Nature and Causes of the Immediate Extinction Deficit: A Brief Review

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Abstract

Recent data in both rodents and humans suggests that the timing of extinction trials after conditioning influences the magnitude and duration of extinction. For example, administering extinction trials soon after Pavlovian fear conditioning in rats, mice, and humans results in minimal fear suppression--the so-called *immediate extinction deficit*. Here I review recent work examining the behavioral and neural substrates of the immediate extinction deficit. I suggest that extinction is most effective at some delay after conditioning, because brain systems involved in encoding and retrieving extinction memories function sub-optimally under stress.

Introduction

Behavioral interventions for pathological fear often involve exposure therapy in which cues or reminders of trauma-related events are used to evoke fear memories in a safe and controlled setting. It is widely believed that exposure therapy relies, at least in part, on extinction learning (Bouton, Mineka, & Barlow, 2001; Craske et al., 2008; Rothbaum & Davis, 2003). In this form of learning, subjects learn that once fearful cues no longer predict an aversive consequence. Extinction procedures do not erase fear memories, but result in new inhibitory associations between the now safe cue and its formerly aversive outcome (Bouton, 1993). The inhibitory associations acquired during exposure therapy lead to a reduction of fear and have considerable therapeutic benefits. Not surprisingly, extinction learning has become an important translational model for developing behavioral interventions for fear and anxiety disorders (Milad & Quirk, 2012).

Curiously, recent data in both rodents and humans suggests that the timing of extinction relative to fear conditioning influences the magnitude of fear reduction after extinction (Golkar & Öhman, 2012; Huff, Hernandez, Blanding, & Labar, 2009; Maren & Chang, 2006; Myers et al., 2006; Norrholm et al., 2008). In many cases, administering extinction

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trials soon after fear conditioning results in no long-term fear suppression at all--the so-called *immediate extinction deficit* (Kim et al., 2010; Maren & Chang, 2006; Chang & Maren, 2009, 2011; Chang et al., 2010; MacPherson et al., 2013). Interestingly, the administration of extinction trials soon after fear conditioning often produces within-session decrements in fear, but this is not maintained over long retention intervals resulting in the spontaneous recovery of fear. The clinical implications of this finding are clear: widely practiced early interventions after psychological trauma may be ineffective in producing long-term fear reduction. Indeed, a review of several studies of early intervention after trauma finds that they are largely ineffective at reducing post-traumatic stress and other anxiety disorders (Bryant, 2002; McNally, Bryant, & Ehlers, 2003). Because of the difficult clinical problem of fear relapse after behavioral therapies, the last several years have witnessed a swell of interest in understanding the factors, including the acquisition-extinction interval, that regulate the recovery of fear after extinction (Maren, 2011).

Here I review recent work in rodents and humans examining the influence of the timing of extinction relative to conditioning on the subsequent suppression of fear. In many cases, delivering extinction trials soon after conditioning produces weak long-term extinction, which, in the case of fear conditioning, is associated with a rapid return of fear responses. I suggest that extinction is most effective at some delay after conditioning, because the severe stress that accompanies trauma engages brain systems involved in acquiring fear memories, and these systems in turn inhibit those involved in fear extinction.

Nature of the Immediate Extinction Deficit

In an extinction procedure, subjects receive non-reinforced presentations of a conditioned stimulus (CS), which ultimately yield suppression of the conditional response (CR). The loss of conditional responding that occurs after extinction is both temporary and context-dependent (Bouton, 1993; Delamater, 2004). That is, extinguished CRs return with the passage of time (i.e., spontaneous recovery) and with changes in context (i.e., renewal). Clearly, spontaneous recovery indicates that the extinction-test interval is a critical determinant of the magnitude of conditional responding after extinction. It has also been suggested that the acquisition-extinction interval might also influence spontaneous recovery. Devenport (1998) argued that the relative recency of different behavioral experiences is a critical determinant of which experience is retrieved, and that short acquisition-extinction intervals might promote retrieval of the conditioning memory (i.e., spontaneous recovery) given the (relatively) recent experience of the CS-US contingency (Devenport, 1998). Rescorla (2004) explored this proposition in a series of appetitive conditioning tasks in both rats and pigeons and found strong evidence that the magnitude of spontaneous recovery varied inversely with the acquisition-extinction interval (Rescorla, 2004). Specifically, spontaneous recovery was greater for the CS whose training was completed one day before extinction, as opposed to eight days before extinction. In other words, delivering non-reinforced trials relatively soon after conditioning produced less long-term suppression of conditional responding.

Interestingly, Myers and colleagues (2006) found the opposite outcome using a shorter (10 minute) acquisition-extinction interval in an aversive conditioning procedure in rats (Myers,

Ressler, & Davis, 2006). After startle habituation, rats were submitted to a fear conditioning procedure (15 light-shock pairings), which was followed after 10 min, 1 hour, or 72 hours by an extinction procedure (90 light-alone trials); fear was tested either 1 day or 21 days after the extinction procedure. In contrast to Rescorla's (2004) results, spontaneous recovery after a long-retention interval (relative to a short-retention interval) was greatest in rats extinguished at the 72-hr delay; rats in the 10-min condition did not exhibit spontaneous recovery. The authors also reported less reinstatement and renewal in animals extinguished at the 10-min delay, suggesting that not only had extinction been effective, but that it had possibly interfered with the fear memory, resulting in an "unlearning" of the conditioning experience. Interestingly, in all of the experiments, fear potentiated-startle during the 1-day retention test was always lowest in the 72-hour groups and highest in the 10-min groups, although the absence of no-extinction controls and the lack of assessment of within-session extinction makes it difficult to determine the magnitude of extinguished conditional responding in any of the groups. Nonetheless, an alternative account of these data is that spontaneous recovery had already occurred in the immediate extinction groups in the 1-day test, leaving little room for additional recovery across the longer 21-day retention interval. This also accounts for the reinstatement and renewal data, insofar as immediate-extinction animals tested in the extinction context exhibited more fear than animals in the delay condition. This would be consistent with the view that there is greater spontaneous recovery of fear in animals after short acquisition-extinction intervals.

To probe this phenomenon further, we examined the extinction of conditional freezing behavior in rats that underwent extinction (45 tone-alone trials) either 15-min or 24 hours after fear conditioning (5 tone-shock trials) (Maren & Chang, 2006). We assessed fear across all phases of training (i.e., conditioning, extinction, and retention testing), and included no-extinction controls to assess the magnitude of extinction in each group. All animals were tested after a 24- or 48- hour retention period. Our results were unambiguous: rats receiving extinction trials 15 minutes after fear conditioning showed similar levels of conditional freezing to no-extinction controls during the retention test, and far less freezing than animals extinguished 24 hours after conditioning, which showed much less freezing than their respective no-extinction control groups. This outcome held true when extinction-test interval was equated, and was even evident after massive amounts of extinction (225 trials with a 12-sec inter-stimulus interval). In subsequent work, we have found that this immediate extinction deficit is found with acquisition-extinction delays of up to 6 hours (Chang & Maren, 2009). Interestingly, the levels of fear at the outset of extinction (and during the extinction session) were much higher in animals extinguished 15-min after conditioning. Consequently, we found that delivering unsignaled shock immediately before a delayed extinction procedure resulted in impaired extinction, and reducing fear before immediate extinction enabled fear suppression (Maren & Chang, 2006). As I discuss in greater detail below, this suggests that one factor regulating the immediate extinction deficit is the high level of acute fear engendered by the conditioning experience.

Consistent with both Rescorla (2004) and Maren and Chang (2006), Woods and Bouton (2008) observed that short (10 min) acquisition-extinction intervals produce weaker extinction in both aversive and appetitive conditioning procedures. In two different experiments in rats, conditioned suppression of lever pressing served as the index of

aversive conditional responding, whereas magazine approach served as the index of appetitive conditional responding; after single-session conditioning in each case, extinction trials were administered either 10 minutes or 24 hours after conditioning and retention was tested 24 hours after extinction (Woods & Bouton, 2008). In both cases, extinction trials administered soon after conditioning produced less suppression of conditional responding on the retention test. Moreover, in an additional aversive conditioning experiment, greater renewal of conditional responding was observed in immediate extinction animals when the CS was tested outside of the extinction context. Interestingly, Woods and Bouton (2008) found lower levels of conditioned suppression during the extinction session in animals undergoing immediate extinction, and manipulating levels of fear (with additional conditioning to a novel CS) before extinction and test did not support a contextual mismatch account of the immediate extinction deficit. Based on this outcome, they argued that levels of fear *per se* are likely not a determinant of the immediate extinction deficit, an outcome supported by their parallel findings in the appetitive task that does not obviously motivate fear (see also (S. C. Kim, Jo, Kim, Kim, & Choi, 2010)).

In other work, Schiller and colleagues (2008) explored, in both rats and humans, whether short acquisition-extinction intervals prevent the reinstatement and spontaneous recovery of fear as suggested by others (Myers et al., 2006). In contrast to earlier reports (Maren & Chang, 2006; Woods & Bouton, 2008), Schiller and colleagues (2008) did not observe an immediate extinction deficit (Schiller et al., 2008); rats receiving extinction trials exhibited within-session extinction that was maintained during a retention test 24 hours later. Interestingly, these animals also exhibited weaker conditional freezing during the extinction session, an outcome that has been observed under some conditions (Maren & Chang, 2006; Woods & Bouton, 2008), but not others (Archbold, Bouton, & Nader, 2010). A similar pattern of behavior during the extinction session has been observed in juvenile rats (PND24) undergoing immediate extinction, which also fail to exhibit an immediate extinction deficit (J. H. Kim & Richardson, 2009). This suggests that low levels of fear during immediate extinction may limit the immediate extinction deficit, as we have previously reported (Maren & Chang, 2006). Nonetheless, despite the absence of an immediate extinction deficit, Schiller and colleagues (2008) found that the reinstatement of extinguished fear in both rats and humans was not influenced by the acquisition-extinction interval indicating that immediate extinction did not eliminate the fear memory. Likewise, Kim and Richardson (2009) have found equivalent renewal of fear outside the extinction context in young rats undergoing immediate or delayed extinction.

Archbold and colleagues (2010) recently examined whether the extinction of *contextual* fear conditioning is also influenced by the acquisition-extinction interval. Using rats as subjects, they found that rats exposed to a shock context 15 minutes after conditioning exhibited higher levels of contextual fear during the extinction session, but that freezing was comparable to delay extinction animals during a 24-hour retention test (Archbold et al., 2010). However, the authors did not include no-extinction controls, so it is not clear how the performance in the animals undergoing extinction would compare to a similarly handled (but non-extinguished) control group. Hence, it is possible that differential spontaneous recovery of extinguished fear in immediate and delay animals was masked by factors

regulating fear other than the extinction contingency. The authors found no evidence that immediate extinction impaired fear memory, insofar as animals receiving either immediate or delayed extinction exhibited evidence of a spared conditioning memory. Indeed, Stafford and colleagues (2013) explored the acquisitioninterval in mice undergoing contextual fear conditioning, and in contrast to Archbold and colleagues (2010), found marked immediate extinction deficits in animals undergoing context-alone extinction immediately after conditioning (Stafford, Maughan, Ilioi, & Lattal, 2013).

Additional work on using immediate extinction procedures in humans has largely supported the notion that immediate extinction is less effective than delayed extinction in suppressing fear. For example, Norrholm and colleagues (2008) found little evidence for differential spontaneous recovery in a single-cue conditioning paradigm in humans; they concluded that "These results are not consistent with work in rodents (Myers et al., 2006)." Moreover,in subjects that underwent immediate extinction after a differential conditioning procedure, Norrholm and colleagues (2008) found *greater* shock expectancy ratings during the retention test relative to those subjects that underwent delayed extinction (Norrholm et al., 2008). However, in a subset of subjects in the immediate and delay conditions that exhibited extinction, there was different pattern of spontaneous recovery of fear-potentiated startle. That is, although subjects in both the immediate and delay conditions exhibited spontaneous recovery of fear-potentiated startle, subjects in the delay condition reportedly exhibited greater discriminative responding between the CS+ and CS on the test (Norrholm et al., 2008). However, inspection of the startle difference scores during the test (Figure 8A, Norrholm et al., 2008) does not suggest a statistically reliable interaction between CS type and training-extinction delay. Collectively, these results are equivocal for their support the notion that immediate extinction is more effective than delay extinction.

In other human work, Huff and colleagues (2009) have shown that immediate extinction is less durable than delayed extinction (Huff et al., 2009). In this case, galvanic skin conductance CRs were much greater during the retention test in subjects that underwent extinction immediately after conditioning, relative to those extinguished 24 hours after conditioning. In addition, greater renewal of fear was observed in subjects undergoing immediate extinction when CSs were presented in a context different from that used during conditioning (Alvarez, Johnson, & Grillon, 2007; Huff et al., 2009). And, as we have observed in our previous work (Maren & Chang, 2006), immediate extinction supports weaker within-session extinction in humans under some conditions (Golkar & Öhman, 2012). Golkar and Öhman (2012) did find less reinstatement of fear-potentiated startle after immediate extinction, when reinstatement was performed immediately after extinction training. This finding is at odds with data in rodents showing that renewal is absent when assessed immediately after extinction (Chang & Maren, 2010). Ultimately, these data support the general picture that immediate extinction is at least no more effective, and possibly less effective, than delay extinction in producing long-term suppression of conditional responding. This conclusion is clearly at odds with the earlier suggestion that immediate extinction is a particularly effective at promoting long-term fear reduction (Myers et al., 2006).

More recent behavioral work in rats has focused on the factors regulating the immediate extinction deficit. Johnson and colleagues (2010), using a conditioned suppression procedure in rats, have recently shown that immediate extinction is associated with greater spontaneous recovery when the retention test is conducted relatively soon after extinction (i.e., 48 hours) (J. S. Johnson, Escobar, & Kimble, 2010). However, they reported the opposite outcome when retention testing was conducted one week after extinction; in this case, immediate extinction was reported to produce more robust extinction than delayed extinction. This rather complicated state of affairs suggests that the expression of extinction may depend on a variety of factors, and that temporal contexts (e.g., acquisition-extinction and extinction-test intervals) may regulate the expression of extinction memories (whether acquired at short or long delays after conditioning) much in the way environmental contexts regulate the expression of extinction memories (Bouton, 1993). In addition, MacPherson and colleagues (2013) have recently examined the immediate extinction deficit using fear conditioning procedures in mice (MacPherson, Whittle, & Camp, 2013). These authors found interesting genetic differences in the effect: 128S1/SvImJ animals exhibited little extinction of cued freezing in either delayed or immediate conditions, whereas C57BL/6J animals exhibited an immediate extinction deficit similar to that reported in rats (Chang & Maren, 2009; Maren & Chang, 2006).

To summarize, in many cases immediate extinction procedures either result in a minimal long-term retention of extinction or yield a normal suppression of conditional responding that exhibits spontaneous recovery, renewal, and reinstatement of similar magnitude to that obtained after delayed extinction. At this juncture, the notion that administering extinction trials soon after conditioning promotes a more durable suppression of fear finds little support (cf., (J. S. Johnson et al., 2010)).

Causes of the Immediate Extinction Deficit

Two general classes of explanations have been offered to account for the spontaneous recovery of conditional responding after immediate extinction (Maren & Chang, 2006). Importantly, these explanations are not mutually exclusive. One class of explanation appeals to the interference of acquisition and extinction memories during memory retrieval at the time of retention testing. The notion that the resolution of interference between competing memories has had considerable success in accounting for many phenomena, including spontaneous recovery and the context-dependence of extinction (Bouton, 1993). Another explanation appeals to differential encoding (or consolidation) of fear and extinction memories as a critical determinant of performance at test. By this view, retention test performance is governed by the relative strength of extinction and fear memories, not by the degree to which similarly strong memories are retrieved. Of course, both encoding and retrieval processes are likely to influence levels of conditional responding on test.

An example of a retrieval-based account of the immediate extinction deficit can be found in Devenport's (1998) temporal weighting model (Devenport, 1998). In this model, Devenport (1998) argues that with short conditioning-extinction intervals, the relatively recent conditioning experience interferes with the extinction experience and promotes spontaneous recovery. In other words, the temporal proximity of two experiences influences the degree to

which they are perceived as unique, thereby increasing retrieval interference. By this view, the extinction-test interval might also be imagined to interact with the immediate extinction deficit and recent evidence confirms this fact (J. S. Johnson et al., 2010). They found that while the immediate extinction deficit was greatest at short extinction-test intervals (48 hours), it was tempered at longer extinction-test intervals (7 days). In fact, at longer extinction-test intervals, immediate extinction was found to produce more CR suppression than delayed extinction. This suggests that animals encode extinction memories (e.g., inhibitory CS-'no US' association), but that their retrieval is influenced by interference from the conditioning memory. There is considerable evidence that this sort of retrieval interference accounts for other forms of CR recovery, including renewal, after extinction (Bouton, 1993). Clearly, additional work is required to understand whether immediate extinction "incubates" over longer retention intervals to ultimately yield more effective fear suppression. If so, this would be at odds with the view presented here that immediate extinction fails to yield long-term fear suppression.

Another possibility is that the immediate extinction deficit results because extinction trials soon after conditioning either enhance consolidation of the fear memory (thereby strengthening it) and/or limit encoding or consolidation of the extinction memory (thereby weakening it) (Myers et al., 2006). There are several pieces of evidence that argue against this possibility. First, within-session loss of conditional responding can be comparable during immediate or delay extinction procedures (Chang & Maren, 2009; Maren & Chang, 2006; cf., Golkar & Öhman, 2012 and Archbold et al., 2012). This suggests that animals encode the extinction contingency, at least in the short-term, although habituation might account for some response loss during extinction training. Second, animals showing spontaneous recovery after immediate extinction procedures exhibit considerable savings when re-extinguished later, suggesting that some aspect of the original extinction experience was encoded (Chang & Maren, 2011). And, third, as noted above, the loss of conditional responding after immediate extinction is more pronounced than that after delay extinction after long extinction-test delays (J. S. Johnson et al., 2010). These results imply that the immediate extinction deficit is not due to a wholesale failure to encode the extinction memory.

Although immediate extinction procedures appear to support encoding of an extinction memory, it has been suggested that they might disrupt consolidation or reconsolidation of fear memories under some cases (Auber, Tedesco, Jones, Monfils, & Chiamulera, 2013; Myers et al., 2006). In particular, it has been suggested that delivering extinction trials soon after the re-activation of a fear memory ultimately weakens that memory. It is beyond the scope of this review to consider the expanding literature on this phenomenon, but it is worth noting that there are several recent reports that have not replicated the effect (Chan, Leung, Westbrook, & Mcnally, 2010; Costanzi, Cannas, Saraulli, Rossi-Arnaud, & Cestari, 2011; MacPherson et al., 2013; Stafford et al., 2013). Indeed, if "active" fear memories are most sensitive to disruption by extinction procedures, then immediate extinction after fear conditioning should yield less spontaneous recovery of fear, which is not the normative case as discussed above.

We have argued in previous work that a major determinant of the immediate extinction deficit may be the high levels of fear expressed by animals as they enter extinction training. For example, freezing behavior in the baseline period before the delivery of extinction trials is often higher in animals extinguished soon after conditioning (Chang & Maren, 2009; Chang, Berke, & Maren, 2010; MacPherson et al., 2013; Maren & Chang, 2006). However, the immediate extinction deficit has also been observed under conditions in which pre-extinction fear, at least as reported by freezing, is low (Chang & Maren, 2011; S. C. Kim et al., 2010). Moreover, the immediate extinction deficit has been obtained in appetitive paradigms in which fear is not a factor (Rescorla, 2004; Woods & Bouton, 2008), or in aversive procedures in which fear is disassociated from extinction learning (Powell, Escobar, & Kimble, 2013). Thus, it would not appear that high levels of fear before extinction training are not necessary for the immediate extinction deficit.

Nevertheless, recent work suggests that arousing fear prior to extinction affects the retrieval of extinction memory and can lead to greater spontaneous recovery (Archbold, Dobbek, & Nader, 2013; Stafford et al., 2013). Animals extinguished in a state of fear may fail to encode the extinction contingency, encode extinction trials in a fear context that prevents retrieval in a safe test situation, or encode the extinction contingency in a context-independent manner that impairs later retrieval of that contingency. There is evidence against the first two possibilities given that animals undergoing immediate extinction show evidence of extinction performance (Chang & Maren, 2009; J. S. Johnson et al., 2010) or savings (Chang & Maren, 2011) and providing a fear context before retention testing does not alleviate the immediate extinction deficit (Woods & Bouton, 2008). The last possibility finds some support in the observation that animals extinguished after hippocampal inactivation exhibit deficits in the retention of extinction, an pattern that parallels with the immediate extinction deficit (Corcoran, Desmond, Frey, & Maren, 2005). In this case, we argued that animals encode extinction memories, but do not couple them to a context that would later aid in their retrieval on test (thereby promoting the expression of the fear memory).

Neural Mechanisms Underlying the Immediate Extinction Deficit

Neurobiological investigation of the immediate extinction deficit has focused on the medial prefrontal cortex (mPFC) given its prominent role in the encoding and retrieval of extinction memories (Herry et al., 2010; Milad & Quirk, 2012; Orsini & Maren, 2012; Quirk & Mueller, 2008). The initial studies to investigate the phenomenon used Fos immunohistochemistry (S. C. Kim et al., 2010) and single-unit recording methods (Chang et al., 2010) to examine neuronal activity in the mPFC after immediate and delay extinction procedures. In the first study (S. C. Kim et al., 2010), rats underwent fear conditioning (5 CS-US trials) followed by extinction (15 CS-alone trials) either 15 min or 24 hours after conditioning; brains were collected 90 minutes after extinction to assess extinction-related neuronal activity in the mPFC. Animals in the delayed extinction group exhibited highly significant increases in the number of Fos-positive nuclei in the infralimbic and prelimbic regions of the medial prefrontal cortex. In contrast, animals in the immediate extinction condition (which failed to extinguish fear) exhibited similar levels of mPFC Fos-immunoreactivity compared to control animals that did not undergo extinction. In a second

experiment, the authors found that pairing immediate extinction trials with high-frequency electrical stimulation of the mPFC eliminated the immediate extinction deficit.

We have used single-unit recording procedures to compare mPFC neuronal activity after immediate and delayed extinction following auditory fear conditioning in rats (Chang et al., 2010). Consistent with the immunohistochemical results of Kim and colleagues (2010) we found that the extinction was associated with greater levels of bursting in infralimbic mPFC neurons. This effect was apparent at the outset of the extinction session and appeared to reflect the behavioral state of the animal before extinction, rather than a consequence of extinction training *per se* (Burgos-Robles, Vidal-Gonzalez, Santini, & Quirk, 2007). Yet infralimbic cortical bursting was dramatically reduced in animals undergoing immediate extinction procedures. Interestingly, CS-evoked spike firing in the infralimbic cortex was relatively normal during immediate extinction training relative to rats in the delay condition, whereas CS-evoked firing was dampened in the prelimbic cortex. Interestingly, we did not observe the development of extinction-related increases in CS-evoked spike firing in the mPFC that have been previously reported (Milad & Quirk, 2002). In fact, CS-evoked firing during retention testing in the infralimbic cortex correlated with the expression of fear--it was highest in animals in the immediate extinction group (which failed to extinguish) and lowest among animals in the delay group (which effectively suppressed fear).

Given the evidence for hypoactivity in the mPFC during extinction (reduced IL bursting, reduced CS-evoked activity in PL, decreased Fos-immunoreactivity), we examined whether pharmacological activation of the mPFC might ameliorate the immediate extinction deficit (Chang & Maren, 2011). Rats were implanted with cannulas targeting the infralimbic cortex and received infusions of the NMDA receptor partial agonist, D-cycloserine, or the GABAA antagonist, picrotoxin, prior to an immediate extinction session conducted one hour after auditory fear conditioning. Although neither drug manipulation eliminated the immediate extinction deficit that was manifest as near complete spontaneous recovery during the earliest period of the retention test, each facilitated the re-extinction of fear during the retention test. This reveals that increasing prefrontal cortical function at the time of extinction learning can facilitate some aspects of extinction performance during later tests (B. M. Thompson et al., 2010).

Collectively, these results suggest that hypoactivity in the mPFC during immediate extinction contributes to later extinction retrieval deficits. However, a recent study of mPFC activity in mice undergoing immediate extinction after contextual fear conditioning has reported the opposite outcome (Stafford et al., 2013). Stafford and colleagues (2013) found greater numbers of Fos-positive neurons in the infralimbic and prelimbic cortex (as well as the basolateral and central nuclei of the amygdala) in animals undergoing immediate extinction after contextual fear conditioning. In other experiments, animals submitted to these procedures exhibited robust immediate extinction deficits, and these deficits were comparable to those found in studies reporting less Fos expression in mPFC (S. C. Kim et al., 2010). The reasons for these discrepancies are not clear, but suggest further work is needed to characterize the relationship of mPFC activity to extinction performance.

One possibility long entertained in the stress literature is that aversive stimuli impair prefrontal cortical function (Akirav & Maroun, 2007; Arnsten, 2009; McEwen & Morrison, 2013). If the mPFC is involved in registering changes in CS-US contingency, and along with the hippocampus, imbues context-dependence to this information (Maren, 2011; Maren & Quirk, 2004), then stressful experiences may render extinction impairments. Indeed, there is substantial evidence that chronic stress causes morphological changes in mPFC neurons that correlate with extinction impairments (Izquierdo, Wellman, & Holmes, 2006; Miracle, Brace, Huyck, Singler, & Wellman, 2006; Wilber et al., 2011). In the case of the immediate extinction deficit, the conditioning experience itself (and the stress it engenders) may cause extinction to fail. For example, animals may fail to detect a change in CS-US contingency during extinction if they are still greatly aroused after the conditioning experience. The impairment of PFC function by stress may be cause by a number of factors, including elevated glucocorticoid levels and noradrenergic hyperarousal (Arnsten, 2009; McEwen & Morrison, 2013). At the circuit level, it has been proposed that the amygdala hyperexcitability that accompanies fear states may dampen mPFC function. For example, Garcia and colleagues (1999) have observed that fear CSs reduce PFC firing during the expression of fear and impair the acquisition of conditioned inhibition (Garcia, Vouimba, Baudry, & Thompson, 1999). More recently, Ji and colleagues (2010) have found that the inactivation of the basolateral complex of the amygdala limits pain-induced decrements in PFC firing (Ji et al., 2010). The inhibitory influence of basolateral amygdaloid activity on mPFC activity has been born out in recent neurophysiological studies (Dilgen, Tejeda, & O'Donnell, 2013; Sun & Neugebauer, 2011), and stress-related impairments in hippocampal function and learning have been linked to the amygdala (J. Kim, Lee, Han, & Packard, 2001). This raises the intriguing possibility that heightened amygdala excitability that is associated with Pavlovian fear conditioning (Goosens, Hobin, & Maren, 2003; Paré & Collins, 2000) and conditioning-related increases in firing to fear CSs (Goosens et al., 2003; Maren, 2000; Quirk, Repa, & LeDoux, 1995; J. C. Repa et al., 2001) might actually inhibit hippocampal-prefrontal cortical circuits and interfere with extinction encoding and retrieval. By this view, manipulations that reduce fear before extinction commences, particularly those that do so by reducing amygdala activity, will increase the efficacy of extinction training by disinhibiting hippocampal-prefrontal cortical circuitry involved in the encoding and retrieval of extinction memory.

Conclusions

A considerable body of evidence now suggests that the timing of extinction after conditioning influences the durability of extinction memory. Short intervals between fear conditioning and extinction result in the spontaneous recovery of fear within 24 hours after extinction. Although the precise mechanisms underlying this effect are under active investigation, mounting evidence suggests that the arousal of fear before extinction may interfere with the brain systems involved in encoding and retrieving extinction memories.

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Highlights

- The timing of extinction after conditioning determines the magnitude and longevity of response loss.
- Delivering extinction trials minutes to hours after conditioning often leads to an ‘immediate extinction deficit’.
- The ‘immediate extinction deficit’ may be mediated by stress-induced impairments in medial prefrontal cortical function.