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de Jong, Rachel; Lommen, Miriam J. J.; de Jong, Peter J.; Nauta, Maaïke H.

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**Using Multiple Contexts and Retrieval Cues in Exposure-Based Therapy to Prevent
Relapse in Anxiety Disorders**

Abstract

Purpose of review: The benefits of exposure-based interventions for anxiety disorders are substantial but not stable for everyone, given that these interventions are often followed by relapse of symptoms. A body of research provides a background on how to add certain strategies in exposure-based therapy to prevent relapse in anxiety disorders. This review summarizes some of these strategies and provides clear-cut clinical implications. **Recent findings:** Studies that provide support for two types of strategies to prevent relapse have been reviewed: the use of multiple contexts and the use of retrieval cues. The use of multiple contexts reduces context and stimulus specificity of extinction learning during exposure, while the use of retrieval cues enhances memory (re-)consolidation and retrieval after exposure. **Summary:** The described strategies to enhance the accessibility and therefore the retrievability of exposure-based learning to prevent relapse in anxiety disorders, can be summarized as an advice to conduct exposure under variable conditions. This way, the generalizability of what is learned during exposure to the patients' daily life after treatment improves. Therefore, adding these strategies in the course of exposure-based treatment of anxiety disorders seems beneficial. However, future replications and translational studies are needed to verify ecological validity.

Keywords: Exposure, Inhibitory learning, Relapse prevention, Anxiety disorders

Highlights

- The use of multiple contexts reduces context and stimulus specificity of extinction.
- The use of retrieval cues enhances memory retrieval of extinction learning.
- Optimizing the generalizability of exposure-based extinction learning prevents relapse.

Introduction

Anxiety disorders are a major concern of mental health given that the worldwide lifetime prevalence estimates of anxiety disorders are 4.8-31.0% (Kessler et al., 2007). In addition to being one of the most prevalent mental health problems, anxiety disorders are also among the most chronic (Barlow, 2004). Depending on the type of anxiety disorder, remission rates vary around 50% post-treatment and around 55% at follow-up (Springer, Levy, Tolin, 2018). Unfortunately, remission from an anxiety disorder does not mean that an individual will remain well, given that relapse of symptoms is frequent and characteristic of anxiety disorders (Bruce et al., 2005).

It is assumed that avoidance behaviors that prevent the extinction of fear, play an important role in the maintenance and recurrence of anxiety disorders. Therefore, exposure-based therapy for anxiety disorders aims to target these maladaptive avoidance behaviors, which allows extinction learning to take place. In the past few years, different strategies to optimize the generalizability of this exposure-based extinction learning have been proposed (f.e. Craske et al., 2008; 2014). Recent findings on the effect of two of these strategies, namely the use of multiple contexts and retrieval cues, will be summarized in this article, followed by implications for the treatment of anxiety disorders in clinical practice.

In the process of extinction, one can distinguish context and cues. A context is broadly defined as the set of circumstances around an aversive event (or unconditioned stimulus: US), and can to a certain extent be separated from cues (or conditioned stimuli: CS) that are considered signals for aversive events. Contexts can be external (e.g., places and times), internal (e.g., physiological or psychological states) or interpersonal (e.g., social and cultural contexts) (Maren, Luan Phan, Liberzon, 2013). During extinction, these cues (CS) are repeatedly presented in the absence of the aversive event (US). This is found to be a powerful

way to reduce fear and avoidance behavior in a laboratory setting. Note that these cues (CS) may occur in different contexts and may therefore also be referred to as contextual cues.

To be able to extinguish fear in a clinical setting, Wolpe (1958) developed an early method of exposure called systematic desensitization, which is derived from the laboratory model of extinction learning. Based on systematic desensitization, different forms of exposure have been developed over the years, which are described in Box 1. All forms of exposure aim to target the maladaptive avoidance behaviors of the patient by asking a patient to repeatedly and systematically approach, instead of avoid, the stimuli that elicit fear in different contexts. During these approaches, the patient is repeatedly exposed to contextual cues (CS) in the absence of the aversive event(s) (US).

Box 1 here.

Nowadays, most psychotherapies for anxiety disorders share exposure techniques as their main ingredient. These exposure-based interventions are generally effective in the treatment of anxiety disorders, considering a success rate around 50% post-treatment and around 55% at follow-up in both children and adolescents (Rapee, Schniering, & Hudson, 2009) as well as in adults (Loerinc, et al., 2015; Springer, Levy, Tolin, 2018).

The ‘emotional processing’ theory (EPT) provides a possible explanation for the positive effects of exposure-based interventions in treating anxiety disorders (Foa & Kozak, 1986; Foa & McNally, 1996; Rachman, 1980). In the development of this theory, two lines of basic science research are reflected. The first line includes research focusing on extinction learning, since - as described above - the extinction of conditioned fear for contextual cues can be viewed as a laboratory analogue of exposure (Mineka, 1985). The second line concerns research focusing on learning and memory, since what is learned in treatment needs to be remembered once therapy is finished.

Based on these two lines, the EPT proposes that reduction of fear throughout treatment by means of habituation is reflective of ‘corrective’ learning and essential to the therapeutic outcome. ‘Corrective’ meaning that the original CS-US association (e.g., CS: dog, US: bite) learned during fear acquisition is erased during extinction of the fear response (or conditioned response: CR). This corrective learning occurs after activation of a ‘fear structure’ and integration of information that is incompatible with this fear structure. This results in the development of a non-fear structure that replaces (Foa & Kozak, 1986) or competes with (Foa & McNally, 1996) the original structure. The fear structure is a set of propositions about a stimulus (e.g., dog), response (e.g., screaming), and their meaning (the aversive event, e.g., “it will bite me to death”) that are stored in memory. The EPT proposes that habituation within and between exposure sessions reflects that the patient integrated the incompatible information (e.g., “this dog doesn’t bite”).

However, Craske and colleagues (2008; 2013) found that habituation within sessions and between sessions does not always seem to be the best predictor of treatment outcome and success. Therefore, it has been argued that inhibitory learning - instead of ‘corrective’ learning - is central to extinction of fear, and thus to exposure (Bouton, 1993; Craske et al., 2008; 2014; Miller, & Matzel, 1988). In this inhibitory learning model, disconfirming expectancies regarding the likelihood of the occurrence of the aversive event(s) (US) are believed to be essential to the therapeutic outcome (Craske, Treanor, Conway, Zbozined, & Vervliet, 2014). Extinction is assumed to follow from a mismatch between the expectancy of an aversive event and the absence of its occurrence (Rescorla & Wagner, 1972), or from the perception of a negative change in the rate at which the aversive event is associated with the contextual cues (CS) (Gallistel & Gibbon, 2000). By repeatedly experiencing that the aversive event does not occur as expected, or at least not as often as expected, the patients’ erroneous expectancies are disconfirmed. This continued disconfirmation leads to the extinction of fear

and provides the patient with an opportunity to learn more adaptive responses to the contextual cues.

Unfortunately, the benefits of exposure-based interventions are not stable for everyone, given that about 40% demonstrate a relapse of symptoms after exposure-based treatment of anxiety (Craske & Mystkowski, 2006; Ginsburg et al., 2014). One of the studies on the long-term effects of psychological treatment of anxiety disorders was conducted by Fava, Zielezny, Savron and Grandi (1995). In this study, many participants who were classified as treatment responders still had some residual avoidance after treatment. Among these, two-thirds relapsed within five years. This finding - that the presence of residual avoidance at the end of behavioral treatment is associated with relapse over time – has been replicated in later studies (e.g., Dow et al., 2007). Moreover, more residual avoidance at the end of behavioral treatment is associated with a shorter time to relapse compared to those with less residual avoidance at the end of treatment (White et al., 2013). In order to prevent relapse of symptoms, this tendency to engage in avoidant coping strategies needs to be addressed in therapy. Given that exposure targets these avoidance behaviors, optimizing exposure techniques might reduce relapse after exposure-based interventions of anxiety disorders.

In the inhibitory learning model it is recognized that inhibitory learning is subject to influences such as context and time (Craske et al, 2008). The model distinguishes three contexts: the pre-exposure context of onset (A), the exposure context (A or B), and the post-exposure context (A or B or C). Inhibitory learning in these contexts means that the original CS-US association learned during fear conditioning (in context A) is not erased during extinction (in context A or B), but is left intact while a new CS-noUS association develops next to it. In this way, extinction is a process in which the CS acquires two meanings: the original excitatory meaning (CS-US: dog - will bite me) as well as a new inhibitory meaning (CS-noUS: dog - will not bite me). In this inhibitory learning model of exposure it is not

necessarily the level of fear reduction throughout exposure that is considered as an index of learning, but the strength of the associations after exposure (in context A or B or C) (Bouton, 2002). This is also shown in Figure 1.

Figure 1 here.

As mentioned above, context is one of the factors that determines whether the original excitatory association or the new inhibitory association is activated after exposure (Bouton, 1993). Therefore, strategies that enhance the strength of the inhibitory association (CS-noUS) in *various* contexts could possibly prevent the return of fear and therefore relapse of symptoms after exposure-based interventions. Suggestions on which strategies could be used to strengthen the inhibitory association have already been proposed by Craske and colleagues (2008; 2014). One of the described approaches suggests conducting exposure in multiple contexts (A and B and C), especially when the feared stimulus is likely to be encountered again once treatment is over (Craske et al., 2008). Another approach to enhance the strength of the acquired inhibitory association is to provide a ‘bridge’ from the exposure context to contexts likely to be encountered after treatment. One such bridge is the use of retrieval cues (of the CS-noUS association) during exposure, that can be used in other contexts once treatment has finished (Bouton, Garcia-Gutierrez, Zilski, & Woody, 2006). Recent findings on the effect of the use of multiple contexts and retrieval cues in attenuating return of fear after exposure will be the focus of this article, followed by clinical implications for the exposure-based treatment of anxiety disorders as illustrated by the descriptive case example of Anna.

Anna was bitten by a large black dog at the age of fifteen. Subsequently, she became fearful of dogs and avoided dogs where- and whenever possible. Anna’s therapist helped Anna to repeatedly expose herself to dogs in six sessions. If the six treatment sessions for Anna’s dog phobia took place in the therapists office only, then Anna may

not fear a dog in the therapists office (safe context: inhibitory meaning of the CS activated). But, she may still fear a dog when encountering one in the park (unsafe context: excitatory meaning of the CS activated) (Maren, Phan, & Liberzon, 2013). As pictured in Figure 1, the inhibitory meaning of the CS does not tend to generalize to contexts that differ from the context of exposure. This implies that if Anna acquired her dog phobia in the park (pre-exposure context of onset A), and is only exposed to dogs in the therapists office during treatment (exposure context B), she might not fear dogs in the therapist office after treatment (same post-exposure context B), but might still fear dogs when encountering one in the park (different [old] post-exposure context A) or that are held as pets at home (different [new] post-exposure context C).

Mechanisms of Relapse in Anxiety Disorders after Exposure-Based Interventions

As an explanation of the high number of relapses after exposure-based treatment of anxiety disorders, Bouton (2002) described four mechanisms of return of fear after extinction. And although relapse can be caused by more than these four mechanisms, their description has inspired researchers to discover ways to prevent relapse by optimizing exposure techniques. The first relapse mechanism as described by Bouton (2002) is spontaneous recovery, meaning that the strength of the CR (fear) increases again with the passing of time after the end of extinction.

Second, recovery of the CR can occur when the context changes after extinction. This context renewal effect can take various forms and is observed when people have acquired certain behaviors in one context (A), learn new behaviors in a different context like therapy (B), then return to the original context of conditioning (A) (ABA renewal) (Neumann & Longbottom, 2007; Vansteenwegen et al., 2005). To a lesser extent, context renewal is also observed when people turn to a new context (C) that differs from both the context of

conditioning (A) and the context of extinction (B) (ABC renewal) (Effting & Kindt, 2007). Another kind of context renewal, that has been found in rodents but remains to be studied in humans, occurs when a new context (B) is encountered that differs from the context in which both conditioning (A) and extinction (A) took place (AAB renewal) (Thomas, Larsen, & Ayres, 2003). In other words, the extinguished response (no fear) learned during exposure does not easily generalize to other contexts than the context in which the exposure took place, while - perhaps for evolutionary reasons - the conditioned response (fear) *does* generalize easily to new contexts (Bouton, 1994).

A third mechanism of relapse as described by Bouton (2002) is reinstatement of the CR, when people are exposed to an *unpaired* US (bite) after extinction (Van Damme, Crombez, Hermans, Koster, & Eccleston, 2006). This implies that the occurrence of an adverse event (bite) following exposure may lead to a return of fear for the previously feared stimulus (dog) even though this bite was not of a dog.

A fourth and final mechanism is rapid reacquisition of the CR when the CS (dog) is *paired* with a US (e.g., bite) again after extinction. In case of dog phobia, this may occur when the patient experiences an adverse event with a dog after treatment, like a bite or other incident.

In sum, to prevent relapse of anxiety symptoms after treatment, therapists using exposure techniques need to anticipate on all four described mechanisms of fear recovery. In line with this, recent studies investigated ways to prevent these mechanisms of relapse in different conditioning paradigms, to inform us about clinical implications for exposure-based interventions. Although most of these studies focused on preventing fear renewal, we will also review studies on the other mechanisms of relapse wherever applicable. Following every paragraph, we summarize the clinical implications we can derive from these findings for the treatment of anxiety disorders. To illustrate these implications, we refer to a case example of

phobic fear, although the same principles apply to other anxiety disorders like panic disorder, generalized anxiety disorder and social anxiety disorder. Regarding these insights we can provide therapists with evidence-based recommendations for enhancing the maintenance of the benefits of exposure and preventing relapse after successful treatment.

Luckily, Anna's therapist conducted the first three treatment sessions in his office, and the second three sessions in a park. After these six sessions, Anna was able to be around dogs with minimal discomfort and she no longer avoided them. Both Anna and her therapist regarded this treatment outcome as a success and decided that no further therapy was necessary. A year later, Anna experienced some moments of fear again when walking in a different park, and her tendency to avoid dogs was renewed. As a consequence, Anna experienced a relapse of her dog phobia. Anna's fear of dogs may have extinguished through exposures to dogs in the park near the therapist's office, but may have reemerged when she entered a different park (renewal). Anna's fear may also have reemerged after not seeing dogs for a while (spontaneous recovery). Or Anna's fear of dogs may have reemerged after she experienced a bite of another animal like a cat (reinstatement). Finally, Anna's fear may have reemerged after another adverse event with a dog other than a bite, for example a dog peeing over her shoes (rapid reacquisition). As seen in Anna, return of fear – and therefore relapse of her dog phobia - results from a failure to activate the inhibitory meaning of the CS in a different context than the exposure context (AAB, ABA, or ABC renewal).

Preventing Relapse in Anxiety Disorders after Exposure-Based Interventions

Using Multiple Contexts

Bouton (1993) proposed that the context of the CS determines whether the excitatory (bite) or inhibitory meaning (no bite) of the CS (dog) is activated after exposure. The exposure context can be divided into four domains. The first one includes (1) the exposure stimuli themselves (i.e., the specific situations and stimuli that patients confront; e.g., exposure to multiple spiders). The following three context domains are the ones described previously (Maren, Phan, Liberzon, 2013), (2) the external environment (i.e., the surroundings in which exposure occurs; e.g., exposure to multiple spiders outdoors and indoors), (3) the internal environment (i.e., the physiological or psychological states of the patients during exposure; e.g., exposure to multiple spiders after drinking coffee versus after drinking water), and (4) the interpersonal environment (i.e., the surrounding people or culture in which exposure occurs; e.g., exposure to multiple spiders alone versus with a therapist) (Jacoby & Abramowitz, 2016).

Context of exposure stimuli. Given that what is learned during exposure does not easily generalize while conditioned fear *does* generalize easily, it is expected that patients who receive all exposure sessions with the same exposure stimulus (e.g., the same dog) show failed generalization of inhibitory learning when they are confronted with a novel stimulus (e.g., a different dog). This is especially salient since patients with anxiety disorders show deficits in inhibitory learning (Duits et al., 2015). Change in the stimulus after extinction has indeed been found to cause return of fear in a human conditioning paradigm (Vervliet, Vansteenwegen, Baeyens, Hermans, & Helen, 2005). A first clinical study on this subject found that conducting exposure using four spiders of different size, appearance and quickness, compared to exposure using a single spider, resulted in similar improvements in the short-

term, yet less return of fear three weeks later (Rowe & Craske, 1998). Another study of contamination anxiety, however, showed trends regarding less return of fear only (Kircanski et al., 2012). A more recent study on the use of multiple virtual reality stimuli (four different virtual spiders instead of a single virtual spider) has been found to reduce short and long term return of fear (Shiban, Schelhorn, Pauli, & Muhlberger, 2015).

In the context of treating Anna's dog phobia, different approaches may be helpful to enhance generalizability of what she learns during exposure. For instance, practicing handling different dogs who may all react differently. These dogs can be different in size, color, level of activity and training, while their reactions can differ in predictability. As a therapist, consider to let Anna decide on forehand to approach every fifth dog she encounters: regardless of how friendly or threatening it comes across.

External contexts. Recent animal and human conditioning studies found the use of different surroundings to attenuate fear renewal in both ABA designs (Balooch & Neumann, 2011) and ABC designs (Balooch, Neumann, & Boschen, 2012; Bustamante, Uengoer, Thorwart, & Lachnit, 2016; Gunther, Denniston, & Miller, 1998). However, Gunther et al. (1998) showed that extinction in multiple contexts failed to reduce fear renewal when fear conditioning had occurred in the same number of contexts. This implies that the number of exposure contexts should exceed the number of contexts in which the fear is acquired. However, no human studies have evaluated the number of exposure trials or contexts needed to offset spontaneous recovery, renewal or reinstatement. In addition, although the context of onset (acquisition) might be clear in a laboratory setting, it is often hard for individuals to recollect the context of initial fear conditioning in real life settings.

Although two other conditioning studies in humans failed to find that the use of multiple external contexts attenuates fear renewal (Bouton, Garcia-Gutierrez, Zilski, &

Moody, 2006; Neumann, Lipp, & Cory, 2007), positive results have been found in studies resembling clinical practice. For example, exposure conducted in multiple *real-life* contexts (different locations within the university campus), reduced both short-term and long-term fear of spiders (Bandarian-Balooch, Neumann, & Boschen, 2015). Treatment of spider phobia using virtual reality exposure in which spider-phobic participants were exposed to spiders in multiple contexts (different rooms) was more effective in reducing return of fear than exposure to spiders in a single context (same room) (Shiban, Pauli, & Muhlberger, 2013). However, this effect of exposure in multiple *virtual* contexts was only evident on the short-term, but not on the long term (Dunsmoor, Ahs, Zielinski, & LaBar, 2014; Shiban, Schelhorn, Pauli, & Muhlberger, 2015; Vansteenwegen et al., 2007). The effect on the short term was stronger for reinstatement of fear than fear renewal, and the absence of an effect on the long term implies that the use of multiple *virtual* contexts may not prevent spontaneous recovery.

So, the reducing effect of exposure on return of fear partially depends on the degree of context similarity between the context of onset (A), the context in which the exposure is conducted (A or B), and the contexts encountered thereafter (A or B or C). Therefore, exposure conducted in multiple contexts may have a stronger reducing effect on return of fear when the exposure (i.e., extinction) contexts are more similar to the contexts likely to be encountered after treatment (AAB or ABB) than when they are different (ABA or ABC). In line with this, an animal conditioning study varying odor and location showed that fear renewal can be attenuated by making the extinction context resemble the acquisition context (AAB) (Thomas, Larsen, & Ayres, 2003). In addition, a human conditioning study varying the lightning level showed that fear renewal was completely abolished when multiple extinction contexts that were similar to the test context were combined (ABB) (Balooch & Neumann, 2011). Thus, not only the use of multiple external contexts that are *dissimilar* to the context of onset (ABA or ABC), but also multiple external contexts that are *similar* to either

the context of onset (AAB) or the context most likely to be encountered after treatment (ABB) seem to be effective in reducing fear renewal. However, as mentioned before, it is often hard for individuals to recollect the context of initial fear acquisition in real life settings.

During treatment, Anna and her therapist should use multiple external contexts in which places and times are varied. For Anna, this implies practicing handling dogs in small and big parks, during quiet and busy hours, during daytime and possibly also night time (with parental supervision), in her own neighbourhood and possibly also in unknown parts of town (with parental supervision), in open and more grown areas of the parks. For the therapist, this implies integrating contexts into treatment that resemble the context(s) in which Anna thinks she acquired her dog phobia, as well as contexts that she is likely to encounter once the therapy is over. In the case of Anna, who has been bitten by a large black dog at the age of fifteen, this means she will need to practice with a similar dog. Also, she knows that a family in her neighbourhood has a black dog, which makes her nervous for the yearly neighbourhood BBQ. She is encouraged to also practice with this particular dog.

Internal contexts. In 1991, Bouton and Swartzentruber already proposed that when the context changes, fear responding often restores. They described these contexts not only as external, but also as internal physical or psychological states, like arousal or mood. Arousal can be induced by giving caffeine to participants. It is hypothesized that fear is more likely to return in a dissimilar level of arousal. In line with this, it has been found that spider-phobic participants experiencing incongruent arousal states during treatment and follow-up (only caffeine intake during either treatment *or* follow-up), showed greater return of fear than those experiencing congruent states of arousal (caffeine intake during both treatment *and* follow-up or no caffeine intake during both) (Mystkowski, Mineka, Vernon, & Zinbarg, 2003). This

state dependent learning phenomenon as first described by Girden and Culler (1937) can thus be applied to inhibitory learning, and therefore to exposure as well.

In the context of exposure, learning may also take place state-dependently, and it may require a large variability in levels of arousal during exposure exercises. Although one study failed to find this (Meuret, Siedel, Rosenfield, Hofmann, & Rosenfield, 2012), other studies have found that variability in subjective fear during exposure predicted lower subjective fear levels at follow up in a group of patients with fear of public speaking (Culver, Stoyanova, & Craske, 2012) and contamination (Kircanski et al., 2012). Thus, patients who learned to tolerate varying levels of fear-induced arousal during exposure showed better long-term treatment outcomes compared to patients who learned to tolerate just one level of fear arousal.

In the course of treating Anna, we suggest the use of multiple internal contexts in which physiological and psychological states are varied. For Anna, this implies practicing handling dogs before and after caffeine intake, like coffee, tea, soda or dark chocolate. As a therapist, it is important to explain to Anna why practicing both before and after caffeine intake is important, because caffeine intake increases arousal and could possibly cause unwanted physical sensations like a racing heart or dizziness. Practicing before, in and just after this physical state will help Anna to realise that unregarding her physical state or level of arousal, dogs don't bite. However, it is important that exposure before and after caffeine intake is only conducted when consent is obtained from both Anna and her parents. In addition, it is especially relevant to help Anna tolerate not only varying levels of caffeine-induced arousal, but also varying levels of fear and fear-induced arousal during treatment. Regarding practicing by herself, the therapist will explain to Anna that she needs to practice in different emotional states. For instance, she is encouraged to do her exposures despite feeling tired, down or irritated. It is helpful to plan the exposure tasks and have Anna

conduct them irrespective of her emotional state. Otherwise, Anna may only do exposure when feeling “strong enough”. Then, she may not learn that she can also handle the situation when feeling tired, down or irritated, and the chances of relapse may increase.

Interpersonal contexts. As described before, conditioned safety does not easily generalize while conditioned fear *does* generalize easily. It is therefore expected that patients who receive all exposure sessions within the same social context (e.g., the same therapist), show failed generalization of inhibitory learning when they are confronted with a new social context (e.g., another therapist or no therapist at all). Change in the therapist presence during or after exposure has indeed been found to cause return of fear in a clinical analogue study with spider-phobic participants (Mystkowski, Craske, & Echiverri, 2002). Varying not only the presence of a therapist but also varying different therapists over the course of the treatment might thus have beneficial effects on the outcome of exposure.

Considering the overall course of therapy, we suggest to let Anna practice with different therapists and by herself with no therapist present at all. In addition to varying the interpersonal context, we suggest varying the sociocultural context in which she practices, and also taking into account social and cultural reality of her daily life. For Anna, adding social and cultural diversity to her exercises implies practicing in different neighborhoods, in school and outside of school, and with dogs from families from different cultures. Taking into account the social and cultural context, a therapist will look for exercises that are relevant and appropriate for the patient. One patient may want to be able to have a dog as a pet in her house, while for other patients it may be enough to tolerate dogs in a park. Moreover, only contexts in which fear is disproportional are appropriate for exposure exercises. For example, practicing in a dangerous neighborhood, in a hostile school environment or with an

aggressive dog that is known to bite often, are no good exposure exercise options. As a therapist, one should always aim for minimizing objective health and safety risks when practicing with a patient. It may be helpful to get information about what is socially and culturally appropriate in the context of the patient, either by asking the patient or by having the patient and the family gain information from important others about the safety of certain parks, neighborhoods, schools or dogs. In Anna's case, this means that she decides to practice walking in a park in some neighborhoods only at daytime and not during nighttime, like others of her peer group.

In sum, it is advised to conduct exposure in multiple contexts that are in some ways similar and in some ways dissimilar to the context of onset and the contexts likely to be encountered after treatment (A and B and C). It seems recommendable to conduct exposure outdoors and indoors, in familiar and unfamiliar places and at varying times and days. In addition, using different stimuli to induce various levels of arousal seems to be beneficial. And possibly most importantly: let the patient practice together with a therapist *and* alone, considering that the therapist will not be there anymore once the treatment has finished (Craske, Treanor, Conway, Zbozined, & Vervliet, 2014).

Using Retrieval Cues

Bouton (1993) suggested that return of fear may also be due to a failure to retrieve a memory of extinction. So when returning to the fear conditioning context, the patient recalls a memory of conditioning, not of extinction, and reacts accordingly (i.e., shows the CR: fear). The more contexts that are used in exposure, the more diverse the conditions under which inhibitory learning takes place. These more diverse conditions generate a greater number of retrieval cues, which trigger memories of the extinction that occurred during exposure. By this means, retrieval cues function as a bridge from the exposure context to the contexts likely to

be encountered once treatment has finished, which improves the generalizability of inhibitory learning (Jacoby & Abramowitz, 2016). Like contexts, retrieval cues can be divided in external and internal cues.

External retrieval cues. The described bridge from the exposure context to other contexts can be provided by instructing patients to wear a retrieval cue (e.g., a bracelet or necklace) during (for (re-)consolidation) and after exposure therapy (for retrieval). Although such external retrieval cues seem to be able to attenuate fear renewal in some human conditioning studies (Dibbets, Havermans, & Arntz, 2008; Vansteenwegen et al., 2006) especially when positive retrieval cues like a smiley are used (Dibbets & Maes, 2011), other studies found only a weak effect of the use of retrieval cues upon fear renewal reduction using a similar conditioning paradigm (Culver, Stoyanova, & Craske, 2011). In addition, in clinical analogue studies in which patients with spider phobia or public speaking fear wore a retrieval cue during exposure therapy and thereafter at home until follow-up, no effect of these cues on fear renewal was found (Dibbets, Moor, & Voncken, 2013; Laborda et al. 2016). However, a recent clinical analogue study showed that retrieval cues failed to reduce renewal, but were able to reduce spontaneous recovery in participants with fear of public speaking (Shin, & Newman, 2017). Interestingly, the reducing effect of these retrieval cues on spontaneous recovery was stronger when cues reminded the participants of feeling anxious during exposure instead of when cues reminded participants of feeling comfortable. In sum, external retrieval cues like reminder objects seem to have only limited effect on reducing fear renewal after exposure-based interventions, although they may have a reducing effect on spontaneous recovery of fear.

Internal retrieval cues. A second and possibly more effective retrieval cue can be provided by instructing patients to actively recall the exposure contexts when encountering an anxiety provoking situation after treatment. A clinical analogue study evaluating the role of

mental rehearsal of the therapy context on return of fear found that participants with spider phobia who mentally rehearsed the treatment context before encountering the phobic stimulus (spider) in a different context after treatment, showed less return of fear than those who did not rehearse the treatment context (Mystkowski, Craske, Echiverri, & Labus, 2006). The same was found in a study evaluating the effect of mentally rehearsed retrieval cues on dental phobia (Elsesser, Wannemuller, Lohrmann, Jhren, & Sartory, 2013). However, a more recent study failed to replicate this effect for fear of public speaking (Laborda et al., 2016).

These findings suggest that internal retrieval cues (e.g., mentally rehearsing the treatment context) have a more robust effect on reducing fear renewal than external retrieval cues (e.g., objects to remind one of what is learned in the treatment context). In addition, mentally rehearsing the exposure context may have more practical value than reminder objects, since the CS might be encountered at times after treatment when the reminder object is not available (Mystkowski & Mineka, 2007). Moreover, a risk of retrieval cues is that they may acquire an inhibitory value and become a safety signal or safety behavior (Dibbets, Havermans, & Arntz, 2008).

Safety behavior is the use of avoidance during exposure, which enhances feelings of safety in the presence of perceived threat (Salkovskis, 1991). However, when a patient engages in safety behavior, the absence of the feared outcome will be falsely attributed to this safety behavior. In other words, it could be argued that safety behavior prevents an individual from gaining realistic information that contradicts their existing beliefs about the feared situation or object (Hedtke, Kendall, & Tiwari, 2009). Although patients who use safety behaviors during exposure will experience less fear, their erroneous fear beliefs will not be disconfirmed. Their threat beliefs are preserved, which causes fear to return later on (Meulders, van Daele, Volders, & Vlaeyen, 2016).

Retrieval cues differ from safety signals in that they inform the patient about the CS-noUS association, whereas safety signals directly inform the patient about the nonoccurrence of the US. This is an unfavorable outcome, as it is counterproductive to the effect of exposure to create dependence on safety signals or behaviors. In fact, breaking dependence on safety signals is often a primary goal of exposure-based treatment, given that safety signals and behaviors can be maladaptive in the long term by prolonging anxiety and fear of nonthreatening situations (Vervliet, Craske, & Hermans, 2013).

In Anna's case, we suggest her to wear certain jewelry, or carry a certain keychain or little object in her wallet during and after treatment of her dog phobia. This will remind her of her experiences handling dogs during treatment, and help her remember that she can also handle dogs after treatment. In addition, she can take a photo or video of herself during one of the exposures in treatment. Looking at this photo or video after treatment will remind her of the exposure context and what she learnt from the exposure exercise(s). However, there is also a chance that Anna starts to attribute the nonoccurrence of the bite to wearing the 'lucky object' or the ritual of mentally rehearsing. If this happens, the retrieval cue has become a safety signal. In that case, Anna is encouraged to stop using the retrieval cues that have become safety signals and engage in exposures without them, in line with handling safety signals in general. For instance, she notices that her jogging trousers - that she started wearing to the park because it reminded her of feeling strong - became a safety signal when she got reluctant to go to the park in skirts, expecting that dogs were more likely to run after skirts than after jogging trousers. Retrieval cues that function as an encouragement to engage in exposure can be contained.

In sum, any retrieval cue should be used with care to avoid their likelihood of negatively impacting treatment progress. Preferably, patients are prompted to remind

themselves of the context of exposure and the anxiety they felt and tolerated in this context, each time they encounter previously feared stimuli, in order to reduce return of fear and prevent relapse of symptoms.

Considerations for future research

Overall, the empirical literature evaluating hypotheses derived from the inhibitory learning approach to exposure is still in an early stage. Multiple questions regarding the use of the described strategies to improve inhibitory learning and how these findings can be translated to actual clinical practice still need to be addressed in future research. First of all, replications of the reviewed studies are needed to test the utility and effectiveness of the described strategies by themselves and their additional value when used in combination with each other or with new strategies (Bouton, 2002; Pittig, van den Berg, Vervliet, 2016). In addition, the described strategies are aimed at optimizing *exposure-based* interventions. It should be noted however, that exposure is just one element in the different psychotherapies for anxiety disorders. Future studies should investigate whether optimization of other elements in psychotherapy for anxiety could also reduce return of fear and relapse after treatment.

Second, future research aimed at enhancing the therapeutic outcome of exposure therapy should consider the validity of laboratory-based treatment research when translating findings from animal or human conditioning paradigms to exposure in clinical practice (Scheveneels, Boddez, Vervliet, & Hermans, 2016). As described above, extinction training is used as the laboratory analogue of exposure, since in both, the repeated confrontation with a CS results in a decrease in outcome variables that are indicative of the CR. In addition, return of fear is considered the laboratory analogue of relapse, because a context switch between the extinction phase and the test phase causes a return of the CR, similar to a clinical relapse after successful treatment when the CS is encountered outside the therapy context (Effting & Kindt, 2007). However, there are mechanisms that are at work in exposure but not in the extinction model, like the valence of the CR and CS, US-habituation and counterconditioning (McConnell & Miller, 2014), and social- and cultural factors that do not play a role in the lab.

Future studies should therefore aim to optimize the ecological validity of the conditioning paradigms used for translation from the laboratory to the clinic, in addition to gaining more ecological valid results by studying strategies to prevent relapse directly in the clinic (Vervliet, Baeyens, van den Bergh, & Hermans, 2013)

In line with this, future research should aim to define what constitutes a context in the laboratory and how this translates to the clinical field. There are three main approaches to define contexts: 1) context as perceptual cue(s) (Rudy, 2009), 2) context as temporal cue(s) (Grillon, 2002) and 3) context as functional cue(s) (Bouton, 2002). These different levels of contexts have been studied in the laboratory as distinct features, but co-occur in clinical practice. For example, contexts can be very local perceptually (e.g., the therapist office in a certain building in a certain city) but at the same time very global temporally (e.g., therapy during the three years of living in a certain city). Considering that learning will be more general when it is linked to a global context, or more specific when it is linked to a local context (Vervliet, Craske, & Hermans, 2013), research into co-occurrence of contexts during extinction in conditioning paradigms and exposure in clinical analogue studies could possibly provide us with more insight into ways to optimize the use of multiple contexts to tackle return of fear.

Thirdly, the relatively young field of neuroscience research might also be able to provide us with new strategies to offset return of fear and therefore relapse. Given that context specificity of extinction is largely dependent on the hippocampus (Fanselow, 2000), the use of strategies aimed at downregulating the hippocampus during extinction offers the potential to increase generalization of extinction learning (Craske, 2015). A neuroscientific review of a series of small-scale studies described promising results for the use of pharmacological interventions such as d-cycloserine, yohimbine, cortisol and L-DOPA as downregulators of the hippocampus (De Carvalho Myskiw, Furini, Benetti, & Izquierdo, 2014). However, a

more recent review of larger-scale studies yields more mixed results, with some studies showing only weak or no effects of d-cycloserine (Otto et al., 2016). Exposure to a novel context briefly before or after extinction to downregulate the hippocampus seems to have more promising effects (De Carvalho Myskiw, et al., 2014). Future research should investigate whether these pharmacological enhancers and the use of novelty contexts can attenuate the context specificity of exposure by weakening the fear memory itself (Singewald, Schmuckermair, Whittle, Holmes, & Ressler, 2015).

It is important to note, that the described strategies used in conditioning and clinical analogue studies aim at reducing return of *fear*, and not the return of *anxiety* per se. Fear, in this sense, can be seen as the result of cued fear conditioning: a cue (e.g., tone or dog) is followed by an aversive outcome (e.g., shock or bite). Anxiety, on the other hand, can be seen as the result of context conditioning: a context (e.g., certain box or park) is followed by the anticipation of an aversive event (e.g., shock or bite). It is this anticipatory anxiety that often causes the residual avoidance or return of fear and thus relapse (Rodriguez, Craske, Mineka, & Hladek, 1999). Therefore, future research should not only aim at finding new or adapting current strategies to reduce the return of fear directly, but also strategies that could reduce anticipatory anxiety and thereby reducing return of fear indirectly.

Finally, the described strategies to tackle return of fear have mainly been studied in anxiety disorders. However, exposure is applied in treatment for a variety of other disorders as well, like obsessive-compulsive disorders, trauma, addiction, feeding and eating disorders and psychopathologies in which aggression- and emotion regulation problems play a central role. Although it is expected that findings from the above described studies generalize to these psychopathologies, future research needs to study these strategies directly in these specific patient populations. Only this will allow the drawing of conclusions about their long term effectiveness on exposure-based treatment outcome, which can be used to provide therapists

with evidence-based recommendations for enhancing the maintenance of the benefits of exposure-based interventions for these patients too.

Conclusion

In conclusion, it can be suggested that extinction is relatively easy to *learn* but difficult to *remember* (Vervliet, Craske, & Hermans, 2013). The described strategies to enhance the accessibility and therefore the retrievability of exposure-based learning to prevent relapse of anxiety disorders, can be summarized as an advice to conduct exposure under variable conditions. This can make inhibitory learning and retrieval of the inhibitory (CS-noUS) association more difficult on the short-term, but might lead to long-term benefits for the following reasons. First, repeated practice provides more opportunities for inhibitory learning, and therefore promotes greater storage and retrieval strength to enhance long-term retention. Second, the more diverse the conditions in which the inhibitory learning takes place, the more retrieval cues can be generated. These cues can trigger memories of the learning that occurred during exposure, and therefore improve the generalizability of this learning. Finally, to develop a strategy for handling aversive (like phobic) stimuli across different contexts, engaging in analysing, evaluating and synthesizing what is learned - instead of only remembering - seems to be beneficial (Jacoby & Abramowitz, 2016). In sum, this transfer-appropriate processing (Morris, Bransford, & Franks, 1977), will not only help the patient to *learn*, but also to *remember*.

So, although relapse remains a pressing problem for the long-term efficacy of exposure-based treatment for anxiety disorders, the use of multiple contexts and retrieval cues in and after exposure has promising effects. And with relapse prevention being a major focus in both laboratory-based and clinical research, novel ways to tackle the context dependency of inhibitory learning are waiting to be discovered (Vervliet, Craske, & Hermans, 2013).

References

- Barlow, D. H. (2004). *Anxiety and its disorders: The nature and treatment of anxiety and panic*. Guilford press. ISBN: 978-1593850289
- Balooch, S. B., & Neumann, D. L. (2011). Effects of multiple contexts and context similarity on the renewal of extinguished conditioned behaviour in an ABA design with humans. *Learning and Motivation*, 42, 53-63. <https://doi.org/10.1016/j.lmot.2010.08.008>
- Balooch, S. B., Neumann, D. L., & Boschen, M. J. (2012). Extinction treatment in multiple contexts attenuates ABC renewal in humans. *Behaviour Research and Therapy*, 50, 604-609. <https://doi.org/10.1016/j.brat.2012.06.003>
- Bandarian-Balooch, S., Neumann, D. L., & Boschen, M. J. (2015). Exposure treatment in multiple contexts attenuates return of fear via renewal in high spider fearful individuals. *Journal of Behavior Therapy and Experimental Psychiatry*, 47, 138-144. <https://doi.org/10.1016/j.jbtep.2014.12.006>
- Bouton, M. E. (1993). Context, time and memory retrieval in the interference paradigms of Pavlovian learning. *Psychological Bulletin*, 114, 90-99. <http://dx.doi.org/10.1037/0033-2909.114.1.80>
- Bouton, M. E. (1994). Context, ambiguity, and classical conditioning. *Current Directions in Psychological Science*, 3, 49-53. <http://dx.doi.org/10.1111/1467-8721.ep10769943>
- Bouton, M. E. (2002). Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biological Psychiatry*, 52, 976-986. [http://dx.doi.org/10.1016/S0006-3223\(02\)01546-9](http://dx.doi.org/10.1016/S0006-3223(02)01546-9)
- Bouton, M. E., García-Gutiérrez, A., Zilski, J., & Moody, E. W. (2006). Extinction in multiple contexts does not necessarily make extinction less vulnerable to relapse. *Behaviour Research and Therapy*, 44, 983-994. <http://dx.doi.org/10.1016/j.brat.2005.07.007>
- Bouton, M. E., & Swartzentruber, D. (1991). Sources of relapse after extinction in Pavlovian and instrumental learning. *Clinical Psychology Review*, 11, 123-140. [http://dx.doi.org/10.1016/0272-7358\(91\)90091-8](http://dx.doi.org/10.1016/0272-7358(91)90091-8)

- Brooks, D. C., & Bouton, M. E. (1993). A retrieval cue for extinction attenuates spontaneous recovery. *Journal of Experimental Psychology: Animal Behavior Processes*, 19, 77-89.
<http://dx.doi.org/10.1037/0097-7403.19.1.77>
- Bruce, S. E., Yonkers, K. A., Otto, M. W., Eisen, J. L., Weisberg, R. B., Pagano, M., ... & Keller, M. B. (2005). Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *American Journal of Psychiatry*, 162, 1179-1187.
<https://doi.org/10.1176/appi.ajp.162.6.1179>
- Bustamante, J., Uengoer, M., Thorwart, A., & Lachnit, H. (2016). Extinction in multiple contexts: Effects on the rate of extinction and the strength of response recovery. *Learning & Behavior*, 44, 1-12. <http://dx.doi.org/10.3758/s13420-016-0212-7>
- Craske, M. G. (2015). Optimizing exposure therapy for anxiety disorders: an inhibitory learning and inhibitory regulation approach. *Verhaltenstherapie*, 25, 134-143.
<http://dx.doi.org/10.1159/000381574>
- Craske, M. G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., & Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. *Behaviour Research and Therapy*, 46, 5-27. <http://dx.doi.org/10.1016/j.brat.2007.10.003>
- Craske, M. G., & Mystkowski, J. (2006). Exposure therapy and extinction: Clinical studies. In M. G. Craske, D. Hermans, & D. Vansteenwegen (Eds.), *Fear and Learning: Basic Science to Clinical Application* (pp. 213–233). Washington, DC: APA Books.
ISBN: 978-1-59147-414-2
- Craske, M. G., Treanor, M., Conway, C. C., Zbozinek, T., & Vervliet, B. (2014). Maximizing exposure therapy: an inhibitory learning approach. *Behaviour Research and Therapy*, 58, 10-23. <http://dx.doi.org/10.1016/j.brat.2014.04.006>
- Culver, N. C., Stoyanova, M., & Craske, M. G. (2011). Clinical relevance of retrieval cues for attenuating context renewal of fear. *Journal of Anxiety Disorders*, 25, 284-292.
<http://dx.doi.org/10.1016/j.janxdis.2010.10.002>
- Culver, N. C., Stoyanova, M., & Craske, M. G. (2012). Emotional variability and sustained arousal during exposure. *Journal of Behavior Therapy and Experimental Psychiatry*, 43, 787-793. <http://dx.doi.org/10.1016/j.jbtep.2011.10.009>

- De Carvalho Myskiw, J., Furini, C. R. G., Benetti, F., & Izquierdo, I. (2014). Hippocampal molecular mechanisms involved in the enhancement of fear extinction caused by exposure to novelty. *Proceedings of the National Academy of Sciences*, *111*, 4572-4577. <http://dx.doi.org/10.1073/pnas.1400423111>
- Dow, M. G., Kenardy, J. A., Johnston, D. W., Newman, M. G., Taylor, C. B., & Thomson, A. (2007). Prognostic indices with brief and standard CBT for panic disorder: I. Predictors of outcome. *Psychological Medicine*, *37*, 1493-1502. <http://dx.doi.org/10.1017/S0033291707000670>
- Dibbets, P., Havermans, R., & Arntz, A. (2008). All we need is a cue to remember: the effect of an extinction cue on renewal. *Behaviour Research and Therapy*, *46*, 1070-1077. <http://dx.doi.org/10.1016/j.brat.2008.05.007>
- Dibbets, P., & Maes, J. H. (2011). The effect of an extinction cue on ABA-renewal: Does valence matter?. *Learning and Motivation*, *42*, 133-144. <http://dx.doi.org/10.1016/j.lmot.2010.12.003>
- Dibbets, P., Moor, C., & Voncken, M. J. (2013). The effect of a retrieval cue on the return of spider fear. *Journal of Behavior Therapy and Experimental Psychiatry*, *44*, 361-367. <http://dx.doi.org/10.1016/j.jbtep.2013.03.005>
- Duits, P., Cath, D. C., Lissek, S., Hox, J. J., Hamm, A. O., Engelhard, I. M., & Baas, J. M. (2015). Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depression and Anxiety*, *32*, 239-253. <http://dx.doi.org/10.1002/da.22353>
- Dunsmoor, J. E., Ahs, F., Zielinski, D. J., & LaBar, K. S. (2014). Extinction in multiple virtual reality contexts diminishes fear reinstatement in humans. *Neurobiology of Learning and Memory*, *113*, 157-164. <http://dx.doi.org/10.1016/j.nlm.2014.02.010>
- Effting, M., & Kindt, M. (2007). Contextual control of human fear associations in a renewal paradigm. *Behaviour Research and Therapy*, *45*, 2002-2018. <http://dx.doi.org/10.1016/j.brat.2007.02.011>
- Elsesser, K., Wannemüller, A., Lohrmann, T., Jöhren, P., & Sartory, G. (2013). Mental retrieval of treatment context in dental phobia. *Behavioural and Cognitive Psychotherapy*, *41*, 173-187. <http://dx.doi.org/10.1017/S1352465812000318>

- Fanselow, M. S. (2000). Contextual fear, gestalt memories, and the hippocampus. *Behavioural Brain Research*, 110, 73-81. [http://dx.doi.org/10.1016/S0166-4328\(99\)00186-2](http://dx.doi.org/10.1016/S0166-4328(99)00186-2)
- Fava, G. A., Zielezny, M., Savron, G., & Grandi, S. (1995). Long-term effects of behavioural treatment for panic disorder with agoraphobia. *The British Journal of Psychiatry*, 166, 87-92. <http://dx.doi.org/10.1192/bjp.166.1.87>
- Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: exposure to corrective information. *Psychological Bulletin*, 99, 20-35. <http://dx.doi.org/10.1037/0033-2909.99.1.20>
- Foa, E. B., & McNally, R. J. (1996). Mechanisms of change in exposure therapy. In M. Rapee (Ed.), *Current Controversies in the Anxiety Disorders* (pp. 329–343). New York: The Guilford Press. ISBN: 978-1572300231
- Gallistel, C. R., & Gibbon, J. (2000). Time, rate, and conditioning. *Psychological review*, 107, 289-344. <http://dx.doi.org/10.1037/0033-295X.107.2.289>
- Ginsburg, G. S., Becker, E. M., Keeton, C. P., Sakolsky, D., Piacentini, J., Albano, A. M., & Peris, T. (2014). Naturalistic follow-up of youths treated for pediatric anxiety disorders. *Journal of the American Medical Psychiatry Association*, 71, 310-318. <http://dx.doi.org/10.1001/jamapsychiatry.2013.4186>
- Girden, E., & Culler, E. (1937). Conditioned responses in curarized striate muscle in dogs. *Journal of Comparative Psychology*, 23, 261-274. <http://dx.doi.org/10.1037/h0058634>
- Grillon, C. (2002). Startle reactivity and anxiety disorders: aversive conditioning, context, and neurobiology. *Biological psychiatry*, 52(10), 958-975. [https://doi.org/10.1016/S0006-3223\(02\)01665-7](https://doi.org/10.1016/S0006-3223(02)01665-7)
- Gunther, L. M., Denniston, J. C., & Miller, R. R. (1998). Conducting exposure treatment in multiple contexts can prevent relapse. *Behaviour research and therapy*, 36(1), 75-91. [https://doi.org/10.1016/S0005-7967\(97\)10019-5](https://doi.org/10.1016/S0005-7967(97)10019-5)
- Hedtke, K. A., Kendall, P. C., & Tiwari, S. (2009). Safety-seeking and coping behavior during exposure tasks with anxious youth. *Journal of Clinical Child & Adolescent Psychology*, 38, 1-15. <https://doi.org/10.1080/15374410802581055>

- Jacoby, R. J., & Abramowitz, J. S. (2016). Inhibitory learning approaches to exposure therapy: A critical review and translation to obsessive-compulsive disorder. *Clinical Psychology Review*, 49, 28-40. <http://dx.doi.org/10.1016/j.cpr.2016.07.001>
- Kessler, R. C., Angermeyer, M., Anthony, J. C., De Graaf, R. O. N., Demyttenaere, K., Gasquet, I., ... & Kawakami, N. (2007). Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry*, 6, 168-176.
- Kircanski, K., Mortazavi, A., Castriotta, N., Baker, A. S., Mystkowski, J. L., Yi, R., & Craske, M. G. (2012). Challenges to the traditional exposure paradigm: Variability in exposure therapy for contamination fears. *Journal of Behavior Therapy and Experimental Psychiatry*, 43, 745-751. <http://dx.doi.org/10.1016/j.jbtep.2011.10.010>
- Laborda, M. A., Schofield, C. A., Johnson, E. M., Schubert, J. R., George-Denn, D., Coles, M. E., & Miller, R. R. (2016). The Extinction and Return of Fear of Public Speaking. *Behavior Modification*, 40, 901-921. <http://dx.doi.org/10.1177/0145445516645766>
- Loerinc, A. G., Meuret, A. E., Twohig, M. P., Rosenfield, D., Bluett, E. J., & Craske, M. G. (2015). Response rates for CBT for anxiety disorders: need for standardized criteria. *Clinical Psychology Review*, 42, 72-82. <http://dx.doi.org/10.1016/j.cpr.2015.08.004>
- Maren, S., Phan, K. L., & Liberzon, I. (2013). The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nature Reviews Neuroscience*, 14, 417-428. <http://dx.doi.org/10.1038/nrn3492>
- McConnell, B. L., & Miller, R. R. (2014). Associative accounts of recovery-from-extinction effects. *Learning and Motivation*, 46, 1-15. <http://dx.doi.org/10.1016/j.lmot.2014.01.003>
- Meulders, A., Van Daele, T., Volders, S., & Vlaeyen, J. W. (2016). The use of safety-seeking behavior in exposure-based treatments for fear and anxiety: Benefit or burden? A meta-analytic review. *Clinical psychology review*, 45, 144-156. <https://doi.org/10.1016/j.cpr.2016.02.002>
- Meuret, A. E., Seidel, A., Rosenfield, B., Hofmann, S. G., & Rosenfield, D. (2012). Does fear reactivity during exposure predict panic symptom reduction?. *Journal of Consulting and Clinical Psychology*, 80, 773-785. <http://dx.doi.org/10.1037/a0028032>

- Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J., & Rauch, S. L. (2007). Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biological Psychiatry*, 62, 446-454.
<http://dx.doi.org/10.1016/j.biopsych.2006.10.011>
- Miller, R. R., & Matzel, L. D. (1988). The comparator hypothesis: A response rule for the expression of associations. In G. H. Bower (Ed.), *The Psychology of Learning and Motivation: Advances in Research and Theory*, 22 (pp. 51–92). San Diego: Academic Press, Inc. ISBN: 978-0125433280
- Mineka, S. (1985). Animal models of anxiety-based disorders: Their usefulness and limitations. In A. H. Tuma, & J. D. Maser (Eds.), *Anxiety and the Anxiety Disorders*. England: Lawrence Erlbaum Associates, Inc. ISBN: 978-0898595321
- Mineka, S., & Oehlberg, K. (2008). The relevance of recent developments in classical conditioning to understanding the etiology and maintenance of anxiety disorders. *Acta psychologica*, 127, 567-580. <https://doi.org/10.1016/j.actpsy.2007.11.007>
- Mineka, S., & Zinbarg, R. (2006). A contemporary learning theory perspective on the etiology of anxiety disorders: it's not what you thought it was. *American Psychologist*, 61, 10-26.
<http://dx.doi.org/10.1037/0003-066X.61.1.10>
- Morris, C. D., Bransford, J. D., & Franks, J. J. (1977). Levels of processing versus transfer appropriate processing. *Journal of Verbal Learning and Verbal Behavior*, 16, 519-533.
[http://dx.doi.org/10.1016/S0022-5371\(77\)80016-9](http://dx.doi.org/10.1016/S0022-5371(77)80016-9)
- Mowrer, O. H. (1948). Learning theory and the neurotic paradox. *American Journal of Orthopsychiatry*, 18, 571-610. <http://dx.doi.org/10.1111/j.1939-0025.1948.tb05122.x>
- Mystkowski, J. L., Craske, M. G., & Echiverri, A. M. (2002). Treatment context and return of fear in spider phobia. *Behavior Therapy*, 33, 399-416. [http://dx.doi.org/10.1016/S0005-7894\(02\)80035-1](http://dx.doi.org/10.1016/S0005-7894(02)80035-1)
- Mystkowski, J. L., Craske, M. G., Echiverri, A. M., & Labus, J. S. (2006). Mental reinstatement of context and return of fear in spider-fearful participants. *Behavior Therapy*, 37, 49-60. <http://dx.doi.org/10.1016/j.beth.2005.04.001>

- Mystkowski, J. L., & Mineka, S. (2007). Behavior therapy for specific fears and phobias: Context specificity of fear extinction. *Psychological Clinical Science: Papers in honor of Richard M. McFall*, 197-222. ISBN: 978-1138873063
- Mystkowski, J. L., Mineka, S., Vernon, L. L., & Zinbarg, R. E. (2003). Changes in caffeine states enhance return of fear in spider phobia. *Journal of Consulting and Clinical Psychology*, 71, 243-250. <http://dx.doi.org/10.1037/0022-006X.71.2.243>
- Neumann, D. L., Lipp, O. V., & Cory, S. E. (2007). Conducting extinction in multiple contexts does not necessarily attenuate the renewal of shock expectancy in a fear-conditioning procedure with humans. *Behaviour Research and Therapy*, 45, 385-394. <http://dx.doi.org/10.1016/j.brat.2006.02.001>
- Neumann, D. L., & Longbottom, P. L. (2008). The renewal of extinguished conditioned fear with fear-relevant and fear-irrelevant stimuli by a context change after extinction. *Behaviour Research and Therapy*, 46, 188-206. <http://dx.doi.org/10.1016/j.brat.2007.12.004>
- Otto, M. W., Kredlow, M. A., Smits, J. A., Hofmann, S. G., Tolin, D. F., de Kleine, R. A., & Pollack, M. H. (2016). Enhancement of psychosocial treatment with d-cycloserine: models, moderators, and future directions. *Biological psychiatry*, 80(4), 274-283. <https://doi.org/10.1016/j.biopsych.2015.09.007>
- Pittig, A., van den Berg, L., & Vervliet, B. (2016). The key role of extinction learning in anxiety disorders: behavioral strategies to enhance exposure-based treatments. *Current Opinion in Psychiatry*, 29, 39-47. <http://dx.doi.org/10.1097/YCO.0000000000000220>
- Rachman, S. (1980). Emotional processing. *Behaviour Research and Therapy*, 18, 51-60. [http://dx.doi.org/10.1016/0005-7967\(80\)90069-8](http://dx.doi.org/10.1016/0005-7967(80)90069-8)
- Rapee, R. M., Gaston, J. E., & Abbott, M. J. (2009). Testing the efficacy of theoretically derived improvements in the treatment of social phobia. *Journal of Consulting and Clinical Psychology*, 77, 317-327. <http://dx.doi.org/10.1037/a0014800>
- Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. *Classical conditioning II: Current research and theory*, 2, 64-99. ISBN: 978-0390718013

- Rodriguez, B. I., Craske, M. G., Mineka, S., & Hladek, D. (1999). Context-specificity of relapse: effects of therapist and environmental context on return of fear. *Behaviour research and therapy*, 37(9), 845-862. [https://doi.org/10.1016/S0005-7967\(98\)00106-5](https://doi.org/10.1016/S0005-7967(98)00106-5)
- Rowe, M. K., & Craske, M. G. (1998). Effects of varied-stimulus exposure training on fear reduction and return of fear. *Behaviour Research and Therapy*, 36, 719-734. [http://dx.doi.org/10.1016/S0005-7967\(97\)10017-1](http://dx.doi.org/10.1016/S0005-7967(97)10017-1)
- Rudy, J. W. (2009). Context representations, context functions, and the parahippocampal–hippocampal system. *Learning & memory*, 16(10), 573-585. <http://dx.doi.org/10.1101/lm.1494409>
- Salkovskis, P. M. (1991). The importance of behaviour in the maintenance of anxiety and panic: A cognitive account. *Behavioural Psychotherapy*, 19, 6-19. <http://dx.doi.org/10.1017/S0141347300011472>
- Scheveneels, S., Boddez, Y., Vervliet, B., & Hermans, D. (2016). The validity of laboratory-based treatment research: Bridging the gap between fear extinction and exposure treatment. *Behaviour Research and Therapy*, 86, 87-94. <http://dx.doi.org/10.1016/j.brat.2016.08.015>
- Shiban, Y., Pauli, P., & Mühlberger, A. (2013). Effect of multiple context exposure on renewal in spider phobia. *Behaviour Research and Therapy*, 51, 68-74. <http://dx.doi.org/10.1016/j.brat.2012.10.007>
- Shiban, Y., Schelhorn, I., Pauli, P., & Mühlberger, A. (2015). Effect of combined multiple contexts and multiple stimuli exposure in spider phobia: A randomized clinical trial in virtual reality. *Behaviour Research and Therapy*, 71, 45-53. <http://dx.doi.org/10.1016/j.brat.2015.05.014>
- Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*, 35, 169-191. <http://dx.doi.org/10.1038/npp.2009.83>
- Shin, K. E., & Newman, M. G. (2017). Using Retrieval Cues to Attenuate Return of Fear in Individuals With Public Speaking Anxiety. *Behavior Therapy*, In Press. <https://doi.org/10.1016/j.beth.2017.07.011>

- Singewald, N., Schmuckermair, C., Whittle, N., Holmes, A., & Ressler, K. J. (2015). Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. *Pharmacology & Therapeutics*, 149, 150-190. <http://dx.doi.org/10.1016/j.pharmthera.2014.12.004>
- Springer, K. S., Levy, H. C., & Tolin, D. F. (2018). Remission in CBT for adult anxiety disorders: A meta-analysis. *Clinical Psychology Review*, *In Press*. <https://doi.org/10.1016/j.cpr.2018.03.002>
- Thomas, B. L., Larsen, N., & Ayres, J. J. (2003). Role of context similarity in ABA, ABC, and AAB renewal paradigms: Implications for theories of renewal and for treating human phobias. *Learning and Motivation*, 34, 410-436. [http://dx.doi.org/10.1016/S0023-9690\(03\)00037-7](http://dx.doi.org/10.1016/S0023-9690(03)00037-7)
- Tolin, D. F. (2010). Is cognitive-behavioral therapy more effective than other therapies?: A meta-analytic review. *Clinical Psychology Review*, 30, 710-720. <https://doi.org/10.1016/j.cpr.2010.05.003>
- Van Damme, S., Crombez, G., Hermans, D., Koster, E. H., & Eccleston, C. (2006). The role of extinction and reinstatement in attentional bias to threat: A conditioning approach. *Behaviour Research and Therapy*, 44, 1555-1563. <http://dx.doi.org/10.1016/j.brat.2005.11.008>
- Vansteenwegen, D., Hermans, D., Vervliet, B., Francken, G., Beckers, T., Baeyens, F., & Eelen, P. (2005). Return of fear in a human differential conditioning paradigm caused by a return to the original acquisition context. *Behaviour Research and Therapy*, 43, 323-336. <https://doi.org/10.1016/j.brat.2004.01.001>
- Vansteenwegen, D., Vervliet, B., Hermans, D., Beckers, T., Baeyens, F., & Eelen, P. (2006). Stronger renewal in human fear conditioning when tested with an acquisition retrieval cue than with an extinction retrieval cue. *Behaviour Research and Therapy*, 44, 1717-1725. <http://dx.doi.org/10.1016/j.brat.2005.10.014>
- Vansteenwegen, D., Vervliet, B., Iberico, C., Baeyens, F., Van den Bergh, O., & Hermans, D. (2007). The repeated confrontation with videotapes of spiders in multiple contexts attenuates renewal of fear in spider-anxious students. *Behaviour Research and Therapy*, 45, 1169-1179. <http://dx.doi.org/10.1016/j.brat.2006.08.023>

- Vervliet, B., Baeyens, F., Van den Bergh, O., & Hermans, D. (2013). Extinction, generalization, and return of fear: a critical review of renewal research in humans. *Biological Psychology*, 92, 51-58.
<http://dx.doi.org/10.1016/j.biopsycho.2012.01.006>
- Vervliet, B., Craske, M. G., & Hermans, D. (2013). Fear extinction and relapse: state of the art. *Annual Review of Clinical Psychology*, 9, 215-248.
<http://dx.doi.org/10.1146/annurev-clinpsy-050212-185542>
- Vervliet, B., Vansteenwegen, D., Baeyens, F., Hermans, D., & Eelen, P. (2005). Return of fear in a human differential conditioning paradigm caused by a stimulus change after extinction. *Behaviour Research and Therapy*, 43, 357-371.
<http://dx.doi.org/10.1016/j.brat.2004.02.005>
- White, K. S., Payne, L. A., Gorman, J. M., Shear, M. K., Woods, S. W., Saksa, J. R., & Barlow, D. H. (2013). Does maintenance CBT contribute to long-term treatment response of panic disorder with or without agoraphobia? A randomized controlled clinical trial. *Journal of Consulting and Clinical Psychology*, 81, 47-57.
<http://dx.doi.org/10.1037/a0030666>
- Wolpe, J. (1958). *Psychotherapy by reciprocal inhibition*. Stanford, CA: Stanford University Press. ISBN: 978-0804705097