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# Impaired action-safety learning and excessive relief during avoidance in patients with anxiety disorders

R.A. De Kleine [a,b,*], M.H.M. Hutschemaekers [b,c], G.J. Hendriks [b,c,d], M. Kampman [b,c], S. Papalini [f], A. Van Minnen [c,e], B. Vervliet [f,g]

[a] Department of Clinical Psychology, Leiden University, The Netherlands
[b] Pro Persona Mental Health Care, The Netherlands
[c] Behavioral Science Institute, Radboud University, The Netherlands
[d] Department of Psychiatry, Radboud University Medical Centre, The Netherlands
[e] PSYTREC, The Netherlands
[f] Laboratory of Biological Psychology, KU Leuven, Belgium
[g] Leuven Brain Institute, KU Leuven, Belgium

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ABSTRACT

Anxiety-related disorders are characterized by high levels of avoidance, but experimental research into avoidance *learning* in patients is scarce. To fill this gap, we compared healthy controls (HC, $n = 47$) with patients with obsessive-compulsive disorder (OCD, $n = 33$), panic disorder with agoraphobia (PDA, $n = 40$), and post-traumatic stress disorder (PTSD, $n = 66$) in a computer-based avoidance learning task, in order to examine (1) differences in rates of avoidance responses, (2) differences in action-safety learning during avoidance, and (3) differences in subjective relief following successful avoidance. The task comprised aversive negative pictures (unconditional stimulus, US) that followed pictures of two colored lamps (conditional stimuli, CS+), but not a third colored lamp (safety stimulus, CS-), and could be avoided by pressing a button during one CS+ (CS+ avoidable) but not the other (CS+ unavoidable). Participants rated their US-expectancy and level of relief on a trial-by-trial basis. Compared to the HC group, patient groups displayed higher levels of avoidance to the safety stimulus, and higher levels of US-expectancy and relief following the safety and avoidable danger stimulus. We propose that patients with anxiety disorders have low confidence in the safety consequences of avoidance actions, which induces increased relief during US omissions that reinforce the avoidance action.

## 1. Introduction

Excessive avoidance is a cardinal symptom across the anxiety disorders and a diagnostic criterion for phobia, social anxiety, panic disorder, and extending to anxiety-related disorders such as posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD; American Psychiatric Association, 2013; Craske & Stein, 2016). It is widely acknowledged that excessive avoidance is a major contributor to the individual suffering of the patient and possibly to disability as well (the anxiety disorders combined are the 6th leading cause of disability worldwide; Baxter, Vos, Scott, Ferrari & Whiteford, 2014). The term avoidance is a functional description of those behaviors that serve to prevent or mitigate confrontations with a threatening situation and provide safety instead. In face of real danger, avoidance can be adaptive. But, when real danger is absent and fears are irrational, avoidance is unnecessary, and importantly, precludes the opportunity to learn that fears are unsubstantiated.

Avoidance behaviors have been heavily investigated in patients suffering from anxiety disorders and are thought to play a central role in the development and maintenance of anxiety disorders (Krypotos, Efftting, Kindt & Beckers, 2015; Pittig, Treanor, LeBeau & Craske, 2018). In experimental psychopathology research, avoidance tendencies are often assessed by approach-avoidance tasks (AAT), behavioral avoidance tasks (BAT), or decision-making tasks (Pittig et al., 2018). These types of tasks gauge the degree to which an individual tends to avoid fear-evoking stimuli or what avoidance is worth, but do not shed light on the learning mechanisms involved in the development of maladaptive avoidance. This is unfortunate, because insight in the basic mechanisms

* Correspondence to: Wassenaarsweg 52, 2333 AK Leiden, The Netherlands.
*E-mail address:* r.a.de.kleine@fsw.leidenuniv.nl (R.A. De Kleine).

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by which excessive avoidance behaviors are acquired and maintained may inform optimization strategies for anxiety treatments. Over the last decades, a wealth of experimental fear conditioning studies has greatly improved our understanding of fear learning mechanisms, which has resulted in clinical recommendations on exposure delivery (Craske, Treanor, Conway, Zbozinek & Vervliet, 2014). Similarly, a greater insight into the underlying learning processes of excessive avoidance could give guidance to treatment augmentation strategies.

The gold standard for investigating learning mechanisms in avoidance is a combined Pavlovian and operant conditioning task. During the Pavlovian phase, a neutral stimulus (conditional stimulus, CS) precedes an aversive stimulus (unconditional stimulus, US) a number of times, so that it becomes a reliable signal of the occurrences of that US. Next, an avoidance behavior is made available that can prevent US delivery if executed during the CS. Increasing frequency of the avoidance behavior during the CS reflects an operant learning process that is driven by the contingency between the avoidance behavior and the omission of the US. Although different views exist on what exactly is being learned in avoidance (Krypotos et al., 2015), one straightforward interpretation is that the executed avoidance behavior becomes associated with the subsequent omission of the US, so that the correct behavior can be selected when the US is expected on a next CS encounter (Lovibond, 2006; Moutoussis, Bentall, Williams & Dayan, 2008; Seligman & Johnston, 1973). For example, during an avoidance conditioning task, a participant learns that executing an avoidance action during the presentation of a neutral stimulus (e.g. a certain picture or sound) will prevent the occurrence of a mild electric shock. These action → safety associations are thought to guide avoidance behavior.

We know of only two studies that have examined avoidance learning in patients with anxiety-related disorders. First, Gillan et al. (2014) observed that patients with obsessive-compulsive disorder (OCD) continued to engage in a learned avoidance action when the feared outcome was clearly no longer possible (the cable that previously administered the aversive electrical stimulation US, was visibly removed). Healthy controls, on the other hand, immediately stopped avoiding. This pattern of results suggests that patients with OCD are prone to develop habitual avoidance behaviors that no longer serve the initial goal (safety from shock, in this case). Second, Pittig, Boschet, Gluck, and Schneider (2021) added a response cost (money loss) to a learned avoidance action and found that patients suffering from anxiety disorders (mixed sample) continued to engage in the avoidance action, while healthy controls stopped avoiding and collected the money. Together, these results suggest that patients with anxiety-related disorders are less sensitive to devaluation of the threat value of a feared outcome or inflation of the cost of avoidance. However, while these studies shed light on the situations in which patients suffering from anxiety disorders continue to avoid, less is known about potential differences in the initial learning process of avoidance.

The main goal of the current study was to investigate avoidance learning in pathological anxiety by comparing performance on a newly developed avoidance conditioning task (Vervliet & Indekeu, 2015; Vervliet, Lange, & Milad, 2017) between patients with anxiety disorders and healthy controls. During the task, participants are presented with stimuli that signal safety (CS-) or danger (CS+), and avoidance behavior is made available during both CS types. Crucially, there are two danger stimuli, and avoidance is only effective when executed during one of these stimuli. Consequently, avoidance behavior can be either unnecessary (during CS-), effective (during CS+avoidable) or ineffective (during CS+unavoidable). We expected that patients with anxiety disorders would exhibit more widespread avoidance behavior (Klein, Berger, Vervliet & Shechner, 2021; San Martin, Jacobs, & Vervliet, 2020), and thus show more avoidance when this was unnecessary or ineffective.

Aside from avoidance behaviors, we aimed to investigate differences between patients with anxiety disorders and controls with respect to what they learn from their behavior. Previous work (Briscione, Jovanovic, & Norrholm, 2014; Duits et al., 2015) has convincingly shown that those suffering from anxiety have difficulties in the learning to feel safe and inhibit fear in situations of objective safety (CS-). The current paradigm extends this work by investigating how patients with anxiety disorders learn from their own behavior. Specifically, we wanted to know whether they can learn to feel safe when applying an avoidance action that reliably cancels a feared threat. For that purpose, we tracked the acquisition of action → safety associations during the paradigm, by asking after each avoidance action to what extent they still expected to receive the US. A high expectancy of the US would indicate a weak action → safety association, whereas a shift towards low expectancy of the US after execution of the avoidance behavior would indicate that the participant has acquired the action → safety association. We expected that, as participants learned that executing the avoidance action would effectively cancel the US, their residual expectancy of the US would decrease accordingly. Granted the hampered safety learning observed in those suffering from anxiety (Duits et al., 2015), and given that weaker action → safety learning has been observed in an unselected sample with higher levels of social anxiety (Ly & Roelofs, 2009), we expected to see weaker action → safety learning in anxiety patients as well, expressed by higher US-expectancies following effective avoidance in patients in comparison to controls.

Next to avoidance rates and action → safety learning, we also probed the relief that participants experience when an expected US is successfully omitted. Arguably, a pleasant feeling of relief contributes to the reinforcement of avoidance actions (Vervliet et al., 2017). We previously found that self-reported relief is high during early avoidance trials and then gradually decreases over later avoidance trials. This suggests that relief relates to surprise: it is especially high when an aversive outcome is expected and its non-occurrence is surprising (Vervliet et al., 2017). Because computational models of avoidance learning point to surprise as the critical reinforcer of action → safety learning (Moutoussis et al., 2008) we use relief ratings during successful US avoidance to gauge the dynamics of this surprise signal (also termed the prediction error signal or expectancy violation) over the course of learning. If patients would display impaired action → safety learning, as hypothesized above, the actual omissions of the US would remain surprising and continue to trigger relief, which might further reinforce the avoidance action up to a point where it becomes excessive.

Taken together, we adapted the standard avoidance learning task in order to test differences between healthy controls and patients with anxiety disorders in avoidance learning and reinforcing mechanisms. We investigated three anxiety groups, those suffering from panic-disorder, obsessive compulsive disorder and posttraumatic stress disorder. We tested the hypotheses that, in comparison to healthy controls, patients with anxiety disorders would show:

(1) more avoidance, specifically when this was unnecessary (during the CS-) or ineffective (during the CS+unavoidable) as witnessed by a significant CS-type by Group interaction on avoidance rate.
(2) impaired action → safety learning, that is, we expected to find higher danger expectancies following the safety (CS-) or avoidable danger stimulus (CS+avoidable), as shown by significant interaction between CS-type and Group on the US-expectancy scores.
(3) more relief following US omissions (i.e., after the CS- or CS+avoidable), evidenced by a significant Group effect on relief ratings.

## 2. Methods

### 2.1. Participants

Hundred and eighty-six participants ($M_{age}$ =37.03, SD = 13.03; 66.7% female) completed the experimental task between January 2016 and April 2017. Participants from the patient groups (OCD: $n = 33$; PDA:

$n = 40$; PTSD: $n = 66$) were recruited at an outpatient clinic specializing in the treatment of anxiety-related disorders. Inclusion criteria were: 1) satisfying DSM-IV based diagnostic criteria for OCD, PD or PTSD; 2) enrollment in intensive exposure treatment (see Hendriks, de Kleine, Broekman, Hendriks & van Minnen, 2018); 3) ≧ 18 years old; 4) master Dutch language; 5) estimated IQ > 80. Psychiatric diagnoses were established by experienced clinicians through the Mini International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998). Establishing the primary diagnosis (most severe and impairing) was pivotal as participants were assigned to a disorder-specific exposure program after intake. However, there was some overlap in diagnoses between groups. In the OCD group, four participants were diagnosed with a comorbid PDA. In the PDA group, one participant was diagnosed with comorbid PTSD. In the PTSD group, 19 participants were diagnosed with a comorbid PDA ($n = 7$), OCD ($n = 9$) or both ($n = 3$). The healthy control (HC) group was ascertained to have no mental disorder by assessment of the MINI. See Table 1 for sample demographics and clinical characteristics. The specific size per group was a convenience size. For all participants, written informed consent was obtained prior to participation. Ethical approval was obtained from the Ethical Committee of the Faculty of Social Sciences of the Radboud University (ECSW2015–0903–295). The study was not pre-registered.

### 2.2. Study procedure

Participating patients completed the study prior to the start of their exposure treatment. All patients completed a baseline measurement (including clinical interviews and questionnaires (including the BAI, IDS)) as part of routine outcome monitoring. Those eligible and willing to participate in the study, completed an extra assessment. The current study was part of a larger research project on emotional learning in treatment-seeking patients suffering from various anxiety-related disorders. Participants successively completed a task on contextual modulation of fear and extinction,[1] a probabilistic learning task (both will be reported elsewhere), and the current avoidance learning paradigm. Upon completion of the experimental tasks, they completed a working memory and attention test. Next, they filled-out online questionnaires. In total, the research-related assessment took approximately 1,5 h to complete. All tasks and questionnaires were completed on a laptop computer, and the assessment took place at the outpatient clinic. A research assistant was present during the entire assessment. For the healthy control group, a research assistant visited participants at their home address (or location of choice) and reassured that the room was quiet and with minimum distraction. Those in the healthy control group completed the experimental tasks and questionnaires in similar order as the patient groups.

### 2.3. Task procedure

Before the task started, we instructed participants on how to use the expectancy and relief rating scales. Moreover, we told them that the red and blue lamp colors (CS+avoidable and CS+unavoidable, respectively) would be followed by the aversive US but the yellow lamp color (CS-) not. This was done in order to speed up learning during the Pavlovian phase (as we were only interested in the next phase of avoidance learning).

During the **Pavlovian phase** (see Fig. 1), participants saw each of the three CSs twice. One second after each CS onset, the expectancy rating-scale appeared. The CS remained on screen until the participant clicked the scale (with a 500 ms delay). The aversive US appeared immediately after each CS+. The CS- was followed by the relief-rating scale after a delay of 2 s and remained on the screen until clicked by the participant (with a 500 ms delay).

Prior to the avoidance phase, the participant received additional instructions about the use of the avoidance button. They were told that they would be able to sometimes prevent the aversive US by clicking on the red button, and that it was their task to figure out *when* they could prevent the US. They were also warned that the duration of each red button was only 2 sec, so that if they wanted to click on the button, they should do it relatively fast.

The **Avoidance phase** consisted of 12 presentations of each CS, divided into two blocks of six presentations. During each CS presentation, the red button appeared one second after CS onset and remained on screen for 2 sonds (irrespective of an avoidance response). The US-expectancy scale appeared 500 ms after removal of the red button. The CS remained on screen until the participant clicked the US-expectancy scale (with a 500 ms delay). The aversive US appeared immediately after the CS+ unavoidable, irrespective of button clicking. Appearance of the aversive US after the CS+avoidable depended on whether the red button was clicked appropriately. When indeed no aversive US followed (after an avoided CS+avoidable and after all presentations of the CS-), the relief-rating scale appeared 2 s after CS offset.

In between the two blocks (i.e., after 18 trials), two CS+avoidable presentations were added during which clicking the red button had no effect (temporarily unavoidable, not announced to the participant). These presentations were inserted to create uncertainty in the task and investigate the re-learning of the association between CS+avoidable and US omission in the second block.

Throughout the entire task, inter-trial intervals were set at 2 s.

### 2.4. Measures

#### 2.4.1. Self-report measures

Beck Anxiety Inventory (BAI; Beck, Epstein, Brown & Steer, 1988). The BAI is a 21-item self-report instrument that assesses both physiological (e.g., shaky; difficulty breathing) and cognitive components (e.g., fear of dying) of anxiety. Participants indicate to what level (0 = not at all; 3 = severely) they have experienced each anxiety symptom over the past week. The psychometric quality of the BAI was found to be good ($\alpha = 0.92$; (Steer, Ranieri, Beck & Clark, 1993)).

Inventory of Depressive Symptoms (IDS-SR; Rush, Gullion, Basco, Jarrett & Trivedi, 1996). Severity of depressive symptoms was assessed with the 30-item self-report version of the IDS. The IDS measures depression symptoms on a 4 point scale, with total scores ranging between 0 and 90. The IDS has shown high correlations with clinician rated depressive symptom inventories and the psychometric qualities are good (Rush et al., 1996).

Spielberger State and Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970; Van der Ploeg, Defares, & Spielberger, 1980). The STAI consists of two 20-item scales: one scale measuring the level of anxiety at the moment (state anxiety; STAI-S), and one the level of anxiety one generally feels (trait anxiety; STAI-T). Each item is scored on a 4-point Likert scale (1 = not at all; 4 = very), total scores range from 20 to 80, and higher scores indicate increased levels of anxiety. For the current study, we used the STAI-trait scores. The psychometric qualities of the STAI-trait are shown to be good ($\alpha = 0.91$ (Van der Ploeg et al., 1980)).

[1] In this task, participants saw avatars (CS's) in different contexts (office rooms). In the acquisition phase, participants learned that one avatar (CS+) was followed by a loud noise (95DB), provided through a noise-canceling headphone; US), whereas the other avatar was never followed by the loud noise. During extinction, none of the CS's was followed by the loud noise. Crucially, the context wherein acquisition and extinction took place differed, such that there was a "danger" and "safety" context. In the test-phases, expectancies and subjective fear to both CS's were examined in three contexts, assessing extinction generalization (i.e. novel context), extinction retention (i.c. safety context) and acquisition retention (i.c. danger context). This task took 20 min to complete. In between this fear learning task and the avoidance learning task, participants completed a probabilistic learning task

**Table 1**
Demographic and clinical characteristics of HC, OCD, PDA and PTSD groups and significant between-group comparisons.

| | HC ($n$ = 47) | OCD ($n$ = 33) | PDA ($n$ = 40) | PTSD ($n$ = 66) | One-way Anova/Kruskall Wallis or Chi-Square Test | Pair-wise comparisons |
|---|---|---|---|---|---|---|
| Demographic variables | | | | | | |
| Gender (female) ($n$, %) | 25 (53.2) | 19 (57.6) | 26 (65.0) | 54 (81.8) | $\chi^2(3) = 11.94$, $p = .008$ | HC < PTSD |
| Age | 38.30 (14.21) | 35.18 (14.51) | 33.70 (10.27) | 39.06 (12.57) | $\chi^2(3) = 5.059$, $p = .168$ | |
| Higher education ($n$, %) | 23 (48.9) | 15 (45.5) | 14(36.8)[a] | 18 (27.7)[b] | $\chi^2(3) = 6.10$, $p = .107$ | |
| Married or cohabitating ($n$, %) | 27 (57.4) | 15 (45.5) | 17(42.5) | 25 (37.9) | $\chi^2(3) = 4.39$, $p = .222$ | |
| Clinical variables | | | | | | |
| Mood disorder ($n$, %) | - | 14 (42.4) | 18 (45.0) | 43 (65.2) | $\chi^2(2) = 6.39$, $p = .041$ | OCD, PD < PTSD |
| Psychotropic medication (any) ($n$, %) | - | 18 (54.5) | 27 (69.2)[c] | 57 (87.7)[b] | $\chi^2(2) = 13.43$, $p = .001$ | OCD < PTSD |
| SSRI/SNRI | - | 13 (39.4) | 16 (41.0)[c] | 31 (47.7)[b] | $\chi^2(2) = 0.67$, $p = .676$ | |
| Benzodiazepine | | 5 (15.2) | 16 (41.0)[c] | 32 (49.2)[b] | $\chi^2(2) = 10.84$, $p = .004$ | OCD < PD, PTSD |
| Antipsychotic drugs | | 4 (12.1) | 4 (10.3)[c] | 27 (41.5)[b] | $\chi^2(2) = 16.66$, $p < .001$ | OCD, PD < PTSD |
| Self-report questionnaires | | | | | | |
| BAI | 4.02 (4.78)[d] | 20.67 (13.71) | 30.45 (12.49) | 31.24 (10.75) | $\chi^2(3) = 106.04$, $p < .001$ | HC < OCD, PD, PTSD; OCD < PD, PTSD |
| IDS | 6.37 (5.67)[d] | 28.73 (14.39) | 34.65 (14.57) | 46.13 (11.74) | $\chi^2(3) = 116.54$, $p < .001$ | HC < OCD, PD, PTSD; OCD, PD < PTSD |
| STAI-trait | 33.51 (8.66) | 55.03 (9.99) | 58.45 (10.65)[a] | 63.42 (9.09)[b] | $\chi^2(3) = 101.03$, $p < .001$ | HC < OCD, PD, PTSD; OCD < PTSD |
| IAPS unpleasantness | 1.70 (1.36)[d] | 1.91 (1.47) | 2.53 (1.45)[a] | 3.12 (1.32)[b] | $\chi^2(3) = 28.07$, $p < .001$ | HC, OCD < PTSD |

Notes. $n$ = sample size. Due to missing values there were small variations in sample sizes: [a] $n$ = 38; [b] $n$ = 65; [c] $n$ = 39; [d] $n$ = 46. Abbreviations: HC = healthy controls; OCD = obsessive compulsive disorder; PDA = panic disorder with agoraphobia; PTSD = Posttraumatic Stress Disorder; SD = standard deviation; BAI = Beck Anxiety Inventory; IDS = Inventory of Depressive Symptoms. STAI-T = Spielberger State Trait Anxiety Inventory – Trait; IAPS = International Affective Picture System.

#### 2.4.2. *Avoidance learning task*

We programmed the avoidance learning task with Affect4 software (Spruyt, Clarysse, Vansteenwegen, Baeyens & Hermans, 2010), which also recorded the main outcome variables.

*2.4.2.1. Conditional stimuli.* These were pictures of an office room that contained a desktop lamp, which could be illuminated in three clearly distinct colors (red, blue, yellow;). Each picture presentation started with the desktop lamp unlit (1 s), after which it switched on in of the three colors (conditional stimuli, CS).

*2.4.2.2. Unconditional stimulus.* On each trial, the aversive unconditional stimulus (US) was taken from a set of 12 negative pictures and presented for 500 ms. The pictures were selected as mildly aversive from the international affective picture system (snake, spider, aggressive dog, shark, gun, dirty toilet, crying child, fighting politicians, knife to throat, dirty toilet, dog cadaver, dental treatment; Lang, Bradley, & Cuthbert, 2005).

*2.4.2.3. Avoidance response.* A red button that was superimposed at the bottom of the room picture signaled the availability of the avoidance response (as instructed to the participants). The designated avoidance response consisted of clicking the red button via the computer mouse that guided a cursor on the screen.

*2.4.2.4. Expectancy-rating.* An 11-point scale ranged from 0 (“certainly no picture”) over 5 (“uncertain”) to 10 (“certainly picture”). The scale appeared at the bottom of the screen, participants used the computer mouse to move the cursor to the desired position and entered their rating by clicking the left mouse-button.

*2.4.2.5. Relief-rating.* An 11-point scale ranged how much relief they felt from 0 (“no relief”) over 5 (“moderate relief”) to 10 (“strong relief”). The scale appeared on the left of the screen, participants used the computer mouse to move the cursor to the desired position and entered their rating by clicking the left mouse-button.

#### 2.4.3. *Additional measurement*

IAPS unpleasantness rating. Upon completion of the task a research assistant enquired after a participant’s experience (open-answer question). Next, participants were asked to rate the level of the unpleasantness of the pictures seen during the task on a 5-point scale (0 not unpleasant at all; 5 extremely unpleasant).

### 2.5. *Statistical approach*

Differences between all groups (HC, PDA, OCD, PTSD) on descriptive variables were analyzed using chi-square, independent one-way ANOVA’s or Kruskal-Wallis in case of non-normality.

We investigated group differences (HC, PDA, OCD, PTSD) with repeated measures analysis of variance (RM-ANOVA) and univariate ANOVA models appropriate for the test at hand (see Results section). Each ANOVA model also included three covariates to control for differences in age, gender and education level. Significant ANOVAs were replicated with US-unpleasantness added as covariate-of-interest to estimate the influence of this variable on the main and/or interaction effects. Significant between group differences were tested with post-hoc pair-wise comparisons with Bonferroni correction.

## 3. Results

### 3.1. *Descriptive variables*

There were no between group differences in age and educational level. There were however differences in gender distribution $\chi^2(3) = 11.94$, $p = .008$: more participants in the PTSD group self-identified as woman ($n$ = 54; 81.8%) than in the HC group ($n$ = 25; 53.2%). As expected, the patient groups had higher scores on the pathology measures (i. e. BAI, IDS, STAI-T) than the HC group (see Table 1). There were also some differences between patient groups, with the PTSD group showing

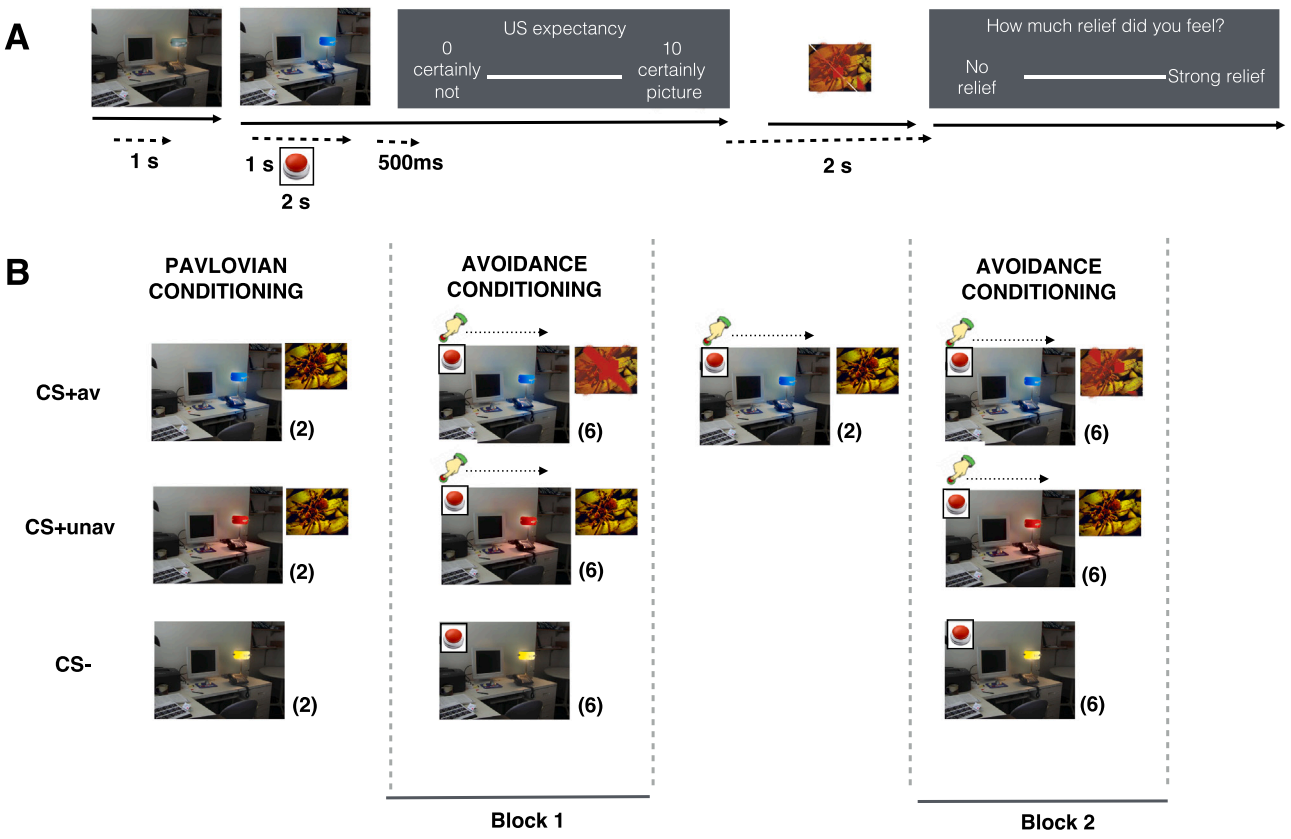


**Fig. 1.** Overview of the timeline of a successful avoidance trial and experimental design. (A): Avoidance trials began with 1 s of office room picture until the lamp unlit in one of three colors (CS). The red button appeared 1 s following color onset and remained on screen for 2 s. Expectancy rating scale appeared on screen 500 ms after removal of the red button. The CS stayed on screen until the expectancy scale was clicked. The relief scale appeared 2 s after CS offset and remained on the screen until the participants clicked the rating scale. (B): Two colors were paired with an aversive IAPS picture during Pavlovian Conditioning. All three colors included a red button during Avoidance Conditioning; clicking the computer mouse canceled the IAPS picture to one color (CS+avoidable), but not the other (CS+unavoidable). Clicking was unnecessary to the safety stimulus (CS-). After 18 trials (block 1), two CS+avoidable trials were presented wherein the avoidance button had no effect. Followed by 18 trials identical to Block 1.
Figure adapted from Vervliet et al. (2017).

more co-occurring depressive symptoms (both clinical diagnosis and self-reported symptom severity) than the PDA and OCD group. The OCD group reported lower anxiety symptoms than the PDA and PTSD group (on both anxiety indices, i.c. BAI and STAI-T).

### 3.2. Avoidance learning task

#### 3.2.1. Between group comparisons

##### 3.2.1.1. Pavlovian learning

*3.2.1.1.1. Expectancy ratings.* Within the Group (HC; PDA; OCD; PTSD) × CS (CS-; CS+avoidable; CS+unavoidable) ANOVA, CS+avoidable and CS+unavoidable elicited higher US-expectancy than CS-, as indicated by a main effect of CS, $F(1.59, 281.40) = 17.55$, $p < .001$, $eta = 0.09$, and follow-up pairwise comparisons (CS+avoidable > CS-, $p < .001$; CS+unavoidable > CS-, $p < .001$). There was no main effect of Group, $F(3177) = 0.89$, $p = .45$, or a Group × CS interaction, $F(4.77, 281.40) = 1.51$, $p = .19$, indicating that there were no between group differences on the US-expectancy ratings during the Pavlovian phase. Unexpectedly, we also observed significant effects of the covariates, CS × Age, $F(1.59, 281.40) = 4.61$, $p = .017$, $eta = 0.03$, and CS × Education, $F(1.59, 281.40) = 5.63$, $p = .007$, $eta = 0.03$, but not CS × Gender, $F(1.59, 281.40) = 0.13$, $p = .83$.

*3.2.1.1.2. Relief ratings.* A one-way ANOVA with Group as independent variable and average relief rating to CS- revealed a main effect of Group, $F(3, 177) = 15.95$, $p < .001$, $eta = 0.21$ (no effect of the covariates). Bonferonni corrected follow-up pairwise comparisons showed that the PDA and the PTSD group had significant higher relief levels than the HC group ($p = .004$ and $p < .001$, respectively), and the PTSD group also than the PDA and OCD group ($p = .031$ and $p = .001$, respectively, see Fig. 2).

##### 3.2.1.2. Avoidance learning

*3.2.1.2.1. Avoidance actions.* Within the Group (4) × CS (3) × Block (2) ANOVA, we found no significant three-way interaction ($F(5.91, 349.21) = 0.52$, $p = .79$). Moreover, there were no main effects of CS, $F(1.38, 244.72) = 1.32$, $p = .26$, or Group, $F(3, 177) = 1.09$, $p = .36$, but there was a significant Group × CS interaction, $F(4.15, 244.72) = 4.90$, $p = .001$, $eta = 0.08$. Bonferroni-corrected follow-up Group comparisons per CS showed that the interaction was driven by significant differences between the HC group and the OCD and PTSD group in reaction to the CS- ($p = .004$ and $p = .028$, respectively). No significant differences between groups were found in reaction to the CS+ 's (see Fig. 3A).

Adding US-unpleasantness to the co-variates in the Group (4) × CS (3) × Block (2) ANOVA left the Group × CS interaction intact, $F(4.17, 239.07) = 3.92$, $p = .004$, $eta = 0.06$, and did not reveal a main effect of US-unpleasantness, $F(1, 172) = 1.65$, $p = .201$.

*3.2.1.2.2. Expectancy ratings.* Firstly, we tested whether there were Group by CS-type interactions on expectancy ratings regardless of participants' avoidance actions. This RM-ANOVA with Group (4) × CS (3) × Block (2) revealed no significant three-way interaction ($F(5.66, 333.93) = 0.94$, $p = .46$), but main effects of CS, ($F1.81, 320.53$)

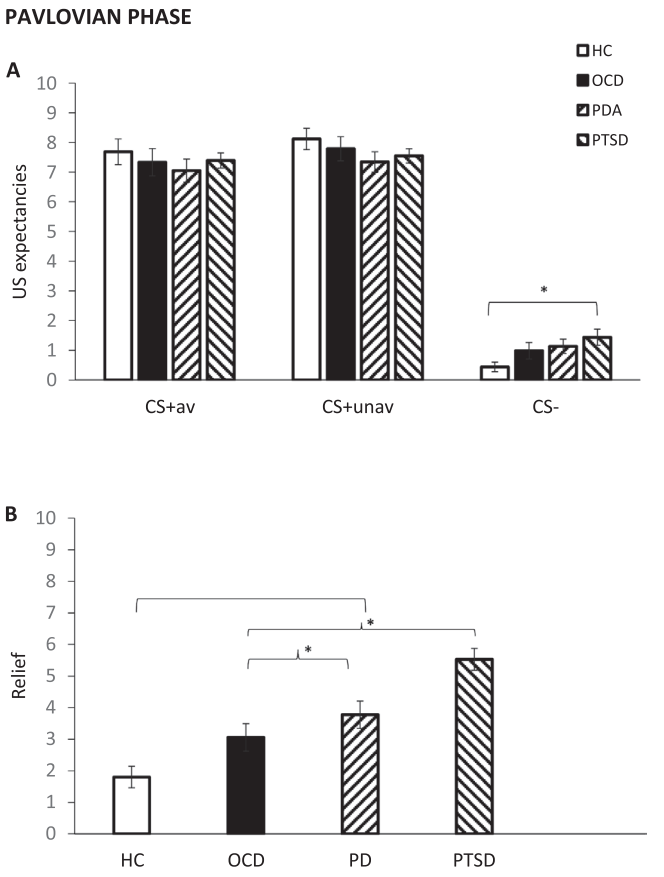


**Fig. 2.** Results from the pavlovian learning phase. White bars represent the Healthy Control group; Black bars the OCD group, right striped bars the PDA group, and left striped bars the PTSD group. (A). Expectancies were lower for the CS- than for both CS+'s across all groups, indicating successful discriminative learning. (B). All patients reported more relief than healthy controls and the highest levels of relief were reported by PTSD patients. Error bars represent standard errors of the mean; *$p < .05$.

$= 13.11$, $p < .001$, $eta = 0.07$, and Group, $F(3, 177) = 8.73$, $p < .001$, $eta = 0.13$, as well as a Group × CS interaction, $F(5.43, 320.53) = 3.50$, $p = .003$, $eta = 0.06$. Bonferroni-corrected follow-up Group comparisons per CS revealed that the interaction was driven by significant differences between the HC and the OCD and PTSD group for both the CS- and CS+avoidable ($p$'s $< 0.05$). There were no between group differences for the CS+unavoidable (all $p$'s $= 1$; see Fig. 3B). Adding US-unpleasantness to the covariates left the main effect of CS intact, $F(1.79, 307.34) = 12.76$, $p < .001$, $eta = 0.07$, as well as the main effect of Group, $F(3, 172) = 5.49$, $p = .001$, $eta = 0.09$; and the interaction between CS and Group $F(5.36, 307.34) = 2.81$, $p = .015$, $eta = 0.05$. Moreover, it revealed a main effect of US-unpleasantness, $F(1, 172) = 6.78$, $p = .01$, $eta = 0.04$, without interaction with CS, $F(1.79, 307.34) = 1.17$, $p = .31$. Thus, in comparison to healthy controls, those suffering from OCD and PTSD showed higher expectancies following the safety stimulus and the avoidable conditioned stimulus.

Secondly, we tested whether there were between group differences in expectancy ratings on selected trials when participants had clicked the avoidance button during the CS+avoidable. This ANOVA again revealed a main effect of Group, $F(3, 161) = 8.43$, $p < .001$, $eta = 0.14$. Post-hoc Bonferroni corrected pair-wise comparisons showed that the OCD and PTSD group had significantly higher US expectancies following successful avoidance than healthy controls ($p = .045$ and $p < .001$, respectively). This shows that, in comparison to healthy controls, both patients with OCD and PTSD were marked by elevated expectancies following effectively avoided CS+ trials. When US-unpleasantness was

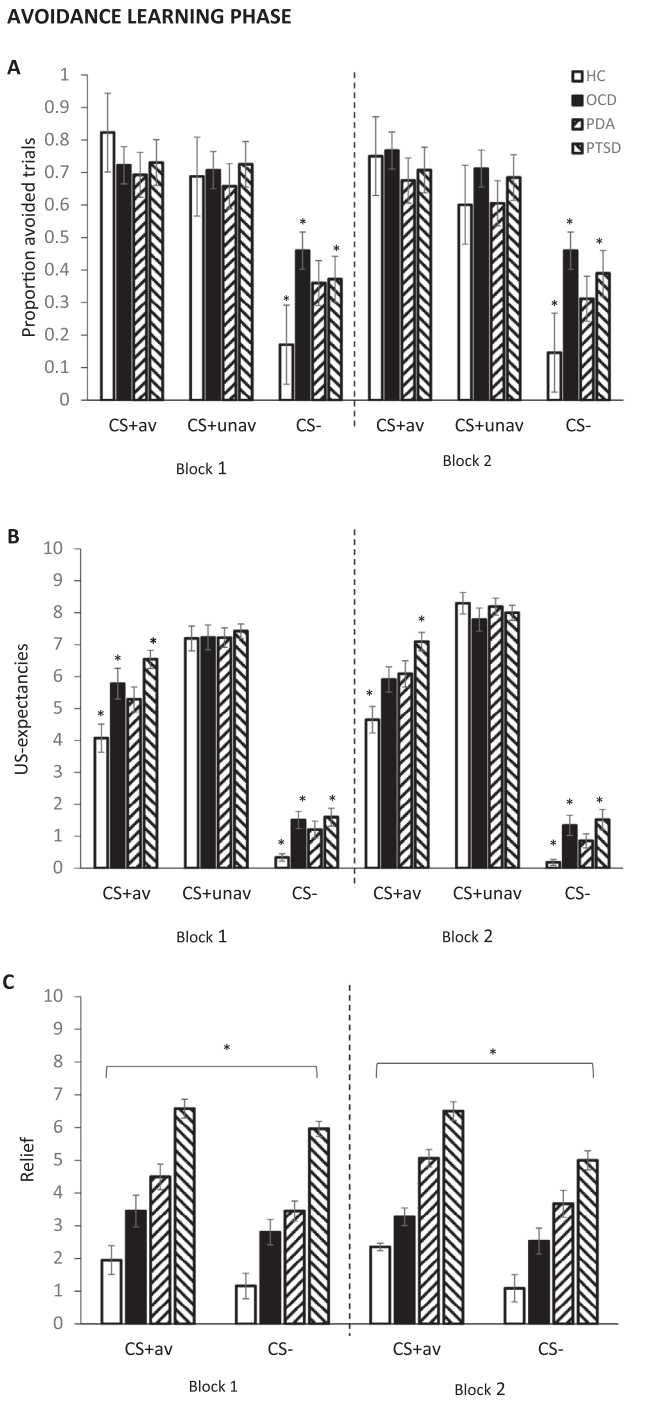


**Fig. 3.** Results from the avoidance learning phase. White bars represent the Healthy Control group; Black bars the OCD group, right striped bars the PDA group, and left striped bars the PTSD group. CS+av = CS+avoidable; CS+unav = CS+unavoidable. The left panel reflects responding during the first block, the right panel during the second block. (A). There was a significant CS x Group interaction, driven by higher unnecessary avoidance (i.e. to the CS-) in the OCD and PTSD group compared to the HC. (B). Both OCD and PTSD patients had higher US expectancies than HC's for both the avoidable danger stimulus (CS+av) as well as the safety stimulus (CS-). (C). Irrespective of stimulus, groups significantly differed in relief ratings, with the highest levels of relief (in comparison to all other groups) reported by PTSD patients. Error bars represent standard errors of the mean; *$p < .05$.

added to the covariates, the main effect of Group remained, $F(3, 156) = 5.72$, $p = .010$, $eta = 0.10$, in combination with a main effect of US-unpleasantness, $F(1, 156) = 5.28$, $p = .023$, $eta = 0.03$.

*3.2.1.2.3. Relief ratings.* Within the Group (4) × CS (2) × Block (2) ANOVA, there was no significant three-way interaction ($F(3, 141) = 0.82$, $p = .48$), no main effect of CS, $F(1, 141) = 0.38$, $p = .54$, but a main effect of Group, $F(3, 141) = 28.71$, $p < .001$, $eta = 0.38$, without a Group × CS interaction, $F(3, 141) = 0.58$, $p = .63$. There was a Group × Block interaction, $F(3, 141) = 4.17$, $p = .007$, $eta = 0.08$, in the absence of a main effect of Block, $F(1, 141) = 0.74$, $p = .39$. Bonferroni-corrected follow-up comparisons revealed that the main effect of Group was driven by differences between the HC and the PDA and PTSD group ($p$'s $< .001$), and the PTSD group had higher relief ratings than both the PDA ($p = .006$) and OCD group ($p < .001$). This shows that, regardless of CS-type, patients with anxiety disorders (specifically PTSD patients) had higher levels of relief, especially during the first half of the task (see Fig. 3C).

Adding US-unpleasantness to the RM-ANOVA revealed a significant main effect of US-unpleasantness, $F(1, 136) = 25.87$, $p < .001$, $eta = 0.16$, while leaving the main effect of Group intact, $F(3, 136) = 17.98$, $p < .001$, $eta = 0.28$.

## 4. Discussion

Patients with anxiety disorders go at great lengths to avoid the things they fear. Many studies have investigated excessive avoidance in patients, but how they *learn* to avoid the things they fear, has been addressed less often (Hofmann & Hay, 2018; Pittig et al., 2018). This study used a validated computer task to probe avoidance learning in patient suffering from panic disorder with agoraphobia (PDA), obsessive compulsive disorder (OCD) or posttraumatic stress disorder (PTSD), compared to healthy controls. We expected patients with anxiety disorders, in comparison to healthy controls, to be marked by 1) more avoidance; 2) impaired action → safety learning; and 3) heightened levels of relief.

In line with the first hypothesis, we found more frequent avoidance actions in the anxiety patients compared to the healthy controls, but only when avoidance was unnecessary, i.e., to the safety stimulus (CS-). One explanation for this finding could be that anxiety participants did not fully learn that the CS- was safe and were therefore more motivated to engage in avoidance. However, we did not find higher ratings of US-expectancy to the CS- during the preceding Pavlovian phase, suggesting that patients did acquire explicit knowledge that the CS- was safe. A remaining possibility is that, during the avoidance learning phase, the presence of the avoidance cue (a red button) or the act of pressing that button (behavior-as-information, see Gangemi, Mancini, & van den Hout, 2012) conferred a threat meaning to the otherwise safe CS- (see also van Dis, Krypotos, Zondervan-Zwijnenburg, Tinga & Engelhard, 2022; Vervliet & Indekeu, 2015; Xia, Eyolfson, Lloyd, Vervliet & Dymond, 2019). But why this would have occurred more in the anxiety patients than in the healthy controls, remains unclear (see Gangemi et al., 2012, for a related finding). Irrespective of the underlying mechanism, the observation of more unnecessary avoidance is in line with clinical observation that anxiety patients tend to avoid situations that do not pose actual threat. In fact, avoiding stimuli that do not objectively pose any threat to an individual is deemed a hallmark of maladaptive avoidance (Arnaudova, Kindt, Fanselow & Beckers, 2017).

Our second hypothesis was that anxiety patients display impaired action→ safety learning, as shown by higher threat-expectancies following the safety and avoidable danger stimulus. This is indeed what we observed. Although patients with anxiety disorders and healthy controls did not differ in their use of the avoidance button during the CS+avoidable, patients with anxiety disorders (especially those suffering from OCD or PTSD), were less certain that the avoidance action would prevent the aversive picture: their ratings of US-expectancy were higher than those of the healthy controls. A similar pattern was found for the CS-, where avoidance was unnecessary. We interpret these findings as indicating that the anxiety patients had less confidence in the avoidance action. Although they were (more) motivated to click the avoidance button, they were less certain of its outcome. This may relate to the impaired sense of control that is often observed in patients with anxiety disorder (Gallagher, Naragon-Gainey, & Brown, 2014). In essence, perceived control is the idea that one's actions can produce the desirable outcome (Gallagher et al., 2014), and our findings suggests that those suffering from anxiety disorders have lower confidence in their control over the aversive stimulus.

Our third hypothesis was that anxiety patients would report more relief during omissions of the threat US. The results showed indeed between-group differences in the level of relief: those belonging to the PDA or PTSD group reported significantly more relief than the healthy controls (there was no difference between omissions following the safety stimulus or avoidable danger stimulus). Importantly, this effect remained when we controlled for individual differences in perceived aversiveness of the threat US. Relief is proposed to be a function of both the *intensity (aversiveness)* and *expectancy* of an omitted threat (Willems & Vervliet, 2021). Indeed, our findings implicate that the heightened level of relief observed in patients suffering from anxiety disorders could not merely be explained by higher US-intensity (aversiveness) levels in these groups. We argue that the impaired action→ safety learning by patients with anxiety disorders left successful omissions more surprising, leading to a greater sense of relief.

Taken together, the combined profile of patients with anxiety disorders in our study is: (1) more avoidance, (2) less confidence that the avoidance action will effectively omit the aversive picture, and (3) stronger relief upon actual omissions of the aversive picture. Our interpretation of this set of findings is as follows. Less confidence in the avoidance action implies that successful omissions of the US will be more surprising and, therefore, elicit more relief. This increased relief reinforces the avoidance action further, thereby leading to higher levels of avoidance, but apparently not by strengthening the action → safety association (which is weakened in the patients). What, then, is the mechanism by which increased relief leads to more avoidance? One, untested, possibility is that the continuously elevated relief promotes the development of a CS → action association instead. This association would lead to increased levels of avoidance behavior upon viewing the threat CS, but more in a habitual manner (detached from the goal of obtaining safety). Interestingly, it has been suggested elsewhere that, in patients with anxiety disorders, avoidance behaviors become habitual over time, resulting in maladaptive forms of avoidance (LeDoux & Daw, 2018; LeDoux, Moscarello, Sears & Campese, 2017). We speculate here that continuously elevated relief may a play a role in this process. More research is clearly needed here as a better understanding of the development of avoidance and its function could help selecting the appropriate clinical interventions to reduce excessive avoidance in those suffering from anxiety disorders (see also Hofmann & Hay, 2018; Pittig, Wong, Gluck & Boschet, 2020).

We found that the aversive pictures worked well to study Pavlovian and avoidance learning in a computer-based task, which opens the possibility of investigating threat learning abnormalities remotely (McGregor et al., 2021). Of note, the content of the pictures seemed to matter. These were aversive situations, such as an attacking dog, an animal corpse, a fight, an assault, etc. It is not surprising that these were rated as more aversive in the patients with anxiety disorders, particularly the PDA and PTSD group, given that patients with anxiety disorders are marked by heightened threat appraisal (Arnaudova et al., 2017). This pattern mirrored the relief ratings, which were also highest for the PTSD patients and lowest for the healthy controls. This begs the question whether the differences between the groups are the result of differences in US aversiveness (threat appraisal) rather than learning processes per se. Indeed, it is conceivable that a more intense US triggers stronger motivation to avoid, less confidence in one's ability to control the US, and more relief. One argument against this possibility is that group

differences remained when the analyses controlled for individual ratings of US aversiveness. Nevertheless, to fully explore this possibility, we should increase US aversiveness in healthy individuals and investigate whether this pushes avoidance, confidence, and relief more in line with the profile that we obtained here in patients with anxiety disorders. Both perceived US aversiveness (i.e., threat-appraisal) and weakened avoidance → safety association learning may be key factors in understanding maladaptive avoidance.

This study has several limitations. We used a cross-sectional design, which does not allow testing whether the observed effects and proposed mechanism are causal to the disorder. We did not fully match the healthy controls to the anxiety patients, although we statistically controlled for important demographic variables. The conditioned stimuli were not counterbalanced between participants. The experiment did not include psychophysiological measures that could additionally inform psychobiological mechanisms of avoidance, expectancy, and relief in patients. We did not explicitly assess fear, although fear may be an important driver of avoidance. There was no cost attached to the avoidance action, although participants were instructed to use the avoidance button *only* when they expected it to effectively cancel the US. The fact that we did not observe differences in the use of the avoidance button between the avoidable and non-avoidable stimulus could be related to this lack of costs (i.e. there was no incentive to not use the avoidance button following the CS+unavoidable). It would be interesting to learn whether similar patterns would occur when avoidance actions were related to costs, as the level of costs might affect specifically unnecessary avoidance behavior (Wong & Pittig, 2022) and pathological avoidance might be specifically related to persistence despite its costs (Pittig et al., 2021).

We conclude from our results that patients with anxiety disorders learn to avoid in a different way than healthy control participants. Patients used the avoidance action more often during a signal of safety, had less confidence in the effectiveness of the avoidance action, and reported more relief when it was effective. Future experiments should examine the role of perceived US aversiveness in the observed profile of avoidance learning in patients with anxiety disorders.

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## Conflict of interest

All authors declare to have no conflict of interest related to the presented work.

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