Behaviour Research and Therapy 137 (2021) 103788

Contents lists available at ScienceDirect

Behaviour Research and Therapy

journal homepage: www.elsevier.com/locate/brat

Individual differences in costly fearful avoidance and the relation to psychophysiology

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ARTICLE INFO

Keywords:
Avoidance
Anxiety
Psychophysiology
Individual differences
Reward
Threat

ABSTRACT

Excessive avoidance behaviour is a cardinal symptom of anxiety disorders. Avoidance is not only associated with the benefits of avoiding threats, but also with the costs of missing out on rewards upon exploration. Psychological and psychophysiological mechanisms contributing to these costly avoidance decisions in prospect of mixed outcomes remain unclear. We developed a novel Fearful Avoidance Task (FAT) that resembles characteristics of real-life approach-avoidance conflicts, enabling to disentangle reward and threat effects. Using the FAT, we investigated individual differences in avoidance behaviour and anticipatory psychophysiological states (i.e. startle reflex and skin conductance) in a relatively large sample of 343 (78 females) participants. Avoidance under acute threat of shock depends on a trade-off between perceived reward and threat. Both increased startle and skin conductance in the absence of threat of shock emerged as predictors of increased avoidance (potentially indicative of fear generalization). Increased avoidance was also associated with female sex and trait anxiety, dependent on reward and threat levels. Our findings highlight distinct possible predictors of heightened avoidance and add to mechanistic understanding of how individual propensity for costly avoidance may emerge. Distinct avoidance typologies based on differential reward and threat sensitivities may have different mechanistic origins and thereby could benefit from different treatment strategies.

1. Introduction

Excessive avoidance behaviour is a key symptom of anxiety disorders (Aupperle, Sullivan, Melrose, Paulus, & Stein, 2011; LeDoux, Moscarello, Sears, & Campese, 2017; Mkrtchian, Aylward, Dayan, Roiser, & Robinson, 2017). In contrast to emotional and cognitive elements of these disorders, avoidance is a critical, yet scientifically understudied factor in both emergence and maintenance of anxiety disorders (Beckers & Craske, 2017). Recent converging findings indicate that excessive avoidance is a better predictor of disorder outcome than current anxiety levels (Hendriks, Spijker, Licht, Beekman, & Penninx, 2013; Pittig, Alpers, Niles, & Craske, 2015). However, most previous mechanistic studies of anxiety did not assess behavioural responses, such as avoidance (Beckers, Krypotos, Boddez, Effting, & Kindt, 2013; Kirlic, Young, & Aupperle, 2017). Therefore, it remains unclear what drives excessive avoidance behaviour.

Recently, there has been a renewed interest in avoidance research (Arnaudova, Kindt, Fanselow, & Beckers, 2017; Krypotos, Effting, Kindt, & Beckers, 2015; LeDoux et al., 2017). These studies imply an important role for psychobiological processes leading up to the decision to approach or avoid (Bach et al., 2014; Choi & Kim, 2010; Hashemi et al., 2019; Kirlic et al., 2017; Löw, Weymar, & Hamm, 2015; Wendt, Löw, Weymar, Lotze, & Hamm, 2017). However, the majority of studies do not explicitly take into account that real-life approach-avoidance decisions are often made under mixed outcome prospects involving both potential reward and threat (Krypotos, Vervliet, & Engelhard, 2018; Pittig, Treanor, LeBeau, & Craske, 2018). Particularly in patients, avoidance is often not only associated with benefits of avoiding threats (e.g. relieving anxiety), but also with great costs (e.g. inability of maintaining jobs and relationships). Thus, the decision to approach or avoid in the context of pathological anxiety is driven by an interaction between appetitive and defensive motives (McNaughton & Corr, 2004). However, only few studies have tested this interaction under conditions that resemble psychophysiological states of real-life

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https://doi.org/10.1016/j.brat.2020.103788
Received 6 June 2020; Received in revised form 2 December 2020; Accepted 16 December 2020
Available online 21 December 2020

approach-avoidance (Beckers et al., 2013; Brown, Chorpita, & Barlow, 1998; Krypotos et al., 2018).

Due to scarcity of research into costly avoidance with adequate statistical power for addressing individual differences, the link between avoidance and individual differences relevant for anxiety disorders remains unclear (Krypotos et al., 2018; Pittig et al., 2018). Therefore, the aim of the current study was to identify determinants of individual differences in costly avoidance and to assess underlying psychophysiological mechanisms. To simulate costly avoidance as it occurs in pathological anxiety, we recently developed a *Fearful Avoidance Task* (FAT). This task assesses acute avoidance under multiple reward and threat levels while assessing anticipatory psychophysiology indexed by skin conductance and eye-blink startle reflex. A relatively large sample of healthy participants allowed us to investigate subclinical variation without confounds of medication use (N = 343). With this dimensional approach, we first verified that two factors conferring risk for developing anxiety disorders, namely female sex and high trait anxiety, are associated with a relative increase in costly avoidance behaviour (Aupperle, Melrose, Francisco, Paulus, & Stein, 2015; Maner & Schmidt, 2006; Pittig, Pawlikowski, Craske, & Alpers, 2014; Pittig, Schulz, Craske, & Alpers, 2014; Sheynin, Moustafa, Beck, Servatius, & Myers, 2015; Vervliet & Indekeu, 2015). Critically, we next explored which individual patterns of anticipatory psychophysiological responding were most predictive of individual differences in avoidance.

2. Methods

2.1. Participants

Participants partook in the longitudinal 'Police-in-Action' study, consisting of repeated waves of data assessment to evaluate predictors of trauma symptom development in police recruits (see Koch et al., 2017 for the research protocol). The current experiment was conducted in the second wave only, permitting a cross-sectional approach. The sample consisted of 269 police recruits (62 females) and 74 matched (age, sex, educational level) civilians (16 females), leading to a final sample of 343 subjects (78 females; $M_{age} = 25.52$, $SD_{age} = 5.09$, range = 19–45 years). The civilian group was required for analyses in the longitudinal study that are not relevant for the currently reported analyses, with the main goal to control for unspecific time effects, such as test-retest effects. Exclusion criteria include any current psychiatric or neurological disorder, history or current endocrine or neurological treatment, current use of psychotropic medication and current drug or alcohol abuse (see research protocol for a full overview Koch et al., 2017). Police recruits were financially compensated with up to EUR 50, while civilian participants received up to EUR 120 (depending on the number of tests they participated in). The difference in financial compensation is based on the fact that police recruits were allowed to participate during working hours, while civilians participated on their own time. Both groups earned an additional bonus between EUR 0–5 depending on their performance in the Fearful Avoidance Task (described below). All provided written informed consent. This study was carried out in compliance with the declaration of Helsinki and approved by a local medical-ethical committee (Independent Review Board Nijmegen).

2.2. Experimental procedure

First, participants filled out several questionnaires that were part of the overarching longitudinal study (see Koch et al., 2017 for a detailed description of all measures). For the current paper, to prevent multiple comparison issues, we only analysed the questionnaire that we had the strongest a priori expectations on, i.e. the State-Trait Anxiety Inventory (STAI; Spielberger, Gorusch, and Lushene (1970)). Next, to later determine the bonus payout, participants selected 10 random numbers, which were linked to specific trial numbers by a mathematical formula that was unknown to the participant. The participants were instructed that if they received a reward on these payout trials, they would receive this amount as a bonus payout at the end.

Subsequently, participants underwent a standardized shock work-up procedure (described in Klumpers et al., 2010) consisting of five consecutive electric shock administrations to set shock intensity to an individual level that was maximally uncomfortable without being painful (see Supplement 1). Finally, the participants performed the fearful avoidance task.

2.3. Fearful avoidance task (FAT)

Participants received on-screen instructions for the task. Each trial consisted of a cascade of four stages (Fig. 1A). In the *reward-context phase*, a context was presented, indicating the reward level of the trial (low: €0.20, high: €1.00; lasting 3–4s, Fig. 1B). In the successive *threat-cue phase*, an avatar appeared, indicating whether participants could receive a shock in that trial (shock safety: no electric shock, shock threat: electric shock; lasting 3–5s, Fig. 1B). Reward and threat level were combined in a full factorial manner, leading to four trial types in total: low reward/shock safety, low reward/shock threat, high reward/shock safety, high reward/shock threat. Subsequently, the avatar disappeared from the screen and a response window was presented. Participants then had to decide to approach or avoid by pressing the up or down arrow, respectively. Immediately after responding, the outcome of their decision was displayed. Approaching the avatar led to a 50% chance of a negative outcome (displayed by the avatar drawing a gun and shooting) and a 50% chance of receiving a positive outcome (displayed by the avatar offering a stack of bank notes). Getting shot by the shock threat avatar additionally led to receiving an aversive electrical shock, whereas getting shot by the shock safety avatar did not. A timely avoidance response (<1s after response window onset) always led to a neutral outcome, indicating safety from receiving the negative outcome (including the shock in the shock threat condition). At the same time, however, avoidance also led to the omission of the positive outcome because the avatar disappeared from the screen. Late responses (>1s) always led to the negative outcome, i.e. getting shot and - depending on the threat level of the trial - receiving electrical stimulation. Participants received explicit instructions on the association between contexts/avatars and reward/threat levels. These contingencies were all clearly explained to the participants before starting the task and comprehension was verified during a short practice session (see Supplement 1). After receiving the outcome, a fixation cross was presented during the inter-trial interval. Participants completed 40 trials (10 trials for each trial type).

2.4. Physiological recording

Full details of psychophysiological recording and processing are described in Supplement 1. In short, startle probes were 50 ms, ±106DbA white noise bursts presented 2500 ms after *reward-context phase* or *threat-cue phase* onset (see Fig. 1A). In each of the four task conditions there were 10 startle probes: 5 in the *reward-context phase* and 5 in the *threat-cue phase*. After filtering and automatic artefact rejection, magnitudes of the eye-blink startle response were scored using previous guidelines and in-house developed scripts, leading to an average startle response score per condition (Blumenthal et al., 2005; Klumpers et al., 2010).

To account for events in the Fearful Avoidance Task that are overlapping and/or close in time, skin conductance response (SCR) amplitudes to reward and threat cues were derived using dynamic causal modelling in PsPM (version 4.0.2 available at pspm.sourceforge.net, Bach and Friston (2013)). The model included both events with a fixed latency (i.e. events that are assumed to elicit an immediate response) and events with a flexible latency (i.e. events that are assumed to elicit sympathetic arousal within a known response window, but with unknown amplitude, latency, and duration). The events of interest

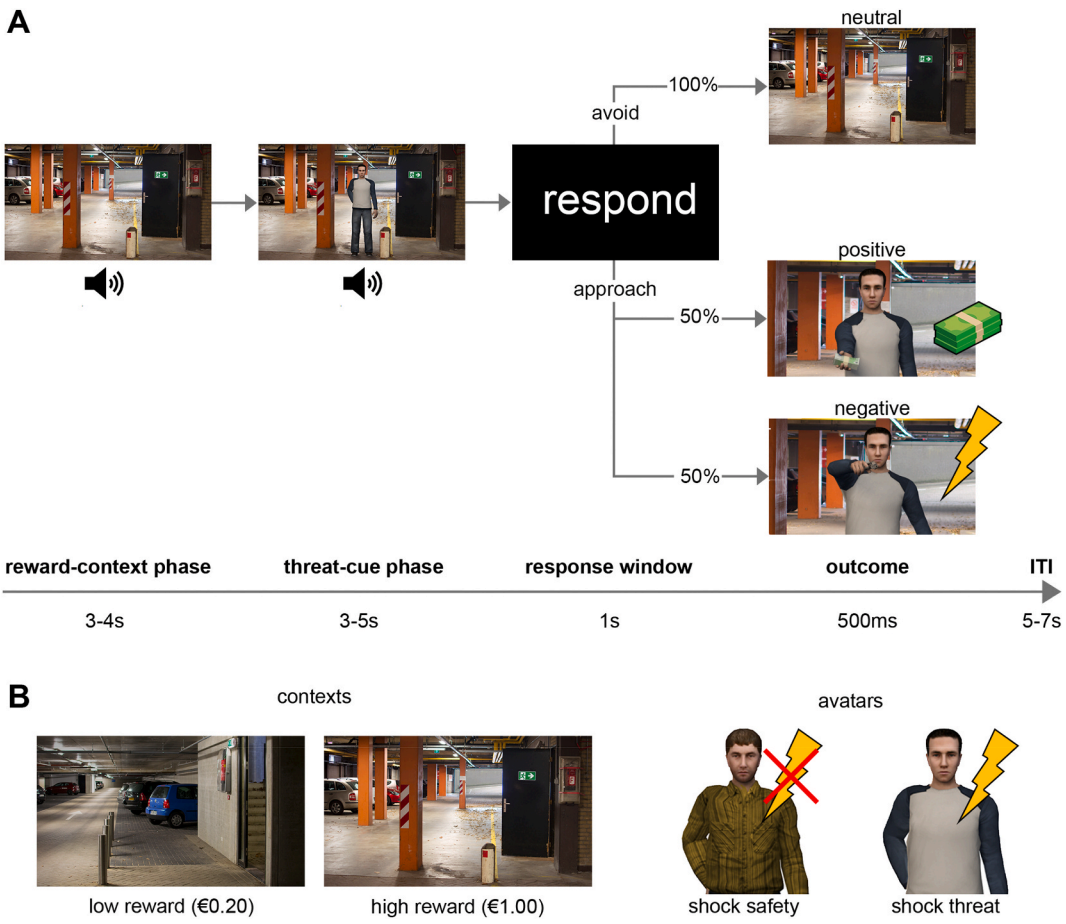

Fig. 1. Fearful avoidance task (FAT). **(A)** Example of the FAT trial structure for a high reward/shock threat trial. In each trial, a context was presented, indicating the reward level (reward-context phase). Next, an avatar appeared, indicating shock threat or shock safety (threat-cue phase). Subsequently, a response window was presented and participants decided to approach or avoid by pressing a button. Immediately after responding, the outcome of their decision was displayed. After receiving the outcome, a fixation cross was presented during the inter-trial interval (ITI). Startle probes were presented 2500 ms after context or cue phase onset. **(B)** Overview of the cues signalling reward and threat. Two background pictures indicated the reward level of the trial (low: €0.20, high €1.00). Two distinct avatars signalled the shock threat level for the trial. Stimulus contingencies were counterbalanced across participants.

concerned the entire *reward-context phase* and the entire *threat-cue phase*. Parameter estimates for all events were extracted for each participant. For both our events of interest (i.e. skin conductance responses during the *reward-context phase* and the *threat-cue phase*) this led to 10 parameter estimates per condition. For each event of interest, these parameter estimates were averaged per condition. See Supplement 1 for a full overview of the modelled events.

2.5. Analyses of task effects on behaviour and physiology

Statistical analyses were carried out in R (Version 3.5.1; R Core team, 2016) in RStudio (Version 1.0.453; RStudio Inc., 2009–2018). To allow accurate modelling of both binary avoidance data and continuous psychophysiological responses within the same analytical framework, we conducted Bayesian mixed-effects models in R using the brms package (Version 2.10.0, Bürkner (2013) and Carpenter et al. (2017)). We investigated the influence of reward, threat, and their interaction on each dependent variable i.e., proportion of avoidant decisions, startle reflex response amplitude, skin conductance response amplitude, using binomial, Gaussian, and skew-normal models, respectively. Model choice for the latter two dependent variables was informed by visual inspection of the data.

During the *reward-context phase*, we only expected an effect of reward. Therefore, the physiological models concerning this phase included reward (low, high) as a fixed effect. Upon threat cue appearance, we expected an effect of both threat and reward. Therefore, behavioural and physiological models concerning the *threat-cue phase* included reward (low, high), threat (shock safety, shock threat), and their interaction as fixed effects. In all models, group (police recruits vs. civilians) and sex (male vs. female) were added as fixed effects. For the basic analyses, group was a factor of no interest, while sex was a factor of interest in the individual differences analyses (see next section). Accordingly, for the basic analyses, we present results related to sex in the supplement. Importantly, all results remained highly similar when we performed control analyses without group or sex in the models.

All continuous predictors were standardized and all categorical predictors were coded using sum-to-zero contrasts. To account for the repeated-measures nature of the data, the models included a random intercept per participant and random slopes for the within-subject effects of reward, threat, and their interaction; all possible bivariate covariances among the random effects were also estimated. We fitted the models using 10 chains with 2000 iterations each (1000 warm-up). In case of non-convergence, iterations were increased with 1000 (with a maximum of 6000 iterations). A coefficient was deemed statistically significant when the associated 95% posterior credible intervals were non-overlapping with zero. As recommended for analyses with an effective sample size <10.000 (Kruschke, 2014), this was supplemented with 90% posterior credible intervals when the 95% credible intervals were overlapping with 0, given that these intervals may produce more stable results (Makowski, Ben-Shachar, & Lüdecke, 2019). The latter

results were reported as trends when the 90% intervals were non-overlapping with zero. Post-hoc tests were conducted using the emmeans package (Lenth, Singmann, Love, Buerkner, & Herve, 2018).

2.6. Analyses of individual differences

To test whether individual differences in avoidance behaviour were related to risk factors of pathological anxiety, sex and trait anxiety score were added as fixed effects to the previously described Bayesian mixed-effects model of avoidance behaviour.

Visual inspection of the proportion avoidant decisions over conditions across individuals suggested a multimodal distribution rather than a normal distribution, suggesting distinct strategic patterns of avoidance. Therefore, K-means cluster analyses were conducted to additionally identify subgroups based on individual differences in the proportion avoidant decisions over conditions.

2.7. Relations between psychophysiology and avoidance

We investigated the relations between psychological responses to reward and threat and avoidance in two ways. First, we explored whether anticipatory physiological responses were associated with subsequent avoidance decisions. Results from an initial model, in which avoidance was predicted from startle reflex amplitude and skin conductance response did not return significant results (reported in Supplement 1). However, mixed-effects models with categorical dependent variables (i.e. binomial models) can have lower statistical power and more often lead to non-convergence than models with continuous dependent variables (Eager & Roy, 2017). Therefore, given the correlational (non-causal) nature of the statistics and to prevent increasing type II errors and thus avoid overlooking potentially relevant effects, we subsequently ran models with physiological responses as the dependent variable and avoidance behaviour as independent variable. For the startle reflex model (N = 267) we used a Gaussian distribution and for the skin conductance model (N = 293) we used a skew-normal distribution. These results are reported below.

Second, we investigated whether membership of a behavioural cluster (explained in section 3.5.3) was associated with a specific pattern of physiology. The previously mentioned basic models (section 2.5) on startle reflex and skin conductance response during the *threat-cue phase*, were repeated with avoidance cluster (*non-avoiders, low-cost threat avoiders, all-cost threat avoiders*) as an additional fixed factor to test for interactions. Each cluster was contrasted with the *non-avoiders* cluster, which served as a logical baseline due to its low avoidance rates.

3. Results

3.1. Task effects - avoidance behaviour

Reward ($B = 0.67$, 95% CI [0.51, 0.85]) and threat ($B = -1.56$, 95% CI [-1.84, −1.28]) had the expected opposing main effects on the proportion avoidant decisions (Fig. 2), with more avoidance in the low reward and the shock threat conditions. This was qualified by a significant interaction between reward and threat ($B = -0.35$, 95% CI [-0.51, −0.20]) which indicated that threat-of-shock effects on avoidance diminished when rewards were high. Post-hoc analyses demonstrated that threat of shock was associated with increased avoidance within each reward level ($B_{\text{low reward}} = -3.81$, 95% CI [-4.41, −3.28], $B_{\text{high reward}} = -2.40$, 95% CI [-3.13, −1.78]). Conversely, increased reward was associated with reduced avoidance independent of shock threat ($B_{\text{shock safety}} = 0.63$, 95% CI [0.12, 1.19], $B_{\text{shock threat}} = 2.04$, 95% CI [1.68, 2.40]). Together, the opposing influence of reward and threat on avoidance suggests that the task successfully induced conflicting approach- and avoidance tendencies.

3.2. Task effects - startle reflex

The anticipatory *reward-context* and *threat-cue phases* allowed us to assess anticipatory psychophysiological responses, prior to decision making. In the *reward-context phase*, when the cue signalling shock threat was not presented yet and the potentially rewarding outcome was still relatively distal, startle reflex amplitude showed no significant main effect of reward ($B = 0.02$, 90% CI [-0.04, 0.08]).

However, in the *threat-cue phase*, when both reward and threat level were presented, the mean startle reflex was increased under threat of shock compared to shock safety ($B = -0.24$, 95% CI [-0.30, −0.17]). There was no significant main effect of reward ($B = 0.01$, 90% CI [-0.04, 0.06]), however a significant interaction between reward and threat was observed ($B = -0.23$, 95% CI [-0.30, −0.17]), partly mimicking the behavioural effects (Fig. 2). In line with previous literature (Bach, 2015; Bradley, Zlatar, & Lang, 2017), the mean startle reflex amplitude was increased by shock threat anticipation in low reward conditions ($B =$

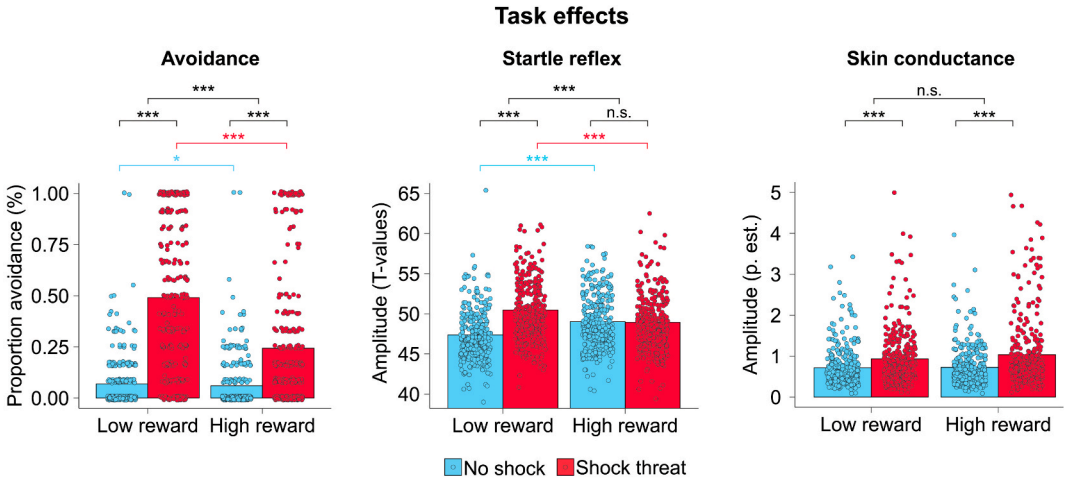

Fig. 2. Overview task effects. Mean behavioural (proportion avoidant decisions) and anticipatory physiological (startle reflex, skin conductance) responses as a function of reward and threat level, overlaid with individual data points to illustrate variance between subjects. For avoidance behaviour, results showed the expected decreasing and increasing influences of reward and threat respectively. All post-hoc contrasts were significant. Startle reflex results showed that the mean amplitude was increased by threat in low reward conditions, whereas it was increased by reward in shock safety conditions. These reward and threat effects were diminished when the other factor (reward/threat) was high. Skin conductance results only showed an effect of threat. * = 95% and *** = 99.9% posterior credible intervals non-overlapping with zero.

−0.94, 95% CI [-1.12, −0.76]), whereas it was increased by reward anticipation when participants were safe from receiving electrical stimulation (B = −0.44, 95% CI [-0.61, −0.27]). These reward and threat effects were attenuated when the opposite factor (reward/threat) was high, leading to an absence of threat effects under high reward (B = −0.02, 90% CI [-0.16, 0.13]) and a reversal of reward effects under threat of shock (B = 0.49, 95% CI [0.32, 0.67]).

3.3. Task effects - skin conductance response

In *the reward-context phase,* similar to the startle reflex, skin conductance response amplitude showed no main effect of reward (B = 0.01, 90% CI [-0.02, 0.03]).

However, in the *threat-cue phase*, when participants decide to approach or avoid, the mean skin conductance response amplitude was increased by shock threat (B = −0.11, 95% CI [-0.16, −0.07], Fig. 2). While skin conductance was increased for high rewards (M = 0.88) compared to low rewards (M = 0.82), the main effect of reward did not reach (trend) significance (B = −0.02, 90% CI [-0.05, 0.00]). In contrast to the behavioural and startle reflex responses, no reward by threat interaction was observed for skin conductance (B = 0.01, 90% CI [-0.02, 0.03]). In conclusion, skin conductance response amplitude increased with anticipation of threat of shock, with no evidence for a reward effect nor additive or opposing influences of both factors.

3.4. Anticipatory threat physiology is associated with subsequent avoidance

There was no relation between overall avoidance and the overall physiological responses ($B_{startle}$ = 0.06, 90% CI [-0.02, 0.15], B_{SCR} = 0.04, 90% CI [-0.02, 0.10]), nor an interaction between avoidance and reward-related changes in physiology ($B_{startle}$ = 0.06, 90% CI [−0.02, 0.14], B_{SCR} = −0.01, 90% CI [-0.01, 0.09]), nor a three-way interaction between avoidance, reward, and threat on physiology ($B_{startle}$ = −0.02, 90% CI [.-10, 0.06], B_{SCR} = −0.02, 90% CI [-0.06, 0.02]). However, for both startle and skin conductance, we found a significant interaction between threat and avoidance ($B_{startle}$ = 0.12, 95% CI [0.02, 0.22], B_{SCR} = 0.11, 95% CI [0.05, 16], see Fig. 3).

Post-hoc analyses consistently showed that for both startle and skin conductance, more avoidance was associated with increased psychophysiological responses in anticipation of shock safety ($B_{startle}$ = 0.18, 90% CI [0.02, 0.34], B_{SCR} = 0.15, 95% CI [0.05, 0.25]). These findings indicate that high psychophysiological responsiveness in conditions where threat is relatively low is predictive of avoidance. In shock threat conditions the pattern was not consistent across measures. If anything, decreased skin conductance response amplitudes were predictive of increased avoidance in the shock threat conditions but this effect was not observed for startle ($B_{startle}$ = −0.06, 90% CI [-0.12, 0.01], B_{SCR} = −0.06, 95% CI [-0.12, −0.01]).

3.5. Individual differences in avoidance behaviour

3.5.1. Trait anxiety

Mean trait anxiety scores were relatively low (M = 31.56, SD = 7.39), yet our large sample showed a wide range of scores (range: 20–61), including those in the high anxiety range (score ≥40, 13.41% of the participants). There was no main effect of trait anxiety on avoidance (B = 0.11, 90% CI [-0.14, 0.36]) nor an interaction between trait anxiety and threat (B = 0.05, 90% CI [-0.13, 0.24]). However, there was a significant interaction between trait anxiety and reward on avoidance (B = 0.11, 95% CI [0.00, 0.22]), which signified a more positive association between trait anxiety and avoidance for low reward (B = 0.22, 90% CI [-0.01, 0.45]) than high reward (B = −0.00, 90% CI [-0.30, 0.29]). Moreover, there was a marginally significant three-way interaction between trait anxiety, reward, and threat (B = −0.08, 90% CI [-0.02, −0.00], see Fig. 4A).

Follow-up analyses for the three-way interaction showed that for shock threat, there was a significant interaction between reward and trait anxiety on avoidance (B = .38, 95% CI [0.08, 0.69]), which was not present for shock safety (B = 0.07, 90% CI [-0.15, 0.27]). The low reward/shock threat condition showed a more positive relationship between avoidance and trait anxiety (B = 0.25, 90% CI [-0.10, 0.58]) than the high reward/shock threat condition (B = −0.14, 90% CI [-0.49, 0.26]). Control analyses did not show a relationship between trait anxiety and shock level after work-up ($r(302)$ = −0.054, p = .348), indicating that the observed trait anxiety effect in avoidance was not confounded by differences in shock level. These findings support the relevance of systematically varying threat and reward conditions, showing that under shock threat conditions, high trait anxiety is associated with increased avoidance decisions, particularly when gains are low.

3.5.2. Sex

There was a marginally significant main effect of sex (B = −0.30,

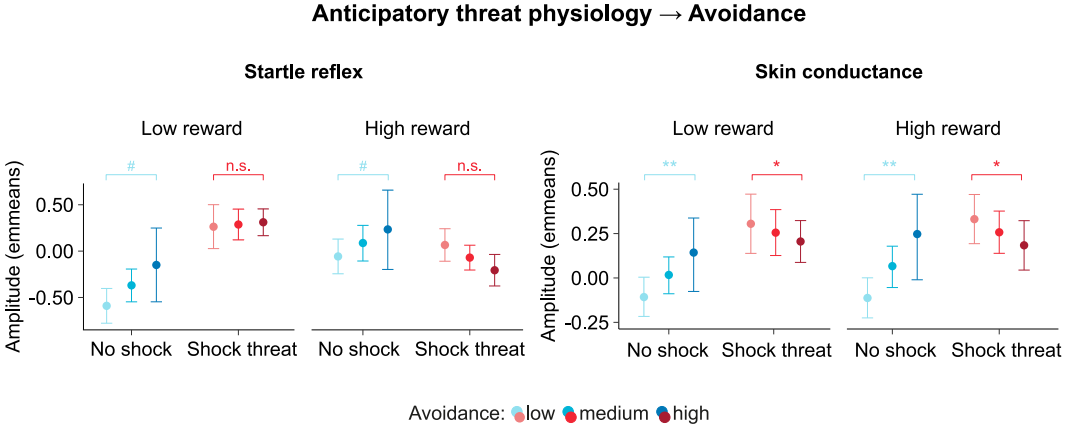

Fig. 3. Marginal effects plots of the relationship between threat physiology and avoidance. For visualization purposes only, avoidance was subdivided in low, medium, and high scores (i.e. one standard deviation below the mean, the mean, one standard deviation above the mean, respectively). The colour coding represents the amount of avoidance. Startle reflex data showed that more avoidance was associated with increased startle amplitudes in the shock safety conditions. Skin conductance response data showed that more avoidance was associated with increased skin conductance amplitudes in the shock safety conditions opposed to decreased amplitudes in the shock threat conditions. In conclusion, threat physiology is predictive of avoidance behaviour. # = 90%, * = 95%, and ** = 99% posterior credible intervals non-overlapping with zero. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

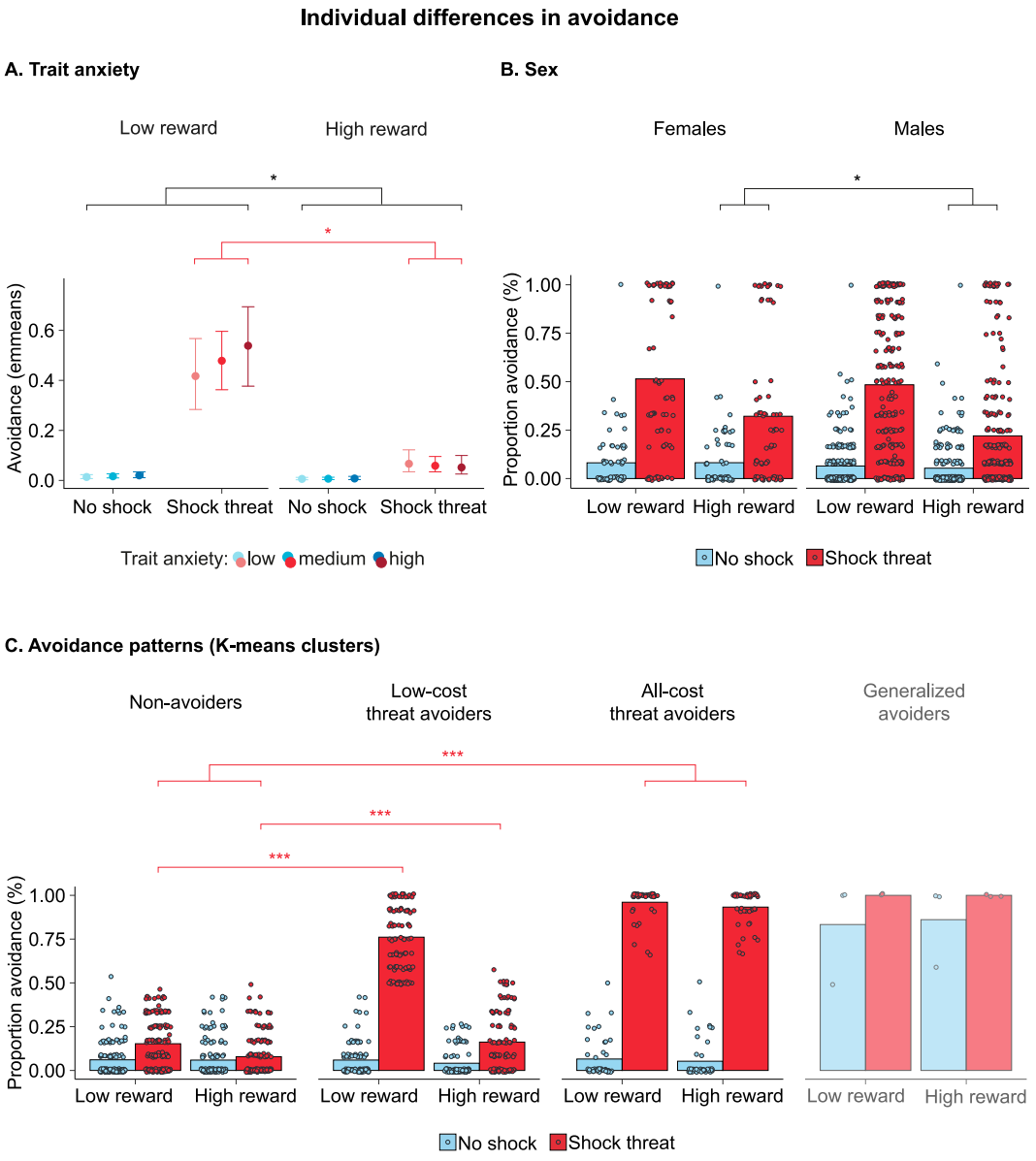

Fig. 4. **(A)** Marginal effects plot for the interaction between reward, threat, and trait anxiety on avoidance. For visualization purposes only, trait anxiety was subdivided by low, medium, and high scores (i.e. one standard deviation below the mean, the mean, one standard deviation above the mean, respectively). The colour coding represents the trait anxiety score. Results showed that high trait anxiety leads to more avoidance under shock threat conditions, but contrary to our hypotheses, only when costs are low. **(B)** Mean proportion avoidant decisions as a function of reward, threat, and sex. Females engaged more often in relatively costly threat avoidance (i.e. avoidance in high reward threat conditions) than males. **(C)** Mean behavioural (proportion avoidant decisions) responses per cluster of participants as identified by the K-means clustering procedure. Results confirmed distinct avoidance patterns in different clusters of participants depending on threat and reward levels (differences with the *generalized avoidance* cluster not tested statistically). The results of post-hoc tests indicating differences between the clusters are marked using significance annotations: * = 95% and *** = 99.9% posterior credible intervals non-overlapping with zero. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

90% CI [-0.58, −0.02]), qualified by a significant interaction between sex and reward ($B = 0.15$, 95% CI [0.02, 0.27]). Neither the interaction between sex and threat ($B = 0.08$, 90% CI [-0.11, 0.31]) nor the interaction between sex, threat, and reward ($B = -0.06$, 90% CI [-0.16, 0.02]) was significant. Post-hoc analyses confirmed our hypotheses (Aupperle et al., 2015; Maner & Schmidt, 2006; Pittig, Pawlikowski, et al., 2014; Pittig & Scherbaum, 2020; Pittig, Schulz, et al., 2014; Sheynin et al., 2015; Vervliet & Indekeu, 2015) that females avoided more frequently than males when high rewards were available ($B = -0.89$, 95% CI [-1.68, −0.10], see Fig. 4B), but not when low rewards were available ($B = -0.30$, 90% CI [-0.84, 0.20]). Control analyses showed that even though females avoided more frequently than males, their shock levels were lower ($F(1,302) = 8.380$, $p = .004$, $\eta^2_p = .027$).

3.5.3. *Avoidance patterns (K-means cluster analysis)*

K-means cluster analyses identified four clusters of participants with distinct patterns of avoidance behaviour across conditions, labelled as *non-avoiders* (49.7%; mainly driven by reward), *low-cost threat avoiders* (34.4%; driven by a combination of reward and threat), *all-cost threat avoiders* (14.9% mainly driven by threat), *generalized avoiders* (1.0%; generalizing avoidance beyond threat), see Fig. 4C. We expected that these avoidance patterns might be linked to distinct physiological response patterns. However, while we demonstrated above that physiological responses were associated with subsequent avoidance in a continuous manner, physiological responses were not significantly different between clusters with diverging behavioural patterns. Thus, there were no main effects of cluster nor interactions between cluster

and reward/threat on psychophysiology (see Supplement 1, section 3.5.3).

4. Discussion

The aim of the current study was to enhance mechanistic insight in inter-individual differences in avoidance, an important maintaining factor of anxiety disorders. The use of a recently developed fearful avoidance task under acute threat revealed four findings with theoretical and potential clinical implications. First, in accordance with risky decision making literature (Figner & Weber, 2011; Loewenstein, Weber, Hsee, & Welch, 2001), avoidance does not only depend on perceived threat but also on perceived reward. Importantly, this is still largely ignored in current exposure treatment models (Zbozinek & Craske, 2017). Second, strong psychophysiological arousal in relatively low-threatening conditions is predictive of costly avoidance. Third, trait anxiety and female sex independently predict avoidance under low and high reward conditions respectively. Fourth, a cluster analysis indicated that individual differences in reward and threat responsiveness can lead to distinct individual approach-avoidance patterns. Together, these findings (I) suggest that theories of avoidance in anxiety should not only take into account threat but also reward responsiveness; (II) provide a first biomarker for the occurrence of costly avoidance behaviour, and (III) suggest that for individualized treatment both dimensions of reward and threat may need to be taken into account when tackling an individual's avoidance propensity.

The observed interactive influence of reward and threat on avoidance is in line with previous work (Aupperle et al., 2011; Bublatzky, Alpers, & Pittig, 2017; Talmi, Dayan, Kiebel, Frith, & Dolan, 2009), confirming a role for potential rewarding outcomes in reducing threat avoidance. Most theoretical models of avoidance do not consider this reward-threat trade-off (Löw et al., 2015; Sege, Bradley, & Lang, 2018; Wendt et al., 2017), while previous empirical studies often used anticipation of negatively-valenced affective pictures or small monetary losses (Aupperle et al., 2015; Schlund et al., 2016; Sheynin et al., 2015), which have been shown to produce less arousal and lack of amygdala engagement respectively compared to electrical shocks (Delgado, Jou, & Phelps, 2011). We extend previous findings by assessing the role of reward under acute and more arousing levels of threat (Delgado et al., 2011), resembling conditions in which patients with anxiety usually take approach-avoidance decisions more closely (Brown et al., 1998).

Contributing to the face validity of our task and demonstrating the importance of assessing reward-threat interactions, avoidance tendencies were associated with well-known individual difference factors associated with real-life avoidance, namely the female sex and subjective trait anxiety, which depended on reward and threat levels (Aupperle et al., 2015; Maner & Schmidt, 2006; Pittig, Pawlikowski, et al., 2014; Pittig & Scherbaum, 2020; Pittig, Schulz, et al., 2014; Sheynin et al., 2015; Vervliet & Indekeu, 2015). While these findings need replication in an independent sample and most importantly in patients, these dimensional findings suggest that current biological theories about fear responding in anxiety disorders may need to be complemented with insight on how biological mechanisms of reward-threat trade-offs influence avoidant decision making.

Overall, physiological patterns evoked by the FAT where consistent with previous research as they demonstrated increases in startle and skin conductance with reward and threat (Bach, 2015; Bradley et al., 2017; Klumpers et al., 2010; Klumpers, Heitland, Oosting, Kenemans, & Baas, 2012; Löw et al., 2015; Wendt et al., 2017), though, in line with previous research, skin conductance did not show significant reward effects (Pittig & Dehler, 2019). Interestingly, both startle and skin conductance did emerge as significant correlates of avoidance. More subsequent avoidance was associated with stronger anticipatory physiological responses, independent of reward level and only in absence of threat of shock. This suggests that strong physiological responses might be particularly predictive of avoidance under more ambiguous threat, a situation where individual differences in anxiety have previously been shown to emerge in passive fear tasks (Duits et al., 2015; Lissek, Pine, & Grillon, 2006; Stegmann et al., 2019). Patients tend to generalize anxiety to low threatening situations (Duits et al., 2015; Lissek et al., 2005). Whether this link is related to overlapping neural circuitry associated with both fear generalization and avoidance requires additional neuroimaging research.

Subsequently, we explored whether different combinations of reward and threat sensitivity would lead to distinct avoidance patterns. Indeed, we discovered four discrete clusters of participants with varying reward and threat sensitivity. This observation provides further support for theoretical models of avoidance that besides threat also include appetitive processing. Interestingly, unlike the continuous relation between psychophysiology and avoidance, these categorical avoidance clusters were not significantly tied to differences in anticipatory physiological responses. The fact that behavioural avoidance and anticipatory psychophysiological responses here do not correlate provides support for the well-known observation that avoidance may not always be driven by (neuro)physiological and subjective fear responses (Arnaudova et al., 2017; Aupperle et al., 2015; Beckers et al., 2013; Bublatzky et al., 2017; LeDoux et al., 2017; Pittig & Dehler, 2019). This leaves open the question what biological mechanisms are driving these individual differences that we observed. Future investigations should also test what patterns are observed in patients with clinical anxiety and depression.

To conclude, our findings show the relevance of assessing avoidance on the basis of reward-threat conflict. Besides theoretical implications such as the introduction of reward or cost anticipation as a factor influencing maladaptive avoidance behaviour, these findings could have potential clinical implications. The current findings need to be replicated in healthy controls and extended in patients, who likely show more extreme avoidance levels, to support the idea that individualized treatment might be warranted for avoidance dependent on the mechanistic origins of the behaviour. Concretely, one could foresee that the traditional approaches involving exposure based psychotherapy to reduce threat expectancy could be supplemented for some individuals by strategies that make rewards more salient, e.g. through the use of counter conditioning (Keller, Hennings, & Dunsmoor, 2020).

5. Acknowledgements and disclosures

This study was funded by the Netherlands Organization for Scientific Research (Research Talent Grant No. 406-18-540 [to AMH], VICI Grant No. 453-12-0010 [to KR]) and a consolidator grant from the European Research Council (Grant No. ERC_CoG-2017_772337 [to KR]). We gratefully acknowledge excellent contributions from Vanessa van Ast, Annika Smit, Ingrid Kersten, Tiele Döpp, Naomi de Valk, Leonore Bovy, and Lisanne Nuijen in setting up the study, participant recruitment and data acquisition. All authors report no biomedical financial interests or potential conflicts of interest. Netherlands Trial Registry: Police-in-Action: The Role of Automatic Defensive Responses in the Development of Posttraumatic Stress Symptoms; https://www.trialregister.nl/trial/5989; NTR6355.

6. Data availability

Data are available from the Donders Institute for Brain, Cognition and Behaviour repository at: https://doi.org/10.34973/y8rn-nw02.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2020.103788.

Author Contributions

Study concept and experimental design was done by: A.M.H., K.R.,

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Data acquisition was done by: R.K., M.M.H., W.Z., and S.B.J.K. Analysis was performed by A.M.H. and F.K. after consultation with B.F. The manuscript was drafted by A.M.H., K.R., and F.K.

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