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The relevance of accounting for parasympathetic as well as sympathetic arousal in threat conditioning: Methodological and clinical considerations

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ABSTRACT

Alterations in associative threat learning have been thought to underlie the aetiology and maintenance of anxiety disorders. Recent insights into the facilitatory role of parasympathetic arousal for threat coping have raised the question whether individual differences in sympathetic versus parasympathetic dominance during threat learning may shed light on the complex relationship with anxiety vulnerability versus resilience. We applied an established differential-cue delay threat conditioning paradigm in 78 neurotypical individuals and assessed parasympathetic responses (threat-induced bradycardia), as well as sympathetic responses (threat-induced tachycardia and increased skin conductance responses-SCR). We found evidence that patterns of threat-induced bradycardia as well as tachycardia are present during associative learning. Threat bradycardia was linked to weaker initial conditioned SCRs (mainly driven by responses to the CS+), a finding that may be relevant for current common practice in the field of threat learning: namely participants with weak differential skin conductance responses - who according to frequently applied 'SCR non-learner' criteria are often considered non-learners and sometimes even excluded from analyses - were in fact showing successful learning in terms of parasympathetic arousal. Additionally, the *presence* of threat bradycardia as well as the *magnitude* of overall conditioned heart rate responses were linked to relatively lower trait anxiety. These findings not only have practical research implications but also clinical implications when assessing markers for anxiety vulnerability versus resilience.

1. Introduction

Deviations in associative threat learning are thought to underlie the development and maintenance of anxiety-related psychopathology (Duits et al., 2015; Marin et al., 2017; Mineka and Oehlberg, 2008). Indeed, individual differences in associative learning, assessed by increased sympathetic arousal to conditioned threat, have been linked to trait anxiety (Sjouwerman et al., 2020), a trait that has been linked to vulnerability for anxiety disorders (Nordahl et al., 2019; Weger and Sandi, 2018). However, these associations between altered conditioned responses and trait anxiety do not always replicate (Haaker et al., 2015) and have been largely based on one sympathetic arousal measure, namely skin conductance response (SCR). While heart rate (HR) can capture both sympathetic as well as parasympathetic arousal (Coote, 2013), it is much less frequently used as an outcome measure in threat conditioning studies, and SCR has become the most widely used outcome measure (see Lonsdorf et al., 2017).

Previous studies have indicated that the conditioned response to threat at the group level can be reflected in HR acceleration (or tachycardia; e.g., Forsyth et al., 2000), as well as in HR deceleration (or bradycardia; e.g., Bradley et al., 2005; Castegnetti et al., 2016). Those differences could of course be related to differences in task context between studies, but they have also been reported *within* studies, where some individuals show threat bradycardia and some show threat tachycardia (e.g., Hodes et al., 1985; Moratti and Keil, 2005). For instance, threat tachycardia and failure to reach parasympathetic dominance (and bradycardia) have been observed in anxiety disorders (e.g., Adenauer et al., 2010). However, these individual differences in cardiac responses have not been investigated in relation to threat learning. In general, the literature on individual differences in autonomic nervous system (ANS) responses during threat learning lacks integration with the extensive literature on the relation between anxiety

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and associative threat learning. This constitutes a missed opportunity to investigate the conditions under which successful threat learning may be a protective factor, or is instead signalling vulnerability. Namely threat bradycardia may indicate more than just the absence of a strong sympathetic response, it may reflect parasympathetic learning (for a review, see Battaglia et al., 2024), a cardiac defensive state which has been associated with optimized coping behaviour (Bradley, 2009; Lang and Davis, 2006; Roelofs and Dayan, 2022). Here, we assess whether threat responses can indeed be manifested in a pattern of sympathetic as well as parasympathetic arousal, and whether these individual differences are meaningfully related to trait anxiety. Such finding could advance insights into the role of threat learning in anxiety vulnerability and resilience.

Acute threat activates both the parasympathetic and sympathetic branch of the autonomic nervous system (e.g., Carrive, 2006; Nijsen et al., 1998). The relative balance of activity in the ANS (i.e., which branch of the ANS predominates, see Berntson et al., 1994) is associated with distinct response patterns, including defensive freezing and fight-flight reactions, respectively (Roelofs, 2017; Trott et al., 2022). Freezing is a parasympathetically dominant state accompanied by motor inhibition and threat bradycardia (Niermann et al., 2015; Noordewier et al., 2020; Roelofs et al., 2010; Schipper et al., 2019), while fight-or-flight reactions reflect a sympathetically dominant state accompanied by threat tachycardia (Hagenaars et al., 2014; Iwata and LeDoux, 1988; Waxenbaum et al., 2021). Which branch is more dominant within an individual can depend on situational factors, such as threat proximity (Mobbs, 2018; Mobbs et al., 2020), escape possibilities (Qi et al., 2018), or whether a later action is required (Gladwin et al., 2016; Roelofs and Dayan, 2022).

However, an observation less frequently highlighted in the threat conditioning literature, is that in addition to situational factors, there are also inter-individual differences in which of the two ANS branches is more dominant in response to acute threat. Namely, some individuals exhibit relative threat bradycardia in response to threat, while others show threat tachycardia to the same threat context (Cohen and Randall, 1984; de Echegaray and Moratti, 2021; Hodes et al., 1985; Moratti and Keil, 2005; Sevenster et al., 2015). For instance, Hodes et al. (1985) classified tachycardic as well as bradycardic responders based on the HR waveform during threat conditioning and showed the latter group to display stronger extinction in terms of SCR. de Echegaray and Moratti (2021) showed similar differential HR patterns in a passive viewing task, with bradycardia linked to stronger visual attention processing.

While it is not yet clear what underlies these different response patterns, these findings are in line with other studies, linking defensive freezing and threat bradycardia to enhanced perception and decision-making under threat (Bradley, 2009; de Voogd et al., 2022; Klaassen et al., 2024; Lang and Davis, 2006). Moreover, parasympathetically dominant (threat) responses, such as freezing, threat bradycardia, or higher HR variability have also been linked to resilience and reduced manifestation of vulnerability factors underlying anxiety-related psychopathology (Minassian et al., 2015). For instance, shorter freezing duration or no freezing at all in response to an acute threat during early childhood is predictive of later internalizing symptom development (Held et al., 2022; Niermann et al., 2017). Also, ANS responses are often altered in individuals with (or at risk for) anxiety-related psychopathology (Vinkers et al., 2021), who oftentimes exhibit dysregulated sympathetic responding (Blechert et al., 2007). For instance, PTSD patients tend to show threat tachycardia to threatening stimuli compared to controls who typically show threat bradycardia (Adenauer et al., 2010; Fragkaki et al., 2017). Finally, pre-deployment parasympathetic dominance in resting HR variability has been linked to increased stress-resilience in marines (Minassian et al., 2015), while higher resting HR after traumatic injury predicted subsequent PTSD development in children (Bryant et al., 2007).

Together these findings suggest that parasympathetically dominant threat-responding constitutes an important factor to consider when studying (between-subjects) individual differences in anxiety vulnerability and resilience. Here we explore the possibility that inter-individual differences in the magnitude of threat bradycardia vs. tachycardia in threat conditioning reflect differences in associative learning processes that in turn may be related to differential vulnerability underlying anxiety-related psychopathology.

Investigating these relations is not only relevant to advance our understanding of threat learning, but could also impact methodological considerations in threat conditioning paradigms, where exclusion criteria are often hinged on sympathetic measures (i.e., skin conductance, see Bach et al., 2023; Lonsdorf et al., 2017). Previous work has indicated that exclusion practices based on non-learning could greatly affect the conclusions drawn from such studies (Lonsdorf et al., 2019). Here we explore an additional issue, namely the possibility that those non-learners based on SCRs may in fact show learned responses on HR in terms of threat bradycardia, a pattern that may be relevant for optimal coping and reduced anxiety (Roelofs and Dayan, 2022). Therefore, measurement choices may not be arbitrary but may reflect qualitative different processes. We hypothesize that learning may not only be expressed in sympathetically (SCR) but also in parasympathetically sensitive measures (threat bradycardia). Furthermore, based on the role of threat bradycardia in threat coping, we speculate that the presence of threat bradycardia may be linked to reduced anxiety.

To test our hypotheses, we used an established differential delay threat conditioning paradigm (Jaswetz et al., 2022), during which both HR and SCR were measured. Our first aim was to verify that associative threat reactions can be manifested in both threat bradycardia as well as tachycardia. Second, we additionally assessed whether those HR response patterns were also correlated to sympathetically driven SCR, and to various classes of SCR-based "non-learners". Thirdly, we tested the possibility that the magnitude of both threat-induced bradycardia as well as tachycardia may be related to trait anxiety, a marker that has been linked to vulnerability to develop anxiety-related psychopathology.

2. Method

2.1. Preregistration

This study was preregistered on the open science framework (Link: https://osf.io/48eqs). As this study was part of a previous project on threat memory reconsolidation (Jaswetz et al., 2022), the preregistration was written after visual inspection of the data, but before conducting any statistical analyses of the data relevant to this study.

2.2. Participants

We recruited healthy individuals through the online recruitment system of the Radboud University. Inclusion criteria were: above the age of 18, with normal or corrected to normal vision, no acute mental disorder, no skin disease that would prohibit the use of electrodes, and no history of brain trauma or brain surgery. In total, 78 individuals (49 females, 29 males, 18–60 years [$M = 24.73$, $SD = 7.05$]) completed the entire study. There was one individual who terminated the experiment early. All participants provided informed consent and received €16 as a compensation for their participation.

2.3. Procedure

Participants were tested in a differential-cue delay threat conditioning paradigm (Jaswetz et al., 2022). Participants came to the lab and filled in an informed consent for the entire study, as well as a screening list, and two questionnaires (see below). Next, participants were instructed to wash their hands to clean off any soap or disinfectant and, in case their hands were cold, to warm up their hands. Next, participants completed a standardised shock workup procedure to calibrate the

intensity of the electric shock (see below). Afterwards, participants were subjected to the acquisition phase of threat conditioning paradigm. Finally, participants filled in a five-point rating scale concerning their shock expectancy and subjective feelings regarding the likeability of each stimulus. The data presented here was collected as part of a project on memory reconsolidation and included two more testing sessions (Jaswetz et al., 2022) not included here.

2.4. Material

2.4.1. Conditioned stimuli

The conditioned stimuli (CS) consisted of three rectangles in the colours blue, green, and yellow. Two of these stimuli were paired with an electrical shock (CS+). We used two CS+ because the data reported here are part of a larger project on memory reconsolidation with a within-subjects design, which necessitates the use of two CS+ (see Jaswetz et al., 2022). Additionally, one stimulus was never paired with a shock (CS−). Assignment of colours to the different CS types was counterbalanced across participants. For this study, we averaged responses across the two CS+ trials (see Supplementary Results).

2.4.2. Differential delay threat conditioning paradigm

Participants were instructed to discover the relationship between the CSs and the UCS (electrical shock). The acquisition phase consisted of 48 trials in total (32 CS+ trials, 16 CS− trials). The stimuli were presented in a pseudo randomised order, with no more than three stimuli of the same type being presented in succession. Each CS (4 s duration) was followed by an inter-trial interval (ITI) during which a fixation cross was shown (jittered 6–10 s, $M = 8$ s duration). For the CS+ trials, the shock (200 ms duration) was delivered at 3.8 s after stimulus onset. Reinforcement rate was set at 37.5 % for each CS+, meaning that 12 out of 32 CS+ presentations were paired with a shock. This was done to prevent the participants to habituate to the shock and to preserve a level of uncertainty with each CS+ presentation. The first presentation of each CS+ was always paired with a shock to facilitate immediate and equal learning for both CS+ types. The remainder of the shocks were pseudo randomly distributed across the first and second half of the acquisition phase. This was done to ensure that the shocks were spread evenly across the whole acquisition phase.

2.4.3. Unconditioned stimulus

The unconditioned stimulus (UCS) was an electrical shock that was delivered via two Ag/AgCl electrodes attached to the distal phalanges of the second and third finger of the left hand. The shock was delivered via a MAXTENSE 2000 (Bio-Protech) electrical stimulation machine, with a frequency of 140 Hz and a duration of 200 ms. The shock intensity was set during a standardised shock workup procedure (Jaswetz et al., 2022) and remained the same throughout the whole experiment. In this procedure all participants received five shocks. After each shock, participants subjectively rated the experienced unpleasantness on a scale ranging from 1 (not painful at all) to 5 (very painful), based on which the subsequent shock was adjusted, in order to arrive at a shock intensity that was unpleasant, but not painful (for the shock workup table, see Supplementary Table 1). The intensity varied in 10 intensity steps between 0 and 40 V/0–80 mA. The average intensity step was M = 4.48 (SD = 1.87).

2.4.4. Physiological measures

Electrodermal activity (EDA) and HR were measured throughout the experiment (5000 Hz, no online filters) using a BrainVision EXG MR 16 channel amplifier, an EXG aux device, and BrainVision Recorder software. EDA was measured via two Ag/AgCl electrodes attached to distal phalanges of the first and second finger of the right hand. The raw EDA signal was low-pass filtered (2 Hz) and smoothed using a moving average filter (window of 0.25 s/50 samples). HR was measured via a pulse sensor attached to the third finger of the right hand. Additionally, a woolen gauntlet was pulled over the participant's right hand to keep the hand warm during the experiment.

2.4.5. Questionnaires

Trait anxiety was measured with the trait scale of the State Trait Anxiety Inventory (STAI-T; Spielberger, 1983) and childhood adversity with the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1998). Since the CTQ scores were right-skewed and leptokurtic (skewness = 1.48, kurtosis = 5.06) we were unable to use CTQ scores as an inter-individual difference measure (see Blanca et al., 2013). The STAI-T scores were not skewed and only slightly platykurtic (skewness = 0.38, kurtosis = −0.31). In our sample, the STAI-T showed a Cronbach's alpha of $\alpha = 0.89$, indicating good reliability (Tavakol and Dennick, 2011). The STAI-T sum scores were computed by first inversing all item scores of mirrored items and then adding all item scores.

2.5. Pre-processing

The raw physiological data were first pre-processed using inhouse software (brainampconverter: https://github.com/can-lab/brainampconverter). The downsampled (100 Hz) HR data were then scored using inhouse software (hera: https://github.com/can-lab/hera) for peak detection (with additional manual supervision). The resulting inter-beat interval (IBI) time course data was then exported to R (R Core Team, 2020) and transformed into beats per minute (BPM). For each trial, a baseline window (1 s before trial onset up to trial onset; de Voogd et al., 2022) was taken and subtracted from the trial window (1–3.8 s after trial onset), resulting in a baseline corrected average BPM per trial.

After down sampling (200 Hz), skin conductance responses (SCR) data were scored with additional manual supervision using Autonomate (Green et al., 2014) implemented in Matlab (*MATLAB*, 2018). Here, the amplitude of a rise in SCR was scored. The rise had to start between 0.5 s after stimulus onset and 0.5 s after stimulus offset, with a minimum rise time of 0.5 s and a maximum rise time of 5 s after response onset. The SCRs from the acquisition phase were normalised to the average shock SCRs during the acquisition phase and square root transformed. All reinforced trials were excluded from the analyses involving SCR but were included in analyses involving HR as the shock was delivered outside the analysis window.

Grouping participants into threat-induced bradycardia and tachycardia groups was done based on the average deceleration and acceleration response per participant. These were determined by subtracting the average BPM to the CS+ minus the average BPM to the CS−, where a negative value indicates threat bradycardia, and a positive value indicates threat tachycardia.

2.6. Data-analyses

The data were analysed with Bayesian Mixed Effects Models in R (R Core Team, 2020) using the *brms* package (Bürkner, 2018). For all parameter estimates we used weakly regularising default priors. These include improper flat priors for the group-level effects, LKJ-correlation priors for the random correlations, and weakly informative Student t-priors for the random intercepts and slopes. Since Bayesian analyses do not yield *p*-values but instead work with 95 % confidence intervals (CI), effects were considered “significant” in the traditional sense when the 95 % confidence interval of the posterior distribution did not include zero. In addition to the confidence interval, we also report the estimate. The estimate is the mean of the posterior distribution, which is the probability distribution of the parameters conditional on the data. We opted not to use Bayes Factors as the test statistic since we did not have informative priors. We tried to use a maximal model approach for our random effects structure (Barr, 2013), however, we sometimes had to forego random slopes due to convergence issues.

To assess successful conditioned HR responses, we first ran a model with baseline corrected BPM as the dependent variable and included CS

type (CS+, CS−) and trial number (1–16) as fixed effects, with a random slope for both fixed effects over a random intercept for participant ID. To investigate the association between HR and our other variables of interest, we split up the group based on whether participants expressed a threat-induced bradycardia versus tachycardia response pattern (similar to de Echegaray and Moratti, 2021). Additionally, we also analysed whether these groups differed in terms of uncorrected HR as well as the average HR across the whole experiment (i.e., autonomic tone, see Supplementary Fig. 1).

Next, to assess the relation between parasympathetically and sympathetically dominant response patterns, we investigated the relationship between HR and SCR. We ran a model with SCR as the dependent variable and CS type (CS+, CS−) and in addition HR groups (threat bradycardia and threat tachycardia group) as fixed effects and with a random slope for CS type over a random intercept for participant ID. We then followed this up by including trial number as a fixed effect in that model (not preregistered) to assess time effects as well. We ran follow-up models, in case of significant main or interaction effects. We deviated from the preregistration in which we mentioned HR as the dependent variable. In order to test our hypotheses, it is more intuitive to test whether HR groups differ in SCR, with SCR as dependent variable.

The aim of our next analysis was to assess the relation between HR response patterns and Trait Anxiety. Therefore, we ran a model with HR as the dependent variable and CS type (CS+, CS−) and trait anxiety as an additional fixed effect, with a random slope for CS type over a random intercept for participant ID. Because there is also the possibility that the magnitude of both threat bradycardia and threat tachycardia (regardless of the direction of HR change) is linked to trait anxiety, we ran an additional model (as preregistered) with the absolute difference score between the CS+ and CS− on HR as the dependent variable and trait anxiety as the fixed effect, with a random intercept for participant ID.

Finally, the results from the 2nd model gave rise to a further (not preregistered) analysis of whether classifications of SCR non-learners also followed non-learning in HR. To better understand the consequences of the results of the first step we first computed SCR difference scores between the CS+ and CS−. In order to assess the impact of different SCR learning criteria, we followed an approach similar to Lonsdorf et al. (2019). To that end, we employed three increasingly strict learning criteria similar to Lonsdorf et al. (2019) that would exclude a similar percentage of participants as "non-learners" (see Lonsdorf et al., 2019, Fig. 3 – Fig. Supplement 1 Panel B). Following this approach yielded three cut-offs that would exclude 25 %, 37 %, and 50 % of the participants. To clarify, individuals included in the lenient cut-offs were also included in the stricter cut-offs, therefore these analyses were not independent. We then analysed whether there was significant differentiation on HR responses within the SCR non-learner groups by running a simple brms model per cut-off score with HR as the outcome variable and CS type (CS+, CS−) as the fixed effect, with a random slope for CS Type over a random intercept for Participant ID.

Lastly, we also assessed whether the absolute magnitude, rather than the direction (i.e., threat related threat bradycardia/tachycardia) of the HR threat response was associated with individual differences in sympathetic arousal. To that end, we ran models with the absolute difference between the CS+ and CS− in BPM per participant as the dependent variable and SCR as the fixed effect. We preregistered additional exploratory analyses but opted not to report them here.

3. Results

3.1. Conditioned HR responses can be expressed in threat-induced bradycardia as well as tachycardia

First, we tested whether overall differential threat learning was expressed in HR responses. In line with previous work (Battaglia et al., 2024; Castegnetti et al., 2016; Klorman and Ryan, 1980), our results showed that the CS+ elicited overall significantly lower HR than the CS− (CS Type: estimate = −0.84, 95 % CI [−1.38; −0.31]). Furthermore, our results showed that the overall HR significantly rose across trials (Trial Number: estimate = 0.11, 95 % CI [0.04; 0.19]), but that the change in HR across trials did not differ between CS+ and CS− across the whole group (CS Type * Trial Number: estimate = −0.02, 95 % CI [−0.11; 0.06]). In line with expectations, we observed both patterns of threat-induced bradycardia (n = 49) and tachycardia (n = 29), when numerically dividing participants based on their BPM difference score between the CS+ and CS- (i.e., de Echegaray and Moratti, 2021– see Fig. 1). There was no difference in shock intensity (Group: $F = 1.27$, $p = 0.263$) between the bradycardia group ($M = 4.27$, $SD = 1.47$) and the tachycardia group ($M = 4.76$, $SD = 2.40$), rendering it unlikely that the heart rate response patterns differences were driven by shock intensity levels. Gender distribution did not differ across both groups ($X = 0.02$, $df = 1$, $p = 0.891$), making it likewise unlikely that differences in HR response types were driven by gender differences.

3.2. Threat-induced tachycardia is associated with heightened sympathetic arousal

Next, we tested whether sympathetically dominant response patterns of HR in the threat tachycardia group are related to the sympathetic index SCR. Across the entire time course, there was no significant difference in average conditioned response (CS+ vs CS−) between the threat bradycardia and tachycardia group (CS Type * Group: estimate = 0.03, 95 % CI [−3.02; 3.11]). However, the change in conditioned response (CS+ vs CS−) across time was significantly different between the groups (CS Type * Group * Trial Number: estimate = −0.0134, 95 % CI [−0.0187; −0.00236]). Follow-up analyses indicated that the differences in the change in SCRs across time between HR groups (threat bradycardia and tachycardia) was significantly different for the CS+ (Group * Trial Number: estimate = 0.00252, 95 % CI [0.00258; 0.00856]), but not for the CS− (Group * Trial Number: estimate = −0.00, 95 % CI [−0.00; 0.00]). The difference in conditioned SCRs between the groups was more pronounced during the first compared to the second half of the trials (CS Type * Group * Half: estimate = −0.0211, 95 % CI [−0.0322; −0.00626]) indicating the groups to mainly differ in SCRs during early learning (See Fig. 2a for a representation of the whole time course, and 2b/2c for a comparison between the first and second half of the trials).

We also assessed whether the absolute difference in HR between the CS+ and CS− (i.e., the magnitude of the threat response, regardless of direction) was related to SCR. Here, we analysed the absolute BPM difference between the CS+ and CS− across SCR. The results showed that there was no significant relation between the absolute HR difference and SCR (estimate = −1.72, 95 % CI [−4.36; 0.92]).

Thus, there was a difference between the threat bradycardia and tachycardia groups in the specific pattern of conditioned SCRs (characterized by a steeper slope over trials) that was mainly driven by the CS+ in the first half of the trials in the threat tachycardia group. Together, these results indicate that individual differences in threat bradycardia and tachycardia response patterns are also characterized by specific differences in SCR patterns, a main measure of sympathetic arousal.

3.3. SCR non-learners show learning in terms of parasympathetic arousal

Fig. 2 shows the variation in SCR responses, with most individuals showing a conditioned response but also many showing an absence of stronger SCR for CS+ versus CS−. In the next analysis, we assessed whether those individuals who fail to show a differential SCR response (CS+ > CS−) may nevertheless show a differential HR response (i.e., on an index that is sensitive to parasympathetic arousal). We used three increasingly liberal (with respect to including only learners in the sample) cut-off values to assess differentiation between the CS+ and CS− on HR responses within the excluded group ("SCR non-learners").

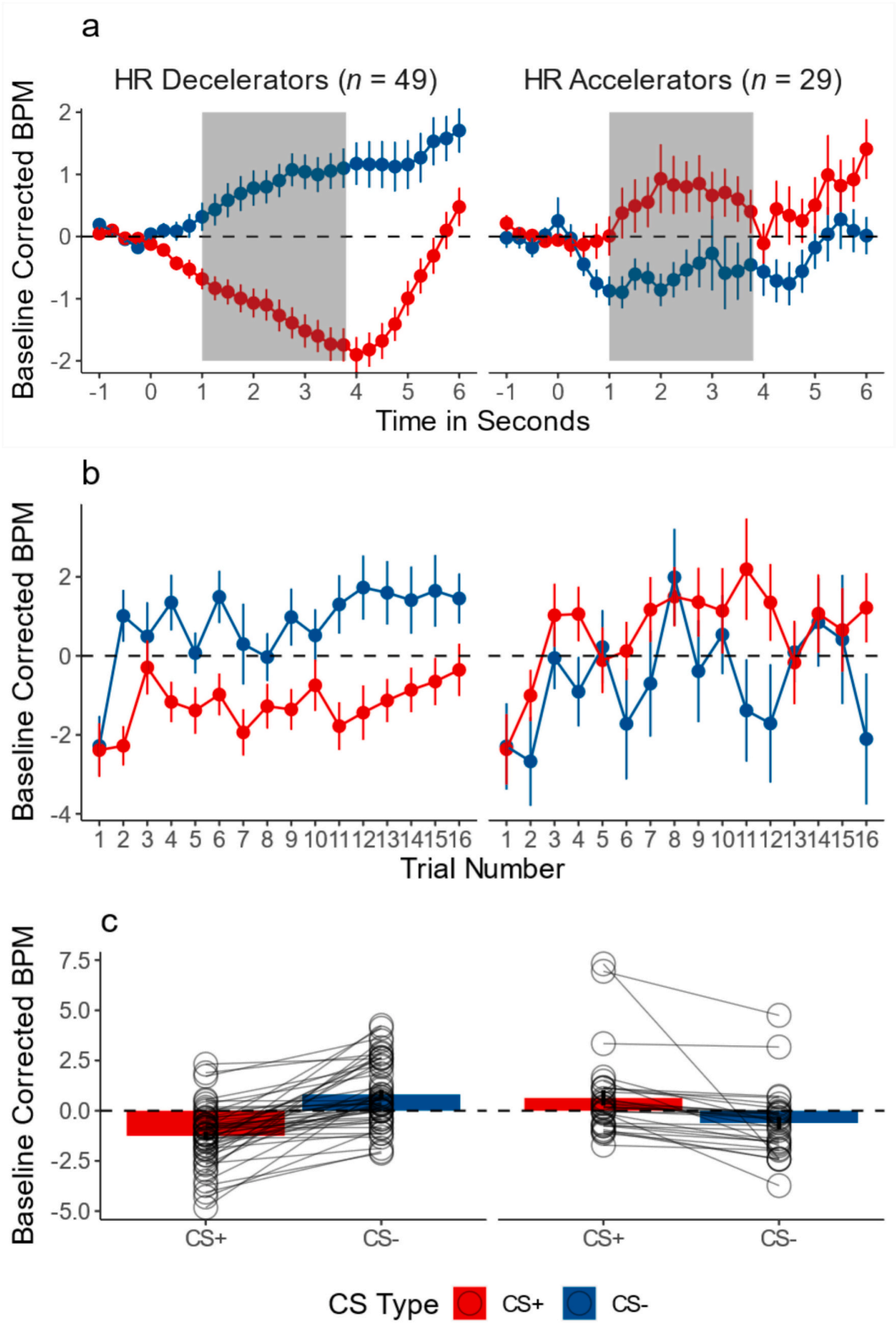

Fig. 1. HR responses in threat-conditioned bradycardia and tachycardia response groups. a) Average time course of the HR across a trial, split by CS type and threat-induced bradycardia and tachycardia groups. The shaded area shows the analysis window used to determine the HR response. b) HR across all trials, split by CS type and threat-induced bradycardia and tachycardia groups. Note that the first trial per CS is not shown here, as no learning has taken place yet. c) Paired observations of the average HR response split by CS type and HR groups.

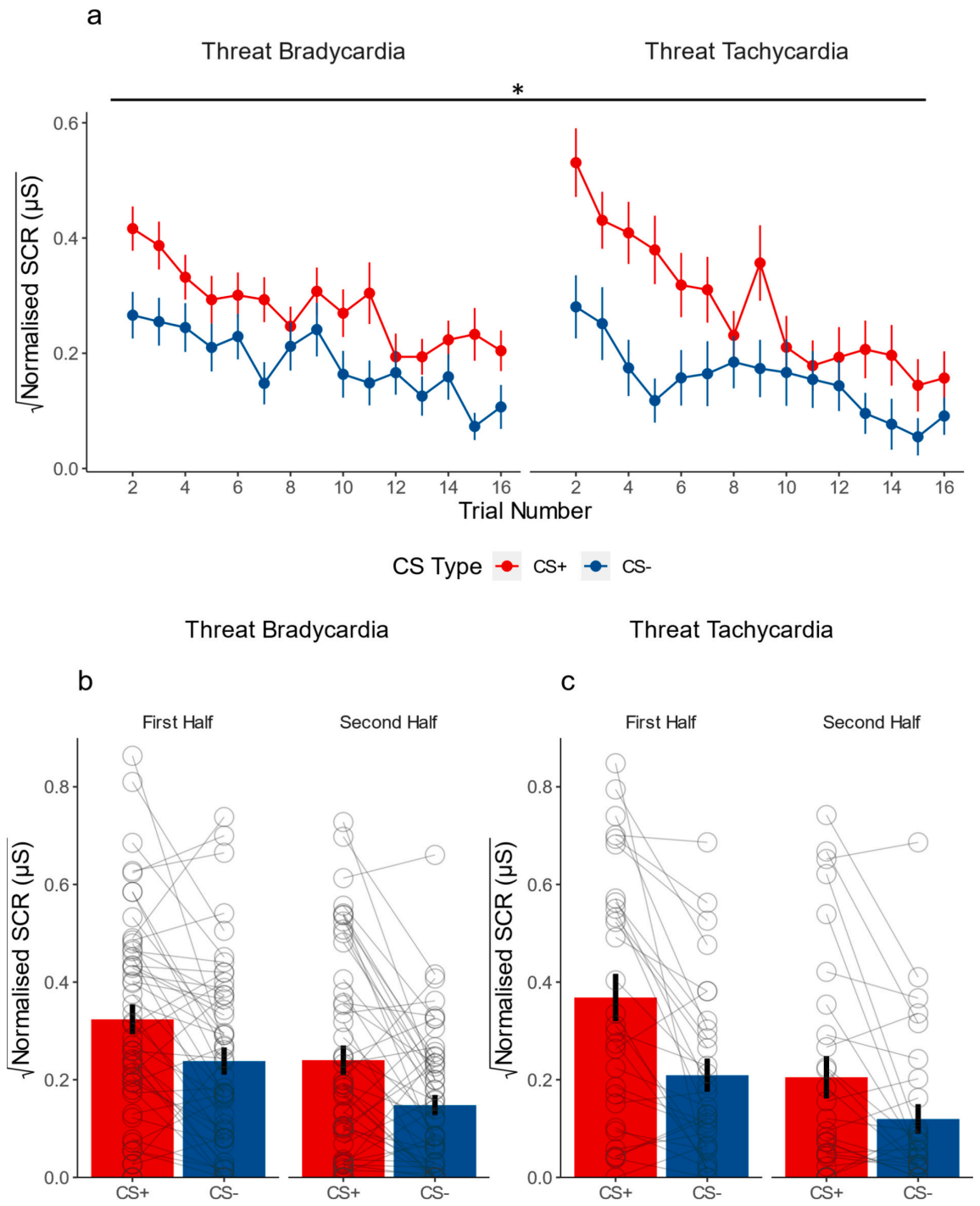

Fig. 2. a) SCR across all trials split by CS type and threat-induced bradycardia and tachycardia groups. Note that the first trial per CS is not shown here, as no learning has taken place yet. The figure illustrates stronger conditioned skin conductance responses (SCR) for the CS+ trials in the threat tachycardia vs. threat bradycardia group, at the start of the experiment in particular. b) and c) Paired observations of the SCR split by CS type and HR groups, for the first (trial number 1–8) and second (trial number 9–16) half of trials.

For the most conservative cut-off value excluding 50 % of the participants as "non-learners"), which included 39 participants as "SCR non-learners", the CS+ evoked significantly lower HR compared to the CS− (CS Type: estimate = −1.20, 95 % CI [−1.90; −0.51], see Fig. 3a). Next, with a more lenient cut-off (excluding 37 % of the participants as "non-learners", n = 29), we also found that the CS+ evoked significantly lower HR compared to the CS− (CS Type: estimate = −1.28, 95 % CI [−2.12; −0.45], see Fig. 3b). Lastly, even for the most lenient cut-off (excluding 25 % of the participants as "non-learners", n = 21), which represents the smallest group of "SCR non-learners", we still found that the CS+ evoked significantly lower HR compared to the CS− (estimate = −1.08, 95 % CI [−1.94; −0.22], see Fig. 3c). These results indicate

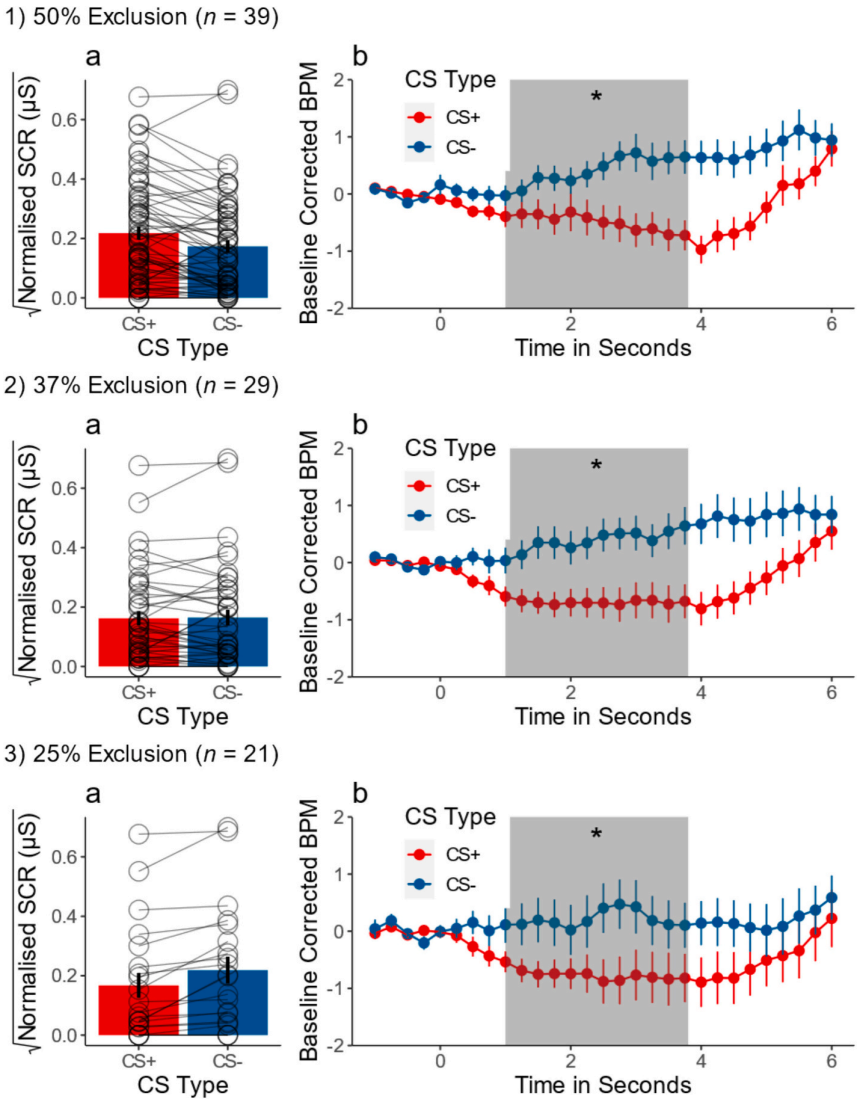

Fig. 3. Heart rate responses in SCR-based 'non-learners' indicate learning in terms of parasympathetic arousal instead of sympathetic arousal. a) SCR to the CS+ and CS− within the non-learner group (i.e., difference between CS+ and CS− scoring below the respective cut-off value) with paired observations. b) HR response to the average CS+ and CS− trial within the SCR non-learner group. Shaded area represents the analysis window. 1), 2), and 3) represent the respective SCR cut-off values. The figure illustrates that sympathetic 'non-learners' according to varying previously defined SCR-criteria do show learning on a parasympathetic arousal measure: threat bradycardia.

that SCR non-learners, i.e., individuals who do not show a differential SCR response, do seem to show differential HR responses that on average are manifested as threat bradycardia.

3.4. *Threat-induced bradycardia responders have relatively low trait anxiety*

After having established that associative threat learning can be reflected in both parasympathetic as well as sympathetic arousal, we verify the clinical relevance of both types of response patterns. In light of previous conflicting results for predictability of trait anxiety by threat conditioned SCR responses, we assessed the relationship between threat-induced bradycardia and tachycardia responses and trait anxiety (for a visual representation of the results, see Fig. 4a). First, we ran a group-based model assessing whether threat-induced bradycardia and tachycardia groups differed in their levels of trait anxiety. The results showed that the groups differed significantly, with the threat bradycardia responders showing lower trait anxiety scores as compared to the threat tachycardia responders (Group: estimate = −3.85, 95 % CI [−5.81, −1.89], see Fig. 4b).

Next, we ran a model, assessing whether HR responses to the CS+ and CS− were related to trait anxiety, across individuals rather than between groups. Similar to the previous analysis, overall lower HR response patterns were related to lower trait anxiety (Trait Anxiety: estimate = −0.05, 95 % CI [−0.09; −0.01]). Importantly, there was a significant interaction effect, indicating that the relation between trait anxiety and HR differed between the CS+ and CS− (CS Type * Trait Anxiety: estimate = 0.10, 95 % CI [0.04; 0.16]). Follow-up analyses show, that the relation between HR and trait anxiety was significant for the CS− (Trait Anxiety: estimate = −0.05, 95 % CI [−0.09; −0.01]) and marginally significant for the CS+ (Trait Anxiety: estimate = 0.05, 95 % CI [−0.002; 0.09], 90 % CI [0.01; 0.08]). With increasing trait anxiety, the CS− elicited significantly lower HR responses while the CS+ elicited marginally significant higher HR responses, see Fig. 4a.

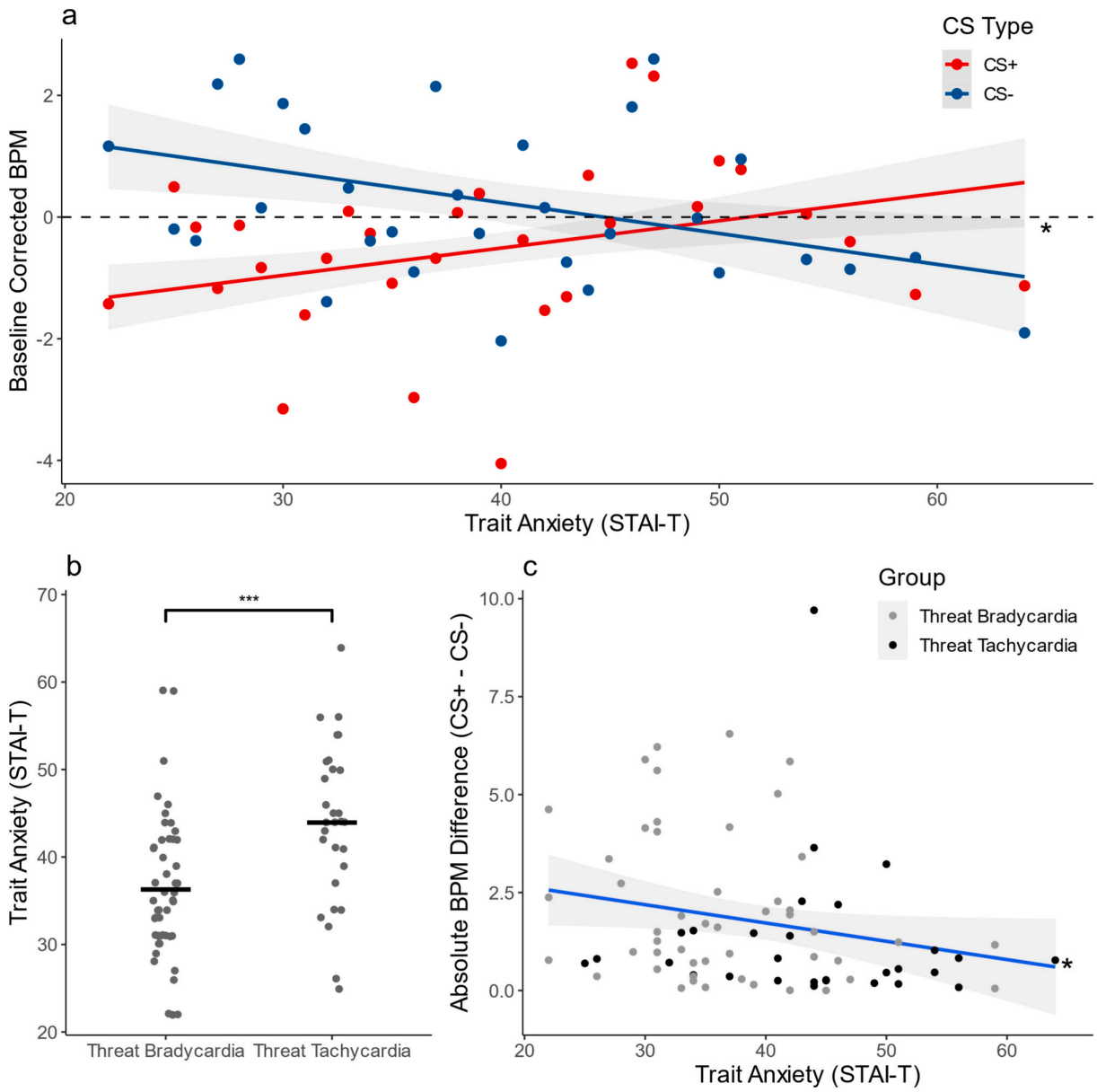

Fig. 4. Threat conditioned threat tachycardia is linked to low trait anxiety a) Relation between HR (Baseline corrected BPM) and trait anxiety scores split by CS type. This panel illustrates, that participants with stronger CS Type discrimination (hence stronger threat-induced bradycardia) have lower Trait Anxiety scores. b) Trait anxiety levels of threat bradycardia and tachycardia groups. Black lines indicate mean values per group. c) Absolute baseline corrected BPM differences between CS+ and CS− (i.e., the magnitude of the difference between the two stimuli, rather than the direction) are correlated to trait anxiety scores.

Finally, we assessed whether trait anxiety was linked to altered differentiation between the CS+ and CS− in terms of HR responses *regardless of the direction*. To that end, we analysed the *absolute* difference in HR responses between the CS+ and the CS−. The results showed a significant main effect of trait anxiety (Trait Anxiety: estimate = −0.05, 95 % CI [−0.09; −0.01]), indicating that also the absolute difference in HR responses between CS+ and CS− decreased with increasing trait anxiety (see Fig. 4c). Following up on this, we furthermore explored (not preregistered) whether the absolute HR response (magnitude of the response regardless of direction) for either the CS+ or CS− (i.e., not the difference between them) was associated with trait anxiety. The results show that there is no overall effect of trait anxiety on the absolute HR responses (Trait Anxiety: estimate = −0.01, 95 % CI [−0.06; 0.04) as well as no interaction effect with CS Type (CS Type * Trait Anxiety: estimate = −0.00, 95 % CI [−0.03; 0.03]). These results indicate that the magnitude of the HR responses per stimulus does not significantly increase or decrease with trait anxiety. Together these findings suggest that acceleratory HR response patterns constitute an important marker for relatively high trait anxiety and that with increasing anxiety, the discriminative ability (between CS+ and CS−) is impaired in terms of HR responses.

4. Discussion

This study demonstrates that threat conditioning can be reflected in threat bradycardia as well as tachycardia response patterns and that those response types are differentially linked to skin conductance responses (SCR) and subjective measures. Specifically, and supporting the

relevance to consider parasympathetic as well as sympathetic arousal indices during threat conditioning, threat tachycardia responders showed stronger initial conditioned SCRs and higher trait anxiety compared to threat bradycardia responders. Critically, we tested the relevance of these findings for current common practice in the extensive field of threat learning where 'non-learners' are typically exclusively based on sympathetic arousal indices (SCR) and are sometimes even excluded from analyses. Using frequently applied 'SCR non-learner' criteria (Lonsdorf et al., 2019), we showed that individuals previously classified as 'non-learners' were in fact showing successful learning in terms of parasympathetic arousal.

The finding that both parasympathetically dominant (indicated by threat bradycardia) and sympathetically dominant (threat tachycardia) threat responses can be observed during associative threat learning is in line with earlier observations (de Echegaray and Moratti, 2021; Hodes et al., 1985; Sevenster et al., 2015), where such patterns were found in individuals confronted with various forms of (learned) threat. We extend these findings by showing that threat tachycardia is related to altered SCR patterns, namely stronger initial conditioned responses, which then quickly habituate. Distinguishing HR response types is not only meaningful in terms of SCR responses and CS discrimination but also in terms of trait anxiety levels. Based on these findings we advocate for considering both sympathetic and parasympathetic threat responses in threat learning studies, allowing for direct comparisons between sympathetic and parasympathetic dominant learners.

Such direct comparisons between parasympathetic and sympathetic dominant threat responses may serve several purposes. First, during anticipation of acute threat, sympathetic and parasympathetic ANS are both activated but parasympathetic arousal is dominant in most cases (Roelofs, 2017; Roelofs and Dayan, 2022; van Ast et al., 2022). There is mounting evidence that threat-anticipatory parasympathetic responding occurs during associative threat learning (Battaglia et al., 2022; Battaglia et al., 2024; Castegnetti et al., 2016) and is relevant for active threat coping (Gladwin et al., 2016; Klaassen et al., 2024; Roelofs, 2017). Second, we see an association between the HR response patterns and the sympathetic measure SCR that is most used in threat learning studies: Threat-induced tachycardia responders showed stronger sympathetically driven conditioned SCRs (during early learning) compared to threat-induced bradycardia responders. Therefore, the combination of both measures can provide additional information about the relative sympathetic vs. parasympathetic dominance, which can be valuable in the context of threat learning and defensive responses. Third, and most critically, when we classified individuals as SCR "non-learners" according to several exclusion criteria that are commonly used in the field (Lonsdorf et al., 2019), we show that SCR non-learners still showed discriminatory threat bradycardia responses. Thus, SCR "non-learners" should not be treated as non-learners per se, since these individuals could just as well show a learned parasympathetically dominant response instead. Fourth, threat bradycardia and tachycardia responders showed differential trait anxiety levels, with threat bradycardia responders reporting lower trait anxiety. In light of the well-established association between high trait anxiety and vulnerability to stress (e.g., Weger and Sandi, 2018), threat bradycardia observed in the low trait anxious participants could potentially be a sign of relative resilience. Such interpretation would be in line with prospective longitudinal studies linking low HR and/or high HR variability to resilience against the negative effects of trauma (e.g., Minassian et al., 2015; Pyne et al., 2016). Previous work has established the relevance of threat bradycardia and tachycardia groups in the context of circa-strike responses (Battaglia et al., 2024; López et al., 2009). Here, we extend these findings by showing that threat bradycardia and tachycardia groups are also relevant when assessing post-encounter threat responses. Taken together, these findings suggest it is important for future studies to take parasympathetic response patterns in addition to sympathetic response patterns into account when assessing individual differences in associative threat learning.

An open question remains regarding the mechanism behind the individual differences in parasympathetic and sympathetic dominant threat responses. One possibility is that parasympathetic dominance this is caused by increased parasympathetic outflow (Battaglia et al., 2022), as the heart is strongly under parasympathetic control via the nervous vagus (Levy et al., 1993; for a review see Roelofs and Dayan, 2022). However, it is also possible this is caused by sympathetic withdrawal. Moreover, it is also possible that parasympathetic dominance is indirectly caused by breathing patterns. Indeed, HR fluctuates with breathing patterns (i.e. HR increases during inhalation and decreases during exhalation), a phenomenon referred to as respiratory sinus arrhythmia (e.g. Grossman, 2024; Yasuma and Hayano, 2004). Another important aspect to consider in future work is the preprocessing strategy employed to assess HR responses. Several studies have demonstrated consistent threat bradycardia in response to (conditioned) threat, but even among those studies, different preprocessing strategies have been employed (for an overview, see Battaglia et al., 2024). For instance, Battaglia et al. (2022) and Castegnetti et al. (2016) have used the heart period (i.e., inter beat interval) during the tri-phasic HR response to threat (an initial deceleration, followed by a quick acceleration, after which a larger deceleration follows), whereas we, similar to de Echegaray and Moratti (2021), used the average BPM within a given analysis window to determine the threat bradycardia or tachycardia response. Future studies are needed to shed more light on the exact mechanisms behind threat bradycardia and, possibly linked, the impact of divergent preprocessing strategies. Furthermore, a limitation that future studies could rectify, is that we did not explicitly screen for possible heart conditions and/or medication use. While we screened for medication use related to mental illness, we cannot fully rule out the possibility that individuals were using medication related to heart conditions.

The observed link between trait anxiety and HR threat responses can bare clinical relevance. Our results are broadly in line with an earlier review on threat conditioned HR responses in PTSD patients and trauma-exposed individuals with subthreshold PTSD (Battaglia et al., 2023). In the majority of the reviewed literature, not threat *bradycardia*, but threat *tachycardia* was the dominant response to conditioned threat. Also, outside of threat conditioning studies, our results are broadly in line with earlier research on ANS reactivity in anxious psychopathology, showing that indices of anxious psychopathology are related to less parasympathetic and more sympathetic ANS activity (Adenauer et al., 2010; Held et al., 2022; Niermann et al., 2017). In the context of threat, one explanation for these differences in ANS responses could be, that anxious individuals mobilise for avoidance (Hodes et al., 1985; Van Diest et al., 2009), which is accompanied by sympathetic dominance (i.e., flight or fight reactions). Cardiac accelerations in response to unpleasant stimuli in highly anxious individuals might be interpreted as defensive action preparation (Hamm et al., 1993). Indeed, previous literature on avoidance behaviour under threat shows that anxious psychopathology is associated with more pronounced avoidance tendencies (Hulsman et al., 2021; Pittig et al., 2021). In studies with unavoidable and avoidable threat, threat tachycardia occurred when participants took action to avoid threat, whereas threat bradycardia occurred when facing unavoidable threat (Löw et al., 2015; Wendt et al., 2017). It is therefore possible that highly anxious individuals under threat prepare for action (i.e., avoidance), even when no action can be taken. Thus, threat bradycardia and tachycardia can both be seen as ANS reactions to learned threat, whereby threat tachycardia may contain an impulsive action preparation component that is related to fearful avoidance, whereas bradycardia has been linked to more context-adaptive selection of coping strategies (Klaassen et al., 2024).

The finding that differences in HR responses between the threatening and the safe stimuli decreased with increasing trait anxiety might be indicative of threat generalisation, which is characterized by threat responses to innocuous stimuli (for a review, see Dymond et al., 2015). Interestingly, our results also showed that the absolute HR response for either stimulus alone did not significantly vary across trait anxiety,

which shows, that overall HR reactivity in terms of magnitude is not altered in highly anxious individuals. Together, these results show that highly anxious individuals do not show an overall blunted HR response, but that their discriminatory ability to discern between threatening and safe stimuli is diminished. In line with this notion, a recent meta-analysis has indicated that indices of anxious psychopathology are linked to threat generalisation in threat learning (Sep et al., 2019). Therefore, it is possible that the ANS responses we found in the participants with relatively high trait anxiety are indicative of avoidance reactions and generalisation to innocuous stimuli. One last note with respect to the specificity of these findings should be made: The trait anxiety scale of the STAI measures not only anxiety but is also sensitive to depressive symptomatology (Knowles and Olatunji, 2020), potentially capturing a broader range of negative affectivity. In this context, future research could explore whether alterations in threat learning are specific to anxiety or extend to depressive disorders, thus addressing a more transdiagnostic aspect of negative affectivity.

In conclusion, our results highlight the importance of including parasympathetic and sympathetic contributions in the threat response when assessing individual differences in physiological responses to threat. Threat-induced bradycardia and tachycardia each constitute unique indices of learned threat that are differentially linked to individual differences in trait anxiety. Because threat learning processes can yield insights into the aetiology, maintenance, and treatment of anxiety disorders (Mineka and Oehlberg, 2008; VanElzakker et al., 2014), adequate measures of threat responses are needed to best inform clinical practice (Bach et al., 2023). When employing paradigms assessing individual differences in threat responding, we advocate to not classify, nor exclude, participants based on the absence of SCR responses alone. Defensive responses to threat vary across a larger spectrum than sympathetic arousal alone. This is particularly relevant for studies that aim to link threat learning processes to resilience.

CRediT authorship contribution statement

Lars Jaswetz: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lycia D. de Voogd:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Eni S. Becker:** Writing – review & editing, Supervision, Conceptualization. **Karin Roelofs:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

The author(s) did not use generative AI technologies for preparation of this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpsycho.2025.112561.

Data availability

Data will be made available on request.

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