Tackling Costly Fearful Avoidance using Pavlovian Counterconditioning

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Abstract

Avoidance behaviour constitutes a major transdiagnostic symptom that exacerbates anxiety. It hampers fear extinction and predicts poor therapy-outcome. Pavlovian counterconditioning with a reward could alleviate avoidance better than traditional extinction by reducing negative valence of the feared situation. However, scarce previous studies did not consider that pathological avoidance is often costly and typically evolves from an approach-avoidance conflict. Therefore, we used an approach-avoidance conflict paradigm to model effects of counterconditioning on costly avoidance (i.e., avoidance that leads to missing out on rewards). Results from our preregistered Bayesian Mixed Model analyses in 51 healthy participants (43 females) indicated that counterconditioning was more effective in reducing negative valuation and decreasing costly avoidance than traditional extinction. This study supports application of a simple counterconditioning technique, shows that its efficacy transfers to more complex avoidance situations, and suggests treatment may benefit from increasing reward drive in combination with extinction to overcome avoidance.

1. Introduction

Anxiety disorders are among the most prevalent and costly disorders worldwide (Craske & Stein, 2016; Kessler et al., 2005; Kessler et al., 2010). Although exposure-based CBT interventions have high success rates of 50-60% (Loerinc et al., 2015), a substantial proportion of patients profit insufficiently and/or show a return of symptoms. One key transdiagnostic factor that not only severely impairs patients' everyday functioning but also reduces therapy efficacy is avoidance behaviour (Craske et al., 2017; Kashdan et al., 2008; Pittig et al., 2018). Avoidance counter-acts the effect of exposure therapies by protection from extinction (Lovibond et al., 2009; Rattell et al., 2017; Vervliet & Indekeu, 2015) and predicts clinical outcomes better than anxiety (Castriotta, 2013; Hendriks et al., 2013; Pittig et al., 2015). Therefore, treatments to more successfully tackle this 'costly' avoidance behaviour are sorely needed. Here we used an approach-avoidance conflict paradigm to model effects of counterconditioning on so-called 'costly avoidance' and compared it to 'extinction alone' in reducing negative valuation and avoidance.

A promising avenue to innovate anxiety treatment has been shifting focus from mere exposure to actively changing the evaluation of the feared situation (Baeyens et al., 1992; De Houwer et al., 2000; Dirikx et al., 2004; Engelhard et al., 2014; Hermans et al., 2002). Traditional exposure therapy predominantly focuses on changing negative outcome expectations. This change is triggered by extinction procedures, where individuals are repeatedly exposed to the feared situation without the expected negative outcome to generate a newly-learned safety association that inhibits the original fear response (Bouton, 2004; Pittig et al., 2018). However, whereas extinction often effectively changes the *expectancy* of the negative situation, it is typically less effective in changing the *disliking* of that situation (Gawronski et al., 2015; Kerkhof et al., 2011; van Dis et al., 2019; Vansteenwegen et al., 2006). Since the negative evaluation associated with feared situations predicts the return of fear and other debilitating symptoms such as avoidance, dampening remaining negative feelings could be key in enhancing treatment success (Dirikx et al., 2004).

An effective way to manipulate the evaluation of a stimulus is counterconditioning (CC). Ever since the seminal studies by Mary Cover Jones (1924), the CC procedure is used to reverse negative valence of a disliked stimulus by associating it with a pleasant stimulus through Pavlovian conditioning. Whereas ground-breaking early studies provided clear evidence of its clinical potential (Bandura, 1961), counterconditioning has ever since been studied considerably less than extinction (see Keller et al., 2020 for review). This is surprising because indeed CC-based interventions also in more recent studies resulted in robust improvements in a variety of outcomes, sometimes even in direct comparison to traditional extinction-based interventions (Gatzounis et al., 2021; Hendriks et al., 2021; Kang et al., 2018; Keller & Dunsmoor, 2020; Kerkhof et al., 2011; Newall et al., 2017; Raes & De Raedt, 2012; Reynolds et al., 2018; van Dis et al., 2019; Zenses et al., 2021).

Previous studies have suggested that CC may also help overcome avoidance (de Jong et al., 2000; Hendriks et al., 2021; Jones, 1924; Reynolds et al., 2018) and thereby constitutes an attractive path for improving success in treating anxiety-related psychopathology (Dymond, 2019). However, these previous studies did not account for the fact that in psychopathology, avoidance is often costly, evolving from an approach-avoidance conflict caused by a mixed-outcome prospect (Bach, 2015; Pittig et al., 2018). That is, direct benefits of avoidance, such as reduced threat exposure, increased feelings of control (Boeke et al., 2017) and relief (Vervliet et al., 2017) usually co-occur in anxiety patients with significant negative long term consequences. Indeed what defines pathological avoidance is that it can lead to profound social isolation, impairments in professional life, and missed opportunities for personal development (Kashdan et al., 2008). Therefore in severe anxiety not only threat appraisals inform the decision to avoid but also appraisal of the foregone rewards typically weigh in to avoidance decisions (Aupperle et al., 2015; Ball & Gunaydin, 2022; Krypotos et al., 2018; Pittig et al., 2014). To date the vast majority of empirical and theoretical work, including work on CC, has however focussed on how anxious individuals process threats, leaving the potential influence of reward processing in avoidance and anxiety understudied (Arnaudova et al., 2017; LeDoux & Daw, 2018; Pittig et al., 2018). It therefore remains critically unclear whether CC

could effectively reduce avoidance during the more representative and ecologically valid situation of approach-avoidance conflict generated by mixed-outcome prospects.

We investigated the effects of CC on costly fearful avoidance behaviour, as assessed by our Fearful Avoidance Task (FAT). This task probes instrumental avoidance of aversive electrical stimulation at the expense of monetary rewards, and shows external validity in that higher real-life anxiety predicts stronger avoidance behaviour in the task (Hulsman et al., 2021). We hypothesised that CC is successful in reducing negative valence as well as avoidance under mixed outcome prospects. Additionally, we tested whether CC produces changes in basic physiological emotional stance indexed by eye-blink startle. Amplification of the eye-blink startle reflex is a cross-species measure for defensive responses (Bradley & Lang, 2000; Grillon & Baas, 2003; Lang et al., 1990) and could therefore be used to track changes in basic defensive physiology after the counter conditioning.

2. Transparency and Openness

2.1 Preregistration

All hypotheses, methods, and analyses were pre-registered on the Open Science Framework (<https://osf.io/p8gyn>). After the first preregistered analyses confirmed our effects (as documented in this 2019 preprint: <https://psyarxiv.com/h85ay/>), it became apparent that we may have been underpowered. Therefore, even though we obtained the expected key results, to confirm the reliability of our findings we decided at that point to amend our preregistration to include an extended data collection that more than doubled the sample size. Prior to the additional data collection, we also changed the analysis methods from standard mixed models to Bayesian Mixed models to provide more sensitive analyses and to better assess null findings. Importantly, and as can be verified from the 2019 preprint, all our key findings from the original preregistration were replicated in the extended sample with the new analyses.

2.2 Data, materials, code and online resources

All data and code are available from the Donders Institute for Brain, Cognition and Behaviour repository at <https://doi.org/10.34973/1tvv-wa16>

2.3 Reporting

We report how we determined our sample size, all data exclusions, all manipulations, and all measures in the study

2.4 Ethical approval

This study was carried out in compliance with the declaration of Helsinki and approved by a local medical-ethical committee (CMO Arnhem-Nijmegen).

3. Methods

3.1 Participants

Power calculations indicated a sample of at least $N=45$ would be required to detect the critical effect of counter conditioning on avoidance (for $>80\%$ power as indicated by formal simulations using SIMR; (Green & MacLeod, 2016)). The final sample for the analyses consisted of 51 participants (39 females, $M_{age} = 22.88$, $SD_{age} = 4.26$). In total, 57 participants participated in the testing session (43 females, $M_{age} = 22.68$, $SD_{age} = 4.15$). One participant failed to complete the testing session due to inability to cope with the startle sound. Six additional participants were excluded from the analyses based on their behavioural data suggesting they did not understand the task or showed almost no avoidance already before counterconditioning (detailed criteria specified below in section 3.8). Importantly, these exclusion criteria were specified a priori in our preregistration and we additionally confirmed that excluding these subjects did not affect the main results. Further exclusion criteria included lifetime diagnosis of mental, cardiologic or neurologic disorders, non-Dutch language speakers, hearing problems, insufficient (corrected) vision, use of psychoactive medication, epilepsy, and pregnancy. Additionally, participants were requested to refrain from eating three hours prior to the

experiment to enhance the effect of the counterconditioning (Andreatta & Pauli, 2015). At the start of the experiment, all participants reported to have followed this instruction. Participants were financially compensated with EUR 10 and received an additional bonus between EUR 0-5 depending on their performance in the Fearful Avoidance Task (described in section 3.5). All participants provided written informed consent.

3.2 General procedure

First, electrodes for physiology recordings and shock administration were applied. Subsequently, participants underwent *titration procedures* to determine the shock and reward levels for the Fearful Avoidance Task (FAT) at an individual level (see section 3.3). This was followed by *CS valence ratings* in which participants rated the pleasantness of each CS-type included in the FAT prior to conditioning (see below for details on the CS-types). Next, *baseline startle* measurements were taken to correct for individual differences in baseline startle response and to habituate subjects to the procedure. Subsequently, participants performed the FAT to assess baseline approach-avoidance behaviour prior to the counterconditioning. The FAT was followed by a second CS valence rating. Next, the *counterconditioning and extinction training* took place, in which one of the CS-types of the FAT was counterconditioned (CS+CC) and another was extinguished (CS+EXT) (see section 3.6). After the training, another CS valence rating was taken and participants completed the FAT a second time to assess the impact of the counterconditioning and extinction training on avoidance. The study ended with a last CS valence rating and baseline startle measurement. The overall procedure is summarized in Figure 1.

Figure 1. Study timeline. Shock work-up: procedure to set shock level intensity to an individual level that is maximally uncomfortable, but not painful. Reward-threat titration: procedure to titrate the subjective experience of the reward levels in the FAT to the subjective experience of shock intensity. CS valence rating: valence rating of all CS types. Startle baseline: seven startle probes at the beginning and end of the experiment to measure baseline startle amplitude. FAT = Fearful Avoidance Task. Training: counterconditioning and extinction training.

3.3. Titration procedures

3.3.1 Shock work-up procedure

A standardized *shock work-up procedure* was performed to set shock intensity to an individual level that was maximally uncomfortable, but not painful. After receiving a test-stimulation on the lowest shock level, participants rated each shock on a scale of 1 (*not painful/annoying*) to 5 (*very painful/annoying*). Intensities were adjusted step by step, aimed at a final level of 4 (uncomfortable but not painful) after 5 shocks were administered (Klumpers et al., 2010). Electrical shocks were delivered via two Ag/AgCl electrodes attached to the distal phalanges of the second and third fingers of the left hand using a MAXTENS 2000 (Bio-Protech) device. Shock duration was 250ms at 150Hz, and intensity varied in 10 intensity steps between 0–38 mA.

3.3.2 Titration of monetary reward

The Fearful Avoidance Task consisted of low and high reward conditions (explained in detail in section 3.5). To ensure that these low and high reward conditions had similar subjective value across participants relative to the shock and would lead to sufficient variation in avoidance, monetary rewards were titrated beforehand to the individual indifference point of each subject (Talmi et al., 2009). In this titration procedure, participants repeatedly made a hypothetical approach/avoid decision by button press. Participants were instructed that, just as in the FAT that would follow, an approach response was associated with a larger chance of receiving either a monetary reward or electrical shock (both 40%) and a smaller chance of a neutral outcome (no reward/shock; 20%). On the other hand, an avoidance response was associated with a larger chance on a neutral outcome (no reward/shock; 80%), a smaller chance of receiving a monetary reward or electrical shock (both 10%). These outcomes were hypothetical, i.e., participants did not receive any shocks or rewards during the titration procedure. The lowest amount that could be chosen was €0.20, and the highest was €10.00. In total 12 different amounts were presented in a fixed, semi-random order (€2.00, €0.20, €8.00, €0.50, €10.00, €1.00, €6.00, €0.80, €3.00, €5.00, €4.00, €7.00). The individual indifference point was operationalized as the average of the lowest monetary reward for which the participant chose to approach and the amount immediately below it. For example, when the lowest amount for which a participant approached was €2.00, the indifference point was set to €1.50 as the level directly below would be €1.00. This indifference value was subsequently used to calculate a low and high reward value for the ensuing FAT. The average indifference point was EUR 1.44 ($SD = 1.97$).

3.4 Valence ratings

The FAT consisted of four different CS-types (see sections 3.5 and 3.6). To investigate whether the counterconditioning and extinction training had an effect on the subjective valence of the CS-types, participants were asked to rate all four CS-types that were shown during the FAT on a scale ranging from -100 ('*Very unpleasant*') to 100 ('*Very pleasant*'), where 0 was a neutral

score. To account for order effects, participants rated the CS-types in a random order. Ratings were taken at four different time-points throughout the experiment (see Figure 1).

3.5 Fearful Avoidance Task (FAT)

The Fearful Avoidance Task (Hulsman et al., 2021) was used to assess approach-avoidance behaviour under competing reward and threat prospects. The task was programmed using Presentation® (Version 20.0; Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com). Participants received on-screen instructions for the task. Each trial in the FAT consisted of a cascade of three phases: i.e., the offer, anticipation, and outcome phase.

In the *offer phase*, a monetary amount and male avatar were presented. Participants were instructed that the monetary amount indicated the potential reward that could be earned on this trial, whereas the avatar indicated the threat level. There were two reward levels (low/high). The low and high reward levels were set at 40, 45, and 50% below and above the individual difference point, respectively. The jitter within each reward level was intended to create variability over trials to keep subjects attentive. To illustrate, with an indifference point of EUR 1.50 the low reward value ranged between EUR 0.75 and EUR 0.90 and the high reward values ranged between EUR 2.10 and EUR 2.25. Threat levels (low/high) were indicated with four different avatars (representing the CS-types), one signalling absence of shock threat (CS-) and three signalling threat of shock (CS+CC, CS+EXT, CS+Control, see Figure 2). Unbeknownst to the participants, each of these high threat avatars was pre-determined to be counterconditioned (CS+CC), to be extinguished (CS+EXT), or to serve as a non-extinguished control (CS+Control) during the subsequent training. Reward and CS-types were combined in a full factorial manner, leading to eight trial types in total: low reward/CS-, low reward/CS+CC, low reward/CS+EXT, low reward/CS+Control, high reward/CS-, high reward/CS+CC, high reward/CS+EXT, high reward/CS+Control. After the onset of the offer phase, participants had 4 seconds to decide to approach or avoid by pulling the joystick towards them or pushing the joystick away from them, respectively. As confirmation of a timely response (<4s), a white square appeared around the reward.

Next, a 2-4s *anticipation phase* started. In all trials, startle probes (50ms white noise, $\pm 105\text{dB}$) were presented 1500ms after the response to measure the eye-blink response during outcome anticipation.

After the anticipation phase, participants received the *outcome* of their decision. The outcome could either be positive (avatar offered money), negative (avatar drew a gun), or neutral (avatar disappeared; Figure 2B). As in the titration, participants were explicitly instructed before the task that when they decided to approach, there was a 40/40% chance of receiving the positive or negative outcome and a 20% chance on receiving the neutral outcome. If the participants decided to avoid, there was a 10/10% chance of receiving the positive or negative outcome and an 80% chance of receiving the neutral outcome. Participants were further instructed that in contrast to trials with the CS- avatar, the CS+ avatars (CS+CC, CS+EXT, CS+Control) signalled that the negative outcome would be accompanied by an electric shock. If participants did not give a timely response ($<4\text{s}$), they always received the negative outcome. After receiving the outcome, a 5-7s inter-trial interval occurred in which a fixation cross was presented.

The FAT was administered twice: before and after the counterconditioning and extinction training. For both administrations, the FAT consisted of 6 blocks, with each block comprising all 8 trial types, leading to a total of 48 trials per FAT administration. The order of the reward levels and CS-types was pseudo-randomised so that both could not be repeated more than once within a block. Before the first administration of the FAT, participants completed a practice session. The practice session consisted of 8 trials (one of each trial type), without the risk of receiving an electric shock. The experimenter monitored their responses, and verified that participants understood the task. To determine the bonus pay-out on the FAT, participants selected six random numbers prior to the first FAT. Each number was linked to a specific trial number by a mathematical formula that was unknown to the participants when they selected the numbers. Participants received the total amount of rewards received on these six trials as a bonus at the end, with a maximum of EUR 5.

Figure 2. Fearful Avoidance Task (FAT) **A.** Example of the FAT trial structure. In the offer phase, a monetary reward (low/high relative to the participant's individual difference point) and an avatar indicating the shock threat level (low/high) were presented. The participant had to decide to approach or avoid by pulling the joystick towards themselves or away from them, respectively. After an anticipation phase, participants received a neutral, positive or negative outcome. Each trial ended with an inter-trial interval (ITI) during which a fixation cross was presented. **B.** One avatar indicated safety from receiving electrical shock (CS-); three avatars indicated threat of shock and were subsequently counterconditioned, extinguished or not shown during the training following the FAT (CS+CC, CS+EXT, CS+Control). **C.** Overview of the outcome contingencies when choosing to approach or avoid.

3.6 Counterconditioning and Extinction training

With our training, we aimed to compare the effect of counterconditioning training directly with the effect of extinction training (Keller et al., 2020). We based our training on studies by Kerkhof et al. (Kerkhof, 2010; Kerkhof et al., 2011), who showed that a picture-taste paradigm was

most effective in changing the valence of a negative stimulus. During the training, one avatar previously associated with risk of shock in the FAT was counterconditioned with a rewarding snack (CS+CC), while another was extinguished yet never paired with reward (CS+EXT). The third high threat avatar of the FAT was not included in the training to assess effects of repeating the FAT (CS+Control).

Before the start of the training, a plate with small 1x1 cm cookies was placed in front of the participants, together with a glass of water. The cookies were made using 200 grams of oats, 150 grams of butter, and 100 grams of sugar. The plate and cookies were removed right after the training.

Each trial started by showing the avatar (CS+CC or CS+EXT). After one second, a prompt appeared instructing participants to eat a cookie and drink a sip of water (CC trials) or to wait to continue (EXT trials; see Figure 3). Meanwhile, the avatar remained on the screen. In both conditions participants were able to continue after 20s by pressing enter. After each trial there was a 2s fixation cross. In total, participants completed 20 trials, 10 trials for each type of training (CC vs. EXT). The trial order was pseudorandomized and CS-types were never repeated more than once. Associations between specific avatar identities and conditions were counterbalanced across participants

To assess the behavioural effects of the CC-training without an impact of shock reinforcement (i.e., receiving shocks after the CC-training might reinstate anxiety and quickly overshadow CC effects), the first block of the FAT after the training unbeknownst to the participant only consisted of either monetary reward (80% chance when deciding to approach, 20% chance when deciding to avoid) or the neutral outcome (20% chance when deciding to approach, 80% chance when deciding to avoid).

Figure 3. Counterconditioning and extinction training trial structure. Schematic overview with one example of a CS+CC and one example of a CS+EXT trial. Each trial type was presented 10 times. The CS+Control was not presented during the CC-training.

3.7 Eye-blink startle recording

Electrodes for recording eye-blink electromyography (EMG) were placed on the lower orbicularis oculi muscle of the left eye, with the active electrode beneath the pupil, as close to the eyelid as possible, and the reference electrode approximately 1-2 cm lateral to the first (Blumenthal et al., 2005). The ground electrode was placed on the right cheek. EMG electrode impedance was held below 30kOhm. Physiological recording and amplification were carried out using BrainAmp ExG (BrainProducts GmbH, brainproducts.com) and BrainVision Recorder software (Version 1.21.0201, BrainProducts GmbH, brainproducts.com) at a sampling frequency of 2500 Hz.

Participants with missing and/or a null-response in more than half of the trials were excluded from the analyses concerning eye-blink startle data. This exclusion resulted in a sample size of 43 participants. In part of the sample, the Post-Auricular Reflex (PAR) was measured as well. However, due to a high number of null-responses (i.e., no significant

response could be detected for this more subtle response), the PAR results are not included in this manuscript. More information can be found in the supplementary materials.

The raw EMG data were processed with Vision Analyzer software (Version 2.1; BrainProducts GmbH, brainproducts.com) and in accordance with previously published guidelines (Blumenthal et al., 2005). The data was filtered with a bandpass filter (low frequency = 28 Hz, high frequency = 500 Hz), and segmented into epochs from 50ms before and 200ms after startle probe onset. Further, the signal was rectified, and a low-frequency filter of 14 Hz was applied for smoothing and was baseline corrected. Responses were scored as the maximum peak amplitude within 25ms – 100ms after startle probe onset subtracted by baseline EMG activity, consistent with previous work (Klumpers et al., 2015). Using an in-house developed pipeline in Matlab, (www.matlab.com), trials in which there was excessive activity in the 50ms baseline period preceding the startle probe and where the peak amplitude latencies were outside the normal range were set to missing. Trials with less than 10% increase in standard deviation relative to a 50ms baseline preceding the response were scored as null responses.

Before the start of the experiment, participants received seven startle probes to index baseline startle and to habituate to the sound. This was repeated at the end of the experiment to standardise the magnitudes of the startle measures and control for individual variation in magnitude (Blumenthal et al., 2005). The startle probe consisted of a 105dB 50ms white noise burst with instantaneous rise time. Raw mean startle amplitudes during the habituation phase of the startle and after the completion of the FAT were used to identify the unconditioned startle amplitude and to correct for individual differences in baseline startle. These 14 trials (7 before and 7 after the experiment) were included together with all the FAT trials to calculate the *z*-scores per participant to control for individual differences in baseline startle (Blumenthal et al., 2005; Klumpers et al., 2015).

Peak amplitudes of all trials in the FAT were subsequently converted into *T* scores ($T = z \cdot 10 + 50$) for further statistical analysis. Raw eye-blink startle magnitudes were also statistically analysed, since in some rare cases standardization may produce unintended

results (Bradford et al., 2015). However, the results for the raw amplitudes showed identical patterns to the standardized amplitudes and therefore are not discussed.

3.8 Analyses

Six participants were excluded from behavioural data analyses following our a priori registered exclusion criteria: i.e., more than 50% missing responses, more than three trials more avoidance on CS- than CS+ trials, more than three trials more avoidance on high than on low reward trials. These patterns were observed in three participants and potentially indicated that the participants did not understand the FAT correctly or did not seriously make decisions as there was no reason to consistently avoid CS- trials more than CS+ trials or avoid low reward more than high rewards after the instructions. Further, participants with less than 10% avoidance in the first FAT were excluded to diminish floor effects (i.e., avoidance could not be robustly decreased further with CC and EXT training). This criterium led to the exclusion of an additional three participants. Please note that none of these criteria bias our results in the expected direction, because the expectation was to observe a stimulus specific reduction in avoidance only for the CS+CC stimulus. We verified however that all the main results reported as significant below remained significant when repeating the analyses without any exclusion of participants.

Statistical analyses were carried out in R (Version 3.6.2; R Core team, 2019) in RStudio (Version 1.2.5033; RStudio Inc., 2019). Bayesian mixed models were used to estimate the effects for all dependent variables, using the package brms (Version 2.10.0; Burkner, 2017). All models included a maximum random-effects structure. This consisted of a random intercept per participants and random slopes for the within-subject effects of the same variables that were fixed effects in all the models described below (both main effects and interactions). All continuous predictors were standardized and all categorical predictors were coded using sum-to-zero contrasts. For all models we used the generic, default priors of the brms package to give fast and accurate model convergence, without making study-specific assumptions on the data. These are improper flat priors for population-level (i.e., fixed) effects, weakly informative

Student-t priors for group-level effects (i.e., random intercepts and slopes), and LKJ-Correlation priors for random correlations (Bürkner, 2017, 2018). For the behavioural analyses, a binomial distribution was used. For the eye-blink startle and valence analyses a Gaussian distribution was used.

Models were fitted using 6 chains with 5000 iterations each (1000 warm-up). A coefficient is deemed “significant” when the associated 95% posterior credible intervals is non-overlapping with zero. In the case results did not reach “significance”, 90% CI’s are reported to investigate whether a marginally significant effect is observed with a narrower interval. When effects were significant at the 95% level, we additionally tested 99% and 99.9% CI’s to explore in more detail the robustness of the effects (akin to reporting $p < .01$ and $p < .001$ respectively rather than only $p < .05$). All post-hoc analyses were conducted using the emmeans package (Version 1.4.5; Russel, Henrik, Jonathon, Paul, & Maxime, 2020).

3.8.1 Baseline (pre-conditioning)

First, three separate Bayesian mixed-effects models were performed to inspect the effects of threat and/or reward on stimulus valence, avoidance, and eye-blink startle at baseline before the training. Threat (low: CS- vs high: all CS+) was a predictor in all these models. Since the valence data was not acquired per reward level but per avatar, reward (low, high) was only a predictor in the avoidance and eye-blink startle models.

3.8.2. Counter-conditioning effects

Subsequently, the effects of the counter-conditioning training were investigated. Again, three Bayesian mixed effects models (section 3.8) were performed. CS+-type (CS+CC, CS+EXT, CS+Control) was a predictor in all these models. In addition, time was added as a predictor to all models. For the valence data, time had 4 levels (before FAT1, after FAT1, before FAT2, after FAT2). For the avoidance data and eye-blink startle data, time had 2 levels (before CC-training, after CC-training). Again, reward (low, high) was a predictor in the avoidance and eye-blink startle models.

4. Results

4.1 Baseline effects (before training)

4.1.1 Stimulus Valence (pre FAT1 vs post FAT1)

As expected, valence ratings for the CS+ stimuli were overall significantly more negative than for the CS- (Threat: $B = 0.47$, 99.9% CI [0.28, 0.67]). In addition, there was a significant decrease in valence after FAT administration (Time: $B_{\text{pre FAT1 vs post FAT1}} = -0.11$, 99% CI [-0.21, -0.01]) that was further qualified by a significant interaction between Threat and Time ($B = 0.32$, 99.9% CI [-0.49, -0.14]). Before the first FAT administration, the valence of the CS+ stimuli was already more negative than the low threat (CS-) stimulus ($B = 0.29$, 95% CI [0.07, 0.52]), likely due to instructed CS-type contingencies. This difference was further enhanced after FAT administration and accompanying shock exposure ($B = 1.58$, 99.9% CI [0.98, 2.20]). Indeed, the CS- was rated more positively over time ($B = -.88$, 99.9% CI [-1.38, -0.34]), while CS+ ratings decreased ($B = 0.42$, 99.9% CI [0.07, 0.76]; see Figure 4A).

Although no distinction was made between the CS+ types at baseline (i.e., before the counterconditioning and extinction training), we unexpectedly found a marginally significant interaction between CS-type and Time for CS+CC vs. CS+Control ($B = 0.11$, 90% CI [0.01, 0.21]). No such effect was found for CS+EXT vs. CS+CC ($B = -0.03$, 90% CI [-0.13, 0.07]). Post-hoc analyses showed that before the first FAT administration, valence for the CS+Control was more positive than for CS+CC and CS+EXT ($B_{\text{CS+CC vs. CS+Control}} = 0.39$, 95% CI [0.08, 0.69]; $B_{\text{CS+EXT vs. CS+Control}} = 0.33$, 95% CI [0.02, 0.63]). Importantly however, after the first FAT administration, these differences were no longer apparent ($B_{\text{CS+CC vs. CS+Control}} = 0.001$, 90% CI [-0.26, 0.25]; $B_{\text{CS+EXT vs. CS+Control}} = 0.05$, 90% CI [-0.20, 0.31]). Thus, before the CC and EXT training took place, all CS+-types had a comparable valence rating ($M_{\text{CS+CC}} = -30.61$; $M_{\text{CS+EXT}} = -32.33$; $M_{\text{CS+Control}} = -30.59$; see Figure 4A).

Figure 4. A. Average rated valence per CS-type as a function of time: pre FAT1, post FAT2 (before CC and EXT training), pre FAT2 (after CC and EXT training), and post FAT2. Valence ratings ranged from -100 (very unpleasant) to 100 (very pleasant) and show a positive effect of counter conditioning. **B.** Average proportion avoidant decision per CS-type over time (collapsed across reward level as the training effect did not vary as a function of reward). Avoidance decreased more for the CS+CC compared to the CS+EXT and CS+Control. **C.** Average eye-blink startle magnitude *T*-scores per CS-type over time (collapsed across reward levels given no interaction between reward and time). Startle showed a reduction over time across all CS+ types that was statistically indistinguishable. * 95%, ** 99%, *** 99.9% posterior credible intervals non-overlapping with zero.

4.1.2 Avoidance behaviour (FAT1)

The task elicited the expected behaviour, as evidenced by opposing effects of Threat ($B_{\text{high vs low threat}} = 0.21$, 99.9% CI [0.15, 0.28]) and Reward ($B_{\text{high vs low reward}} = 0.16$, 99.9% CI [0.11, 0.21]), with more avoidance in high threat and low reward conditions. Given that training was found not to interact with reward level (see below), results are collapsed across reward levels in Figure 4 but reward effects are illustrated in the supplement (Figure S2). As expected, there was also an interaction between shock threat and reward ($B = 0.13$, 99.9% CI [0.08, 0.17]). For both CS- and CS+ stimuli, participants avoided more in the low than high reward conditions ($B_{\text{low threat}} = 0.07$, 95% CI [0.01, 0.12]; $B_{\text{high threat}} = 0.58$, 99.9% CI [0.42, 0.74]). However, this effect of reward was stronger for high threat (CS+) stimuli (Figure S2).

Importantly, there was no difference in overall avoidance rates for the CS+ types before the CC and EXT training ($B_{\text{CS+CC vs CS+Control}} = -0.15$, 90% CI [-0.38, 0.08], $B_{\text{CS+CC vs CS+EXT}} = 0.13$, 90% CI [-0.09, 0.36]), and there was also no interaction between CS-type and Reward ($B_{\text{CS+CC vs CS+Control}} = -0.11$, 90% CI [-0.34, 0.12], $B_{\text{CS+CC vs CS+EXT}} = .04$, 90% CI [-0.19, .26]).

4.1.3 Eye-blink startle (FAT1)

In line with our hypotheses, startle magnitude was increased for CS+ stimuli compared to CS- ($B = -0.11$, 99.9% CI [-0.21, -0.01]). There was no significant main effect of Reward ($B = 0.01$, 90% CI [-0.04, 0.05]). There was a significant interaction between Threat and Reward ($B = -0.10$, 99% CI [-0.18, -0.02]; see supplement Figure 2). We found threat-potentiated startle in high reward conditions ($B = -0.42$, 99.9% CI [-0.71, -0.13]) but not in low reward conditions ($B = 0.21$, 90% CI [-0.15, 0.12]) where most avoidance occurred and therefore shock threat was low.

Importantly, before the CC and EXT training, there was no difference in startle magnitudes between CS+-Types ($M_{\text{CS+CC}} = 52.24$; $M_{\text{CS+EXT}} = 52.59$; $M_{\text{CS+Control}} = 52.64$; $B_{\text{CS+CC vs CS+Control}} = 0.02$, 90% CI [-0.05, 0.08]; $B_{\text{CS+CC vs CS+EXT}} = 0.02$, 90% CI [-0.05, 0.08]).

Summarizing, prior to the CC and EXT training the task overall produced the expected results, and importantly there was no significant difference between the to be-conditioned CS-types in avoidance rates, valence ratings or startle directly before the training commenced.

4.2 Training effects (comparisons between CS-types before and after training)

4.2.1 Stimulus Valence

As expected, compared to the CS+EXT and CS+Control, the CS+CC showed a significant increase in valence from before to after training (i.e., post FAT1 vs pre FAT2; $B_{\text{CS+CC vs CS+Control}} = 0.14$, 99% CI [0.01, 0.26]; $B_{\text{CS+CC vs CS+EXT}} = 0.17$, 95% CI [0.04, 0.29]). This difference decreased again after administration of the second FAT (i.e., pre FAT2 vs post FAT2; $B_{\text{CS+CC vs CS+Control}} = -0.15$, 99% CI [-0.29, -0.02]; $B_{\text{CS+CC vs CS+EXT}} = -0.17$, 99% CI [-0.32, -0.02]).

Post-hoc analyses revealed that only for the CS+CC there was a significant effect of time ($B = -0.93$, 99.9% CI [-1.35, -0.49]), reflecting an more positive valence after the CC training ($M = 2.25$, $SD = 36.17$) compared to the timepoint immediately preceding it ($M = -30.61$, $SD = 32.70$). After shock threat was reinstated in FAT2, the CS+CC valence rating decreased again ($B = 0.33$, 95% CI [0.07, 0.59]; $M = -9.64$, $SD = 35.10$). For both the CS+EXT and CS+Control there were no significant changes in valence following the training (all 90% CI's overlapping with zero; see Figure 4A).

Comparing conditions directly per timepoint, subjects reported significantly higher valence for CS+CC compared to both other CS+-types after the training (i.e., pre FAT2; CS+CC vs CS+EXT: $B = -1.00$, 99.9% CI [-1.68, -0.36]; CS+CC vs CS+Control: ($B = -0.90$, 99.9% CI [-1.45, -0.35])). Although the CS+CC decreased in valence after the second FAT, it was still rated significantly more positive in the last rating than CS+EXT ($B = -0.50$, 95% CI [-0.88, -0.11]), and CS+Control ($B = -0.41$, 99% CI [-0.81, -0.01]). The CS+Control and the CS+EXT did not differ at any timepoint following the training ($B = .09$, 90% CI [-0.16, 0.34] and $B = 0.09$, 90% CI [-0.16, 0.34], respectively).

Thus, results indicated that the CC and EXT training produced a robust and specific increase in positive valence of the CS+CC with incomplete extinction of this effect upon shock threat re-exposure during FAT2.

4.2.2 Avoidance behaviour

There was a significant main effect of Time indicating overall avoidance was lower after the CC and EXT training than before ($B = 0.72$, 99.9% CI [0.19, 1.39]). There were trends for overall reduced avoidance for the CS+CC compared to the other high threat (CS+) conditions across both timepoints ($B_{\text{CS+CC vs CS+EXT}} = 0.24$, 90% CI [0.03, 0.47]; $B_{\text{CS+CC vs CS+Control}} = 0.47$, 90% CI [0.001, 0.98]). Importantly, there was also a significant interaction between CS-type and Time for CS+CC versus CS+Control ($B = -0.25$, 95% CI [-0.48, -0.04]), reflecting stronger reductions in avoidance after CC-training compared to before (Figure 4B). EXT training showed intermediate success in reducing avoidance as it did not produce significantly stronger avoidance reductions than the passive control condition ($B_{\text{CS+EXT vs CS+Control}} = -0.34$, 90% CI [-0.93, 0.29]) but the reduction in avoidance was also not significantly different compared to the counterconditioned stimulus ($B_{\text{CS+CC vs CS+EXT}} = -0.08$, 90% CI [-0.32, 0.15]). Planned comparisons in fact showed significant decreases in avoidance after the training for all conditions ($B_{\text{CS+CC}} = 2.13$, 99.9% CI [0.70, 3.79]; $B_{\text{CS+EXT}} = 1.28$, 99% CI [0.13, 2.53]; $B_{\text{CS+Control}} = 0.94$, 95% CI [0.18, 1.74]). Critically, while there were no differences in avoidance before training between CS-types, after the training avoidance on the CS+CC ($M = .40$, $SD = .49$) was significantly lower compared to both the CS+EXT ($M = 0.46$, $SD = 0.50$, $B = 1.00$, 95% CI [0.15, 1.85]), and the CS+Control ($M = 0.45$, $SD = 0.50$, $B = 1.01$, 99% CI [0.11, 1.98]). There was no significant difference between the CS+EXT and the CS+Control after the training ($B = 0.01$, 90% CI [-0.50, 0.55]).

While we hypothesized that the effect of counterconditioning might be strongest in the low reward condition where there was potentially most room for improvement, the three-way interaction between CS+-type, time and reward returned non-significant ($B_{\text{CS+CC vs CS+Control}} =$

0.14, 90% CI [-.04, .32]; $B_{CS+CC \text{ vs } CS+EXT} = -0.08$, 90% CI [-0.32, 0.12]; full descriptives per reward level can be found the supplement (table S1).

Together, results demonstrated that CC training reduced avoidance compared to the passive control, while EXT training did not. While the reduction over time was not significantly stronger for the counterconditioned stimulus than for traditional extinction, subjects reached a significantly lower level of avoidance after counterconditioning (Figure 4B).

4.2.3 Eye-blink startle

In contrast to subjective valence and avoidance, startle was not affected by CC. There was a significant main effect of time ($B = -.05$, 99.9% CI [-0.06, -.03]), with eye-blink magnitude lower after the training ($M = 47.92$, $SD = 8.95$), than before ($M = 52.49$, $SD = 9.48$; Figure 4C). There was also a main effect of reward, with amplitudes for high reward larger ($M = 50.92$, $SD = 9.66$), than for the low reward condition where most avoidance occurred ($M = 49.51$, $SD = 9.29$, $B = 0.01$, 99.9% CI [0.002, 0.03]).

More importantly, there was no significant main effect of CS+-type ($B_{CS+CC \text{ vs } CS+Control} = 0.01$, 90% CI [-0.002, 0.01]; $B_{CS+CC \text{ vs } CS+EXT} = -0.00$, 90% CI [-0.01, 0.003]) nor interactions between CS-type and time ($B_{CS+CC \text{ vs. } CS+Control} = 0.00$, 90% CI [-0.01, 0.01]; $B_{CS+CC \text{ vs } CS+EXT} = -0.01$, 90% CI [-0.02, .0002]). The three-way interaction between CS-type, time and reward was also not significant ($B_{CS+CC \text{ vs. } CS+Control} = 0.00$, 90% CI [-0.01, 0.01]; $B_{CS+CC \text{ vs } CS+EXT} = -0.00$, 90% CI [-0.01, 0.01]). These results indicate that the CC-training, while effective in changing subjective valence and avoidance did not influence the startle reflex amplitude and startle simply seemed to habituate similarly for all CS-types.

5. Discussion

This study investigated if a training based on counterconditioning could reduce the negative valence of a threatening stimulus and more effectively reduce avoidance behaviour during approach/avoid conflicts, compared to extinction. We found that the CC-training successfully reduced the negative valence and more importantly led to significantly decreased avoidance

for the appetitively conditioned stimulus compared to an extinction control. Contrary to our expectations, there was no concomitant change in eye-blink startle potentiation. Our findings (I) provide a proof-of-principle demonstration of the effectiveness of counterconditioning as a pathway for reducing costly avoidance, (II) thereby demonstrate a causal role for reward processing in costly fearful avoidance under mixed outcome possibilities and (III) suggest that reductions in avoidance may take place in the absence of changes in basic reflex physiology indexed by eye-blink startle.

Our FAT paradigm produced the intended negative valence for stimuli associated with shock. We showed that only counterconditioning reduces the negative valence of the CS+CC whereas an extinguished stimulus (CS+EXT) or a passive control (CS+Control) did not show such changes. Although such effects are not universal and likely dependent on exact study procedures (Gatzounis et al., 2021; Kang et al., 2018), these findings are in line with the majority of previous studies (Hofmann et al., 2010; Keller et al., 2020; Kerkhof et al., 2011; Newall et al., 2017; van Dis et al., 2019). We show that this reduction generalises to the case of an acute approach-avoidance conflict and that it is robust, even under acute threat of shock while previous studies have typically tested under extinction conditions or after reinstatement.

Our paradigm also successfully elicited costly avoidance behaviour, with avoidance levels varying dependent on the combination of threat and reward levels as expected (Hulsman et al., 2021; Pittig et al., 2014). After CC-training we found reduced avoidance behaviour for all CS-Types. Counterconditioning however led to a significantly lower level of avoidance than extinction. There was also a smaller reduction in avoidance over time for the CS+Control stimulus that was neither counter conditioned nor extinguished, likely due to habituation to the shock-US (Hall & Rodríguez, 2017) although also generalization of CC or extinction cannot be ruled out. The observed superiority of counterconditioning is in line with recent work by Newall et al. (2017) and Reynolds et al. (2018) who found a reduction in avoidance behaviour after CC in children. We extend these previous findings by including (I) a different population (i.e., adults), (II) subjective valence scores, and (III) a potentially more ecologically valid avoidance measure (Krypotos, Vervliet, & Engelhard, 2018).

While our study showed the expected benefits of CC in reducing negative valence and avoidance, we in addition tested whether the effects of the CC-training would be visible on a measure that is not dependent on contingency awareness: eye-blink startle. Startle reflex modulation has been shown to provide an index of subconscious conditioned emotional responding (Hamm & Vaitl, 1996; Sevenster et al., 2014) and we added this measure to investigate effects on a more basic physiological level. Startle did show the expected potentiation under high threat on high reward trials, where conflict was highest and avoidance lowest. However, the CC-training did not decrease the eye-blink magnitude for the CS+CC compared to the control conditions, as would be expected based on previous studies that suggested startle potentiation reflects hedonic impact or “liking” (Hebert et al., 2015). Credible intervals were centred closely around zero for the CS effects, which suggests that our null finding is not a result of being underpowered to detect small effects. While care is required in interpreting the null finding, this is in line with a recent study (Stussi et al., 2018) that found that counterconditioning with a pleasant odour also resulted in subjective effects in the absence of eye-blink effects. Thus, a difference in subjective valence and choice behaviour does not necessarily imply a decrease in more automatic defensive emotional stance reflected by startle. Together, these findings may suggest that the behavioural effects of counterconditioning take place at a neural implementation level that is, at least to some extent, independent of the neural circuits driving startle potentiation. Such dissociations provide support for recommendations to study affective processes at subjective, physiological and behavioural levels simultaneously (Beckers et al., 2013; Lang, 1994).

While our lack of a reduction of startle might lead to speculation that counterconditioning may not be of added benefit to change basic physiological aspects of anxiety, several recent studies have found superior effects of counterconditioning on skin conductance responding (Keller & Dunsmoor, 2020; Raes & De Raedt, 2012). An alternative hypothesis to be considered for the discrepancy between startle physiology on the one hand and choice behaviour and ratings on the other, is that the reduction in avoidance rates after counterconditioning led to higher shock exposure for the CS+CC. These effects could have

led to a quick reinstatement of conditioned startle compensating any reductions in startle due to the counterconditioning. There are two reasons why we think such an interpretation is unlikely. First, the probabilistic nature of the task leads to an increase in uncertainty about threat even when avoiding and thereby dampens any impact of an avoidant strategy on the perceived threat (Krypotos, Vervliet, & Engelhard, 2018). Second, post-hoc analyses did not find evidence for an association between startle and avoidance levels during the baseline (pre-counterconditioning) phase. What then drives the change in avoidance observed after counterconditioning? This is an important question for future research as more knowledge of the working mechanisms could help understand for whom counterconditioning-based treatments may be most successful and how they can be improved. Recent studies seem to indicate that changes in subjective valence are not required (Kang et al., 2018) nor sufficient (van Dis et al., 2019) for robust changes after counterconditioning. A potential working mechanism besides the observed change in subjective valence could be that counterconditioning facilitates attention towards the CS+CC, which could boost learning and provide a robust and more resistant inhibitory memory trace (Keller et al., 2020). Indeed, recent studies indicate that counter conditioning may boost explicit memory compared to extinction (Keller & Dunsmoor, 2020; Keller et al., 2022).

The current study has several strengths and limitations. As far as the strengths, we measured avoidance in a more representative context of approach-avoidance conflict, using a well-established task that was demonstrated to be sensitive to individual differences (Hulsman et al., 2021), a well powered sample and consideration of conditioning effects using subjective, behavioural as well as physiological measures. As far as limitations, it has to be noted that the decrease in avoidance after counterconditioning vs. extinction was significant but small. Indeed, It is important to point out however that both renewal (due to removal of the plate of cookies) and reinstatement (due to shock exposure) likely counteracted the effects of the counterconditioning and extinction in our setup. Nevertheless, that counterconditioning was superior to extinction under these circumstances might underline the potential relevance for real-life where continued positive reinforcement after treatment is not always feasible and

exposure to reminders of the threat may be a problem. Further, while there is evidence that counterconditioning effects can last up to month (Keller et al., 2022; Kerkhof et al., 2011), it would for the clinical potential be important in future work to also assess the long term impact of counterconditioning on avoidance by using multi-day protocols (Dis et al., 2019; Kang et al., 2018). Finally, we did not formally assess gender or ethnic, cultural, and socioeconomic backgrounds of our participants. Our study population consisted predominantly of a young, white, highly-educated female population and therefore the findings of this study require exploration in more diverse populations. For instance, it has been found in multiple studies that females generally show more or longer avoidance behaviour than males (Hulsman et al., 2021; McLean & Anderson, 2009; Pittig et al., 2018; Sheynin et al., 2015). Since the incidence of anxiety disorders is overall higher in females, the current results are promising, but more work in larger more diverse samples is needed to understand the impact of such individual differences on the efficacy of counterconditioning training.

Besides theoretical implications, this study may have implications for the treatment of anxiety disorders. Our finding should be seen as a promising proof-of-concept which requires more exploration to investigate clinical utility. Current standard treatment of anxiety disorders does not typically involve an explicit counterconditioning component (Craske & Stein, 2016; Stein & Craske, 2017). Translation of counterconditioning to treatment may be especially challenging also because higher levels of anxiety would likely require a sufficiently potent appetitive stimulus to counter the higher levels of negative valence. That said, therapeutic presence and feedback might already provide some implicit counterconditioning of threat. Our study, while in healthy participants, suggests together with recent studies (Newall et al., 2017; Reynolds et al., 2018) and promising work in spider phobics (De Jong, Vorage, & Van Den Hout, 2000) that counterconditioning strategies might be used more explicitly in clinical treatment of anxiety and avoidance. One consideration for its application would be that for the inhibitory extinction learning to be effective, the appetitive stimulus should not distract from the exposure and may best be presented in the background or immediately following exposure as was done here so that no competition arises. Future studies are needed to investigate such

boundary conditions more. Also, it would be highly relevant for future work to study how a CC-training approach compares to extinction in the reduction of avoidance behaviour in a population with clinical anxiety levels.

In conclusion, our training based on counterconditioning was successful in reducing negative valence and avoidance behaviour in a mixed-outcome fearful approach-avoidance task. As excessive avoidance is one of the key predictors of clinical outcomes, this study should be an impetus for further investigation of counterconditioning as a potential treatment for anxiety disorders.

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7. Conflicts of interest

The authors declare that there were no conflicts of interest with respect to the authorship or the publication of this article.

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9. Author contributions

Conceptualization: IvdP, AH, KR, FK; Methodology: IvdP, AH, KR, FK; Formal analysis: AH, IvdP; Investigation: IvdP & AH; Original draft preparation: AH, IvdP, FK; Validation: IvdP & AH; Review & Editing: AH, KR, FK; Supervision: KR & FK;

10. Prior versions

Preprints of earlier drafts of the article can be found at <https://psyarxiv.com/h85ay/>.

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