention to the effects of recent trials and trial spacing. Control of fear extinction by physical context involves interactions between the dorsal hippocampus and the lateral nucleus of the amygdala. This interaction may be mediated by gamma-aminobutyric acid (GABA)-ergic and adrenergic mechanisms.

Key Words: Context, extinction, behavioral mechanisms, brain mechanisms

In extinction, an organism learns that a conditional stimulus (CS), a signal for a psychologically potent unconditional stimulus (US), no longer predicts the US. The consequence is that the behavior elicited by the CS declines. Although extinction involves a decrease in responding, it is clear that it usually entails new learning rather than unlearning (e.g., Bouton 2004; Rescorla 2001). One reason we know this is that there are several behavioral phenomena to indicate that responding can return after extinction, suggesting that extinction has not destroyed the original learning. These phenomena follow from the principle that extinction involves new learning that is especially context-dependent (e.g., Bouton 2002, 2004). The purpose of the present article is to review and discuss what we know about the behavioral and neurobiological mechanisms underlying the contextual modulation of extinction performance.

Contextual Modulation of Extinction Performance: Behavioral Mechanisms

Physical Context

At least two behavioral phenomena show that responding to the CS after extinction depends on the current context, typically defined as the apparatus or chamber in which CSs (e.g., a tone) and USs (e.g., a footshock) are presented to rats. In the renewal effect, testing the CS in a context other than the context in which extinction has occurred can cause a recovery of responding (e.g., see Bouton 2002, 2004 for reviews). The renewal effect takes several different forms. In ABA renewal, conditioning (CS-US pairings) occurs in Context A, extinction (CS presentations without the US) occurs in Context B, and then the CS is tested in the original context (Context A). In ABC renewal, conditioning occurs in Context A, extinction occurs in Context B, and testing occurs in a third, neutral context (Context C). Finally, in AAB renewal, conditioning and extinction both occur in Context A and then testing occurs in Context B. In each of these procedures, responding that is completely lost in extinction is restored when the CS is tested outside the extinction context. Each form of renewal suggests that extinction does not destroy the original learning but instead creates a performance that is modulated by the current context. ABC and AAB renewal further suggest that extinction performance depends, at least in part, on the animal being in the context in which extinction was learned. However, because renewed responding is not to the level shown by subjects that have never received extinction (Bouton and King 1983), extinction is only partly context-specific. There may be generalization between contexts, and/or there may be a component of extinction that is context-free.

Further, behavioral studies of renewal have identified how contexts modulate extinction performance. One view is that the context is merely a second CS that is present in compound with the CS whenever conditioning and extinction occur (e.g., Pearce and Hall 1980; Rescorla and Wagner 1972; Wagner 1981). Context B in the ABA design might therefore acquire a direct inhibitory association with the US during extinction, and Context A might acquire an excitatory association. Such inhibition or excitation would summate with the CS to produce extinction and renewed performance in the extinction and conditioning contexts, respectively. However, renewal can occur without evidence of inhibition in Context B or excitation in Context A (e.g., Bouton and King 1983; Bouton and Swartzentruber 1986, 1989), and a strongly conditioned context does not influence performance to a CS unless the CS is under the influence of extinction (Bouton 1984; Bouton and King 1986). In short, direct associations between the context and US are neither necessary nor sufficient for a context to influence responding to a CS. Instead, the contexts appear to activate or retrieve the current relationship between the CS with the US (see Bouton 1993). They modulate or "set the occasion" for the current CS-US or CS-no US association (e.g., Bouton and Swartzentruber 1986; see Holland 1992). Thus, after extinction, the CS has two available "meanings" (i.e., CS-US and CS-no US) and like an ambiguous word, its current meaning and the response it evokes depend crucially on the current context (e.g., Bouton 1994).

The second illustration of the role of context in extinction is reinstatement. In this phenomenon, the response returns to the CS after extinction if the animal is merely reexposed to the US (e.g., Pavlov 1927; Rescorla and Heth 1975). Evidence suggests that when the US is presented after extinction, it is associated with the context, and this context conditioning then triggers responding when the CS is presented there again. For example,

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if the reinstating USs are presented in an irrelevant context, there is no reinstatement when the CS is tested (e.g., Bouton 1984; Bouton and Bolles 1979; Bouton and King 1983; Frohardt et al 2000; Wilson et al 1995). Independent measures of contextual conditioning also correlate with the strength of reinstatement (Bouton 1984; Bouton and King 1983). And, if the animal receives extensive extinction exposure to the context after US-alone exposures, reinstatement is not observed (Baker et al 1991; Bouton and Bolles 1979). Reinstatement is thus another example of modulation by the context, although in this case responding to the CS depends on the context's direct association with the US.

As noted above, this effect of context is especially robust with an extinguished CS. Bouton (1984) compared the effects of US exposure in the same or a different context on fear of a partially extinguished CS or another CS that had reached the same low level of fear through simple CS-US pairings (and no extinction). Although contextual conditioning enhanced fear of the extinguished CS, it had no impact on the nonextinguished CS (see also Bouton and King 1986), suggesting that an extinguished CS is especially sensitive to manipulations of the context. One reason is that contextual conditioning constituted part of the background under which the CS-US association was originally acquired; its presence during a test may cause a return of responding after extinction because of another ABA renewal effect (Bouton et al 1993). Westbrook et al (2002) have suggested an additional mechanism through which the context might modulate CS responding in reinstatement. During extinction, the organism can associate the CS with the context in which it is being presented. When the US is then presented in that context, it might reinstate responding to the CS in the following way: when the CS is presented again, it activates a representation of the associated context, which now activates a representation of the US because of the new context-US association.

Drug, Emotion, and Trial Contexts

Most research investigating contextual modulation has investigated the effects of "physical context," the chamber in which conditioning and/or extinction occur. However, extinction performance is also modulated by other types of background cues. For example, context can include interoceptive cues provided by the ingestion of drugs. Bouton et al (1990) found that after extinction was conducted while rats were under the influence of benzodiazepine tranquilizers (chlordiazepoxide or diazepam), fear was renewed when the rat was tested in the sober state. Thus, the drug provided a context that exerted familiar control over extinction (see also Cunningham 1979). There is an extensive literature on state-dependent learning that is consistent with the idea that interoceptive cues produced by drug ingestion may play the role of context (e.g., Overton 1985).

Studies of human memory suggest that moods and emotions may also function as contexts; information learned in the presence of an emotion can be difficult to retrieve in its absence (e.g., Bower 1981; Eich 1995). Consistent with this, there is evidence that emotions modulate extinction performance in animals. For example, administration of the stress hormone adrenocorticotropin (ACTH) causes an extinguished avoidance response to return in rats (Richardson et al 1984). This effect appears to depend on ACTH being part of the conditioning context; if ACTH release is suppressed during the original avoidance conditioning (through negative feedback caused by administration of dexamethasone), it has no effect when it is administered after extinction (Ahlers and Richardson 1985). From a theoretical standpoint, the reinstatement effect may also depend on an emotional context. That is, one effect of conditioning the context might be to arouse the emotion that also prevailed during conditioning. Recent research has suggested that the reinstatement of extinguished fear might be mediated, in part, by anxiety elicited by the conditioned context. Specifically, lesions of the bed nucleus of the stria terminalis, a brain site thought to mediate anxiety (e.g., Davis et al 1997), can abolish reinstatement (Bouton 2005; Waddell et al 2006). The precise mechanism is not known. One possibility is that anxiety is part of the context of conditioning, and its presence during testing creates a renewal effect (see above). Alternatively, anxiety may unconditionally potentiate fear of an extinguished CS in a manner analogous to the way conditioned fear potentiates startle responding to a sudden stimulus (Bouton 2005; cf. Konorski 1967; Wagner and Brandon 1989).

Recent research has also investigated the "trial context," the context provided by the memory of immediately preceding trials. Ricker and Bouton (1996)) noted the importance of the trial context in rapid reacquisition, another behavioral effect indicating that extinction does not destroy the original learning. In this phenomenon, resuming CS-US pairings after extinction can cause a very rapid return of the conditioned response. One explanation is that the first few reconditioning trials return a part of the context of conditioning; conditioning trials have usually followed in the context of previous conditioning trials. (In contrast, extinction trials have typically followed previous extinction trials.) Consistent with a role for a trial context, experiments that provide many initial conditioning trials and thus allow ample opportunity to learn that reinforced trials follow other reinforced trials, appear especially likely to yield rapid reacquisition (Ricker and Bouton 1996).

Bouton et al (2004) recently tested an implication of a trial context account of rapid reacquisition. Presenting an occasional conditioning trial during extinction should make a recent conditioning trial a part of the extinction context, as well as the conditioning context, and thus less likely to retrieve conditioning (as opposed to extinction) during reacquisition. Consistent with this idea, reacquisition was less rapid following an extinction procedure that included occasional trials when the CS was paired with the US. Recent experiments have extended this finding to operant conditioning (Woods and Bouton, unpublished data). Here, rats first learned to lever press for food pellets and then received either extinction (sessions in which lever pressing no longer yielded pellets) or a procedure in which the response was infrequently but occasionally paired with the pellet. Reacquisition was often slower after the latter procedure. The rate of reacquisition is thus at least partly controlled by the trial context.

Trial context also plays a role in the partial reinforcement extinction effect (PRE), in which conditioning with a mixture of reinforced and nonreinforced trials makes responding difficult to eliminate in extinction. One explanation of this well-known phenomenon is that a partially reinforced subject persists because it has learned that reinforced trials occur in the context of recent nonreinforced trials (e.g., Capaldi 1994). When a series of nonreinforced trials occurs in extinction, there is relatively little detectable change in the trial context. Bouton and Woods (unpublished data) recently found that this account of the PRE fares better than an alternative view that presenting a mixture of reinforced and nonreinforced trials during conditioning causes the animal to expect the reinforcer after a greater accumulated amount of time in the CS, making it harder to discriminate extinction from acquisition (Gallistel and Gibbon 2000). Interest-

ingly, the PRE is logically similar to the effect of partial reinforcement in extinction on reacquisition just described (Bouton et al 2004; Woods and Bouton, unpublished data): the addition of nonreinforced trials in conditioning encourages generalization between conditioning and extinction, just as the addition of reinforced trials in extinction encourages generalization between extinction and reacquisition. Both phenomena illustrate the importance of trial context.

Temporal Context

We have also noted that the passage of time may cause a gradually changing context (e.g., Bouton 1993). Thus, a long temporal gap (or retention interval) can change the "temporal context" and influence behavior accordingly. This idea provides an explanation of spontaneous recovery, a fourth behavioral phenomenon indicating that extinction does not destroy original learning (e.g., Pavlov 1927). In this effect, responding can recover after extinction if some interval of time elapses before the CS is tested again. Although several explanations of spontaneous recovery are available (e.g., Rescorla 2004), one of the most straightforward is that it is another example of renewal: it occurs because the CS is tested outside the temporal extinction context.

Consistent with this view, spontaneous recovery can be attenuated if a brief visual cue that is presented between trials in extinction is also presented just before the spontaneous recovery test (e.g., Brooks and Bouton 1993; Brooks 2000). In effect, the cue ameliorates the failure to retrieve extinction that is caused by the temporal context change. Importantly, presenting a similar retrieval cue also attenuates the renewal effect (Brooks and Bouton 1994), which encourages the view that renewal and spontaneous recovery are caused by the same mechanism. Another finding consistent with a common mechanism is that the effects of temporal and physical context change are additive (e.g., Rosas and Bouton, 1998; Rosas et al 2001; Westbrook et al 2000). For example, if animals receive both a temporal change and a physical context change after extinction, they show a stronger recovery of responding than after either manipulation alone (Rosas and Bouton 1998). The fact that retention interval and physical context interact this way and are similarly influenced by retrieval cues is consistent with the idea that elapsing time produces a functional change in context.

Bouton and García-Gutiérrez (2006) have recently extended the idea of temporal context to the effects of intertrial interval (ITI), the time between successive trials. For example, the time between successive extinction trials might be encoded as part of the extinction context. If the next trial occurred after a new and different temporal interval, a renewal of responding might be observed–another possible cause of spontaneous recovery. Consistent with this possibility, Bouton and García-Gutiérrez (2006) found that rats that had received extinction trials spaced by 4 minutes showed spontaneous recovery when a retention interval of 16 minutes was introduced. In contrast, a group that received its extinction trials separated by the 16-minute interval showed no recovery after a 16-minute interval. Thus, time between trials may be part of the context that controls extinction performance. (Previous experiments had shown that extinction trials spaced by 4 minutes and 16 minutes produced equivalent spontaneous recovery after 72 hours [Moody et al, in press].)

Further research on the ITI context uncovered an interesting anomaly. When a 16-minute ITI was followed by a 4-minute retention interval, there was no spontaneous recovery despite the mismatch of intervals. A similar asymmetry in how animals generalize extinction over ITIs was evident when the ITI was used as an explicit signal for whether the next CS would be paired with the US or not. Specifically, when the CS was reinforced after 16-minute ITIs but not reinforced after 4-minute ITIs, rats learned the discrimination: they inhibited responding after 4 minutes but responded after 16 minutes. However, when the CS was reinforced after 4 minutes but not after 16 minutes, the discrimination was far more difficult to learn; there was little evidence that the same ITIs controlled performance. One implication is that although stimuli that correlate with time are indeed coded as part of the extinction context, there may be theoretical constraints on how they are coded and/or how they are used (Bouton and García-Gutiérrez 2006).

Trial massing or trial spacing can have effects on extinction performance for other reasons. For example, massed extinction trials may not allow the physical context to extinguish much between trials. In fear extinction, one consequence is that the context will remain dangerous between trials. Exposure to a dangerous context before a CS is presented can enhance responding to an extinguished CS. Morris et al (2005a) extinguished fear reactions to a CS and then shocked rats in a second context. They then re-exposed the rats to this context alone before testing fear of the extinguished CS in a third context. The interval (spent in the home cages) between re-exposure and test was either short (2 minutes) or long (24 hours). Fear was reinstated to the extinguished CS after the shorter interval but not the longer interval. Fear was not reinstated when testing occurred shortly after exposure to a safe context. Reinstatement also depended on rats being tested with an extinguished CS rather than a CS that had not been conditioned or a CS that had been conditioned but not extinguished. Thus, a recent exposure to a dangerous context acted selectively on fear of an extinguished CS. Morris et al (2005a) suggested that the fear elicited by exposure to the dangerous context restored the background under which the original CS-US association had been formed, thereby favoring retrieval by the CS of the conditioning rather than the extinction memory (e.g., Bouton 2002).

The reinstatement of fear to an extinguished CS presented shortly after exposure to the dangerous context can persist as long as 24 hours. That is, rats exposed to an extinguished CS soon after exposure to a dangerous context still showed reinstated fear when the CS was tested 24 hours later. This long-term effect might depend on the adrenergic system's enhancement of aversive memories (van Stegeren et al 1998; Liang et al 1986; for review, see McGaugh 1989). Consistent with this suggestion, Morris et al (2005b) have shown that rats injected with a β-adrenergic antagonist (propranolol) before exposure to the context and extinguished CS failed to show long-term reinstatement of freezing. Conversely, rats injected with the adrenergic agonist epinephrine and simply exposed to the extinguished CS (i.e., in the absence of dangerous context exposure) showed long-term reinstatement of freezing. Morris et al (2005b) suggested that exposure to the dangerous context serves two functions. First, it acts as a retrieval cue that favors activation by the extinguished CS of the conditioning memory. Second, it increases adrenergic activity that promotes further consolidation of the conditioning memory and thereby renders that memory more salient than the extinction memory at a later test.

Similar effects were obtained when a physical box played the role of CS. Morris et al (2005a) shocked rats in a context and then re-exposed them to that context without shock on two occasions. Rats received either a short (2-minute) or long (24-hour) interval between these two extinction trials. Rats from each condition were then given a test trial either 2 minutes or 24 hours after the

second extinction trial. Consistent with the results just described, rats tested 2 minutes after the second extinction trial exhibited more freezing than rats tested 24 hours later. However, if the extinction trials had been spaced by only 2 minutes, the rats froze substantially at either test interval. As argued above, the fear elicited by a recent exposure to the context may cue retrieval of the conditioning memory and promote its reconsolidation, whereas a remote trial favors retrieval of the extinction memory and, presumably, its consolidation.

Li and Westbrook (in preparation) have confirmed that shorter intervals between context extinction trials produce less long-term response loss than longer intervals. In these studies, rats were trained to discriminate between a shocked (A) and a safe (B) context. One group then received nonshocked exposures to context A with an ITI of 24 hours. A second group of rats received the equivalent number of extinction trials with an ITI of a few minutes. (The interval was spent in the home cages. In addition, all rats received complementary exposures to the safe context B in a manner that equated the groups on experimenter handling.) Finally, rats from each of these conditions were tested for freezing to context A. The interval between test trials was either a few minutes or 24 hours. Rats trained with a 24-hour interval between extinction trials exhibited very little freezing during testing (Figure 1). In contrast, the rats trained with the short interval between extinction trials also exhibited little freezing when tested with short intervals but an almost complete recovery of freezing when the tests were separated by 24 hours. Thus, the spaced extinction trials yielded more extinction performance during testing at the 24-hour test interval.

It should be noted that these results contrast with the results of other tests of ITI effects in extinction (e.g., Moody et al, in press). In particular, they are the opposite of those reported for the extinction of an appetitive response in pigeons (Rescorla and Durlach 1987) and a fear response in mice (Cain et al 2003): in these studies, the shorter the interval between CS extinction trials the greater the loss of the learned responding when subjects were tested at common intervals. One of the many differences between these experiments is the location where the subjects spent the interval between extinction trials. In the experiments studying extinction of contextual conditioning (Li and Westbrook, in preparation), subjects spent the interval in their home cages; in experiments studying extinction with explicit CSs (e.g., Rescorla and Durlach 1987; Cain et al 2003), they spent it in an experimental chamber. The difference is potentially important, because according to conditioning models like the Rescorla and Wagner (1972) model, learning resulting on any trial is influenced by the associative strength of the context in which conditioning is conducted. Specifically, learning on any trial is determined by the discrepancy between the outcome predicted on that trial and the outcome that actually occurs; the outcome predicted on a trial is determined by the summed associative strengths of the CS plus the context. Since short ITIs allow less extinction of the context between trials, short ITIs create a greater discrepancy between what is predicted (CS plus context) and what actually occurs (no US), and this may produce a greater decrease in the associative value of the CS.

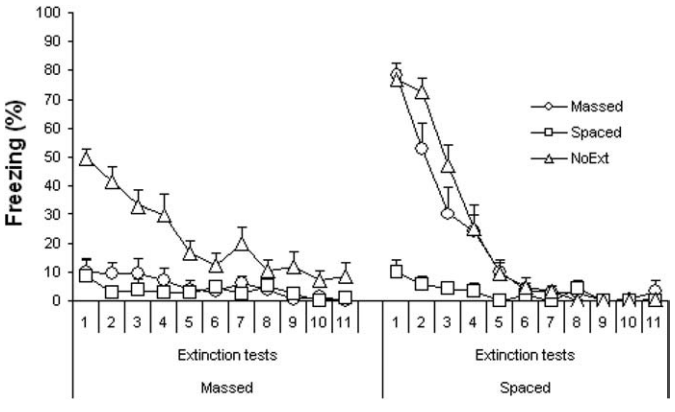

Figure 1. Mean (± SEM) percentage of time spent freezing across massed and spaced extinction tests. The rats spent the ITI across extinction training and extinction tests in the home cage. Rats in Group Massed (circles) received a 4-minute ITI across extinction training and either a 4-minute or 24-hour ITI across extinction tests; those in Group Spaced (squares) received a 24-hour ITI across extinction training and either a 4-minute or 24-hour ITI across extinction tests; rats in Group No Ext (triangles) received either a 4-minute or 24-hour ITI across extinction tests in the absence of prior extinction training. ITI, intertrial interval.

One advantage of the method used by Li and Westbrook (in preparation) (Figure 1) is that the subject spent the ITI in a context different from the one where extinction occurred, effectively eliminating the mechanism just described. Their finding that short intervals between context extinction trials impaired long-term extinction is consistent with at least four sorts of explanations. One assumes that massed exposures to the context might promote consolidation of the conditioning as opposed to extinction memory (Morris et al 2005a, 2005b). Another assumes that attention or processing of the CS that is required for extinction learning is reduced with shorter ITIs because of the dynamics of short-term memory (e.g., Wagner 1978, 1981; see Moody et al, in press, for discussion). A third supposes that the differences in long-term extinction could be due to differences in the consolidation of extinction learning. If consolidation occurs gradually over time, then longer intervals might yield better consolidation of extinction than shorter intervals. Finally, the extinction ITI might become part of the context associated with extinction. Short ITIs might impair long-term extinction learning because the short ITI is absent when subjects are shifted to spaced testing (Bouton and García-Gutiérrez 2006). Regardless of the explanation, under at least some conditions, spaced extinction trials can yield more persistent extinction performance than massed extinction trials.

Contextual Modulation of Extinction: Brain Mechanisms

Hippocampus and Amygdala

Across levels of analysis, from systems to cellular to molecular mechanisms of extinction, we have only begun to uncover how the brain mediates the effects of context on extinction. There is considerable evidence that the hippocampus is involved in developing cognitive representations of contexts during Pavlovian fear conditioning (Fanselow 2000; Maren and Holt 2000; Rudy and O'Reilly 1999, 2001). Therefore, the hippocampus has naturally been the target of several studies investigating the neurobiology of the contextual encoding and retrieval of fear extinction. However, permanent lesions of the fimbria/fornix (Wilson et al 1995) made prior to fear conditioning revealed no deficits in the acquisition of extinction or in the context-dependency of extinction retrieval. This result was subsequently replicated in rats with complete excitotoxic hippocampal lesions (Frohardt et al 2000). In contrast, reversible inactivation of the dorsal hippocampus with muscimol, a gamma-aminobutyric acid $(GABA)_A$ receptor agonist, prior to retention testing impaired

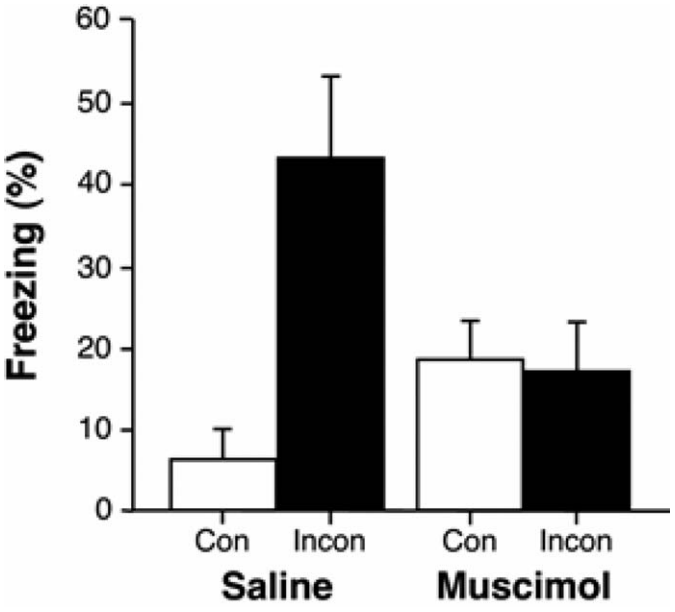

Figure 2. Muscimol infusion into the dorsal hippocampus disrupts the context-specific retrieval of extinction. Mean (± SEM) percentage of freezing during the first minute after CS onset during a test for extinction retrieval. Rats were tested either in a context consistent with extinction of the CS (CON, open bars) or in a context inconsistent with extinction (INCON, filled bars). Retrieval testing took place 20 to 25 minutes after an intrahippocampal infusion of either muscimol or saline. (Adapted with permission from Corcoran and Maren 2001.)

renewal of conditioned freezing in AAB and ABC renewal experiments (Figure 2; Corcoran and Maren 2001, 2004). Moreover, recent work reveals that electrolytic lesions of the dorsal hippocampus impair the renewal of conditional freezing in AAB and ABA renewal experiments, whether those lesions are made before or after extinction (Ji and Maren 2005). In both cases, dorsal hippocampal impairment causes the extinction memory to dominate responding and the context-dependence of extinction is lost. As suggested previously (Maren et al 1997; Maren and Holt 2000), the nature and location of hippocampal damage may be a critical variable in determining the influence of hippocampal manipulations on contextual memory. Interestingly, whereas muscimol inactivation suggests that the dorsal hippocampus is necessary for the context-specificity of extinction retrieval in some renewal designs (AAB and ABC but not ABA) (Corcoran and Maren 2001, 2004), dorsal lesion experiments disrupt renewal regardless of design (Ji and Maren 2005). Nonetheless, permanent lesions of the fimbria/fornix and full hippocampus effectively eliminated reinstatement of conditional responding after extinction (Frohardt et al 2000; Wilson et al 1995), consistent with a role for the hippocampus in forming context-US associations (Kim and Fanselow 1992). Interestingly, none of these studies reported an influence of hippocampal dysfunction on extinction per se, although pretraining hippocampal lesions can result in slower and less complete extinction of an appetitive conditioned response (Benoit et al 1999).

Based on these data, it appears that one function of the hippocampus is to control the context-specific expression of extinction. But is the hippocampus also required to encode extinction or the relationship between the extinction context and the CS as extinction is taking place? To address this issue, a recent study examined the influence of pre-extinction inactivation of the dorsal hippocampus on the acquisition and contextual encoding of extinction memory (Corcoran et al 2005). In a pattern of effects similar to those seen by Benoit et al (1999), muscimol infused into the dorsal hippocampus shortly before extinction training did not prevent rats from learning extinction but rather slowed its acquisition, as evidenced by higher freezing at the end of the extinction session as compared with saline-infused control rats (Figure 3). Rats in each of these conditions were then tested (in the absence of hippocampal inactivation) either in the context where extinction occurred or in a different context. Rats that had been extinguished under saline exhibited the renewal phenomenon: freezing was low when the CS was tested in the extinction context but renewed when it was tested outside that context. Rats extinguished under hippocampal inactivation exhibited similar levels of freezing in either context, indicating an inability of the extinction context to facilitate extinction retrieval. Thus, the hippocampus is not critical for acquiring new learning across CS-alone presentations but does appear to be critical for linking this learning to its associated context. It is worth noting, though, that freezing in the rats whose hippocampus had been inactivated during extinction was lower during the test than it had been at the outset of extinction. Thus, freezing was partly under the influence of extinction. This result suggests that the hippocampus may be involved in that portion of extinction learning that is context-specific but not a possible component that may be context-free.

In spite of the data suggesting a role for the hippocampus in mediating the contextual encoding and retrieval of extinction, it is unlikely that the hippocampus stores the extinction memory itself. While some early theories posited that extinction memory is acquired and stored in the hippocampus (e.g., Douglas 1967), recent evidence suggests instead that fear extinction learning is linked to the amygdala (Falls et al 1992; Lu et al 2001; Walker et al 2002), as fear conditioning itself is known to be (Davis et al 1994; Maren 1996, 1998; Rogan and LeDoux 1996). In fact, neuronal activity in the amygdala encodes conditional fear memories and

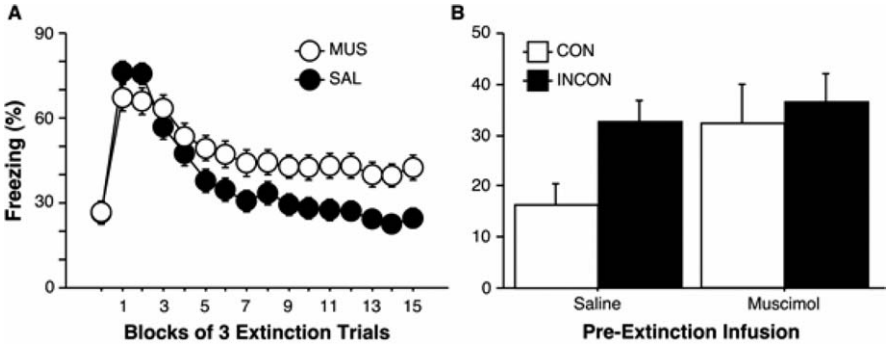

Figure 3. (A) Hippocampal inactivation disrupts the acquisition of extinction. Mean (± SEM) percentage freezing across 3 pre-CS and 45 post-CS minutes during an extinction session. Rats were given intrahippocampal infusions of muscimol (open circles) or saline (filled circles) prior to the extinction session. **(B)** Hippocampal inactivation prior to extinction disrupts the contextual encoding of extinction. Testing for fear to the CS occurred either in a context consistent with extinction (CON; open bars) or in a context inconsistent with extinction (INCON; filled bars) for a subset of rats from **(A)** that were matched for freezing levels at the end of extinction. Note change in y axis. (Adapted with permission from Corcoran et al 2005.)

is correlated with the behavioral responses to a fearful CS (for review, see Maren and Quirk 2004). It is reasonable, then, to propose that shifts in context produce not only robust renewal of fear but also changes in amygdalar neuronal activity in response to an extinguished CS and that these context-dependent shifts in neuronal activity require a functional hippocampus.

To test these proposals, rats were fear conditioned to two distinct CSs, which were subsequently and separately extinguished in two novel contexts. All rats were then tested with each CS in each extinction context while neuronal activity was recorded from the lateral nucleus of the amygdala. During testing, single amygdalar neurons responded more to the CS when they were presented in a context that was inconsistent with the extinction of that CS, relative to CS-evoked responses observed when the same CSs were tested in their extinction contexts. This "renewal" of neuronal activity was mirrored by renewed fear to the CSs when each was tested in the other's extinction context (Hobin et al 2003). Moreover, when the same tests were performed on similarly conditioned and extinguished rats, inactivation of the dorsal hippocampus via muscimol attenuated the cellular renewal that had previously been observed (Figure 4). In this case, CS-evoked lateral amygdala responses were similarly low when CSs were tested either in a context consistent with their extinction or in an extinction-inconsistent context (Hobin and Maren, unpublished data, 2003); this pattern matches the pattern of fear behavior previously seen after hippocampal inactivation (Corcoran and Maren 2001, 2004).

Collectively, these data suggest an important role for the hippocampus in the modulation of extinction by physical context. Other studies suggest that the hippocampus is also vital for using internal contexts, such as hunger and thirst (Hirsh 1974; Kennedy and Shapiro 2004). While the investigations of Maren and Corcoran and their collaborators, using reversible inactivation and electrophysiological techniques, have begun to shed light on the neurobiology of context effects in renewal, many questions remain. What is the neural circuitry by which context signals from the hippocampus regulate fear responses? The ventromedial prefrontal cortex, which receives ample hippocampal inputs and projects strong inhibitory control over the amygdala, is involved in the consolidation (Santini et al 2004) and retrieval (Milad and Quirk 2002; cf. Garcia et al 2006) of extinction. During fear extinction, it may come to inhibit cells in the lateral amygdala that otherwise excite fear responses; one effect of hippocampus might be to inhibit ventromedial prefrontal cortex activation when an extinguished CS is presented outside the extinction context (Maren 2005). At this point in time, we do not know what causes the hippocampus to be activated when the CS is presented in the wrong context or why extinction makes the hippocampus ready to be activated this way. There are also little data to suggest how the brain manages information about internal contexts, such as time, which are just as effective at modulating fear behavior as hunger, thirst, and physical contexts. Thus, we are only beginning to bridge the gap between the behavioral and neurobiological mechanisms that underlie the contextual control of extinction.

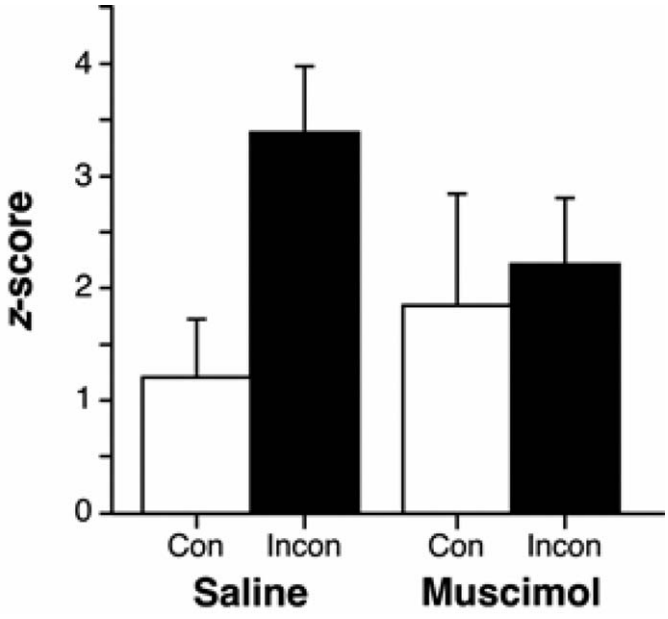

Figure 4. Muscimol infusion into the dorsal hippocampus disrupts the context-specific firing of neurons in the lateral amygdala. Mean (± SEM) *z*-scores for amygdala units that fired preferentially to CSs presented outside their extinction contexts. After saline infusions, "neuronal renewal" is clearly seen as increased activity in response to a CS presented in a context inconsistent with extinction (INCON) relative to activity evoked by CSs presented in their extinction context (CON). The context-preferential firing of the same amygdala units was eliminated by intrahippocampal infusion of muscimol. (Adapted with permission from Hobin et al 2003 and Hobin and Maren, unpublished data, 2003.)

GABA Influences

One pharmacological candidate for the hippocampal suppression of the amygdaloid activity is the inhibitory neurotransmitter GABA. The amygdaloid circuit mediating the acquisition and expression of Pavlovian conditioned fear reactions are controlled by GABA. For example, the acquisition and expression of such reactions are reduced by an intra-amygdaloid infusion of either a $GABA_A$ receptor agonist (muscimol) (Helmstetter and Bellgowan 1994; Muller et al 1997) or a benzodiazepine (e.g., midazolam) that facilitates the inhibitory effects of GABA at the $GABA_A$ receptor without activating these receptors in the absence of GABA (Harris and Westbrook 1995, 1998).

There are various possible roles for GABAergic mechanisms in the normal functioning of the fear system. For example, GABA could be released in response to danger and thereby provide negative feedback as part of a homeostatic system that regulates the level of activity within the amygdaloid fear circuits. This feedback may enable the rat to deal more effectively with learned or innate sources of danger by preventing the escalation of low levels of fear into panic or by reducing the high levels of threat to the manageable levels required for adaptive responses. A related possibility is that the intra-amygdaloid release of GABA is triggered when the rat detects that an event is no longer associated with danger or that some other stimulus or location signals such a relation between the event and danger. This GABAergic modulation of the circuits controlling fear would enable the rat to switch its responses from those required by danger to those appropriate for satisfying the demands of other motivational systems, such as feeding and drinking.

The β-carbolines are a class of compounds that bind to the benzodiazepine site on the $GABA_A$ receptor complex, but in contrast to the benzodiazepines, β-carbolines antagonize the inhibitory effects of GABA (Haefely 1991). Harris and Westbrook (1998) reasoned that if GABA transmission underlies the inhibition of fear reactions, β-carbolines would be especially

likely to promote fear reactions under conditions (such as extinction) where these reactions are suppressed. Rats were exposed to pairings of a CS and shock and then repeatedly exposed to that CS in the absence of shock under the influence of a systemic injection of the β-carboline FG 7142 or saline. Rats from each of these conditions were then tested under either FG 7142 or saline. The test results were clear: rats extinguished and tested under saline exhibited little fear, but rats either extinguished or tested with FG 7142 exhibited high levels of fear. Thus, FG 7142 impaired the development of extinction, and this impairment was evident during tests with saline. Moreover, the drug also impaired the expression of extinction during testing among rats that had been extinguished under saline.

Further experiments indicated that the effects of FG 7142 interact with the contextual control of extinction. Rats received fear conditioning in Context A, extinction in Context B, and then tests under either FG 7142 or saline in the extinction context (B) or a context where no CS had been presented (C). The results were again clear: rats tested under saline exhibited less fear when tested with the CS in the extinction context (B) than outside that context (C). But this difference was erased among rats tested under FG 7142: rats tested in the extinction context (B) froze just as much as did such rats tested outside that context (C), and these levels of freezing were similar to those shown by control rats tested outside the extinction context (C). FG 7142 thus increased freezing in the extinction context (B) without increasing freezing elsewhere (C). In further support for this conclusion, FG 7142 did not disrupt the context-specificity of latent inhibition, the phenomenon in which initial nonreinforced exposure to the CS interferes with subsequent conditioning. These findings suggest that the context-gated inhibitory CS-US association that appears to develop in extinction is mediated by GABA binding to $GABA_A$ receptors.

As noted previously, this inhibitory process may be mediated by GABA transmission within the amygdala, as GABA transmission within the amygdala impairs both the acquisition and expression of fear reactions. Consistent with such a role, Chhatwal et al (2005) reported that fear conditioning downregulates both messenger RNA (mRNA) and protein levels for the $GABA_A$ receptor clustering protein gephyrin, as well as the number of $GABA_A$ receptors in the basolateral amygdala (BLA). In contrast, extinction of fear exerts the opposite effect, upregulating mRNA and protein levels of gephyrin, as well as increasing the number of $GABA_A$ receptors available at the cell surface. Moreover, Jami and Barad (described in Barad 2005) have found that infusion of the $GABA_A$ receptor antagonist picrotoxin into the BLA increases fear reactions to an extinguished CS while failing to increase equivalent levels of fear reactions to a conditioned but not extinguished CS. The use of the renewal paradigm to explore these findings might be especially informative with regard to whether GABA transmission within the amygdala is critical for the development and expression of contextually controlled extinction.

Conclusions and Implications

A variety of behavioral evidence points to a critical role of context in extinction (e.g., Bouton 2002, 2004). As illustrated by the renewal effect, behavior after extinction is at least partly under the influence of a context-specific form of inhibitory learning. This article has summarized the behavioral evidence supporting the role of context in extinction, as well as what we know about its neurobiological mechanisms. Activity in the hippocampus seems critical in controlling the context-specific component of fear extinction, and that component is also mediated, at least in part, by GABAergic activity. At the present point in time, we know considerably less about the brain mechanisms behind the effects of other types of contexts that behavioral research indicates are important in extinction, such as drug and emotion contexts, as well as trial and temporal contexts.

Popular treatments for clinical disorders of fear and anxiety in humans typically revolve around exposure to the fearful stimulus in conjunction with drug administration, and yet humans are potentially as susceptible to relapses after extinction as rats (Mineka et al 1999; Mystkowski et al 2002; Rachman 1989). We have previously noted that the inherent context-specificity of extinction may be an important contributor to lapse and relapse processes (e.g., Bouton 2002). Understanding the basic behavioral and neurobiological mechanisms of extinction will one day contribute to the success of therapy and relapse prevention. But in the absence of understanding the role of context, that knowledge will be incomplete. For example, recent preclinical and clinical research has suggested the promise of combining exposure therapy with the administration of the partial *N*-methyl-D-aspartate (NMDA) receptor agonist D-cycloserine, which may facilitate extinction after an abbreviated number of trials (e.g., Ressler et al 2004). However, the behavioral consequences of extinction with D-cycloserine have not been characterized. We have yet to determine how the drug influences extinction and whether it influences the role of the context. Will it prevent renewal and other forms of relapse (see Ledgerwood et al 2004)? In this regard, it is worth noting that recent behavioral research suggests that treatments that "bridge" connections between the extinction context and potential relapse contexts may be more effective at preventing relapse effects than treatments designed to "optimize" extinction learning (Bouton et al, in press). Our understanding of extinction and its long-term effectiveness will not be adequate without an understanding of how the various forms of context control and modulate it. Harris et al 2000.

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