Neurobiology of Learning and Memory 113 (2014) 19–24

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Review

Nature and causes of the immediate extinction deficit: A brief review

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ARTICLE INFO

Article history:
Available online 29 October 2013

Keywords:
Fear conditioning
Extinction
Spontaneous recovery
Rat
Human
Freezing
Time

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.

1. 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, Ressler, & Davis, 2006; Norrholm et al., 2008). In many cases, administering extinction trials soon after fear conditioning results in no long-term fear suppression at all – the so-called immediate extinction deficit (Chang, Berke, & Maren, 2010; Chang & Maren, 2009, 2011; Kim, Jo, Kim, Kim, & Choi, 2010; MacPherson et al., 2013; Maren & Chang, 2006). 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.

2. 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

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1074-7427/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nlm.2013.10.012

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 min) acquisition–extinction interval in an aversive conditioning procedure in rats (Myers et al., 2006). After startle habituation, rats were submitted to a fear conditioning procedure (15 light-shock pairings), which was followed after 10 min, 1 h, or 72 h 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-h 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-h 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 h 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-h retention period. Our results were unambiguous: rats receiving extinction trials 15 min 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 h 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-s inter-stimulus interval). In subsequent work, we have found that this immediate extinction deficit is found with acquisition–extinction delays of up to 6 h (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 min or 24 h after conditioning and retention was tested 24 h 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 (Kim et al., 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 h 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 (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.