

COMMENTARY

Hippocampal Involvement in Contextual Modulation of Fear Extinction

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ABSTRACT: Extinction of fear conditioning in animals is an excellent model for the study of fear inhibition in humans. Substantial evidence has shown that extinction is a new learning process that is highly context-dependent. Several recovery effects (renewal, spontaneous recovery, and reinstatement) after extinction suggest that the contextual modulation of extinction is a critical behavioral mechanism underlying fear extinction. In addition, recent studies demonstrate a critical role for hippocampus in the context control of extinction. A growing body of evidence suggests that the hippocampus not only plays a role in contextual encoding and retrieval of fear extinction memories, but also interacts with other brain structures to regulate context-specificity of fear extinction. In this article, the authors will first discuss the fundamental behavioral features of the context effects of extinction and its underlying behavioral mechanisms. In the second part, the review will focus on the brain mechanisms for the contextual control of extinction. © 2007 Wiley-Liss, Inc.

KEY WORDS: fear conditioning; extinction; context; behavioral mechanisms; brain mechanisms; hippocampus; amygdale; prefrontal cortex

INTRODUCTION

In the context of normal human life, fearful situations are regularly encountered; characteristically, these are managed successfully and then forgotten. However, in some individuals, the fearful situation is overwhelming, such as military combat, motor vehicle accident, or sexual assault. These fearful experiences persist and contribute to, such as, psychological disturbances, post-traumatic stress disorders (PTSD), and panic disorders (Friedman et al., 1994; Maren and Chang, 2006; Feldner et al., 2007). Understanding the precise neural mechanisms of anxiety is necessary for developing selective and effective treatments.

Pavlovian fear conditioning and its extinction are the most extensively studied models that provide the laboratory tools to understand the neural mechanisms of fear and anxiety disorders in humans (Myers and Davis, 2002; Kim and Jung, 2006). Pavlovian fear conditioning is a

form of associative learning, in which an animal (typically a rat) is exposed to pairings of a neutral conditional stimulus (CS), such as a tone or light, with an aversive unconditional stimulus (US), such as a foot-shock; this procedure yields a conditioned fear response to the CS. Extinction training, in which CSs are repeatedly presented in the absence of USs, suppresses the amplitude and probability of the conditional response (Pavlov, 1927). As a result, an animal learns that a CS no longer predicts that aversive US. Since Pavlov (1927) observed that extinguished conditional response could recover with the passage of time, extinction has been widely interpreted not to be a process of erasing the original excitatory association (i.e., CS-US), but instead a process of learning a new inhibitory association (i.e., CS-no US) (Myers and Davis, 2002; Bouton, 2004; Delamater, 2004). By the competition between an inhibitory CS-“no-US” association and excitatory CS-US association, the conditional fear response is suppressed (Myers and Davis, 2002; Bouton, 2004; Delamater, 2004).

During this competition, context appears to play an important role to modulate the suppression of extinction memories (Bouton, 2002, 2004). For example, one of the fundamental context effects is the renewal effect, in which changing the context favors recall of extinguished fear memory (Bouton, 1993, 1994). Other context effects of extinction include spontaneous recovery and reinstatement, in which an extinguished response can be recovered following the passage of time or re-exposure to an un signaled US in a relevant context (Myers and Davis, 2002; Bouton, 1993, 1994). These behavioral features of extinction therefore indicate that extinction involves new learning that is particularly dependent on context.

In this review, we will first summarize some fundamental behavioral features of context effects in extinction, and discuss behavioral mechanisms underlying contextual modulation of fear extinction. Since there is a growing body of research uncovering the neural mechanisms enabling this modulation, in the second part, we will discuss the data concerning the roles of the brain structures that mediate the context-specific expression of extinction, especially the involvement of hippocampus, and hippocampal interactions with pre-

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frontal cortex and amygdala network in the contextual regulation of extinction.

BEHAVIORAL MECHANISMS OF EXTINCTION

New Learning Rather than Erasure Process

Considerable evidence has emerged to show that extinction does not erase original learning but instead is an active learning process. There are three impressive behavioral features of extinction (including renewal, spontaneous recovery, and reinstatement) that favor the view that extinction is a form of new learning. In each case, the extinguished conditional response returns after extinction. One property of extinction, known as the renewal effect, has been extensively studied. In this phenomenon, an extinguished conditional response returns if the CS is presented outside of the extinction context in animals (Bouton and Bolles, 1979a; Bouton and King, 1983) or humans (Rodriguez et al., 1999). Another effect is spontaneous recovery, in which the extinguished conditional response recovers with a passage of time after extinction (for reviews, see Robbins, 1990; Brooks and Bouton, 1993). The third phenomenon is reinstatement, in which an extinguished conditional response is partially restored if the subject is exposed to the US alone following extinction (e.g., Rescorla and Heth, 1975; Bouton, 1993, 2002). Both renewal and spontaneous recovery indicate that a CS retains its ability to drive conditional responding following extinction, and must therefore retain at least some of the strength it acquired upon being paired with an US. In reinstatement, contextual conditioning after extinction can reinstate fear to the CS suggesting that extinction does not destroy the CS-US association. Therefore, all these behavioral features indicate that extinction does not erase the original CS-US association. Meanwhile, all of these phenomena indicate that the expression of extinction memories is also context-dependent (Bouton 1993, 2002). Extinction involves new learning; therefore, it leaves the CS with two available “meanings” or associations with the US.

Context-Dependence of Fear Extinction Memory

Renewal

The renewal effect is perhaps the most fundamental and impressive context effect in extinction. There are several different forms of renewal effects, including ABA, AAB and ABC renewal (each letter denotes conditioning, extinction, or testing context). Thus, in ABA renewal, conditioning (CS-US pairings) occurs in context A, extinction (CS presentation in the absence of US) in context B, and then CS is tested in original conditioning context (context A). In AAB or ABC renewal, all retrieval testing is conducted outside of the conditioning context as well as occurred in a context different from the extinction, in that the CS is tested in a neutral context that has no history of CS exposure. However, whether the animal is presented an extinguished CS in the conditioning context (ABA) or in a

neutral context (AAB or ABC), renewal is demonstrated by greater conditional response relative to the extinction context (AAA or ABB). Hence, the expression of extinction is context-dependent (Bouton, 2004; Bouton et al., 2006).

The renewal effect has been demonstrated in many conditioning paradigms (Bouton, 1994, 2002; Bouton et al., 2006). It has been demonstrated in appetitive conditioning (Brooks and Bouton, 1994), taste aversion learning (e.g., Rosas and Bouton, 1998; Chelonis et al., 1999), and operant conditioning (for review, see Nakajima et al., 2000; Bouton, 2002), as well as fear conditioning (e.g., Bouton and Swartzentruber, 1989; Wilson et al., 1995; Frohardt et al., 2000; Corcoran and Maren, 2001, 2004; Ji and Maren, 2005). It has also been demonstrated in a causal judgment task in humans (Rosas et al., 2001). In addition, it appears that the renewal effect can be induced by many kinds of contexts. In one experiment, for example, alcohol was used as an interoceptive drug “context” (Cunningham, 1979). In another experiment, Bouton et al. (1990) obtained similar results that extinction under the influence of benzodiazepine tranquilizers renewed when rat was tested in a drug-free state. Moreover, administration of adrenocorticotropic hormone prior to testing yields renewal of fear in the avoidance performance when rats are returned to the hormonal conditional context (Richardson et al., 1984; Ahlers and Richardson, 1985). All of these observations suggest that the renewal effect is fairly general.

The renewal effect is not only well studied in animals but has also been studied in humans (Mineka et al., 1999; Rodriguez et al., 1999; Rosas et al., 2001; Kalisch et al., 2006). In one study, a causal judgment task in humans was shown to be modulated by context after retroactive interference (extinction) (Rosas et al., 2001). In another experiment, Rodriguez et al. (1999) examined the context-specificity of fear extinction among the patients undergoing exposure treatment for spider phobia. The results demonstrated a context-specific return of fear after the exposure session. The renewal effect is also very robust. In fear conditioning (bar suppression), Bouton and Swartzentruber (1986) observed it after 84 extinction trials following eight conditioning trials. Corcoran and Maren (2001) and others (Gunther et al., 1998; Rauhut et al., 2001) found it occurred after as many as 180 extinction training trials, although Denniston et al. (2003) have reported that “massive” extinction training with 800 trials eliminates renewal.

Some models have been proposed to illustrate the behavioral mechanisms underlying contextual modulation of extinction. One model is that contextual stimuli can modulate the performance of Pavlovian conditional response in extinction (Bouton, 1993, 1994). According to Bouton (1994), an association between a CS and an US is formed during conditioning. In extinction, a new inhibitory CS-“no US” association that is formed blocks the activation of the original CS-US association, thereby limiting the conditional responding to the CS. The meaning of the CS is now ambiguous, and requires the context to disambiguate the meaning of extinguished CS. That is, the excitatory CS-US association established during conditioning is not context-specific and generalizes in all test

contexts. In contrast, the inhibitory CS-“no US” association established during extinction is context-specific. Therefore, the inhibitory association is “gated” so that its activation requires the simultaneous presence of the CS and the extinction context. This “gated” activation allows the expression of inhibitory association memory when the CS is presented in the extinction context. In contrast, presenting the CS outside of the extinction context would reduce activation of the inhibitory link, therefore causing a renewal of conditional response to the CS (Bouton, 1994).

Similar to the “gating” model, context may be “on occasion setter” for the current CS-US or CS-“no US” associations (Bouton and Swartzentruber, 1986; Holland, 1992). In negative occasion setting, a discrete cue stimulus (the feature) precedes a CS (a target) stimulus when the US does not follow the target. Hence, the extinction context may act as a “negative occasion setter” by signaling the CS not followed by the US (Bouton, 1993). In situations in which a CS acquires multiple meanings (both an excitatory CS-US association and an inhibitory CS-“no-US” association after extinction training), retrieval context serves as the feature or occasion setter for the selective retrieval of the appropriate meaning of the target CS (Bouton, 1993).

Another view is that the context can serve as another CS, in addition to participating in contextual encoding and retrieval. That is, contexts themselves can signal US and enter into compound associations or configurations with other stimuli (Rescorla and Wagner, 1972; Pearce and Hall, 1980; Wagner and Brandon, 1989). It therefore enters into simple excitatory or inhibitory associations with US during conditioning or extinction. In the ABA renewal, for example, context B might acquire inhibitory associations with US during extinction, and context A might acquire excitatory associations. Either kind of association would summate with the CS to produce extinction and renewal performance in the extinction and conditioning contexts, respectively. Nevertheless, a context does not need to acquire excitatory or inhibitory associative strength itself to modulate conditional response. That is, the context-specific expression of Pavlovian memories is not simply because of excitatory or inhibitory context-US associations, but rather can occur in the absence of the demonstrable excitation in context (A) or inhibition in context (B) (Bouton and King, 1983; Bouton and Swartzentruber, 1986; Bouton et al., 2006). Nonetheless, the context specificity of memory might arise from the configurative or conjunctive association of a context with a CS (O’Reilly and Rudy, 2001).

Spontaneous recovery

One of Pavlov’s most famous discoveries was the return of conditional responding with the passage of time (Pavlov, 1927). Pavlov noted that if time elapses after extinction, the extinguished response could recover “spontaneously” when CS was tested again. There are several basic empirical properties of spontaneous recovery that are widely accepted. First, spontaneous recovery, similar to the renewal effect, has been dem-

onstrated in virtually every conditioning method (for review, see Brooks et al., 2001). Moreover, spontaneous recovery has been well documented to increase in a negatively accelerated fashion over time (Rescorla, 2004). That is, the longer the delay between extinction termination and testing, the greater the recovery. This feature has been found in fear conditioning in rats (Quirk, 2002), eyelid conditioning in rabbits (Haberlandt et al., 1978), and sign-tracking in pigeons (Robbins, 1990). In addition, recovery declines with repeated extinction (Rescorla, 2004).

Although there are several models available to explain spontaneous recovery, it can be viewed as a forum of context-dependent inhibitory learning (Bouton, 1993, 1994). According to memory theorists (e.g., Spear, 1981), the passage of time may provide a gradually changing context (also see Bouton, 2004). Given this possibility, Bouton (1993) has argued that just as extinction is spatial context specific in renewal, it might also be “temporal context” specific in the spontaneous recovery. In the “gating” mechanism proposed by Bouton (1994), if the CS is associated with the passage of time (temporal context), the model also predicts spontaneous recovery. As time passes after extinction (temporal context gradually changes), shifts in temporal context would reduce the activation of the inhibitory association, leading to the occurrence of spontaneous recovery. Therefore, spontaneous recovery is another “renewal effect”, that occurs when the CS is tested outside its “temporal extinction context”, relative to the “physical context” (Bouton, 1993, 1994).

This idea suggests that both renewal and spontaneous effects are controlled by a common mechanism: a failure to retrieve a memory of extinction outside of the extinction context (Bouton, 2004; Bouton et al., 2006). If this is true, either effect should be attenuated if a retrieval cue that reminds the subjects of extinction memories is presented just prior to the recovery test. It appears that there have been several studies supporting this view. For example, Brooks and Bouton (1993) and Brooks (2000) presented a brief visual cue intermittently during extinction and then presented the cue before the retrieval testing long after extinction. The results showed that the cue presentation prior to testing attenuated spontaneous recovery. Importantly, a reduced renewal effect was also found when a similar retrieval cue was presented before testing outside of the extinction context (Brooks and Bouton, 1994). These data suggest that renewal and spontaneous recovery result from a similar control mechanism, which is due to the failure to retrieve a memory of extinction outside of the extinction context (Bouton, 2004). In another experiment, animals with both temporal and spatial context shifts after extinction showed a stronger recovery of extinguished responding than after either manipulation alone (Rosas and Bouton, 1998). This indicates that the spatial and temporal contexts produce similar effects in modulation of extinction, further supporting the view that renewal and spontaneous recovery share a common mechanism (Bouton, 2004).

A recent study extends the idea of temporal context by examining the interaction of temporal context and extinction

intertrial interval (ITI) (Bouton and Garcia-Gutierrez, 2006). In this study, it was hypothesized that extinction ITI might be encoded as the extinction context, and the interaction of the ITI and retention interval (temporal context) could modulate extinction memories. If the last extinction trial shifted the temporal context, spontaneous recovery might occur. The results confirmed this hypothesis in that rats receiving 4-min ITI extinction trials showed spontaneous recovery when presented with a 16-min ITI during the retention test. However, other rats that received 16-min ITI extinction trial failed to show recovery in this test. Therefore, ITI might also be encoded as part of the context to modulate extinction memories. However, further study demonstrated that spontaneous recovery did not occur if a longer extinction ITI was followed by a shorter temporal context (i.e., 16-min ITI followed by a 4-min ITI) despite that the intervals are mismatched (for review, see Bouton et al., 2006).

Reinstatement

In addition to renewal and spontaneous recovery, the extinguished response returns after extinction if the animal is merely re-exposed to the US alone (Pavlov, 1927; Rescorla and Heth, 1975; Bouton and Bolles, 1979b). In a typical fear reinstatement task, animals first undergo conditioning and extinction. Following extinction, an aversive US is presented a few times in a distinct context. When fear to the CS is tested again, the conditional response is reinstated (Bouton and Bolles, 1979b; Bouton, 1993, 2002). In this case, evidence strongly suggests that the reinstatement effect is due to context conditioning. The context-US associations after extinction promote reinstatement (Bouton, 1993, 2004). Similar to renewal and spontaneous recovery, reinstatement also demonstrates the context-dependence of extinction. That is, reinstatement only occurs when the USs are presented in the context, in which the extinguished CS is tested but not when reinstating USs are presented in a novel or irrelevant context (Bouton and Bolles, 1979b; Bouton and King, 1983; Bouton, 1984; Wilson et al., 1995; Frohardt et al., 2000; Bouton, 2004).

Besides the context-specificity of extinction, there are several other empirical properties in reinstatement. The first one is that the strength of reinstatement is correlated with the strength of contextual conditioning (Bouton and King, 1983; Bouton, 1984, 2004). The second one is that reinstatement is attenuated by exposure to the context, in which reinstatement shock was delivered (Bouton and Bolles, 1979b; Baker et al., 1991; Bouton, 1993). The third property is that the reinstatement shock has a stronger effect on extinguished CSs compared with nonextinguished CSs (Bouton, 1984, 1993). For example, Bouton (1984) delivered reinstatement shock in the same or different context under a comparable condition, in which the fear of one group of rats was partially extinguished; whereas the other group of rats reached the same level of fear by simple CS-US conditioning but without extinction. The data showed that contextual conditioning resulted in an impressive reinstatement for the extinguished CS, but had no discernable effect on

performance to a nonextinguished CS (Bouton and King, 1986).

The results that extinguished CSs are particularly sensitive to contextual control suggest that the reinstatement may be due to a similar mechanism underlying other context effects of extinction (i.e., renewal and spontaneous recovery) (Bouton, 1993). Bouton (1993) proposed that contextual conditioning may constitute part of a background associated with conditioning and thus may act as another feature of the conditioning "context". When extinguished CS is returned to that conditioning context, a feature of the conditioning "context" will activate the original CS-US memory, leading to the reinstatement of extinguished conditional responding, just like another ABA renewal (Bouton, 1993, 2004).

THE BRAIN MECHANISMS UNDERLYING CONTEXT DEPENDENCE OF EXTINCTION

Hippocampus

As theoretical studies in conjunction with recent empirical discoveries reveal a role of context in regulating expression of extinction, it has become important to understand the brain mechanisms underlying the contextual control of extinction. Considering the established role of the hippocampus in several memory processes, including episodic memory (Squire and Zola, 1996; Eichenbaum, 2000, 2001; Burgess et al., 2002), researchers have begun to explore how it mediates context effects on learning.

Hirsh (1974) proposed one of the first theories to account for context effects in memories. He suggested that the hippocampus was a critical substrate for contextual memory retrieval (Hirsh, 1980; Ross et al., 1984; Good and Honey, 1991; Honey and Good, 1993; Holt and Maren, 1999). Meanwhile, an abundance of evidence reveals that the hippocampus is also involved in encoding and consolidating representations of contexts, as well (e.g., Kim and Fanselow, 1992; Philips and LeDoux, 1992; Antagnostaras et al., 1999). Therefore, it is believed that the hippocampus is critical for using contextual representations to guide behavior (Rudy and O'Reilly, 1999, 2001; Fanselow, 2000; Maren and Holt, 2000). Based on these findings, the hippocampus has been explored for its role in contextual modulation of extinction.

Hippocampal involvement in context-dependent retrieval after extinction

As a first attempt to examine the role of the hippocampus in contextual modulation of extinction, Wilson et al. (1995) made permanent lesions of the fimbria/fornix prior to conditioning and observed its influence on several context effects after extinction, including renewal, spontaneous recovery, and reinstatement. The results showed that rats with hippocampal lesions did not show reinstatement, but exhibited normal in

renewal and spontaneous recovery. This result was subsequently replicated in another experiment (Frohardt et al., 2000), showing that complete hippocampal lesions made before conditioning interfered with the reinstatement to fear to an extinguished CS, but left renewal of fear to an extinguished CS intact. These two studies suggest that the hippocampus is not necessary for the context-specific expression of extinguished fear. However, these conclusions are tempered by the fact that all these studies used permanent pretraining lesions of the hippocampus, which necessarily confound the hippocampal role in retrieval processes with its possible role in encoding process (Maren et al., 1997; Maren and Holt, 2000). To overcome these problems, Corcoran and Maren (2001) reversibly inactivated the dorsal hippocampus (DH) with muscimol, a gamma-aminobutyric acid receptor agonist prior to retention testing and examined its effect on context-dependent expression of extinction. In this experiment, intact rats exhibited context-specific retrieval after multiple extinction training sessions, in that they displayed low levels of freezing when presented in the extinction context but showed high levels of freezing when tested outside of the extinction context. The renewal of fear by the context shift was so robust that the elevated fear reached a similar level to that in nonextinguished rats. However, intrahippocampal muscimol infusions prior to testing disrupted this context-specificity, eliminating the renewal of fear to an extinguished CS that occurred outside of the extinction context. This experiment strongly suggests, in contrast to the earlier work (Wilson et al., 1995; Frohardt et al., 2000), that the hippocampus is involved in the context-dependent expression of extinction.

One factor that might account for this discrepancy is that Corcoran and Maren (2001) used an ABC renewal design (Experiment 2), whereas Bouton and colleagues used an ABA design (Wilson et al., 1995; Frohardt et al., 2000). It remains a question, therefore, whether hippocampal lesions influence different types of contextual control in different ways. To address this question, Corcoran and Maren (2004) examined the role of the hippocampus in different renewal paradigms. Consistent with their earlier findings, muscimol inactivation of DH prior to testing resulted in impaired contextual memory retrieval after extinction, eliminating the renewal of conditional responding when animals were tested in a novel, neutral context (AAB renewal). However, if animals were returned to the conditional context during testing (ABA renewal), the context-specificity was minimally affected by hippocampal inactivation, which is consistent with the earlier lesion results (Wilson et al., 1995; Frohardt et al., 2000). It is therefore interesting to understand why the hippocampus plays a role in ABB or ABC renewal, but not in ABA renewal. One possibility Corcoran and Maren (2004) proposed is that the ambiguity in the relationship between the test context and the CS in different renewal conditions is not the same, and this may be differentially sensitive to hippocampal manipulations. Therefore, ABA renewal is not susceptible to hippocampal impairments because the testing context reliably predicts the CS-US association and thus has an unambiguous relationship with the CS. By contrast, in AAB and ABC tests, the context has no history of CS exposure, and

therefore the meaning of the CS in testing contexts is ambiguous. This may yield more interference between the retrieval of CS-US and CS-"no US" memories and thus results in more susceptibility to hippocampal disruption.

In a subsequent study, Ji and Maren (2005) further compared the nature and timing of the hippocampal lesions in determining their influence on different renewal paradigms. They made electrolytic lesions of the DH either before conditioning or after extinction, and examined their effects on context-specific expression of fear memory after extinction. The results showed that DH lesions impaired the context-dependence of extinction, independent on whether lesions were made prior to conditioning or after extinction, and independent on whether retrieval testing returned to the conditioning context (ABA renewal) or occurred in a neutral context (AAB renewal). These data are consistent with the inactivation reports (Corcoran and Maren, 2001, 2004), indicating a critical role for the hippocampus in contextual fear memory retrieval. On the other hand, these results are in contrast to lesion studies (Wilson et al., 1995; Frohardt et al., 2000), which demonstrate unaffected ABA renewal by pretraining fornix or hippocampus lesions. One possible interpretation for the disparities, for example, may be that Bouton and colleague used bar-suppression (Wilson et al., 1995; Frohardt et al., 2000), whereas Ji and Maren (2005) used freezing to index fear. These responses have been demonstrated to be neuroanatomically dissociated, and rats can continue to suppress bar pressing in the absence of freezing under some conditions (Amorapanth et al., 1999).

Interestingly, ABA renewal is not affected by hippocampal inactivation, which is inconsistent with the results showed by Ji and Maren (2005). One possibility to account for this discrepancy may be that the electrolytic lesions clearly disrupt more neurochemical systems than muscimol alone (Ji and Maren, 2005). Another possibility may be the difference in the effects between pretraining and pretesting hippocampal manipulations on the contextual memory retrieval as suggested by Maren et al. (1997). This possibility has been supported by a recent study showing that hippocampal inactivation impaired renewal of fear regardless of testing context occurred when the inactivation was conducted before extinction training (Corcoran et al., 2005).

Nonetheless, the findings from permanent lesions (Ji and Maren, 2005) are consistent with the studies with pharmacological inactivation of DH (Corcoran and Maren, 2001, 2004), suggesting the critical requirement of DH in using contextual stimuli to regulate the expression of fear to a Pavlovian CS after extinction. Based on Bouton's extinction model (Bouton, 1994), Maren and Holt (2000) have posited a model to illustrate hippocampus engagement in latent inhibition (LI). According to Maren and Holt (2000), the DH is necessary for the contextual "gating" of inhibitory CS-"no event" associations in LI. Extinction and LI are similar phenomena in that contextual retrieval cues disambiguate conflicting CS memories and guide behavior. Therefore, this model is also suitable to reveal a role for the DH in contextual "gating" of inhibitory CS-"no US" association in extinction. In this model, the functional hippocampus allows contextual gating of the inhibitory association, leading to the

expression of CS-“no US” association memory in the extinction context. This contextual gating of the CS-“no US” association, however, is mitigated by the absence of a functional hippocampus. Hence, the expression of the CS-“no US” memory becomes context-independent, and conditional responding to the CS is reduced in all test contexts.

Hippocampal involvement in encoding context-specificity of extinction

Collectively, it seems that one function of the hippocampus is to control the context-specific expression of extinction. But it still remains unclear whether the hippocampus is also required to encode extinction or the context-specificity of extinction. To address this question, recent work has investigated the impact of pre-extinction inactivation of the DH by muscimol on encoding the context specificity of extinction (Corcoran et al., 2005). DH inactivation prior to extinction training attenuated extinction learning and disrupted contextual encoding of extinction memory. Rats that underwent extinction training after hippocampal inactivation showed renewal of fear irrespective of the context, in which testing context occurred. Therefore, it appears that the hippocampus plays a role in acquiring extinction, and is required in encoding the CS-context relationship to guide behavior after extinction. Similarly, the context-dependency of extinction was abolished by hippocampal inactivation when muscimol was administered before testing. Interestingly, it did so by diminishing renewal of fear when retrieval occurred outside of extinction context. This contrasted with those rats treated with muscimol before extinction, which exhibited renewal of fear, independent of the context, in which retrieval testing took place (Corcoran et al., 2005). The reasons for the differential effects between pre- and post-extinction hippocampal inactivation on context-specificity of extinction might be due to different hippocampal mechanisms. Corcoran et al. (2005) argued that when hippocampus is engaged in encoding context-specificity of extinction, it plays a role in mediating negative occasion setting, which signals the CS-“no US” associations in extinction as suggested by Holland et al. (1999). A deficit in an occasion-setting process produced by hippocampal inactivation prior to extinction would engender the rats' inability to retrieve extinction memories in the contexts, in which they were learned. However, this model does not account for the effects of pretesting hippocampal inactivation on context-specific expression of extinction. Instead, it is because hippocampal inactivation removes the contextual gating and thus cause the extinction memory to prevail during retrieval (Holt and Maren, 1999; Maren and Holt, 2000), leading to conditional responding reduced in all contexts.

This study, along with previous data, further elaborates an important role for the hippocampus in mediating contextual control of extinction. In addition to animal research, there is emerging evidence indicating hippocampal involvement in mediating context-dependent human extinction memory (Charney et al., 1993; Mineka and Zinbarg, 1996; LaBar and Phelps, 2005; Kalisch et al., 2006). For example, many patients

with anxiety disorders, including phobias and PTSD, are characterized by hippocampal dysfunction and inappropriate context control of the expression of acquired fear response. Recently, Kalisch et al. (2006) examined context-dependent retrieval of human extinction memory with the use of fMRI. They showed that CS-evoked brain activity is context-dependent, and this context-dependent brain activity specifically exhibited in ventromedial prefrontal cortex (vmPFC) and the hippocampus. Also, this activity positively correlated between vmPFC and hippocampus. The role of the hippocampus as supporting context-dependent retrieval of extinction memory has also been strengthened by the finding of impaired context-specific reinstatement in two patients (LaBar and Phelps, 2005). In this report, LaBar and Phelps (2005) used environmental cues as context to investigate how it regulates recovery of conditional fear following extinction. The results showed the context-specificity in the recovery of extinguished fear response after reinstating shock in normal participants. However, two amnesic patients with bilateral ischemic hippocampal damage failed to exhibit recovery following reinstatement in the same context after extinction, despite performing intact fear acquisition and extinction. These results suggest that human hippocampus not only provides for context-dependent retrieval of extinction memory, but also is essential in this memory retrieval.

Amygdala

Although the earlier data suggest an important role for the hippocampus in mediating the contextual modulation of extinction, extinction memory is not stored in the hippocampus. Instead, evidence from animal and human studies indicates that the amygdala is involved in the acquisition and extinction of fear memory (Maren et al., 1996; Rogan and LeDoux, 1996; Goossens et al., 2003; for review, see Davis et al., 1994; Maren, 2001; Sotres-Bayon et al., 2004), and seems to have a pivotal role in the extinction of learned fear (Falls et al., 1992; Lu et al., 2001; for review, see Walker and Davis, 2002; Sotres-Bayon et al., 2004). The mediation of extinction by the amygdala is manifested in the firing of lateral amygdala (LA) neurons. The neuronal activity of LA encodes conditional fear memories and is correlated with the behavioral responses to a fearful CS (Maren, 2000; for review see, Maren and Quirk, 2004). Therefore, it is reasonable to hypothesize that amygdala neuronal activity would be contextually modulated after extinction training, as well as that a renewal of fear occurs in the animal's behavioral performance. In addition, the hippocampus would contribute to the context regulated effects for the CS-evoked neuronal activity.

To test this idea, Hobin et al. (2003) trained rats using a fear extinction procedure that yields context-specific memories for two different CSs, in which they could record CS-elicited firing in LA neurons in two different contexts. The results of this experiment showed that LA neuronal activity exhibited context-dependent spike firing, in that CS-evoked LA firing responded more to the CS when presented outside of extinc-

tion context, compared with CS-evoked firing observed when the same CS was tested in its own extinction context. Similarly, conditional freezing was context-dependent, in which rats demonstrated renewal of fear to an extinguished CS when tested in a context different from extinction (Hobin et al., 2003). In addition, rats with hippocampal inactivation prior to testing were incapable of being recorded the context-dependent spike firing, in that they lost the ability to get the renewal of CS-evoked LA responses that normally observed in intact rats (Maren and Hobin, 2007). In this case, CS-evoked LA neuronal activity diminished in all contexts, which matches the pattern of behavioral performance modulated by context after hippocampal inactivation that was previously reported (Corcoran and Maren, 2001, 2004).

Hippocampus-prefrontal cortex-amygdala interactions

Collectively, these data suggest that context-dependent neuronal activity in the LA may be an important mechanism for disambiguating the meaning of fear signals, thereby enabling appropriate behavioral responses to such stimuli. This contextual modulation of amygdala neuronal activity requires a functional hippocampus to implement. However, it is not clear what the mechanisms are, by which the hippocampus interacts with the amygdala, to regulate CS-evoked firing and context-specific behavioral response. Because there are reciprocal connections between amygdala and hippocampus (Maren and Fanselow, 1995; Pitkanen et al., 2000), one model suggests that a direct projection from hippocampus to LA subserves contextual modulation of neuronal activity (Maren and Quirk, 2004). Alternatively, the medial prefrontal cortex (mPFC) has been anatomically identified to receive strong hippocampal projection, and exerts strong inhibitory control over the amygdala (Jay and Witter, 1991; Conde et al., 1995; Rosenkranz and Grace, 1999, 2001, 2002; Ishikawa and Nakamura, 2003; for review, see Tamminga, 2006), substantial evidence suggests that mPFC plays a critical role in the representation of fear extinction (Quirk et al., 2000; Milad and Quirk, 2002; for review, see Stotres-Bayon et al., 2004; Quirk et al., 2006), and hippocampal modulation of mPFC may control LA projections to the central amygdala (Thierry et al., 2000; Hobin et al., 2003; Stotres-Bayon et al., 2004). This model proposes that the hippocampus performs an executive role in the balance of excitation and inhibition in the fear circuits, in which mPFC may come to inhibit LA neuronal activity during fear extinction that otherwise excite fear response (Hobin et al., 2003; Stotres-Bayon et al., 2004; Maren, 2005). Also, the regulation of this fear is dependent on the context, in which fear stimuli are encountered (Hobin et al., 2003; Maren, 2005). When animals are tested in the extinction context, the hippocampus drives mPFC inhibition of LA. However, if animals are presented with an extinguished CS outside the extinction context, the hippocampus may inhibit mPFC activation and thus promote excitation in the LA to renew extinguished fear under these conditions (Hobin et al., 2003; Maren, 2005). This point of

view is supported by a recent study in humans demonstrating that CS-evoked brain activity is context-dependent after extinction, and this activity is particularly observed in vmPFC and the hippocampus (Kalisch et al., 2006). In addition, CS-evoked in the hippocampus and the vmPFC is positively correlated, which is consistent with the view that the hippocampus may confer contextual information to vmPFC during the expression of extinction (Hobin et al., 2003; Kalisch et al., 2006).

Although the network of the hippocampus, prefrontal cortex, and amygdala is involved in regulating conditional response performance after extinction (Hobin et al., 2003; Maren and Quirk, 2004; Maren, 2005), it is not clear what causes the hippocampus to be activated when the CS is presented outside the extinction context. It is also unclear whether the prefrontal cortex itself is engaged in the context-dependency of extinction, and if so, how prefrontal cortex uses the contextual information to regulate extinction memories. Thus, there is considerable work to do to uncover the brain mechanisms that underlie the contextual control of extinction.

CONCLUSION

In summary, a variety of research indicates that responding to an extinguished CS is susceptible to many recovery effects, suggesting that extinction involves new learning, and this new learning is especially sensitive to manipulations of context. Substantial evidence supports a critical role for the hippocampus in mediating contextual control of extinction. These data reveal that the DH is involved in the acquisition, contextual encoding, and context-dependent retrieval of fear extinction (Corcoran et al., 2005; Ji and Maren, 2004). Moreover, emerging evidence suggests that the context-dependence of extinguished fear involves the interactions between the hippocampus, amygdala, and prefrontal cortex (Hobin et al., 2003). Although the hippocampus plays an important role in the contextual modulation of extinction, it is not required for storing extinction memories. Instead, the amygdala appears to be a critical site for storing and expressing of fear extinction, and mPFC may play a critical role in regulating the expression of fear extinction by inhibiting the amygdala. The hypothesis that LA neurons encode fear memories and CS-elicited LA firing is contextually modulated after extinction has been demonstrated to require the functional hippocampus. According to this result, it has been proposed that contextual modulation of CS-evoked spike firing could be implemented by hippocampal modulation of mPFC to exert control over the amygdala (Hobin et al., 2003; Maren and Quirk, 2004; Stotres-Bayon et al., 2004). Alternatively, direct projections from the hippocampus to the amygdala may regulate fear expression after extinction (Maren and Quirk, 2004). Because the hippocampus has strong reciprocal connections with mPFC and the amygdala, it is yet unclear, which of these connections is important for the contextual modulation of extinction. Nevertheless, it is without doubt that the hippocampus plays a central role in contextual control of fear extinction.

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