Breaking the Cycle of Learned Fear

An Experimental Approach

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An Experimental Approach

De Cirkel van Angst Doorbreken

Een Experimentele Benadering

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 8 oktober 2021 des ochtends te 10.15 uur

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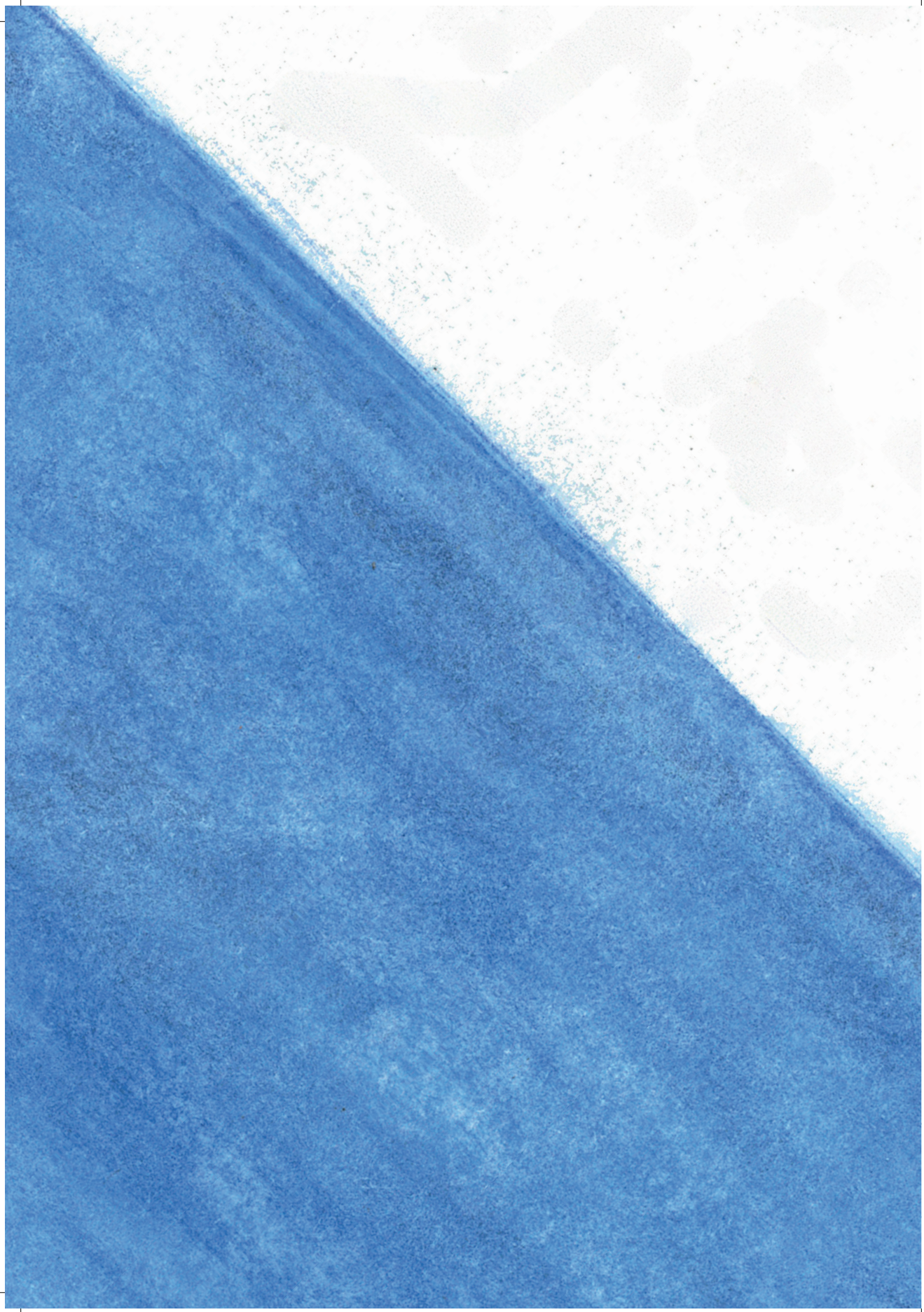
Table of Contents



Chapter 1

General introduction

Breaking the Cycle of Learned Fear: An Experimental Approach

Fear lies at the heart of our existence. In threatening situations, fear-related responses such as fight, flight, or freeze reactions allow fast reactions to promote survival in the short run and the long run when such situations are reencountered (e.g., Fanselow, 2018). Because threatening situations are never identical, we need to generalize fear to stimuli and situations that resemble the original situation (Asok et al., 2019). However, extreme fear in relatively safe situations is not adaptive, which is the case in anxiety-related disorders (Rosen & Schulkin, 1998). Anxiety-related disorders can generally be characterized by three core criteria (see American Psychiatric Association, 2013). First, fear levels should be chronic and disproportionally high, given the actual threat. For example, patients with health anxiety may fear life-threatening illnesses, even after medical tests have not detected bodily anomalies. Second, there should be avoidance or safety behaviors aimed at reducing the occurrence or severity of the threat. As an example, patients with panic disorder may avoid crowded places because they may fear fainting. Third, the fear and avoidance should cause significant personal suffering or functional impairment. To illustrate, patients with social anxiety disorder may struggle with finding a job because they fear and avoid job interviews. Anxiety-related disorders are highly prevalent. Approximately one out of 10 individuals will meet diagnostic criteria for an anxiety-related disorder at some point in their lives (Kessler et al., 2005). In Europe, the estimated total annual costs attributed to anxiety-related disorder diagnoses are more than €74 billion (Gustavsson et al., 2011). Moreover, patients with anxiety-related disorders have higher natural and unnatural mortality rates than individuals from the general population (Meier et al., 2016). Together, this exemplifies the tremendous personal and societal burden associated with these disorders.

Anxiety-related disorders can be treated successfully with pharmacological (Baldwin et al., 2014) or psychological interventions (Cuijpers et al., 2016; Loerinc et al., 2015), but patients usually prefer receiving psychological treatment (McHugh et al., 2013). Cognitive-behavioral therapy (CBT) is currently the best empirically supported psychological treatment for anxiety-related disorders and typically includes a combination of cognitive restructuring and behavioral (e.g., exposure) techniques (Hofmann & Smits, 2008). CBT is considered more effective than other *bona fide* psychological interventions (d = 0.43), such as psychodynamic psychotherapy (Tolin, 2010), and is therefore recommended as psychological treatment of choice (e.g., Benedek et al., 2009; Stein et al., 2009). A

review of nine meta-analyses on underlying mechanisms of CBT showed that therapy gains were positively related to both cognitive and behavioral changes (Kazantzis et al., 2018). Despite its relative efficacy, some caution is warranted. First of all, CBT effects are modest, especially for high-quality studies that compared CBT effects with active comparison groups (*g*s = 0.30-0.57; Cuijpers et al., 2016). In fact, about half of the patients with anxiety-related disorders do not fully recover after CBT (Loerinc et al., 2015) and empirically supported interventions, including CBT, only reduce the years lived with disability by 35% (Andrews et al., 2004). In addition, some studies suggest that 13% to 23% of patients may experience relapse after successful treatment (Fava, Grandi, et al., 2001; Fava, Rafanelli, et al., 2001). This aligns with findings from clinical research revealing that approximately 19-62% of patients experience a return of fear after successful brief exposure training (Craske & Mystkowski, 2006). Thus, there is a need to optimize CBT interventions.

In this light, the Lancet Psychiatry Commission on psychological treatments research in tomorrow's science recommended to "maximize research on mechanisms by firmly framing it within a clinical treatment context to: a) understand how existing treatments work; b) improve these treatments; and c) derive new treatments" (Holmes et al., 2018). Thus far, our understanding of active treatment ingredients is relatively limited. Meta-analytic evidence on treatment mechanisms is correlational and, hence, does not allow causal inferences (Cuijpers et al., 2019). For unraveling specific treatment mechanisms, direct experimental manipulation of these mechanisms is crucial (Cuijpers et al., 2019; Holmes et al., 2018; Kazdin, 2007; van den Hout et al., 2017). As van den Hout and colleagues (2017) pointed out, when a mechanism (A) co-varies with a particular outcome (B), this does not imply that it has *caused* the outcome. Indeed, A may cause B, but it is also possible that B causes A or that the relation between A and B is caused by a third variable. Experimental psychopathology research can elucidate such causalities and reveal *how* a given mechanism contributes to the maintenance or treatment of psychopathology. This dissertation stands in the experimental psychopathology tradition and predominantly describes experimental research on mechanisms involved in the onset, maintenance, and treatment of clinical anxiety. We present a model based on the contemporary learning theory and use this as a departure point to identify and test relevant treatment mechanisms.

Entering the Cycle of Learned Fear

The contemporary learning theory is among the most influential models on the etiology

and maintenance of clinical anxiety (Craske et al., 2018; De Houwer, 2020; Vervliet et al., 2013). Although it clearly overlaps with cognitive theories (e.g., Clark, 1986; Ehlers & Clark, 2000; Rachman, 1997; Salkovskis et al., 2003), it stems from a long tradition of Pavlovian fear conditioning research (Vervliet & Boddez, 2020). According to the contemporary learning theory, patients with anxiety-related disorders may have learned that an innocuous stimulus or situation (e.g., crowded place in panic disorder example) can predict a threatening outcome (e.g., fainting or heart attack). Contemporary learning theory purports that the intensity of conditioned fear is determined by 1) this associative strength (i.e., threat expectancy) and 2) the evaluation of the mental representation of threat (i.e., threat severity), see Figure 1. Fear learning can be modeled in the lab using Pavlovian fear conditioning paradigms. These paradigms typically start with a fear learning phase in which one innocuous stimulus (e.g., a tone) is followed by a threatening stimulus (e.g., mild electrical shock), while another innocuous stimulus (e.g., a light) is not. After several trials, the tone becomes a 'danger cue' that signals the pending shock, whereas the light becomes a 'safety cue' that signals the absence of the shock.

Fear in response to a danger cue is, of course, essential for survival. Likewise, it may be adaptive to generalize fear to stimuli that resemble the danger cue, as they may be more likely to predict threat as well. Yet, the lesser the perceptual or symbolic overlap between the original danger cue and a novel innocuous cue, the lower the functional value to fear a novel stimulus (Asok et al., 2019). Interestingly, fear conditioning research has shown that patients with anxiety-related disorders, relative to healthy comparisons, show stronger threat responding toward novel innocuous stimuli that only slightly resembled the danger cue and were not paired with the threatening outcome in the task (e.g., Kaczkurkin et al., 2017; Lissek et al., 2010, 2014). Likewise, during the fear learning phase, they generally exhibit elevated threat responding to *safety cues* that were never paired with a threatening outcome (Duits et al., 2015). Impaired safety learning during a fear conditioning task predicts later anxiety-related symptoms in soldiers deployed to Afghanistan (Lommen et al., 2013; Sijbrandij et al., 2013), as well as worse CBT outcomes in patients with anxiety-related disorders (e.g., Duits et al., 2021). Therefore, understanding and improving impaired safety learning will be central to this dissertation.

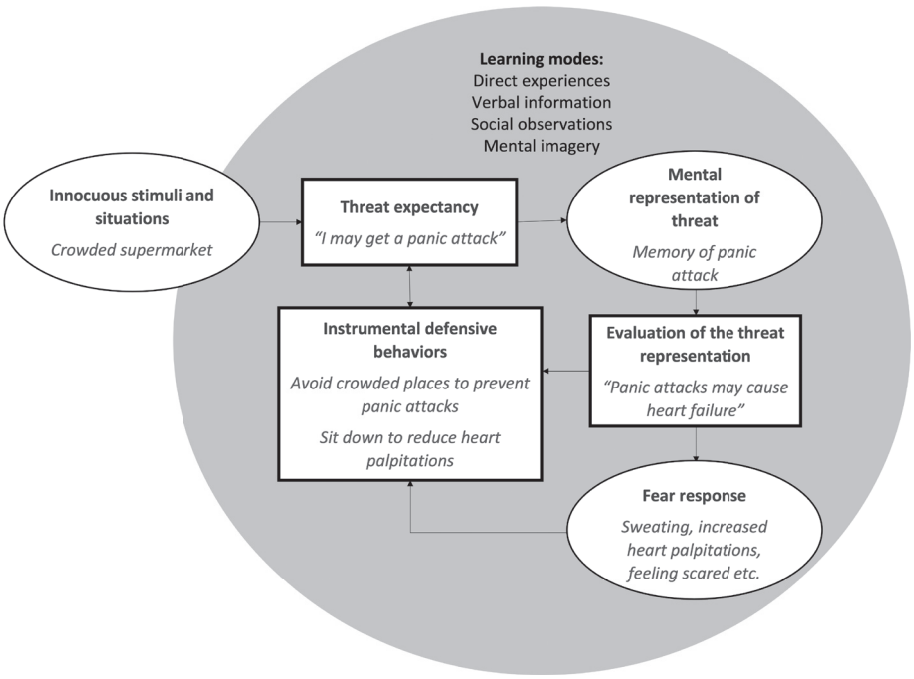
Even though the contemporary conditioning theory has considerably improved our understanding of fear learning, two limitations are worth noting. First of all, the theory does not address instrumental defensive behaviors, such as avoidance or safety behaviors, which play a crucial role in the onset and maintenance of clinical anxiety (Krypotos et al., 2018; Pittig et al., 2020; van Uijen et al., 2018). They have often been neglected in fear

conditioning research (Krypotos et al., 2015), even though they may directly affect threat expectancies (e.g., Deacon & Maack, 2008; Engelhard et al., 2015; van Uijen & Toffolo, 2015), see Fig. 1. In addition, the learning theory pays little attention to emotional episodic memory (Dunsmoor & Kroes, 2019) and mental imagery of threat (Mertens et al., 2020), even though the cognitive representation of threat is one of its central elements. In fact, recent research has shown that aversive mental imagery may also affect threat expectancy (Mertens et al., 2020) and acquisition of instrumental behavior (Krypotos et al., 2020), see Fig. 1.

Section 1 of this thesis **(Chapters 2 and 3)** examines three central components in the extended version of the contemporary learning theory of learned fear: threat expectancy, evaluation of the threat representation, and instrumental defensive behaviors (Fig. 1). We tested to which extent these components are involved in the onset of learned fear to innocuous cues.

Figure 1

The Cycle of Learned Fear: The Contemporary Learning Model (e.g., Davey, 1997) Extended With Instrumental Defensive Behaviors



Breaking the Cycle of Learned Fear

The recommended treatment for anxiety-related disorders is exposure-based CBT (e.g., National Institute for Health and Care Excellence, 2011, 2013). In this treatment, patients are repeatedly exposed to fear-relevant yet innocuous stimuli, such as a crowded supermarket, to disconfirm their expected negative outcome (i.e., risk or severity), such as a heart or panic attack (Abramowitz et al., 2019). However, as outlined earlier, a substantial number of individuals who start with exposure therapy do not benefit from it. For example, some patients show no symptom reduction (e.g., Loerinc et al., 2015), while others show a return of symptomatology *after* successful treatment (i.e., relapse; e.g., Fava, Grandi, et al., 2001; Fava, Rafanelli, et al., 2001).

Why do some patients not benefit from exposure therapy? According to the inhibitory learning model (Bouton, 2002; Bouton & King, 1983; Craske, 2015), patients do not *unlearn* the association between fear-relevant stimuli and the feared outcome (Fig. 1), but they learn a new safety association between fear-relevant stimuli and the absence of threat, which needs to be strengthened to become dominant (Craske et al., 2008, 2014). The stronger the mismatch, or prediction error, between one's expectancies of what will happen and the actual outcome, the stronger the learning effects will be (Rescorla & Wagner, 1972). Therefore, to optimize new learning, therapists are advised to aim for high expectancy violations (Craske et al., 2014). Research has shown that new safety associations are "relatively easy to 'learn' but difficult to 'remember'" (Vervliet et al., 2013), particularly after a time lapse (i.e., spontaneous recovery), a context switch (i.e., contextual renewal), or new encounters with stress(ors) (i.e., reinstatement; Bouton, 2002; see also Dunsmoor et al., 2018). Therefore, strategies have been proposed to strengthen new safety learning during exposure, such as positive valence training (e.g., Craske et al., 2014). Testing whether these are indeed more effective is an empirical issue that awaits rigorous research.

As outlined above, exposure and return of fear can also be modeled with the Pavlovian fear conditioning paradigms. After the fear learning phase, an extinction phase follows (the analog of exposure therapy), in which danger and safety cues are repeatedly presented without a threatening stimulus. In this phase, fear and threat responses toward the danger cue typically decrease. Finally, in a next phase, return of fear can be induced by a time lapse (i.e., spontaneous recovery; e.g., extinction recall at 1-day follow-up), a context switch (i.e., contextual renewal; e.g., extinction recall with a different virtual background than during extinction), or unsignaled presentations of a threatening stimulus (e.g., electrical shocks), followed by extinction recall (i.e., reinstatement).

The findings of the laboratory fear conditioning studies with respect to reduced extinction (retention) effects in patients with clinical anxiety align with clinical observations of limited exposure effects. In some studies, patients with anxiety-related disorders, relative to healthy comparisons, exhibited elevated fear responses to the danger cue throughout the extinction phase (Duits et al., 2015). Similarly, deficient extinction learning toward the danger cue predicted worse CBT outcomes in patients with anxiety-related disorders (Duits et al., 2021). In other studies, patients with anxiety-related disorders, relative to healthy comparisons, had similar fear responses during extinction training but elevated responses during extinction recall (Milad et al., 2008, 2013; but see Pöhlchen et al., 2020). Therefore, it is critical to address both the short- and long-term effects of exposure-based therapy and extinction and test how these may be optimized.

Section 2 of this thesis **(Chapter 4, 5, and 6)** examines safety learning during CBT or extinction training and how this learning is retained over time. **Chapter 4** describes a meta-analysis on the short- and long-term effects of CBT for anxiety-related disorders. **Chapters 5 and 6** predominantly focus on improving safety learning during and after exposure.

Aims and outline

The research in this dissertation aimed to elucidate underlying mechanisms in the development and treatment of learned fear. The first aim was to test how threat expectancy, evaluation of threat representations, and instrumental defensive behaviors may increase fear toward innocuous cues (**Chapters 2 and 3**). The second aim was to examine the immediate and long-term effects of CBT in anxiety-related disorders (**Chapter 4**). The third aim was to test whether a novel intervention would enhance extinction learning and would reduce the return of fear in the lab (**Chapter 5**). Finally, we aimed to develop a more ecologically valid procedure to test exposure and return of fear in a virtual reality paradigm (**Chapter 6**). These studies will be described in more detail below.

Chapter 2 describes a fear conditioning study that examined whether imagery-based rehearsal of threat in the presence of an innocuous cue increases fear generalization and whether threat inflation moderates this effect. It was expected that imagery-based threat rehearsal (versus no threat rehearsal) combined with threat inflation (versus no inflation) would lead to fear generalization. Participants (N = 120) first completed an acquisition phase, in which a danger cue was paired with a mildly aversive sound, whereas a safety

cue was not. Then, in the threat inflation phase, the sound was presented 11 times at an increasing (i.e., threat inflation) or constant volume (i.e., no threat inflation). Finally, during the rehearsal phase, some participants were instructed to imagine the last sound (i.e., threat rehearsal), and others were not given this instruction (i.e., no threat rehearsal) during the presentation of a generalization stimulus (which perceptually resembled the danger cue). Dependent variables were online threat expectancy and online distress ratings. Hypotheses were tested with Bayesian informative hypotheses tests.

Chapter 3 includes two studies on the effects of safety behaviors toward an innocuous stimulus on threat beliefs. The aim of Study 1 was to replicate a fear conditioning study (N = 68) in which one stimulus (i.e., CS+) was followed by a shock, while two other stimuli were not (i.e., CSs-). At some point, the experimental, but not the control group, received the opportunity to perform safety behavior toward one of the CSs-. It was hypothesized that the experimental group, relative to the control group, would show higher threat expectancy and skin conductance response toward this CS- after the removal of the safety behavior. Study 2 aimed to examine individual differences in threat beliefs from before to after the performance of safety behavior. To this end, we performed a multi-dataset latent class analysis on threat expectancy data from Study 1 and two earlier studies (N = 213).

Chapter 4 describes a systematic review and meta-analysis aimed to assess the immediate and long-term outcomes after CBT for anxiety-related disorders (compared with care-as-usual, relaxation, psychoeducation, pill placebo, supportive therapy, or waiting list). Two independent researchers screened and selected publications published between 1980 and January 2019. Included articles reported randomized clinical trials on post-treatment and at least 1-month follow-up effects of cognitive-behavioral therapy compared with control conditions among adults with generalized anxiety disorder, panic disorder with or without agoraphobia, social anxiety disorder, specific phobia, PTSD, or OCD. We calculated Hedges g for anxiety symptoms immediately after treatment and at 1 to 6 months, 6 to 12 months, and 12 months or more after treatment completion.

The aim of **Chapter 5** was to examine whether positive valence training reduces negative stimulus valence and the return of fear. Participants were 87 students in Experiment 1 (three-day paradigm) and 90 students in Experiment 2 (one-day paradigm). They first underwent a differential acquisition phase, in which one of three pictures was paired with an electric shock. They were then randomly allocated to one of the three intervention groups: 1) counterconditioning with positive film clips; 2) standard extinction training; 3) extinction training with non-contingent exposure to the positive film clips.

Afterward, they underwent a test phase in which pictures were presented without shock (to measure spontaneous recovery of fear), followed by unsignaled shocks to induce reinstatement of extinguished fear. Outcome variables were self-reported stimulus valence, shock expectancy, skin conductance, and fear-potentiated startle.

Chapter 6 describes a novel virtual reality procedure to examine spontaneous recovery (i.e., a return of fear over time) and fear renewal (i.e., the return of fear after a context switch) in individuals with fear of public speaking. On Day 1, 32 participants received exposure training before a virtual audience. On Day 8, they completed a spontaneous recovery phase, followed by a fear renewal test, in which they gave a presentation in front of a new (context switch) or the same audience (no context switch). Outcome measures were heart rate, subjective distress, negative valence, and arousal. Finally, **Chapter 7** presents a summary and discussion of the findings from **Chapters 2 to 6**.

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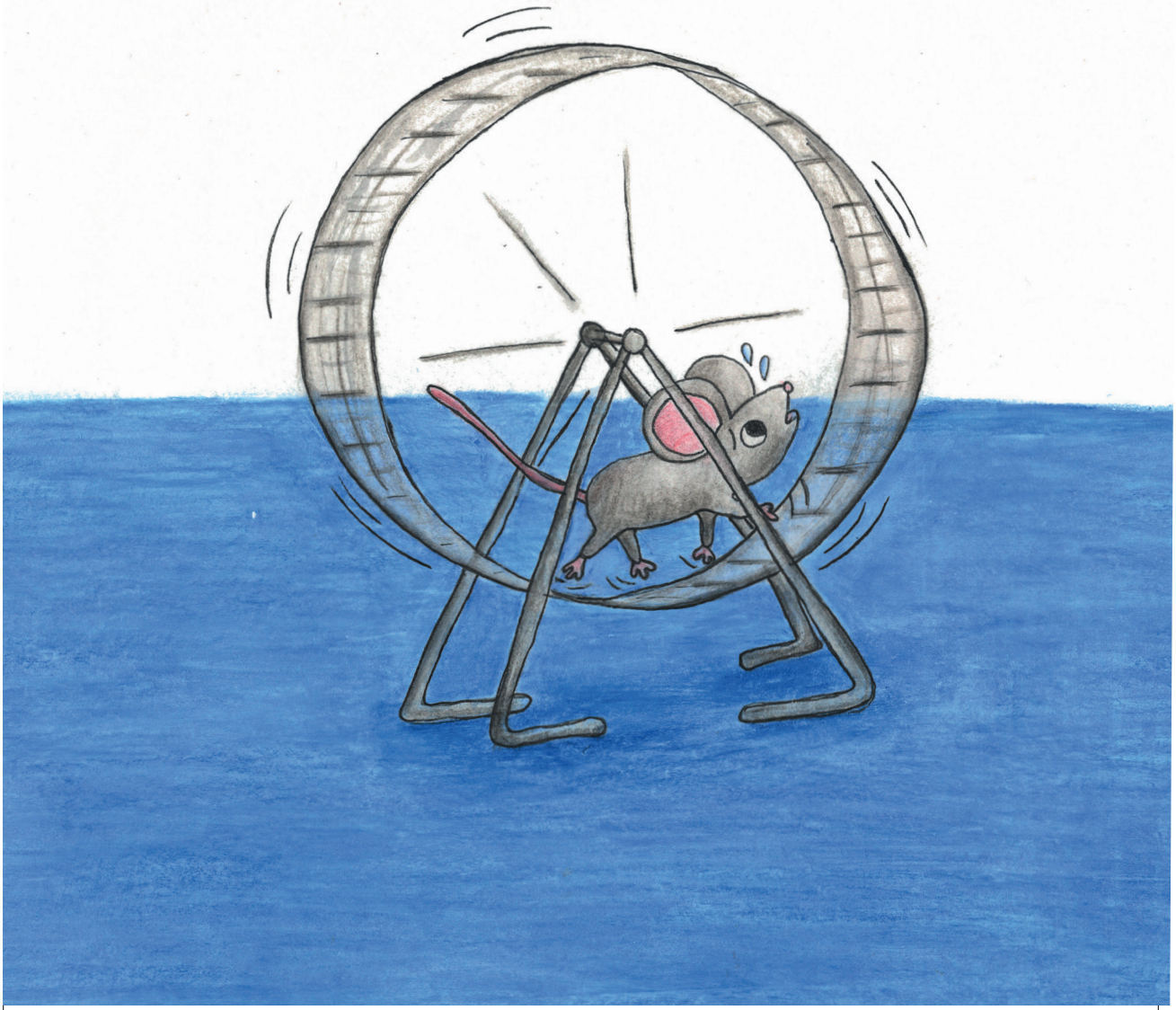
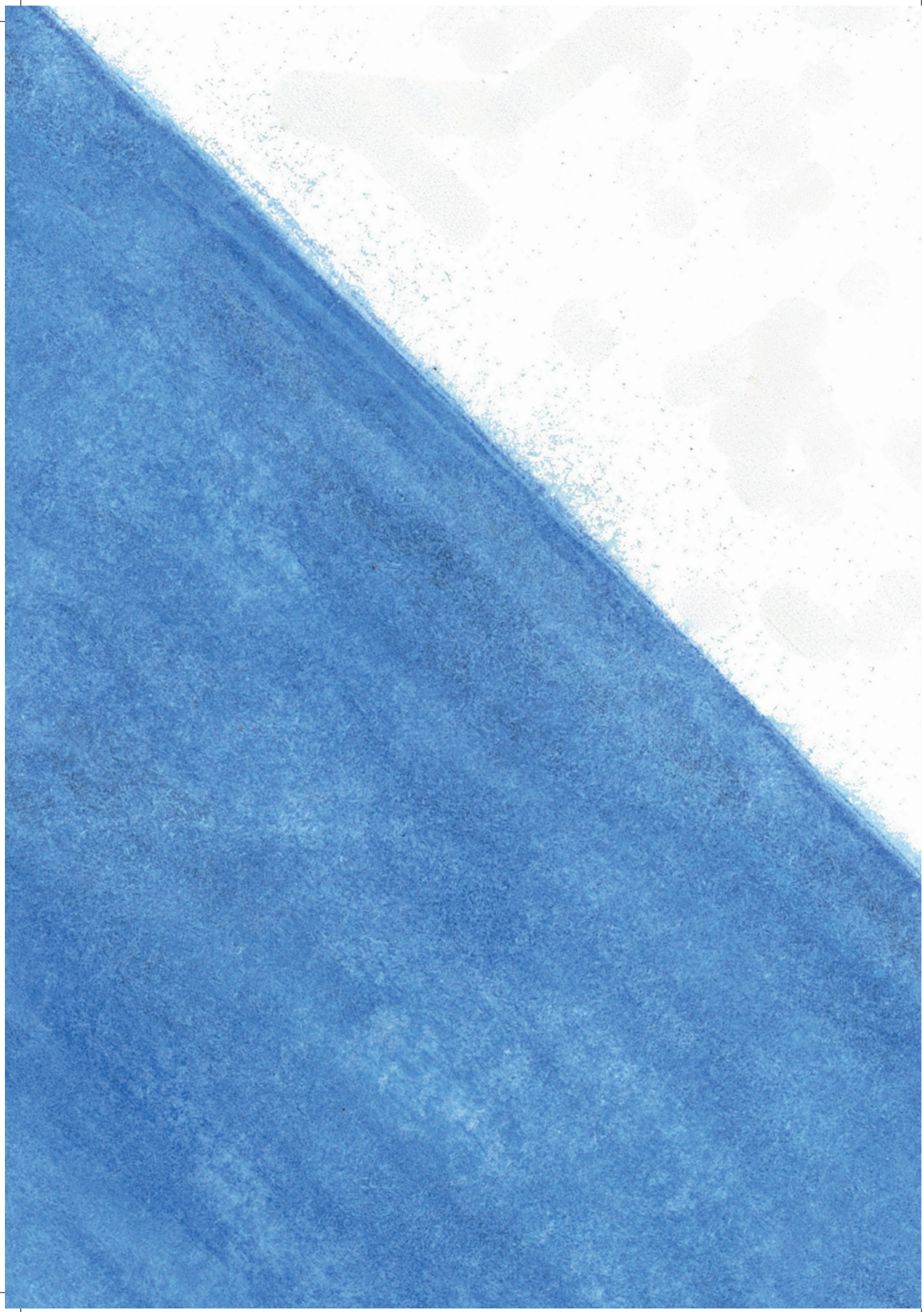
Section 1

Entering the cycle of learned fear





Chapter 2

Mental threat rehearsal increases fear generalization

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Manuscript under review

Abstract

Fear generalization to harmless stimuli characterizes anxiety-related disorders, but much remains unknown about its determinants. Based on studies showing that mental imagery of threat can increase conditioned fear responding, we tested whether it also facilitates fear generalization, and whether threat inflation moderates this effect. In a fear conditioning study, 120 participants first completed an acquisition phase, in which one of two pictures was followed by an aversive sound (human scream). Then, the sound was presented 11 times at an increasing (threat inflation) or constant volume (no threat inflation). Finally, a generalization stimulus was presented, and some participants were asked to imagine the last sound (threat rehearsal) and others were not (no threat rehearsal). Bayesian informative hypotheses tests indicated that imagery-based threat rehearsal increased generalization of threat expectancy, and, combined with threat inflation, it also resulted in stronger generalized distress. Future studies should examine whether modulating imagery may prevent clinical anxiety.

Keywords: mental imagery, rehearsal, threat inflation, fear generalization, anxiety disorders

Introduction

Fear is vital to survival. Yet aversive experiences are never identical, so we must generalize the fear we learned for a particular stimulus to future encounters that resemble the original event to a sufficient degree (Asok et al., 2019). This allows us to respond quickly to novel relevant stimuli (Dunsmoor et al., 2009). However, overgeneralization of fear to harmless stimuli or situations is a hallmark of anxiety-related disorders (American Psychiatric Association, 2013). For example, if a child has learned to fear a white rat, it can also exhibit fear of a white rabbit or a fur coat (Watson & Rayner, 1920). Therefore, an important theoretical and clinical question is how fear generalizes to harmless stimuli.

Fear generalization can be modeled in the lab with fear conditioning paradigms (Dymond et al., 2015). These paradigms usually start with a fear acquisition phase in which an innocuous stimulus, such as a picture of a neutral face, is repeatedly followed by a threat, such as a loud scream (i.e., unconditioned stimulus; US). After several pairings, the picture has become a conditioned stimulus (CS+) that typically excites strong subjective and physiological fear responses. In a subsequent fear generalization phase, one or more pictures that are perceptually or conceptually similar to the CS+ (i.e., generalization stimuli; GSs), such as morphs of different faces (Leer et al., 2017), are presented without the US. GSs that resemble the CS+ generally elicit fear responses, even though they have never been paired with the threatening stimulus (e.g., Dymond et al., 2015). Notably, during this phase, patients with anxiety-related disorders typically show elevated fear generalization (i.e., also to GSs that bear less similarity to the CS+), relative to healthy comparison groups (e.g., Kaczkurkin et al., 2017; Lissek et al., 2010), which underscores the paradigm's validity.

Research has shown that fear acquisition and generalization are complex phenomena that go beyond the mere pairing of stimuli (Asok et al., 2019; Dymond et al., 2015). For example, they also depend on verbal instructions (Mertens et al., 2018), abstract processing (Van Lier et al., 2014, 2015), observational learning (Cameron et al., 2015), and inductive reasoning (Dunsmoor & Murphy, 2015). Another way in which fear generalization could be modulated is by mental imagery: the experience of "seeing with the mind's eye, or hearing with the mind's ear etc." (Holmes & Mathews, 2010; Kosslyn et al., 2001). Mental imagery can be considered as a weak form of sensory perception (Pearson, 2019), sharing brain regions involved in actual perception (Ganis et al., 2004). It has functions, such as revisiting the past to learn from consequences, or projecting oneself in a future situation to adjust decision-making strategies and behavior (Bulley et

al., 2017; Libby et al., 2007; Schacter & Addis, 2007). Yet, aversive mental imagery (e.g., vivid involuntary images of threat) may be dysfunctional and is considered a maintaining factor of clinical anxiety (Berntsen, 2010; Brewin et al., 2010; Holmes & Mathews, 2010). Clinical and lab studies have found compelling evidence that mental imagery of threat can enhance fear acquisition and impede extinction learning (e.g., Hirsch et al., 2003, 2004; Mertens et al., 2020). For example, Joos and colleagues (2012a, 2012b) demonstrated that individuals who were asked to repeatedly imagine the CS+/US association after acquisition showed more elevated fear responses to the CS+ than individuals who did not imagine this association. Reversely, mental imagery of *safety learning* may promote extinction learning. In a study by McGlade and Craske (2021), students with fear of spiders received two exposure training sessions with a tarantula in a terrarium. On three separate days after each exposure session, participants in the "exposure rehearsal" group were asked to retrieve their exposure memory and rehearse how their negative outcome expectancy had been violated. They were also asked to relive their experience with the spider. Participants in the "control rehearsal" group were asked to rehearse the last time they were in class. Results showed that, relative to the control rehearsal group, the exposure rehearsal group showed more substantial symptom reductions and less subjective distress before and less avoidance during a behavioral approach test.

Thus far, to our knowledge, only one study has examined whether mental imagery of threat facilitates fear generalization. Krypotos et al. (2020) tested whether repeatedly imagining a CS-/US association amplifies the generalization of fear and avoidance from a CS+ to CS-. In the acquisition phase, one colored square (CS+) was followed by a shock, and two differently colored squares (CS-) were not. During a subsequent rehearsal phase, participants were asked to mentally rehearse "as vividly as possible" one of the CSs- together with either the shock ("shock group") or a neutral tone ("tone group"). Results showed that the "shock group" exhibited higher shock expectancy, subjective fear, and avoidance responses to that CS-, compared to the "tone group". They suggest that repeated mental imagery of the CS-/US association created a new association between a safe and an aversive stimulus. It remains unknown whether imagery-based threat rehearsal facilitates fear generalization toward a novel stimulus.

Threat intensity is another important factor in fear acquisition, and it also affects generalization of fear (e.g., Leer & Engelhard, 2015). For example, a fear conditioning study showed that individuals displayed more distinct fear generalization when they had a fear acquisition phase with a high relative to a low-intensity threat (Dunsmoor et al., 2017). Moreover, anecdotal evidence from case studies suggests that individuals without an aversive conditioning experience may be more susceptible to developing anxiety

symptoms when a threat evaluation becomes more negative (i.e., threat inflation; Davey et al., 1993). Several lab studies indeed demonstrated that threat inflation leads to increased conditioned fear (e.g., Hosoba et al., 2001; White & Davey, 1989). As far as we know, no lab studies have tested whether threat inflation may also increase fear generalization.

The current fear conditioning study had three aims. First, we aimed to examine whether mental rehearsal of threat in the presence of a novel (perceptually similar) GS would show increased threat expectancy and distress to this GS relative to no rehearsal. Second, we examined whether threat inflation would lead to increased threat expectancy and distress to the GS relative to no threat inflation. Third, we tested whether mental rehearsal combined with threat inflation would lead to higher threat expectancy and distress to this GS, relative to the other three conditions.

Methods

Participants

A total of 128 Dutch-speaking students aged between 18 and 30 were recruited via Utrecht University, Facebook, and Proefbunny.nl. Exclusion criteria were: visual impairment, color blindness, hearing problems, psychoactive medication, diagnosis of mental disorder, or neurological problems. Participants were randomly assigned (stratified for gender) to one of the four conditions: 1) threat rehearsal with threat inflation; 2) threat rehearsal without threat inflation; 3) no threat rehearsal with threat inflation; 4) no threat rehearsal without threat inflation. After participation, we excluded eight participants from analyses due to: unsuccessful fear learning (n = 4), familiarity with the stimuli and procedure (n = 2), non-adherence to instructions (n =1), and an equipment failure (n = 1). The final sample comprised 120 participants (80 females and 40 males; mean age = 21.30, SD = 2.02). The study protocol was approved by the ethics committee of the Faculty of Social and Behavioral Sciences at Utrecht University (FETC16-054) and was carried out in accordance with the provisions of the World Medical Association Declaration of Helsinki. This study was preregistered (including a power analysis) on the Open Science Framework (https://osf.io/xgmk8/).

Stimuli

Conditioned stimuli (CSs) were a neutral female and male face (387 × 511 pixels), which were selected from the Radboud Face database (Langner et al., 2010). They randomly

served as CS+ or CS-. The generalization stimulus (GS) was a morph of the CS+ with another same-gender morph (using Abrosoft Fantamorph software); see Figure S1 in the Supplementary Materials. The unconditioned stimulus (US) was a 2-s scream, which was presented binaurally at 60 dB during the acquisition phase.

Trial Procedure

Each trial consisted of a 12-s CS or GS presentation (in the middle of the computer screen on a black background). Participants rated threat expectancy during the first 4 s and distress during the following 4 s. Throughout the acquisition phase, the scream was presented 8 s after CS+ onset. CSs and GSs were presented in a pseudorandom order (i.e., a maximum of two consecutive presentations per phase). The 4 to 5-s inter-trial interval (ITI) was a black screen with a white fixation cross (Joos et al., 2012a).

Measures

Neuroticism Scale of the Eysenck Personality Questionnaire (EPQ-N)

Neuroticism was measured with a validated Dutch translation of the EPQ-N (Eysenck & Eysenck, 1991; Sanderman et al., 2012). This questionnaire consists of 22 questions (e.g., "Are you often troubled about feelings of guilt?") that are answered on a dichotomous scale (0 = *no*, 1 = *yes*). Cronbach's α was .82 in this study.

Anxiety Sensitivity Index (ASI)

Anxiety sensitivity was assessed with a validated Dutch translation of the ASI (Reiss et al., 1986; Vujanovic et al., 2007). The scale has 16 items (e.g., "It scares me when my heart beats rapidly") which are rated on a 5-point Likert scale, ranging from 0 (*very little*) to 4 (*very much*). Cronbach's α was .78 in this study.

Plymouth Sensory Imagery Questionnaire (PsiQ)

The vividness of mental imagery was assessed with a self-translated Dutch version of the PsiQ (Andrade et al., 2014). The 21-item scale contains seven modalities of imagery (visual, audio, taste, touch, smell, emotions, and bodily sensations) that are measured with three items (e.g., "Imagine the sound of a car horn"). Items are rated on an 11-point Likert scale ranging from 0 (*no image at all*) to 10 (*as vivid as real life*). Cronbach's α was .90 in this study.

Threat Expectancy

Participants rated threat expectancy on a visual analog scale (VAS) with three anchors: 0 (*certainly no scream*), 50 (*uncertain*), and 100 (*certainly a scream*).

Distress

Participants indicated their distress level ("How distressed do you feel at this moment?") on a visual analog scale (VAS) that ranged from 0 (*not distressed at all*) to 100 (*very distressed*).

Post-Experimental Questions

Manipulation Check for Threat Rehearsal. Participants were asked to rate on a binary scale whether they rehearsed the US during the GS in the rehearsal phase ("Did you imagine the scream when you saw this picture?" 1 = *yes*, 2 = *no*). If they answered yes, they were asked to indicate the frequency, vividness, and unpleasantness of their rehearsal. VASs ranged from 0 (frequency: *never;* vividness: *not at all vivid;* unpleasantness: *not at all unpleasant*) to 100 (frequency: *always;* vividness: *very vivid;* unpleasantness: *very unpleasant*).

Manipulation Check for Threat Inflation. Following Leer and Engelhard (2015), participants were asked to indicate whether they thought the intensity of the scream had changed, using three answer options: 1 = *no, the scream did not change in intensity*, 2 = *yes, the scream became louder*, or 3 = *yes, the scream became weaker*. If their answer was "yes", they were asked to indicate whether they had the impression that 1) *the original scream was presented weaker/stronger*, or that 2) *at some point, another, new scream was presented*. This was done to check whether participants updated their US representation or whether they perceived a new stimulus. US unpleasantness was also rated for the 60dB and 100 dB scream ("How unpleasant was the last scream you heard?") on a scale from 0 (*not unpleasant at all*) to 100 (*extremely unpleasant*).

Procedure

Table 1 provides an overview of the experimental procedure. In the habituation phase, the CS+ and CS- were presented twice. In the acquisition phase, there were six presentations of each CS, with a 100% reinforcement rate of the CS+ (see Jones & Davey, 1990). Next, in the threat inflation phase, there were 11 unsignaled scream presentations (with a 5-s inter scream interval) at the same volume (no threat inflation) or at an increasing volume

Table 1
Overview of Experimental Design

Group	Habituation	Acquisition	Inflation	Rehearsal
Threat rehearsal + threat inflation	CS+ (2) CS- (2)	CS+ (6) CS- (6)		GS (6) CS- (6)
Threat rehearsal + no threat inflation	CS+ (2) CS- (2)	CS+ (6) CS- (6)		GS (6) CS- (6)
No threat rehearsal + threat inflation	CS+ (2) CS- (2)	CS+ (6) CS- (6)		GS (6) CS- (6)
No threat rehearsal + no threat inflation	CS+ (2) CS- (2)	CS+ (6) CS- (6)		GS (6) CS- (6)

Note. CS = conditioned stimulus; GS = generalization stimulus.

(threat inflation; 60, 65, 70, 75, 80, 85, 90, 95, 100, 100, 100 dB). In the rehearsal phase, the GS and CS- were each presented six times. Half of the participants was instructed that, whenever they would see a male/female face (i.e., GS which was congruent with the gender of the CS+), they first had to complete the threat expectancy (4 s) and distress (4 s) ratings and then had to imagine the last scream they had heard (i.e., threat rehearsal). They were asked to imagine this scream and their reactions to it as vividly as possible (see Jones & Davey, 1990) until the face disappeared (i.e., for 4 s). The other half of the participants was not asked to rehearse the US during this phase (i.e., no threat rehearsal). Next, in the test phase, each CS and multiple GSs were presented. Data of this test phase could not be analyzed due to a technical problem, but this did not affect the analyses of the preregistered hypotheses regarding fear generalization during the rehearsal phase. Finally, participants were asked to complete the post-experimental questions and were thanked, debriefed, and remunerated.

Data-Analysis

Randomization and Manipulation Checks

Four checks were carried out. First, to examine whether randomization was successful,

we performed four one-way ANOVAs with Group (4: threat rehearsal with/without threat inflation and no threat rehearsal with/without threat inflation) as the independent variable and age, anxiety sensitivity scores, neuroticism scores, and mental imagery vividness scores as dependent variables. Second, to test whether the imagery-based threat rehearsal was successful, we conducted a Bayesian Contingency Tables Test with Group (2: threat rehearsal, no threat rehearsal) as the independent variable and the binary rehearsal question as the dependent variable. We also conducted three one-way ANOVAs with Group (2: threat rehearsal with/without threat inflation) as independent variable and frequency, vividness, and unpleasantness of US imagery as dependent variables. Third, to examine whether the threat inflation manipulation was successful, we conducted a Bayesian Contingency Tables Test with Group (US-inflation, no threat inflation) as the independent variable and the threat inflation question as the dependent variable. Finally, to examine whether differential acquisition occurred, we performed two mixed ANOVAs with Stimulus (2: CS+, CS-), Time (6: acquisition trials 1-6), and Group (4: threat rehearsal with/without threat inflation and no threat rehearsal with/without threat inflation) as the independent variables, and threat expectancy and distress as the dependent variables.

Analyses were conducted within the Bayesian hypothesis testing framework using JASP (Version 0.14.1.0; default settings). Bayes factors (BFs) denote the likelihood of the data under one hypothesis versus another hypothesis. Bayesian inference allows quantifying evidence for the null hypothesis (Krypotos et al., 2017; Wagenmakers, Marsman, et al., 2018). For example, $BF_{10} = 3$ indicates that the data are three times more likely under H1 than H0 (and vice versa for $BF_{10} = 0.33$; Wagenmakers, Love, et al., 2018). A commonly used benchmark is that BF_{10} between 1 and 3 indicates anecdotal evidence in favor of H1 relative to H0, values between 3 and 10 indicate moderate evidence, and values greater than 10 indicate strong evidence. Likewise, BFs_{10} below 0.33 indicate evidence in favor of the null hypothesis (Wagenmakers, Love, et al., 2018).

Hypotheses Testing and Deviations From Preregistration

The relative evidence for three hypotheses was tested. Hypothesis 1 was that threat rehearsal, relative to no threat rehearsal, leads to higher threat expectancy and distress toward the GS in the rehearsal phase. Hypothesis 2 was that threat inflation, relative to no threat inflation, results in higher threat expectancy and distress toward the GS in the rehearsal phase. Hypothesis 3 was that threat rehearsal combined with threat inflation, relative to the other three conditions would lead to higher threat expectancy and distress toward the GS in the rehearsal phase.

The BAyesian INformative hypotheses evaluation (BAIN) module in JASP (JASP Team, 2020) was used. For example, $BF_{12} = 3$ means that the data are three times more likely under H1 than H2. Two alternative hypotheses were used as a reference. The fourth hypothesis was that threat rehearsal and/or threat inflation are superior to no threat rehearsal combined with no threat inflation. Finally, the fifth hypothesis was that all groups are similar. A two-step approach was used to test the hypotheses: the Bayes Factor was calculated for each hypothesis relative to its complement and the hypothesis with the highest Bayes Factor was compared to all other hypotheses. Tables 2 and 3 report the formulas and descriptions of hypotheses.

There were three deviations from the preregistration for this study. First, because the data of the test phase could not be analyzed, we could only test two of the three preregistered hypotheses. Second, although the preregistration mentions using BIEMS software, we decided to use the more recently developed and advanced BAIN module instead, which yields similar Bayes Factors and is more robust to outliers and distributional assumptions (Hoijtink et al., 2019). Third, the preregistration mentions analysis of all the rehearsal trials, but BAIN and BIEMS do not allow testing mixed ANOVAs. Therefore, we decided to use trials at the beginning (i.e., average of the first two trials and the end of the rehearsal phase (i.e., average of the last two trials).

Results

Randomization Checks

There was strong evidence that the groups were similar in age, and ASI, EPQ-N, and PsiQ scores ($BFs_{10} < 0.08$). This suggests successful randomization.

Manipulation Checks

Threat Rehearsal

More participants in the rehearsal groups (47/60; 78%) compared to the no-rehearsal groups (24/60; 40%) indicated that they had rehearsed the US during the GS in the rehearsal phase ($BF_{10} > 1000$). For the rehearsal groups, frequency ($BF_{10} = 0.33$) and vividness ($BF_{10} = 0.30$) of threat rehearsal ratings were similar, but for the rehearsal with threat inflation group, relative to the rehearsal without threat inflation group, unpleasantness of rehearsal ratings was higher ($BF_{10} = 12.73$). This suggests the rehearsal manipulation was successful.

Threat Inflation

More participants in the inflation groups (43/60; 72%), compared to the no-inflation groups (8/60; 13%), reported that the scream had become louder during the experiment (BF_{10} > 1000), and most of them (39/43; 91%) correctly indicated that the original scream had become louder, while a minority (4/43; 9%) indicated that at some point, a new scream had been presented. All participants rated the 100-dB scream as more unpleasant (*M* = 93.69, *SD* = 9.79) than the 60-dB scream (*M* = 44.44, *SD* = 26.50; BF_{10} > 1000), with no group differences (BFs_{10} < 0.21). Together, these findings suggest that the threat inflation manipulation was successful.

Acquisition

Participants showed higher expectancies of the scream after CS+ than after CS- (Stimulus × Time: BF_{10} > 1000; Stimulus: BF_{10} > 1000, and there were no group differences (all BFs_{10} < 0.16). They also had higher distress levels during CS+ than CS- presentations (main effect Stimulus: BF_{10} > 1000), which did not change over time (Stimulus × Time: BF_{10} = 0.01). Groups did not differ in these effects (all BFs_{10} < 0.25). This indicates successful differential learning (see Figure 1).

Hypotheses

Threat Expectancy

For the first trials of the rehearsal phase, the strongest evidence was found for H4; see Table 2 for BF_{XC} values. So groups that engaged in threat rehearsal and/or underwent threat inflation had higher threat expectancy ratings then, relative to the 'no rehearsal and no inflation' group. All other hypotheses were supported to a lesser extent. Informative hypothesis tests showed that the data were most likely under H4 relative to any other hypothesis (BF_{41} = 3.58; BF_{42} = 8.03; BF_{43} = 10.89; BF_{45} = 3.62); see Table S1 for direct comparisons.

For the last trials of the rehearsal phase, the data were most likely under H1, followed by H4 and H5; see Table 2 for BF_{XC} values. This means that after threat rehearsal (with or without inflation), these threat expectancy ratings were higher. Tests of informative hypotheses showed that the data were more likely under H1 than under any alternative hypothesis (BF_{12} = 98.15; BF_{13} = 30.37; BF_{14} = 7.37; BF_{15} = 12.52); see Table S2 for other direct comparisons.

Distress

On the first trials of the rehearsal phase, the data were most likely under H2 (see Table 3). This means that threat inflation (with or without threat rehearsal) led to higher distress ratings than no threat inflation. Tests of informative hypotheses indicated that the data were more likely under H2 relative to any other hypothesis ($BF_{21} > 1000$; $BF_{23} = 15.50$; $BF_{24} = 291.39$; $BF_{25} > 1000$); see Table S3 for other comparisons.

At the end of the rehearsal phase, the data were most likely under H3 followed by H2 (see Table 3 for BF_{XC} values). Informative hypothesis tests (see Table S4) demonstrated that H3 received more support than H1 ($BF_{31} = 281.07$), H4 ($BF_{34} = 59.60$), and H5 ($BF_{35} = 409.10$). The evidence for H3 relative to H2 was inconclusive ($BF_{32} = 1.60$). This means that at the end of the rehearsal phase, rehearsal of the inflated US resulted in higher distress levels to the GS than all other groups. Yet, this hypothesis was not evidently stronger than the hypothesis stating that threat inflation (with or without rehearsal) results in higher distress to the GS than no threat inflation.

Exploratory Analyses

To explore the specificity of threat rehearsal and inflation effects, we performed Bayesian Informative analyses on CS- (see Tables S5 and S6). For threat expectancy, there was no compelling evidence for any hypothesis at the start of the rehearsal phase (all $BFs_{XC} < 0.39$), but at the end of this phase, the strongest evidence was found for similarity between groups ($BF_{5c} = 33.87$; see Table S5). The data were most likely under H5 relative to any other hypothesis (all $BFs_{5X} > 10.24$).

For distress ratings, there was strong evidence that ratings were higher after threat inflation (with or without rehearsal) at the beginning ($BF_{2c} = 63.08$) and at the end ($BF_{2c} = 27.92$) of the rehearsal phase (see Table S6). The data were more likely under H2 than the other hypotheses at the beginning of the rehearsal phase (all $BFs_{2X} > 277.17$). Yet, at the end of the rehearsal phase, H2 was more likely than H1, H3, and H4 ($BFs_{2X} > 4.57$), but not H5 ($BF_{25} = 1.58$). Together, these findings suggest that threat rehearsal did not affect threat expectancy and distress to CS-. In contrast, threat inflation resulted in higher distress, but not threat expectancy, to CS-, but this effect was uncertain at the end of the rehearsal phase.

Figure 1

Unconditioned Stimulus (US) Expectancy and Distress Ratings to Conditioned (CSs) and Generalization Stimuli (GSs)

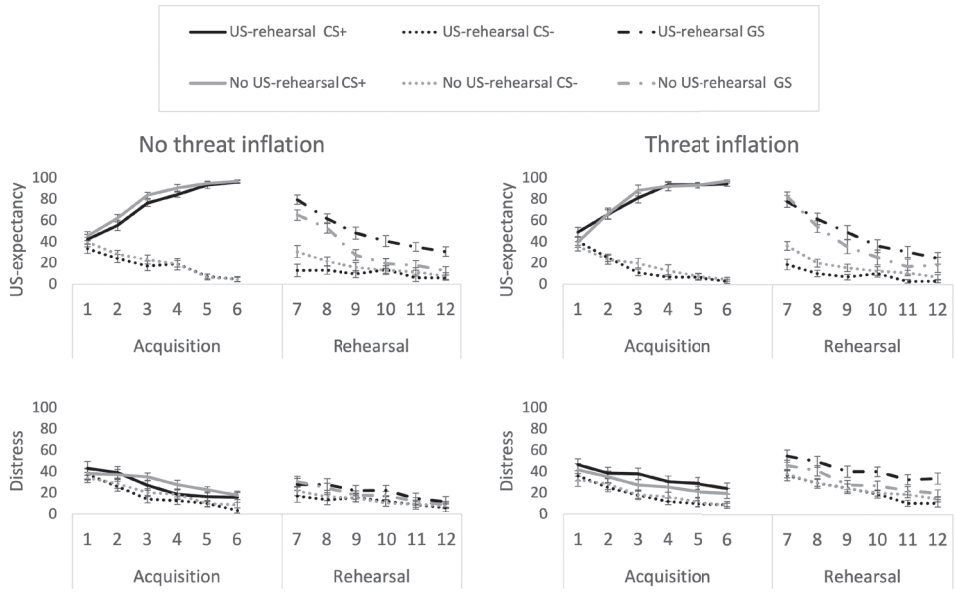

Table 2

Group Differences in Threat Expectancy to the GS at the Beginning and End of the Rehearsal Phase

Hypothesis	Description	First trials	Last trials
1. R+I = R+noI > noR+I = noR+noI	Threat rehearsal leads to higher threat expectancy towards the GS than no threat rehearsal.	BF_{1c} = 20.49	**BF_{1c} = 56.48**
2. R+I = noR+I > R+noI =noR+noI	Threat inflation leads to higher threat expectancy towards the GS than no threat inflation.	BF_{2c} = 9.13	BF_{2c} = 0.58
3. R+I > R+noI = noR+I = noR+noI	Threat rehearsal combined with threat inflation leads to higher threat expectancy towards the GS than all other groups.	BF_{3c} = 6.73	BF_{3c} = 1.86
4. R+I = R+noI = noR+I > noR+noI	Threat rehearsal and/or threat inflation lead to higher threat expectancy towards the GS.	**BF_{4c} = 73.27**	BF_{4c} = 7.66
5. R+I = R+noI = noR+I = noR+noI	Threat rehearsal and/or threat inflation do not affect threat expectancy towards the GS.	BF_{5c} = 20.24	BF_{5c} = 4.51

Note. BF = Bayes Factor; GS = generalization stimulus; I = Inflation; R = Rehearsal.

Table 3
Group Differences in Distress to the GS at the Beginning and End of the Rehearsal Phase

Hypothesis	Description	First trials	Last trials
1. R+I = R+noI > noR+I = noR+noI	Threat rehearsal leads to higher distress during the GS than no threat rehearsal.	BF_{1c} = 0.01	B_{1c} = 0.05
2. R+I = noR+I > R+noI =noR+noI	Threat inflation leads to higher distress during the GS than no threat inflation.	**BF_{2c} = 35.46**	BF_{2c} = 8.85
3. R+I > R+noI = noR+I = noR+noI	Threat rehearsal combined with threat inflation leads to higher distress during the GS than all other groups.	BF_{3c} = 2.29	**BF_{3c} = 14.15**
4. R+I = R+noI = noR+I > noR+noI	Threat rehearsal and/or threat inflation lead to higher distress towards the GS.	BF_{4c} = 0.12	BF_{4c} = 0.24
5. R+I = R+noI = noR+I = noR+noI	Threat rehearsal and/or threat inflation do not affect distress during towards the GS.	BF_{5c} = 0.02	BF_{5c} = 0.04

Note. BF = Bayes Factor; GS = generalization stimulus; I = Inflation; R = Rehearsal.

Discussion

The aim of this preregistered experiment was to examine whether threat rehearsal, threat inflation, or both would increase threat expectancy and distress toward a generalization stimulus (GS). Manipulation checks showed that these manipulations were successful. The hypotheses were tested separately for the two outcome variables: threat expectancy and distress ratings. There were two key findings. First, in the beginning of the rehearsal phase, threat expectancy ratings towards the GS were higher after threat rehearsal, threat inflation, or both, compared to the passive control condition. At the end of the rehearsal phase, only rehearsal (with or without inflation) resulted in higher threat expectancy. Second, for subjective distress, our findings indicated that threat inflation (with or without threat rehearsal) resulted in higher distress ratings toward the GS at the start of the rehearsal phase. At the end of this phase, threat inflation resulted in higher distress ratings, and there was inconclusive evidence whether threat rehearsal amplifies this effect.

To our knowledge, this is the first study showing that imagery-based mental threat rehearsal in the presence of a novel stimulus increases threat expectancy toward this stimulus in healthy individuals. It extends earlier work showing that threat rehearsal also increases threat expectancy to a safety cue (Krypotos et al., 2020). Although there was no

specific effect for rehearsal versus inflation at the beginning of the rehearsal phase, we did find higher threat expectancy ratings for the rehearsal versus no rehearsal groups at the end of the rehearsal phase, presumably resulting from repeated rehearsal. Interestingly, threat rehearsal did not materialize on subjective distress at the start of the rehearsal phase, but only at the end when it had been combined with threat inflation. Thus, threat intensity likely augments the effects of repeated threat rehearsal on subjective distress. Taken together, the findings suggest that particularly repeated threat rehearsal may be involved in fear overgeneralization and may hamper extinction learning. Interestingly, a parallel finding was recently reported in a clinical study showing that rehearsal of safety learning strengthens extinction learning (McGlade & Craske, 2021). Yet, they did not use a no rehearsal comparison group, so it is unclear how to interpret their imagery-based rehearsal effects.

This study also found that threat inflation was followed by increased subjective distress toward a generalization stimulus, both at the start and the end of the rehearsal phase. At the end of the rehearsal phase, this effect of threat inflation was even more substantial for participants who rehearsed the inflated US. Thus, threat inflation may play a crucial role in overgeneralization of distress, perhaps especially when people repeatedly imagine an inflated threat. These effects of threat inflation were specific for distress. This suggests that threat inflation may be better quantified with distress rather than threat expectancy outcome measures. Perhaps the use of expectancy measures, which do not necessarily reflect *severity* of threat, may explain some null findings of previous threat inflation studies (e.g., de Jong et al., 1996).

The findings highlight several clinically relevant implications. That is, repeated mental imagery of threat, and especially in case of an inflated threat, may play an important role in the overgeneralization of fear. Thus, mental rehearsal of threat may potentially play an important role in the etiology of clinical anxiety, but more research is needed to further examine its exact role. Perhaps, interventions that target mental imagery of threat may prevent the development of clinical anxiety in high-risk individuals (e.g., after trauma exposure). Our findings also suggest that threat rehearsal may conceivably hamper exposure learning and, therefore, may need to be addressed in patients seeking treatment for anxiety disorders. For example, imagery of desired behavior or outcomes may help to maximize treatment effects. Indeed, rehearsal of safety information (Carpenter et al., 2021; McGlade & Craske, 2021) or the addition of imagery-based interventions, such as imagery-rescripting (e.g., Dibbets et al., 2012; Morina et al., 2017) or positive mental imagery (Landkroon, van Dis, et al., 2021), have proven to boost exposure effects.

Our study brings forth several directions for research. For example, an interesting

new avenue for future research could be to examine to which extent effects of threat rehearsal depend on mental imagery. That is, some studies have shown that (abstract) verbal threat rehearsal could facilitate the generalization of fear potentiated startle (Gazendam & Kindt, 2012) and threat expectancy (Van Lier et al., 2014, 2015). On the one hand, abstract verbal threat rehearsal (e.g., worry) may advance overgeneral autobiographical memories which have been associated with heightened fear generalization (Lenaert et al., 2012). On the other hand, following the findings of Krypotos et al. (2020) and the current study, specific imagery-based threat rehearsal may amplify generalization by directly creating new fear-relevant associations. So future studies could directly compare whether and how different forms of threat rehearsal (e.g., verbal versus imagery-based; specific versus general) differently affect fear generalization. Another relevant direction for future research could be to examine the role of involuntary mental imagery in fear generalization, because anxiety patients typically suffer from intrusive, involuntary mental imagery of threat (Holmes & Mathews, 2010; Pearson & Westbrook, 2015). Future studies could, for example, add measures of involuntary mental imagery (e.g., Hagenaars & Arntz, 2012) or a conditioned-intrusion paradigm (e.g., Landkroon, Salemink, et al., 2021).

Some limitations of the current study should be noted. First, the test phase could not be used, in which CSs and multiple GSs, were presented, so it is unclear whether our effects are restrained to the rehearsed generalization stimulus, transfer to other GSs, and persist beyond the manipulation phase. In addition, it is unclear whether the threat inflation effects can be attributed to actual threat inflation or whether the presentation of the aversive stimulus would have created a threatening context. This should be further examined, as some scholars question the role of threat inflation in the etiology of clinical anxiety (Armfield, 2006). Finally, we cannot be sure whether our findings may differ across individuals with different ethnic identifications or geographic backgrounds. The strengths of our study are the trial-by-trial measurement of threat expectancy and distress, and the advanced statistical analyses, allowing direct comparisons between hypotheses.

Overall, our findings suggest that repeated threat rehearsal increases generalization of threat expectancy. In combination with threat inflation, it also increases generalized distress. Future studies should replicate the findings and examine the potential clinical utility of modulating imagery to prevent clinical anxiety.

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Author Contributions

All authors developed the study concept and contributed to the study design. EvD supervised the data collection and performed the data analysis. All authors were involved in the interpretation of the data. EvD drafted the paper and MH and IE provided critical revisions. All authors approved the final version of the paper for submission.

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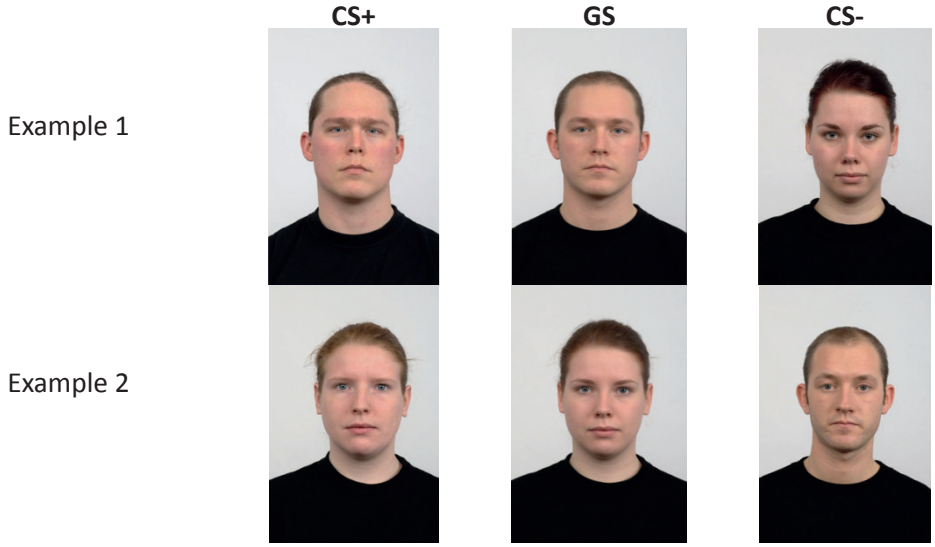
Supplementary Materials

Figure S1
Two Examples of Conditioned and Generalization Stimuli



Note. These faces were fully randomized across participants, with the restriction that the gender of the GS and CS+ were congruent. CS = conditioned stimulus; GS = generalization stimulus.

Table S1

Bayes Factor Matrix of Informative Hypothesis for Threat Expectancy at the Beginning of the Rehearsal Phase

	H1	H2	H3	H4	H5
H1	1.000	2.245	3.046	0.280	1.013
H2	0.446	1.000	1.357	0.125	0.451
H3	0.328	0.737	1.000	0.092	0.332
H4	**3.575**	**8.026**	**10.891**	**1.000**	**3.620**
H5	0.988	2.217	3.008	0.276	1.000

Table S2

Bayes Factor Matrix of Informative Hypothesis for Threat Expectancy at the End of the Rehearsal Phase

	H1	H2	H3	H4	H5
H1	**1.000**	**98.146**	**30.368**	**7.374**	**12.520**
H2	0.010	1.000	0.309	0.075	0.128
H3	0.033	3.232	1.000	0.243	0.412
H4	0.136	13.309	4.118	1.000	1.698
H5	0.080	7.839	2.426	0.589	1.000

Table S3

Bayes Factor Matrix of Informative Hypothesis for Distress at the Beginning of the Rehearsal Phase

	H1	H2	H3	H4	H5
H1	1.000	2.200e -4	0.003	0.064	0.408
H2	**4545.504**	**1.000**	**15.501**	**291.391**	**1853.854**
H3	293.242	0.065	1.000	18.798	119.597
H4	15.599	0.003	0.053	1.000	6.362
H5	2.452	5.394e -4	0.008	0.157	1.000

Table S4

Bayes Factor Matrix of Informative Hypothesis for Distress at the End of the Rehearsal Phase

	H1	H2	H3	H4	H5
H1	1.000	0.006	0.004	0.212	1.455
H2	175.855	1.000	0.626	37.291	255.953
H3	**281.073**	**1.598**	**1.000**	**59.604**	**409.095**
H4	4.716	0.027	0.017	1.000	6.864
H5	0.687	0.004	0.002	0.146	1.000

Table S5

Group Differences in Threat Expectancy to the CS- at the Beginning and End of the Rehearsal Phase

Hypothesis	Description	First trials	Last trials
1. R+I = R+noI > noR+I = noR+noI	Threat rehearsal leads to higher threat expectancy towards the CS- than no threat rehearsal.	BF_{1c} = 0.01	BF_{1c} = 1.92
2. R+I = noR+I > R+noI =noR+noI	Threat inflation leads to higher threat expectancy towards the CS- than no threat inflation.	BF_{2c} = 0.09	BF_{2c} = 3.30
3. R+I > R+noI = noR+I = noR+noI	Threat rehearsal combined with threat inflation leads to higher threat expectancy towards the CS- than all other groups.	BF_{3c} = 0.02	BF_{3c} = 2.02
4. R+I = R+noI = noR+I > noR+noI	Threat rehearsal and/or threat inflation lead to higher threat expectancy towards the CS-.	BF_{4c} = 0.02	BF_{4c} = 2.51
5. R+I = R+noI = noR+I = noR+noI	Threat rehearsal and/or threat inflation do not affect threat expectancy towards the CS-.	**BF_{5c} = 0.39**	**BF_{5c} = 33.87**

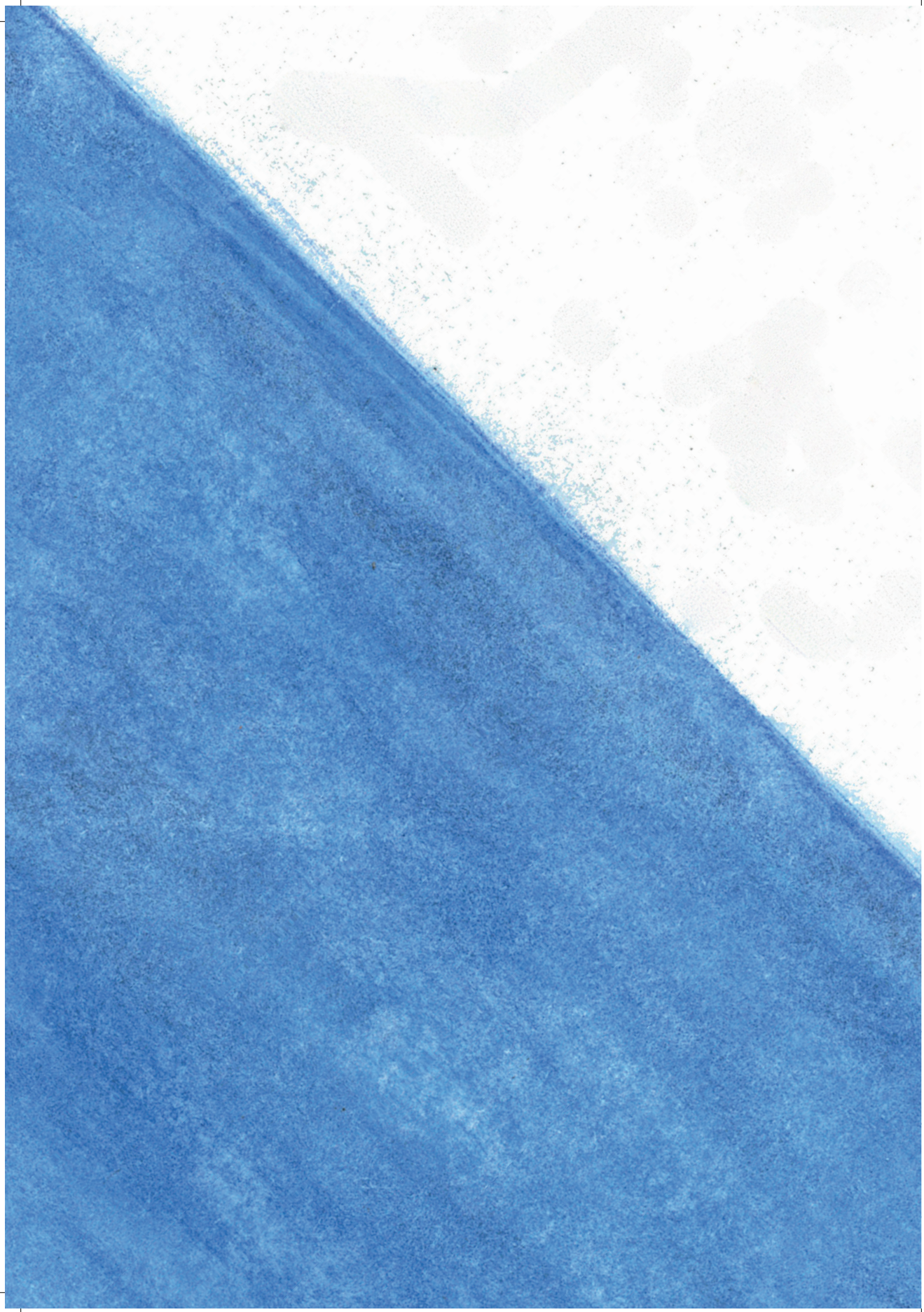
Note. BF = Bayes Factor; CS = conditioned stimulus; I = Inflation; R = Rehearsal.

Table S6

Group Differences in Distress to the CS- at the Beginning and End of the Rehearsal Phase

Hypothesis	Description	First trials	Last trials
1. R+I = R+noI > noR+I = noR+noI	Threat rehearsal leads to higher distress during the CS- than no threat rehearsal.	BF_{1c} = 0.01	BF_{1c} = 1.33
2. R+I = noR+I > R+noI =noR+noI	Threat inflation leads to higher distress during the CS- than no threat inflation.	**BF_{2c} = 63.08**	**BF_{2c} = 27.92**
3. R+I > R+noI = noR+I = noR+noI	Threat rehearsal combined with threat inflation leads to higher distress during the CS- than all other groups.	BF_{3c} = 0.23	BF_{3c} = 2.61
4. R+I = R+noI = noR+I > noR+noI	Threat rehearsal and/or threat inflation lead to higher distress towards the CS-.	BF_{4c} = 0.09	BF_{4c} = 6.11
5. R+I = R+noI = noR+I = noR+noI	Threat rehearsal and/or threat inflation do not affect distress during towards the CS-.	BF_{5c} = 0.06	BF_{5c} = 17.73

Note. BF = Bayes Factor; CS = conditioned stimulus; I = Inflation; R = Rehearsal.



Chapter 3

Safety behaviors toward innocuous stimuli can maintain or increase threat beliefs

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Abstract

Safety behaviors can prevent or minimize a feared outcome. However, in relatively safe situations, they may be less adaptive, presumably because people will misattribute safety to these behaviors. This research aimed to investigate whether safety behaviors in safe situations can lead to increased threat beliefs. In Study 1, we aimed to replicate a fear conditioning study (N = 68 students) in which the experimental, but not the control group, received the opportunity to perform safety behavior to an innocuous stimulus. From before to after the availability of the safety behavior became unavailable, threat beliefs persisted in the experimental group, while they decreased in the control group. In Study 2, we examined whether threat beliefs had actually increased for some individuals in the experimental group, using a multi-dataset latent class analysis on data from Study 1 and two earlier studies (N = 213). Results showed that about a quarter of individuals who performed safety behavior toward the innocuous stimulus showed increased threat expectancy to this cue, while virtually nobody in the control group exhibited an increase. Taken together, safety behavior in relatively safe situations may have maladaptive effects as it generally maintains and sometimes even increases threat beliefs.

Keywords: safety behavior, fear conditioning, anxiety disorders, individual differences

Introduction

Safety behaviors involve precautions to prevent or minimize a feared outcome. Many people regularly engage in such behaviors, such as frequent hand washing and avoidance of contact with potential contaminants (Deacon & Maack, 2008), particularly during the current pandemic to slow the spreading of the coronavirus. Safety behaviors that reduce threat are obviously essential to survival. However, they may also be used in low threat situations. For example, consider people who knock on wood to avert bad outcomes or patients with a panic disorder who sit down when they feel dizzy because they are afraid to faint. Although safety behaviors in such situations may be considered benign ("better safe than sorry"), there may be costs to performing them. Specifically, they may ironically lead to an increased threat perception because people may accommodate their cognitions to their behavior to reduce cognitive dissonance (Festinger & Carlsmith, 1959; Harmon-Jones et al., 2015). In addition, safety behaviors are also thought to prevent the disconfirmation and updating of threat beliefs (akin to "protection from extinction"; see Clark, 1999; Lovibond et al., 2009). For example, when patients with a panic disorder sit down when they fear fainting, they will not learn that dizziness is not a harbinger of fainting (Telch & Zaizar, 2020). Therefore, studies have been conducted to find out whether safety behaviors actually enhance threat beliefs.

Laboratory experiments (e.g., Lovibond et al., 2009; van Uijen et al., 2018; Vervliet & Indekeu, 2015) have demonstrated that safety behaviors can maintain or increase threat beliefs in "high-threat" situations. That is, individuals did or did not apply safety behavior toward cues that signaled impending threat. Less is known, however, about the causal relationship between safety behaviors and threat beliefs in "low-threat" or relatively safe situations, which are more typical for clinical anxiety than high-threat situations (e.g., Lissek et al., 2006). Several field studies found evidence for a causal relation between safety behavior and threat beliefs in low threat situations. For example, college students who were instructed to apply contamination-related safety behaviors for a week (e.g., washing and disinfecting hands repeatedly; Deacon & Maack, 2008; Olatunji et al., 2011) showed increased contamination concerns a week later. Likewise, applying checking behaviors for a week led to increased safety concerns (van Uijen & Toffolo, 2015). However, these studies did not manipulate actual threat or safety. Therefore, a controlled lab study was conducted to examine whether safety behavior toward a safe stimulus increases threat beliefs when that behavior is no longer available (Engelhard et al., 2015). This experiment started with a fear learning phase, in which one neutral cue (i.e., "danger cue") was

followed by a mild electrical shock, whereas two other neutral cues were not (i.e., "safety cues"). In a subsequent safety behavior learning phase, participants could prevent the shock by pressing a button in response to the danger cue. Next, in the safety behavior *shift* phase, participants in the experimental group, but not in the control group, received the opportunity to perform safety behavior toward one of the two *safety* cues. Finally, in a *test* phase, the danger and safety cues were presented without the opportunity to perform safety behavior. The results of the test phase showed that participants in the experimental group, relative to the control group, exhibited higher threat expectancy to the safety cue to which they previously applied safety behavior. In other words, from before to after the safety behavior shift phase, threat expectancy to this safety cue persisted in the experimental group while it decreased in the control group (Engelhard et al., 2015). This suggests that safety behavior toward safe stimuli does not increase but maintains threat beliefs. These findings were recently replicated (Xia et al., 2019).

Even though these two studies (Engelhard et al., 2015; Xia et al., 2019) provided evidence that safety behavior toward innocuous stimuli maintains threat beliefs, two problems remain. First, they excluded about 28% of participants in the experimental group who did not apply safety behavior toward the safety cue (Engelhard et al., 2015; Xia et al., 2019), potentially resulting in a selection bias. Second, they used statistical methods to analyze mean differences, which may neglect relevant heterogeneity in performance (Krypotos et al., 2018; Lonsdorf & Merz, 2017). Advanced modeling techniques (see Bonanno et al., 2012; Galatzer-Levy et al., 2013) could elucidate whether and for whom safety behaviors to safe stimuli may also lead to increased threat beliefs, but such techniques require larger sample sizes.

The aim of the current research was twofold. First, in Study 1, we sought to replicate and extend Engelhard et al. (2015) by employing a design that would prevent the high exclusion rates in the experimental group. To reduce exclusion rates, we increased stimulus ambiguity (i.e., partial reinforcement and fewer safety cues presentations), which could motivate participants to apply safety behavior toward the safety cue (see Lissek et al., 2006). Second, in Study 2, we performed a multi-dataset analysis on all three studies (Engelhard et al., 2015; Xia et al., 2019; current Study 1) using meaningful change scores and latent class analyses to examine heterogeneity in threat expectancy over time. We predicted that the experimental group would predominantly show a maintained or increased threat expectancy to the safety cue when the safety behavior is no longer available, while the control group would mainly show decreased threat expectancy to this safety cue.

Study 1

Methods

Participants

One-hundred Dutch-speaking undergraduate students were recruited and tested at Utrecht University. Of these, 32 were excluded (see below), resulting in a final sample size of 68 participants (14 males; 54 females; mean age = 20.85; *SD* = 2.02) who were randomly assigned to the experimental (*n* = 34) and control group (*n* = 34). The sample size (*N* = 68) was set before data collection using G*Power 3.1 (Faul et al., 2009; settings: repeated measures analysis of variance; within-between interaction, $\eta_p^2 = 0.025$, $\alpha = 0.05$, power = 0.80, 2 groups, 3 measures). We aimed to detect a small to medium effect (see Engelhard et al., 2015; Xia et al., 2019). The study adhered to the Dutch legal requirements and was approved by the Faculty of Social and Behavioral Sciences ethics committee at Utrecht University (FETC15-014).

Measures

Shock unpleasantness and threat expectancy. Shock unpleasantness was assessed with an 11-point scale, ranging from 0 (not unpleasant at all) to 10 (very unpleasant). Threat expectancy was rated on a visual analog scale ranging from 0 (certainly no shock) to 100 (certainly a shock); following Engelhard et al. (2015).

Neuroticism Scale of the Eysenck Personality Questionnaire (EPQ-N). Neuroticism was measured using the Dutch EPQ-N version (Eysenck & Eysenck, 1991; Sanderman et al., 2012), which may be relevant to explore individual differences in safety behavior (Lommen et al., 2010). It includes 22 self-report items (e.g., "Are you often troubled about feelings of guilt?") that are rated on a dichotomous scale (0 = no, 1 = yes). Cronbach's α was 0.88 in the current study.

Skin Conductance

Skin conductance activity was recorded using two 8-mm passive Nihon Kohden electrodes that were placed on the index and middle fingers of the non-dominant hand. Two 4-mm Ag-AgCl reference electrodes were attached to the forehead. Skin conductance signals were amplified with a Biosemi system and were recorded with a separate computer running ActiView 7.06 at 5 samples/s.

Stimuli and Apparatus

The conditioned stimuli (i.e., CSs: A+, B-, and C-) consisted of 6 × 6 cm blue, yellow, and pink squares (randomized for each participant) and were presented in the middle of the screen. The unconditioned stimulus (US) was a 0.5-s tone (95 dB) combined with a 0.5-s electric shock (range 0.2-4.0 mA), which was delivered by a Coulbourn Transcutaneous Aversive Finger Stimulator [E13-22] through electrodes attached to the index and middle finger of the dominant hand. The combination of a shock with a tone may prevent US habituation (Lovibond et al., 2009). A serial response box (model 200A) with five lights and corresponding buttons was placed in front of the monitor. The experimental paradigm and response collection were controlled by Python 2.7.

Trial Procedure

Trials started with an 8-s CS presentation, after which participants received 5 s to rate their threat expectancy. Trials ended with a 0.5-s period during which the US could be presented. Inter-trial intervals (ITIs) randomly varied between 15 s and 36 s. In some phases, a response box light illuminated during a CS presentation, which provided participants with the opportunity to prevent the US (i.e., "if you press the button below the light, the shock will not occur"). Trials were presented in a pseudorandom order with a maximum of two identical trials in sequence. A maximum of 3 successive presentations of the same trials was allowed during the safety behavior acquisition phase.

The methodology differed from Engelhard et al. (2015) in three significant ways. First, we added skin conductance measures, a physiological measure of arousal, and, therefore, prolonged the CS presentations and ITIs. Second, we aimed to reduce the exclusion rate of participants who do not show a safety behavior shift by including fewer safety cue trials. Presumably, this would increase stimulus ambiguity, which may instigate fear (Lissek et al., 2006) and, thereby, safety behavior. Finally, we reduced the reinforcement rate to A+ from 100% to 75%. This way, we did not have to exclude participants who applied safety behavior toward C- only three out of four times.

General Procedure

Table 1 displays the general experimental procedure. After providing informed consent, participants were attached to skin conductance and shock electrodes. Participants selected a "certainly annoying, but not painful" shock level through a work-up procedure (Engelhard et al., 2015). Throughout the experiment, they wore headphones that played an 80-dB white noise to mask external sounds. Participants were instructed to learn the

Table 1
Design of Study 1

Pavlovian acquisition	Safety behavior acquisition	Safety behavior shift	Test
A+ (4)	A*(+) (6)	A+ (4)	A+ (1)
B- (2)	A+ (1)	B- (4)	B- (1)
C- (2)	B- (1)	C(*)- (4)[a]	C- (1)
	C- (1)		

Note. A+, B-, and C- refer to visual stimuli; * refers to the availability of safety behavior; (+) indicates that shock only occurred if the participant failed to perform safety behavior; numbers in parentheses give the number of trials.
[a] The experimental, but not the control group, received the opportunity to perform safety behavior during this stimulus.

relationship between the blocks' color and shock occurrence. After six practice trials, they started with a Pavlovian acquisition phase in which A+ was followed by the US in 3 out of 4 trials (random reinforcement order), while B- and C- were never followed by the US. In the safety behavior acquisition phase, one of the response box lights illuminated during 6 out of 7 A+ trials (i.e., A+*). If participants pressed a button below the light, the US did not follow. In the safety behavior shift phase, response box lights illuminated during C- trials (i.e., C-*) in the experimental group, but not in the control group. In this phase, no safety behavior could be performed to A+. In the test phase, each stimulus was presented once without illuminated response box lights. C+ was always shown last. Finally, participants filled out the EPQ-N and were debriefed and reimbursed.

Data Preparation

We based all our exclusion criteria on Engelhard et al. (2015). Participants were excluded if they showed no CS-US contingency awareness (i.e., a higher threat expectancy rating to A+ than to B- in the test phase), no safety behavior acquisition (i.e., at least four button presses during A+* trials), or no safety behavior shift (i.e., in our study, at least three button presses during C-* trials). Data of 32 participants were excluded: 7 were unaware of the CS-US contingency, 16 showed no successful safety behavior acquisition, and 9 showed no safety behavior shift (i.e., 21% of the experimental group). Outliers were defined as more than 3 *SD* from the mean and were replaced with $M \pm 3$ *SD* (see Engelhard et al., 2015).

Similar to Lovibond et al. (2008, 2009), we computed the change in mean skin conductance level (SCL) by subtracting the mean SCL during the 10-s pre-CS baseline

period from the mean SCL during the 5-s pre-US presentation. SCL data were mean-corrected following Lovibond (1992; Exp. 2).

Data-Analysis

First, to inspect group differences in baseline variables, one-way ANOVAs were performed on age, neuroticism scores, shock level, and shock unpleasantness. A Chi-squared test assessed gender differences across groups. Second, to test whether Pavlovian acquisition was successful for threat expectancy and SCL, we used two 3 (Stimulus: A+, B-, C-) × 2 (Time: first, final acquisition trial) × 2 (Group: experimental, control) mixed ANOVAs. Third, to examine safety behavior acquisition effects on threat expectancy and SCL, we performed two 2 (Stimulus: A+, first A+* trial) × 2 (Group: experimental, control) mixed ANOVAs. To examine how threat responding to A+* developed over time, we used two 6 (Time: all A+* trials) × 2 (Group: experimental, control) mixed ANOVAs. Fourth, to test group differences to C- in the safety behavior shift phase, we conducted two 4 (Time: all C-/C-* trials) × 2 (Group: experimental, control) mixed ANOVAs with threat expectancy and SCL as dependent variables. Fifth, to test group differences in threat expectancy and SCL in the test phase, we performed two 3 (Stimulus: A+, B-, C-) × 2 (Group: experimental, control) mixed ANOVAs. To test whether threat expectancy and SCL to C- changed from the safety behavior acquisition phase to the test phase, we used two 2 (Time: C- trial safety behavior acquisition, C- trial test) × 2 (Group: experimental, control) mixed ANOVAs.

All analyses were performed within a frequentist ($\alpha = .05$) and Bayesian hypothesis testing framework (using JASP Version 0.12.2.0; JASP Team, 2020). When the sphericity assumption was violated, we used Huynh-Feldt ($\varepsilon > 0.75$) or Greenhouse-Geisser ($\varepsilon < 0.75$) corrections. Holm–Bonferroni methods were used for all simple effects tests. Bayes factors (BFs) indicate that the data are BF times more likely under the alternative relative to the null hypothesis (Dienes, 2014). $BFs_{10} > 3$ indicate stronger evidence of data coming from the alternative than the null hypothesis, whereas $BFs_{10} < 0.33$ indicate the reverse. BFs_{10} between 0.33 and 3 can be interpreted as anecdotal or inconclusive evidence (Jeffreys, 1961).

Results

Randomization Checks

We found no evidence that the groups differed in gender distribution, $\chi^2(1) = 3.24$, $p = .072$, $BF_{10} = 1.69$, age, neuroticism scores, shock level, or shock unpleasantness, (all Fs < 2.11, all ps > .151, all $BFs_{10} < 0.61$), which suggests a successful randomization.

Pavlovian Acquisition Phase

Throughout this phase, participants had higher shock expectancy during A+ than B- or C- (Stimulus × Time), $F(1.60, 105.88) = 28.04$, $p < .001$, $\eta_p^2 = .30$, $BF_{10} > 1000$, see Figure 1. Similarly, SCL was stronger for A+ than B- and C-, Stimulus × Time: $F(1.82, 120.09) = 2.68$, $p = .078$, $\eta_p^2 = .04$, $BF_{10} = 0.40$; Stimulus, $F(1.82, 120.36) = 12.68$, $p < .001$, $\eta_p^2 = .16$, $BF_{10} > 1000$. Groups did not differ in threat expectancy and SCL (interaction effects with group: Fs < 2.81, all ps > .099, $BFs_{10} < 0.20$), which indicates a successful acquisition on threat expectancy and SCL for both groups.

Safety Behavior Acquisition Phase

Participants had lower threat expectancy ratings to the first response box trial (A+*) than to A+, $F(1, 66) = 126.94$, $p < .001$, $\eta_p^2 = .66$, $BF_{10} > 1000$, which suggests that they learned that safety behavior canceled the shock. Throughout this phase, threat expectancy ratings and SCL during the safety behavior trials continued to decline (Fs > 8.82, ps < .001, $BFs_{10} > 842.30$). There were no interactions with group (Fs < 1.61, ps > .168, $BFs_{10} < 0.07$).

Safety Behavior Shift

Groups significantly differed in threat expectancy to C- across all trials (Time × Group), $F(2.13, 140.78) = 3.20$, $p = .041$, $\eta_p^2 = .05$, $BF_{10} = 1.66$, but there was no evidence that they differed on the first and last trial of C- (both ts < 1.70, ps > .999, $BFs_{10} < 0.70$). For SCL, there was no Time × Group interaction, $F(3.07, 202.50) < 1$, $p = .735$, $\eta_p^2 = .01$, $BF_{10} = 0.07$, nor a main effect of Time, $F(3.07, 202.50) < 1$, $p = .770$, $\eta_p^2 = .01$, $BF_{10} = 0.03$, but a main effect of Group, $F(1, 66) = 17.54$, $p < .001$, $\eta_p^2 = .21$, $BF_{10} = 217.74$.

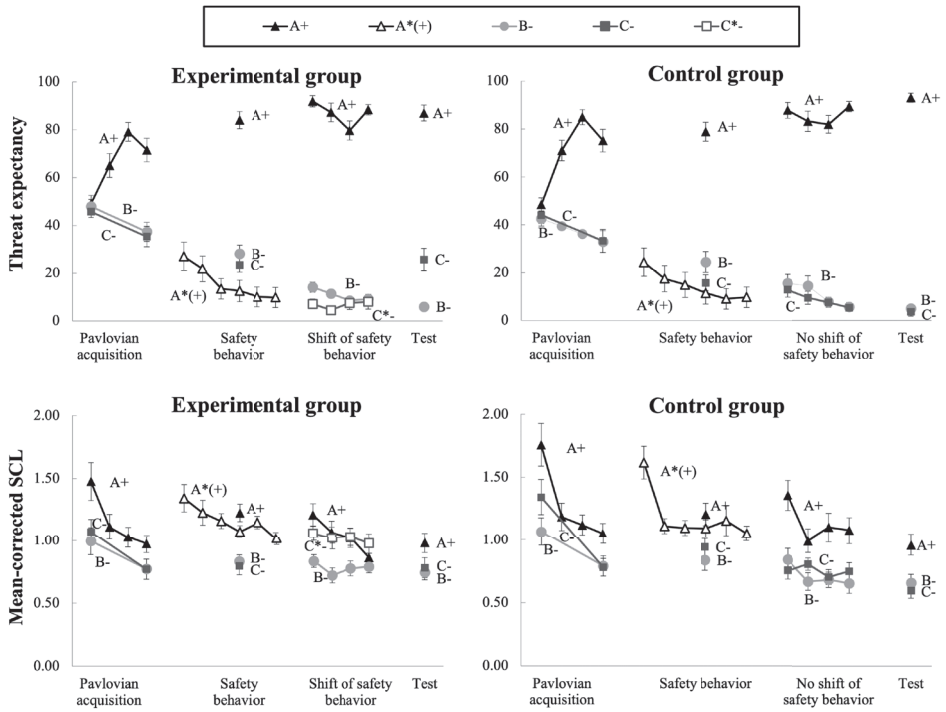
Test Phase

In this phase, groups differed in threat expectancy across stimuli, Stimulus × Group: $F(1.85, 121.83) = 15.53$, $p < .001$, $\eta_p^2 = .19$, $BF_{10} > 1000$. For both groups, threat expectancy ratings were higher for A+ than for B- and C-, ts > 16.50, ps < .001, $BFs_{10} > 1000$. Crucially, the experimental group showed higher ratings during C- compared to the control group, $t = 5.72$, $p < .001$, $BF_{10} = 446.37$. Also, ratings to C- were higher than B- in the experimental group, $t = 5.32$, $p < .001$, $BF_{10} = 190.21$, but not in the control group, $t < 1$, $BF_{10} = 0.22$.

Furthermore, from the safety behavior acquisition phase to the test phase, ratings to C- did not change in the experimental group ($t < 1$, $BF_{10} = 0.20$), while they decreased in the control group ($t = 2.72$, $p = .034$, $BF_{10} = 9.55$), $F(1, 66) = 5.20$, $p = .026$, $\eta_p^2 = .07$, $BF_{10} = 2.64$ (Time × Group), suggesting that safety behavior maintained threat expectancy.

Figure 1

Threat Expectancy Ratings and Skin Conductance Level (SCL) During Study 1



In contrast to the expectancy ratings, we found no evidence that the groups differed in SCL, Stimulus × Group: $F(1.84, 121.63) < 1$, $p = .512$, $\eta_p^2 = .01$, $BF_{10} = 0.15$; Group: $F(1, 66) = 2.35$, $p = .130$, $\eta_p^2 = .03$, $BF_{10} = 0.49$. SCL did differ across stimuli, $F(1.84, 121.63) = 9.87$, $p < .001$, $\eta_p^2 = .13$, $BF_{10} = 541.78$. Simple effects showed that SCL was higher to A+ than to B- and C- ($ts > 3.76$, $ps < .001$, $BFs_{10} > 22.55$), while B- and C- did not differ ($t < 1$, $BF_{10} = 0.14$). Thus, safety behavior did not result in stronger SCL to C- when the safety behavior was made unavailable.

Discussion

Study 1 demonstrated that safety behavior toward a safety cue maintains threat expectancy when the safety behavior becomes unavailable. This replicates previous studies (e.g., Engelhard et al., 2015; Xia et al., 2019). Our findings were not substantiated

on a skin conductance level (in line with Xia et al., 2019), perhaps because this measure is not sensitive enough to detect differences between responses to two innocuous stimuli. Indeed, a previous study on safety behavior toward a *danger* cue did show group differences in skin conductance (Lovibond et al., 2009).

In Study 2, we set out a multi-dataset analysis using meaningful change scores and latent class analyses to test heterogeneity in threat expectancy from before to after the performance of safety behavior to a safety cue. We hypothesized that the experimental group would predominantly show maintained or increased threat expectancy to the safety cue after removing the safety behavior and that the control group would mainly show decreased threat expectancy to this cue. In addition, we performed sensitivity analyses to explore whether our results would change when different exclusion criteria were applied.

Study 2

Methods

The Faculty of Social and Behavioral Sciences ethics committee at Utrecht University (FETC-20-347) approved this study. It was preregistered on the Open Science Framework (https://osf.io/3vyrc/).

Study Selection

We combined datasets from the three studies that used the same basic paradigm (i.e., Engelhard et al., 2015; Xia et al., 2019; current Study 1). There were minor variations in the number of stimulus presentations, stimuli nature, trial duration, and outcome measures (see Table S1 in the Supplementary Materials).

Participants

We applied the same exclusion criteria as in Study 1 (i.e., no contingency awareness; no safety behavior acquisition; no safety behavior shift) and excluded 87 participants out of 311 (i.e., n = 20 of 101, Engelhard et al. 2015; n = 35 of 110, Xia et al. 2019; and n = 32 of 100, Study 1 of this paper). Data of 11 participants were missing (Engelhard et al., 2015: n = 1; Xia et al., 2019: n = 10). Complete case analyses are reported because the missingness might not be completely at random (van Buuren, 2012). The final sample included N = 213 students (n = 99 experimental; n = 114 control) with 57 males and 156 females.

Outcome Measure

The outcome measure comprises a change score in threat expectancy to C- from the final trial of the safety behavior acquisition phase to the first trial of the test phase. For the Chi-Square and Bayesian Contingency Tables tests (see below), we computed meaningful change scores following Copay et al. (2007). Change scores ranging between 0 ± 0.5 *SD* were the *no-change* category, change scores smaller than 0 – 0.5 *SD* were the *decrease* category, and change scores larger than 0 + 0.5 *SD* were the *increase* category.

Data-Analysis

First, to test whether we needed to control for between-study heterogeneity in our multi-dataset analysis, we calculated the Diamond Ratio (DR; see Cairns et al., 2020). Specifically, we calculated the DR for group effects on change scores in threat expectancy to C-. DR = 1 means no or little heterogeneity, DR = 1.40 indicates moderate heterogeneity, and DR of 2 and higher means large heterogeneity (Cairns et al., 2020). Second, to test group differences in the *no-change*, *decrease,* and *increase* categories, we performed a Chi-Square test and a Bayesian Contingency Tables test with Group (Experimental vs. Control) as an independent variable and the change score categories (i.e., *no-change*, *decrease*, and *increase*) as the dependent variable. These analyses were run in JASP Version 0.12.2.0 using the default settings (JASP Team, 2020). Follow-up analyses were run in MedCalc using the "N-1" Chi-squared test, as suggested by Campbell (2007) and Richardson (2011). Third, to explore how individuals are categorized based on their change score (i.e., how many categories best fit the data) and whether these categories differ across groups, we performed a latent class analysis in Mplus (Version 8.4). We used the three-step procedure (Asparouhov & Muthén, 2014) with Group as a predictor. This method takes the uncertainty with respect to participants' class allocations into account in the subsequent multinomial regression analysis. The number of latent classes was determined by evaluating the combination of the Lo-Mendell-Rubin test (LMR), adjusted LMR, bootstrap likelihood ratio test (BLRT), the Bayesian information criterion (BIC; Tein et al., 2013), sample size, and interpretability. The LMR, adjusted LMR, and BLRT result in *p*-values, where *p*-values $<.05$ suggest that *k* classes are preferred over *k*-1 classes. The BIC can be compared between *k* and *k*-1 classes, where lower BIC values are preferred. The sample size criterion means that there cannot be many small categories in the final selection, as the third step of the analysis is a multinomial regression with group as a predictor and class as a dependent variable. The final criterion was interpretability

(Geiser, 2013), which means that we prefer a *k*-class solution when we can also give meaning to it. Fourth, we explored whether a change in threat expectancy to C- is related to anxiety-related personality trait measures.

Results

Meaningful Change

We used a fixed-effects model for all analyses because the between-studies heterogeneity was small (DR = 1; 95% CI: 1.00, 4.49). As displayed in Figure 2, groups significantly differed in meaningful change scores to C- from the safety behavior acquisition phase to the test phase, $\chi^2(2, N = 213) = 25.44$, $p < .001$; $BF_{10} > 1000$. Further examination showed that more participants in the experimental group (26/99; 26.26%) exhibited a meaningful *increase* in threat expectancy to C-, relative to the control group (3/114; 2.63%), while more participants in the control group showed *no change* in threat expectancy (experimental: 54/99; 54.55%; control: 78/114; 68.42%). Unexpectedly, groups did not significantly differ in the percentage of *decreased* threat expectancy (experimental: 19/99; 19.19%; control: 33/114; 28.95%). A sensitivity analysis using different exclusion criteria showed similar results (see Table S2 in the Supplementary Materials).

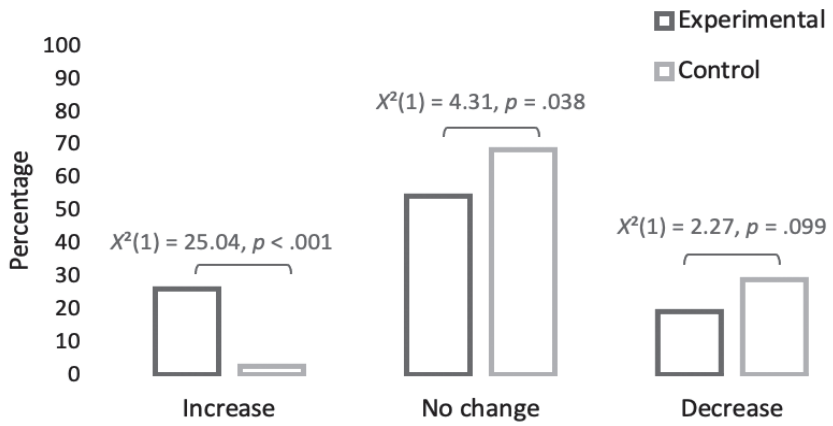
Latent Class Analysis

Figure S1 in the Supplementary Materials displays the change score distributions across groups. The best solution with interpretable and analyzable classes was the three-class solution (see Table 2 and Figure 3). The classes could be labeled as *decrease* (class 1; *n* = 10), *no-change* (class 2; *n* = 183), and *increase* (class 3; *n* = 20). Sensitivity analyses demonstrated that these results did not meaningfully change when different exclusion criteria were applied (see Table S3 in the Supplementary Materials).

To compare group differences in classes, we calculated odds ratios (ORs). Participants in the experimental group, relative to the control group, were 14.63 times more likely to exhibit change scores that fell into in the *increase* rather than the *decrease* class (95% CI = 1.93, 110.93; $p = .009$) and were 7.63 times more likely to have change scores in the *increase* rather than the *no-change* class (95% CI = 2.11, 27.60; $p = .002$). Groups did not significantly differ in OR of change scores in the *decrease* rather than the *no-change* class (OR = 1.91; 95% CI = 0.37, 9.93; $p = .438$). Thus, these results suggest that safety behavior increases the likelihood of an increased threat expectancy to safety cue C- when the safety behavior is unavailable.

Figure 2

Percentage of Participants who Showed an Increase, no Change or Decrease in Threat Expectancy to C- From the Safety Behavior Acquisition Phase to the Test Phase (Study 2)



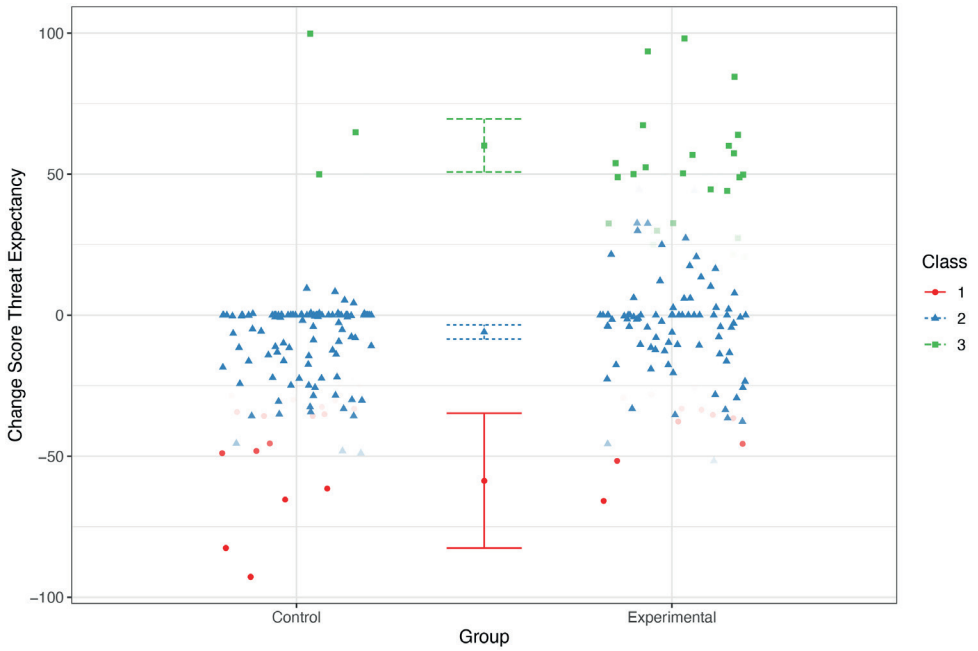
Note. The labels represent meaningful change categories.

Exploratory Analyses

We executed Pearson correlation analyses to test a relation between change scores in threat expectancy to C- and *z*-transformed trait anxiety (Xia et al., 2019) and neuroticism scores (current Study 1). These analyses did not reveal a relationship between change scores in threat expectancy to C- and *z*-transformed anxious personality traits (r = -0.17, p = .056, BF_{10} = 0.66).

Figure 3

Solution with Three Classes by Group Resulting from a Three-Step Latent Class Analysis (Study 2)



Note. Change scores represent the difference in threat expectancy to C- from the safety behavior acquisition phase to the test phase.

Table 2

Latent Class Analyses on Change Scores in Study 2

Classes	LMR	V-LMR	BLRT	BIC	Entropy	Min n	Max n
1	-	-	-	2025.55	-	213	213
2	.033	.027	<.001	1988.28	.96	20	193
3	.034	.026	<.001	1960.66	.95	10	183
4	.618	.605	<.001	1957.97	.95	4	180
5	.008	.006	< .001	1932.22	.95	4	149
6	.157	.136	< .001	1924.37	.96	4	145

Note. Change scores represent the difference in threat expectancy to C- from the safety behavior acquisition phase to the test phase.

General Discussion

We examined whether safety behavior toward a safety cue maintains or increases threat beliefs when the behavior becomes unavailable. In Study 1, we replicated and extended earlier fear conditioning studies on safety behavior to a safety cue (Engelhard et al., 2015; Xia et al., 2019). Our results showed that safety behavior toward a safety cue maintains threat beliefs, although skin conductance data did not corroborate this result (see also Xia et al., 2019). In Study 2, we performed a multi-dataset analysis (using meaningful change scores and latent class analyses) to explore heterogeneity in threat expectancy to a safety cue before and after the performance of safety behavior. This revealed that about a quarter of individuals who performed safety behavior toward a safety cue showed increased threat expectancy to this cue, while virtually nobody in the control group exhibited an increase. Thus, the present research, together with prior clinical studies (e.g., Deacon & Maack, 2008; van Uijen & Toffolo, 2015), indicates that safety behavior in relatively safe situations may culminate in the increase or perseverance of threat beliefs.

Several findings warrant further discussion. First, in Study 2, participants strongly differed in their threat responses when the safety behavior was no longer available, which may indicate resilience or risk for clinical anxiety (Krypotos et al., 2018; Lonsdorf & Merz, 2017). Future research may elucidate whether these response patterns are related to specific traits (e.g., harm avoidance; Gazendam et al., 2020) or symptom profiles (e.g., obsessive-compulsive symptoms; Hunt et al., 2020) that are involved in clinical anxiety. If, for example, individuals who exhibit increased threat expectancy after safety behavior are more likely to develop anxiety symptoms, this paradigm can be used to identify such individuals to offer them preventive treatment (Paulus, 2015).

Another noteworthy finding in Study 2 was that a substantial number of individuals showed *increased* threat expectancy to the safe stimulus (that was never paired with an unpleasant stimulus) when the safety behavior was no longer available. This is in line with previous field studies (e.g., Deacon & Maack, 2008) and with recent work showing that people who see police patrolling in safe situations may ironically feel less safe (van de Veer et al., 2012). How could these findings be explained? On the one hand, following the cognitive-dissonance theory, these individuals may have sought consistency in their attitudes and safety behaviors (Festinger & Carlsmith, 1959; Harmon-Jones et al., 2015; van Uijen et al., 2017). Indeed, previous work showed that patients with clinical anxiety rate objectively safe scenarios as more dangerous when the person in the scenario uses safety behavior (Gangemi et al., 2012; van den Hout et al., 2014). Future research could directly manipulate cognitive dissonance to test whether more cognitive dissonance is

indeed related to increased threat perception. On the other hand, the increased threat beliefs could also result from higher-order conditioning (Seymour et al., 2004). Specifically, in the test phase, some individuals may have based their threat beliefs on the removal of the safety behavior rather than the safety cue itself (see Klein et al., 2021).

Our findings suggest that safety behaviors in relatively safe situations may potentially be detrimental for some individuals. Note that there is an ongoing debate whether safety behaviors during exposure-based therapy are deleterious or beneficial. For example, a meta-analysis on experimental studies among fearful individuals demonstrated that self-reported fear at post-intervention did not differ between groups that did or did not use safety behaviors (Meulders et al., 2016). However, another systematic review reported that 15 out of 18 *clinical treatment studies* demonstrated that safety behaviors negatively affected treatment outcomes (Blakey & Abramowitz, 2016). Potentially, safety behaviors may occasionally be beneficial in lowering the threshold for starting with exposure (e.g., Rachman et al., 2008, 2011; van den Hout et al., 2011), but they may be detrimental in the long-term (Craske et al., 2008; Meulders et al., 2016). This is an empirical question that needs to be further investigated.

Several limitations of this research should be mentioned. First, in Study 1, 21% of participants in the experimental group were excluded because they did not apply safety behavior toward the safety cue. This may limit the generalizability of these findings (see Lonsdorf et al., 2017). However, sensitivity analyses in Study 2 showed that the results did not meaningfully change when we applied different exclusion criteria. A second limitation could be that our test phase only included one trial; hence our effects may be short-lived (see Xia et al., 2019). Therefore, future research should examine individual differences throughout an extended test phase. Third, we did not collect data on racial/ethnic identifications and culture/geographic background, which may limit the generalizability of our findings. Strengths of the present research include the well-controlled paradigm and advanced statistical analyses to explore individual heterogeneity.

To conclude, accumulated evidence suggests that safety behavior in relatively safe situations may have maladaptive effects: it generally maintains and sometimes even increases threat beliefs. Future research should test whether and for whom safety behavior in relatively safe situations culminates in clinical anxiety.

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Author Contributions

EvD, AT, and IME designed Study 1. EvD and AT collected data and performed statistical analyses for Study 1. EvD, AK, MZ, and IME designed Study 2. EvD and MZ performed statistical analyses for Study 2. EvD drafted the manuscript and all authors critically revised the manuscript.

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Supplementary Materials

Data-Analysis Study 1

Latent Class Analysis Study 2

Exploratory Analyses Study 2

Table S1. *Study Characteristics of Included Experiments (Study 2)*

Table S2. *Sensitivity Analyses of Group Differences in Meaningful Change Using Different Exclusion Criteria (Study 2)*

Table S3. *Sensitivity Analyses of Latent Class Analyses on Change Scores in Threat Expectancy to C- Using Different Exclusion Criteria (Study 2)*

Figure S1. *Rain Cloud Plot of Change Scores (With Mean ± 95% Confidence Interval) in Threat Expectancy to C- From the Safety Behavior Acquisition Phase to the Test Phase (Study 2)*

Data-Analysis Study 1

First, to inspect group differences in baseline variables, one-way ANOVAs were performed on age, neuroticism scores, shock level, and shock unpleasantness. A Chi-squared test assessed gender differences across groups. Second, to test whether Pavlovian acquisition was successful for threat expectancy and SCL, we used two 3 (Stimulus: A+, B-, C-) × 2 (Time: first, final acquisition trial) × 2 (Group: experimental, control) mixed ANOVAs. Third, to examine safety behavior acquisition effects on threat expectancy and SCL, we performed two 2 (Stimulus: A+, first A+* trial) × 2 (Group: experimental, control) mixed ANOVAs. To examine how threat responding to A+* developed over time, we used two 6 (Time: all A+* trials) × 2 (Group: experimental, control) mixed ANOVAs. Fourth, to test group differences to C- in the safety behavior shift phase, we conducted two 4 (Time: all C-/C-* trials) × 2 (Group: experimental, control) mixed ANOVAs with threat expectancy and SCL as dependent variables. Fifth, to test group differences in threat expectancy and SCL in the test phase, we performed two 3 (Stimulus: A+, B-, C-) × 2 (Group: experimental, control) mixed ANOVAs. To test whether threat expectancy and SCL to C- changed from the safety behavior acquisition phase to the test phase, we used two 2 (Time: C- trial safety behavior acquisition, C- trial test) × 2 (Group: experimental, control) mixed ANOVAs.

Latent Class Analysis Study 2

This method takes the uncertainty with respect to participants' class allocations into account in the subsequent multinomial regression analysis. The number of latent classes were determined by evaluating the combination of the Lo-Mendell-Rubin test (LMR), adjusted LMR, bootstrap likelihood ratio test (BLRT), the Bayesian information criterion (BIC; Tein et al., 2013), sample size and interpretability. The LMR, adjusted LMR and BLRT result in *p*-values, where *p*-values <.05 suggest that *k* classes are preferred over *k*-1 classes. The BIC can be compared between *k* and *k*-1 classes, where lower BIC values are preferred. The sample size criterion means that there cannot be many small categories in the final selection, as the third step of the analysis is a multinomial regression with group as a predictor and class as a dependent variable. The final criterion was interpretability (Geiser, 2013), which means that we prefer a *k*-class solution when we can also give meaning to it.

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Exploratory Analyses Study 2

We executed Pearson correlation analyses to test a relation between change scores in threat expectancy to C- and *z*-transformed trait anxiety (Xia et al., 2019) and neuroticism scores (current Study 1). These analyses did not reveal a relationship between change scores in threat expectancy to C- and *z*-transformed anxious personality traits (r = -0.17, p = .056, BF_{10} = 0.66).

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Table S1

Study Characteristics of Included Experiments (Study 2)

	Experimental phases				US	CSs	ITI	Outcome measures
	Acquisition	Safety behavior acquisition	Safety behavior shift	Test				
Engelhard et al. (2015)	A+ (2) B- (4) C- (2)	A* (+) (6) A+ (1) B- (2) C- (1)	A+ (2) B- (2) C(*)- (6)[a]	A+ (1) B- (1) C- (1)	500-ms electrical shock + 95-dB tone	3-s blue, yellow, and pink squares	2-4 s	Threat expectancy
Xia et al. (2019)	A+ (4) B- (4) C- (4)	A* (+) (6) A+ (1) B- (2) C- (2)	A+ (2) B- (2) C(*)- (6)[a]	A+ (4) B- (4) C- (4)	250-ms electrical shock	15-s male, neutral Caucasian faces	6-10 s	Threat expectancy, SCR, FPS
van Dis et al. (Study 1)	A+ (4) B- (2) C- (2)	A* (+) (6) A+ (1) B- (1) C- (1)	A+ (4) B- (4) C(*)- (4)[a]	A+ (1) B- (1) C- (1)	500-ms electrical shock + 95-dB tone	8-s blue, yellow, and pink squares	15-36 s	Threat expectancy, SCL

Note. CSs = conditioned stimuli; FPS = fear potentiated startle response; US = unconditioned stimulus; SCL = skin conductance level; SCR = skin conductance response. + denotes trials with US presentations; - denotes trials without US presentations; *denotes the availability of safety behavior

[a] The experimental group received the opportunity to perform safety behavior during this stimulus.

Table S2

Sensitivity Analyses of Group Differences in Meaningful Change Using Different Exclusion Criteria (Study 2)

		CS-US contingency			
		Yes		***No***	
		Safety behavior acquisition		**Safety behavior acquisition**	
		Yes	***No***	***Yes***	***No***
Safety behavior shift	***Yes***	BF_{10} = 24,304.89; $\chi^2(2) = 25.44^a$; *N* = 213	BF_{10} = 254,383.98; $\chi^2(2) = 30.37^a$; *N* = 227	BF_{10} = 1,654.16; $\chi^2(2) = 21.21^a$; *N* = 230	BF_{10} = 7,158.17; $\chi^2(2) = 24.49^a$; *N* = 244
	No	BF_{10} = 476.48; $\chi^2(2) = 17.68^a$; *N* = 256	BF_{10} = 497.99; $\chi^2(2) = 17.95^a$; *N* = 282	BF_{10} = 19.89; $\chi^2(2) = 12.65^b$; *N* = 274	BF_{10} = 24.78; $\chi^2(2) = 13.29^b$; *N* = 300

Note. Yes = exclusion criterion applied; No = exclusion criterion not applied. Reported analyses are Bayesian Contingency Tables and Chi-square tests with Group as an independent variable and meaningful change scores as a dependent variable.

[a] $p < .001$; [b] $p < .05$.

Table S3

Sensitivity Analyses of Latent Class Analyses on Change Scores in Threat Expectancy to C- Using Different Exclusion Criteria (Study 2)

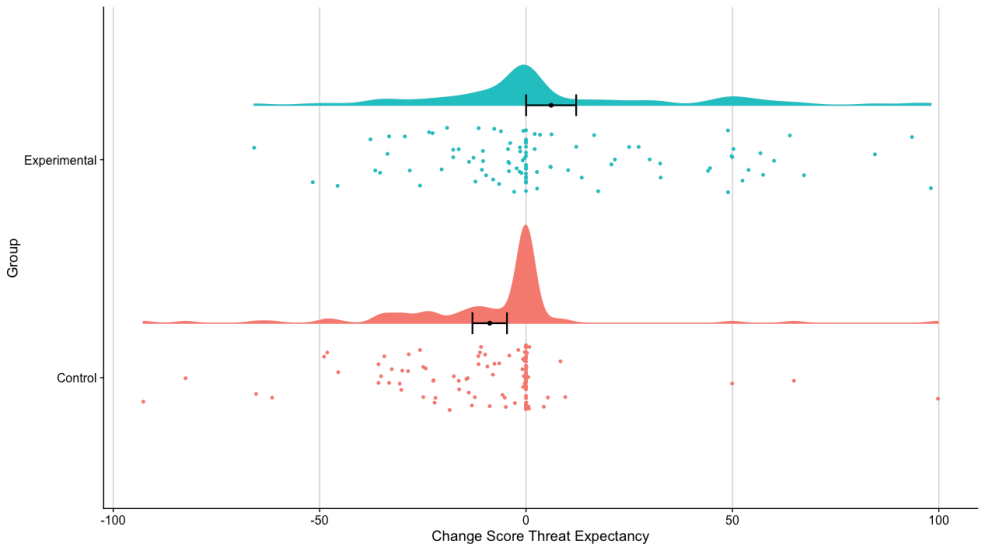
		CS-US contingency			
		Yes		***No***	
		Safety behavior acquisition		**Safety behavior acquisition**	
		Yes	***No***	***Yes***	***No***
Safety behavior shift	***Yes***	*k* = 3; Min *n* = 10; Max *n* = 183	*k* = 3; Min *n* = 10; Max *n* = 197	*k* = 3; Min *n* = 11; Max *n* = 195	*k* = 3; Min *n* = 11; Max *n* = 209
	No	*k* = 2[a]; Min *n* = 20; Max *n* = 236	*k* = 2[a]; Min *n* = 20; Max *n* = 262	*k* = 3; Min *n* = 12; Max *n* = 238	*k* = 3; Min *n* = 15; Max *n* = 261

Note. Yes = exclusion criterion applied; No = exclusion criterion not applied; *k* = number of latent classes; Reported analyses are latent class analyses on change scores for both groups. All *p*-values of bootstrap likelihood ratio tests were < .001; all *p*-values of (Vuong-) Lo-Mendell Rubin likelihood ratio tests were < .05; all entropy values were > 0.95.

[a] Class 1 could be labeled as *decrease or no change* and class 2 as *increase*.

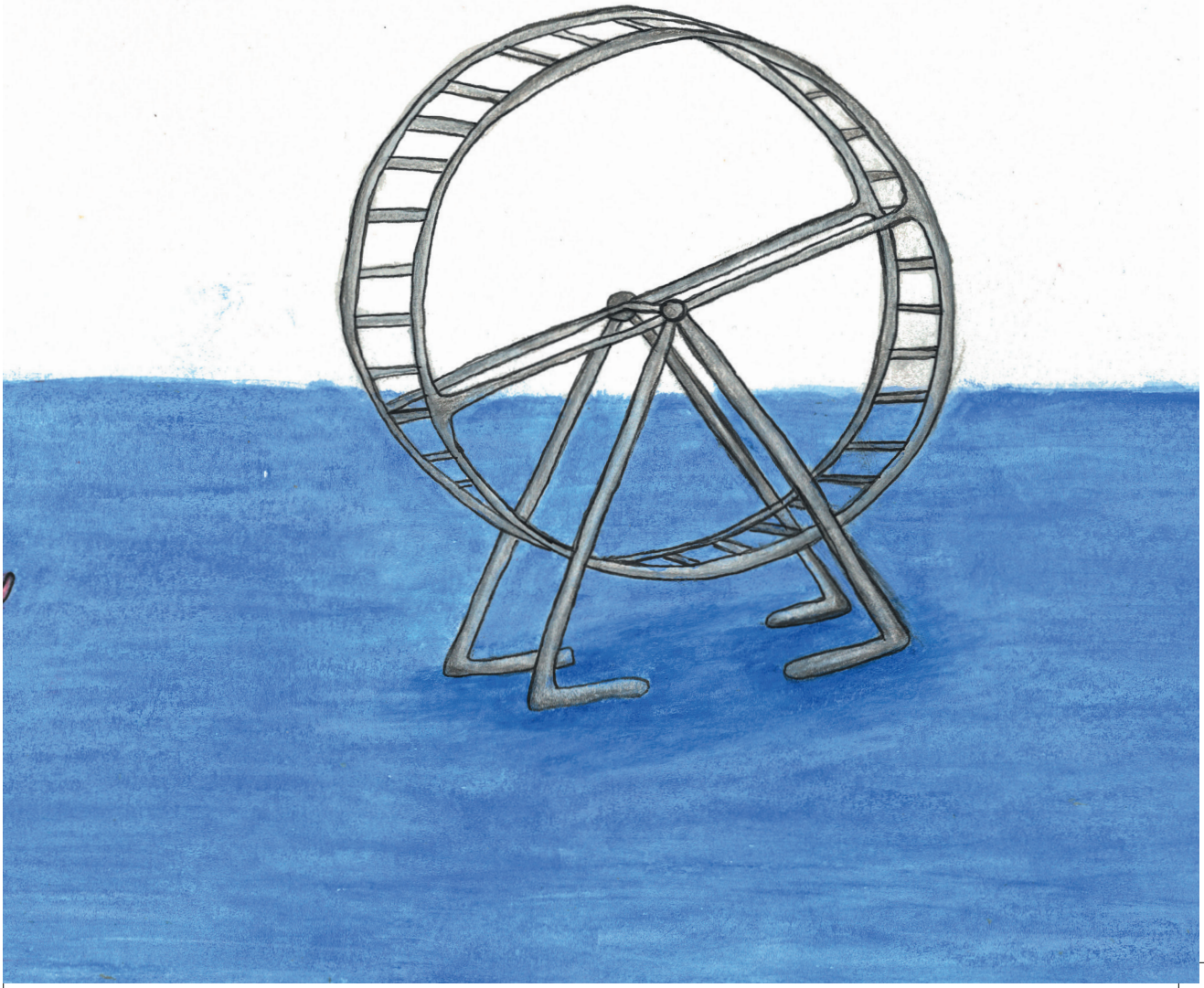
Figure S1

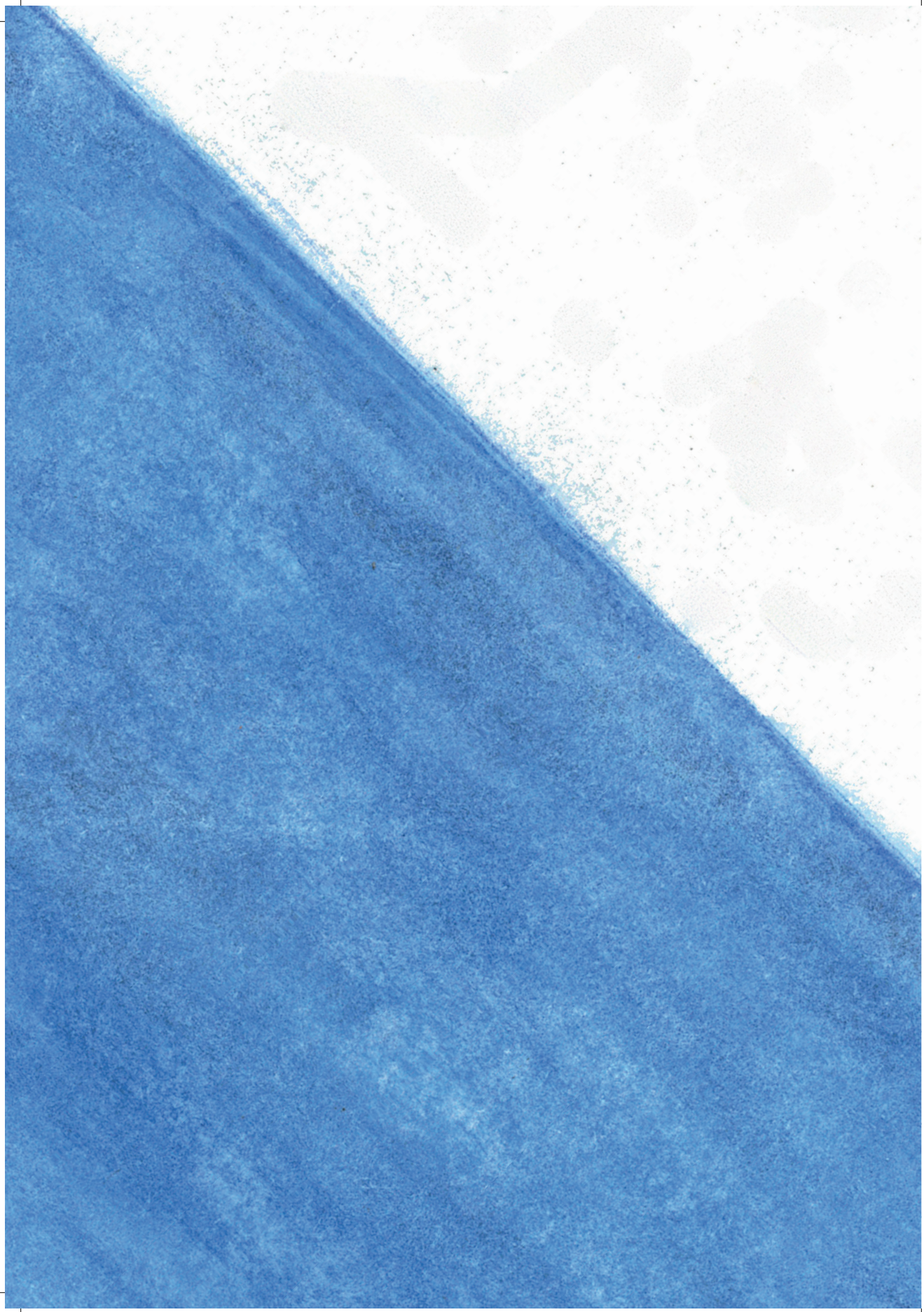
Rain Cloud Plot of Change Scores (With Mean ± 95% Confidence Interval) in Threat Expectancy to C- From the Safety Behavior Acquisition Phase to the Test Phase (Study 2)



Section 2

Breaking the cycle of learned fear





Chapter 4

Long-term outcomes of cognitive behavioral therapy for anxiety-related disorders: A systematic review and meta-analysis

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Abstract

Importance: Cognitive behavioral therapy is recommended for anxiety-related disorders, but evidence for its long-term outcome is limited. **Objective:** This systematic review and meta-analysis aimed to assess the long-term outcomes after cognitive behavioral therapy (compared with care as usual, relaxation, psychoeducation, pill placebo, supportive therapy, or waiting list) for anxiety disorders, posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD). **Data Sources:** English-language publications were identified from PubMed, PsycINFO, Embase, Cochrane, OpenGrey (1980 to January 2019), and recent reviews. The search strategy included a combination of terms associated with anxiety disorders (e.g., *panic* or *phobi**) and study design (e.g., *clinical trial* or *randomized controlled trial*). **Study Selection:** Randomized clinical trials on post-treatment and at least 1-month follow-up effects of cognitive behavioral therapy compared with control conditions among adults with generalized anxiety disorder, panic disorder with or without agoraphobia, social anxiety disorder, specific phobia, PTSD, or OCD. **Data Extraction and Synthesis:** Researchers independently screened records, extracted statistics, and assessed study quality. Data were pooled using a random-effects model. **Main Outcomes and Measures:** Hedges' *g* was calculated for anxiety symptoms immediately after treatment and at 1 to 6 months, 6 to 12 months, and 12 months or more after treatment completion. **Results:** Of 69 randomized clinical trials (4118 outpatients) that were mainly of low quality, cognitive behavioral therapy compared with control conditions was associated with improved outcomes after treatment completion and at 1 to 6 months and at 6 to 12 months of follow-up for a generalized anxiety disorder (Hedges' *g*, 0.07-0.40), panic disorder with or without agoraphobia (Hedges' *g*, 0.22-0.35), social anxiety disorder (Hedges' *g*, 0.34-0.60), specific phobia (Hedges' *g*, 0.49-0.72), PTSD (Hedges' *g*, 0.59-0.72), and OCD (Hedges' *g*, 0.70-0.85). At a follow-up of 12 months or more, these associations were still significant for generalized anxiety disorder (Hedges' *g*, 0.22; number of studies [*k*] = 10), social anxiety disorder (Hedges' *g*, 0.42; *k* = 3), and PTSD (Hedges' *g*, 0.84; *k* = 5), but not for panic disorder with or without agoraphobia (*k* = 5) and could not be calculated for specific phobia (*k* = 1) and OCD (*k* = 0). Relapse rates after 3 to 12 months were 0% to 14% but were reported in only 6 randomized clinical trials (predominantly for panic disorder with or without agoraphobia). **Conclusions and Relevance:** The findings of this meta-analysis suggest that cognitive behavioral therapy for anxiety-related disorders is associated with improved outcomes compared with control conditions until 12 months

after treatment completion. At a follow-up of 12 months or more, effects were small to medium for generalized anxiety disorder and social anxiety disorder, large for PTSD, and not significant or not available for other disorders. High-quality randomized clinical trials with 12 months or more of follow-up and reported relapse rates are needed.

Key Points

Question: What is the long-term outcome of cognitive behavioral therapy for anxiety disorders, posttraumatic stress disorder, and obsessive-compulsive disorder?

Findings: In this systematic review and meta-analysis of 69 randomized clinical trials including 4118 patients, cognitive behavioral therapy was associated with better outcomes compared with control conditions among patients with anxiety symptoms within 12 months after treatment completion. At longer follow-up, significant associations were found only for generalized anxiety disorder, social anxiety disorder, and posttraumatic stress disorder; relapse rates (predominantly for panic disorder with or without agoraphobia) after 3 to 12 months were 0% to 14%.

Meaning: The findings suggest that compared with control conditions, cognitive behavioral therapy was generally associated with lower anxiety symptoms within 12 months after treatment completion, but few studies have examined longer-term outcomes.

Introduction

Anxiety disorders, posttraumatic stress disorder (PTSD), and obsessive compulsive disorder (OCD) are highly prevalent (Baxter et al., 2013; Kessler et al., 2005) and are associated with substantial personal (Whiteford et al., 2013) and societal costs (Greenberg et al., 1999; Layard & Clark, 2015; Smit et al., 2006). Clinical practice guidelines recommend psychological and pharmacological interventions for anxiety-related disorders (Benedek et al., 2009; Koran & Simpson, 2013; National Institute for Health and Care Excellence, 2005, 2011, 2013, 2018; Stein et al., 2009), but most patients favor psychotherapy over pharmacotherapy (McHugh et al., 2013). Cognitive behavioral therapy (CBT) for these disorders has been associated with reduced symptoms at short-term (Cuijpers et al., 2016; Hofmann & Smits, 2008), with small to medium effect sizes adjusted for publication bias and when studies with waiting list comparisons were not taken into account (Cuijpers et al., 2016). However, regarding its long-term outcome, little meta-analytic evidence is available. Such evidence is important, because the course of anxiety-related disorders is typically chronic (Klein Hofmeijer-Sevink et al., 2012). Evidence on long-term outcome is particularly vital for researchers to prioritize research directions (e.g., further examining variables associated with treatment success and ways to optimize treatment) and for clinicians to give patients realistic information.

Four recent meta-analyses have addressed the long-term outcome of CBT for anxiety-related disorders, and they generally indicate a medium symptom reduction up to two years following treatment completion (Bandelow et al., 2018; Carpenter et al., 2018; Montero-Marin et al., 2017; Springer et al., 2018). However, in two of these (Bandelow et al., 2018; Springer et al., 2018), CBT outcome was only calculated over time (pretreatment vs. post-treatment vs. follow-up), and not relative to a control condition. Therefore, these meta-analyses could not disentangle treatment outcome from placebo effects or spontaneous remission. Moreover, because pretreatment and post-treatment correlations of individual studies are often unknown, there may be substantial errors in these effect size estimations (Cuijpers et al., 2017). The other two meta-analyses did use comparison interventions, but these were limited to placebo (Carpenter et al., 2018) or relaxation (Montero-Marin et al., 2017), resulting in 23 and 27 studies, respectively. The number of studies would be at least twice as large if other comparison groups were also included (e.g., a care-as-usual group). In addition, no meta-analysis has examined the association between CBT and relapse rates in anxiety-related disorders, to our knowledge. Cross-sectional findings indicate that approximately 31% to 55% of patients with remitted anxiety meet diagnostic criteria of the same or another disorder within

four years (Scholten et al., 2016). Research on relapse and the return of fear has become a major focus of fundamental fear and anxiety research (Vervliet et al., 2013), but the evidence for clinical relapse after psychotherapy in anxiety-related disorders is limited.

Our aim was to conduct a comprehensive meta-analysis to establish a reliable estimate of the long-term outcome of CBT relative to passive and active comparison groups in anxiety disorders, PTSD, and OCD. We examined (1) long-term effects (at least one month post-treatment) and (2) relapse rates after successful treatment in patients with generalized anxiety disorder (GAD), panic disorder with or without agoraphobia (PD), social anxiety disorder (SAD), specific phobia (SP), PTSD, and OCD.

Methods

The systematic review and meta-analysis was preregistered at PROSPERO (registration no. CRD42017067363), and it adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (Moher et al., 2009).

Search Strategy

Relevant English-language publications were identified by systematically searching PubMed, PsycINFO, Embase, Cochrane, and OpenGrey (from 1980 until January 2019). The search strategy included a combination of terms related to anxiety disorders (e.g. *panic* or *phobi**) and study design (e.g., *clinical trial* or *randomized controlled trial*). Table S1 in the Supplementary Materials provides the exact search strategies. The electronic database search was supplemented with a bibliography screening of four relevant meta-analyses (Bandelow et al., 2018; Carpenter et al., 2018; Montero-Marin et al., 2017; Springer et al., 2018) and one systematic review (Loerinc et al., 2015).

Inclusion Criteria

Randomized clinical trials were included that examined effects of CBT (i.e., any therapy with cognitive restructuring and/or a behavioral therapy, such as exposure, as core component; Cuijpers et al., 2016), including third generation CBTs (i.e., acceptance and commitment therapy and metacognitive therapy), at least one month after treatment completion, in an individual, group or internet treatment format. Comparison groups included care-as-usual (CAU; i.e., anything patients would normally receive as long as it was not a structured type of psychotherapy, such as primary care at medical centers or case management with educational groups; Cuijpers et al., 2016), relaxation,

psychoeducation, pill placebo, supportive therapy, or waiting list. Studies were included if they tested adult patients (or samples consisting mostly of adults but also some adolescents aged 16 years or older) who received a diagnosis of GAD, PD, SAD, specific phobia, PTSD, or OCD based on results of a structured diagnostic interview.

Studies were excluded if they did not use CBT (e.g., applied relaxation, eye movement desensitization and reprocessing, or interpersonal therapy) or did not report symptoms separately for each disorder. To reduce clinical heterogeneity, studies were also excluded if they had done any of the following: 1) used self-guided therapy without any guidance, 2) used CBT combined with medication or pill placebo, or 3) tested inpatients.

Study Selection

Titles and abstracts of the records were independently screened by two of us (EvD and SvV) with the use of the Covidence systematic review tool (www.covidence.org). The full-text screening and data extraction were independently performed by two of us (EvD and RvdH). In case of disagreements during the screening or data extraction process, a consensus was reached through discussion or by the decision of a third person (PC). If full-text records were inaccessible, authors and/or libraries were contacted (k = 12; response rate = 33%). If crucial statistics were missing, study authors were contacted (k = 8; response rate = 38%).

Quality Assessment

To assess the quality of the included studies, five criteria of the Cochrane Collaboration's risk of bias tool were used: adequate generation of allocation sequence, concealment of allocation to conditions, blinding of outcome assessment, adequately dealing with incomplete outcome data (this was evaluated as being of high quality when we could use intention-to-treat analyses), and no selective outcome reporting (based on whether authors referred to trial registrations or study design publications; Higgins et al., 2011). In addition, quality of treatment implementation was evaluated according to four criteria outlined by Chambless and Hollon (1998): 1) the use of a treatment protocol, 2) training of therapists, 3) monitoring of therapy (integrity check), and 4) researcher allegiance. Researcher allegiance was defined as one of the authors' involvement in developing the treatment under investigation, except when collaborators had mixed allegiances (Munder et al., 2013). All quality assessments were independently completed by EvD and RvdH, and disagreement was solved through discussion or by the decision of a third person (PC).

Data Analysis

Comprehensive Meta-Analysis software (Version 3; Borenstein et al., 2013) was used to calculate the pooled effect sizes separately for each disorder. If studies used multiple symptom measures, these outcomes were pooled within studies (Borenstein et al., 2009), except for a sensitivity analysis that included one outcome measure (based on a frequency ranking). Random-effects models were selected in all analyses and available intention-to-treat data were used. Power analyses were conducted with the online Power Calculator Tool (Harrer et al., 2019). The primary outcome variable was anxiety symptoms. Hedges' *g* was calculated to indicate differences between treatment and comparison groups at post-treatment and follow-up. Follow-up measurements were categorized into three periods: 1–6 months, 6-12 months, and 12 months or more of post-treatment follow-up. Relapse rates were defined as the percentage of relapse after treatment response at follow-up (treatment group vs. comparison group). Relative risk was calculated to indicate dropout differences between treatment and comparison groups. Subgroup analyses were performed on treatment approaches, comparison groups, and study quality using a mixed-effects model and meta-regression. Analyses with at least three studies per subgroup are reported.

To assess potential publication bias, the Egger's test of the intercept was used, which is a significance test based on the asymmetry of funnel plots (Egger et al., 1997). The funnel-plot-based method of Duval and Tweedie (2000) was used to test and adjust for publication bias through a trim and fill technique. To estimate heterogeneity across studies, the I^2 statistic with 95% confidence intervals (using the HETEROGI module for Stata, Version 8; Orsini et al., 2006) was calculated, which displays the proportion of the observed variance that would remain if we could remove the sampling error. A common benchmark for interpretation is 25% for small, 50% for medium, and 75% for large heterogeneity (Borenstein et al., 2009). We also calculated 95% prediction intervals to estimate the effect size range in future studies (Borenstein et al., 2017).

Results

Selection and Characteristics of Included Studies

Figure 1 displays the PRISMA flowchart of the selection and inclusion process. We screened 10,857 titles and abstracts and retrieved 715 full-text records, of which 69 published studies (reported in 73 records) met our inclusion criteria: 14 studies on GAD,

13 studies on PD, 7 studies on SAD, 3 studies on specific phobia, 30 studies on PTSD, and 2 studies on OCD (Table S2 in the Supplementary Materials presents characteristics of these studies). A total of 4,118 unique patients were enrolled. The studies examined cognitive-behavioral therapy (CBT; *k* = 42), exposure therapy, (*k* = 26), cognitive therapy (*k* = 10), cognitive reprocessing (*k* = 1), metacognitive therapy (*k* = 1), applied tension (*k* = 1), and acceptance and commitment therapy (*k* = 1). Comparison groups consisted of CAU (*k* = 13), relaxation (*k* = 24), psychoeducation (*k* = 2), pill placebo (*k* = 5), supportive therapy (*k* = 14), waiting list (*k* = 12), and tension-only (*k* = 1). Multiple treatment or comparison groups within one study were pooled together (*k* = 9). We found 41 studies reporting outcomes at 1-6 months, 34 studies on 6-12 months, and 24 studies at 12 months or more of follow-up. Groups did generally not differ in dropout (relative risk range, 0.97-1.03; *p*s > .50), but for PTSD, there was slightly more dropout in the comparison group (relative risk, 0.95; *p* = .01).

Figure 1
PRISMA Flow Diagram of Selection and Inclusion Process

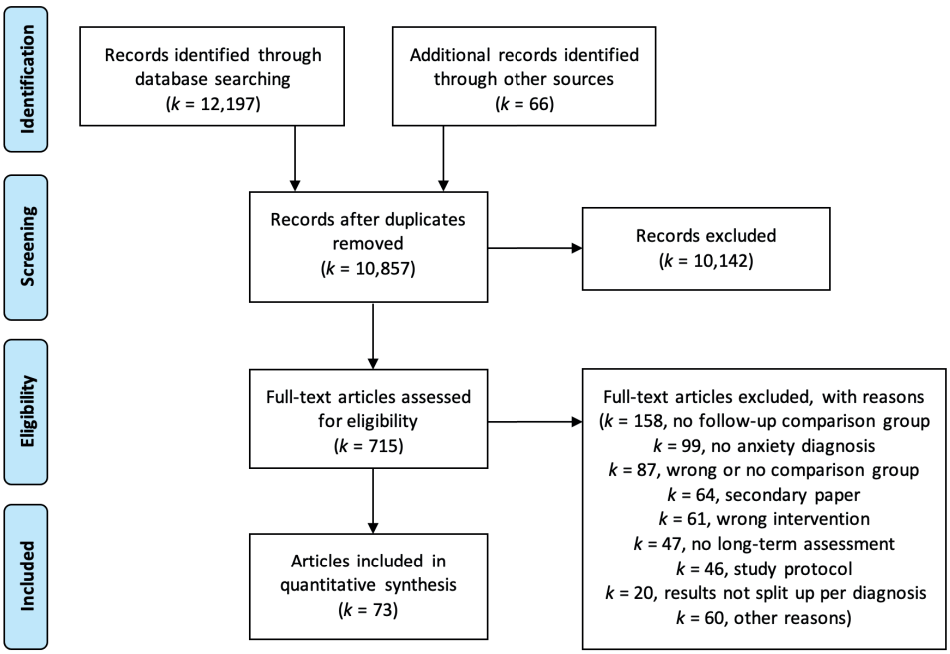
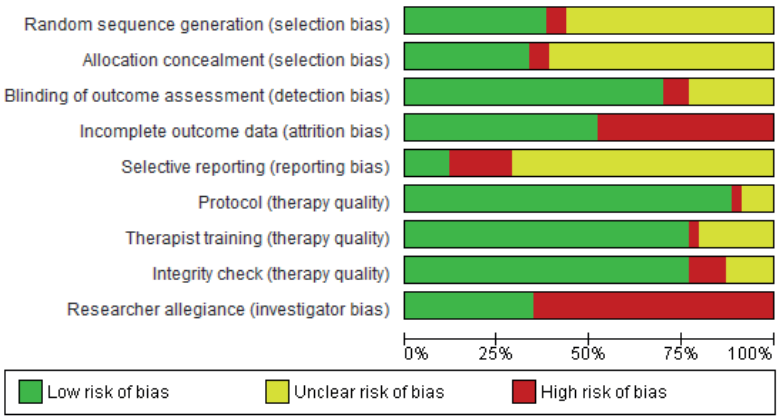


Figure 2

Summary Graph of Study Design Quality, Therapy Quality, and Researcher Allegiance



Quality Assessments

Figure 2 and Figure S1 in the Supplementary Materials present the study and treatment quality assessments. Only 12 studies met criteria for high quality (i.e., at least 4 of 5 criteria). Nineteen of the studies (27.5%) applied random sequence generation and allocation concealment. In 44 studies (63.8%), the outcome assessments were blinded, and 35 studies (50.7%) applied intention-to-treat analyses. Only 21 studies (30.4%) reported a preregistration or a design protocol, and in 13 cases, the outcomes were not reported in accordance with their preregistration. The overall treatment implementation quality was high and most studies had a high risk of researchers' allegiance.

Main Analyses

Table 1 presents effect sizes, heterogeneity indices, and adjusted effect sizes for risk of publication bias based on Duval and Tweedie's trim and fill procedure for all disorders across time; see Supplementary Materials for forest plots (Figures S2-7) and funnel plots (Figures S8-12). A sensitivity analysis with one outcome measure yielded similar results (see Table S3 in the Supplementary Materials). After treatment, the pooled effect size of CBT relative to control conditions was small for PD (Hedges' g = 0.22; 95% CI: 0.01-0.43), medium for GAD (Hedges' g = 0.39; 95% CI: 0.12-0.66), SAD (Hedges' g = 0.38; 95% CI: 0.19-0.57), and specific phobia (Hedges' g = 0.49; 95% CI: 0.13-0.84); and medium to large for PTSD (Hedges' g = 0.72; 95% CI: 0.52-0.93) and OCD (Hedges' g = 0.70; 95% CI: 0.29-

1.12). Egger's test of the intercept was only significant for PTSD (intercept $\beta = 3.13$; 95% CI: 1.78-4.49, $p < .001$; all other βs < 2.34, ps > .201). The trim and fill procedure yielded lower adjusted effect sizes for all disorders except OCD (see Table 1). Heterogeneity was low to moderate for PD, SAD, specific phobia, and OCD, and it was moderate to large for GAD and PTSD.

At 1 to 6 months of follow-up, the relative pooled estimate of CBT was small for GAD (Hedges' $g = 0.07$; 95% CI: -0.50-0.63) and PD (Hedges' $g = 0.27$; 95% CI: -0.01-0.55), medium for SAD (Hedges' $g = 0.60$; 95% CI: 0.36-0.85), and medium to large for specific phobia (Hedges' $g = 0.72$; 95% CI: 0.01-1.44), PTSD (Hedges' $g = 0.67$; 95% CI: 0.46-0.88), and OCD (Hedges' $g = 0.85$; 95% CI: 0.47-1.22). Egger's test of the intercept was significant for GAD (intercept $\beta = -10.45$; 95% CI: -16.15-4.76, $p = .027$) and PTSD (intercept $\beta = 3.10$; 95% CI: 1.28-4.92, $p = .002$; all other βs < 4.22, ps > .084), and Duval and Tweedies' trim and fill procedure resulted in a lower adjusted effect size only for PTSD (Hedges' $g = 0.50$; 95% CI: 0.27-0.73). Heterogeneity was low for PD, SAD, and OCD; moderate for specific phobia; and moderate to large for GAD and PTSD.

At 6 to 12 months of follow-up, the pooled effect size of CBT relative to control conditions was small to medium for GAD (Hedges' $g = 0.40$; 95% CI: 0.13-0.67), PD (Hedges' $g = 0.35$; 95% CI: 0.11-0.59), and SAD (Hedges' $g = 0.34$; 95% CI: 0.07-0.61), and it was medium for PTSD (Hedges' $g = 0.59$; 95% CI: 0.42-0.77). No pooled effect sizes could be calculated for specific phobia ($k = 0$) and OCD ($k = 0$). Egger's test of the intercept did not indicate a risk of publication bias for any disorder (all βs < 2.74, ps > .057). The trim and fill procedure resulted in a lower adjusted effect sizes only for SAD and PTSD (Table 1). Heterogeneity was low for PD, SAD, and PTSD, and moderate for GAD.

After a follow-up of 12 months or more, CBT was still associated with a better outcome than control conditions for GAD (Hedges' $g = 0.22$; 95% CI: 0.02-0.42; $k = 10$), SAD (Hedges' $g = 0.42$; 95% CI: 0.04-0.79; $k = 3$), and PTSD (Hedges' $g = 0.84$; 95% CI: 0.03-1.64; $k = 5$), but this effect was not significant for PD (Hedges' $g = 0.14$; 95% CI: -0.19-0.47; $k = 5$) and could not be calculated for specific phobia ($k = 1$) and OCD ($k = 0$). Egger's test of the intercept did not indicate a risk of publication bias (all βs < 3.51, ps > .091), but the trim and fill procedure yielded a lower nonsignificant effect for PTSD (Hedges' $g = 0.54$; 95% CI: -0.20-1.29). Heterogeneity was low for PD, SAD, and GAD, but large for PTSD.

Table 1

Treatment Effects (Hedges' g), Heterogeneity Indices, and Effect Sizes Adjusted for Publication Bias Across Time and Disorders

Diagnosis	*k*	Hedges' *g* (95% CI)	95% Prediction interval	I^2 (95% CI)	Adjusted *g* (95% CI)
Post-treatment					
GAD	14	0.39 (0.12-0.66)	-0.55-1.33	67 (42-81)	0.34 (0.05-0.62)
PD	13	0.22 (0.01-0.43)	-0.30-0.74	29 (0-63)	0.19 (-0.02-0.41)
SAD	7	0.38 (0.19-0.57)	0.04-0.72	11 (0-63)	0.22 (-0.01-0.44)
SP	3	0.49 (0.13-0.84)	-1.80-2.78	0 (0-90)	0.34 (0.04-0.63)
PTSD	30	0.72 (0.52-0.93)	-0.26-1.71	74 (62-81)	0.50 (0.28-0.72)
OCD	2	0.70 (0.29-1.12)	N/A	17 (N/A)	N/A
1-6 months FU					
GAD	3	0.07 (-0.50-0.63)[a]	-6.48-6.61	73 (10-92)	
PD	6	0.27 (-0.01-0.55)	-0.22-0.76	8 (0-64)	
SAD	4	0.60 (0.36-0.85)	0.06-1.15	0 (0-68)	
SP	2	0.72 (0.01-1.44)	N/A	39 (N/A)	N/A
PTSD	24	0.67 (0.46-0.88)	-0.19-1.52	63 (38-75)	0.50 (0.27-0.73)
OCD	2	0.85 (0.47-1.22)	N/A	0 (N/A)	N/A
6-12 months FU					
GAD	11	0.40 (0.13-0.67)	-0.41-1.22	59 (20-79)	
PD	9	0.35 (0.11-0.59)	-0.08-0.77	12 (0-60)	
SAD	3	0.34 (0.07-0.61)	-1.40-2.08	0 (0-73)	0.22 (0.01-0.45)
SP	0	N/A	N/A	N/A	N/A
PTSD	11	0.59 (0.42-0.77)	0.28-0.90	12 (0-57)	0.55 (0.35-0.75)
OCD	0	N/A	N/A	N/A	N/A
≥12 months FU					
GAD	10	0.22 (0.02-0.42)	-0.18-0.61	18 (0-59)	
PD	5	0.14 (-0.19-0.47)[a]	-0.40-0.67	0 (0-64)	
SAD	3	0.42 (0.04-0.79)	-2.00-2.83	0 (0-73)	
SP	1	N/A	N/A	N/A	N/A
PTSD	5	0.84 (0.03-1.64)	-2.13-3.80	88 (71-93)	0.54 (-0.20-1.29)
OCD	0	N/A	N/A	N/A	N/A

Note. Underlined effect sizes are statistically significant ($p < .05$). Empty cells indicate no adjustment for publication bias based on Duval and Tweedies' trim and fill procedure. Abbreviations: CI, confidence interval; FU, follow-up; GAD, generalized anxiety disorder; N/A, not available; OCD, obsessive compulsive disorder; PD, panic disorder with or without agoraphobia; PTSD: posttraumatic stress disorder; SAD, social anxiety disorder; SP, specific phobia.

[a] Post-hoc statistical power beneath 80% ($\alpha = 0.05$).

Subgroup Analyses

Tables S4-5 in the Supplementary Materials present exploratory subgroup analyses for treatment approaches and comparison groups. For specific phobia and OCD, subgroup analyses could not be performed (<2 studies per comparison group). Meta-regression analyses revealed no significant differences across treatment approaches for any disorder at any time (Qs < 1.92, *p*s > .385).

For GAD and SAD, the comparison groups did not significantly differ at any time. For PD, subgroup analyses showed a significant medium treatment effect of CBT relative to pill placebo at post-treatment (Hedges' *g* = 0.42) and at 6-12 months follow-up (Hedges' *g* = 0.73). There were no significant treatment effects relative to any other active comparison group at any time (all *p*s > .057; see Table S5). For PTSD, CBT appeared to be generally more effective relative to all comparison groups until 12 months of follow-up (Hedges' *g*s > 0.73; *p*s < .021), but not compared with supportive therapy after 12 months or more (Hedges' *g* = 0.08; *p* = .440). At treatment completion, studies that used a waiting list comparison group yielded significantly larger effect sizes (Hedges' *g* = 1.25; *p* =.001), while studies using a supportive therapy comparison condition yielded significantly lower effect sizes (Hedges' *g* = 0.27; *p* = .023).

Exploratory subgroup analyses on study quality could only be performed for PTSD (high-quality studies: *k* = 8) and showed larger effect sizes at all times for high-quality studies (Hedges' *g* = 0.65-2.10) compared with the other studies (Hedges' *g* = 0.51-0.57). There were no high-quality studies for SAD and specific phobia, and only a few for PD (*k* = 1), GAD (*k* = 2), and OCD (*k* = 1).

Relapse

A total of six studies (seven comparisons) reported relapse rates after successful treatment. Of these, five studies were about PD (Arntz & van den Hout, 1996; Barlow et al., 2000; Öst et al., 1993; Öst & Westling, 1995; Shear et al., 2001) and one was on OCD (Simpson et al., 2004). An additional study described relapse of PD as a comorbid condition after PTSD treatment, and this study was not included (Vaughan et al., 1994). All six studies used small sample sizes (*N* < 28), and most operationalized successful treatment using ambiguous treatment response criteria rather than reliable remission criteria (e.g., the absence of a disorder based on a clinical interview). Therefore, we refrained from statistically pooling these results and instead presented outcomes per study in Table 2. Overall, relapse rates were relatively low: in three of seven comparisons, relapse occurred after successful CBT and relapse rates ranged from 0 to 14%.

Table 2
Number of Relapses After Successful CBT

Study	Diagnosis	Instrument	Criterion		Follow-up	No. of relapse/N	
			Response	Relapse		Treatment	Control
Arntz 1996	PD	Diary	No panic attack in 2 weeks	Pretest panic attack frequency	7 months	CT (2/14)	AR (0/9)
Barlow 2000	PD	PDSS	40% reduction from baseline on PDSS	Not meeting response criterion	12 months	CBT (1/24)	Pill placebo (0/3)
Öst 1993	PD	Percentage of BAT completed	Clinically significant improvement (Jacobson et al., 1984) on BAT	Not meeting response criterion	12 months	Exposure (0/12) CT (0/9)	AR (0/13)
Öst 1995	PD	Diary	No panic attack in 3 weeks	Not meeting response criterion	12 months	CBT (0/14)	AR (0/11)
Shear 2001	PD	CGI	CGI improvement: >2 (much improved) and CGI severity: <3 (mild)	Not meeting response criterion	6 months	CBT (0/16)	Pill placebo (0/3)
Simpson 2004[a]	OCD	CGI	Much or very much improved relative to Week 0, as measured by the CGI Improvement scale	1) a return to pretreatment severity or worse in the past week on the CGI-Severity scale; or 2) an unsafe clinical state based on the clinical judgment of the treating clinician.	3 months	EX/RP (2/18)	Pill placebo (0/1)

Note. AR, applied relaxation; BAT, behavioral avoidance test (based on agoraphobic situations hierarchy); CGI, Clinical Global Impression scale; CBT, cognitive behavioral therapy; CT, cognitive therapy; EX/RP, exposure with response prevention; OCD, obsessive compulsive disorder; PD, panic disorder with or without agoraphobia; PDSS, Panic Disorder Severity Scale.
[a] This study was not included in the meta-analysis, because it only examined treatment responders at follow-up.

Discussion

Summary of Results

This systematic review and meta-analysis examined the long-term outcome of CBT for anxiety disorders, PTSD, and OCD across 69 randomized clinical trials. Overall, CBT was associated with moderate symptom reductions up to 12 months after treatment. Longer effects were still significant for GAD, SAD, and PTSD, but not for PD, and could not be calculated for specific phobia and OCD. Because this meta-analysis included a limited number of high-quality studies and English-language articles only, our reported effect estimates should be interpreted with caution. Because statistical heterogeneity was considerable in GAD and PTSD studies, our effect estimates for these disorders are uncertain. Future meta-analyses should aim to explain this heterogeneity as more studies become available. Although post-hoc power analyses generally demonstrated sufficient statistical power of our main analyses, simulation studies showed that at least 40 studies per analysis are needed to reach sufficient power (López-López et al., 2014). Therefore, non-significant findings, especially of the subgroup analyses, should be interpreted as the absence of evidence rather than evidence of absence.

Our overall findings were in line with CBT outcomes for depression (Cuijpers et al., 2013), and suggest that skills and insights acquired during CBT are relatively stable until 12 months after treatment but do not improve further. Nevertheless, evidence for CBT outcomes at 12 months or more after treatment is scarce. Given the chronic trajectories of anxiety-related disorders (Klein Hofmeijer-Sevink et al., 2012) and because longer illness duration may increase the odds of developing comorbidity (van Oudheusden et al., 2018), it is important to examine whether treatment effects are maintained 12 months or more after treatment. Thus, more research on CBT efficacy at 12 months follow-up and beyond and on ways to optimize effects is urgently needed.

Relapse rates after successful CBT were relatively low (0-14%) compared to uncontrolled trials that indicated a maximum relapse of 13% for SAD (Fava, Grandi, et al., 2001) and 23% for PD (Fava, Rafanelli, et al., 2001). However, only a few studies reported them (five studies for PD and one for OCD), in contrast to studies on pharmacotherapy for anxiety-related disorders that frequently report clinical relapse after treatment discontinuation (Batelaan et al., 2017). Also, these studies calculated relapse rates based on ambiguous response criteria rather than relative to complete remission. Therefore, future research should carefully define and report relapse criteria (e.g., a return of the full symptomatology; Rachman, 1989; Vervliet et al., 2013; based on a structured

interview). Future research may also give insight into risk factors for relapse, which could identify patients at risk who may benefit from additional or more intensive therapy or from pharmacotherapy to prevent relapse. Relapse prevention after psychotherapy is still relatively uncharted in the field of anxiety-related disorders but is quite common and effective in depressive disorders (Bockting et al., 2015). For example, studies have demonstrated the efficacy of well-being therapy (Fava et al., 1998; Ruini & Fava, 2009) as second-line relapse prevention strategy in patients with GAD (Fava et al., 2005).

For PD, when corrected for publication bias, CBT outcome did not significantly differ from control conditions (except for a small to medium effect at 6-12 months follow-up). This may be explained by the frequent use of applied relaxation as a control condition, which may involve some exposure (Öst et al., 1993). Relaxation appeared to be as effective as CBT in a previous meta-analysis (Montero-Marin et al., 2017). Subgroup analyses across comparison groups revealed a medium treatment effect for PD within 12 months post-treatment when CBT was compared to pill placebo, but not relative to other active comparison groups. However, the subgroup analyses should be interpreted with caution because of the small subsample sizes.

For specific phobia and OCD, only a few studies met our inclusion criteria, and treatment effect estimates could not be calculated beyond a 6-month follow-up. Most previous studies on OCD treatment with long-term assessments have tested the efficacy of pharmacotherapy (augmented with CBT; Fineberg et al., 2012; Sharma et al., 2014). Because approximately 50% of patients with OCD do not respond to pharmacotherapy and many patients relapse after medication discontinuation (Fineberg et al., 2012), more research is needed on the long-term efficacy of CBT as an alternative stand-alone treatment.

Regarding PTSD, after correcting for publication bias, we observed medium treatment effects favoring CBT over control conditions at post-treatment until 12 months of follow-up. At 12 months of follow-up and beyond, there was a nonsignificant medium effect adjusted for publication bias, which probably did not reach statistical significance because of limited statistical power.

Strengths and Limitations

Strengths of this meta-analysis are the inclusion of more comparison groups, which yielded more studies than previous meta-analyses (Bandelow et al., 2018; Carpenter et al., 2018; Montero-Marin et al., 2017; Springer et al., 2018), and the investigation of long-term outcomes (including relapse rates) after CBT for anxiety-related disorders.

Furthermore, we conducted a comprehensive literature search, an independent screening and data extraction, and treatment and study quality assessments. Several limitations should also be noted. First, meta-analyses are inherently associated with heterogeneity regarding methodological aspects (e.g., outcome measures) and clinical aspects (e.g., CBT approaches and samples). Therefore, future research is needed to test which specific methodological or treatment factors explain the reported effects (Cuijpers et al., 2019). Second, because of limited experimental control during follow-up periods, confounding factors may have threatened the validity of our long-term effect estimates (e.g., due to additional treatment or adverse life events). Third, symptom outcome measures were averaged to handle dependent outcomes, which may have resulted in overestimated standard errors (Moeyaert et al., 2016). Fourth, most studies had suboptimal designs (or these criteria were poorly reported), and a high risk of researcher allegiance bias, which may have affected the reliability of our effect estimates.

Conclusions

Anxiety-related disorders are characterized by a chronic course, so sustainable treatment effects are important. The results of this meta-analysis suggest that, on average, CBT was associated with moderate symptom reductions in anxiety disorders, PTSD, and OCD until 12 months after treatment completion. At a follow-up of 12 months or more, these effects were still present for GAD, SAD, and PTSD, but not for PD. For specific phobia and OCD, no follow-up data beyond 6 months after treatment completion were available. Studies on relapse were scarce but gave the preliminary impression that relapse rates after successful treatment, predominantly for PD, may be relatively low (0-14% at 3-12 months following treatment completion). More high-quality randomized clinical trials on long-term treatment effects (preferably ≥ 12 months after treatment completion) and relapse are warranted to facilitate more reliable long-term effect size estimations.

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Author Contributions

EvD, SvV, MH, NB, CB, PC, and IE designed the meta-analysis. EvD and SvV screened titles and abstracts. EvD and RvdH (supervised by MH, NB, PC, and IE) completed the full-text screening, data-extraction and quality assessments. EvD (Utrecht University) performed statistical analyses and drafted the manuscript (supervised by IE). SvV, MH, NB, CB, RvdH, PC, and IE critically revised the manuscript. EvD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplementary Materials

Table S1. Search strategy and number of hits per search engine

Table S2. Characteristics of included studies

Table S3. Sensitivity analysis of treatment effects based on symptom outcome measures

Table S4. Subgroup analyses across treatment approaches

Table S5. Subgroup analyses across comparison groups

Figure S1. Study design quality, therapy quality and researcher allegiance per study

Figure S2. Standardized effect sizes of comparisons between CBT and comparison groups on symptoms for generalized anxiety disorder

Figure S3. Standardized effect sizes of comparisons between CBT and comparison groups on symptoms for panic disorder with or without agoraphobia

Figure S4. Standardized effect sizes of comparisons between CBT and comparison groups on symptoms for social anxiety disorder

Figure S5. Standardized effect sizes of comparisons between CBT and comparison groups on symptoms for specific phobia

Figure S6. Standardized effect sizes of comparisons between CBT and comparison groups on symptoms for posttraumatic stress disorder

Figure S7. Standardized effect sizes of comparisons between CBT and comparison groups on symptoms for obsessive compulsive disorder

Figure S8. Funnel plots of standard error by Hedges' g of symptom level after cognitive behavioral therapy relative to comparison groups for generalized anxiety disorder

Figure S9. Funnel plots of standard error by Hedges' g of symptom level after cognitive behavioral therapy relative to comparison groups for panic disorder with or without agoraphobia

Figure S10. Funnel plots of standard error by Hedges' g of symptom level after cognitive behavioral therapy relative to comparison groups for social anxiety disorder

Figure S11. Funnel plots of standard error by Hedges' g of symptom level after cognitive behavioral therapy relative to comparison groups for specific phobia

Figure S12. Funnel plots of standard error by Hedges' g of symptom level after cognitive behavioral therapy relative to comparison groups for posttraumatic stress disorder

Table S1
Search Strategy and Number of Hits per Search Engine

PubMed: 4783

1. (panic[tiab] OR phobi*[tiab] OR agoraphobi* [tiab] OR acrophobi* [tiab] OR emetophobi* [tiab] OR cynophobi* [tiab] OR trypanophobi* [tiab] OR claustrophobi* [tiab] OR (obsess*[tiab] AND compuls*[tiab]) OR OCD[tiab] OR posttrauma*[tiab] OR post-trauma*[tiab] OR traumatic stress[tiab] OR generalized anxiety[tiab] OR generalized anxiety[tiab] OR social anxiety[tiab] OR "Stress disorders, Traumatic"[MeSH] OR "Anxiety disorders"[MeSH])
2. ("Child"[MeSH] OR ("Animals"[MeSH] NOT "Humans"[MeSH]))
3. ("Chemicals and Drugs Category"[MeSH] NOT "Psychotherapy"[MeSH])
4. ("Clinical Trial"[Publication Type] OR "Randomized Controlled Trial" [Publication Type])
5. #1 NOT #2 NOT #3
6. #4 AND #5 Filters: Publication date from 1980/01/01

PsycINFO: 1881

1. ("panic" or "*phobi*" or ("obsess*" and "compuls*") or "OCD" or "posttrauma*" or "post-trauma*" or "traumatic stress" or "generalized anxiety" or "generalized anxiety" or "social anxiety").ab,id,ti.
2. anxiety disorders/ or generalized anxiety disorder/ or obsessive compulsive disorder/ or panic disorder/ or phobias/ or post-traumatic stress/ or posttraumatic stress disorder/ or performance anxiety/ or social anxiety/ or speech anxiety/ or test anxiety/
3. 1 or 2
4. limit 3 to (childhood <birth to 12 years> or adolescence <13 to 17 years>)
5. 3 not 4
6. limit 5 to animal
7. limit 5 to human
8. 6 not 7
9. 5 not 8
10. drug therapy/ not psychotherapy/
11. 9 not 10
12. limit 11 to ("0300 clinical trial" or "2100 treatment outcome")
13. limit 12 to yr="1980-Current"

(Table continues on the next page)

EMBASE: 1571

1. 'panic':ab,ti OR 'phobi*':ab,ti OR 'agoraphobi*':ab,ti OR 'acrophobi*':ab,ti OR 'emetophobi*':ab,ti OR 'cynophobi*':ab,ti OR 'trypanophobi*':ab,ti OR 'claustrophobi*':ab,ti OR '(obsess*':ab,ti AND 'compuls*)':ab,ti OR 'ocd':ab,ti OR 'posttrauma*':ab,ti OR 'post-trauma*':ab,ti OR 'traumatic stress':ab,ti OR 'generalized anxiety':ab,ti OR 'generalised anxiety':ab,ti OR 'social anxiety':ab,ti OR 'anxiety disorder'/exp
2. 'juvenile'/exp
3. ('animal model'/exp OR 'animal'/exp OR 'animal experiment'/exp) NOT 'human experiment'/exp
4. ('drug'/exp OR 'drug therapy'/exp) NOT 'psychotherapy'/exp
5. #1 NOT #2 NOT #3 NOT #4
6. #5 AND ('clinical trial'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'randomized controlled trial'/de) AND [1980-2019]/py

Cochrane Library: 3941

1. (panic or *phobi* or (obsess* and compuls*) or OCD or posttrauma* or post-trauma* or traumatic stress or generalized anxiety or generalized anxiety or social anxiety):ti,ab,kw (Word variations have been searched)
2. MeSH descriptor: [Stress Disorders, Traumatic] explode all trees
3. MeSH descriptor: [Anxiety Disorders] explode all trees
4. #1 or #2 or #3
5. MeSH descriptor: [Child] explode all trees
6. MeSH descriptor: [Animals] explode all trees
7. MeSH descriptor: [Humans] explode all trees
8. #6 not #7
9. #5 or #8
10. #4 not #9
11. MeSH descriptor: [Drug Therapy] explode all trees
12. MeSH descriptor: [Anxiety Disorders] explode all trees and with qualifier(s): [Drug therapy – DT]
13. MeSH descriptor: [Anxiety] explode all trees and with qualifier(s): [Drug therapy – DT]
14. MeSH descriptor: [Chemical Actions and Uses] explode all trees
15. MeSH descriptor: [Psychotherapy] explode all trees

(Table continues on the next page)

16. #11 or #12 or #13 or #14
17. #16 not #15
18. #10 not #17
19. "randomized controlled trial":pt
20. #19 and #20
21. With Cochrane Library publication date from Jan 1980 to present

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OpenGrey: 21

1. (anxiety disorder* OR panic OR phobi* OR agoraphobi* OR acrophobi* OR emetophobi* OR cynophobi* OR trypanophobi* OR claustrophobi* OR (obsess* AND compuls*) OR OCD OR posttrauma* OR post-trauma* OR traumatic stress OR generalized anxiety OR generalized anxiety OR social anxiety)
2. (Controlled trial OR Clinical trial OR RCT)
3. 1 AND 2

Note. This search query was conducted at January 2, 2019.

Table S2

Characteristics of Included Studies

Study	Diagnosis	Country	Population	Age[a]	Sex (M/F)	Conditions	N	Sessions	Format	Outcome	Analysis	Registered
Acosta 2017	PTSD[b]	USA	OEF-OIF veterans	22-64	151/11	1. CBT	81	24	INT	PCL-M	ITT	Y
						2. CAU	81	/	/			
Andersson 2012	GAD	Sweden	Adults	19-66	12/42	1. CBT	27	8	INT	GAD-Q-IV, PSWQ	ITT	N
						2. WL	27	/	/			
Arntz 1996	PD	Netherlands	Adults	21-52	22/14	1. CT	18	12	INDIV	Composite score[c]	ITT	N
						2. AR	19	12	INDIV			
Arntz 2003	GAD	Netherlands	Adults	20-60	15/30	1. CT	25	12	INDIV	Composite score[c]	ITT	N
						2. AR	20	12	INDIV			
Barlow 1989, Craske 1991	PD	USA	Adults	18-65	16/39	1. CBT	16	15	INDIV	*ADIS-R*	COMPL	N
						2. CBT + Relax	24	15	INDIV			
						3. AR	15	15	INDIV			
Barlow 2000	PD	USA	Adults	18-65	35/66	1. CBT	77	11	INDIV	*CGI, PDSS*	ITT	N
						2. PP	24	11	INDIV			
Baruah 2018	OCD	India	Adults	18-45	35/29	1. ERP	30	6	Family	*CGI-S, Y-BOCS*	ITT	Y
						2. Relax	34	6	Family			
Basoglu 2007	PTSD	Turkey	Earthquake survivors	18-65	4/27	1. Exposure	16	1	INDIV	*CAPS,* FAQ, *GIS-A*, GIS-S	ITT	N
						2. WL	15	/	/			
Beck 1994	PD	USA	Adults	18-65	11/31	1. CT	22	10	Group	*ADIS-R*, FQ-Ag	COMPL	N
						2. Relax	20	10	Group			
Borkovec 1993	GAD	USA	Adults	37.5 (11.8)	30/36	1. CBT	23	12	INDIV	*ADIS-R*, PSWQ	COMPL	N
						2. ST	20	12	INDIV			
						3. AR	23	12	INDIV			

(Table continues on the next page)

Study	Diagnosis	Country	Population	Age[a]	Sex (M/F)	Conditions	N	Sessions	Format	Outcome	Analysis	Registered
Borkovec 2002	GAD[d]	USA	Adults	37.1 (11.7)	31/45	1. CT	25	14	INDIV	*ADIS-R*, PSWQ	COMPL	N
						2. CBT	26	14	INDIV			
						3. Relax	25	14	INDIV			
Brenes 2015, 2017	GAD	USA	Rural older adults	60-87	26/115	1. CBT	70	9-11	Phone	GAD-7, PSWQ	ITT	Y
						2. ST	71	10	Phone			
Christensen 2014	GAD	Australia	Adults	18-30	3/12	1. CBT	8	10	INT	GAD-7, *MINI*	COMPL	N
						2. ST	7	10	INT			
Cottraux 2008	PTSD	France	Adults	18-65	28/32	1. CBT	31	10-16	INDIV	PCL	COMPL	N
						2. ST	29	16	INDIV			
Dugas 2010	GAD	Canada	Adults	18-64	21/43	1. CBT	33	12	INDIV	*ADIS-IV*, *CGI-I*, PSWQ, WAQ	COMPL	N
						2. AR	31	12	INDIV			
DuHamel 2010	PTSD[e]	USA	Survivors of HSCT	19-74	48/41	1. CBT	52	10	Phone	PCL-C	ITT	N
						2. WL	37	/	/			
Echeburua 1997	PTSD	Spain	Victims sexual aggression	15-41	0/20	1. CBT	10	6	INDIV	*SSPSDS*	ITT	N
						2. Relax	10	6	INDIV			
Ehlers 2003	PTSD	UK	Motor vehicle accident survivors	18-65	N/A	1. CT	28	2-12	INDIV	*CAPS*, PDS-S	ITT	N
						2. WL	29	/	/			
Ehlers 2014	PTSD	UK	Adults	18-66	38/53	1. CT	31	8-12	INDIV	*CAPS*, PDS-S	ITT	Y
						2. CT (intensive)	30	8-12	INDIV			
						3. ST	30	8-12	INDIV			
Engel 2015	PTSD	USA	Veterans	36 (N/A)	85/15	1. CBT	43	18	INT	PCL-C	ITT	N
						2. CAU	37	3	INDIV			

(Table continues on the next page)

Study	Diagnosis	Country	Population	Age[a]	Sex (M/F)	Conditions	N	Sessions	Format	Outcome	Analysis	Registered
Feldman 2016	PD	USA	Asthmatic Latino adults	43 (N/A)	8/45	1. CBT + biofeedback	27	8	INDIV	ACQ, BSQ, *CGI, PDSS*	ITT	Y
						2. Relax	26	8	INDIV			
Feske 2008	PTSD	USA	Minority women	29-55	3/24	1. PE	13	9-12	INDIV	*PDS-I*	COMPL	N
						2. CAU + AM	14	9-12	INDIV + group			
Foa 1991	PTSD	USA	Rape victims	32 (N/A)	7/21	1. PE	14	9	INDIV	*Symptom severity interview*, RAST	COMPL	N
						2. ST	14	9				
Franklin 2017	PTSD	USA	Veterans	46.1 (15.5)	23/2	1. PE	10	12	Phone	*CAPS,* PDS-S	COMPL	N
						2. PE	7	12	TC			
						3. CAU	8	/	/			
Furmark 2009	SAD	Sweden	Adults	20-63	17/41	1. CBT	29	9	INT	LSAS, SIAS, SPS, SPSQ	ITT	N
						2. AR	29	9	INT			
Gersons 2000	PTSD	Netherlands	Police officers	36.4 (4.9)	37/5	1. BEP	22	16	INDIV	*SI-PTSD*	ITT	N
						2. WL	20	/	/			
Heimberg 1990, 1993	SAD	USA	Adults	30.4 (N/A)	27/22	1. CBT	25	12	Group	*ADIS*, FNE, FQ-SP, PRCS, SADS	COMPL	N
						2. ST	24	12	Group			
Hien 2009	PTSD[f]	USA	Women with substance use disorder	39.2 (9.3)	0/353	1. CBT (SS)	176	12	Group	PSS-S	ITT	N
						2. ST	177	12	Group			
Himle 2014	SAD	USA	Unemployed job-seekers	19-60	39/19	1. Work-related CBT	29	8	Group	BFNE, *CGI,* LSAS, Mini-SPIN, *SCID-I*, WSA	ITT	N
						2. CAU	29	/	/			

(Table continues on the next page)

Study	Diagnosis	Country	Population	Age[a]	Sex (M/F)	Conditions	N	Sessions	Format	Outcome	Analysis	Registered
Hinton 2011	PTSD	USA	Treatment-resistant Latino women	49.5 (7.1)	0/24	1. CBT	12	14	Group	PCL-C	ITT	N
						2. AR	12	14	Group			
Hoyer 2009	GAD	Germany	Adults	45.4 (12.48)	16/52	1. WE	32	15	INDIV	PSWQ, MCQ, WBSI	COMPL	N
						2. AR	36	15	INDIV			
Hui 2017	GAD	China	Older adults	65.4 (4.4)	36/27	1. CBT	32	12	Group	CAQ, GAD-Q-IV, GADSS, PSWQ, WW-II	COMPL	N
						2. WL	31	/	/			
Johnson 2011	PTSD[g]	USA	Battered women living in shelters	32.6 (8.8)	0/70	1. CBT	35	12	INDIV	*CAPS*	ITT	N
						2. CAU	35	/	/			
Johnson 2016	PTSD[h]	USA	Battered women living in shelters	33.3 (10.4)	0/60	1. CBT	30	10	INDIV	*CAPS*	COMPL	N
						2. CAU	30	/	/			
Lessard 2012	PD	Canada	Adults	21-81	31/27	1. Brief CBT	24	1	INDIV	ACQ, *ADIS-IV*, BSQ, CAQ, PAS	ITT	N
						2. CBT						
						3. CAU	19	7	INDIV			
							15	?	INDIV			
Litz 2007	PTSD	USA	Service members of Defense Department	21-65	35/10	1. CBT	24	56	INT	*PSS-I*	COMPL	N
						2. ST	21	56	INT			
Marks 1998	PTSD	UK	Adults	16-65	56/31	1. Exposure	23	10	INDIV	*CAPS*, *GIS-A*, GIS-S	COMPL	N
						2. CR	19	10	INDIV			
						3. Exposure + CR	24	10	INDIV			
						4. Relax	21	10	INDIV			

(Table continues on the next page)

Study	Diagnosis	Country	Population	Age[a]	Sex (M/F)	Conditions	N	Sessions	Format	Outcome	Analysis	Registered
McNamee 1989	PD	UK	Housebound agoraphobics	29-60	7/16	1. Exposure	13	12	Phone	*Assessor ratings*[i]	COMPL	N
						2. Relax	10	12	Phone			
Monson 2006	PTSD	USA	Veterans	54.0 (6.3)	54/6	1. Cognitive processing	30	12	INDIV	*CAPS*, PCL	ITT	N
						2. WL	30	/	/			
Mueser 2008	PTSD	USA	Adults with severe mental illness	44.2 (10.6)	23/85	1. CBT	54	12-16	INDIV	*CAPS*, PTCI	ITT	N
						2. CAU	54	/	/			
Nacasch 2011	PTSD	Israel	Veterans	34.3 (11.7)	30/0	1. PE	15	9-15	INDIV	*PSS-I*	ITT	Y
						2. CAU	15	/	/			
Neuner 2004	PTSD	Uganda	Sudanese refugees	34.8 (12.8)	18/26	1. NET	17	5	INDIV	*CIDI*, *PDS-I*	COMPL	N
						2. ST	15	5	INDIV			
						3. Psycho-education	12	1	INDIV			
Oosterbaan 2001	SAD	Netherlands	Adults	18-65	34/21	1. CT	28	12	INDIV	*ADS*, FQ-SP, IIS, LSAS, SCI	COMPL	N
						2. PP	27	7	INDIV			
Öst 1991	SP	Sweden	Adults	18-55	9/21	1. AT	10	5	INDIV	FQ-BI, FSS-III-blood, MQ	COMPL	N
						2. Exposure	10	5	INDIV			
						3. Tension only	10	5	INDIV			
Öst 1995	PD	Sweden	Adults	23-45	12/26	1. CBT	19	12	INDIV	BSQ, *HEF*[j]	COMPL	N
						2. AR	19	12	INDIV			
Öst 2000	GAD	Sweden	Adults	22-60	10/26	1. CT	19	12	INDIV	*ADIS-R*, PWSQ, severity rating	COMPL	N
						2. AR	17	12	INDIV			

(Table continues on the next page)

Study	Diagnosis	Country	Population	Age[a]	Sex (M/F)	Conditions	N	Sessions	Format	Outcome	Analysis	Registered
Pacella 2012	PTSD	USA	People with HIV	31-61	42/24	1. PE	41	10	INDIV	PTCI, *PSS-I*	ITT	N
						2. WL	25	5	Phone			
Pelland 2011	PD	Canada	People with chest pain at emergency department	18-80	18/16	1. CBT	19	17	INDIV	ACQ, *ADIS-IV*, CAQ, PAS	ITT	N
						2. CAU	15	?	?			
Power 1990, Durham 2003	GAD	UK	Adults	18-65	11/29	1. CBT + Relax	21	7	INDIV	*CGI*, SRT[k], symptom change	COMPL	N
						2. PP	19	/	/			
Rakowska 2011	SAD	Poland	Adults	18-36	50/70	1. Exposure	60	10	INDIV	*ADIS-IV*, SCL-90-R	ITT	N
						2. ST	60	10	INDIV			
Reiss 2017	SAD[l]	Germany	Students with test anxiety	27.1 (5.6)	28/110	1. CBT + ImR	48	5	Group	TAQ	COMPL	N
						2. CBT + Relax	42	5	Group			
						3. Guided SH (ST)	48	5	Group			
Sharp 1996	PD	Scotland	Adults	18-70	36/44	1. CBT	43	8	INDIV	FQ-Ag, SRT	COMPL	N
						2. PP	37	8	/			
Shear 1994	PD	USA	Adults	30.0 (9.1)	29/37	1. CBT	37	15	INDIV	*ADIS-R*, BFQ-Ag, MI	COMPL	N
						2. ST	29	15	INDIV			
Shear 2001	PD	USA	Adults	34.5 (11.5)	23/36	1. CBT	36	12	INDIV	*CGI*, *PDSS*	ITT	N
						2. PP	23	/	/			
Sloan 2012	PTSD	USA	Motor vehicle accident survivors	40.7 (13.1)	16/30	1. Written exposure	22	5	INDIV	CAPS	ITT	N
						2. WL	24	/				

(Table continues on the next page)

Study	Diagnosis	Country	Population	Age[a]	Sex (M/F)	Conditions	N	Sessions	Format	Outcome	Analysis	Registered
Smits 2006	SAD	USA	Students	21.0 (5.1)	30/47	1. Exposure + VFB	20	1	INDIV	LSAS	COMPL	N
						2. Exposure + VFB	19	1	INDIV			
						3. Exposure	23	1	INDIV			
						4. Relax	15	1	INDIV			
Stanley 2009	GAD	USA	Older adults	66.9 (5.8)	29/105	1. CBT	70	10	INDIV	GADSS, PSWQ	ITT	N
						2. CAU	64	6	Phone			
Stenmark 2013	PTSD	Norway	Refugees and asylum seekers	35.3 (11.1)	56/25	1. NET	51	10	INDIV	CAPS	COMPL	N
						2. CAU	30	10	INDIV			
Taylor 2003	PTSD	Canada	Adults	37.0 (10.0)	10/31	1. Exposure	22	8	INDIV	*CAPS*	COMPL	N
						2. Relax	19	8	INDIV			
Thom 2000	SP	Germany	Adults	30.4 (8.7)	35/26	1. CBT	25	1	INDIV	DAS, DFS	COMPL	N
						2. WL	36	/	INDIV			
Twohig 2010	OCD	USA	Adults	18-67	31/48	1. ACT	41	8	INDIV	*Y-BOCS*	ITT	N
						2. Relax	38	8	INDIV			
van den Berg 2015	PTSD	Netherlands	Adults with psychotic disorder	18-65	46/54	1. PE	53	8	INDIV	*CAPS*, PTCI, PSS-S	ITT	N
						2. WL	47	/	/			
Vaughan 1994	PTSD[m]	Australia	Adults	20-78	9/15	1. Imaginal exposure	13	3-5	INDIV	IES, *SI-PTSD*	ITT	N
						2. AR	11	3-5	INDIV			
Wells 2010	GAD	UK	Adults	25-78	8/12	1. Meta-cognitive therapy	10	8-12	INDIV	MCQ, PSWQ, *SCID-I*	COMPL	N
						2. AR	10	8-12	INDIV			

(Table continues on the next page)

Study	Diagnosis	Country	Population	Age[a]	Sex (M/F)	Conditions	N	Sessions	Format	Outcome	Analysis	Registered
Wetherell 2003	GAD	USA	Older adults	67.1 (8.2)	10/42	1. CBT	26	12	INDIV	PSWQ	COMPL	N
						2. ST/ Discussion group	26	12	INDIV			
Wolitzky 2009	SP	USA	Agoraphobic adults	18-64	25/56	1. Exposure + OA	28	1	INDIV	AQ	COMPL	N
						2. Exposure	28	1	INDIV			
						3. Relax	25	1	INDIV			

Note. Outcomes in italics are clinician-administered measures. Abbreviations: ACQ, Agoraphobia Cognitions Questionnaire; ADS, Anxiety Discomfort Scale; ADIS-R, Anxiety Disorders Interview Schedule – Revised; AM, anger management; AQ, Acrophobia Questionnaire; AR, applied relaxation; AS, Agoraphobia Scale; AT, applied tension; BEP, brief eclectic psychotherapy including CBT; BFNE, Brief Fear of Negative Evaluations Scale; BFQ-Ag, Brief Fear Questionnaire (Agoraphobia); BSQ, Body Sensations Questionnaire; CAPS, Clinician-Administered PTSD Scale; CAQ, Cognitive Avoidance Questionnaire; CAU, care as usual; CBT, cognitive behavioral therapy; CGI, Clinical Global Impression Scale (I = improvement; S = severity); CIDI, Composite International Diagnostic Interview; CR, cognitive restructuring; CT, cognitive therapy; DAS, Dental Anxiety Scale; DFS, Dental Fear Survey; ERP, exposure and response prevention; F, female; FAQ, Fear and Avoidance Questionnaire; FNE, Fear of Negative Evaluation Scale; FQ, Fear Questionnaire (Ag = Agoraphobia, BI = Blood Injury, SP = Social Phobia); FSS-III-blood, Fear Survey Schedule-III blood items; GAD, Generalized Anxiety Disorder; GAD-7, Generalized Anxiety Disorder Scale; GAD-Q-IV, Generalized Anxiety Disorder Questionnaire IV; GADSS, Generalized Anxiety Disorder Severity Scale; GIS, Global Improvement Scale (A = Assessor, S = Self); HSCT, Hematopoietic stem cell transplantation; IES, Impact of Event Scale; IIS, Inventory of Interpersonal Situations; ImR, imagery rescripting; INDIV, individual; INT, internet; LSAS, Liebowitz Social Anxiety Scale; M, male; MCQ, Metacognition Questionnaire; MI, Mobility Inventory for Agoraphobia; MINI, Mini-International Neuropsychiatric Interview; Mini-SPIN, Mini Social Phobia Inventory; MQ, Mutilation Questionnaire; N, no; N/A, not available; NET, narrative exposure therapy; OA, oppositional actions; OCD, obsessive compulsive disorder; PAS, Panic and Agoraphobia Scale; PCL, PTSD Checklist (5 = DSM-5, M = Military, C = Civilian); PD, panic disorder with or without agoraphobia; PDS, Posttraumatic Diagnostic Scale (I = interview, S = self-report); PDSS, Panic Disorder Severity Scale; PE, prolonged exposure; PP, pill placebo; PRCS, Personal Report of Confidence as a Speaker; PSS, Post Traumatic Stress Disorder Symptom Scale (I = interview, S = self-report); PSWQ, Penn State Worry Questionnaire; PTCI, Posttraumatic Cognitions Inventory; PTSD, posttraumatic stress disorder; RAST, Rape Aftermath Symptom Test; Relax, Relaxation; SAD, social anxiety disorder; SADS, Social Avoidance and Distress Scale; SCI, Social Cognitions Inventory; SCID-I, Structured Clinical Interview for DSM-IV Axis-1 Disorders; SCL-90-R, Symptom Checklist (Interpersonal Sensitivity and Phobic Anxiety subscales); SH, self-help; SIAS, Social Interaction Anxiety Scale; SI-PTSD, Structured Interview for PTSD; SP, specific phobia; SPS, Social Phobia Scale; SPSQ, Social Phobia Screening Questionnaire; SRT, Symptom Rating Test; SS, Seeking Safety; SSPSDS, Scale of Severity of PTSD Symptoms; ST, supportive therapy;

TAQ, Test Anxiety Questionnaire; TC, teleconference; VFB, video feedback; WAQ, Worry and Anxiety Questionnaire; WBSI, White Bear Suppression Inventory; WL, waiting list; WSA, Work-related Social Anxiety Scale; WW-II, Why Worry-II; Y, yes; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.
[a] Age is provided in range or mean (standard deviation).
[b] 34 participants (21%) did not meet full diagnosis of PTSD.
[c] The authors only reported a composite score of the Fear of Fear questionnaire, the FQ, the STAI, and the Depressive Symptoms Inventory.
[d] 2 participants (3%) did not meet full diagnosis of GAD.
[e] 23 participants (28%) did not meet full diagnosis of PTSD.
[f] 69 participants (20%) did not meet full diagnosis of PTSD.
[g] 9 participants (13%) did not meet full diagnosis of PTSD.
[h] 3 participants (5%) did not meet full diagnosis of PTSD.
[i] Including global phobia, global impression, and fear to 4 phobic targets.
[j] High end-state functioning (HEF) was defined as being panic free and having <3 rating on ADIS-R severity scale.
[k] This was the only measure at follow-up and was not used at post-test.
[l] 10 participants (7%) did not meet full diagnosis of SAD.
[m] 22 participants (22%) did not meet full diagnosis of PTSD.

Table S3

Sensitivity Analysis of Treatment Effects Based on Symptom Outcome Measures

Diagnosis		Hedges' *g* (95% CI)	
	k	**One outcome measure**	**All outcome measures combined**
Post-treatment			
GAD	14	0.50 (0.13-0.86)	0.39 (0.12-0.66)
PD	13	0.26 (-0.04-0.56)	0.22 (0.01-0.43)
SAD	7	0.41 (0.21-0.61)	0.38 (0.19-0.57)
SP	3	0.50 (0.15-0.85)	0.49 (0.13-0.84)
PTSD	30	0.70 (0.49-0.91)	0.72 (0.52-0.93)
OCD	2	0.67 (0.19-1.15)	0.70 (0.29-1.12)
1-6 months FU			
GAD	3	0.32 (-0.38-1.02)	0.07 (-0.50-0.63)
PD	6	0.34 (-0.03-0.70)	0.27 (-0.01-0.55)
SAD	4	0.56 (0.32-0.81)	0.60 (0.36-0.85)
SP	2	1.24 (-0.53-3.02)	0.72 (0.01-1.44)
PTSD	24	0.66 (0.43-0.88)	0.67 (0.46-0.88)
OCD	2	0.72 (0.35-1.09)	0.85 (0.47-1.22)
6-12 months FU			
GAD	11	0.47 (0.11-0.82)	0.40 (0.13-0.67)
PD	9	0.42 (0.20-0.65)	0.35 (0.11-0.59)
SAD	3	0.35 (0.09-0.62)	0.34 (0.07-0.61)
SP	0	N/A	N/A
PTSD	11	0.59 (0.42-0.77)	0.59 (0.42-0.77)
OCD	0	N/A	N/A
≥12 months FU			
GAD	10	0.28 (0.02-0.54)	0.22 (0.02-0.42)
PD	5	0.11 (-0.23-0.45)	0.14 (-0.19-0.47)
SAD	3	0.46 (0.08-0.83)	0.42 (0.04-0.79)
SP	1	N/A	N/A
PTSD	5	0.93 (0.07-1.80)	0.84 (0.03-1.64)
OCD	0	N/A	N/A

Note. Underlined effect sizes are statistically significant ($p < .05$). CI = confidence interval; FU = follow-up; GAD = generalized anxiety disorder; N/A = not available; OCD = obsessive compulsive disorder; PD = panic disorder with or without agoraphobia; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder; SP = specific phobia.

Table S4

Subgroup Analyses Across Treatment Approaches

	Post-treatment		1-6 months FU		6-12 months FU		≥12 months FU	
	k	**Hedges' *g* (95% CI)**	***k***	**Hedges' *g* (95% CI)**	***k***	**Hedges' *g* (95% CI)**	***k***	**Hedges' *g* (95% CI)**
GAD[a]								
CR[b]	4	0.31[c] (-0.33-0.96)	1		3	0.54 (-0.40-1.47)	3	0.35[c] (-0.50-1.20)
BT	1		0		1		1	
Mixed	10	0.49 (0.24-0.74)	2		8	0.45 (0.21-0.96)	7	0.28 (0.08-0.47)
PD[d]								
CR	3	0.15[c] (-0.40-0.69)	2		2		1	
BT	2		1		0		1	
Mixed	9	0.21 (-0.03-0.45)	3	0.09[c] (-0.27-0.44)	7	0.40 (0.11-0.69)	4	0.26[c] (-0.13-0.64)
SAD								
CR	1		1		0		1	
BT	2		2		1		0	
Mixed	4	0.32 (0.02-0.62)	1		2		2	
PTSD[e]								
CR[f]	4	0.87 (0.50-1.23)	3	0.63 (0.32-0.93)	2		0	
BT	13	0.83 (0.47-1.20)	10	0.79 (0.42-1.15)	2		2	
Mixed	15	0.55 (0.30-0.80)	13	0.60 (0.31-0.89)	7	0.52 (0.27-0.77)	3	0.49 (-0.42-1.41)

Note. Underlined effect sizes are statistically significant ($p < .05$). Empty cells indicate insufficient studies ($k < 3$) for subgroup analyses. BT = behavioral therapy (all exposure-based); CAU = care-as-usual; CI = confidence interval; CR = cognitive restructuring; FU = follow-up; GAD = generalized anxiety disorder; OCD = obsessive compulsive disorder; PD = panic disorder with or without agoraphobia; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder; SP = specific phobia.

[a] Groups did not significantly differ at any time (Qs < 0.61, *p*s > .439).

[b] Including 1 study on metacognitive therapy.

[c] Post-hoc statistical power beneath 80% (α = 0.05).

[d] Groups did not significantly differ at post-treatment (Q = 0.05, $p = .822$).

[e] Groups did not significantly differ at any time (Qs < 1.92, *p*s > .385).

[f] Including 1 study on cognitive processing therapy.

Table S5

Subgroup Analyses Across Comparison Groups

	Post-treatment		1-6 months FU		6-12 months FU		≥12 months FU	
	k	**Hedges' *g* (95% CI)**	***k***	**Hedges' *g* (95% CI)**	***k***	**Hedges' *g* (95% CI)**	***k***	**Hedges' *g* (95% CI)**
GAD[a]								
Relaxation[b]	7	0.15[c] (-0.22-0.51)	1		6	0.26 (-0.12-0.64)	6	0.15[c] (-0.20-0.50)
ST[b]	4	0.58 (0.25-0.92)	0		4	0.41 (0.15-0.68)	3	0.35 (0.06-0.64)
Other[d]	4	0.66 (0.04-1.28)	2		2		2	
PD[e]								
Relaxation	7	0.19 (-0.19-0.57)	4	0.39 (-0.01-0.79)	3	0.29[c] (-0.15-0.72)	3	-0.02[c] (-0.43-0.40)
Pill placebo	3	0.42 (0.11-0.74)	0		3	0.73 (0.34-1.12)	2	
Other[f]	3	0.07[c] (-0.29-0.43)	2		3	0.06[c] (-0.30-0.41)	0	
SAD[g]								
ST	3	0.36 (-0.06-0.77)	1		3	0.34 (0.07-0.61)	1	
Other[h]	4	0.43 (0.16-0.70)	3	0.55 (0.18-0.91)	0		2	
PTSD[ij]								
CAU	9	0.54 (0.28-0.80)	7	0.47 (0.17-0.77)	4	0.49 (0.25-0.74)	1	
Relaxation	5	0.77 (0.28-1.25)	5	0.86 (0.30-1.41)	1		1	
ST	6	0.27 (-0.02-0.57)	4	0.35 (-0.08-0.79)	3	0.54 (0.08-0.99)	3	0.08[c] (-0.22-0.38)
Waiting list	9	1.25 (0.82-1.69)	7	1.04 (0.62-1.46)	3	0.66 (0.33-0.99)	0	

Note. Underlined effect sizes are statistically significant ($p < .05$). Empty cells indicate insufficient studies ($k < 3$) for subgroup analyses. BT = behavioral therapy (all exposure-based); CAU = care-as-usual; CI = confidence interval; FU = follow-up; GAD = generalized anxiety disorder; OCD = obsessive compulsive disorder; PD = panic disorder with or without agoraphobia; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder; SP = specific phobia; ST = supportive therapy.

[a] Groups did not significantly differ at any time (Qs < 1.08, *p*s > .200).

[b] One study was included twice, because it compared CBT to supportive therapy and relaxation.

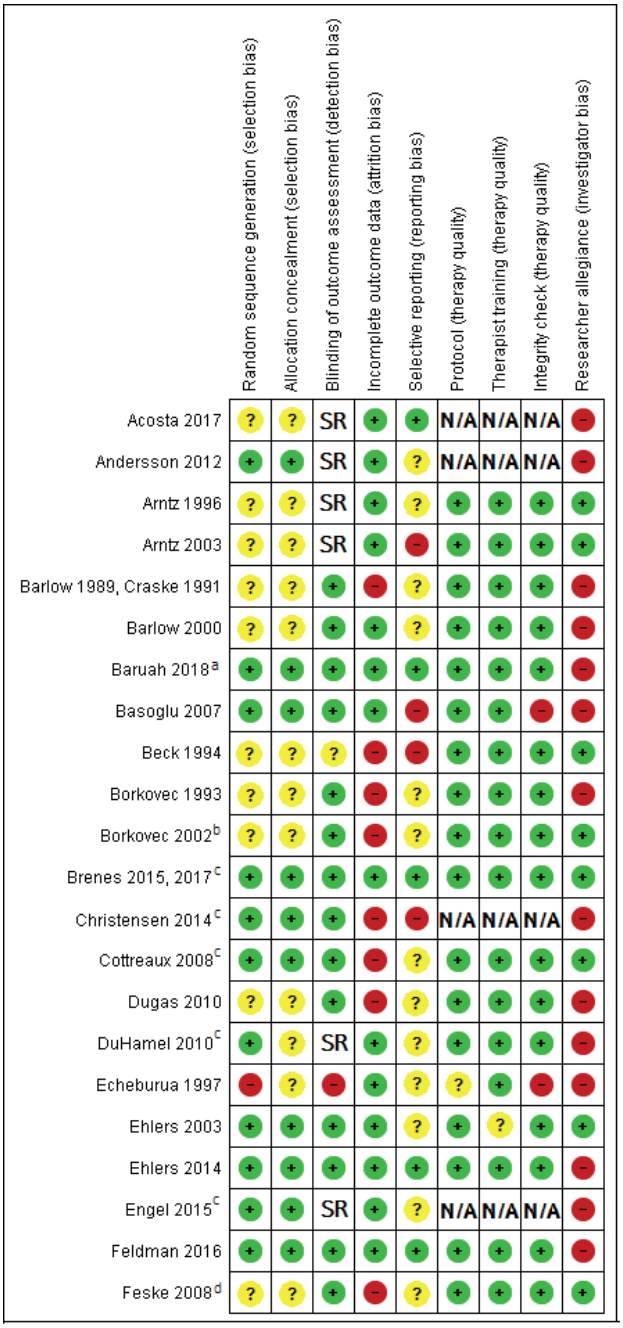
[c] Post-hoc statistical power beneath 80% (α = 0.05).

[d] 2 waiting list, 1 CAU, and 1 pill placebo.

[e] Groups significantly differed at post-treatment (Q = 1.52, *p* = .047) and at 6-12 months follow-up (Q = 6.47, *p* = .039).
[f] 2 CAU and 1 ST.
[g] Groups did not significantly differ at post-treatment (Q = 0.16, *p* = .691)
[h] 2 relaxation, 1 CAU, and 1 pill placebo.
[i] Groups differed significantly at post-treatment (Q = 12.63, p = .006), but not at other times (Qs < 5.92, ps > .115). At post-treatment, supportive therapy yielded a smaller effect size relative to all other groups (Q = 5.19, p = .023); relaxation and CAU did not differ from all other groups (Qs < 1.03, ps > .312); and waiting list resulted in a larger effect size (Q = 10.35, p = .001).
[j] Two studies with psycho-education comparison were excluded from subgroup analyses.

Figure S1

Study Design Quality, Therapy Quality, and Researcher Allegiance per Study



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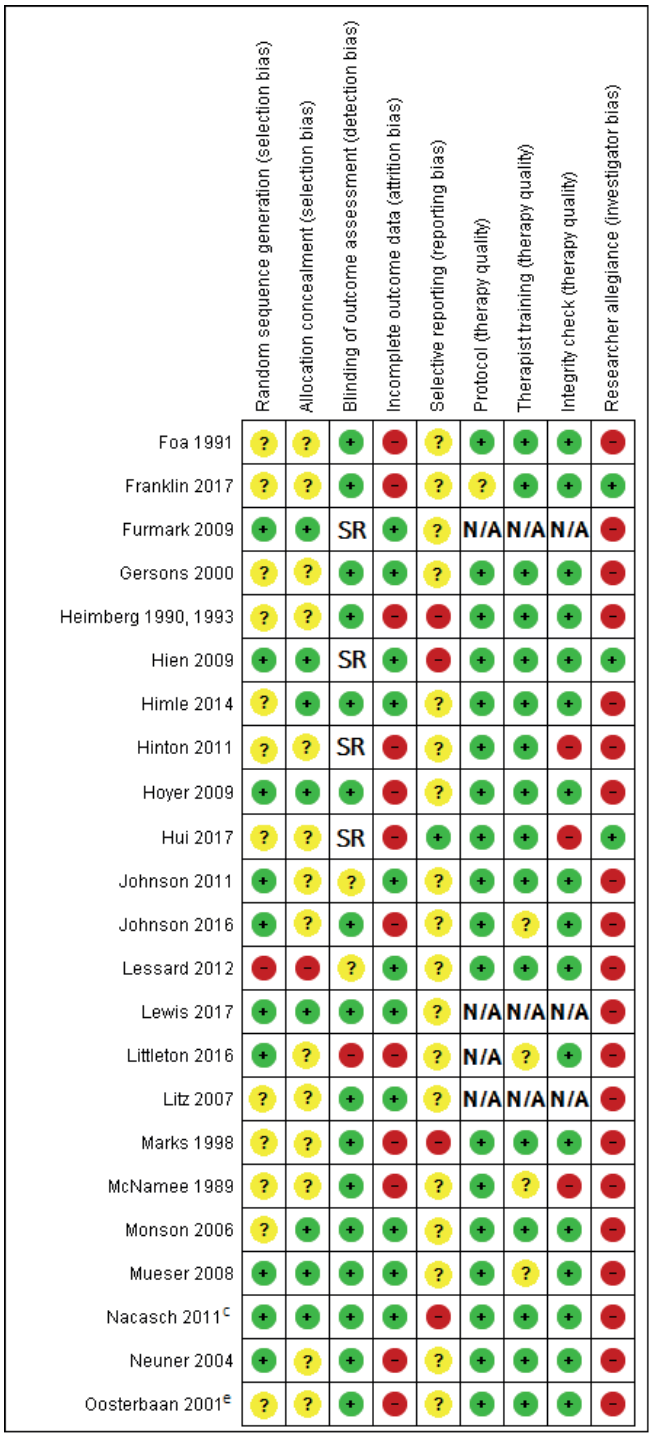

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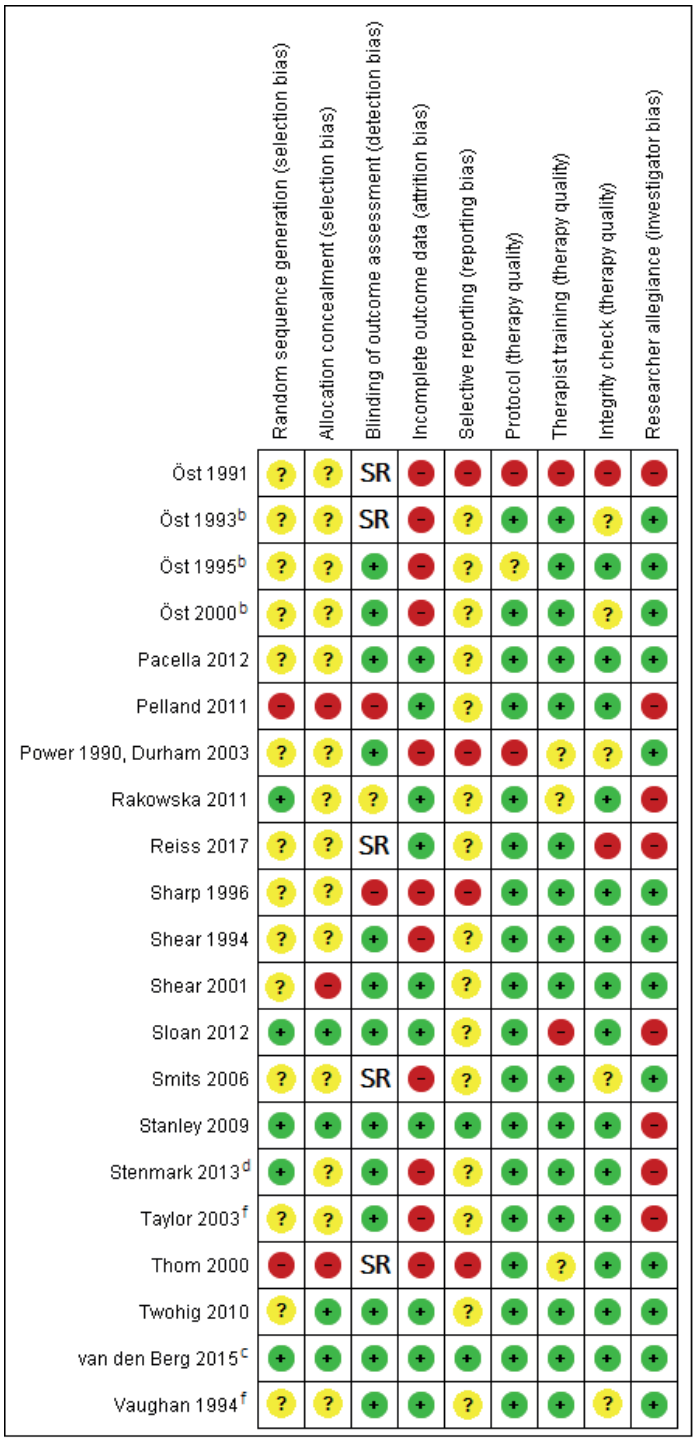

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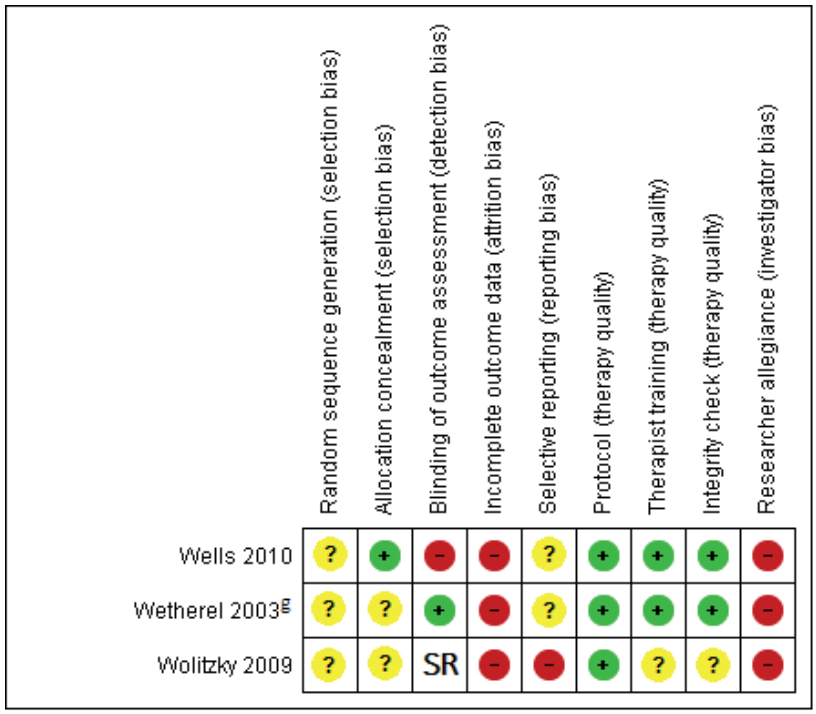


Note. N/A, not applicable due to internet or guided self-help format; SR, only self-report measures on follow-up.

[a] Assessors were not blind for MINI, SCID-I, FAS and FEICS outcomes.

[b] Allegiance to control group.

[c] External party (e.g., statistician or health center) or web-based data management system involved in random sequence generation.

[d] Blind broken in minority of participants.

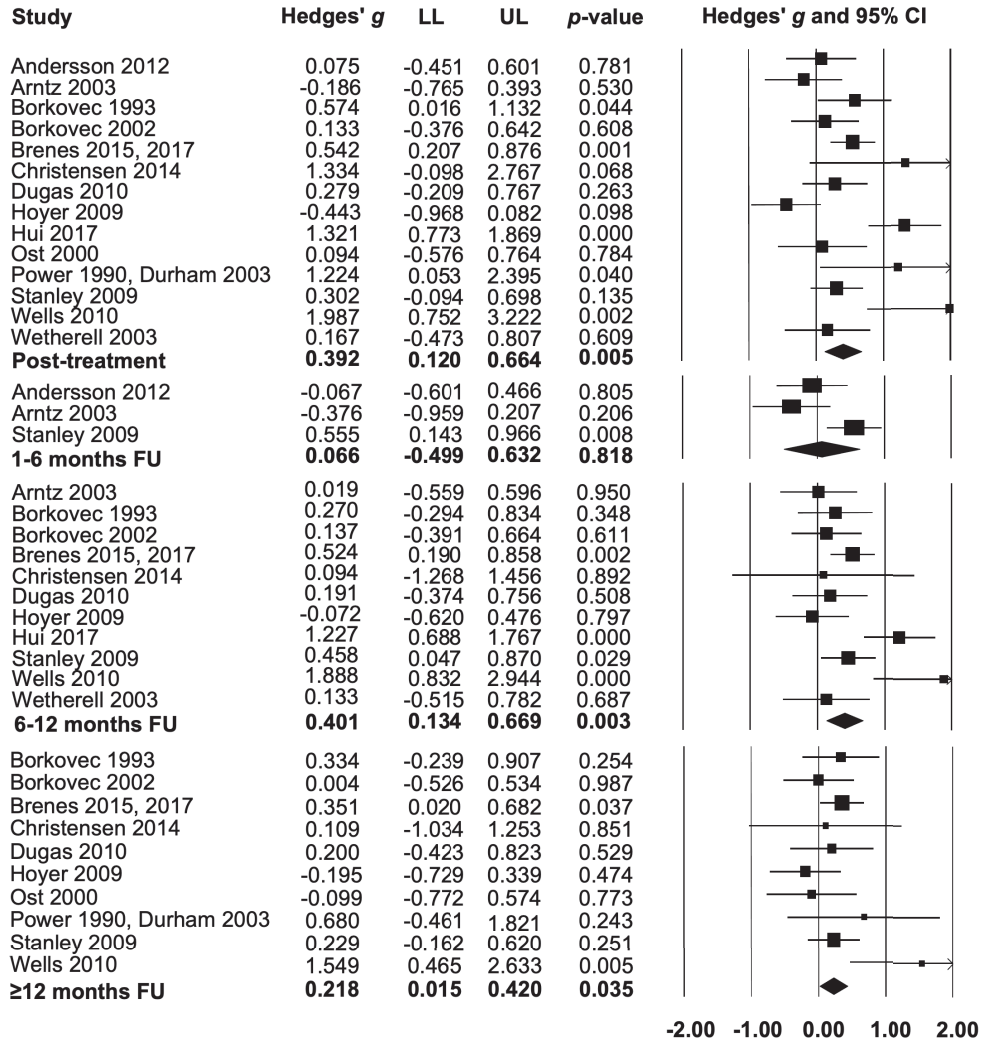
[e] Assessors were not blind for ADS and CIC outcomes.

[f] Therapist training for exposure condition unclear.

[g] Unclear whether all four therapists received training.

Figure S2

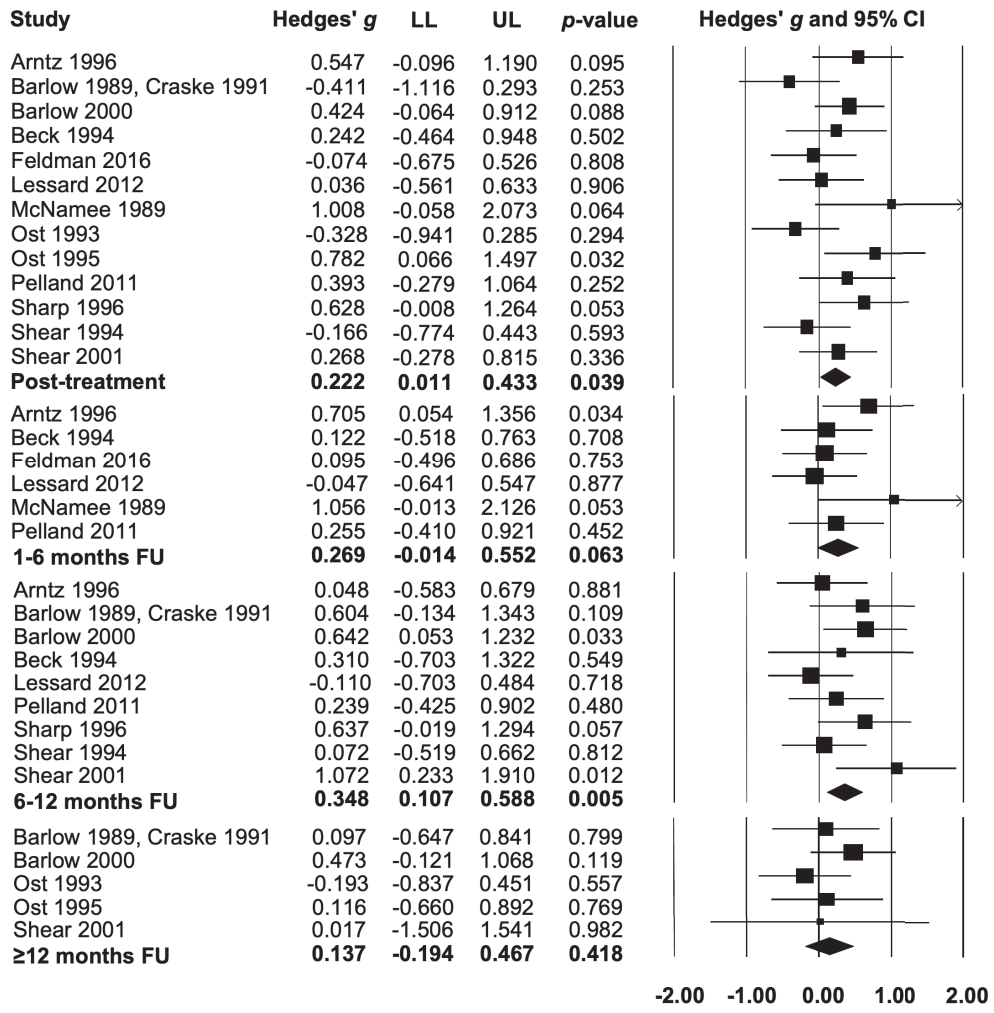
Standardized Effect Sizes of Comparisons Between CBT and Comparison Groups on Symptoms for Generalized Anxiety Disorder



Note. Higher effect sizes favor CBT. CBT = cognitive behavioral therapy; CI = confidence interval; FU= follow-up; LL = lower limit; UL = upper limit.

Figure S3

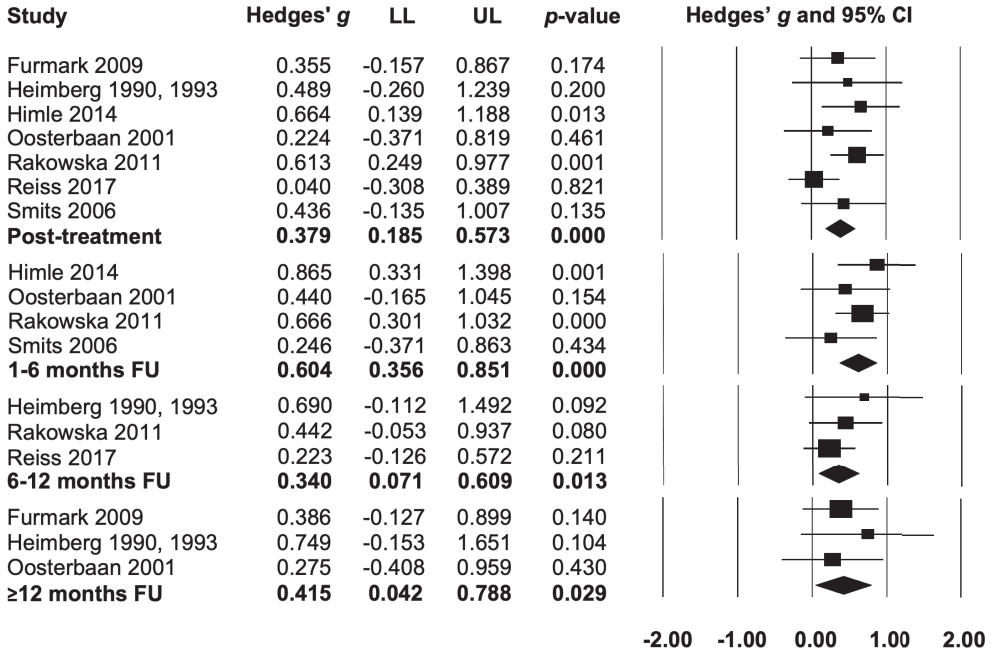
Standardized Effect Sizes of Comparisons Between CBT and Comparison Groups on Symptoms for Panic Disorder With or Without Agoraphobia



Note. Higher effect sizes favor CBT. CBT = cognitive behavioral therapy; CI = confidence interval; FU = follow-up; LL = lower limit; UL = upper limit.

Figure S4

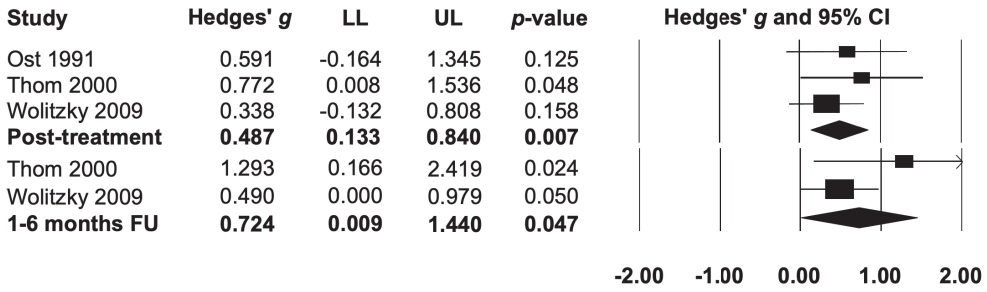
Standardized Effect Sizes of Comparisons Between CBT and Comparison Groups on Symptoms for Social Anxiety Disorder



Note. Higher effect sizes favor CBT. CBT = cognitive behavioral therapy; CI = confidence interval; FU = follow-up; LL = lower limit; UL = upper limit.

Figure S5

Standardized Effect Sizes of Comparisons Between CBT and Comparison Groups on Symptoms for Specific Phobia

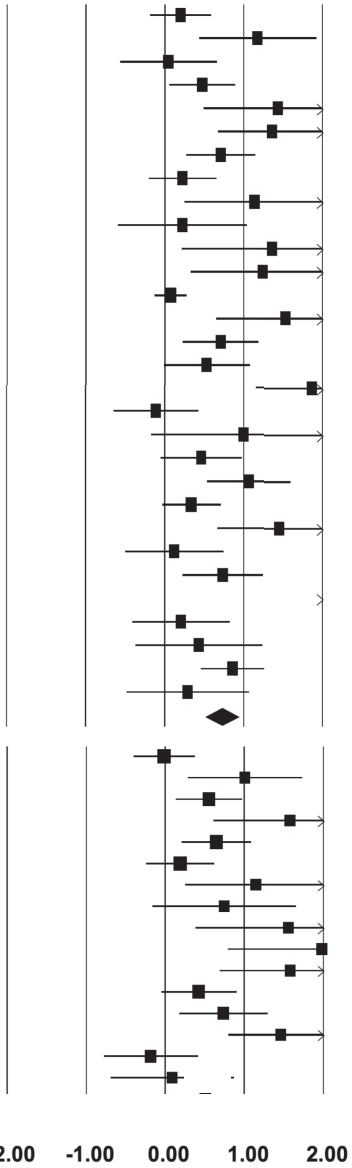


Note. Higher effect sizes favor CBT. CBT = cognitive behavioral therapy; CI = confidence interval; FU = follow-up; LL = lower limit; UL = upper limit.

Figure S6

Standardized Effect Sizes of Comparisons Between CBT and Comparison Groups on Symptoms for Posttraumatic Stress Disorder

Study	Hedges' *g*	LL	UL	*p*-value
Acosta 2017	0.204	-0.188	0.597	0.308
Basoglu 2007	1.181	0.430	1.931	0.002
Cottraux 2008	0.050	-0.569	0.670	0.874
Duhamel 2010	0.478	0.054	0.902	0.027
Echeburua 1997	1.439	0.488	2.389	0.003
Ehlers 2003	1.365	0.671	2.059	0.000
Ehlers 2014	0.713	0.268	1.159	0.002
Engel 2015	0.228	-0.209	0.664	0.307
Feske 2008	1.142	0.243	2.040	0.013
Foa 1991	0.225	-0.600	1.050	0.593
Franklin 2017	1.368	0.214	2.523	0.020
Gersons 2000	1.246	0.327	2.164	0.008
Hien 2009	0.076	-0.133	0.284	0.477
Hinton 2011	1.532	0.646	2.418	0.001
Johnson 2011	0.711	0.226	1.196	0.004
Johnson 2016	0.535	-0.016	1.085	0.057
Lewis 2017	1.867	1.152	2.583	0.000
Littleton 2016	-0.106	-0.650	0.437	0.701
Litz 2007	1.000	-0.175	2.175	0.095
Marks 1998	0.468	-0.051	0.987	0.077
Monson 2006	1.070	0.535	1.605	0.000
Mueser 2008	0.341	-0.036	0.719	0.076
Nacasch 2011	1.454	0.663	2.245	0.000
Neuner 2004	0.126	-0.502	0.754	0.694
Pacella 2012	0.738	0.225	1.252	0.005
Sloan 2012	4.177	2.797	5.557	0.000
Stenmark 2013	0.211	-0.409	0.830	0.505
Taylor 2003	0.436	-0.374	1.247	0.292
van den Berg 2015	0.862	0.455	1.270	0.000
Vaughan 1994	0.298	-0.484	1.080	0.455
Post-treatment	**0.723**	**0.516**	**0.930**	**0.000**
Acosta 2017	-0.013	-0.406	0.380	0.947
Basoglu 2007	1.010	0.278	1.741	0.007
Duhamel 2010	0.555	0.129	0.980	0.011
Echeburua 1997	1.579	0.607	2.551	0.001
Ehlers 2014	0.649	0.206	1.093	0.004
Engel 2015	0.193	-0.245	0.631	0.388
Feske 2008	1.151	0.251	2.050	0.012
Foa 1991	0.746	-0.168	1.661	0.110
Franklin 2017	1.558	0.378	2.738	0.010
Gersons 2000	1.982	0.788	3.175	0.001
Hinton 2011	1.581	0.689	2.474	0.001
Johnson 2011	0.427	-0.056	0.909	0.083
Johnson 2016	0.737	0.171	1.303	0.011
Lewis 2017	1.464	0.793	2.135	0.000
Littleton 2016	-0.180	-0.782	0.422	0.558
Litz 2007	0.091	-0.692	0.875	0.819



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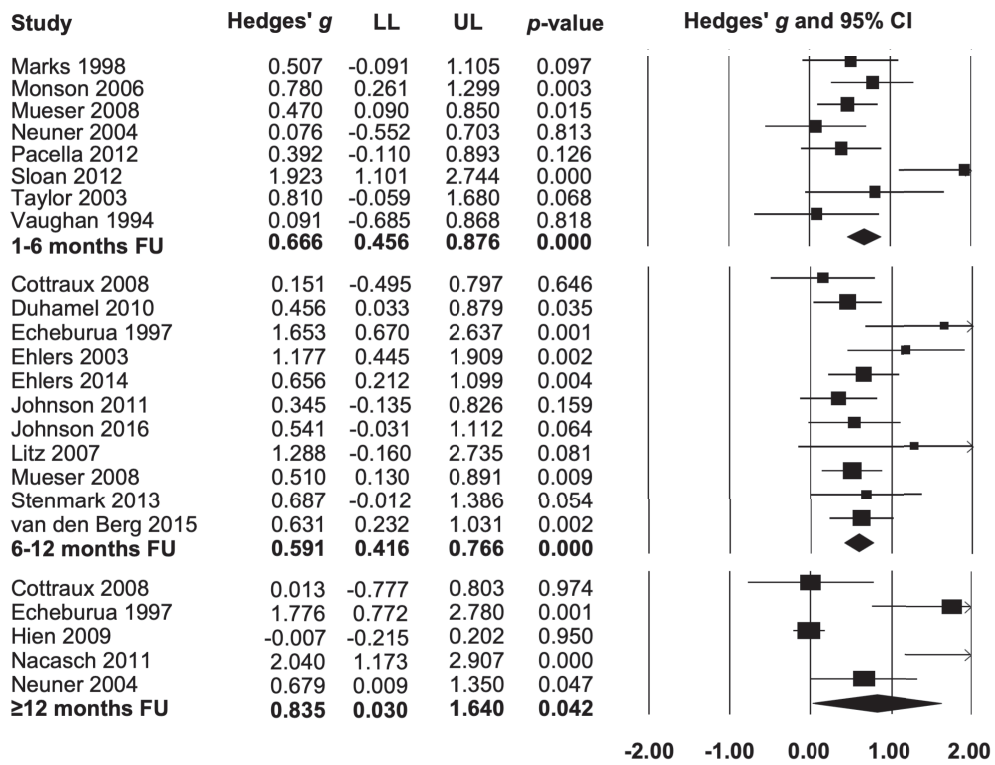
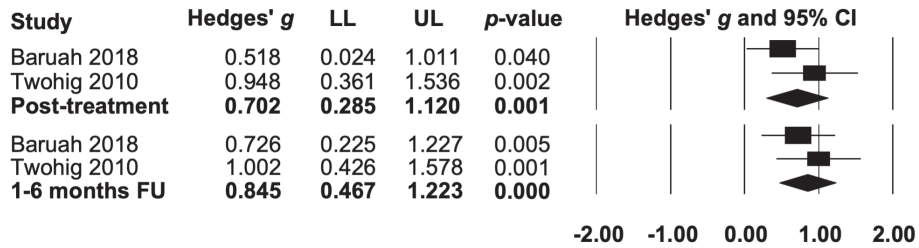


Note. Higher effect sizes favor CBT. CBT = cognitive behavioral therapy; CI = confidence interval; FU = follow-up; LL = lower limit; UL = upper limit.

Figure S7

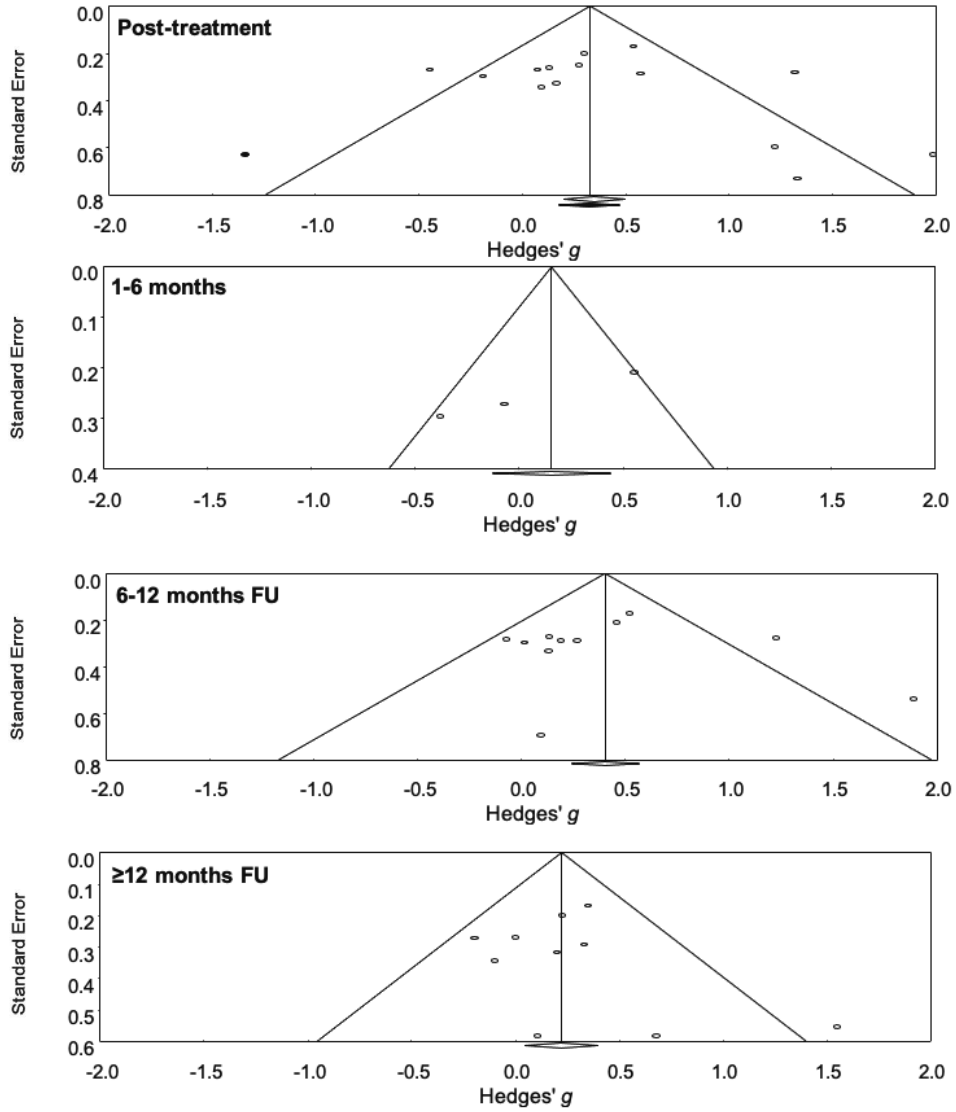
Standardized Effect Sizes of Comparisons Between CBT and Comparison Groups on Symptoms for Obsessive Compulsive Disorder



Note. Higher effect sizes favor CBT. CBT = cognitive behavioral therapy; CI = confidence interval; FU = follow-up; LL = lower limit; UL = upper limit.

Figure S8

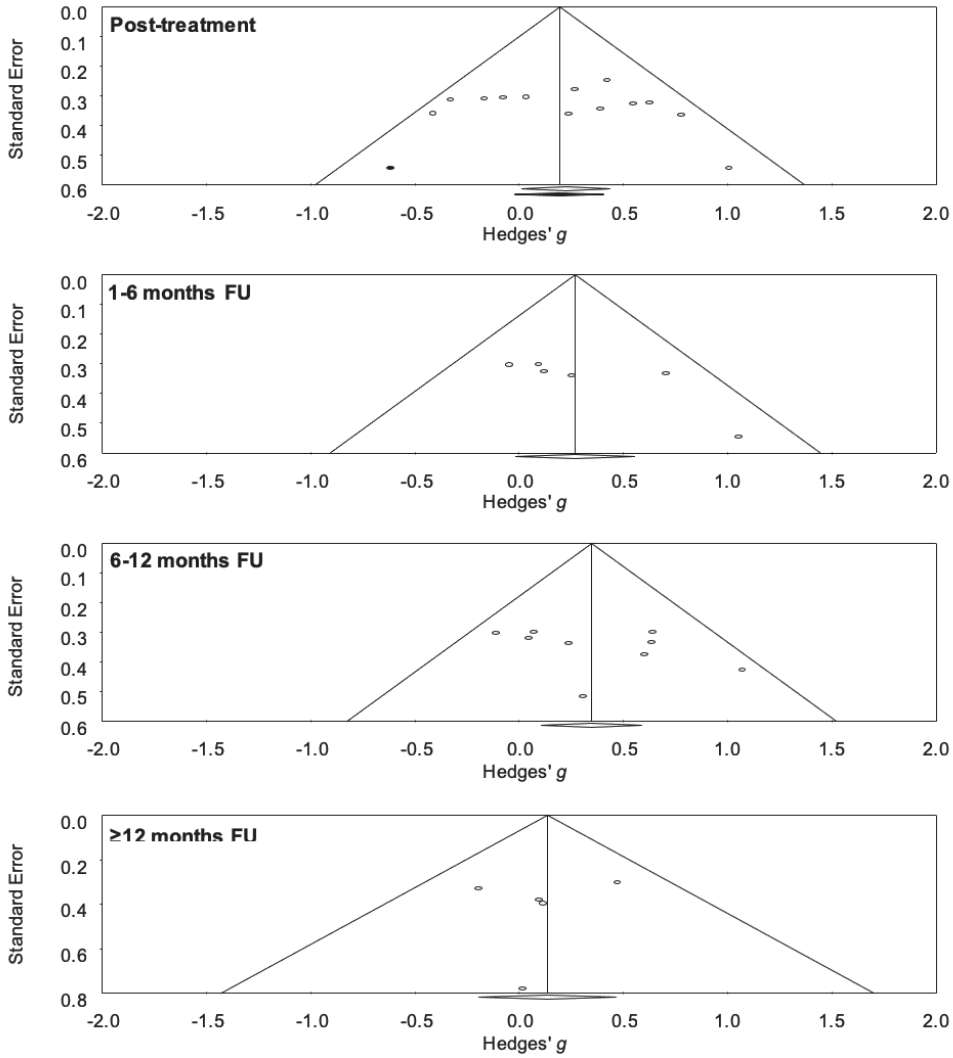
Funnel Plots of Standard Error by Hedges' G of Symptom Level After Cognitive Behavioral Therapy Relative to Comparison Groups for Generalized Anxiety Disorder



Note. Black dots are imputed studies using Duval and Tweedie's trim and fill procedure. FU = follow-up.

Figure S9

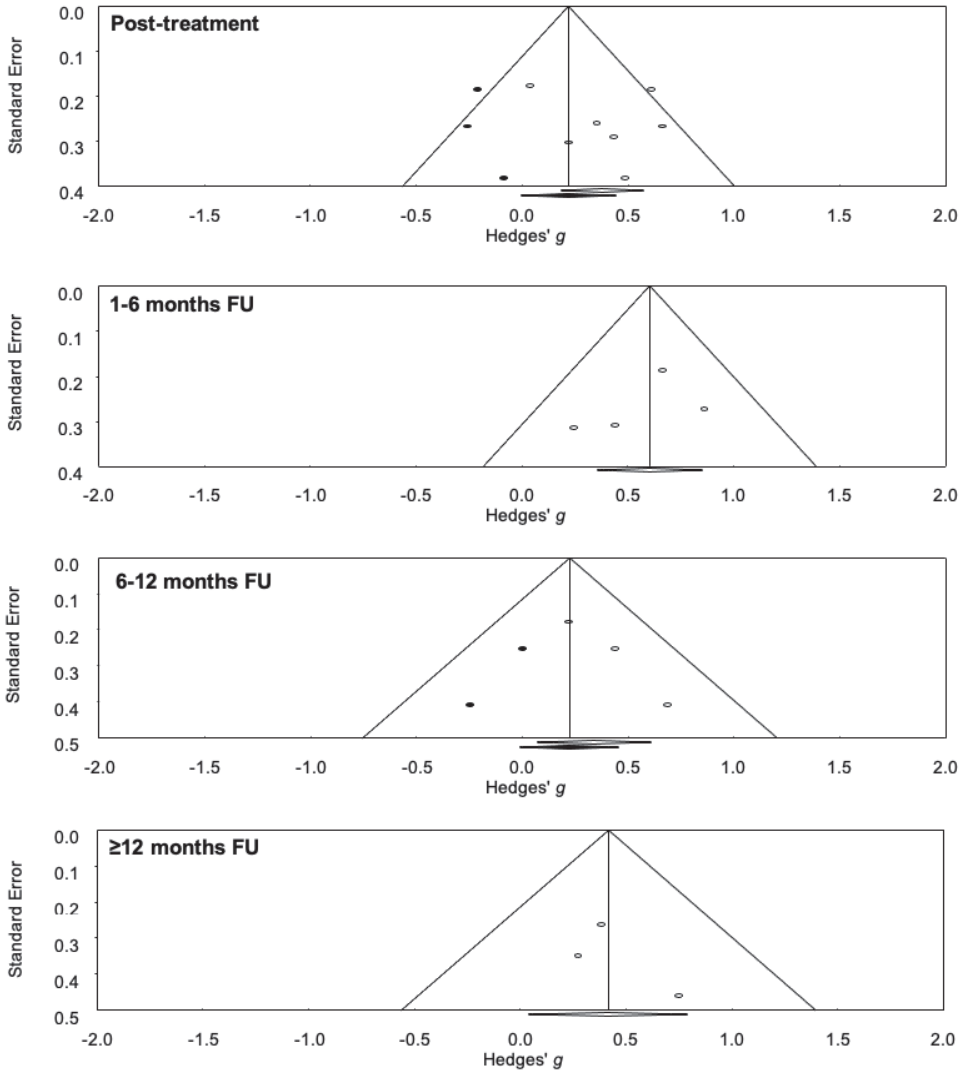
Funnel Plots of Standard Error by Hedges' G of Symptom Level After Cognitive Behavioral Therapy Relative to Comparison Groups for Panic Disorder With or Without Agoraphobia



Note. Black dots are imputed studies using Duval and Tweedie's trim and fill procedure. FU = follow-up.

Figure S10

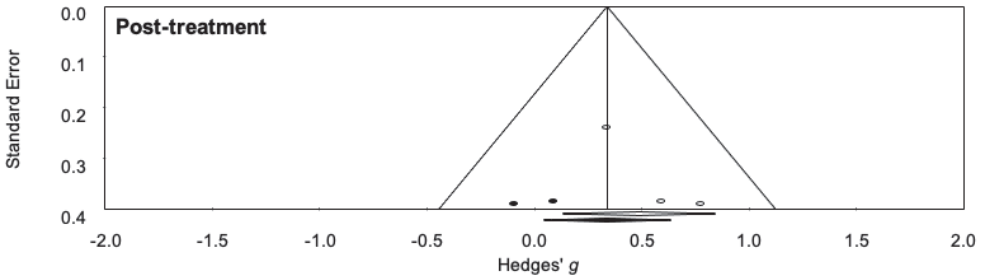
Funnel Plots of Standard Error by Hedges' G of Symptom Level After Cognitive Behavioral Therapy Relative to Comparison Groups for Social Anxiety Disorder



Note. Black dots are imputed studies using Duval and Tweedie's trim and fill procedure. FU = follow-up.

Figure S11

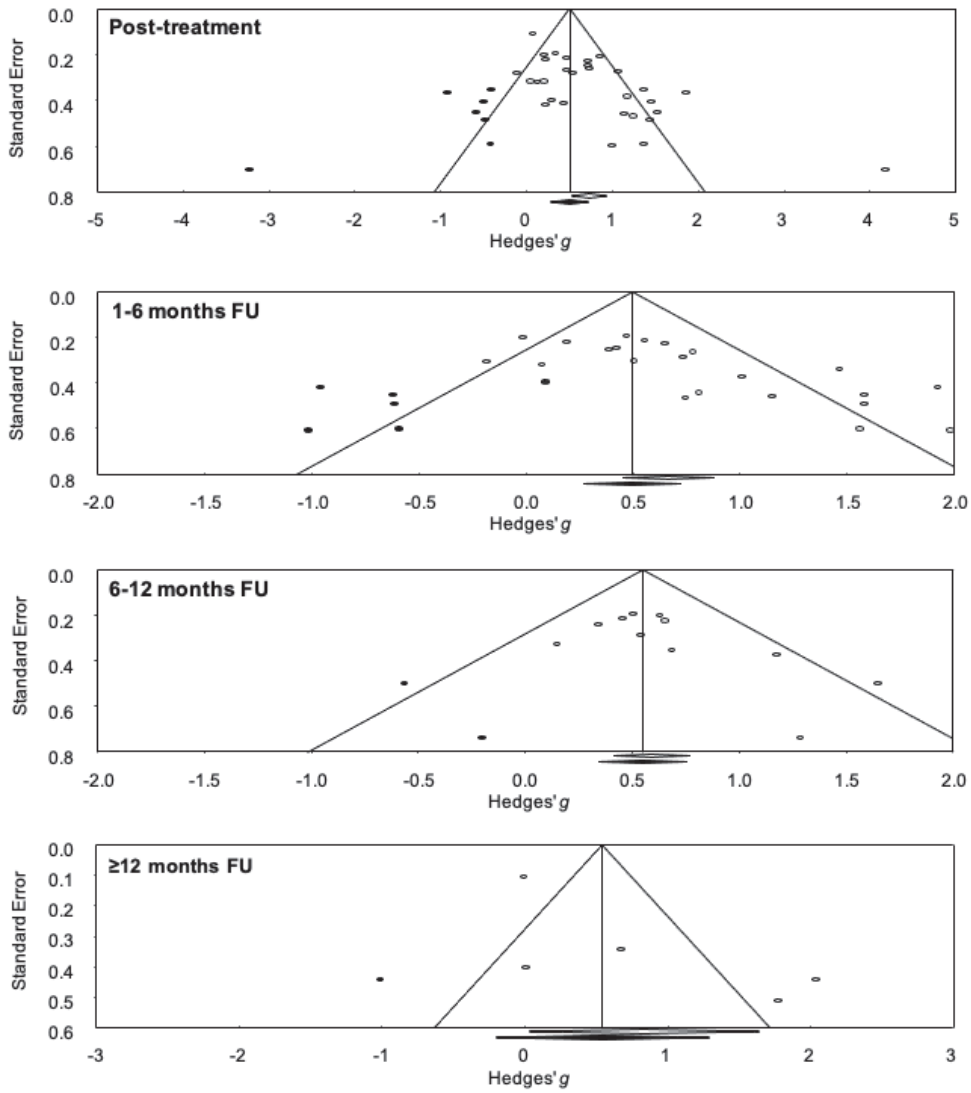
Funnel Plots of Standard Error by Hedges' G of Symptom Level After Cognitive Behavioral Therapy Relative to Comparison Groups for Specific Phobia



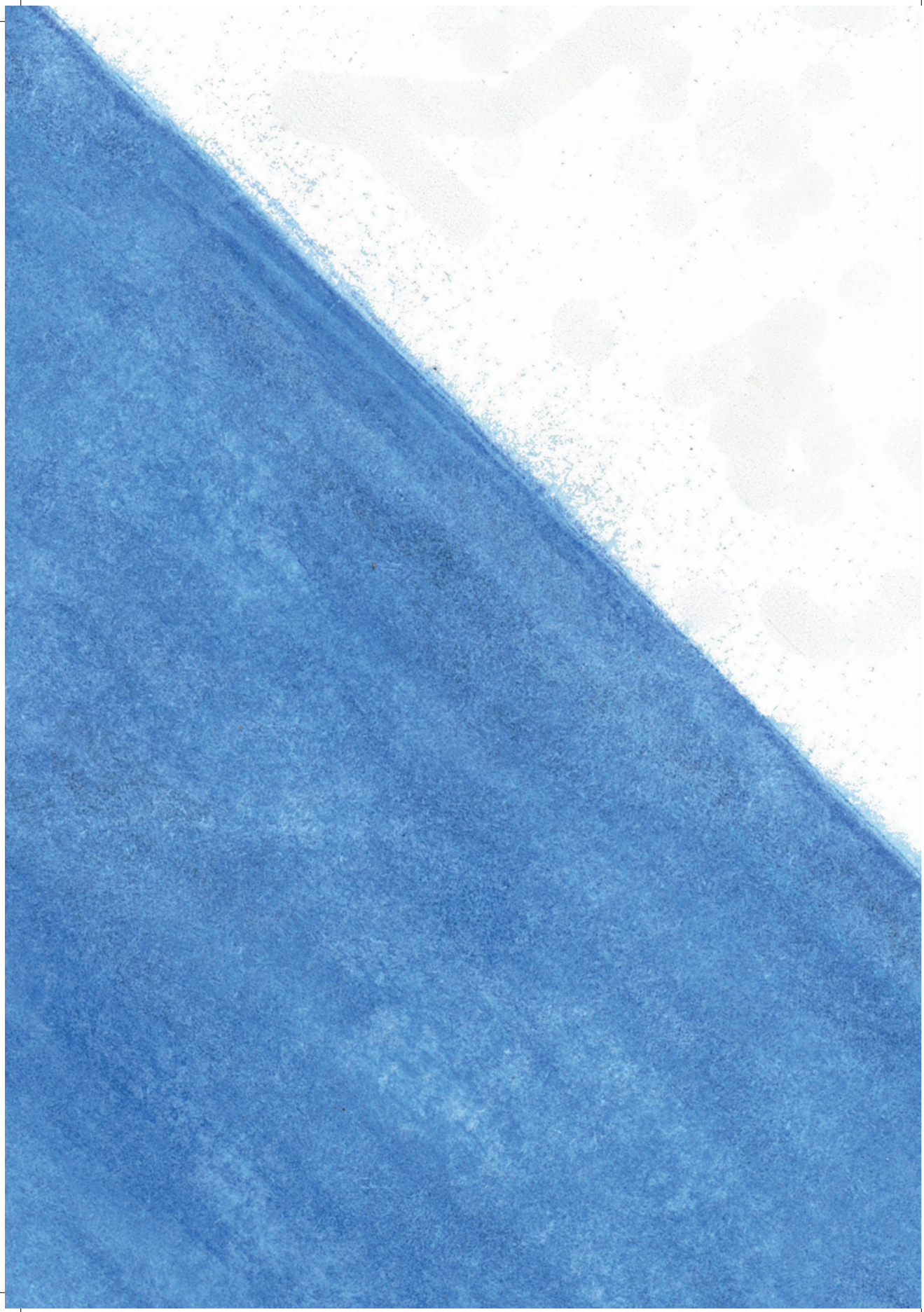
Note. Black dots are imputed studies using Duval and Tweedie's trim and fill procedure. FU = follow-up.

Figure S12

Funnel Plots of Standard Error by Hedges' G of Symptom Level After Cognitive Behavioral Therapy Relative to Comparison Groups for Posttraumatic Stress Disorder



Note. Black dots are imputed studies using Duval and Tweedie's trim and fill procedure. FU = follow-up.



Chapter 5

Reducing negative stimulus valence does not attenuate the return of fear: Two counterconditioning experiments

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Abstract

Exposure-based treatment for anxiety disorders is effective for many patients, but relapse is not uncommon. One predictor of the return of fear is the negative valence of fear-relevant stimuli. The aim of the current experiments was to examine whether counterconditioning with positive film clips reduces this negative stimulus valence as well as the return of fear, compared to standard extinction training and to an extinction training with non-contingent exposure to the positive film clips. Participants were 87 students in Experiment 1 (three-day paradigm) and 90 students in Experiment 2 (one-day paradigm). They first underwent a differential acquisition phase, in which one of three pictures was paired with an electric shock. They were then randomly allocated to one of the three intervention groups. Afterward, they underwent a test phase in which pictures were presented without shock (to measure spontaneous recovery of fear), which was followed by unsignaled shocks to induce reinstatement of extinguished fear. Outcome variables were self-reported stimulus valence, shock expectancy, skin conductance, and fear-potentiated startle. In both experiments, counterconditioning decreased negative stimulus valence relative to the other interventions, but it did not reduce spontaneous fear recovery or fear reinstatement. Overall, our findings do not support the notion that counterconditioning reduces return of fear.

Keywords: counterconditioning; evaluative conditioning; return of fear; fear extinction; positive valence training

Introduction

Anxiety disorders are among the leading causes of the global burden of disease attributable to mental disorders (Whiteford et al., 2013). The gold-standard treatment is exposure-based therapy (Olatunji et al., 2010), in which patients are exposed to fear-relevant, innocuous stimuli or situations to disconfirm their threat expectancy (Craske et al., 2014). Although the treatment is initially effective for many patients (e.g., Cuijpers et al., 2016; Hofmann & Smits, 2008), relapse rates of about 19% to 62% have been reported (Vervliet et al., 2013).

Lab studies using fear conditioning paradigms have examined factors involved in the return of fear. These paradigms typically begin with an acquisition phase in which one neutral stimulus, such as a picture, is repeatedly followed by a negative unconditioned stimulus (US_{neg}), such as a mild electric shock, and another neutral image is not. This usually results in shock expectancy and fear reactions to the first picture, which now serves as the conditioned stimulus (CS). In a subsequent extinction phase (the laboratory analog of exposure therapy), the CS is repeatedly presented without the US_{neg}. This generally extinguishes fear. Extinguished fear can return after the passage of time (i.e., spontaneous recovery), a context switch, or non-signaled US_{neg} presentations (i.e., reinstatement; see Bouton, 2002, and Vervliet et al., 2013).

The return of fear is associated with the person's negative attitude towards fear-relevant stimuli after extinction. This was found in de novo fear conditioning studies (e.g., Dirikx et al., 2004, 2007; Zbozinek, Hermans, et al., 2015) and in subclinical studies (e.g., Huijding & De Jong, 2009; Vasey et al., 2012). This suggests that interventions that decrease negative stimulus valence may reduce the return of fear. Several experiments have examined the effects of positive valence training on the return of fear. First, Zbozinek, Holmes, and Craske (2015) found that positive imagery before extinction training, compared to positive verbal training prior to extinction, reduced negative stimulus valence and reinstatement of fear. However, as suggested by Zbozinek and Craske (2017), increased positive affect during extinction may also have enhanced extinction learning, thereby reducing the return of fear. Therefore, it is unclear whether reduced negative stimulus valence resulted in reduced reinstatement. Second, Dour and colleagues (2016) showed that positive valence training during exposure for spider fear resulted in less negative stimulus valence, less spontaneous recovery of spider fear, and less behavioral avoidance after a reinstatement manipulation. However, the positive valence training group received more exposure to spiders than the control group. Third, a recent fear conditioning study demonstrated that positive, relative to neutral, verbal information

reduced negative stimulus valence but did not attenuate reinstatement (Luck & Lipp, 2018; Exp 2). Fourth, another study used counterconditioning as positive valence training (Kang et al., 2018), in which the CS is paired with a positive US (see De Houwer et al., 2001). Lab experiments have shown that counterconditioning reduces negative stimulus valence (e.g., Engelhard et al., 2014; Kerkhof et al., 2011; Raes & De Raedt, 2012). Kang et al. (2018) found that, compared to extinction training, counterconditioning attenuated the return of fear, which was measured with threat expectancy. Unexpectedly, the groups did not differ in negative stimulus valence, perhaps because the positive US (comic pictures) was not potent enough to affect evaluative learning. Given the mixed results of these studies, more controlled research is needed before positive valence training is implemented in clinical practice to reduce return of fear.

The aim of the current research was to examine whether positive valence training through counterconditioning attenuates the return of fear (while controlling for positive affect and amount of exposure). Participants underwent fear acquisition and were then randomly allocated to one of three groups: counterconditioning (in which the CS was paired with positive film clips, which can be more potent than static images; Rottenberg et al., 2007)(Rottenberg et al., 2007), extinction training, or extinction training with unpaired presentations of positive film clips (to control for positive affect induced by the film clips). We expected that counterconditioning, compared to the other interventions, would reduce post-intervention negative stimulus valence (hypothesis 1) and return of fear (i.e., spontaneous fear recovery and reinstatement; hypothesis 2).

Experiment 1

We used a three-day fear conditioning paradigm, over a period of nine days, with the following phases: Acquisition (Day 1), Intervention (Day 2), Spontaneous Recovery, and Reinstatement (Day 9).

Methods

Participants

One hundred one native Dutch-speaking students aged between 18 and 30 were recruited via Utrecht University, Facebook, and Proefbunny.nl. The exclusion criteria were: self-reported current psychiatric diagnosis, history of heart or epileptic problems, oversensitivity to loud noises, pregnancy, psychoactive medication use, and fear of dogs (see Stimuli below). Six participants were excluded because of unsuccessful fear

acquisition (*n* = 3), negatively rating the positive film clips (*n* = 2), and misunderstanding how to use the US_{neg} expectancy scale (*n* = 1). Five additional participants dropped out: two because of the experimenter falling ill, two because they found the shock/startle probe too unpleasant, and one was a no-show on Day 3. The final sample size comprised 87 participants (72 females and 25 males; mean age = 21.39, *SD* = 2.48) that were randomly assigned to conditions (stratified for gender). This study was approved by the ethics committee of the Faculty of Social and Behavioural Sciences at Utrecht University (FETC16-054) and was preregistered on the Open Science Framework (https://osf.io/bvfx8/).

Stimuli

One CS+ and two CSs- depicted three neutral faces derived from the Chicago Faces Database (Ma et al., 2015) that were presented for 8 s (see below). To enhance stimulus differentiation, the CS+ was a picture of a male face, and the CSs- were pictures of female faces (or vice versa). The stimuli were fully counterbalanced across participants.

The negative US (US_{neg}) was a 2-ms electric shock that was delivered by a Digitimer DS7A through an electrode band that was attached to the wrist of the dominant arm. On Day 1, participants determined a "really annoying, but not painful" shock intensity during a standard work-up procedure (as described by Orr et al., 2000).

The positive US (US_{pos}) consisted of eight different 6-s funny film clips in which a baby laughs at a dog that is trying to catch soap bubbles from the air. The fragments were derived from a 59-s YouTube video (see Jess0rT, 2011).

Measures

Eysenck Personality Questionnaire (EPQ). Neuroticism was measured with the Dutch translation of the Neuroticism scale of the Eysenck Personality Questionnaire (EPQ-N; Sanderman et al., 1991, 2012). It consists of 22 self-report items (e.g., "Are you often troubled about feelings of guilt?") that are rated on a dichotomous scale (0 = *no*, 1 = *yes*). Cronbach's α was .82 in the present study.

US_{neg} Unpleasantness and Expectancy. US_{neg} unpleasantness was rated on an 11-point scale, ranging from 0 (*not unpleasant at all*) to 10 (*very unpleasant*). US_{neg} expectancy was rated with a visual analog scale (VAS) with three anchors: 0 (*certainly no shock*), 50 (*uncertain*), and 100 (*certainly a shock*).

US_{pos} Valence. US_{pos} valence was rated on an 11-point scale, ranging from 0 (*negative*) to 10 (*positive*).

CS Valence, Arousal, and Fear. For each CS rating, the CS was presented on a white background to enhance differentiation between the rating contexts and experimental trials. CS valence ("How negative or positive do you find this picture?") and arousal ("How arousing do you find this picture?") were rated using the Self-Assessment Manikin scale (Bradley & Lang, 1994), ranging from 1 (*negative/not arousing*) to 9 (*positive/arousing*). Fear (i.e., "How fearful are you when seeing this picture?") was rated on a 10-point Likert-scale, ranging from 1 (*not fearful at all*) to 9 (*very fearful*).[1]

Affect Rating. Affect ("How do you feel at this moment?") was rated on a VAS ranging from 0 (*unpleasant*) to 100 (*pleasant*).

Physiological Measures. BioSemi hardware unit and ActiView 7.06 were used to acquire physiological data at a 2048 Hz sampling rate. Two 4-mm Ag-AgCl CMS/DRL electrodes were positioned on the forehead and served as a reference for all physiological measurements.

Skin Conductance Response (SCR). Skin conductance was recorded using two 8-mm passive Nihon Kohden electrodes that were attached to the index and middle fingers of the left hand (all participants were right-handed). SCR was calculated by subtracting the baseline (mean activity during 2 s immediately prior to CS onset) from the peak skin conductance activity between 1 to 7 s after CS onset (Pineles et al., 2009). Negative values and values smaller than 0.01 μS were recoded to 0. We applied a *z*-transformation of each raw SCR across all phases to account for inter-individual variance (as recommended by Lonsdorf et al., 2017).

Fear-Potentiated Startle (FPS). Orbicularis oculi activity was recorded using two 4-mm Ag/AgCl electrodes placed under the left eye (see Blumenthal et al., 2005). FPS was calculated as the difference score between the peak (21 to 150 ms after startle probe onset) from the baseline (mean activity during 50 ms, starting from 30 ms before startle probe onset). We applied an intra-individual *z*-transformation across all phases of the raw FPS data (see Blumenthal et al., 2005)

Post-Auricular Reflex. The post-auricular reflex is an implicit, psychophysiological measure of valence (Benning et al., 2004). It was measured only to explore its value for future studies, but there was no differential responding to CSs during the acquisition phase. Therefore, it is not mentioned further.

Trial Procedure

The trial procedure is largely based on Zbozinek, Holmes, et al. (2015). Each trial began

[1] Results on self-reported arousal and fear are reported in the Supplementary Materials.

with an 8s CS presentation (in the middle of the computer screen on a black background). During the first 6 s, participants rated US_{neg} expectancy. Startle probes (50 ms bursts of white noise at 95 dB) were presented 7 s after CS onset.

During the acquisition phase, the US_{neg} was presented 7.5 s after CS onset during all CS+ presentations. In all phases, CSs were presented in a pseudorandom order (with a maximum of two consecutive CS presentations per phase). Trials ended with a 6 s presentation of a black screen (or a 6 s presentation of US_{pos}, see below). The inter-trial interval (ITI) was a black screen with a white fixation cross that appeared for 15, 20, or 25 s (counterbalanced). Noise alone (NA) trials followed one out of three trials (counterbalanced) to measure baseline startle responding.

General Procedure and Intervention

Table 1 shows the general procedure. On Day 1, participants provided written informed consent. Then they washed their hands without soap, were connected to physiological and shock electrodes, and began the shock work-up procedure. Next, they rated the unpleasantness of the US_{neg} and completed the EPQ-N. Then, they started the Habituation phase, consisting of 6 trials (in which they practiced rating the US_{neg} expectancy scale) and 10 startle probes. Participants then completed CS and affect ratings. Thereafter, the Acquisition phase started, in which each CS was presented 8 times. The CS+ was always paired with US_{neg}, whereas CS1- and CS2- were not. Finally, participants rated CS valence and affect again.

On Day 2, participants were reconnected to physiological and shock electrodes and received 10 startle probes to habituate. They filled out the CS and affect ratings and continued with the intervention phase, in which each CS was presented 8 times and was never followed by the US_{neg}. Reinforcement differed for the groups. In the counterconditioning group (CC), the CS+ was always followed by $US_{pos.}$, in the extinction group (EXT), there was no reinforcement, and in the extinction with positive material group (EXT+), CS2- was always followed by US_{pos}. Participants then rated the CS and affect scales.

On Day 9, participants were again reconnected to physiological and shock electrodes and received 10 startle probes to habituate. After completing the CS and affect ratings, they continued with a spontaneous recovery phase in which each CS was presented twice without reinforcement (see Zbozinek, Holmes, et al., 2015). Participants then completed CS and affect ratings again. Next, they received three non-signaled shocks (same intensity as Day 1) with 15 and 20 s inter-stimulus intervals (fixed order). They continued with a

reinstatement test phase in which each CS was presented twice without reinforcement (Kang et al., 2018; Zbozinek, Holmes, et al., 2015). Participants then completed the CS, affect, and US_{pos} ratings. Finally, they were debriefed and received €20 or course credit.

Data Preparation

Due to technical problems, data were missing completely at random (MCAR; van Buuren, 2012) for SCR, FPS (n = 9), and neuroticism scores (EPQ-N) (n = 27). Multiple imputation techniques were not applied due to an unconnected file matching missing data pattern (e.g., missing data for SCR and FPS during Day 1 and 2, but not for Day 9).

Data Analysis

First, to test whether randomization was successful, one-way ANOVAs were performed on age, neuroticism scores, shock level, US_{neg} unpleasantness, and affect. Second, to examine whether fear acquisition and extinction took place for US_{neg} expectancy, FPS, and SCR, we used three 3 (Stimulus: CS+, CS1-, CS2-) × 8 (Time: all acquisition or intervention trials) × 3 (Group: CC, EXT, EXT+) mixed ANOVAs. Third, to test whether CC and EXT+ groups had higher affect ratings compared to EXT following the Intervention phase, a 2 (Time: pre-intervention, post-intervention) × 3 (Group: CC, EXT, EXT+) mixed ANOVA was used.

To test the first hypothesis on post-intervention group differences in CS valence, a 3 (Stimulus: CS+, CS1-, CS2-) × 2 (Time: pre-intervention, post-intervention) × 3 (Group: CC, EXT, EXT+) mixed ANOVA was conducted. To test the second hypothesis on group differences in spontaneous recovery and reinstatement, separate 3 (Stimulus: CS+, CS1-, CS2-) × 2 (Time: last Intervention trial, first Spontaneous recovery trial; *or* last Spontaneous recovery trial, first Reinstatement trial) × 3 (Group: CC, EXT, EXT+) ANOVAs were used for US_{neg} expectancy, SCR, and FPS. In case sphericity assumptions were not met, we applied Huynh-Feldt ($\varepsilon > .75$) or Greenhouse-Geisser ($\varepsilon < .75$) corrections.

Results

Randomization Checks

Groups did not significantly differ in age, neuroticism scores, shock level, US_{neg} unpleasantness, or baseline affect (all $Fs < 2.14$, all $ps > .123$), which suggests that randomization was successful. Evaluations of positive film clips also did not significantly differ between the CC (M = 8.28, SD = 1.14) and EXT+ (M = 8.44, SD = 1.42) groups, $t(50) < 1$, $p = .649$.

Table 1
Overview of Design in Experiment 1

Group	Day 1		Day 2		Day 9	
	Habituation	**Acquisition**	**Intervention**	**Spontaneous recovery**	**Reinstatement**	**Test**
CC	CS+ (2)	CS+ / US_{neg} (8)	CS+ / US_{pos} (8)	CS+ (2)	US_{neg} (3)	CS+ (2)
	CS1- (2)	CS1- (8)	CS1- (8)	CS1- (2)		CS1- (2)
	CS2- (2)	CS2- (8)	CS2- (8)	CS2- (2)		CS2- (2)
EXT	CS+ (2)	CS+ / US_{neg} (8)	CS+ (8)	CS+ (2)	US_{neg} (3)	CS+ (2)
	CS1- (2)	CS1- (8)	CS1- (8)	CS1- (2)		CS1- (2)
	CS2- (2)	CS2- (8)	CS2- (8)	CS2- (2)		CS2- (2))
EXT+	CS+ (2)	CS+ / US_{neg} (8)	CS+ (8)	CS+ (2)	US_{neg} (3)	CS+ (2)
	CS1- (2)	CS1- (8)	CS1- (8)	CS1- (2)		CS1- (2)
	CS2- (2)	CS2- (8)	CS2- / US_{pos} (8)	CS2- (2)		CS2- (2)

Note. CC = counterconditioning; CS = conditioned stimulus; EXT = extinction; EXT+ = extinction and positive material; US_{neg} = negative unconditioned stimulus.

Acquisition Phase

Acquisition (Stimulus × Time) was reflected by increases in US_{neg} expectancy, SCR, and FPS, with stronger responses to the CS+ over time compared to both CSs- (Stimulus × Time: all *F*s > 4.06, *p*s < .001, simple effects: all *t*s > 2.64, *p*s < .011), see Figure 1. From pre to post acquisition, CS negative valence increased for CS+, but not for CSs-, Stimulus × Time: $F(1.69, 141.72) = 53.58$, $p < .001$, simple effects: $t(86) = 8.67$, $p < .001$, see Table 2. There were no three-way interactions with Group (all *F*s < 1.21, all *p*s > .245).

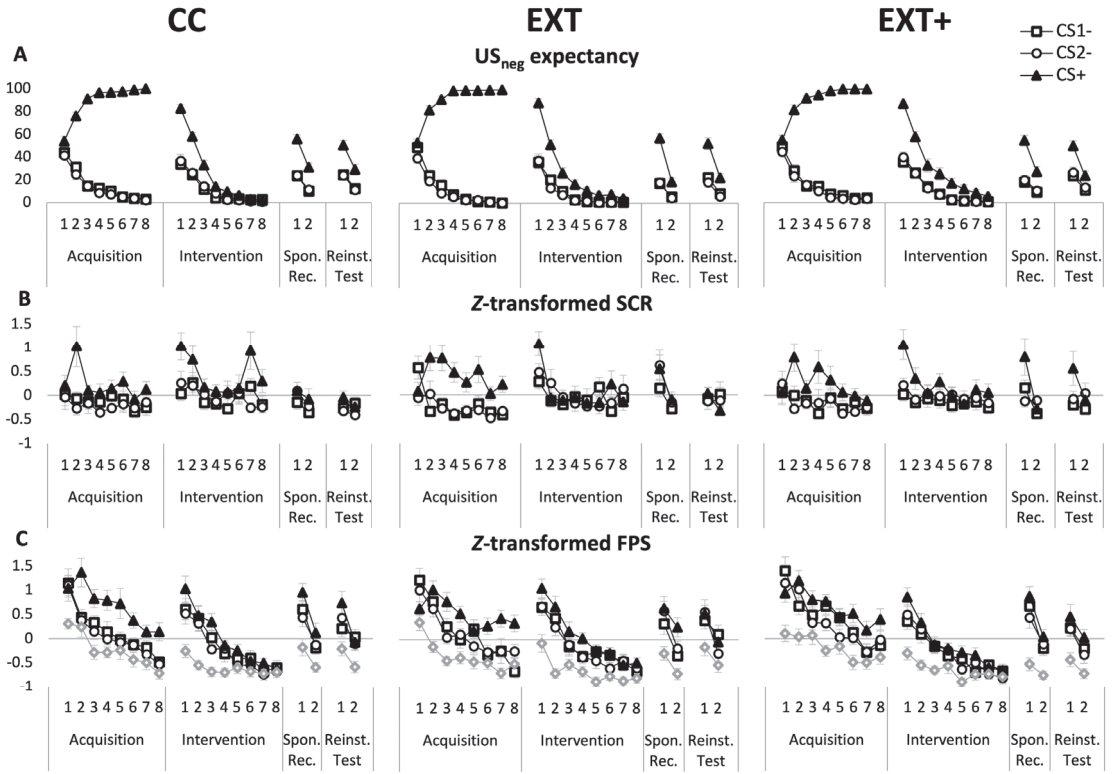
Intervention Phase

US_{neg} expectancy and SCR decreased during the intervention phase, with larger decreases for the CS+ compared to both CSs- (Stimulus × Time: both *F*s > 3.45, *p*s < .001; simple effects: both *t*s > 2.22, *p*s < .030). There was no significant Stimulus × Time interaction for FPS, $F(12.48, 1047.88) < 1$, $p = .487$, but there was a main effect for Time, $F(4.36, 366.27) = 80.45$, $p < .001$, which reflects decreased responding during the intervention phase, and there was a main effect for Stimulus, $F(2, 168) = 15.78$, $p < .001$. There were no significant three-way interactions with Group (all *F*s < 1, all *p*s > .690).

For the affect ratings, there was a trend for a Time (pre, post intervention) × Group interaction, $F(2, 84) = 2.45$, $p = .092$, $\eta_p^2 = .06$. Post-hoc analyses showed that the intervention phase increased positive affect for the CC group ($M = 74.45$, $SD = 13.98$), $t(28) = 2.62$, $p = .014$, and the EXT+ group ($M = 71.52$, $SD = 18.98$), $t(28) = 2.22$, $p = .035$, but not for the EXT group ($M = 64.28$, $SD = 20.99$), $t(28) < 1$, $p = .596$ (see Table 2). The increase in positive affect did not differ between the CC and EXT+ groups, $t(56) < 1$, $p = .585$. Before the Intervention phase, affect ratings did not differ across groups, $F(2, 84) < 1$, $p = .837$, $\eta_p^2 = .00$, but there was a non-significant trend for a Group effect afterwards, $F(2, 84) = 2.39$, $p = .097$, $\eta_p^2 = .05$.

Figure 1

US_{neg} Expectancy, Z-Transformed Skin Conductance Response (SCR), and Fear-Potentiated Startle (FPS) Across Phases and Groups in Experiment 1



Note. CC = counterconditioning; CS = conditioned stimulus; EXT = extinction; EXT+ = extinction and positive material; Spon. Rec. = Spontaneous Recovery; Reinst. = Reinstatement; US_{neg} = negative unconditioned stimulus. Error bars represent the standard error of the mean. Grey diamonds indicate FPS during noise alone trials.

Table 2

Means (Standard Deviations) of CS Valence and Affect Ratings in Experiment 1

		Acquisition		Intervention		Spontaneous Recovery		Reinstatement
		Pre	Post	Pre	Post	Pre	Post	Post
CC	CS+	4.97 (1.43)	3.21 (1.82)	3.79 (1.37)	5.93 (1.33)	5.76 (1.15)	5.76 (1.09)	5.07 (1.16)
	CS1-	4.66 (1.61)	5.41 (1.62)	5.62 (1.21)	5.52 (1.30)	5.38 (1.05)	5.31 (1.23)	4.55 (1.48)
	CS2-	4.83 (1.65)	5.52 (1.60)	5.31 (1.51)	5.72 (1.46)	5.64 (1.37)	5.86 (1.21)	5.43 (1.20)
	Affect	68.79 (16.17)	58.52 (15.77)	68.83 (17.92)	74.45 (13.98)	72.79 (17.95)	74.79 (16.85)	68.38 (17.34)
EXT	CS+	5.24 (1.81)	2.79 (1.76)	3.69 (1.39)	4.97 (1.12)	5.62 (1.40)	6.03 (1.18)	4.72 (1.18)
	CS1-	5.10 (1.61)	5.79 (1.78)	5.66 (1.32)	6.03 (1.30)	5.45 (1.39)	5.66 (1.29)	4.28 (1.31)
	CS2-	5.38 (1.45)	6.14 (1.53)	6.00 (1.49)	6.07 (1.49)	5.79 (1.29)	5.97 (1.21)	4.83 (1.34)
	Affect	60.52 (18.21)	49.93 (20.35)	66.00 (19.81)	64.28 (20.99)	73.38 (18.88)	73.93 (19.95)	65.15 (21.93)
EXT+	CS+	5.00 (1.67)	3.10 (1.52)	3.76 (1.53)	5.00 (1.22)	5.83 (1.20)	6.03 (1.38)	5.10 (1.37)
	CS1-	4.69 (1.61)	5.69 (1.77)	5.79 (1.54)	5.83 (1.73)	5.66 (1.47)	6.14 (1.27)	4.52 (1.30)
	CS2-	5.21 (1.26)	6.03 (1.32)	5.72 (1.58)	6.14 (1.92)	5.89 (1.63)	5.85 (1.35)	4.93 (1.69)
	Affect	60.48 (18.36)	52.24 (18.23)	67.45 (16.26)	71.52 (18.98)	73.83 (17.98)	78.07 (17.67)	65.96 (21.48)

Note. CC = counterconditioning; CS = conditioned stimulus; EXT = extinction; EXT+ = extinction and positive material.

Hypothesis 1: More Positive CS+ Valence After CC, Compared to EXT and EXT+

There was a Stimulus × Time × Group interaction for CS valence, $F(3.55, 149.08) < 1$, $p = .035$, $\eta_p^2 = .06$. The Stimulus × Group interaction was not significant before the intervention, $F(4, 168) < 1$, $p = .523$, $\eta_p^2 = .02$, but it was significant afterwards, $F(4, 168) = 4.69$, $p = .002$, $\eta_p^2 = .10$. Post-hoc analyses with Bonferroni corrections revealed that after the intervention, CS+ valence was more positive in the CC group compared to both control groups ($ps < .015$), and did not differ between the EXT and EXT+ groups ($p = .999$). These results support the hypothesis that negative CS+ valence was more strongly reduced in the CC group relative to the EXT and EXT+ groups, see Table 2. However, on Day 9, the Stimulus × Group effect was no longer significant, $F(4, 162) < 1$, $p = .850$, $\eta_p^2 = .01$.

Hypothesis 2a: Less Spontaneous Recovery in CC Relative to EXT and EXT+

US_{neg} Expectancy. The Stimulus × Time interaction was significant, $F(1.63, 137.12) = 99.04$, $p < .001$, $\eta_p^2 = .54$. The increase in US_{neg} expectancy was stronger for CS+ than for both CSs- (both $ts > 10.36$, $ps < .001$), which demonstrates differential spontaneous recovery (see Figure 1A). However, interaction effects with Group were not significant (all $Fs < 1$, $ps > .407$).

SCR. The Stimulus × Time interaction was not significant, $F(1.85, 155.09) < 1$, $p = .620$, $\eta_p^2 = .01$, but SCR increased over time, $F(1, 84) = 4.02$, $p = .048$, $\eta_p^2 = .05$, which indicates the occurrence of non-differential spontaneous recovery (see Figure 1B). There was also a main effect for Stimulus, $F(1.92, 161.29) = 5.78$, $p = .004$, $\eta_p^2 = .06$. However, again, interaction effects of Group were not significant (all $Fs < 2.17$, $ps > .078$).

FPS. The Stimulus × Time interaction was not significant, $F(2, 168) < 1$, $p = .375$, $\eta_p^2 = .01$, but there was a main effect for Time, $F(1, 84) = 89.83$, $p < .001$, which indicates a non-differential spontaneous recovery effect (see Figure 1C), and for Stimulus, $F(2, 168) = 3.96$, $p = .021$, $\eta_p^2 = .05$. Again, interaction effects with Group were not significant (all $Fs < 1.01$, $ps > .406$).

Hypothesis 2b: Less Reinstatement in CC Relative to EXT and EXT+

US_{neg} Expectancy. The Stimulus × Time interaction was significant, $F(1.33, 111.63) = 9.20$, $p < .001$, $\eta_p^2 = .10$ (see Figure 1A), due to a stronger increase in US_{neg} expectancy following the CS+, compared to both CSs- (both $ts > 2.96$, $ps < .004$). This means that differential reinstatement was successful. However, there were no interaction effects of Group (all $Fs < 1.05$, all $ps > .354$).

SCR. There was no Stimulus × Time interaction, $F(2, 168) = 2.11$, $p = .124$, $\eta_p^2 = .03$, but there was a main effect for Time, $F(1, 84) = 4.45$, $p = .038$, $\eta_p^2 = .05$, which demonstrates non-differential reinstatement (see Figure 1B), and Stimulus, $F(1.94, 162.74) = 3.48$, $p = .034$, $\eta_p^2 = .04$. There were no significant interactions with Group (all Fs < 1.69, all ps > .192).

FPS. Again, the Stimulus × Time interaction was not significant, $F(2, 168) < 1$, $p = .875$, $\eta_p^2 = .00$, but there was a main effect for Time, $F(1, 84) = 35.43$, $p < .001$, $\eta_p^2 = .30$, which indicates non-differential reinstatement (see Figure 1C), and Stimulus, $F(1.91, 160.47) = 7.27$, $p = .001$, $\eta_p^2 = .08$. There were no interaction effects of Group (all Fs < 1, ps > .612).

In summary, spontaneous recovery and reinstatement were differential for US_{neg} expectancy ratings and non-differential for SCR and FPS. However, in contrast to our hypotheses, CC did not attenuate spontaneous recovery or reinstatement of fear relative to the control groups.

Exploratory Analyses

Regression analyses were performed to explore whether post-intervention CS+ positive valence predicted less spontaneous recovery (i.e., difference between CS+ trial 1 in spontaneous recovery phase and CS+ trial 8 in intervention phase) and reinstatement (i.e., difference between CS+ trial 1 in reinstatement phase and CS+ trial 2 in spontaneous recovery phase), measured with US_{neg} expectancy, FPS, or SCR. This was only the case for spontaneous recovery measured with SCR (Beta = -0.22, $p = .039$; all other Betas < 0.17, ps >.136).

Discussion Experiment 1

As predicted, counterconditioning outperformed both extinction procedures in reducing negative stimulus valence at the end of Day 2. However, it did not reduce the return of fear on any of the outcome measures one week later. To our knowledge, only one earlier multiple-day fear conditioning study has been published that showed a correlation between post-extinction CS+ negative valence (Day 2) and reinstatement of fear (Day 3) (Zbozinek, Hermans, et al., 2015). However, their post-extinction CS+ valence ratings did not differ from the pre-spontaneous recovery and pre-reinstatement ratings, whereas, in our experiment, the group effects on CS+ valence did not persist for one week. Other fear conditioning experiments that detected a positive correlation between post-extinction negative stimulus valence and the return of fear used a one-day fear conditioning

paradigm (e.g., Dirikx et al., 2004, 2007; Hermans et al., 2005), in which a reinstatement phase took place immediately after post-extinction CS valence ratings. Hence, in those one-day studies, return of fear may be related to negative stimulus valence right before reinstatement rather than to the valence right after extinction (one week earlier in our experiment). Theoretically, there is no reason to assume that return of fear would be reduced if the stimulus is negative before reinstatement, regardless of whether it was positive before. To test whether return of fear is associated with reduced negative stimulus valence right before a return of fear test, we decided to conduct a replication experiment with all phases on one day.

Experiment 2

Methods

Experiment 2 was a replication of Experiment 1, except that the Acquisition, Extinction, Spontaneous Recovery, and Reinstatement phases took place on one day, and the post-auricular reflex was not measured. Results on self-reported arousal and fear are reported in the Supplementary Materials.

Participants

Ninety-eight participants were recruited at Utrecht University and via the Internet. Two participants dropped out because they found the shock/startle probe too unpleasant. Data from three participants were excluded because they rated the positive film clips negatively (n = 1), did not follow instructions (n = 1), or misunderstood how to use the US_{neg} expectancy scale (n = 1). Due to a counterbalancing error in the Extinction group, and before data analysis, we excluded 33 EXT participants and tested an additional 30 participants in this group. The final sample included 90 participants (75 females and 15 males; mean age = 21.18, SD = 2.01) who were equally distributed across groups. Participants received 12 euros or course credit as compensation for their participation. This study received approval from the ethics committee of the Faculty of Social and Behavioural Sciences at Utrecht University (FETC16-054) and was preregistered on the Open Science Framework (https://osf.io/mxa5z/).

General Procedure

The procedure of Experiment 1 was executed on one day. After participants provided

informed consent, they were connected to physiological and shock electrodes and continued with the shock work-up procedure. Then, they completed the EPQ-N, followed by the Habituation, Acquisition, Intervention, Spontaneous Recovery (starting with a CS1- or CS2- presentation) and Reinstatement phases. Between these phases, they rated CS valence, arousal, and fear and affect. Afterward, participants were thanked and debriefed.

Results

Randomization Checks

There were no significant group differences in age, neuroticism scores, shock level, baseline affect (all *Fs* < 2.71, all *ps* > .072), and gender ($\chi^2 < 1$, $p = .730$). However, groups differed in US_{neg} unpleasantness, $F(2, 87) = 3.77$, $p = .027$, $\eta_p^2 = .08$, with lower shock evaluation in the EXT compared to the EXT+ group (mean difference = 0.50), $t(58) = 2.55$, $p = .013$. There were no other group differences (*t*s < 1.54, *p*s > .128). The evaluation of film clips were not different between the CC ($M = 8.42$, $SD = 0.96$) and EXT+ ($M = 8.55$, $SD = 1.02$) groups, $F(1, 60) < 1$, $p = .609$, $\eta_p^2 = .00$.

Acquisition Phase

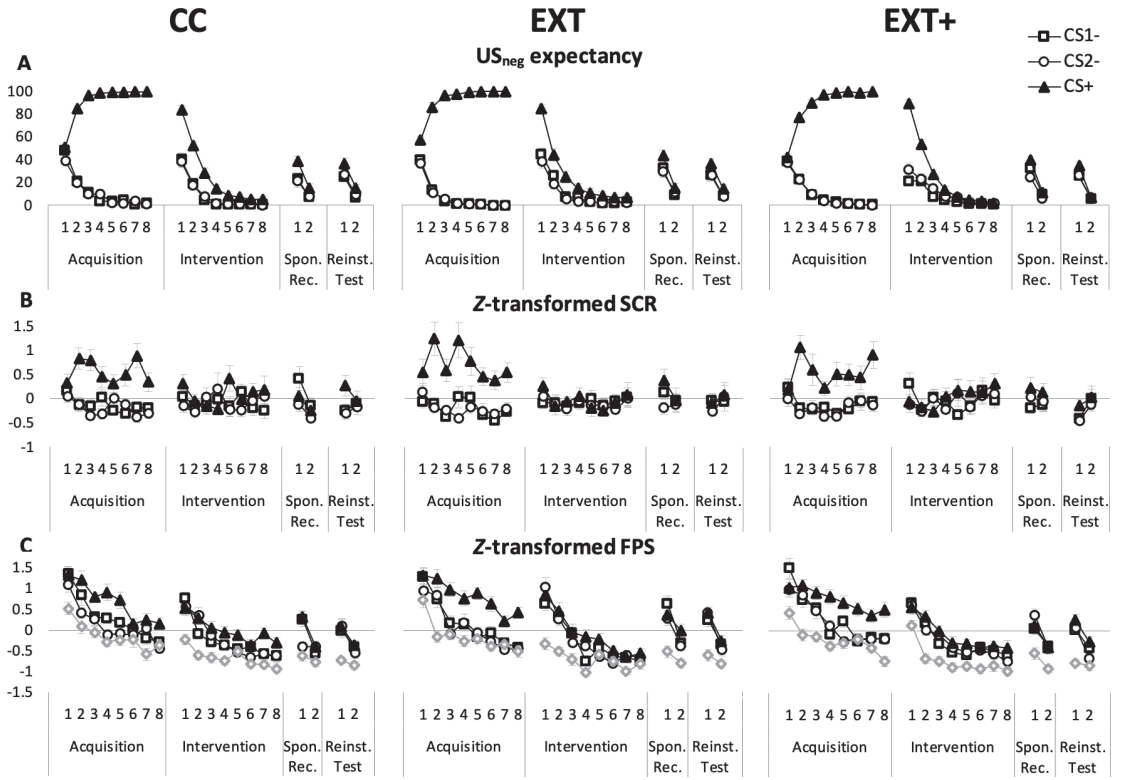
Acquisition was reflected by US_{neg} expectancy, SCR, and FPS variables, with stronger responding over time to the CS+ relative to both CSs- (Stimulus × Time: all *F*s > 3.12, *p*s < .001; simple effects: all *t*s > 2.97, *p*s < .005), see Figure 2. After the acquisition phase, negative valence had increased for CS+ (but not for CSs-), Stimulus × Time: $F(1.70, 169.97) = 97.30$, $p < .001$, simple effects: $t(89) = 11.63$, $p < .001$, see Table 3. There were no three-way interaction effects (all *Fs* < 1.73, all *p*s > .072), indicating that groups did not differ in acquisition.

Intervention Phase

US_{neg} expectancy decreased during the Intervention phase; Stimulus × Time: $F(3.59, 311.97) = 49.82$, $p < .001$, $\eta_p^2 = .36$, simple effects: $t(89) = 10.24$, $p < .001$. For SCR, we did not observe a significant Stimulus × Time interaction, $F(13.66, 1188.39) < 1$, $p = .653$, $\eta_p^2 = .01$, Time, $F(6.61, 575.09) = 1.50$, $p = .169$, $\eta_p^2 = 02$, or main effect for Stimulus, $F(2, 174) = 1.91$, $p = .152$, $\eta_p^2 = 02$. With respect to FPS, there was no Stimulus × Time effect, $F(13.56, 1179.71) = 1.21$, $p = .263$, $\eta_p^2 = .01$, but there were main effects for Time, $F(6.11, 531.13) = 86.00$, $p < .001$, $\eta_p^2 = 50$, and Stimulus, $F(1.93, 168.16) = 14.38$, $p < .001$, $\eta_p^2 = 14$ (see Figure 2). There were no three-way interaction effects (all *Fs* < 1.98, all *p*s > .056).

Figure 2

US_{neg} Expectancy, Z-Transformed Skin Conductance Response (SCR), and Fear-Potentiated Startle (FPS) Across Phases and Groups in Experiment 2



Note. CC = counterconditioning; CS = conditioned stimulus; EXT = extinction; EXT+ = extinction and positive material; Spon. Rec. = Spontaneous Recovery; Reinst. = Reinstatement; US_{neg} = negative unconditioned stimulus. Error bars represent the standard error of the mean. Grey diamonds indicate FPS during noise alone trials.

Table 3

Means (Standard Deviations) of CS Valence and Affect Ratings in Experiment 2

		Acquisition		Intervention	Spontaneous Recovery	Reinstatement
		Pre	Post	Post	Post	Post
CC	CS+	5.13 (1.46)	3.00 (1.46)	5.53 (1.66)	5.53 (1.68)	5.60 1.30)
	CS1-	4.93 (1.72)	6.13 (1.61)	5.97 (1.77)	6.13 (1.76)	5.93 (1.80)
	CS2-	4.93 (1.68)	6.00 (1.68)	5.93 (2.00)	6.00 (1.53)	6.17 (1.60)
	Affect	64.10 (19.78)	55.00 (18.27)	68.23 (15.80)	68.97 (17.66)	64.67 (19.96)
EXT	CS+	4.87 (1.76)	2.70 (1.62)	4.43 (1.43)	4.83 (1.39)	5.30 (1.70)
	CS1-	4.97 (1.52)	6.03 (1.63)	5.60 (1.45)	5.80 (1.30)	5.90 (1.67)
	CS2-	5.50 (1.17)	6.30 (1.49)	5.90 (1.60)	6.07 (1.51)	6.17 (1.62)
	Affect	66.10 (18.76)	55.93 (17.46)	61.67 (15.42)	63.50 (15.57)	63.23 (16.79)
EXT+	CS+	5.17 (1.76)	3.20 (1.52)	5.27 (1.31)	5.33 (1.37)	5.47 (1.53)
	CS1-	4.93 (1.62)	6.10 (1.60)	5.53 (1.61)	5.70 (1.29)	5.70 (1.32)
	CS2-	5.03 (1.59)	5.73 (1.80)	6.64 (1.73)	6.03 (1.50)	6.00 (1.49)
	Affect	61.40 (18.40)	55.23 (19.47)	67.80 (16.39)	65.87 (18.59)	61.43 (16.79)

Note. CC = counterconditioning; CS = conditioned stimulus; EXT = extinction; EXT+ = extinction and positive material.

The Time (pre, post intervention) × Group interaction was not significant for affect ratings, $F(2, 87) = 2.31$, $p = .106$, $\eta_p^2 = .05$. Positive affect increased in all groups from pre to post intervention, $F(1, 87) = 44.38$, $p < .001$, $\eta_p^2 = .34$ (see Table 3).

In summary, extinction occurred for US_{neg} expectancy and FPS. Because SCR did not decrease during the Intervention phase, we did not examine spontaneous recovery and reinstatement effects for SCR (see Figure 2B for visual inspection).

Hypothesis 1: More Positive CS+ Valence After CC, Compared to EXT and EXT+

There was no significant Stimulus × Time (pre, post intervention) × Group interaction for CS valence, $F(3.46, 150.58) = 1.82$, $p = .138$, $\eta_p^2 = .04$, but there was a marginally significant Stimulus × Group effect after the intervention, $F(3.74, 162.60) = 2.47$, $p = .051$, $\eta_p^2 = .05$, see Table 3. Post-hoc analyses adjusted with Bonferroni correction showed that after the intervention phase, the CC group reported more positive CS+ valence compared to the EXT group ($p = .014$), but not compared to the EXT+ group ($p = .999$). CS+ evaluation did not differ significantly between the EXT and EXT+ groups ($p = .093$). These results partially support our hypothesis that negative CS+ valence would be lower after the intervention phase in the CC group relative to the other two groups.

Hypothesis 2a: Less Spontaneous Recovery in CC Relative to EXT and EXT+

US_{neg} Expectancy. There was a significant Stimulus × Time effect, $F(1.88, 163.61) = 10.34$, $p < .001$, $\eta_p^2 = .11$, with a stronger increase in US_{neg} expectancy to the CS+ compared to both CSs-(both ts > 2.64, both ps < .010). This indicates successful differential spontaneous recovery. There were no interaction effects of Group (all Fs < 1, all ps > .561), see Figure 2A.

FPS. There was no significant Stimulus × Time effect, $F(2, 174) = 2.32$, $p = .102$, $\eta_p^2 = .02$. There were main effects for Time, $F(1, 87) = 104.86$, $p < .001$, $\eta_p^2 = .55$, which demonstrates non-differential spontaneous recovery, and Stimulus, $F(2, 174) = 3.27$, $p = .040$, $\eta_p^2 = .04$. The Stimulus × Time × Group effect was also significant, $F(4, 174) = 3.08$, $p = .018$, $\eta_p^2 = .07$. FPS increased over time for all stimuli in all groups (ts > 1.99, ps < .056), but not for CS2- in the CC group, $t(29) = 1.42$, $p = .166$, see Figure 2C.

Hypothesis 2b: Less Reinstatement in CC Relative to EXT and EXT+

US_{neg} Expectancy. A Stimulus × Time interaction, $F(1.73, 150.27) = 3.58$, $p = .037$, $\eta_p^2 = .04$, revealed a stronger increase in US_{neg} expectancy following the CS+ compared to both

CSs- (both *t*s > 2.10, *p*s < .039). This demonstrates successful differential reinstatement. There were no interaction effects including Group (all *F*s < 1, all *p*s > .559), see Figure 2A.

FPS. There was no significant Stimulus × Time effect, $F(2, 174) < 1$, $p = .956$, $\eta_p^2 = .00$. A main effect of Time, $F(1, 87) = 59.36$, $p < .001$, $\eta_p^2 = .41$, indicated non-differential reinstatement. There were no main effect for Stimulus, $F(2, 174) = 2.17$, $p = .118$, $\eta_p^2 = .02$, or interaction effects with Group (all *F*s < 1, all *p*s > .667), see Figure 2C.

These results suggest that spontaneous recovery and reinstatement occurred for US_{neg} expectancy (i.e., differential return of fear) and FPS (i.e., non-differential return of fear). Contrary to our hypothesis, fear responses were not attenuated in the CC group relative to the control groups.

Exploratory Analyses

Following Experiment 1, regression analyses were used to explore whether post-intervention CS+ positive valence predicted less spontaneous recovery and less reinstatement measured with US_{neg}, FPS, or SCR, but it did not (largest Beta = -0.10, $p = .343$).

Discussion Experiment 2

Findings from Experiment 2 were generally in line with Experiment 1. Counterconditioning again reduced negative stimulus valence but only compared to standard extinction training and not compared to extinction training with exposure to positive material. Again, counterconditioning did not reduce the return of fear. In contrast to Experiment 1, SCR did not decrease in the Intervention phase. It is unclear why SCR was low at the start of the intervention.

General Discussion

We conducted two experiments to examine whether positive valence training through counterconditioning reduces negative stimulus valence and return of fear. Overall, our findings do not support the notion that it reduces return of fear. The first main finding is that counterconditioning reduced negative stimulus valence, compared to standard extinction training, which is in line with previous research (e.g., Engelhard et al., 2014; Kerkhof et al., 2011; Raes & De Raedt, 2012). However, some studies did not find this effect. This may be related to methodological differences, such as the use of different

reinforcements (e.g., financial reward: Meulders et al., 2015; comic pictures: Kang et al., 2018), or testing an additional effect of counterconditioning on exposure in vivo, which already includes techniques that may reduce negative stimulus valence, such as therapeutic modeling (de Jong et al., 2000). We also found that negative stimulus valence was reduced directly after counterconditioning but spontaneously recovered after one week (Experiment 1). Thus, counterconditioning did not reduce negative stimulus valence more than extinction did in some studies, and its long-term effects were not found in Experiment 1. Together, these findings may indicate the relevance of testing boundary conditions of counterconditioning as positive valence training. In addition, in Experiment 1, counterconditioning reduced negative stimulus valence more compared to extinction training in which the same positive material was presented (but unrelated to the CS+). This suggests that the effects should not be attributed to general positive mood induction. Nevertheless, this effect was not replicated in Experiment 2, perhaps because negative affect before the intervention was higher in the one-day paradigm than in the three-day paradigm (see Tables 2 and 3).

The second main finding of the current experiments is that counterconditioning did not attenuate return of fear relative to extinction training. To our knowledge, only one human fear conditioning study so far has tested whether counterconditioning reduced the return of fear (Kang et al., 2018). Our findings are at odds with this study, in which counterconditioning did not reduce negative valence but did attenuate spontaneous recovery and reinstatement of threat expectancy (Kang et al., 2018). Two methodological differences may account for these divergent findings. First, we presented the US_{neg} *during* CS presentation throughout the acquisition phase (following Zbozinek, Holmes, et al., 2015) and the US_{pos} right *after* CS offset during the intervention phase, whereas Kang et al. (2018) presented the US_{neg} at CS *offset* in both phases. The same timing of the US presentation in each phase in Kang et al. (2018) may have enhanced learning during counterconditioning. Second, our US_{pos} comprised 6-s film clips, which apparently enhanced the reduction of negative stimulus valence, whereas Kang et al. used 3-s comic pictures. Counterconditioning may not have facilitated associative learning due to the longer US duration or complexity.

Our findings are in line with rodent studies, in which no beneficial effect of counterconditioning (relative to extinction) on the return of fear has been detected (Bouton & Peck, 1992; Brooks et al., 1995; Holmes et al., 2016; Kerkhof et al., 2012). One explanation could be that, as with extinction, counterconditioning creates new, secondary learning about the CS-US relationship. That is, after counterconditioning, the CS possesses

new meanings: its original meaning (CS-US_{neg}), as well as two additional meanings (CS-no US_{neg} and CS-US_{pos}). This may leave the original meaning intact and thereby vulnerable to the return of fear or relapse (e.g., Bouton, 2002; Craske, 2015). The current experiments suggest that the advantages of counterconditioning with respect to reducing negative stimulus valence do not outweigh the disadvantage of creating ambiguity (i.e., two new associations) about fear-relevant stimuli. In this sense, counterconditioning may not be used as a method to prevent the return of fear.

However, this does not necessarily imply that counterconditioning or related procedures are never effective in reducing a return of conditioned responding. First, because individuals tend to learn faster from negative than positive outcomes (Rozin & Royzman, 2001), counterconditioning with a negative (instead of positive) US may yield stronger learning effects and therefore be more effective in reducing a return of appetitive compared to fear responding. Two appetitive conditioning studies indeed found that, relative to extinction, counterconditioning with a negative US (a highly disliked liquid) reduced the return of appetitive responding (i.e., expectancy to eat chocolate and chocolate consumption; Van Gucht et al., 2010, 2013). Second, the "surprise" aspect of counterconditioning may be effective in itself, as it enhances prediction error. Two fear conditioning experiments showed that novelty-facilitated extinction (i.e., extinction in which a CS is followed by a surprising and novel nonthreat outcome) reduced the return of fear more than standard extinction training (Dunsmoor et al., 2015; Lucas et al., 2018; but see Krypotos & Engelhard, 2018). Novelty-facilitated extinction is procedurally akin to counterconditioning (pairing a fear-relevant stimulus with a neutral instead of positive US) but appears to be more effective in reducing return of fear.

Our third main finding is that reduced negative stimulus valence did not lower return of fear. Thus far, attempts to test this hypothesis have yielded inconclusive evidence. Two studies found that positive valence training reduced the spontaneous recovery of spider fear (Dour et al., 2016) and fear reinstatement in a conditioning paradigm (Zbozinek, Holmes, et al., 2015), but another study showed that positive valence training did not reduce reinstatement (Luck & Lipp, 2018). These findings, together with current findings, provide no compelling evidence for a direct causal relationship between post-extinction negative stimulus valence and the return of fear. How may these inconsistencies in evidence be reconciled? One explanation is that the positive correlation between negative stimulus valence and return of fear (e.g., Dirikx et al., 2004, 2007; Hermans et al., 2005; Huijding & De Jong, 2009; Vasey et al., 2012) is spurious. That is, there may be a third variable that explains the relation between post-extinction negative stimulus valence and return of fear, such as individual differences in positive affect. Indeed,

positive valence training increased positive affect and reduced negative stimulus valence and reinstatement in a previous study (Zbozinek, Holmes, et al., 2015; but see van Veen et al., 2020).

Our findings may be relevant for the treatment of anxiety disorders in which negative stimulus valence may impede exposure therapy (e.g., due to disgust in spider phobia, Smits et al., 2002; or blood-injection-injury phobia, Olatunji et al., 2007). About 20% of anxiety patients drop out during treatment, and about 11% even refrain from starting with therapy (Fernandez et al., 2015). Counterconditioning may be a useful additional strategy to reduce negative stimulus valence to lower the threshold for individuals to expose themselves to fear-relevant situations. In that sense, it may increase the therapy's acceptability and reduce avoidance (Chen & Bargh, 1999) and dropout. These are empirical questions that await future clinical research.

Strengths of the current research include the multimodal assessment of fear and replication of results in an independent second experiment, which increases confidence in the robustness of our findings. Several limitations should also be noted. First, we only used an explicit measure of stimulus valence, which may be susceptible to demand characteristics and may reflect judgment-related processes instead of genuine changes in stimulus valence (Gawronski et al., 2015). Future research could include implicit measures, such as affective priming (e.g., Engelhard et al., 2014; Raes & De Raedt, 2012). Second, participants were undergraduates. Future studies may preselect individuals suffering from anxiety or characterized by high neuroticism scores, as there might be more room for improvement in attenuating return of fear in these individuals (see Haaker et al., 2014). Third, the effect of counterconditioning on negative stimulus valence was no longer present after one week. Further research with multiple-day paradigms may use a more powerful manipulation of stimulus valence, for example, by repeatedly exposing participants to the CS/US_{pos} relation throughout the week.

In conclusion, counterconditioning seems to be promising as positive valence training. Our findings do not support the notion that it reduces return of fear, and there was no direct relationship between post-intervention negative stimulus valence and the return of fear. More research is needed to test boundary conditions of counterconditioning effects on stimulus valence and how (sub)clinical groups may profit from counterconditioning.

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Author Contributions

EvD, MH, and IME designed the studies. EvD performed statistical analyses and drafted the manuscript. MH, CB, and IME critically revised the manuscript.

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Supplementary Materials

Table S1. Means (Standard Deviations) of CS Arousal Ratings in Experiment 1

Table S2. Means (Standard Deviations) of Fear Ratings in Experiment 1

Table S3. Means (Standard Deviations) of CS Arousal Ratings in Experiment 2

Table S4. Means (Standard Deviations) of Fear Ratings in Experiment 2

Table S1

Means (Standard Deviations) of CS Arousal Ratings in Experiment 1

		Acquisition		Intervention		Spontaneous Recovery		Reinstatement
		Pre	Post	Pre	Post	Pre	Post	Post
CC	CS+	2.76 (1.83)	4.97 (1.97)	4.41 (2.26)	3.79 (1.76)	2.28 (1.49)	2.24 (1.46)	3.34 (1.88)
	CS1-	3.00 (1.98)	2.59 (1.40)	2.52 (1.53)	2.59 (1.64)	2.55 (1.72)	2.31 (1.39)	4.03 (1.92)
	CS2-	3.03 (2.04)	2.90 (1.88)	2.31 (1.51)	2.52 (1.64)	2.18 (1.31)	2.07 (1.27)	3.39 (1.99)
EXT	CS+	2.83 (1.71)	5.62 (1.92)	4.55 (1.70)	3.55 (1.90)	2.48 (2.01)	2.32 (1.59)	3.21 (1.68)
	CS1-	2.45 (1.40)	2.93 (1.56)	2.24 (1.30)	2.45 (1.66)	2.00 (1.00)	1.97 (1.18)	3.24 (1.77)
	CS2-	2.90 (1.88)	2.90 (1.70)	2.52 (1.43)	2.43 (1.35)	1.93 (1.00)	1.93 (1.13)	2.93 (1.71)
EXT+	CS+	3.41 (1.94)	5.31 (2.09)	4.72 (2.22)	3.34 (1.88)	2.31 (1.31)	2.21 (1.11)	3.17 (1.75)
	CS1-	3.55 (2.01)	3.14 (1.83)	2.90 (1.78)	2.45 (1.38)	2.55 (1.48)	2.69 (1.44)	3.66 (2.06)
	CS2-	2.86 (1.83)	2.93 (1.41)	2.93 (1.67)	2.41 (1.32)	2.26 (1.26)	2.41 (1.19)	2.81 (1.62)

Note. CC = counterconditioning; CS = conditioned stimulus; EXT = extinction; EXT+ = extinction and positive material.

Table S2

Means (Standard Deviations) of Fear Ratings in Experiment 1

		Acquisition		Intervention		Spontaneous Recovery		Reinstatement
		Pre	Post	Pre	Post	Pre	Post	Post
CC	CS+	1.86 (1.57)	4.52 (2.21)	3.90 (2.09)	2.24 (1.43)	3.14 (1.75)	2.11 (1.10)	2.45 (1.57)
	CS1-	2.62 (1.72)	1.86 (0.99)	1.79 (0.94)	1.52 (1.21)	1.72 (1.10)	1.46 (0.69)	1.62 (0.90)
	CS2-	2.41 (1.82)	2.10 (1.47)	1.66 (1.01)	1.28 (0.65)	1.48 (0.99)	1.29 (0.71)	1.38 (0.82)
EXT	CS+	2.00 (1.22)	4.83 (2.24)	4.24 (1.90)	2.86 (1.87)	2.79 (1.62)	2.41 (1.66)	2.83 (1.79)
	CS1-	2.03 (1.24)	1.86 (0.95)	1.55 (0.69)	1.55 (1.02)	1.36 (0.56)	1.48 (0.78)	1.52 (0.78)
	CS2-	2.28 (1.98)	1.97 (1.68)	1.66 (1.08)	1.62 (1.35)	1.43 (0.88)	1.34 (0.67)	1.55 (0.99)
EXT+	CS+	2.10 (1.50)	5.00 (2.31)	4.38 (2.21)	3.07 (2.00)	3.62 (2.08)	2.70 (1.64)	2.76 (1.81)
	CS1-	2.66 (2.18)	2.03 (1.52)	1.97 (1.35)	1.59 (0.82)	1.83 (1.26)	1.44 (0.70)	1.86 (1.22)
	CS2-	1.90 (1.35)	1.79 (1.24)	1.90 (1.14)	1.66 (0.81)	2.00 (1.67)	1.67 (1.30)	1.83 (1.07)

Note. CC = counterconditioning; CS = conditioned stimulus; EXT = extinction; EXT+ = extinction and positive material.

Table S3

Means (Standard Deviations) of CS Arousal Ratings in Experiment 2

		Acquisition		Intervention	Spontaneous Recovery	Reinstatement
		Pre	Post	Post	Post	Post
CC	CS+	2.93 (1.74)	5.70 (1.84)	3.97 (1.96)	3.07 (1.89(	3.27 (2.13)
	CS1-	2.50 (1.20)	2.83 (1.49)	2.37 (1.50)	2.27 (1.66)	2.30 (1.44)
	CS2-	2.80 (1.77)	3.07 (1.82)	2.53 (1.72)	2.43 (1.79)	2.40 (1.52)
EXT	CS+	2.80 (1.88)	5.77 (1.87)	3.17 (1.95)	3.00 (1.74)	2.77 (1.91)
	CS1-	3.10 (1.92)	2.73 (1.74)	2.10 (1.49)	2.17 (1.34)	1.93 (1.20)
	CS2-	2.67 (1.58)	2.53 (1.48)	1.83 (1.29)	2.07 (1.28)	1.93 (1.39)
EXT+	CS+	3.27 (1.68)	6.10 (2.09)	3.40 (1.79)	3.00 (1.93)	2.67 (1.77)
	CS1-	2.80 (1.58)	2.63 (1.67)	2.37 (1.50)	2.10 (1.65)	2.13 (1.72)
	CS2-	2.97 (1.79)	3.00 (1.89)	4.20 (2.54)	2.37 (1.61)	2.30 (1.97)

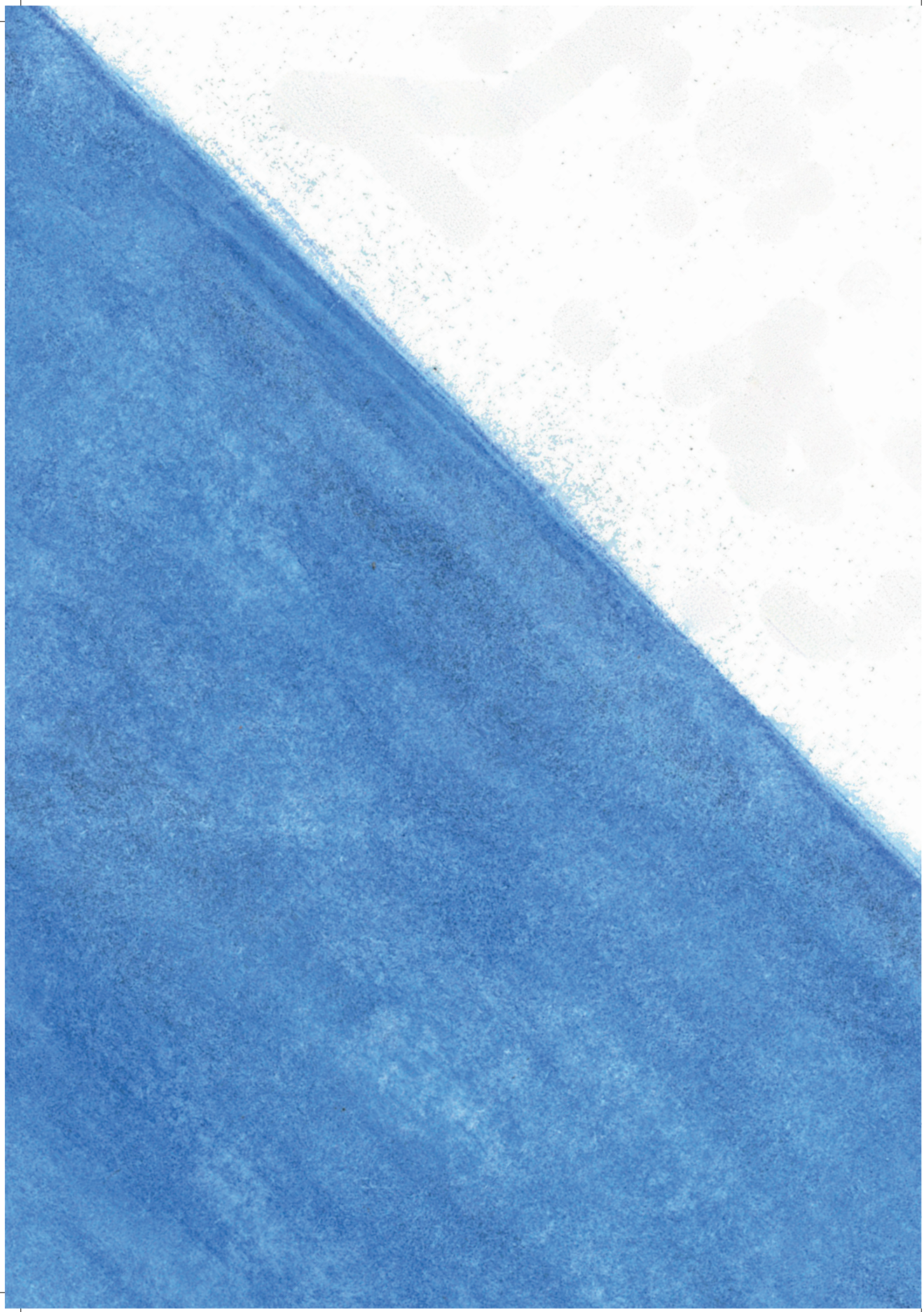
Note. CC = counterconditioning; CS = conditioned stimulus; EXT = extinction; EXT+ = extinction and positive material.

Table S4

Means (Standard Deviations) of Fear Ratings in Experiment 2

		Acquisition		Intervention	Spontaneous Recovery	Reinstatement
		Pre	Post	Post	Post	Post
CC	CS+	2.03 (1.35)	5.10 (2.12)	2.67 (1.81)	2.10 (1.49)	2.17 (1.78)
	CS1-	1.90 (1.27)	1.97 (1.38)	1.43 (0.73)	1.47 (0.90)	1.23 (0.50)
	CS2-	2.07 (1.26)	2.03 (1.59)	1.37 (0.61)	1.40 (0.72)	1.30 (0.60)
EXT	CS+	1.87 (1.41)	5.53 (2.03)	3.00 (2.10)	2.53 (1.74)	2.40 (1.79)
	CS1-	2.27 (1.70)	1.83 (1.29)	1.60 (0.89)	1.60 (0.72)	1.43 (0.68)
	CS2-	2.00 (1.29)	1.60 (0.97)	1.53 (0.97)	1.43 (0.73)	1.37 (0.67)
EXT+	CS+	1.87 (1.63)	5.07 (2.30)	2.33 (1.24)	2.03 (1.19)	2.40 (1.79)
	CS1-	2.00 (1.53)	1.77 (1.55)	1.53 (1.07)	1.33 (0.92)	1.37 (0.85)
	CS2-	2.00 (1.53)	1.77 (1.36)	1.40 (1.16)	1.37 (0.89)	1.23 (0.68)

Note. CC = counterconditioning; CS = conditioned stimulus; EXT = extinction; EXT+ = extinction and positive material.



Chapter 6

Old fears die hard: Return of public speaking fear in a virtual reality procedure

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Abstract

Exposure-based therapy is an effective treatment for social anxiety, but some patients relapse. We used a novel virtual reality procedure to examine spontaneous recovery (i.e., a return of fear over time) and fear renewal (i.e., the return of fear after a context switch) in individuals with fear of public speaking. On Day 1, 32 participants received exposure training before a virtual audience. On Day 8, participants completed a spontaneous recovery phase, followed by a fear renewal test, in which they gave a presentation in front of a new (context switch) or the same audience (no context switch). After exposure, participants exhibited a lower heart rate, subjective distress, negative valence, and arousal. One week later, participants showed spontaneous recovery of heart rate, and the context switch group showed renewal of subjective distress, negative valence, and arousal. Future studies can use this procedure to test interventions aimed at improving long-term exposure effects in individuals with public speaking fear.

Keywords: public speaking anxiety; virtual reality exposure; return of fear; fear renewal

Introduction

About 1 in 10 individuals will meet diagnostic criteria for social anxiety disorder at some point in their lives (Kessler et al., 2012). Social anxiety disorder is characterized by exaggerated fear of social rejections and avoidance of social situations (American Psychiatric Association, 2013). Although many patients with social anxiety disorder benefit from exposure-based therapy (Loerinc et al., 2015; van Dis et al., 2020), about 13% of recovered patients experience relapse (Fava et al., 2001). One commonly accepted explanation for relapse is that fear learning is context-dependent (e.g., Vervliet, Craske, et al., 2013). Specifically, research has shown that the original fear learning (e.g., the belief that other people will judge oneself negatively) is not erased during exposure therapy and can easily resurface in new contexts (i.e., fear renewal; Bouton, 2002). Therefore, research paradigms on fear renewal may be useful for acquiring knowledge to eventually increase long-term treatment success for social anxiety disorder.

Fear renewal has been extensively studied in fear conditioning paradigms (Vervliet, Baeyens, et al., 2013). These usually start with a fear-learning phase in which a danger cue is repeatedly paired with an aversive outcome (e.g., a mild electric shock). Then, in an extinction-training phase, this cue is no longer paired with the aversive outcome, which typically extinguishes fear responses toward the cue. Finally, the danger cue is presented after a time lapse (i.e., spontaneous recovery test) or in a different context (i.e., fear renewal test), generally resulting in a return of fear. Even though fear conditioning studies have substantially contributed to our understanding of learned fear (Vervliet, Craske, et al., 2013), their ecological validity has been criticized. First, most fear conditioning paradigms use simple, generally non-meaningful stimuli (e.g., geometrical shapes) rather than personally meaningful and complex multimodal stimuli that are involved in clinical disorders (Landkroon et al., 2019; Scheveneels et al., 2018). Second, they often rely on passive learning (Scheveneels et al., 2016), while in real-life, individuals actively approach or avoid feared stimuli or situations. Third, fear conditioning paradigms typically instill new fear memories, whereas existing old fear memories are harder to modulate (Eisenberg et al., 2003). Thus, more ecologically valid fear renewal paradigms with complex stimuli, active behavior, and preexisting fear memories are needed.

To our knowledge, only one study has successfully demonstrated fear renewal in individuals with social anxiety using a more ecologically valid procedure (Culver et al., 2011; Study 1). In that study, participants with a fear of public speaking (a type of social anxiety; American Psychiatric Association, 2013) first received exposure training in front of a live audience in Context A. One week later, they received brief exposure

again in the same room (Context A) or a new room (Context B). Participants in Context B showed increased subjective fear and heart rate (HR) during the exposure task 1 week later compared to their initial exposure, while those in Context A did not show an increase in fear or HR from the first exposure to the second (Culver et al., 2011, Study 1). Follow-up studies with this procedure have shown that the use of retrieval cues during exposure slightly reduces fear renewal (Culver et al., 2011, Studies 2 and 3) if participants do not perceive them as safety cues (Shin & Newman, 2018). This illustrates the procedure's potential to reveal mechanisms that may reduce fear renewal. Yet, there is room for improvement—that is, a fear renewal procedure conducted in virtual reality (VR) would allow for more standardization of the audience (Parsons, 2015) and allow more researchers to use the procedure. In addition, the procedure of Culver et al. did not control for spontaneous recovery, even though it may have overshadowed fear renewal in previous studies (Craske et al., 2019; Shin & Newman, 2018).

We aimed to address these issues by developing and validating a 2-day novel VR procedure (following Culver et al., 2011) and testing whether it can be used to examine a return of public speaking fear 1 week after exposure. In our study, participants with a fear of public speaking first received exposure training in VR. After 1 week, they were all tested for spontaneous recovery of fear and they received additional exposure training in the same virtual environment as the previous week. The experimental manipulation was that at the end of the additional exposure training, the virtual context switched for one of the two groups. We expected spontaneous recovery of fear for all participants, but expected fear renewal only for the group that received a context switch relative to the group with no context switch. We also explored the return of subjective negative valence and arousal to delineate the specific emotional responses of this setup.

Methods

Participants

Native Dutch-speaking students were recruited via Utrecht University, Facebook, and Proefbunny.nl to fill out two questions assessing how anxious they thought they would feel when giving a formal speech in front of a live audience and how likely they would avoid taking a class that requires giving an oral presentation, each rated on a 9-point scale (0 = *none/never* and 8 = *extremely/always*; see Culver et al., 2011). If they scored ≥6 on both questions, they were further screened and excluded if they reported heart, respiratory, or neurological problems or 3-D motion sickness. Thirty-seven eligible participants were invited to the first lab session and completed an informed consent procedure. They then

completed the Beck Depression Inventory–II (BDI-II; Beck et al., 1996). If they reported 1 or higher on the item measuring suicidal ideation or had a total score of 18 or higher, they were then excluded from the study (n = 3) to prevent a potential worsening of symptoms. This resulted in 34 participants. Data from one participant were excluded from the final analyses because of a technical issue with the VR equipment, and data from one participant were excluded because of noncompliance. The final sample size comprised 32 participants (10 males, 22 females; mean age = 22.41 years, *SD* = 3.29) who were allocated to Context AA (n = 16) or AB (n = 16) groups (in random order; stratified for gender). The ethics committee of the Faculty of Social and Behavioral Sciences at Utrecht University (FETC17-073) approved this study. We preregistered the study (including a power analysis) on the Open Science Framework (https://osf.io/udny4/).

Power Analysis

A power analysis (using G*Power 3.1.9.2) for a mixed-factorial analysis of variance (ANOVA) with two groups and two measures (f = 0.25, α = .05, power = 0.80) yielded a total sample size of 34 participants (i.e., 17 per group). Although we preregistered a power analysis using a power level of 0.95 (yielding a sample size of 54 participants), a power of 0.80 is often considered preferable (Cohen, 1992). We used an optimal stopping procedure, which allowed us to stop our data collection whenever we found strong evidence in favor of the null or alternative hypothesis (i.e., Bayes factor >10). After testing 32 eligible participants (i.e., the sample size of Culver et al., 2011), we obtained a strong effect on fear renewal for subjective units of distress (SUDS; $BF_{10} > 10.0$) and therefore stopped our data collection. Although stopping rules are considered problematic for frequentist statistics, they are appropriate and commonly used in Bayesian statistics (e.g., Rouder, 2014).

Measures

Questionnaires and Interview

Structured Clinical Interview for DSM-5 Disorders (SCID-5-CV). Social anxiety disorder was assessed using Questions F32–F41 of the SCID-5-CV (First et al., 2016) by trained clinical psychology students. The sections were translated from English to Dutch and back-translated by independent researchers. Independent raters (EvD and EL) evaluated the presence of a diagnosis (interrater reliability κ = 0.79).

Personal Report of Public Speaking Anxiety (PRPSA). Fear of public speaking was assessed with the PRPSA (McCroskey, 1970), which also has been validated in a Dutch sample (Cronbach's α = .83; van Veen et al., 2020). It has good convergent validity (*r* = .41 with a communication apprehension scale) and high internal consistency (α = .94; McCroskey, 1970). This 34-item scale consists of negative and positive statements that are rated on a 5-point Likert scale, ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). Positive items are reverse scored. Cronbach's α was .90 in this study.

Brief Fear of Negative Evaluation Scale–II (BFNE-II). Fear of negative evaluations was measured with a validated Dutch version of the BFNE-II (Carleton et al., 2007; Cieraad & de Jong, 2007). Carleton et al. reported good construct validity (convergent validity with social phobia scales: *r*s = .60–.64; discriminant validity with illness and injury scales: *r*s = .29–.38) and excellent internal consistency (α = .97). This scale consists of 12 statements that are rated on a 5-point Likert scale, ranging from 0 (*not at all characteristic of me*) to 4 (*extremely characteristic of me*). Cronbach's α was .95 in this study.

Behaviors Checklist (BCL). Perceived speech performance of one's speech was assessed with the 18-itmem BCL (derived from Mansell & Clark, 1999; Stopa & Clark, 1993; Vasey et al., 2012). The items were translated from English to Dutch and back-translated by independent researchers. This 18-item scale consists of negative and positive speech characteristics that are rated on a 9-point Likert scale, ranging from 0 (*not at all*) to 8 (*extremely*). Positive items are reverse scored. Cronbach's α was .80–.85 in this study.

Neuroticism Scale of the Eysenck Personality Questionnaire (EPQ-N).[1] Neuroticism was assessed with a validated Dutch version of the EPQ-N (Eysenck & Eysenck, 1991; Sanderman et al., 2012). Its convergent validity is demonstrated by a strong correlation with another neuroticism scale (*r* = .78), and discriminant validity is indicated by a negative correlation with an emotional stability subscale (*r* = –.70). It also has excellent internal consistency (α = .87; Barelds & Luteijn, 2002). This scale has 22 questions that are rated on a dichotomous scale (0 = *no*, 1 = *yes*). Cronbach's α was .90 in this study.

Anxiety Sensitivity Index (ASI).[1] Anxiety sensitivity was measured with a validated Dutch version of the ASI (Reiss et al., 1986; Vujanovic et al., 2007). The convergent and discriminant validity is high: the ASI total score was positively associated with scales

[1] Measures of anxiety-relevant personality traits, such as neuroticism, anxiety sensitivity, emotional reasoning (Arntz et al., 1995; Engelhard et al., 2001), and personalized implicit associations (Vasey et al., 2012) were included in this study to explore whether these predicted return of fear. Yet, our power analysis and stopping rule were aimed at obtaining sufficient statistical power for the renewal analyses. Because the renewal effects were already large after testing 32 participants, we decided to stop testing, and we do not report the return of fear predictors due to limited statistical power.

measuring anxious arousal (r = .42) and negative affectivity (r = .35). It did not show significant correlations with anhedonic depression (r = .07) and positive affectivity (r = .02). In addition, the internal consistency is good (α = .83; Vujanovic et al., 2007). The ASI consists of 16 statements (e.g., "It scares me when my heart beats rapidly") that are rated on a 5-point Likert scale, ranging from 0 (*very little*) to 4 (*very much*). Cronbach's α was .79 in this study.

VR Experiences Scale. A self-constructed seven-item questionnaire assessed three physiological complaints (nausea, headache, and dizziness), realness, immersion, presence, and whether presenting in VR was equally challenging as presenting in real life. Items were rated on a 5-point Likert scale, ranging from 1 (*barely*) to 5 (*very much*).

Subjective Ratings

Subjective Units of Distress Scale (SUDS). Subjective distress was assessed with the SUDS, a 100-point scale with five anchors: 0 (*no distress*), 25 (*mild distress*), 50 (*moderate distress*), 75 (*severe distress*), and 100 (*very severe distress*).

VR Valence and Arousal. VR valence and arousal were assessed by the following two questions: "How positive or negative do you find this audience?" and "How aroused do you feel when seeing this audience?" on an 11-point scale ranging from 0 (*negative/not arousing*) to 10 (*positive/arousing*). VR valence ratings were reverse scored for ease of interpretation.

Speech Topic Difficulty. Speech topic difficulty was measured with the following question: "How difficult do you find it to give a speech on this topic?" that was rated on a 10-point scale, ranging from 1 (*very easy*) to 10 (*very difficult*).

Heart Rate

HR was measured with a Polar H10 chest strap electrocardiogram (ECG) monitor that was connected to the free iOS HRV+ app (ZUZ LLC) on an iPad. Polar wearable HR monitors are reliable (Georgiou et al., 2018) and have often been used in similar research (e.g., Culver et al., 2011). For each day, the average beats per minute (BPM) during the baseline measurement was subtracted from the average BPM during each speech (Culver et al., 2011). We used the final minute of the 5-min baseline period to ensure that participants' HR returned to their baseline level. Following Vasey et al. (2012), we additionally analyzed the average BPM during each speech, without correcting for the baseline measurements (see Supplementary Materials). Data were monitored at 130 Hz and analyzed with Kubios HRV Standard (version 3.2).

Procedure

On Day 1, participants provided informed consent and completed the BDI-II, PRPSA, BFNE-II, EPQ-N, and the ASI, followed by the SCID-5. Next, they put on the Polar chest strap and were instructed to "Please remain seated quietly, without speaking to the experimenter" for a 5-min HR baseline measurement. They then put on the VR headset and practiced for 2 minutes with SUDS, VR valence, and arousal ratings in a neutral VR environment. Hereafter, participants faced the virtual audience for 10 sec (Context A) and completed the baseline VR valence and arousal ratings. This was followed by an exposure phase in which they gave four 5-min speeches. Before each speech, they received three unique topics that were somewhat controversial (e.g., euthanasia, death penalty, and immigration; see Table S1 in the Supplementary Materials). From these, they chose one topic and rated its difficulty. They had 1 minute of preparation time in which they were not allowed to make notes. They then gave a speech in Context A during which they indicated the SUDS rating out loud at the start of the speech and 1-min intervals. If they stopped the presentation within 5 minutes, the experimenter instructed them to continue presenting even if that meant they had to repeat themselves. After each speech, participants took off the VR headset for a 1-min rest. After finishing the last speech, they were asked to complete VR valence and arousal ratings again. Finally, they filled out the BCL regarding the last speech. They also completed an emotional reasoning task and personalized implicit association test,[1] and these data are not reported further.

On Day 8, participants put on the Polar chest strap followed by another 5-min HR baseline measurement. Hereafter, participants gave four 5-min speeches, following the same procedure as Day 1. All participants gave the first three speeches in Context A (i.e., spontaneous recovery test). The fourth speech was either in Context A or Context B (i.e., fear renewal test). Afterward, they completed the VR valence and arousal ratings, the BCL, and the VR questionnaire. When the experiment was finished, participants were asked final questions for exploratory research purposes and were debriefed.

VR Environments

The speech environments were two 360-degree videos depicting an audience (freely derived from https://virtualspeech.com; see Figure S1 in the Supplementary Materials). The virtual audience consisted of either 11 or about 75 individuals with mixed gender and ethnic background. Their facial expressions were neutral to positive, and they had different levels of attentiveness. The environments were fully balanced across

participants. The neutral environment was a 360-degree picture of a room with a couch, a desk, and a computer (purchased from TurboSquid, see https://www.turbosquid.com). The VR environments were presented with an Oculus Rift headset (version CV1; Oculus, USA) and the Oculus Rift App (version 1.19.0.456194).

Data-Analysis

First, to examine whether randomization was successful, we performed one-way ANOVAs to assess the effects of group (Context AA, AB) on age, public speaking fear (PRPSA, BFNE-II), speech performance (BCL Day 1), EPQ-N scores, ASI scores, average speech topic difficulty, HR baseline on Day 1, pre-exposure VR valence and arousal ratings, and the VR questionnaire. A Bayesian Contingency Tables Test assessed group differences in social anxiety disorder diagnosis. Second, to assess whether exposure training was successful (manipulation check), we performed two 4 (Time: four speeches Day 1) × 2 (Group: AA, AB) mixed ANOVAs with HR and SUDS ratings as dependent variables. For each speech, the average HR and the highest SUDS rating were selected for statistical analyses (see Shin & Newman, 2018). We additionally performed two 2 (Time: pre-exposure, post-exposure Day 1) × 2 (Group: AA, AB) mixed ANOVAs with VR valence and arousal ratings as dependent variables. To test whether HR baselines differed across time, we used a repeated-measures ANOVA with time (Day 1, Day 8) as an independent variable. Finally, we tested whether spontaneous recovery occurred for both groups and whether fear renewal occurred for the AB group, with 2 (Time: final speech Day 1, first speech Day 8 [spontaneous recovery]; and third speech Day 8, final speech Day 8 [fear renewal]) × 2 (Group: AA, AB) mixed ANOVAs performed separately for HR and SUDS. We also tested these hypotheses with VR valence and arousal ratings as dependent variables: 2 (Time: post-exposure Day 1, pre-exposure Day 8 [spontaneous recovery]; and pre-exposure, post-exposure Day 8 [fear renewal]) × 2 (Group: AA, AB).

All analyses were performed in JASP version 0.12.2.0 within the Bayesian hypothesis testing framework using the default settings (JASP Team, 2020). Bayes factors quantify the likelihood of the data under one hypothesis relative to another. For example, BF_{10} = 3.0 would mean that the data are three times more likely under the alternative than the null hypothesis (and vice versa for $BF_{10} < 0.33$; Aczel et al., 2020). We interpreted a BF_{10} between 1.0 and 3.0 as anecdotal evidence, values between 3.0 and 10.0 as moderate evidence, and values greater than 10.0 as strong evidence in favor of the alternative hypothesis. A BF_{10} below 0.33 indicates evidence in favor of the null hypothesis (Jeffreys,

1961; Wagenmakers et al., 2018). These classifications should only be used as a general rule of thumb and not as an absolute rule (Wagenmakers et al., 2018).

HR data were missing at random for Day 1 (n = 5) and Day 8 (n = 4). Missing values were imputed in R version 3.6.1. We generated five imputed data sets with predictive mean matching (five iterations) using the mice package version 3.0 (van Buuren & Groothuis-Oudshoorn, 2011) in R. Analyses of these data sets did not differ from complete case analyses (see also Figure S2 in the Supplementary Materials).

Results

Randomization and Manipulation Checks

We found no evidence that groups differed in age (BF_{10} = 0.38), public speaking fear (BFs_{10} = 0.34–0.37), speech performance on Day 1 (BF_{10} = 0.35), EPQ-N scores (BF_{10} = 0.34), ASI scores (BF_{10} = 0.45), average speech topic difficulty (BF_{10} = 0.62), HR baseline on Day 1 (BF_{10} = 0.45), pre-exposure VR valence (BF_{10} = 0.38) and arousal (BF_{10} = 0.59), VR questionnaire items (BFs_{10} = 0.34–1.11), and social anxiety disorder diagnosis (BF_{10} = 0.40), suggesting successful randomization (see Table 1). On Day 1, HR and subjective distress decreased during the four speeches (Time: $BFs_{10} > 8.81$); see Figure 1. There was no evidence for main or interaction effects of group ($BFs_{10} < 1.30$). From pre- to post-exposure, participants rated the VR environment as less negative (BF_{10} = 3.26) and less arousing (BF_{10} = 4.12), with no evidence for group differences ($BFs_{10} < 0.49$); see Figure 2. Thus, for both groups, HR, subjective distress, negative valence, and arousal ratings declined after exposure.

Spontaneous Recovery

HR increased from the final speech on Day 1 to the first speech on Day 8 (BF_{10} = 30,061.15), with a stronger increase for the AA group (Time × Group: BF_{10} = 2.56), but no evidence for a main effect of group (BF_{10} = 0.55); see Figure 1a. Baseline HR did not differ between Day 1 and Day 8 (BF_{10} = 0.52), with no evidence for a main or interaction effect for group ($BFs_{10} < 0.64$). Subjective distress did not change over time (Time: BF_{10} = 0.33) and there was no evidence for group differences (Time × Group: BF_{10} = 0.33; Group: BF_{10} = 0.57); see Figure 1b. In addition, VR negative valence and arousal ratings did not differ from post-exposure Day 1 to pre-exposure Day 8 ($BFs_{10} < 0.26$), with no evidence for main or interaction effects for group ($BFs_{10} < 0.40$); see Figure 2. Thus, both groups demonstrated spontaneous recovery of HR while giving a speech, but not of subjective distress, negative valence, and arousal ratings.

Fear Renewal

Regarding HR during presenting, there was no evidence for a Time × Group effect (BF_{10} = 0.40); see Figure 1a. Yet, for subjective distress, the expected Time × Group effect indicated large differences in renewal between groups (BF_{10} = 400.93); see Figure 1b. Post hoc analyses, using paired samples *t*-tests, showed that the AB group reported an increase in SUDS ratings from the third to final speech on Day 8 (BF_{10} = 82.78), while the AA group did not (BF_{10} = 1.22). We also observed anecdotal evidence for a Time × Group effect for VR valence (BF_{10} = 2.78) and strong evidence for a Time× Group effect for VR arousal ratings (BF_{10} = 14.49); see Figure 2. Post hoc analyses, using paired samples *t*-tests, showed that the AB group reported an increase in negative valence and arousal ratings from pre- to post-exposure on Day 8 (BFs_{10} > 3.68), while there was no evidence for an increase in the AA group (BFs_{10} < 0.86). Robustness checks on these post hoc analyses indicated that effects were robust for SUDS, and to a lesser extent for VR valence and arousal (see Figure S3 in the Supplementary Materials). Thus, fear renewal was not observed for HR, but it was observed for subjective distress, negative valence, and arousal ratings.

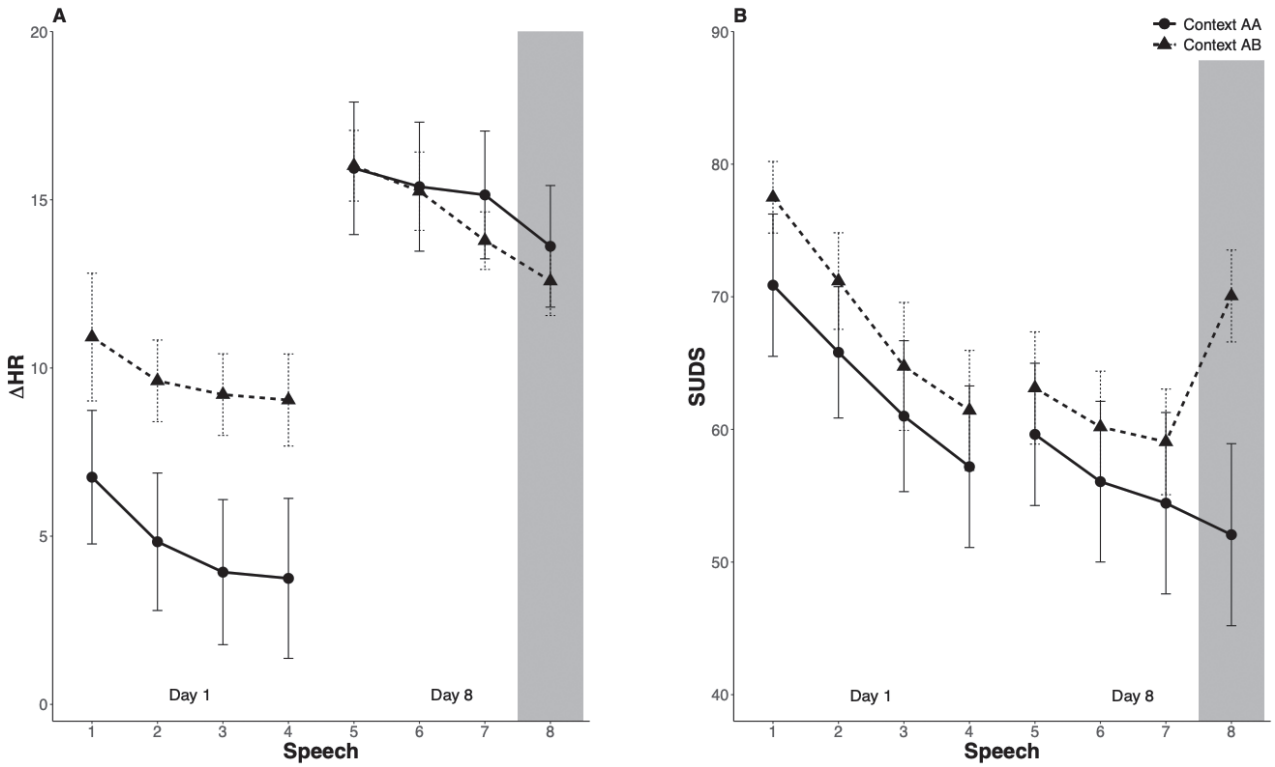
Table 1
Overview of Randomization Variables

		Group	
Questionnaire	**Mean (SD)**	**Context AA**	**Context AB**
Diagnosis; no. (%)	12 (37.50)	6 (37.50)	6 (37.50)
PRPSA	131.63 (16.03)	133.00 (16.98)	130.25 (15.44)
BFNE-II	36.56 (12.76)	37.06 (13.04)	36.06 (12.88)
BCL (Day 1)	83.25 (16.82)	82.31 (17.07)	84.19 (17.07)
EPQ-N	10.75 (5.88)	10.69 (6.34)	10.81 (5.58)
ASI	32.72 (8.22)	31.44 (4.93)	34.00 (10.58)
HR baseline Day 1	84.03 (16.22)	81.73 (18.95)	86.69 (12.58)
Speech topic difficulty	6.44 (1.47)	6.11 (1.58)	6.77 (1.32)
VR negative valence	5.38 (2.21)	5.19 (2.48)	5.56 (1.97)
VR arousal	6.19 (2.04)	6.63 (1.89)	5.75 (2.15)
VR questionnaire			
Physiological complaints	1.18 (0.29)	1.19 (0.32)	1.18 (0.26)
Realness	2.47 (0.86)	2.47 (0.74)	2.47 (0.99)
Immersion	2.80 (1.06)	2.47 (0.99)	3.13 (1.06)
Presence	2.80 (0.89)	2.67 (0.82)	2.93 (0.96)
VR equally challenging as in real-life	2.03 (0.89)	2.07 (0.80)	2.00 (1.00)

Note. SD = standard deviation; PRPSA = Personal Report of Public Speaking Anxiety; BFNE = Brief Fear of Negative Evaluation Scale–II; BCL = Behaviors Checklist; EPQ-N = Neuroticism scale of the Eysenck Personality Questionnaire; ASI = Anxiety Sensitivity Index; HR = heart rate; VR = virtual reality.

Figure 1

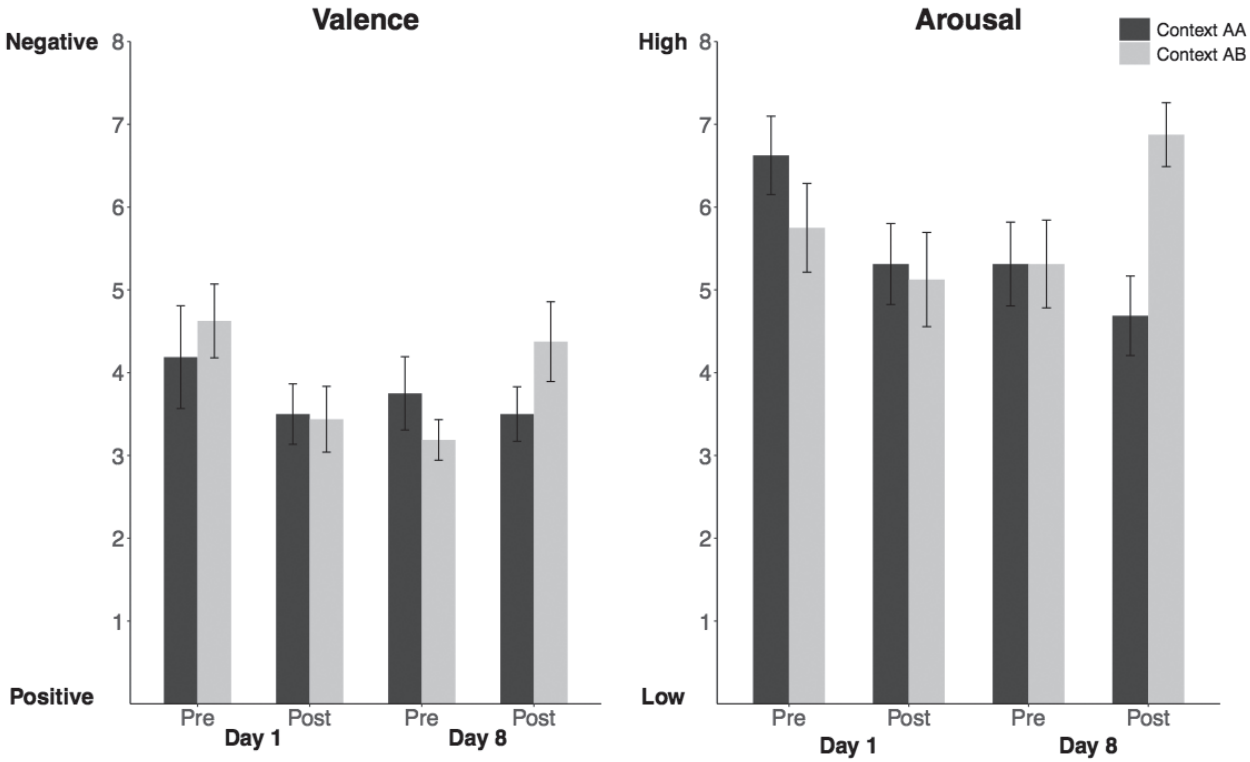
Average Δ HR (Change Scores From Baseline) and Maximum Level of Subjective Distress (SUDS) During the Speeches Across Groups



Note. Error bars reflect standard errors of the mean. The gray shaded areas indicate the context switch; HR = heart rate.

Figure 2

Virtual Reality Audience Valence and Arousal Ratings Across Groups Before and After Exposure on Day 1 and Day 8



Note. Error bars reflect standard errors of the mean; The context switch occurred before the post-measurement on Day 8.

Discussion

This study aimed to validate a newly developed VR paradigm to examine spontaneous recovery and fear renewal in individuals with fear of public speaking. The main findings can be summarized as follows. First, HR, subjective distress, negative valence, and arousal decreased during exposure. Second, 1 week after exposure training, spontaneous recovery occurred for HR during a presentation, which is in line with previous research (Vasey et al., 2012). Third, fear renewal was observed on all subjective measures, which is consistent with Culver et al. (2011, Study 1), except that they also found fear renewal on HR.

Our study expands previous research on the renewal of public speaking fear (Culver et al., 2011; Shin & Newman, 2018) by using VR to enhance experimental control and to facilitate applications in other research labs. One study also tested the renewal of public speaking fear in VR (Craske et al., 2019), but fear renewal did not occur in their setup. One likely explanation for this discrepancy in findings is that, in contrast to our study, they did not control for spontaneous recovery, which may have obscured their fear renewal effect.

Several findings of the current study should be highlighted. First, we found emotional concordance patterns during exposure (reduced HR, subjective distress, negative valence, and arousal ratings), but not during spontaneous recovery and fear renewal tests. This may reflect random variation across response indices and is consistent with findings of similar studies (e.g., Craske et al., 2019; Vasey et al., 2012) and with the general fear conditioning literature (e.g., Mertens et al., 2018) in which subjective and physiological responses also substantially varied. One plausible explanation for this variation is that lab studies may not always evoke sufficient fear for full emotional concordance to occur (Hollenstein & Lanteigne, 2014). Indeed, in our study, we observed high subjective distress ratings and emotional concordance patterns on the first day, whereas 1 week later, lower subjective distress was associated with weaker emotional concordance patterns. Another explanation may be that autonomic fear responding is highly variable across individuals, with high fear associated with HR increases as well as decreases (Hagenaars et al., 2014). It should be noted that spontaneous recovery was observed only for HR (and not subjective distress), while fear renewal occurred only on subjective distress (and not HR). Potentially, a ceiling effect prevented HR renewal effects because HR was already significantly higher during the presentations on the second test day. Future studies that use this procedure could examine whether spontaneous recovery of HR and renewal of subjective distress is a robust pattern or random variation across response indices.

The second finding that should be highlighted is that in our study, participants indicated that they found presenting in VR less challenging than in real life (see Table 1). Nevertheless, our subjective distress ratings were equal to (e.g., Tsao & Craske, 2000) or higher than (Culver et al., 2011; Shin & Newman, 2018) studies with real-life exposure. This is in line with findings among individuals with spider phobia, who exhibited equal fear levels in a VR and real-life setting (Shiban et al., 2015). Taken together, these findings underscore the potential clinical utility of VR in lowering the threshold to start with exposure, albeit being as fear-provoking as real-life exposure.

A third noteworthy finding was that the patterns of subjective valence and arousal closely mirrored those of subjective distress, although effects were stronger for subjective distress. Future research could examine the unique explanatory value of these measures—for example, by testing strategies aimed at reducing negative valence or arousal (e.g., van Dis et al., 2019).

Our VR procedure may pave the way for testing a variety of important research questions. One important question is whether treatment strategies that modulate emotional memories associated with performance anxiety (Kearns & Engelhard, 2015) could reduce fear renewal. In addition, future research may test whether this procedure could help to identify patients with social anxiety who are at risk for clinical relapse after exposure-based therapy (i.e., predictive validity). Another relevant research avenue could be to add a threat expectancy measure (see van Veen et al., 2020) to examine whether within-session fear reduction and renewal can be explained by expectancy violation.

Several limitations of the current study need to be addressed. First of all, statistical power was sufficient for testing the return of fear but limited for exploring individual differences. In addition, our procedure did not measure avoidance responses even though they may play a critical role in relapse (Craske et al., 2018). Future studies may use measures for behavioral and attentional avoidance, such as eye-tracking, to examine whether and when participants avoid facing the audience. Finally, we included only HR as a physiological outcome measure. Skin conductance and fear-potentiated startle measures can be informative additional indices, which may be included in future research (see Constantinou et al., 2021; van Veen et al., 2020). This may also enlighten concordance patterns across fear indices. Strengths include the controlled experimental setup by using VR and the addition of a spontaneous recovery phase using a 2-day procedure.

To conclude, this VR procedure successfully induced spontaneous recovery of HR and renewal of subjective distress, negative valence, and arousal ratings in individuals with a fear of public speaking. Future studies may use this ecologically valid and well-

controlled procedure to test strategies aimed at attenuating the return of fear after exposure in individuals suffering from social anxiety.

Acknowledgments

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Author Contributions

EvD, EL, MH, and IE designed the study. EvD supervised the data collection, performed statistical analyses and drafted the manuscript. FvdD processed the heart rate data. EL, MH, FvdD, and IE critically revised the manuscript. All authors approved the final version of the paper for submission.

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Supplementary Materials

Table S1
Overview of Speech Topics

Set 1	Set 2
Euthanasia	Abortion
President Trump	Nuclear weapons
Death penalty	Smoking in public
Immigration	Violent videogames
Same-sex marriage	Climate change
Animal testing	Organ donation

Note. Topics were balanced across groups and days.

Figure S1
Screenshots of Presentation Contexts in Virtual Reality

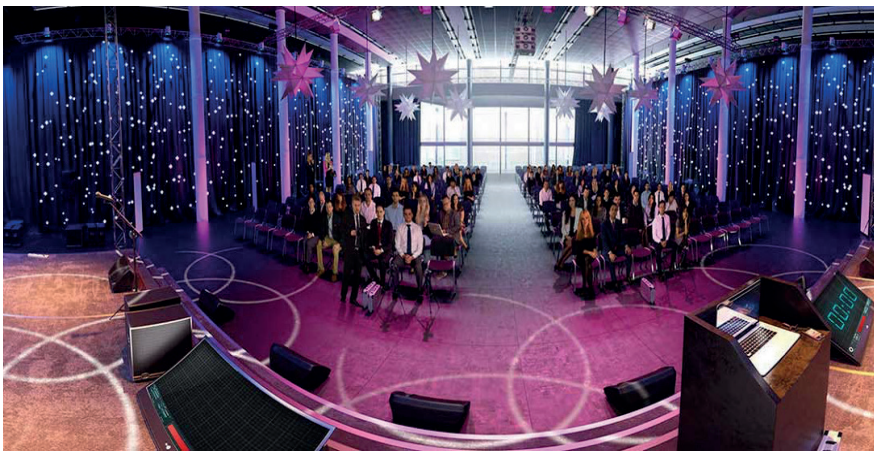
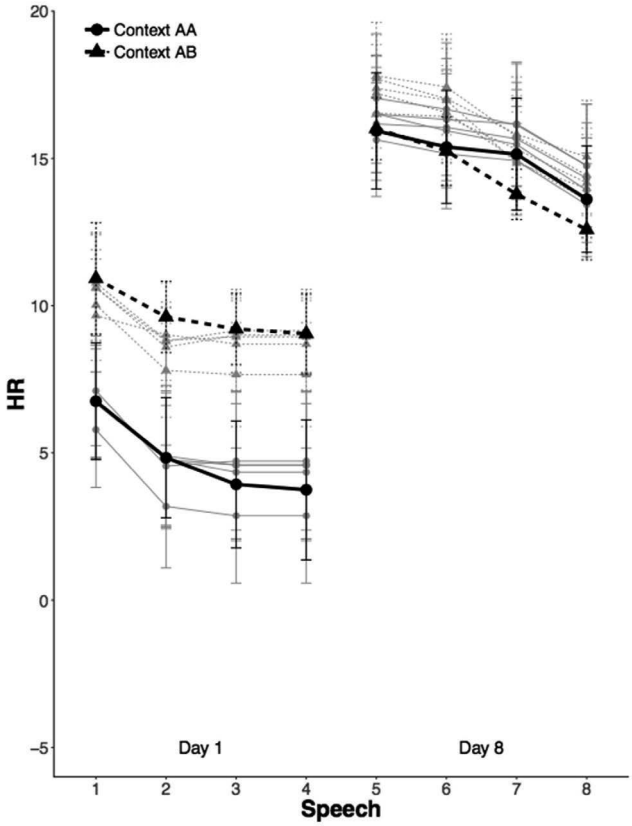


Figure S2

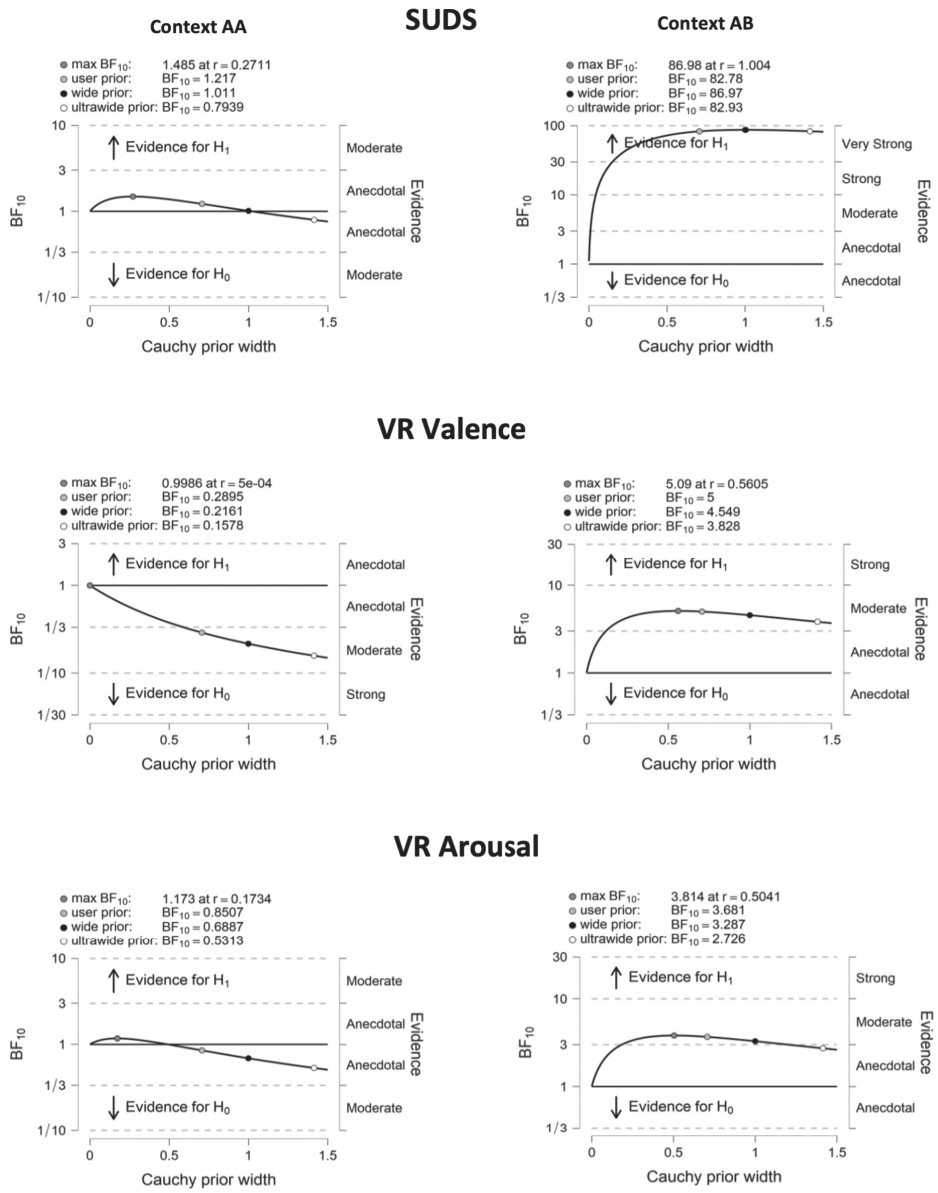
Average Δ HR (Change Scores From Baseline) During Speeches Across Groups



Note. Error bars reflect the standard error of the mean. Gray lines represent five separate heart rate (HR) datasets in which missing data were imputed. The context switch occurred during Speech 8.

Figure S3

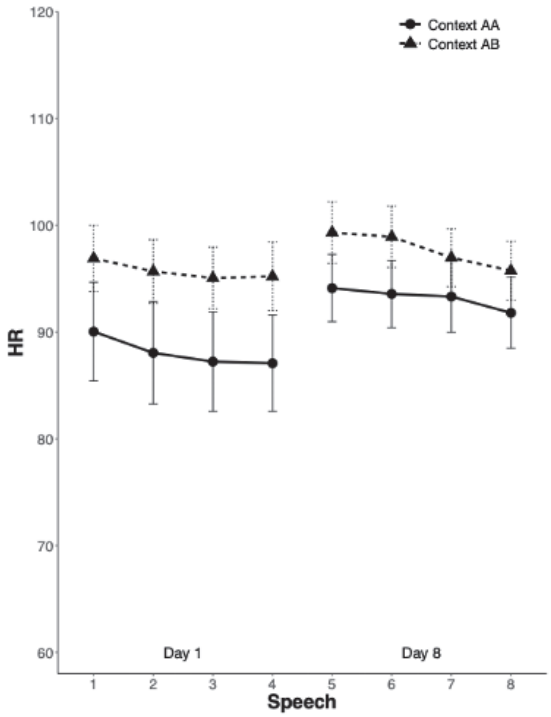
Robustness Analyses for Post-Hoc Paired Samples T-Tests Assessing Renewal Effects for Subjective Distress (SUDS), VR Valence, and VR Arousal Across Groups



Note. VR = virtual reality.

Figure S4

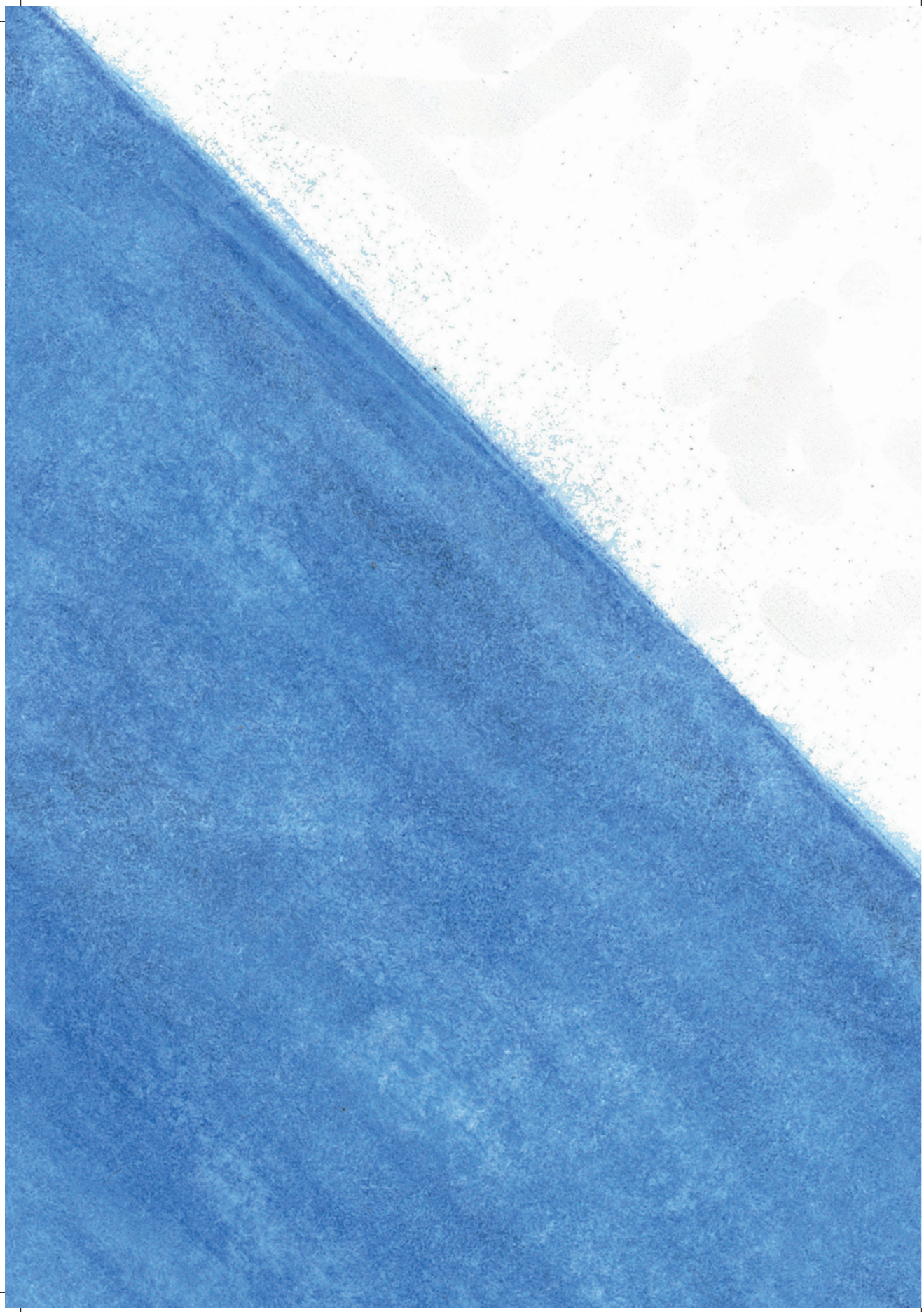
Average Heart Rate (HR) During Speeches Across Groups



Note. Error bars reflect the standard error of the mean. The context switch occurred during Speech 8.

Supplemental Results

On Day 1, HR declined during the four speeches (Time: BF_{10} = 20.49), see Figure S4. There was no evidence for an interaction or main effect of Group (BFs_{10} < 0.50). Hence, for both groups, HR decreased during exposure. Regarding spontaneous recovery, HR increased from the final speech on Day 1 to the first speech on Day 8 (BF_{10} = 5.78), with no evidence for an interaction or main effect for Group (BFs_{10} < 0.88). This indicates that both groups demonstrated spontaneous recovery of HR while giving a speech. Regarding fear renewal, there was no evidence for a Time × Group effect (BF_{10} = 0.37), which suggests fear renewal did not occur on HR (see Figure S4).



Chapter 7

General discussion

Exposure-based cognitive behavioral therapy (CBT) is the recommended treatment for anxiety-related disorders, but a significant number of patients fail to benefit sufficiently from it. To improve treatment effects, rigorous experiments that unravel the underlying mechanisms of these treatments and of novel alternative interventions are crucial. The aim of this dissertation was to unravel mechanisms involved in the development and reduction of learned fear based on the contemporary learning theory. In a series of lab experiments in healthy participants, several proposed mechanisms were manipulated to test their relevance in the development of learned fear (**Chapters 2 and 3**). We also examined the immediate and long-term effects of CBT by conducting a meta-analysis (**Chapter 4**), and we investigated in laboratory experiments how exposure-based interventions could be optimized (**Chapters 5 and 6**). This general discussion starts with a summary of the main findings. This is followed by an integration of our findings into a broader framework of the contemporary learning theory, which will also address the potential clinical implications of the findings. The discussion ends with directions for future research.

Summary of Main Findings

In **Chapter 2**, a study is described that examined whether imagery-based threat rehearsal in the presence of an innocuous cue increases fear generalization and whether threat inflation moderated this effect. Results showed that repeated threat rehearsal increased threat expectancy to a novel innocuous generalization stimulus. After threat inflation, it also increased conditioned distress. Threat inflation did not affect threat expectancy but did increase distress ratings at the start and the end of the rehearsal phase. Thus, repeated mental imagery of threat, especially in the case of an inflated threat, leads to an overgeneralization of fear. If the findings are replicated, then future studies could examine the clinical utility of modulating mental imagery to prevent the development of clinical anxiety in high-risk individuals, such as children of patients with clinical anxiety (Craske, Waters, et al., 2008).

Chapter 3 included two studies that examined whether safety behavior toward an innocuous stimulus maintains or increases threat beliefs when the behavior becomes unavailable. Study 1 showed that from before to after the availability of safety behavior, threat beliefs persisted in the experimental group, while they decreased in the control group. Results were not corroborated on a skin conductance level. In Study 2, it was examined whether threat beliefs had actually increased for individuals in the experimental

group, using a multi-dataset latent class analysis on data from Study 1 and two earlier studies (Engelhard et al., 2015; Xia et al., 2019). Results indicated that about one-fourth of individuals exhibited increased threat expectancy to the innocuous cue when the safety behavior became unavailable. In contrast, almost nobody in the control group exhibited an increase. Collectively, these findings suggest that safety behavior in relatively safe situations may have detrimental effects: it generally maintains and may even increase threat beliefs. An important area for future research would be to examine for whom safety behavior in relatively safe situations leads to learned fear.

In **Chapter 4**, we presented a systematic review and meta-analyse is to estimate the immediate and long-term outcomes after CBT (compared with care-as-usual, relaxation, psychoeducation, pill placebo, supportive therapy, or waiting list) for anxiety-related disorders. The results suggested that CBT for anxiety-related disorders was associated with more substantial symptom reductions than control conditions within 12 months after treatment completion. At longer follow-up, effects were not statistically significant for panic disorder, and the effect size was small to medium for generalized anxiety disorder and social anxiety disorder, large for posttraumatic stress disorder, and not available for specific phobia and obsessive-compulsive disorder (OCD). Relapse rates were predominantly found for panic disorder with or without agoraphobia and were 0-14% 3 to 12 months following treatment completion. There is an urgent need for more high-quality randomized clinical trials with 12 months or more of follow-up to provide more knowledge about long-term efficacy, including relapse rates.

Chapter 5 described two laboratory fear conditioning studies that tested whether counterconditioning (relative to extinction with or without positive material) reduces negative stimulus valence and the return of fear. Both experiments showed that counterconditioning decreased negative stimulus valence compared to the other interventions. Yet, it did not reduce spontaneous recovery or reinstatement of threat expectancy, skin conductance response, and fear-potentiated startle. This suggests that counterconditioning may be promising for reducing negative stimulus valence, which could promote approach behavior, but not for directly attenuating the return of fear.

The final empirical **Chapter 6** contains a validation of a novel two-day virtual reality procedure that we developed to assess the return of public speaking fear following an exposure-based intervention in individuals with public speaking fear. On the first day, participants first received exposure training in front of a virtual audience (Context A). One week later, they received exposure training in front of the same audience (Context A), while half of them ended their exposure session in front of a different virtual context (Context B). Results showed that, on the first day, participants exhibited a lower heart

rate, subjective distress, negative valence, and arousal after exposure. After one week, they showed spontaneous recovery of heart rate, and the context switch group showed renewal of subjective distress, negative valence, and arousal, as predicted. Future studies can use this procedure to test interventions aimed at improving long-term exposure effects in individuals with public speaking fear.

Integration of Findings Into a Broader Framework

Clinical treatment guidelines generally recommend exposure-based CBT for anxiety-related disorders (e.g., National Institute for Health and Care Excellence, 2011, 2013), which has moderate effects immediately after treatment completion (Cuijpers et al., 2016; Hofmann & Smits, 2008). Our meta-analysis (**Chapter 4**) also showed favorable long-term outcomes relative to control conditions, although some of these effects were uncertain. That is, only a few studies included follow-up measures of 12 months or more, so effects were not available for some patient groups (i.e., for specific phobia and OCD), or they were less reliable for these time points due to relatively low statistical power. Furthermore, our systematic review revealed that there is only scant controlled research on relapse after CBT for anxiety-related disorders, and these few studies used ambiguous criteria for response and relapse. Findings from these studies indicated a relapse range between 0-14% (**Chapter 4**), while more recent meta-analyses, which also included uncontrolled studies, estimated relapse rates of approximately 14% (Levy et al., 2021) and 24% (Lorimer et al., 2021). Given the high prevalence of anxiety-related disorders in the general population and mental health care (Bandelow & Michaelis, 2015), this involves large numbers of patients. The findings show that a substantial minority of patients do not benefit from exposure-based CBT in the long run. However, more high-quality studies are needed for more reliable relapse estimations. The observation that symptoms may return after successful exposure-based CBT is in line with findings from fear conditioning and clinical lab studies (Vervliet et al., 2013). For example, in **Chapter 6**, we demonstrated that even though exposure training successfully reduced public speaking anxiety in socially anxious individuals, fear generally returned spontaneously one week later and after a context switch. Thus, even though our meta-analysis demonstrated that CBT may be favorable, there is a need to enhance its immediate and long-term effects. Below, we discuss some strategies examined in this dissertation, which may be relevant for optimizing exposure-based CBT. These focus on threat expectancy, evaluation of threat memory, and instrumental defensive behaviors.

Threat Expectancy

Following contemporary learning theory (Davey, 1997; De Houwer, 2020; Lovibond et al., 2008; Mineka & Zinbarg, 2006) and inhibitory learning model (Bouton, 2004; Craske et al., 2018; Craske, Kircanski, et al., 2008), threat expectancies play an essential role in the etiology, maintenance, and treatment of clinical anxiety. This notion has been supported in studies. For example, individuals who exhibit stronger threat expectancy to novel innocuous generalization cues are more likely to develop anxiety symptoms six-month later (Lenaert et al., 2014). Likewise, soldiers who showed stronger threat expectancies to trauma-related images had more PTSD symptoms over time, even after controlling for initial symptoms (Engelhard et al., 2009). In addition, studies that directly compared exposure therapy aimed at violation of threat expectancy or at fear habituation demonstrated that patients with anxiety disorders profited more from exposure based on expectancy violation (e.g., Deacon et al., 2013). Patients with social anxiety disorder who reported high threat expectancies in the final stages of CBT were also more likely to have more anxiety symptoms at treatment completion (Gregory et al., 2015). Thus, the violation of threat expectancies may be critical for treatment success (but see Scheveneels et al., 2021).

In this dissertation, it was examined whether counterconditioning reduces a return of threat expectancy through reducing negative stimulus valence (**Chapter 5**). The inhibitory learning model advocates reducing negative stimulus valence during exposure because post-extinction negative stimulus valence has been associated with more return of fear and threat expectancy (Craske et al., 2014; Dirikx et al., 2004; Hermans et al., 2005). However, our experiments (**Chapter 5**) demonstrated that although counterconditioning reduced negative stimulus valence, it did not attenuate the return of fear or threat expectancy (see also Luck & Lipp, 2018). Therefore, it may be recommended for reducing negative valence, but not for reducing the return of fear and threat expectancy. The latter finding was contrary to our hypothesis, given that counterconditioning, relative to extinction, could generate a more substantial prediction error (Keller et al., 2020) and strengthen episodic memories of safety learning (Keller & Dunsmoor, 2020), which may be crucial for enhancing inhibitory learning. In fact, two studies showed that counterconditioning reduced a return of fear at 24h follow-up more than extinction (Kang et al., 2018; Keller & Dunsmoor, 2020). How can this discrepancy with our findings be explained? One methodological difference between our experiments (**Chapter 5**) and the other studies (Kang et al., 2018; Keller & Dunsmoor, 2020) was that our experiments used a more complex and salient positive outcome (i.e., film clips instead

of pictures) during counterconditioning. Perhaps, the presence of a salient positive outcome may have enhanced participants' context discrimination, thereby making our counterconditioning effects more context-dependent (see Holmes et al., 2016; Keller et al., 2020). Indeed, novelty-facilitated extinction (in which neutral and less salient instead of positive outcomes are presented) seems a successful strategy to attenuate the return of conditioned fear in healthy individuals (Dunsmoor et al., 2015, 2019; Lucas et al., 2018; but see Krypotos & Engelhard, 2018). Yet, more research is needed to examine boundary conditions and test the potential clinical utility of such strategies. Only a few studies have tested counterconditioning in patients with clinical anxiety, which yielded mixed findings (Keller et al., 2020). Note that the novel clinical technique "association splitting", which shares similarities with novelty-facilitated extinction, seems promising for treating OCD (e.g., Jelinek et al., 2018; Moritz et al., 2007).

Alternatively, the *mental rehearsal* of positive outcomes may reduce threat expectancy, thereby optimizing exposure effects. As demonstrated in **Chapter 2**, mental rehearsal of threat during a novel innocuous stimulus increased threat expectancy to this stimulus. Likewise, prolonged threat rehearsal maintained threat expectancy during exposure training. Therefore, reducing threat rehearsal (e.g., through safety rehearsal) in patients who undergo exposure-based interventions may strengthen extinction learning. Interestingly, a recent fear conditioning study showed that individuals who engaged in positive mental imagery during extinction (i.e., imagery-based counterconditioning) exhibited reduced distress ratings during extinction but not reduced threat expectancy or avoidance behavior (Hendrikx et al., 2021). Potentially, their limited effects of positive rehearsal could be explained by the fact that the positive imagery (e.g., imagining the sound of an exciting crowd) was not necessarily relevant to the threatening stimulus (e.g., a female scream). Indeed, when positive mental imagery is not directly relevant to a task, it may even increase state anxiety relative to a no imagery control group, while task-relevant positive mental imagery reduced state anxiety (Montijn et al., 2021). Likewise, recent studies showed that exposure-relevant positive imagery improved exposure effects in the lab (Carpenter et al., 2021; Landkroon, van Dis, et al., 2021; McGlade & Craske, 2021), including extinction retention (Dibbets et al., 2012).

Even though a central tenet of inhibitory learning model is that stronger expectancy violation improves exposure therapy outcomes, other relevant learning processes should also be recognized. That is, while threat expectancy violation is relevant for sequential learning (*if X happens, then I expect Y*), it is less relevant for referential (*X reminds me of Y*) or evaluative learning (*X is negative because it has been associated with Y*). For example, some anxiety-related disorders, such as posttraumatic stress disorder (PTSD), seem to result

from referential learning, which is relatively resistant to extinction (Baeyens et al., 1988; Engelhard et al., 2014). Indeed, VR exposure training reduced distress and heart rate in socially anxious individuals, but it seemed to diminish negative valence to a lesser extent (**Chapter 6**). This is in line with clinical studies on exposure for spider and blood-injection-phobia, in which the decay slope was also greater for fear than disgust measures (e.g., Olatunji et al., 2007).

In sum, increasing violation of threat expectancy may be important for exposure-based therapy. Yet, to optimize exposure therapy, other mechanisms, such as the evaluation of threat memories (i.e., relevant to referential learning) and instrumental defensive behaviors (i.e., relevant to evaluative learning), should be taken into account (see Figure 1, **Chapter 1**).

Evaluation of Threat Representations

According to the contemporary learning theory, negative evaluations of mental threat representations also contribute to the intensity of learned fear (e.g., Davey, 1997; Vervliet et al., 2013). Fear conditioning research has indeed shown that inflated threat evaluations increase conditioned fear. For example, fear increases after an experience with a threat of similar or greater intensity (e.g., Hosoba et al., 2001; Leer & Engelhard, 2015; White & Davey, 1989), through verbal information (e.g., Davey, 1983), or social observations (e.g., Dunne & Askew, 2013; Reynolds et al., 2015). One of our fear conditioning studies extended these results by showing that threat inflation, particularly in combination with rehearsal, might also lead to distress to a novel stimulus or situation (i.e., generalization; **Chapter 2**). This fits well with observations from studies showing that socially anxious individuals who recalled a threat memory (e.g., poor performance of public speaking) while giving a speech reported more social anxiety symptoms in that novel public speaking situation, relative to individuals who kept a neutral image in mind (Makkar & Grisham, 2011; see also Hirsch & Holmes, 2007). Thus, fundamental and clinical research findings suggest that a negative evaluation of threat maintains or increases learned fear. Reversely, a landslide of studies have shown that reducing the negative evaluation of threat memories (e.g., by disrupting the original fear memory) may attenuate learned fear (e.g., Engelhard et al., 2010; Kindt et al., 2009; Leer, Engelhard, Altink, et al., 2013; Leer, Engelhard, Dibbets, et al., 2013; Soeter & Kindt, 2011), although the exact working mechanisms of such interventions remain disputed (Elsey et al., 2018; Engelhard et al., 2019).

There are at least two reasons to expect that the efficacy of exposure-based therapy may be improved when combined with strategies aimed at reducing these negative

evaluations, such as eye movement desensitization and reprocessing (EMDR; Shapiro, 2017) and imagery rescripting (Morina et al., 2017). A first reason is that, as pointed out earlier, exposure-based CBT may predominantly reduce sequential or expectancy-based learning rather than negative threat representations (e.g., intrusive memories). Therefore, adding threat deflation strategies may also reduce fear related to referential learning. Only a few randomized clinical trials have provided preliminary support for the hypothesis that adding a threat deflation strategy to exposure-based CBT can enhance treatment outcomes. For example, patients diagnosed with PTSD showed stronger reductions of anger and guilt, and reduced dropout after imaginal exposure plus imagery rescripting than following imaginal exposure only (Arntz et al., 2007). Likewise, when CBT for social anxiety disorder was combined with imagery rescripting, symptoms were more substantially reduced at six months following treatment completion than after CBT with relaxation or supportive counseling (Reiss et al., 2017). Another reason to combine exposure-based CBT with threat deflation strategies is that patients may refuse to start with exposure-based CBT or stop with treatment after early sessions (Bentley et al., 2021). Interventions aimed at reducing negative evaluation of threat may lower the threshold for patients to start with exposure-based therapy. Indeed, when individuals with elevated levels of social anxiety were asked to listen to and imagine a public speaking scenario that ended positively, they experienced less anticipatory anxiety before exposure and less distress during exposure training relative to a control condition without positive mental imagery (Landkroon, van Dis, et al., 2021).

Instrumental Defensive Behaviors

The role of instrumental defensive behaviors has been largely ignored in contemporary learning theory of fear and anxiety, even though they may also play a key role in the onset, maintenance, and reduction of clinical anxiety (Krypotos et al., 2018; Pittig et al., 2020). Previous research has shown that safety behavior to danger (e.g., Lovibond et al., 2009) or safety cues (Engelhard et al., 2015; Xia et al., 2019) maintains or increases threat beliefs. In **Chapter 3**, previous experiments were replicated by showing that safety behavior to an innocuous cue generally maintains threat beliefs when the safety behavior had become unavailable. In addition, the data were collapsed with those from two previous studies (Engelhard et al., 2015; Xia et al., 2019) and were jointly analyzed. This uncovered individual differences in the effect of safety behavior on threat beliefs. For most participants, safety behavior maintained threat expectancy, while for approximately a quarter of participants, safety behavior led to increased threat expectancy when the

behavior became unavailable (**Chapter 3**). This implies that safety behavior is only detrimental for specific groups. The results are in line with a recent study demonstrating that individuals with elevated, relative to lower, obsessive-compulsive symptoms perform more safety behavior toward innocuous stimuli and exhibit increased threat expectancies and physiological threat responding to these stimuli (Hunt et al., 2020). Likewise, individuals high in harm avoidance or intolerance of uncertainty are more likely to apply 'better safe than sorry' strategies (Charpentier et al., 2017) and may therefore be more likely to engage in safety behavior (e.g., Flores et al., 2018). These traits may be particularly relevant to investigate in future studies examining trajectories of safety behavior effects.

Exposure-based CBT requires that patients reduce avoiding innocuous fear-related situations. Nevertheless, extinction learning does not necessarily lead to reduced safety behavior (van Uijen et al., 2018; Vervliet & Indekeu, 2015). Therefore, to reduce avoidance or safety behavior, alternative strategies may be needed in addition to exposure-based CBT. One approach could be to target evaluative learning because accumulating evidence suggests that more negative stimulus valence enhances avoidance behavior (Krieglmeyer et al., 2010; Paulus et al., 2017). Perhaps, reducing negative stimulus valence could reduce avoidance and safety behavior, but this is an empirical question that needs to be tested. Another approach could be to reduce the negative evaluation of the threat memory (see the previous section) because when the expected outcome is evaluated less negatively, the motivation for avoidance behavior may decrease. One study demonstrated that threat, but not neutral, rehearsal enhances safety behavior (Krypotos et al., 2020), but future research needs to examine whether threat deflation also decreases avoidance or safety behavior. However, it should be noted that the instrumental behavior of patients has often become habitual, which may be relatively insensitive to changes in expected outcomes (Cain, 2019). Therefore, habit formation strategies such as implementation intentions (Toli et al., 2016) or habit reversal training (Toffolo & Saxena, 2019) may be up-and-coming add-on techniques to CBT.

Note that it remains a debate whether safety behaviors should be eliminated during exposure-based therapy. The inhibitory learning model advocates eliminating these behaviors (Craske et al., 2014; Craske, Kircanski, et al., 2008) because they may interfere with corrective learning (Blakey et al., 2019). Yet, there is only limited evidence for the notion that dropping safety behavior during exposure therapy leads to more substantial reductions in self-reported fear (Meulders et al., 2016). Therefore, more research is needed to test whether and when safety behaviors should be allowed or eliminated during

exposure therapy. A future research avenue would be to examine whether individual differences (e.g., in intolerance of uncertainty) explain when safety behavior during exposure enhances or reduces treatment outcomes (see **Chapter 3**). For example, as Meulders et al. (2016) pointed out, individuals may vary in their motivation and reasons to perform safety behavior. Indeed, safety behavior interfered more strongly with extinction when individuals performed safety behavior to avoid a painful stimulus, but not when they performed the behavior to improve task performance (Volders et al., 2015).

Directions for Future Research

Several novel avenues for future research flow from this dissertation. First, an important next step would be to test whether exposure-based CBT becomes more efficacious when expectancy learning is optimized or combined with additional strategies to modulate threat memories directly. How could this be examined? Following the translational research program on fear extinction (Vervliet et al., 2013), it would be relevant to conduct studies that range from fundamental lab studies to clinical trials. That is, each level on the translational continuum may have certain advantages, such as highly controlled settings in fundamental studies and more ecologically valid settings and populations in clinical trials. In **Chapter 6**, we have presented a novel paradigm that may be the best of both worlds: a highly controlled as well as an ecologically valid setting that included individuals with existing fears. Yet, to facilitate translational research, it is critical to align outcome measures at different levels on the translational dimension. Specifically, most clinical trials on exposure-based therapy use symptoms or distress levels as outcome measures (e.g., **Chapter 4**), but they often do not measure threat expectancy or physiological outcome measures. Conversely, fear conditioning studies predominantly use physiological measures and threat expectancy as main dependent variables, while it may be especially relevant to assess other outcomes, such as distress (**Chapter 2**), instrumental behavior (**Chapter 3**), or threat evaluation (e.g., Leer, Engelhard, Dibbets, et al., 2013; Landkroon, Salemink, et al., 2021). Therefore, future studies that use our validated VR paradigm (**Chapter 6**) may consider adding outcome measures such as threat expectancy, instrumental behavior, and evaluation of threat memories. The inclusion of these outcome measures may help to elucidate and test relevant mechanisms for improving exposure-based CBT.

Second, many experiments along the translational continuum use group-based statistical analyses, which typically apply a rather simplistic 'one size fits all' approach (e.g.,

Chapters 2, 4, 5, and 6). However, as shown in **Chapter 3** (Study 2), individuals may vary substantially in response to experimental manipulations. Careful examination of such individual variations may yield significant insights into disorder- and treatment-specific mechanisms (see Lonsdorf & Merz, 2017; Duits et al., 2021). For example, a pivotal next step of our meta-analysis (**Chapter 4**) could be to perform an individual participant data meta-analysis to unfold who is likely to benefit from CBT and whom not.

Third, it remains important to critically test the predictive and diagnostic validity of our fundamental studies in clinical samples (Scheveneels et al., 2016). It is promising that some studies have clearly demonstrated that performance during fear conditioning tasks predicts the onset and maintenance (e.g., Engelhard et al., 2009; Lenaert et al., 2014; Lommen et al., 2013; Sijbrandij et al., 2013) of anxiety-related symptoms, as well as the treatment success of exposure-based CBT (Duits et al., 2021). Yet, to our knowledge, no studies have examined whether the return of fear in the lab has also been associated with less favorable long-term outcomes after exposure-based CBT.

Conclusion

Exposure-based CBT is, generally, efficacious for the treatment of anxiety-related disorders. However, research along the translational continuum has shown that its effects should be enhanced, given dropout, insufficient benefit, and relapse. The aim of this dissertation was to unravel mechanisms that may be relevant for the development of learned fear and for improving exposure-based CBT. Based on our extended model of the contemporary learning theory, we have examined the role of threat expectancy, evaluations of threat memories, and instrumental defensive behavior. In line with the inhibitory learning model, our findings suggest that interventions aimed at threat expectancy violation (e.g., counterconditioning or mental rehearsal strategies) may improve exposure effects. However, more attention should also be paid to other relevant mechanisms of reducing learned fear, such as modulating threat memories and reducing relapse of avoidance and safety behavior. Future research should examine whether patients who do not benefit from exposure-based CBT may show superior treatment outcomes when they are provided with such alternative or add-on interventions.

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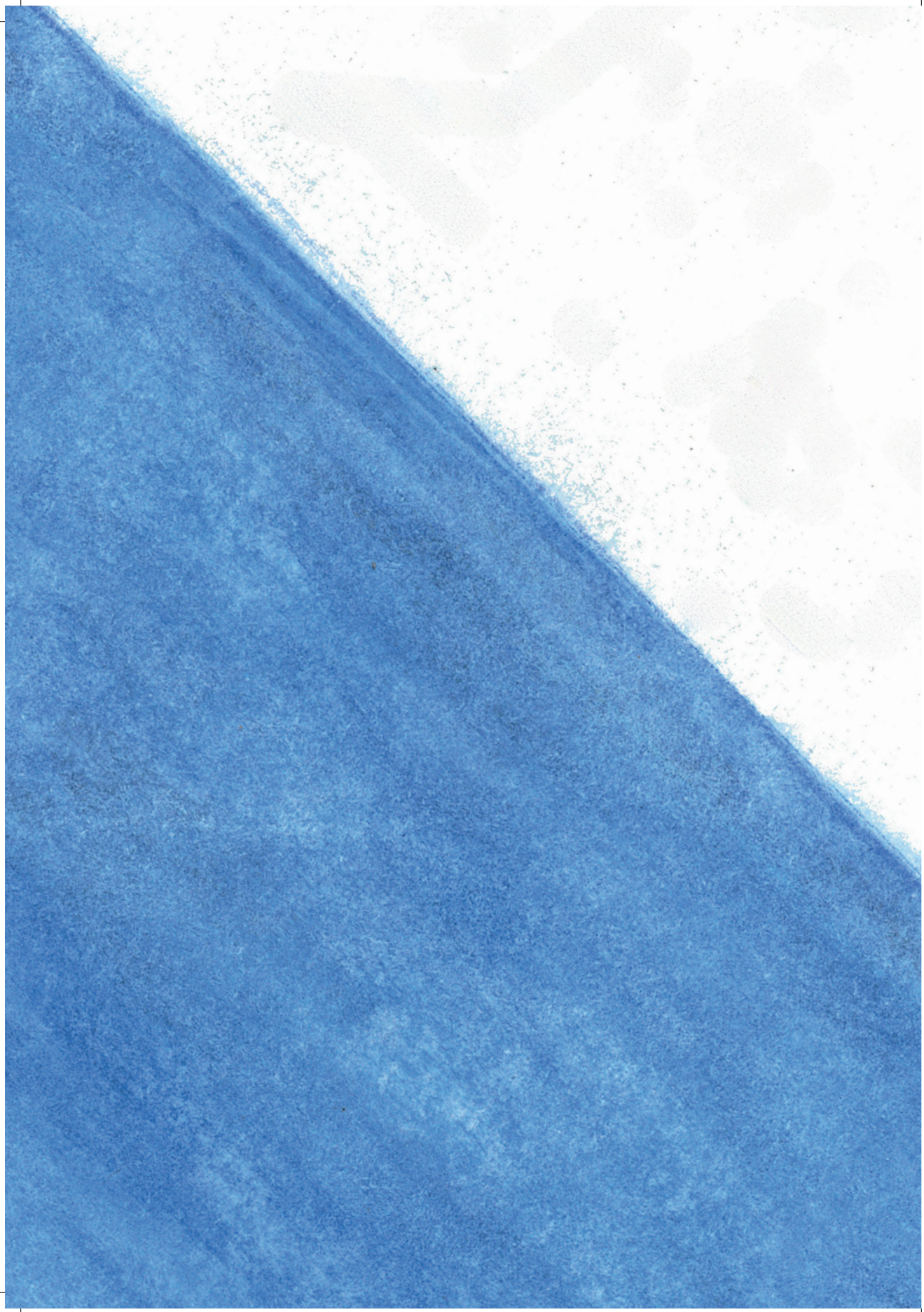


Dutch summary

Nederlandse samenvatting

De Cirkel van Angst Doorbreken: Een Experimentele Benadering

Angst is een essentiële emotie voor onze overleving. Wanneer gevaar dreigt, helpt angst ons om te kunnen vluchten, te vechten of te bevriezen. In relatief veilige situaties is het echter niet nuttig om sterke angstreacties te hebben en dit is precies wat zo kenmerkend is voor patiënten met een angst-gerelateerde stoornis. Deze personen ervaren extreme angstreacties en vertonen vermijdingsgedrag, wat hun dagelijks functioneren beduidend kan beperken. Naar schatting voldoet 1 op de 10 mensen tijdens hun leven aan de diagnostische criteria van een angst-gerelateerde stoornis. De persoonlijke en maatschappelijke lasten van angststoornissen zijn aanzienlijk en daarom is effectieve behandeling nodig. Op dit moment is cognitieve gedragstherapie (CGT) de aanbevolen behandeling. Een cruciaal onderdeel van CGT is exposure. Tijdens exposure worden patiënten herhaaldelijk blootgesteld aan relatief veilige, maar voor hen angstopwekkende stimuli of situaties (bijvoorbeeld een supermarkt), om te leren dat het gevaar dat ze verwachten (bijvoorbeeld flauwvallen) niet optreedt. Hoewel deze behandeling redelijk effectief is op te korte termijn, is er ruimte voor verbetering. Sommige patiënten weigeren de therapie, anderen stoppen voortijdig of verbeteren er weinig door. Ook ervaren sommige patiënten een terugkeer van hun klachten na afloop van de behandeling. Het inhibitoire leermodel stelt dat het disconfirmeren van de gevaarsverwachting in relatief veilige situaties het mechanisme is dat ten grondslag ligt aan de werking van exposure. Klinische en lab studies hebben aangetoond dat de verwachting van gevaar zoveel mogelijk ontkracht moet worden om een goed behandelresultaat of daling in aangeleerde angst te krijgen.

Een veelgebruikte lab methode om mechanismen van de ontwikkeling en behandeling van aangeleerde angst te onderzoeken is angstconditionering. Deze methode begint doorgaans met een zogenaamde 'acquisitiefase', waarbij een neutrale stimulus (bijvoorbeeld een afbeelding) gevolgd wordt door een aversieve stimulus (bijvoorbeeld een milde elektrische prikkel of het geluid van een schreeuw), terwijl een andere neutrale stimulus nooit wordt gevolgd door een aversieve stimulus. Zo leren de participanten doorgaans angst aan voor de neutrale stimulus (gevaar cue) die de aversieve stimulus (gevaar) voorspelt, maar niet voor de neutrale stimulus (veiligheid cue) die de aversieve stimulus *niet* voorspelt. Deze acquisitiefase wordt vaak gevolgd door een zogenaamde 'extinctiefase', het lab model van exposure therapie. In deze fase worden de veiligheid en gevaar cues herhaaldelijk getoond zonder dat de aversieve stimulus volgt. Voor de

meeste mensen daalt de angst gedurende deze fase. Dit model werd gebruikt in diverse onderzoeken die in dit proefschrift zijn beschreven.

Het doel van de onderzoeken in dit proefschrift was een bijdrage leveren aan kennis over het verbeteren van de behandeling van aangeleerde angst. Daartoe zijn manieren onderzocht die de verwachting van gevaar kunnen verminderen. Daarnaast zijn andere mechanismen onderzocht die relevant zijn voor de ontwikkeling en behandeling van aangeleerde angst. Volgens de hedendaagse leertheorie wordt de intensiteit van aangeleerde angst niet alleen bepaald door de verwachting van gevaar, maar ook door mentale voorstellingen van gevaar (bijvoorbeeld herinnering aan een traumatische gebeurtenis). Ook de rol van instrumenteel defensief gedrag bij de ontwikkeling van angst is onderzocht.

In deel 1 van het proefschrift (**Hoofdstukken 2 en 3**) hebben we met name getoetst hoe de verwachting van gevaar, mentale voorstellingen van gevaar en instrumenteel defensief gedrag de aangeleerde angst in stand houden of verergeren. In deel 2 (**Hoofdstukken 4, 5 en 6**) is nagegaan wat de effectiviteit is van (op exposure gebaseerde) cognitieve gedragstherapie en hoe de effecten van exposure geoptimaliseerd kunnen worden. In **Hoofdstuk 7** worden de bevindingen besproken in relatie tot de bestaande literatuur. Tevens wordt ingegaan op theoretische en klinische implicaties van de resultaten en worden aanbevelingen gedaan voor toekomstig onderzoek.

Het Ontstaan van de Cirkel van Angst

Zoals gezegd is bij angst-gerelateerde stoornissen niet alleen de verwachting van gevaar relevant, maar ook de ernst van gevaar. Als je verwacht dat je in een supermarkt flauwvalt zul je doorgaans minder angstig zijn dan als je verwacht dat je daar een hartinfarct gaat krijgen. Zulke mentale voorstellingen van gevaar kunnen de vorm hebben van een flashback van een traumatische gebeurtenis of van een rampfantasie over de toekomst. Eerder onderzoek heeft aangetoond dat het inbeelden van gevaar een rol kan spelen in de ontwikkeling van aangeleerde angst. Het doel van het onderzoek in **Hoofdstuk 2** was om na te gaan of herhaaldelijk inbeelden van gevaar (een aversieve stimulus) tijdens het zien van een nieuwe neutrale stimulus bijdraagt aan angst voor die nieuwe stimulus ('generalisatie'). Er is ook nagegaan of de effecten van het inbeelden van een aversieve stimulus ('gevaar') sterker waren na zogenaamde 'inflatie' van die stimulus, waarbij de intensiteit van de toediening toenam. Deelnemers aan het onderzoek doorliepen een computertaak waarbij ze begonnen met een acquisitiefase, waarin twee neutrale afbeeldingen van een mannen- en vrouwengezicht herhaaldelijk werden getoond. Eén van deze afbeeldingen, bijvoorbeeld het gezicht van een man (de gevaar cue), werd

telkens gevolgd door een nare stimulus (het geluid van een harde schreeuw), maar de andere afbeelding, bijvoorbeeld het gezicht van een vrouw (de veiligheid cue) niet. Daarna volgde een inflatie fase waarbij participanten 11 keer de schreeuw te horen kregen, maar dit keer zonder de aanwezigheid van de gevaar en veiligheid cues. Voor de helft van hen bleef het geluidsniveau van de schreeuw gelijk (60 dB), maar voor de andere participanten nam het geluidsniveau van de schreeuw toe van 60dB naar 100 dB. Hierna kreeg de helft van de participanten de opdracht om tijdens het zien van 'het gezicht van een man' de laatst gehoorde schreeuw zich zo levendig mogelijk in te beelden. Tijdens deze laatste fase van het experiment kregen de deelnemers opnieuw de twee afbeeldingen (zonder schreeuw) te zien: de veiligheid cue en een nieuwe afbeelding (de generalisatiestimulus) die perceptueel leek op de gevaar cue. Er waren dus vier groepen: 1) gevaar inflatie met inbeelding, 2) gevaar inflatie zonder inbeelding, 3) geen gevaar inflatie met inbeelding en 4) geen gevaar inflatie zonder inbeelding. Gedurende het experiment gaven de deelnemers bij elk plaatje aan in hoeverre ze een schreeuw verwachtten en wat hun huidige spanningsniveau was. Uit dit onderzoek kwam naar voren dat participanten die zich herhaaldelijk de schreeuw hadden ingebeeld tijdens de generalisatiestimulus, een sterkere verwachting hadden dat die schreeuw daadwerkelijk zou optreden bij deze nieuwe stimulus. Wanneer participanten zich de schreeuw hadden ingebeeld waarvan het geluid harder was geworden, rapporteerden ze ook meer spanning tijdens het zien van de generalisatiestimulus. Gevaar inflatie (met of zonder inbeelding) leidde niet tot een verhoging van de gevaarsverwachting, maar wel tot een verhoogd spanningsniveau voor de generalisatiestimulus. Kortom, niet alleen daadwerkelijke blootstelling aan een aversieve gebeurtenis kan leiden tot aangeleerde angst, maar ook het eigen voorstellingsvermogen: naarmate gevaar intenser wordt ingebeeld, neemt angst toe. Als deze bevindingen worden gerepliceerd, dan zou toekomstig onderzoek kunnen nagaan of het moduleren van mentale inbeeldingen het ontstaan van klinische angst kan voorkomen bij mensen die een hoog risico hierop lopen (bijvoorbeeld bij kinderen van mensen met een angst-gerelateerde stoornis).

Eén van de kenmerkende symptomen van angst-gerelateerde stoornissen is vermijding- en veiligheidsgedrag. Dit zijn gedragingen die als doel hebben om de kans op gevaar te voorkomen of de ernst ervan te laten afnemen. Zo vermijden sommige patiënten met een paniekstoornis een supermarkt, om te voorkomen dat ze daar zullen flauwvallen. In diverse onderzoeken is echter aangetoond dat dit soort gedrag de angst in stand kan houden of versterken. In **Hoofdstuk 3** zijn twee angstconditionering studies beschreven

die als doel hadden om na te gaan of veiligheidsgedrag (een vorm van instrumenteel defensief gedrag) bij een veiligheid cue kan leiden tot een stijging of instandhouding van angst. In Studie 1 begonnen participanten met een acquisitiefase waarin één stimulus (bijvoorbeeld blauw vierkant; de gevaar cue) op het computerscherm altijd werd gevolgd door een milde elektrische schok op hun vinger, terwijl twee andere stimuli (bijvoorbeeld gele en roze vierkanten; de veiligheid cues) nooit werden gevolgd door de schok. Hierna volgde een 'veiligheidsgedrag' fase, waarbij er tijdens de gevaar cue, maar niet tijdens de andere cues, een lampje ging branden. Wanneer het lampje brandde en de deelnemers op een knop drukten, konden zij daarmee de schok voorkomen. Als ze niet op de knop drukten of het lampje niet ging branden, dan kregen ze alsnog de schok. In de volgende fase kreeg de experimentele groep de mogelijkheid om het veiligheidsgedrag bij een van de veiligheid cues toe te passen (het lampje ging dan bijvoorbeeld tijdens het roze vierkant branden). Bij de controlegroep brandde er geen lampje tijdens deze fase. Daarna volgde een testfase waarin alle cues opnieuw werden getoond, maar dit keer kreeg niemand de mogelijkheid om veiligheidsgedrag toe te passen. De hypothese was dat de experimentele groep, ten opzichte van de controlegroep, in de testfase een hogere verwachting van gevaar en sterkere zweetrespons zou laten zien bij de veiligheid cue waarbij eerder veiligheidsgedrag mogelijk was. Resultaten toonden aan dat de verwachting van gevaar gelijk bleef in de experimentele groep, maar daalde in de controlegroep. Er waren geen effecten op de zweetrespons. Met andere woorden, wanneer mensen in een relatief veilige situatie veiligheidsgedrag toepassen, kan dit de een a priori verwachting van gevaar in stand houden.

Het doel van Studie 2 was om na te gaan of de verwachting van gevaar vaker zou stijgen voor mensen in de experimentele groep vergeleken met de controlegroep. Om dit te onderzoeken zijn de data van Studie 1 en twee vergelijkbare studies die eerder gepubliceerd waren samengevoegd. Uit Bayesiaanse en latente klassenanalyses bleek dat ongeveer een kwart van de deelnemers uit de experimentele groep een stijging van de gevaarsverwachting liet zien vanaf het moment voorafgaand tot na de beschikbaarheid van het veiligheidsgedrag bij de veiligheid cue. Daarentegen liet vrijwel niemand in de controlegroep een dergelijke stijging zien. De bevindingen van deze twee studies suggereren dat veiligheidsgedrag in relatief veilige situaties nadelige effecten kan hebben, namelijk geen daling van angst, maar juist een instandhouding of stijging ervan. Een vervolgstudie zou kunnen nagaan bij welke mensen veiligheidsgedrag in relatief veilige situaties leidt tot aangeleerde angst.

Het Doorbreken van de Cirkel van Angst

Hoewel CGT de aanbevolen behandeling voor angst-gerelateerde stoornissen is, is tot op heden weinig bekend over de lange termijn effectiviteit. Het doel van de studie die in **Hoofdstuk 4** is beschreven was om te onderzoeken wat de lange termijn effectiviteit van CGT is voor angst-gerelateerde stoornissen ten opzichte van controlegroepen, zoals mensen die op een wachtlijst staan of die placebomedicatie krijgen. Hiertoe hebben wij eerst een systematisch literatuuronderzoek gedaan en de statistische gegevens van relevante onderzoeken samengevoegd (ook wel een meta-analyse genoemd). De resultaten van deze meta-analyse lieten zien dat CGT voor angst-gerelateerde stoornissen geassocieerd was met een sterkere symptoomreductie binnen een jaar na afloop van de behandeling ten opzichte van de controlegroepen. Opvallend was dat er slechts weinig studies waren waarbij nametingen van minstens 12 maanden na afloop van de behandeling werden verricht. De studies die dat wel gedaan hadden lieten zien dat de effecten van CGT na 12 maanden of langer afwezig waren voor paniekstoornis (met of zonder agorafobie), en dat de effectgrootte klein tot gemiddeld was voor gegeneraliseerde angststoornis en sociale angststoornis, groot was voor PTSS en onbekend was (doordat er geen beschikbare studies waren) voor specifieke fobie en OCS. Het aantal patiënten dat terugviel na een succesvolle behandeling varieerde van 0 tot 14% tussen 3 tot 12 maanden na afloop van de behandeling, en dit werd met name gerapporteerd voor patiënten met een paniekstoornis. Er is dus meer gerandomiseerd klinisch onderzoek nodig waarin minstens een jaar na afloop van de behandeling terugval wordt onderzocht.

Een van de redenen waarom angst na succesvolle exposure terug kan keren is dat de negatieve valentie van een angst-gerelateerde stimulus of situatie onveranderd is gebleven. Uit eerder onderzoek is inderdaad gebleken dat exposure weliswaar leidt tot een daling van de gevaarsverwachting, maar dat een stimulus of situatie (zoals de supermarkt uit het eerdergenoemde voorbeeld) vaak aversief blijft. Dat kan ertoe leiden dat vermijdingsgedrag terugkeert na de behandeling en de angstklachten weer gaan toenemen. In **Hoofdstuk 5** is daarom middels twee experimenten nagegaan of het verminderen van negatieve stimulus valentie de terugkeer van angst reduceert. In beide experimenten onderzochten we of counterconditionering leidt tot minder negatieve stimulus valentie en minder terugkeer van angst. Bij counterconditionering wordt de acquisitiefase gevolgd door een fase waarin de gevaar cue gepaard wordt met een stimulus die een tegenovergestelde valentie heeft (een positieve stimulus in dit geval). We vergeleken de effectiviteit van een dergelijke procedure met twee controlegroepen:

standaard exposure en exposure waarbij ook de positieve stimuli werden gepresenteerd, maar dan niet gekoppeld aan de gevaar cue. In Studie 1 begonnen participanten met een acquisitiefase waarin een plaatje van een gezicht (gevaar cue) werd gevolgd door toediening van een milde elektrische schok op de pols, en twee plaatjes van andere gezichten (veiligheid cues) niet. Een dag later kwamen de participanten terug in het lab voor de interventiefase. Een week later werd de terugkeer van angst gemeten. Studie 2 was een replicatie van dit onderzoek, waarbij de gehele procedure op één dag plaatsvond. Beide experimenten lieten zien dat de counterconditionering procedure leidde tot een sterkere afname van negatieve stimulus valentie ten opzichte van de andere interventies, maar niet tot minder terugkeer van angst. Deze bevindingen laten zien dat counterconditionering een veelbelovende strategie kan zijn om negatieve stimulus valentie te verminderen en wellicht op die manier vermijdingsgedrag tegen te gaan, maar niet rechtstreeks leidt tot minder terugkeer van angst die in het lab is aangeleerd.

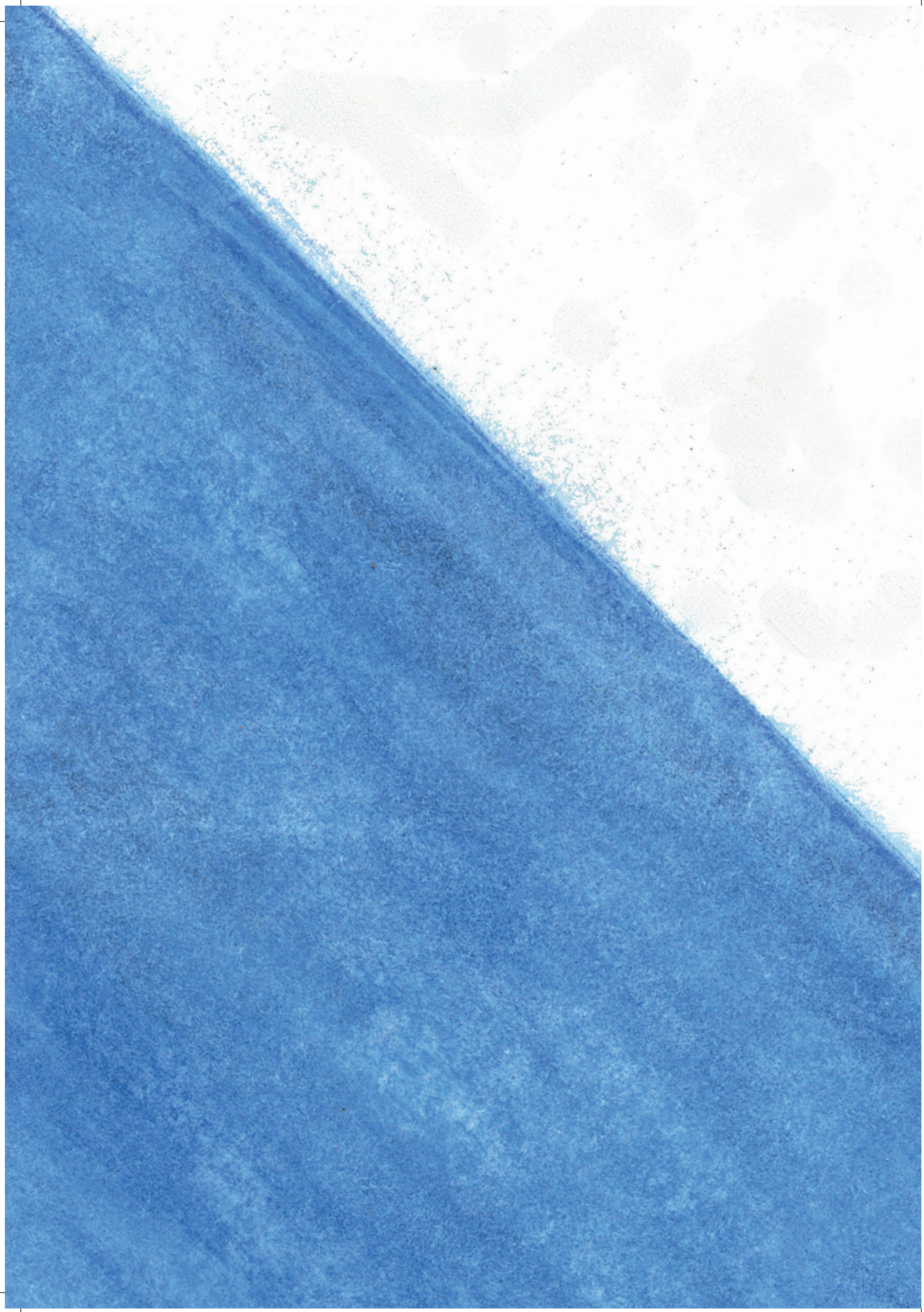
We hebben veelvuldig gebruik gemaakt van een lab model van exposure therapie, omdat daarmee maximale experimentele controle gekregen wordt. Met een goed opgezet lab model kunnen conclusies getrokken worden over causaliteit, maar de ecologische validiteit is deels beperkt, bijvoorbeeld doordat de stimuli niet persoonlijk relevant zijn en de deelnemer geen actieve rol heeft tijdens de taak. Om op een gecontroleerde en meer ecologisch valide manier onderzoek te doen naar exposure hebben we een tweedaagse virtual reality (VR) procedure ontwikkeld om terugkeer van spreekangst na een exposure interventie te toetsen. Angst kan met name terugkeren als iemand aan een nieuwe context wordt blootgesteld dan de context waarin de exposure interventie plaatsvond (dus bijvoorbeeld als een patiënt alleen exposure uitvoert in een therapiekamer en niet thuis). Het laatste empirische **Hoofdstuk 6** beschrijft een validatie studie van deze nieuwe procedure, waarin de context werd gemanipuleerd om terugkeer van angst op te wekken. Participanten met verhoogde spreekangst kregen op de eerste dag een exposure interventie, waarbij zij voor een virtueel publiek (Context A) meerdere presentaties gaven. Een week later ondergingen zij deze exposure interventie opnieuw voor ofwel hetzelfde virtuele publiek (Context A) of een ander virtueel publiek (Context B). Uit dit onderzoek kwam naar voren dat exposure op dag 1 effectief was: tijdens de presentaties nam de hartslag minder sterk toe en namen zelf gerapporteerde spanningsniveaus af. Een week later liet alleen de Context B groep een toename zien in zelf-gerapporteerde spanning. Deze procedure kan dus in toekomstig onderzoek worden gebruikt om na te gaan of de effecten van nieuwe interventies standhouden na een contextverandering.

Conclusie

Het doel van de studies die in dit proefschrift zijn beschreven was om kennis te vergroten over factoren die een rol spelen bij de ontwikkeling en vermindering van aangeleerde angst. Hoewel exposure therapie effectief is voor angststoornissen, laat klinisch onderzoek (**Hoofdstuk 4**) en lab onderzoek (**Hoofdstukken 5 en 6**) zien dat exposure op de lange termijn voor een aanzienlijke minderheid onvoldoende werkt en aangeleerde angst dus kan terugkeren. Volgens het invloedrijke inhibitoire leermodel, is het van belang om tijdens exposure therapie de verwachting van gevaar zoveel mogelijk te doorbreken. Op basis van onze bevindingen zou exposure inderdaad mogelijk effectiever kunnen zijn wanneer er strategieën worden ingezet die de verwachting van gevaar kunnen doorbreken, zoals inbeelding van een positieve gebeurtenis in plaats van gevaar (zie ook **Hoofdstuk 2**). Ook counterconditionering was effectief voor het verminderen van de valentie van een gevaar cue, en dit zou mogelijk vermijdingsgedrag kunnen tegengaan, wat op langere termijn exposure effecten kan versterken (**Hoofdstuk 5**). Deze strategieën dienen uiteraard nader te worden onderzocht in (sub)klinische studies. Resultaten uit dit proefschrift en recente bevindingen uit andere labs suggereren bovendien dat behandeleffecten kunnen worden geoptimaliseerd als niet alleen wordt ingezet op het doorbreken van de gevaarsverwachting (dus de kans op gevaar), maar ook op het moduleren van voorstellingen van gevaar (dus de ernst van gevaar). Het onderzoek zoals beschreven in **Hoofdstuk 2** toonde aan dat de mentale inbeelding van gevaar, vooral na een inflatie procedure, leidde tot verhoogde generalisatie van angst. Er zijn eveneens aanwijzingen dat het verzwakken van mentale voorstellingen van gevaar (bijvoorbeeld door een behandeling als *imagery rescripting* of *Eye Movement Desensitization and Reprocessing; EMDR*) angst kan verminderen. Wellicht kunnen zulke behandelingen ervoor zorgen dat men exposure gemakkelijker durft aan te gaan of dat het effect van exposure mogelijk sterker wordt. Dit is een belangrijk aandachtsgebied voor toekomstig onderzoek. Verder is het van belang dat onderzoek naar nieuwe interventies ook gericht is op het verminderen van instrumenteel defensief gedrag. In **Hoofdstuk 3** kwam bijvoorbeeld naar voren kwam dat veiligheidsgedrag bij een veilige stimulus angst in stand kan houden of versterken. Er waren grote verschillen tussen de deelnemers: bij sommigen steeg de gevaarsverwachting na veiligheidsgedrag, terwijl deze bij de meesten gelijk bleef. Individuele verschillen (bijvoorbeeld in het kunnen verdragen van onzekerheid) kunnen verklaren waarom veiligheidsgedrag soms wel maar niet

altijd nadelig is tijdens exposure therapie. Tot slot is in **Hoofdstuk 6** een lab procedure beschreven die bruikbaar kan zijn bij zulk vervolgonderzoek naar het verminderen van de terugkeer van angst. Metingen met betrekking tot negatieve mentale voorstellingen en instrumenteel defensief gedrag kunnen hierbij worden gebruikt.

Concluderend kan gesteld worden dat, in overeenstemming met het inhibitoire leermodel, interventies gericht op het doorbreken van de gevaarsverwachting de (lange termijn) effecten van exposure mogelijk kunnen verbeteren. Er is echter meer aandacht nodig voor andere mechanismen, zoals het verminderen van negatieve mentale voorstellingen en instrumenteel defensief gedrag. Toekomstig onderzoek zal moeten uitwijzen of patiënten die nu onvoldoende baat hebben bij op exposure gebaseerde CGT meer opknappen door interventies gericht op het versterken van inhibitoir leren en/of interventies die aangrijpen op andere mechanismen, zoals het verminderen van mentale negatieve voorstellingen.



About the author

Over de auteur

Curriculum Vitae

Evi-Anne van Dis was born on February 3, 1990, in Den Haag and has spent her childhood mainly in Nieuwegein. When she was nine years old, she started an Einstein club and published classmates' inventions in a handmade 'scientific' journal. Her passion for science revived when she worked on a research project as part of the honors program of the Clinical and Health Psychology Bachelor at Utrecht University (2008-2011). After that, she attended both the Research Master's program Social and Health Psychology as well as the Master's program Clinical and Health Psychology. During her studies, she also worked as a student assistant at the Psychology Department. After her graduation in 2014, she worked as a junior researcher at Psychotraumacentrum Zuid Nederland and then got a research assistant position in the experimental psychopathology (EPP) lab at Utrecht University. In 2016, she started her PhD project under the supervision of prof. dr. Iris Engelhard and dr. Muriel Hagenaars. During a short visit to the lab of prof. dr. Michelle Craske at the University of California Los Angeles in 2018, she realized she wanted to stay in the US for an extended period of time. In 2020, she received a Fulbright and ZonMw Translational scholarship to visit the ANGST-lab of dr. Shmuel Lissek at the University of Minnesota. In the past years, she has been an active member of the Educational Committee of the Dutch-Flemish EPP postgraduate school. Evi-Anne also has a passion for clinical practice. Since 2018, she has worked at Altrecht Academic Anxiety Centre for one year and completed basic training in cognitive-behavioral therapy and eye movement desensitization and reprocessing. She currently works as a post-doctoral researcher at Utrecht University and as a clinician at GGZ inGeest.

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