



The key role of extinction learning in anxiety disorders: behavioral strategies to enhance exposure-based treatments

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Purpose of review

Extinction learning is a major mechanism for fear reduction by means of exposure. Current research targets innovative strategies to enhance fear extinction and thereby optimize exposure-based treatments for anxiety disorders. This selective review updates novel behavioral strategies that may provide cutting-edge clinical implications.

Recent findings

Recent studies provide further support for two types of enhancement strategies. Procedural enhancement strategies implemented during extinction training translate to how exposure exercises may be conducted to optimize fear extinction. These strategies mostly focus on a maximized violation of dysfunctional threat expectancies and on reducing context and stimulus specificity of extinction learning. Flanking enhancement strategies target periods before and after extinction training and inform optimal preparation and post-processing of exposure exercises. These flanking strategies focus on the enhancement of learning in general, memory (re-)consolidation, and memory retrieval.

Summary

Behavioral strategies to enhance fear extinction may provide powerful clinical applications to further maximize the efficacy of exposure-based interventions. However, future replications, mechanistic examinations, and translational studies are warranted to verify long-term effects and naturalistic utility. Future directions also comprise the interplay of optimized fear extinction with (avoidance) behavior and motivational antecedents of exposure.

Keywords

anxiety disorders, enhancement strategies, exposure therapy, fear extinction, inhibitory learning

INTRODUCTION

The effectiveness of exposure-based interventions for anxiety disorders has been well documented [1–3], but not all patients benefit equally well [4]. Extinction learning is seen as a major mechanism for the reduction of fear during exposure therapy and, thus laboratory extinction procedures are used as experimental models for exposure-based interventions [5]. Current research targets extinction deficits in patients with anxiety disorders and potential strategies to enhance extinction learning to pave the way for treatment optimization. These strategies aim at boosting fear extinction in the short term as well as in the long term to account for the challenges set by relatively high rates of nonresponse and relapse after exposure-based interventions. This review selectively focuses on an overview and most recent findings on innovative behavioral enhancement strategies to provide

tentative clinical implications and open questions for future research.

THE KEY ROLE OF EXTINCTION IN ANXIETY DISORDERS

Extinction of fear occurs when fear decreases during repeated exposure to a previously conditioned

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KEY POINTS

- Extinction learning is a key mechanism of exposure-based interventions. Behavioral strategies to optimize fear extinction may offer cutting-edge clinical implications for psychotherapist conducting exposure exercises.
- Procedural strategies may enhance exposure exercises by focusing on maximized violation of threat expectancies, increasing variability, and regulating specific emotions.
- Flanking strategies may support preparation and post-processing of exposure and thereby enhance general learning, memory consolidation, and retrieval.
- As fear extinction hardly generalizes across stimuli, the next target is to develop and test procedural and flanking strategies to augment extinction generalization.
- Apart from replications and mechanistic examinations, clinical translation calls for an individualized conceptualization of enhancement strategies to balance optimal extinction learning with preceding and subsequent therapeutic strategies and the individual's motivation to conduct exposure.

stimulus which is now presented in the absence of the unconditioned stimulus. The original fear association (excitatory conditioned stimulus–unconditioned stimulus association) and the extinction association (inhibitory conditioned stimulus–no unconditioned stimulus association) now compete and the conditioned stimulus becomes an ambiguous stimulus (even if it currently does not trigger fear; [6–8]). Extinction associations are typically weaker compared to the original fear associations resulting in the recurrence of conditioned fear responding (return of fear) after re-presentation of the unconditioned stimulus (reinstatement; [9]), change of surrounding context (renewal; [10]), or passage of time (spontaneous recovery; [11]).

Previous reviews have concluded that individuals with anxiety disorders generally show impaired extinction learning and memory [12–14,15[■],16,17,18[■]]. Importantly, this is confirmed by a recent meta-analysis on 963 patients from 44 studies [15[■]]. Results demonstrated that patients display increased fear responses to conditioned safety stimuli during fear acquisition. During extinction training, patients showed stronger and longer lasting fear responses to the fear stimulus under extinction. These learning deficits indicate impaired ‘fear inhibition’ under safety and/or increased ‘fear generalization’ to safe stimuli that resemble the conditioned fear stimulus. These findings have since

been further replicated [19–21] and illustrate that individuals with anxiety disorders show deficits in learning processes that are essential for therapeutic change by means of exposure-based interventions. In line with this, extinction response patterns were found to predict treatment outcome in obsessive–compulsive [22] and posttraumatic stress disorder [23,24]. However, more research on other anxiety disorders is needed, especially because the predictive value of fear extinction for exposure-based treatments may crucially support the ecological validity of the experimental model [25].

Apart from fear learning toward a specific stimulus, fear generalization has recently sparked research in preclinical anxiety research, as it addresses the broad array of fear-provoking situations in most anxiety patients [26,27]. Generalization is studied by assessing fear levels, which are elicited by stimuli that resemble the original fear-conditioned stimulus to a variable extent. The main goal is to understand the underlying generalization mechanisms and, eventually, to constrain the over-generalized fears as a means to treat anxiety disorders. Unfortunately, extinction generalization, as the counterpart to fear generalization, has received less attention, despite its relevance for improving exposure effects beyond the specific feared situations used in treatment. Typically, a different but similar stimulus is put to extinction and residual fear to the original fear stimulus is taken as a measure of extinction generalization. Human fear conditioning studies so far revealed little fear reduction to the original stimulus [28,29], even when multiple similar stimuli were extinguished that together contained all its features [10,30]. Equally, low levels of extinction generalization were found between two stimuli that belonged to the same *de novo* created category [31]. Individual differences such as attentional control may, however, influence the amount of extinction generalization [32]. These studies have paved the way for an in-depth analysis of fear extinction generalization and how to overcome its boundaries in extinction-based treatments. However, given the limited findings on extinction generalization, current enhancement strategies are mostly confined to the original fear stimulus.

ENHANCEMENT OF EXTINCTION AND CLINICAL IMPLICATIONS

A variety of strategies to boost extinction are investigated by current research. Neuroscientific approaches unveiled the usefulness of cognitive enhancers and pharmacological agents, such as d-cycloserine, oxytocin, or cannabinoids (for recent reviews see [33[■]–42[■]]) as well as neuromodulation of

Table 1. Overview of behavioral strategies to enhance fear extinction

Keyword	Behavioral strategies	Suggested mechanisms	Exemplary studies
Procedural strategies implemented during extinction training			
Expectancy violation	Increase expectancies regarding the likelihood or intensity of feared aversive outcomes (general strategy)	Maximizes the mismatch between predicted and experienced outcome to augment inhibitory learning	[47]
Safety signals	Removal and prohibition of safety behaviors and signals during extinction training	Increases threat expectancy to augment their violation; shows that safety behaviors/signals are not necessary for safety to occur	[48]
Deepened extinction	Combination of multiple fear stimuli during extinction training, which predict the same aversive consequence (unconditioned stimulus)	Increases threat expectancies to augment their violation; increases salience of fear stimulus	[49 [■]]
Occasional reinforced extinction	Occasional pairing of the fear stimulus with the aversive outcome during extinction training	Increases threat expectancies to augment their violation	[50]
Variability	Varying stimuli, duration, spacing of trials, and anxiety levels during exposure tasks independent of habituation	Reduces context-specificity of extinction	[51 [■]]
Multiple contexts	Varying the external and internal context of the extinction training	Reduces context-specificity of extinction	[51 [■] ,52,53]
Affect labeling	Verbally labeling the emotional content of a stimulus or emotional experiences	Regulates emotions incidentally with similar neural regulation as in fear extinction	[54 [■]]
Sleep	Extinction training during sleep	Induces novel learning during sleep	[55 [■]]
Novelty outcome	Combination of the fear stimulus with novel neutral outcome during extinction training (rather than no outcome as in traditional extinction training)	Increases mismatch between predicted and experienced outcome	[56]
Unconditioned stimulus devaluation	Combine feared stimulus with less aversive, devalued aversive outcome	Weakens the memory of the aversive outcome, resulting in less fear	[57]
Flanking strategies implemented before or after extinction training			
Retrieval cues	Use of external cues or mental rehearsal after extinction training	Enhances retrieval of extinction memory	[58,59]
Sleep	Sleep after extinction training	Enhances memory consolidation	[60 [■]]
Positive affect	Induction of positive mood before extinction training	Reduces negative valence of the fear stimulus after extinction	[61 [■]]
Physical exercise	Physical exercise before extinction training	Enhances learning generally (e.g., by increased BDNF)	[62 [■] ,63 [■]]
Novelty context	Exposure to novel context briefly before or after extinction	Enhances extinction of contextual fear via hippocampal processes (e.g., 'synaptic tagging-and-capture')	[64–66]
Reconsolidation	Activate consolidated fear memory before extinction training	Disrupts fear memory during reconsolidation phase	[67,68]

Most strategies and their corresponding mechanisms are still under critical investigation. BDNF, brain-derived neurotrophic factor.

relevant brain areas [43,44,45[■]]. On the other hand, pharmacological agents that are often prescribed as anxiolytics, such as benzodiazepine, have been found to impair fear extinction [46[■]].

'Behavioral' strategies directly inform psychotherapeutic approaches. Most behavioral strategies are implemented during extinction training and thus inform the specific procedures of exposure

exercises. Additional flanking strategies target intervals before and after extinction training and may thus inform optimal preparation and post-processing of exposure. A selective overview of behavioral strategies and assumed mechanisms is presented in Table 1. Craske *et al.* [69[■]] offer an excellent review of past findings and clinical case formulations for some of these strategies. To maximize impact on

clinical practice, these case formulations and background information have been translated to various languages (German: [70[■]]; Spanish: [71[■]]; French: [72[■]]; Dutch: [73[■]]).

PROCEDURAL STRATEGIES DURING EXTINCTION TRAINING

Procedural strategies generally focus on creating optimal conditions for triggering dysfunctional threat expectancies that are at the core of the anxiety pathology [74[■]]. The goal is then to violate these expectancies via repeated exposures to the feared situations. Thus, increasing expectancies to allow maximal violation may represent a general strategy to augment extinction learning. Recent research, for instance, provided evidence that the combination of multiple fear stimuli during extinction training ('deepened extinction') attenuated the return of fear [49[■]]. Furthermore, although occasionally pairing, the fear stimulus with an aversive outcome causes sustained fear during extinction training ('occasional reinforced extinction'), first evidence suggests that it may also attenuate the return of fear in the long run [50]. Moreover, removal of 'safety signals and behaviors' (such as the presence of other persons, medication, or cell phones) may be another strategy to increase threat expectancies in the short run, but support their violation as the omission of the aversive outcome during extinction training is not associated with the safety signal or behavior (for a critical evaluation see [48,69[■]]).

Another target for augmentation results from findings that fear extinction hardly generalizes to different stimuli and contexts, that is, fear likely returns when a different fear stimulus is encountered or if the current context differs from the extinction context [75,76], see also [77]. Different ways of increasing the 'variability' of extinction training may target this crucial issue. First, fear stimuli during exposure may be varied rather than repeatedly extinguishing the same stimulus (as in habituation protocols). Accordingly, exposing spider-phobic individuals to different spiders enhanced the long-term outcome of virtual reality exposure compared to a single spider exposure only [51[■]]. Second, the level of anxiety itself may represent a source of variability. For example, a spontaneous higher variability in fear levels during exposure tasks predicted better outcome in anxious children [78]. Moreover, greater variability in fear levels throughout exposure positively predicted outcomes in contamination and public speaking anxiety [79,80]. Third, varying the duration and spacing of extinction trials may also enhance

exposure [69[■],81]. Finally, variability may also be increased by varying the context of exposure ('multiple contexts'; e.g., inside vs. outside, different internal contexts), which may attenuate context renewal. Similar to past results on multiple contexts [69[■]], current findings are still mixed. In a conditioning experiment, extinction in multiple context attenuated reinstatement, but not spontaneous recovery and context renewal [53]. Furthermore, exposure in multiple virtual contexts attenuated fear of spiders immediately after exposure, but no impact on the return of fear at a later test was observed [51[■]]. In contrast, exposure in multiple real-life contexts attenuated fear of spiders immediately after exposure and also attenuated the return of behavioral, self-reported, and physiological fear in the long run [52]. Given these mixed results, future research needs to address potential moderators or contextual features that may drive the attenuation of fear renewal.

Some behavioral strategies implemented during extinction training are supposed to target mechanisms other than the violation of expectancies or stimulus and context specificity. Verbally labeling the emotional content of a stimulus or emotional experiences ('affect labeling') may incidentally regulate the corresponding emotion, which involves similar prefrontal-amygdala regulations as in fear extinction [82[■]]. In public speaking anxiety, repeated affect labeling in combination with repeated speech exposures resulted in a steeper decline in physiological arousal following exposure than exposure alone; however, no effect was observed on self-reported anxiety [54[■]]. Further research on the augmentation effect of affect labeling is needed, especially, since this method implicitly is already a part of most exposure manuals.

FLANKING STRATEGIES BEFORE AND AFTER EXTINCTION TRAINING

Flanking strategies aim to provide conditions that support learning during extinction, consolidation of the extinction memory, and retrieval of this memory. For example, 'physical exercise' may increase memory and cognitive functions [83,84]. In line with this, exercising briefly before or after extinction training enhanced extinction of contextual fear in animals [62[■]]. In a pilot clinical trial, patients with posttraumatic stress disorder showed greater improvement after prolonged exposure when they exercised at moderate intensity prior to each exposure session [63[■]]. 'Positive affect induction' has recently been discussed as another strategy before extinction training as it translates recent findings that high dispositional positive

affect may be beneficial for extinction learning [85[■]] into therapeutic strategies. Positive mood induction by means of a positive imagery training indeed reduced the return of fear in a reinstatement test, but not for spontaneous recovery [61[■]]. This attenuation of fear recurrence may be linked to a reduction of negative valence of the fear stimulus under positive mood as sustained negative valence after extinction seems to predict reinstatement of fear [86[■]]. These two examples (physical exercise and positive mood induction) offer first support for an effective augmentation of exposure treatments by strategies that precede the actual exposure session.

Other strategies may specifically support the consolidation and retrieval of the extinction memory after an exposure session. Optimal effects of extinction training require accessibility of the corresponding memory in various contexts. ‘Retrieval cues’ [58] and ‘mental reversal’ [59] may augment this accessibility; however, research is still limited. ‘Sleep’ may represent another simple strategy to augment extinction memory as it improves memory consolidation [87–91]. In support, spider-phobic individuals who slept for 90 min after exposure showed lower self-reported fear and fear-related apprehension while approaching a spider 1 week later [60[■]]. These findings suggest that already acquired extinction learning is strengthened during sleep, so that conditions may be optimized for sufficient sleep after exposure. Interestingly, novel evidence also suggests that completely novel extinction learning may occur during sleep without prior learning under wakefulness. Specifically, participants were reexposed to a previously fear-conditioned tone in the absence of the aversive consequence either during wakefulness (i.e., standard extinction training) or during slow wave sleep [55[■]]. Surprisingly, when exposed to the tone for 10 min, both groups showed attenuated fear responses in a later test. These results provide first evidence for novel extinction learning during sleep. Although these results support a previous study [92], opposite results have also been reported (see [93[■]]). Given these mixed results, future research is required to determine if extinction training during sleep may further support exposure therapy.

Apart from the consolidation of extinction memory, behavioral strategies have also targeted the ‘reconsolidation’ of the original fear memory itself. A reactivation of a consolidated memory trace transfers the memory into a temporarily malleable state before being stored in long-term memory again, that is, reconsolidated [94]. This time window of reconsolidation allows manipulation of the labile memory and has thus become subject to extensive research on the possibility to change fear memories

(for recent reviews see [95,96,97[■]]). Behavioral approaches aim to manipulate fear memories by presenting new or corrective information during malleability of the memory [98,99]. Initially, reconsolidation interference was assumed to actually erase fear-relevant memory traces. However, most recent studies not only found a restriction of the interference to physiological fear levels while leaving declarative knowledge about the unconditioned stimulus–conditioned stimulus association intact [100], but even a full return of fear after manipulation [101]. Thus, reconsolidation more likely appears to be highly dependent on the mismatch between the stored information and actual experience (prediction error). The extent of this mismatch may be the determining factor to evoke either the formation of a new, competitive memory trace (extinction) or the updating of the original trace (reconsolidation) [8,102–104]. Seen in this framework, reconsolidation may be seen as a precursor of or adaptive process alternative to extinction, both mapping onto the same dimension of the processing of corrective information. However, the repeated failures to reliably replicate the reconsolidation effect itself [105–109] constitute a serious problem for clinical translations. Once more, mechanistic research is needed to pinpoint the conditions for a successful augmentation of exposure-based interventions.

CONSIDERATIONS FOR FUTURE RESEARCH AND IMPLEMENTATION IN CLINICAL PRACTICE

Certainly, future research will continue to pinpoint the effects of specific strategies to enhance extinction in anxious individuals. However, several crucial issues need to be addressed to allow a successful clinical translation. First, many strategies have only been supported by a limited amount of studies (e.g., positive affect, affect labeling) and results for other strategies are still mixed (e.g., multiple contexts, removal of safety behaviors). Replications are thus needed to prove reliable augmentation effects. Furthermore, the impact of various strategies has only been tested for immediate learning during extinction training, but needs to be expanded to the return of fear at later test. Second, laboratory extinction procedures need to be replicated in clinical studies with anxious individuals to increase their ecological validity. Third, very little is known about the impact of fear extinction and enhancement strategies on actual behavior. As avoidance behavior is a key feature of all anxiety disorders, future studies need to address potential changes in avoidance. Fourth, to support dissemination,

promising strategies need to be evaluated in a broader context of (cognitive-) behavioral treatments, which may represent the biggest challenge to achieve clinical impact. In therapy, exposure cannot be limited to a single and highly standardized procedure, but rather consists of different stages, such as motivation, preparation, actual exposure, and maintenance of behavioral change [110]. The consequences of enhancement strategies for these stages have rarely been considered. For example, safety signals and behaviors have been discussed to optimize the motivational antecedents of exposure, which are characterized by approach-avoidance conflicts [111[■],112,113[■]]. Despite a potentially detrimental effect on extinction learning, safety signals and behaviors may enhance the acceptability of exposure and, thereby, reduce dropouts and refusals [113[■],114]. Such opposing effects call for an individualized conceptualization of enhancement strategies to balance optimal fear extinction with preceding and subsequent therapeutic strategies. This individualization requires the field of fear extinction research to broaden its scope when investigating enhancement strategies.

CONCLUSION

Fear extinction processes play a crucial role in the development and maintenance of anxiety disorders. Behavioral strategies to enhance extinction may provide powerful clinical applications to further maximize the efficacy of exposure-based treatments. However, for most potential strategies, replications and future research are needed to verify their beneficial effects on fear extinction, increase ecological validity, and test their naturalistic utility. Most importantly, strategies need to be tailored to the individual patient to allow optimal balance between compliance and extinction learning.

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Conflicts of interest

There are no conflicts of interest.

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