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Variability in emotional responsiveness and coping style during active avoidance as a window onto psychological vulnerability to stress

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HIGHLIGHTS

- Human threat responses during active avoidance vary according to coping style.
- Proactive coping is associated with enhanced behavioral avoidance.
- Reactive coping is associated with enhanced autonomic arousal.

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ABSTRACT

Individual differences in coping styles are associated with psychological vulnerability to stress. Recent animal research suggests that coping styles reflect trade-offs between proactive and reactive threat responses during active avoidance paradigms, with proactive responses associated with better stress tolerance. Based on these preclinical findings, we developed a novel instructed active avoidance paradigm to characterize patterns of proactive and reactive responses using behavioral, motoric, and autonomic measures in humans. Analyses revealed significant inter-individual variability not only in the magnitude of general emotional responsiveness but also the likelihood to specifically express proactive or reactive responses. In men but not women, individual differences in general emotional responsiveness were linked to increased trait anxiety while proactive coping style was linked to increased trait aggression. These patterns are consistent with preclinical findings and suggest that instructed active avoidance paradigms may be useful in assessing psychological vulnerability to stress using objective behavioral measures.

1. Introduction

Variability in how persons respond to threat has consistently been identified as a risk factor for the development of mood and anxiety disorders [14,28,55]. Nonetheless, heterogeneity within and between diagnostic categories limits the ability of a single measure to predict which individuals will go on to develop psychopathology. Researchers have suggested that the assessment of action tendencies, such as avoidance behavior, as an index of threat processing can better inform risk for clinical outcomes [6]. Supporting this idea, research has shown that rats bred to exhibit high levels of active avoidance behavior are relevantly resilient to the depressive effects of stress compared to low avoidance rats [47]. Notably, chronic anti-depressant administration rescues the depressive phenotype associated with low levels of active avoidance [47]. These and other data have led researchers to suggest that proactive coping strategies may aid individuals suffering from mood disorders in dealing with threatening stimuli [36]. Yet to date, insufficient preclinical data exists to inform potential treatment strategies employing proactive responses to threat or to determine whether individual differences in active avoidance behavior predicts susceptibility to clinical outcomes in human participants.

Proactive responses to threat are goal directed behaviors that function to directly impact threat exposure. During instrumental avoidance paradigms animals will make shuttling responses in order to terminate the presentation of a conditioned stimulus (CS) that predicts the delivery of an aversive electrical shock [10]. Moreover, animals will exhibit reduced avoidance behavior when the delivery of aversive stimuli is altered so as to be uncontrollable [59]. These data suggest that active avoidance responses are goal directed behaviors and represent a type of proactive response to threat. In contrast, reactive responses to threat, such as freezing or changes in heart rate, might serve adaptive functions by mobilizing bodily resources or preventing detection by predators [19,25] but do not directly impact exposure to the CS. During signaled active avoidance paradigms, the presentation of the CS elicits either proactive avoidance responses or reactive freezing responses, and research

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suggests that variability in the type of response elicited during avoidance paradigms can inform risk for psychopathology.

There is competition between the expression of proactive and reactive responses during active avoidance [42]. For example, there is an inverse relationship between freezing during the first five trials of active avoidance, during which no animals are performing shuttling responses, and future active avoidance [57]. Further, the acquisition of active avoidance is associated with reduced reactive responses to threat, even within novel contexts when no avoidance response is available [31,42]. In addition to illustrating the competition between proactive and reactive responses to threat, prior research suggests that variability in how animals respond during active avoidance paradigms is associated with individual differences in behavioral traits. High levels of reactive freezing responses are associated with generally high levels of anxiety [39,54], whereas heightened proactive avoidance responses are associated with generally high levels of impulsivity and aggression [7,54]. Intriguingly, rats bred to exhibit high levels of aggression and rats bred to exhibit high levels of avoidance are both relatively resilient to the depressive effects of stress [47,56] which may suggest that these behavioral traits reflect a shared proactive coping style [33].

Importantly, prior research suggests that sex differences are critical for understanding the relationship between coping style and inter-individual variation in behavioral traits. Although prior reports have failed to detect different rates of avoidance learning in male and female animals [12,16,17,39,53]; but see Aguilar et al. [60]; Beck, Jiao, Pang, & Servatius [61], research suggests that sex can moderate the relationship between active avoidance and anxiety related behaviors. Rats bred to exhibit high levels of active avoidance behavior more quickly cross the border during the dark/light open field test compared to low avoidance rats, and this relationship is strongest in male animals [53]. Further, prior research has demonstrated that behavioral measures of unlearned anxiety (i.e., black-white box, elevated "zero" maze, and novel cage activity) are negatively associated with two-way avoidance in male but not female animals [39]. As previous research has demonstrated that proactive coping styles are associated with better stress tolerance [47], sex differences may be important in understanding how inter-individual variation in active avoidance behavior is associated with risk for psychopathology.

The general pattern of effects observed in these animal models has led to important insights for posttraumatic stress disorder (PTSD) and other anxiety disorders. However, aversive instrumental conditioning paradigms are limited in their ability to measure naturalistic profiles of active avoidance behavior in humans. First, aversive instrumental paradigms lack real world validity, as conditioning is not necessarily the mechanism by which humans generally learn avoidance responses. Humans frequently avoid threating stimuli, such as downed electrical power lines, not because they have experienced an aversive outcome when encountering these stimuli in the past but because they have cognitively learned that avoidance is the best response to certain situations. Second, the acquisition of an instrumental response is only one possible way to assess proactive responses to potentially harmful stimuli. Previous research has demonstrated that threat can impact the performance on ongoing behavioral processes [41]. However, it is presently unclear if there is competition between proactive and reactive responses during the performance of motivated actions which prevent the delivery of aversive stimuli. Lastly, although some aversive instrumental paradigms are sufficiently challenging to produce individual differences in avoidance behavior [13] others are relatively easy for human participants, resulting in a rapid transition to optimal (i.e., ceiling) performance and a reduced number of trials for analysis [15,18]. Variability in active avoidance behavior is necessary to assess the extent to which individual differences in dispositional traits such as anxiety, impulsivity, and aggression are associated with the likelihood of expressing reactive or proactive responses in humans and, furthermore, the degree to which such differences relate to risk for psychopathology.

Here, we developed a novel instructed active avoidance task – the Active Avoidance of Signaled Threat (AAST) paradigm – to first measure proactive and reactive responses to threat in humans and, subsequently, determine if their expression is inversely related to each other as well as predicted by individual differences in trait personality. Participants listened to auditory stimuli and withdrew their finger when hearing the avoidance cue. Threat was operationalized during the paradigm by manipulating whether performance errors resulted in the delivery of a mildly aversive electrical stimulus. We concurrently measured behavioral withdrawal responses, reaction time, and forearm electromyogram (EMG) responses indexing muscular activity associated with finger withdrawal. Withdrawal during the avoidance cue serves to prevent the delivery of the aversive stimulus and measures of behavior related to withdrawal during the cue may serve as indices of proactive responding.

We also collected physiological measures of threat responsiveness, specifically phasic skin conductance responses (SCRs) to the avoidance cue and changes in salivary alpha-amylase following the avoidance task. SCRs are thought to be a relatively pure measure of phasic sympathetic responses [58] and previous research has shown that following conditioning [38], or following verbal instructions [46], stimuli which predict aversive outcomes elicit increased sympathetic responses. Salivary alpha-amylase, meanwhile, is under control of both the sympathetic and parasympathetic branches of the autonomic nervous system [43]. Previous research has demonstrated that salivary alpha-amylase responses are correlated with changes in systolic blood pressure, heart rate, and cardiac output [26], and, as such, assays of salivary alpha-amylase can provide a broader index of autonomic and physiological response to threat. As autonomic activity has no direct impact on threat exposure or subsequent aversive outcomes, the combination of SCRs and salivary alpha-amylase may better represent reactive responding during avoidance. Lastly, we collected self-reported state anxiety before and after the experiment.

Our data analysis strategy focused on reducing multiple dependent measures of avoidance and anxiety to component clusters that characterize constellations of response patterns, and relating them to individual difference variables. Based on prior research in animal models, we hypothesized that withdrawal to the avoidance cue would be more frequent during the shock condition, and that these withdrawal responses would be associated with faster reaction times and larger muscular responses. Because humans at times will avoid stimuli that pose no threat, and avoidance of non-threatening stimuli and situations is characteristic of dysfunction observed in anxiety disorders [1,4], we also hypothesized that participants would be more likely to withdraw their finger during the shock condition, even during the absence of the avoidance cue, and that participants would exhibit heightened sympathetic activity and state anxiety during the shock condition.

Using principal component analysis to identify the underlying correlational structure of individual differences in threat responses across measures, we further hypothesized that individual differences in threat responses would be characterized by two factors previously identified in animal models, specifically emotional responsiveness and proactive vs. reactive coping style [32,53]. First, we hypothesized that variability in emotional responsiveness would be reflected in a generalized increase in threat responses across all types of measurement. Second, we hypothesized variability in coping style would be reflected in differential loading patterns for proactive and reactive threat responses. Finger withdrawals during the avoidance cue serve to avoid an aversive outcome and we operationally define these responses as proactive responses to threat. Likewise, reaction times and EMG responses are derived from finger withdrawals during the avoidance cue and we hypothesize that these variables will load onto proactive coping style. Withdrawal during the absence of the avoidance cue does not serve to terminate threat exposure and as such we expect this variable to be unrelated to proactive coping. Alternatively, we hypothesize that variability in SCRs and salivary alpha-amylase, which both reflect activity of the

autonomic nervous system [43,58], will load onto reactive coping style and will be inversely related to individual differences in proactive responses.

Lastly, we hypothesized that trait personality would be associated with factor scores derived from our PCA. Based on observations from animals bred for high and low levels of avoidance behavior, we hypothesized that trait anxiety would be associated with high levels of emotional responsiveness and a reactive coping style. We further hypothesized that trait impulsivity and trait aggression would be associated with low levels of emotional responsiveness and a proactive coping style. Given that trait personality differs between men and women [22] and prior preclinical work suggests that sex moderates the relationship between coping style and behavioral traits [39,53], we tested whether trait personality predicted emotional responsiveness and coping style as a function of sex, and we hypothesized that these relationships would be stronger in men based on the prior literature.

2. Methods

2.1. Participants

Sixty-four participants were recruited via email, flyer, and online advertisement from an ongoing parent protocol, the Duke Neurogenetics Study (DNS), which assesses a wide range of behavioral and biological traits among non-patient, 18–22 year old university students. All participants provided informed consent in accordance with Duke University Medical Center Institutional Review Board guidelines prior to participation. The participants were in good general health and free of the following study exclusions: (1) medical diagnoses of cancer, stroke, head injury with loss of consciousness, untreated migraine headaches, diabetes requiring insulin treatment, chronic kidney or liver disease, or current psychotic symptoms; (2) use of psychotropic, glucocorticoid, or hypolipidemic medication; and (3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension). Four participants exhibited present and past diagnosis of mood and anxiety disorders (1 current social phobia and bulimia nervosa, 1 current agoraphobia, 1 past Major Depressive Disorder, 1 recurrent Major Depressive Disorder and past Bipolar II) as identified through clinical interviews using the electronic MINI [50]. All participants additionally reported having no hearing impairments.

2.2. Experimental protocol

All participants first completed the Spielberger State-Trait Anxiety Inventory-State version (STAI-S) [52], provided a saliva sample, and completed a tone recognition test and two practice tasks. Participants then performed the AAST paradigm described below. Next, participants completed a second STAI-S retrospectively reporting state anxiety during the threat condition of the AAST, and provided another saliva sample. After the experiment, participants were debriefed and compensated $20 for their participation.

2.3. Tone recognition test and practice tasks

In order to ensure that participants were capable of performing the AAST, participants were first presented with three 400 ms tones consisting of 700, 1000, and 1300 Hz sinusoidal waveforms three times or until the participant indicated that they could distinguish between the tones. Individual tones were then presented one at a time, and participants were instructed to verbally indicate if the tone was low (700 Hz), medium (1000 Hz), or high (1300 Hz). The order of tone presentation was randomized, and all participants correctly identified ten tone presentations in a row before proceeding with the experiment.

Following the tone recognition test, the first practice task was administered to accustom the participant to both the response required (withdrawal of the index finger) and the window of time provided (400 ms) for correct responses. Participants were instructed to hold down a computer key with the index finger of their dominant hand and to withdraw their finger after hearing the avoidance cue (a pair of two 1000 Hz tones separated by a 250 ms interval). Ten avoidance cues were presented one after the other. A screen with the word "Failure" was presented when participants committed an error to provide feedback regarding performance. No feedback was presented for correct performance.

Subsequent to the first practice task, the second practice task was administered to accustom the participants to the demands of the AAST. The second practice task practice task was identical to a "Safe Block" of the experimental paradigm (see 2.4 Active avoidance of signaled threat paradigm for details) but consisted of 20 randomly selected trials, including 4 response trials signaled by the avoidance cue. After both practice tasks, participants were asked if they had any questions or if they would like to perform the practice task again. After indicating that they had no questions, and did not wish to practice any longer, participants performed the AAST.

2.4. Active avoidance of signaled threat paradigm

Participants were instructed to hold down a computer key with the index finger of their dominant hand and were presented with auditory stimuli, consisting of two 400 ms tones separated by a 250 ms interval. Tone pairs were comprised of all possible combinations of a low tone (700 Hz) a medium tone (1000 Hz) and a high tone (1300 Hz) leading to nine possible combinations. Participants were instructed to withdraw their index finger from the key when hearing the avoidance cue (medium-medium pair), and to refrain from withdrawing their finger during all other times. Participants were instructed that it was important to withdraw their finger as quickly as possible when hearing the avoidance cue, and that they must complete their response before the second medium tone terminated (400 ms). Failure to withdraw their index finger within the 400 ms window, or withdrawal of their finger at any other time resulted in the presentation of a screen that said "Failure" for 2000 ms. After accurately responding to a avoidance cue, or after any erroneous response and subsequent "Failure" screen presentation, participants were presented with text instructing them to "Please place your finger back on the key". This text remained on the screen until participants placed their index finger back on the key, at which point, text instructing participants to "Please Wait" was presented for 10 s. After the "Please Wait" screen the paradigm continued.

Participants completed six blocks of the paradigm, each of which consisted of 30 auditory stimuli interleaved with a variable inter-trial interval (4 ± 2 s). During the blocks a fixation cross was presented in the middle of the computer screen. Each block consisted of 6 response trials signaled by an avoidance cue (medium-medium pairs), and 24 distractor trials. The distractor trials were designed to probe inappropriate avoidance responses and were comprised of 3 medium-low and 3 medium-high pairs, and three each of the following: low-low, low-medium, low-high, high-low, high-medium, and high-high pairs. Variable inter-trial intervals preceded each type of tone pair with equal frequency. The order of tone pair presentation within each block was pseudo-randomized such that no more than two avoidance cues occurred in a row. Three blocks of the paradigm consisted of a neutral condition ("Safe Block") alternated with the three blocks of a threat condition ("Shock Block"). Any error committed during the experiment was followed by feedback ("Failure" screen); however only errors committed during the threat condition resulted in the delivery of an aversive stimulus (Fig. 1). No more than 18 aversive stimuli were administered regardless of performance, and the experiment was terminated if more than 18 errors were committed during the threat condition ($n = 5$). The order of threat and neutral conditions was counterbalanced across participants. Each condition was preceded by text that stated "The next block will be a Safe/Shock block". During the

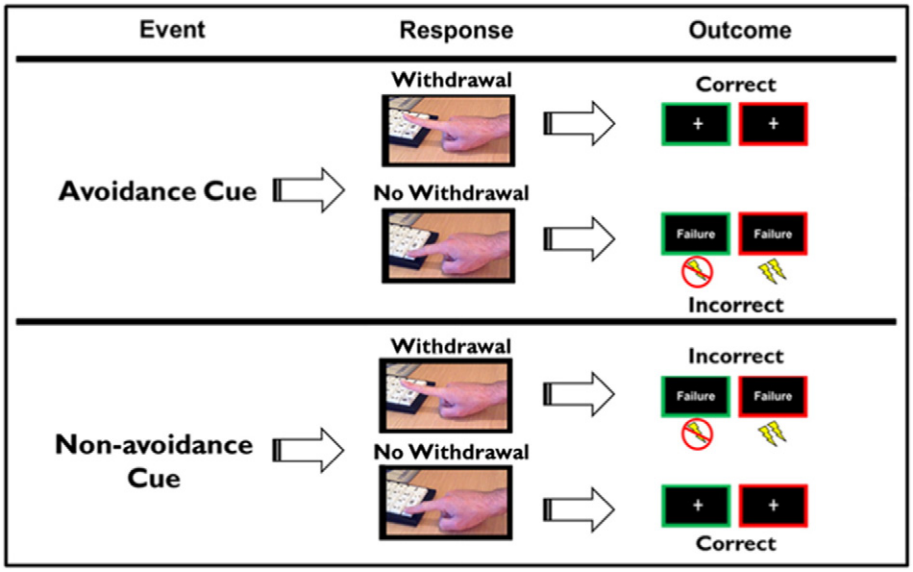

Fig. 1. Task characteristics of the AAST. During avoidance cues finger withdrawals are the correct response, which result in progression to the next trial, and failure to withdraw is the incorrect response, which results in a failure screen and a delivery of an aversive electrical stimulus, but only in the shock condition. During non-avoidance cues maintaining the finger on the key is the correct response, which results in progression to the next trial, and finger withdrawal is the incorrect response.

threat condition the screen was surrounded by a red colored border, while a green colored border surrounded the screen during the neutral condition. Participants were informed of the relationship between the block structure and aversive stimulus contingency, and as such our manipulation was one of instructed fear.

2.5. Electrical stimulation

The aversive stimulus used in the AAST was a mild electrical stimulation. The electric stimulation (200 ms duration delivered at 50 Hz) was administered transcutaneously over the median nerve of the participants' non-dominant wrist by a bipolar surface-stimulating electrode (21 mm electrode spacing: Grass-Telefactor Model F-E 10S2, West Warwick, RI). The electrode leads were secured by a rubber strap and are attached to a Grass-Telefactor SD-9 stimulator via coaxial cable leads that were shielded and grounded through a radiofrequency filter. A saline based gel (Sigma Gel: Parker Laboratories, Fairfield, NJ) was used as an electrolyte conductor. Electrical stimulation was adjusted prior to the start of the experiment according to each subject's tolerance level. The stimulation level chosen was be perceived by each participant as "highly annoying but not painful" according to participant ratings on a 5-point Likert-type tolerance scale. Voltage was initially set at a low level of 20 V and increased in increments of 5–10 V until participants indicated their tolerance level had been reached without inducing pain.

2.6. Salivary alpha-amylase

Participants provided a total of two saliva samples (2 mL). Sample 1 (baseline) was collected approximately 10 min after participants arrived and sample 2 was collected 10 min after participants complete the experimental task. Analyses assessing salivary alpha-amylase were limited to forty two participants who successfully provided saliva samples between the hours of 11:00 a.m. and 4:00 p.m. to limit variability associated with diurnal variation [44]. Saliva samples were collected non-invasively (i.e., passive drool) in polystyrene culture tubes and stored at −20°.

Alpha-amylase concentrations were determined using commercially-available enzyme-linked immunoassay kits (Salimetrics, State College, PA). This assay kit employs a chromogenic substrate, 2-chloro-*p*-nitrophenol, linked to maltotriose. The enzymatic action of salivary alpha amylase on this substrate yields 2-chloro-*p*-nitrophenol, which can be spectrophotometrically measured using a standard laboratory plate reader. The amount of alpha amylase present in the sample is directly related to the increase in absorbance (over a 2 min period) read at 405 nm. Results were computed in U/mL of alpha amylase using the formula: [Absorbance difference per minute × total assay volume (328 mL) × dilution factor (200)] / [millimolar absorptivity of 2-chloro-*p*-nitrophenol (12.9) × sample volume (0.008 mL) × light path (0.97)]. All saliva samples were measured in duplicate. Optical densities were determined using a Perkin Elmer Wallac 1420 plate reader. Intra- and inter-assay coefficients of variation were 5.7% and 11.9%, respectively.

2.7. Physiological recording and analysis

Electrodermal activity and electromyogardiogram signals were recorded via an MR-compatible psychophysiological monitoring system (BIOPAC Systems, Santa Barbara, CA). Signa Gel (Parker Laboratories; Fairfield, NJ) was used as a conductive electrolyte on the recording electrodes. Electrodermal activity was acquired by placing two Ag-AgCl electrodes on the hypothenar eminence of the non-dominant palm and amplified using the GSR 100C module. Subjects were instructed to keep their hand still to avoid movement artifacts in the electrodermal recording electrode. Electrodermal activity was sampled at up to 1000 Hz, amplified, and stored for offline analysis using AcqKnowledge software (BIOPAC Systems, Santa Barbara, CA). Event related skin conductance responses (SCRs) were scored using the automated scoring software, Autonomate [27].

Electromyogardiogram (EMG) signal was collected from the extensor indicis proprius muscle of the forearm of the dominant hand using two Ag-AgCl recording electrodes with 4 mm inner diameter (BIOPAC Systems; Goleta, CA). The raw EMG signal was sampled at 1000 Hz and was gain amplified by 5000. A 60 Hz notch filter was applied to EMG signal, which was then band pass filtered at 28–500 Hz and integrated over 20 samples. EMG responses were calculated using AcqKnowledge software to determine the peak EMG response within 500 ms of the presentation of the second medium tone during response trials.

2.8. Trait measures

The Spielberger State-Trait Anxiety Inventory-Trait (STAI-T) version was used to assess variation in trait anxiety, which reflects the general tendency to perceive situations to be threatening and to respond to such situations with subjective feelings of apprehension and tension [52]. The physical aggression subscale of the Buss-Perry Aggression Questionnaire (BPAQ) was used to assess variation in aggressive behavior [9]. We focused on this subscale because of evidence that rats bred for high and low levels of physical aggression differ in how they perform during active avoidance [7]. Total scores from the Barratt Impulsiveness Scale (BIS) were used to assess variation in trait impulsivity [5].

2.9. Statistical analyses

The experiment was terminated for five participants due to the large number of errors committed during the threat condition. Analyses assessing behavioral performance were limited to the 59 participants who completed the experiment (36 females, age 19.22 ± 1.22 SD). Physiological data were not available for four participants due to hardware and software problems, and analyses assessing EMG responses were limited to 55 participants. Four participants did not exhibit any SCRs during avoidance cues in either the threat or safe condition, limiting analyses to 51 participants. Analyses assessing salivary alpha-amylase were restricted to 42 participants who provided samples between 11:00 am and 4:00 pm to limit the impact of diurnal variation.

Repeated measure ANOVAs were used to assess effects of the threat condition (shock vs. no shock), temporal order (first vs. second vs. third blocks), and interactions between threat condition and temporal order. Greenhouse-Geisser correction was applied when variance was unequal across measurements as assessed by Mauchly's test of sphericity. Post-hoc effects were assessed with paired *t*-tests.

To identify the underlying correlational structure of individual differences in threat responses across measures, we applied principal components analysis (PCA) to difference scores from our dependent variables of interest. We employed this strategy because principal components are easily interpretable, yielding distinct loadings for well-defined correlational structures and non-separable loadings in the absence of clear patterns. Changes in reaction times, withdrawals during response trials, withdrawals during non-response trials, peak EMG responses, and SCRs between threat conditions (shock minus no shock) were calculated for each participant. Difference scores for salivary alpha-amylase were created by calculating the differences between measurement before the AAST and after (post minus pre). One EMG response difference score was >4 SD from the mean, and thus this data point was censored from the PCA analysis. As reaction time was the only variable to decrease during the threat condition, difference scores were multiplied by −1 so that positive values reflected increased responding during the shock condition for all variables. After regressing out variance associated with trial order, the total number of aversive stimuli delivered during the experiment, time of day, and past or present mood diagnosis, residual variables were entered into a PCA with rotated solutions calculated using Direct Oblimin rotation. We utilized oblique rotation so that identified factors were not forced to be orthogonal. Missing values were replaced with the mean.

Multiple regression analyses were used to determine effects of sex and trait personality on factor scores associated with the principal components characterizing variability in patterns of responding during instructed active avoidance while controlling for past or present DSM-IV diagnosis (dummy coded as 0 for no diagnosis and 1 for any mood or anxiety diagnosis). All analyses were conducted using SPSS v22 and moderation analyses were conducted using the PROCESS macro [29].

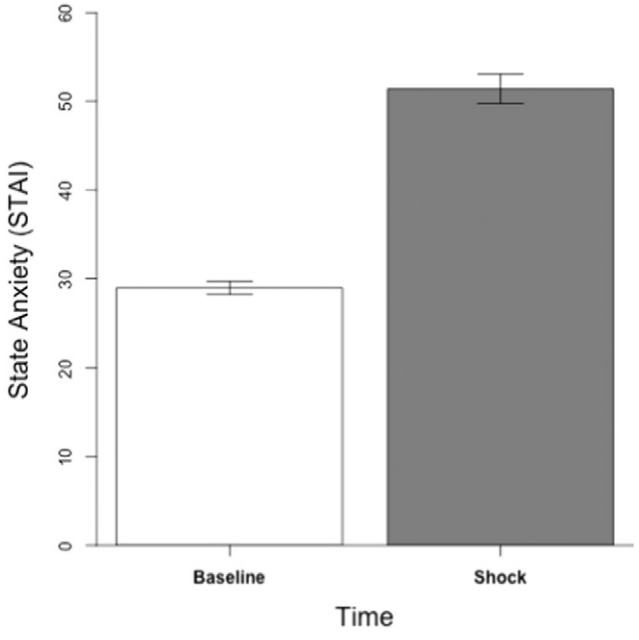

Fig. 2. Self-reported state anxiety (STAI) at baseline (before the AAST) and during the threat condition (reported retrospectively) illustrating an increase in anxiety as a function of the threat condition.

3. Results

3.1. General patterns associated with active avoidance

3.1.1. Self-reported anxiety

As expected, self-reported state anxiety was significantly higher ($t(58) = 14.38$, $p < 0.001$) (Fig. 2) during the shock condition (mean = 51.39, SD = 12.76) than during baseline (mean = 28.98, SD = 5.48).

3.1.2. Responses during active avoidance

Withdrawal in response to the avoidance cue was characterized by a threat × block interaction ($F(2116) = 5.28$, $p < 0.01$, $\eta_p^2 = 0.083$) (Fig. 3), such that there was increased finger withdrawal during the shock condition within the second ($t(58) = 2.57$, $p = 0.013$) and third ($t(58) = 2.10$, $p = 0.041$) blocks, but not within the first block ($t(58) = 1.37$, $p = 0.175$).

Reaction times during successful withdrawals to the avoidance cue were characterized by a threat × block interaction ($F(2112) = 5.42$, $p < 0.01$, $\eta_p^2 = 0.088$) (Fig. 4) such that reaction times were quicker during the shock condition within the second ($t(56) = 4.46$, $p < 0.001$) and third ($t(56) = 4.93$, $p < 0.001$) blocks, but not within the first block ($t(56) = 0.39$, $p = 0.70$).

EMG responses within the extensor indicis proprius muscle during successful withdrawals in response to the avoidance cue were larger during the shock condition compared to the no-shock condition ($F(1.52) = 24.14$, $p < 0.001$ $\eta_p^2 = 0.317$) (Fig. 5). Effects of block and the threat × block interaction did not reach significance (all p's > 0.1).

As predicted, withdrawal during non-response trials was increased during the shock condition ($F(1.58) = 12.36$, $p < 0.001$ $\eta_p^2 = 0.176$) (Fig. 6). Additionally, withdrawals during non-response trials decreased over blocks ($F(2116) = 7.71$, $p < 0.001$ $\eta_p^2 = 0.117$). The threat × block interaction did not reach significance ($p = 0.18$).

SCRs in response to avoidance cues associated with successful withdrawals were larger during the shock condition compared to the no-shock condition ($F(1.48) = 74.38$, $p < 0.001$, $\eta_p^2 = 0.608$) (Fig. 7). Effects of block did not reach significance ($p > 0.1$), and the threat × block interaction trended toward significance ($p = 0.077$).

A trend toward higher salivary alpha-amylase ($t(41) = 1.89$, $p = 0.066$) (Fig. 8) was observed following the AAST (mean = 34.65, SE = 4.98) compared to the baseline measurement before the task (mean = 30.30, SE = 4.29).

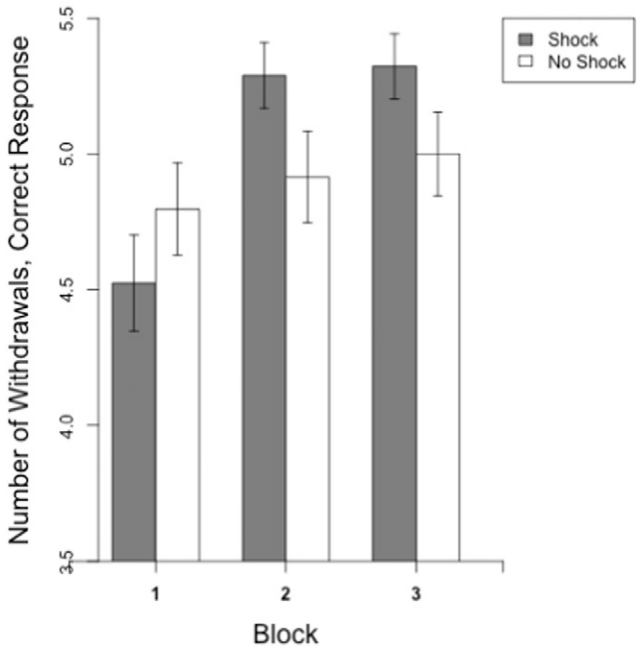

Fig. 3. Correct finger withdrawals in response to the avoidance cue as a function of threat condition (shock vs. no shock) and block. Withdrawals during the avoidance cue were more frequent during the shock condition, but only during blocks 2 and 3.

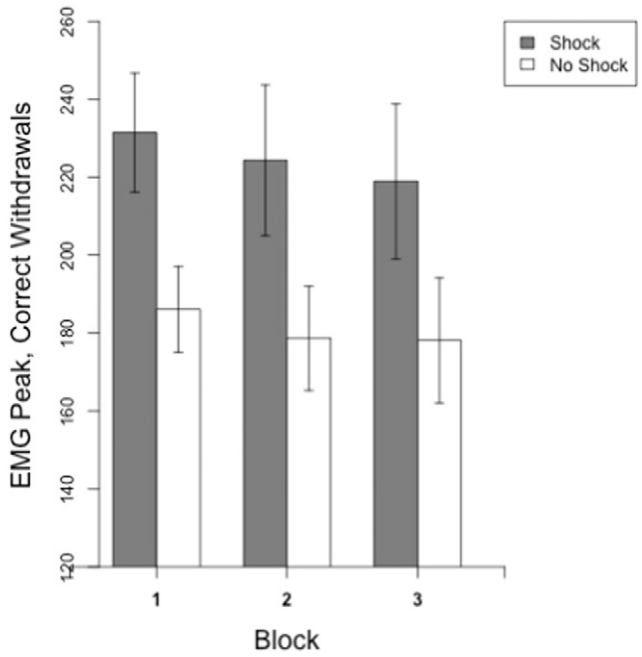

Fig. 5. EMG peak amplitude responses during withdrawals in response to the avoidance cue as a function of threat condition (shock vs. no shock) and block. EMG responses were elevated during the shock condition consistently across all three blocks.

3.2. PCA analysis and integrated patterns of responding to threat

Our measure of sampling adequacy from the PCA (Kaiser-Meyer-Olkin = 0.562) was >0.5, suggesting that our data meets the minimum criteria for PCA. The first and second components accounted for 29.11% and 24.18% of the total variance, respectively, and had eigenvalues >1.

The first principal component loaded onto increased SCRs during avoidance cues, reaction times, EMG responses, and increased withdrawal during non-avoidance cues (Fig. 9 A, Table 1). Individual differences in factor scores associated with this principal component were positively correlated with the change in state anxiety between the shock condition and baseline ($\beta = 0.024$, $p < 0.05$, $\Delta R^2 = 0.101$). (Fig. 10).

The second principal component loaded differentially onto increased withdrawal and quicker reaction times during avoidance cues, versus increased SCRs during avoidance cues and increased salivary alpha-amylase (Fig. 9 B, Table 1). Individual differences in factor scores

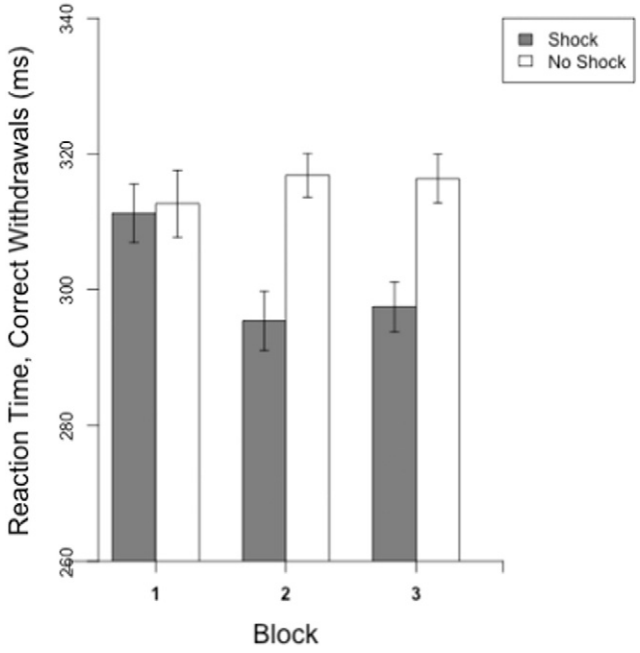

Fig. 4. Reaction times during withdrawals in response to the avoidance cue as a function of threat condition (shock vs. no shock) and block. Reaction times were faster during the shock condition, but only during blocks 2 and 3.

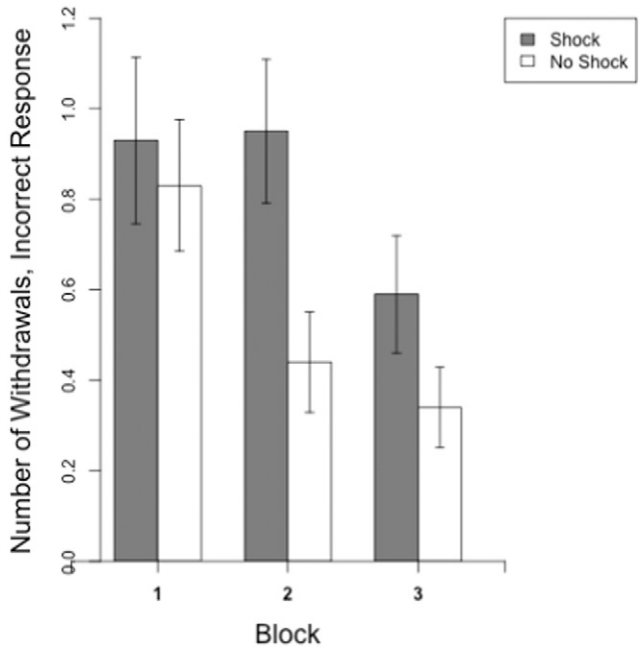

Fig. 6. Incorrect finger withdrawals during the absence of the avoidance cue as a function of threat condition (shock vs. no shock) and block. Withdrawals during the absence of the avoidance cue were more frequent during the shock condition across all three blocks.

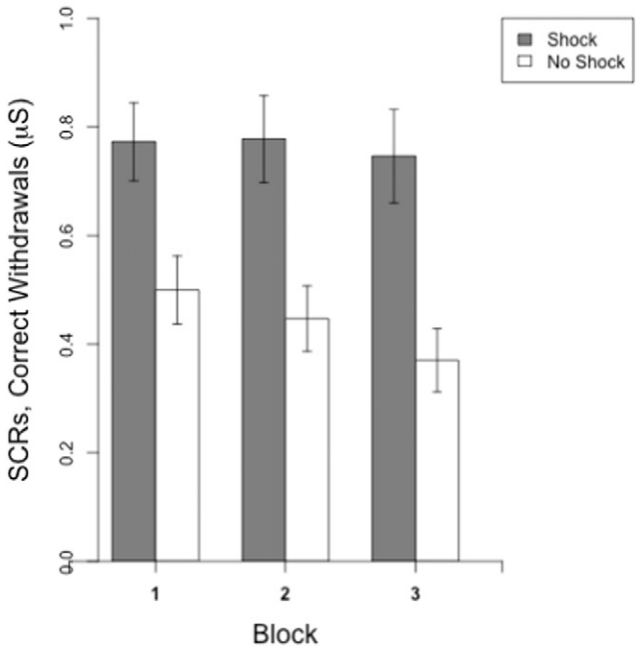

Fig. 7. Skin conductance responses to the avoidance cue as a function of threat condition (shock vs. no shock) and block. Skin conductance responses to the avoidance cue were more frequent during the shock condition across all three blocks.

associated with this principal component were not associated with changes in state anxiety ($p = 0.62$).

3.3. Effects of sex and trait personality

Sex was not associated with factor scores associated with either the first principal component reflecting general emotional responsiveness or second principal component reflecting proactive vs. reactive coping style (all p's > 0.1).

Although there were no main effects of trait anxiety, impulsivity, or aggression on scores from either principal component, trait aggression interacted with sex to predict variability in the second component ($\beta = 0.09$, $p < 0.05$, $\Delta R^2 = 0.087$) with higher trait aggression associated with lower factor scores in men ($\beta = -0.07$, $p = 0.013$) but not women ($\beta = 0.02$, $p = 0.433$) (Fig. 11).

There was also a trend toward an interaction between sex and trait anxiety predicting scores from the first component ($\beta = -0.06$, $p = 0.066$, $\Delta R^2 = 0.059$) with higher trait anxiety associated with higher factor scores in men ($\beta = 0.05$, $p = 0.046$) but not women ($\beta = -0.01$, $p = 0.569$).

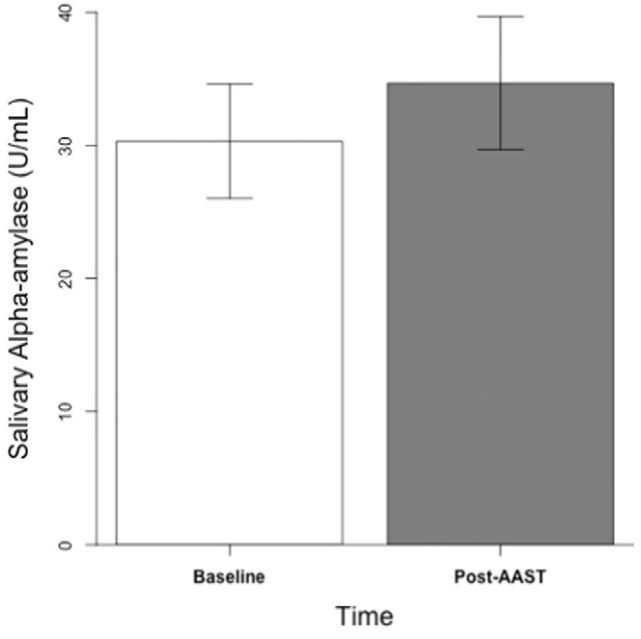

Fig. 8. Salivary alpha-amylase at baseline (before the AAST) and following exposure to threat (after the AAST) illustrating a trend toward an increase in salivary alpha-amylase as a function of the task.

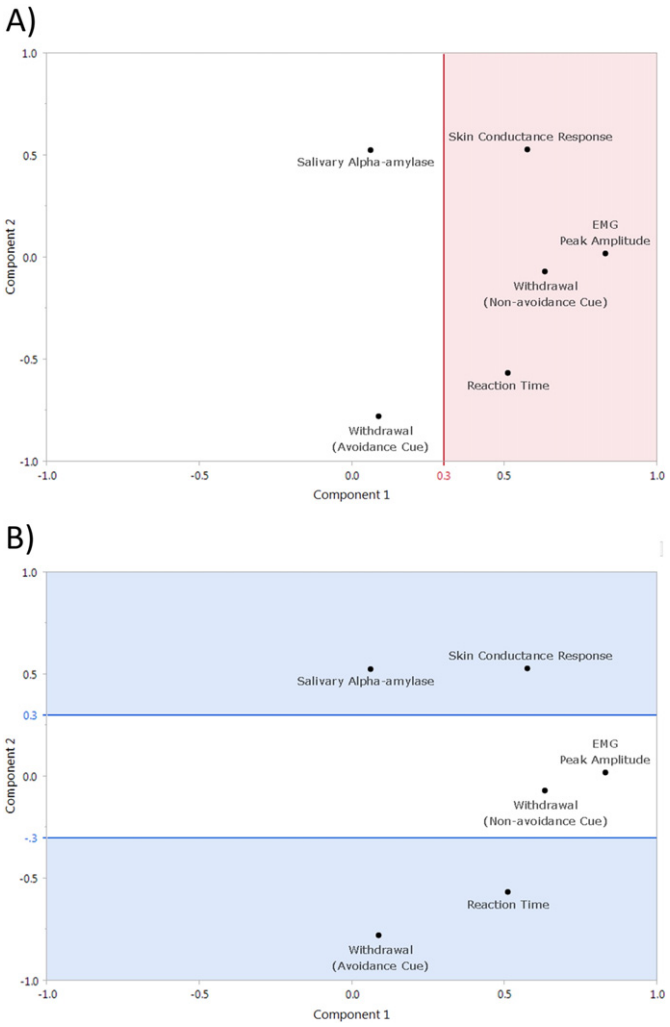

Fig. 9. Factor loadings onto principal components characterizing individual differences during AAST performance. A) Measures significantly loading onto principal component 1 are within the red shaded area; B) Measures which differentially load onto principal component 2 are in the respective areas shaded in blue.

Table 1
Factor loading onto principal components characterizing individual differences during AAST performance.

	Principal component 1	Principal component 2
Skin conductance responses	0.577[a]	0.528[a]
Salivary alpha-amylase	0.060	0.528[a]
Withdrawal (avoidance cue)	0.090	−0.780[a]
Reaction time	0.511[a]	−0.566[a]
EMG peak amplitude	0.834[a]	0.015
Withdrawal (non-avoidance cue)	0.634[a]	−0.071

[a] Values > 0.3 are considered to load significantly onto principal components.

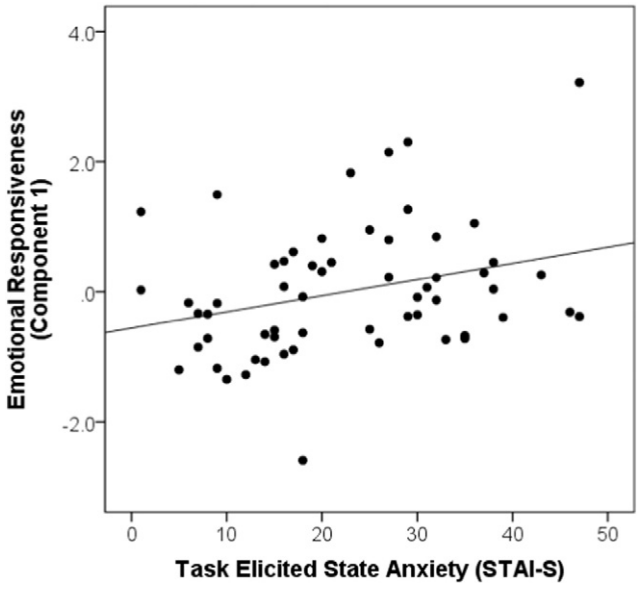

Fig. 10. Relationship between increased state anxiety during the AAST and factor scores associated with the first principal component capturing generalized facilitation in threat responsiveness across measures.

No other interactions between trait personality and sex approached significance.

4. Discussion

Using a novel human active avoidance paradigm, our results demonstrate that individuals differ in their level of emotional responsiveness, the magnitude of their threat response generally, and in their coping style – specifically, the likelihood of exhibiting proactive or reactive responses to threat. Additionally, our results demonstrate that sex and trait personality are important predictors of these individual differences, with higher trait anxiety associated with larger emotional responsiveness, and higher trait aggression associated with more proactive and less reactive responses. Notably, these associations were only observed in men and not women. Prior research suggests that

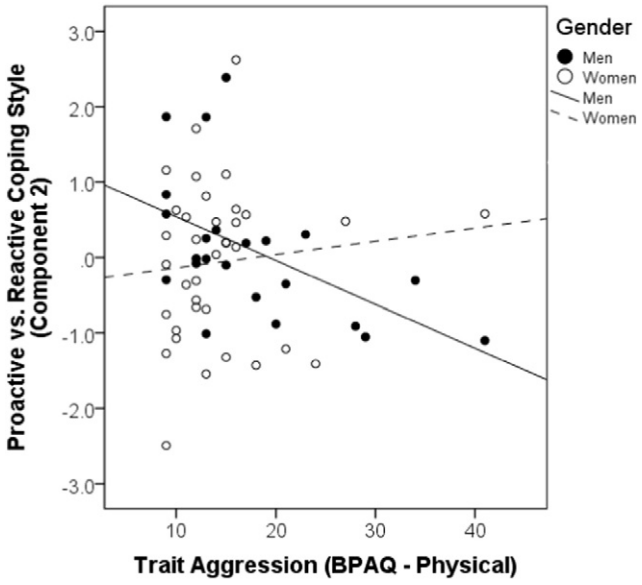

Fig. 11. Relationship between trait aggression and factor scores associated with the second principal component capturing trade-offs between proactive and reactive responses as a function of sex.

patterns of how animals respond to threat represent different styles of coping with environmental challenges, and that animals with proactive coping styles are relatively resilient to adversity [33,47]. Our results suggest that variability in coping style can be observed during instructed active avoidance, and it is possible that these differences in coping style are related to risk for the development of mood and anxiety disorders.

Our strategy to submit multiple measures of threat responsiveness to a PCA produced two complimentary factors that capture individual differences in general emotional responsiveness as well as trade-offs between proactive and reactive responses. The first principal component was associated with increased finger withdrawals during the absence of the avoidance cue, faster reaction times, larger EMG responses, and increased SCRs. Tellingly, increased state anxiety during the shock condition was positively correlated with factor scores from this component. This pattern is consistent with broad increases in threat responsiveness across domains and suggests that shared variability in the magnitude of these responses may represent an index of general emotional responsiveness, which serve a preparatory function and help facilitate behavioral actions [24,37]. Moreover, the pattern associated with our first principal component is consistent with prior studies finding that rats bred for high and low levels of performance during active avoidance differ in their level of emotional responsiveness [54]. Trait anxiety – which reflects the general tendency to perceive stimuli and situations as threatening and experience subjective feelings of apprehension – was positively correlated with factor scores on this first principal component. However, this association was present only in men. This pattern suggests that while both men and women experience higher state anxiety under threat, the general tendency to experience anxiety manifests as greater threat responsiveness in men only.

The second principal component dissociated increased finger withdrawals and faster reaction times during avoidance cues from increased SCRs during the threat condition and heightened salivary alpha-amylase concentrations following the AAST. Thus, individual differences in factor scores on this second principal component likely capture a trade-off between proactive and reactive responses with lower scores indicative of the former and higher scores the latter. Prior work in animal models suggests that during instrumental avoidance, instrumental memories resulting in avoidance compete with Pavlovian memories resulting in freezing [42]. Our current findings suggest that this competition may not be limited to instrumental and Pavlovian responses but extends to proactive and reactive responses to cognitively-instructed threats as well.

Importantly, the variance in salivary alpha-amylase, which is inversely associated with proactive responding, overlaps with the variance in SCRs. Consequently, this shared variance likely reflects sympathetic autonomic responses to threat. These results suggest that in addition to freezing behavior, sympathetic autonomic responses can function as indices of reactive responses to threat during active avoidance. Though freezing responses and phasic sympathetic activity are different types of reactions and are proximally supported by distinct neural structures [2,8], the inverse relationship between these reactive responses and active avoidance behavior may reflect the upstream role of the central nucleus of the amygdala [48]. Prior research suggests that the central nucleus of the amygdala supports freezing behaviors during active avoidance [42] in addition to supporting phasic changes in skin conductance [35]. Research in humans demonstrates that the amygdala supports SCRs during instructed fear [46], and individual variability along the principal component associated with proactive vs. reactive responses in our analyses may reflect the relative contributions of the central nucleus of the amygdala, which likely drives reactive autonomic responses.

The use of sympathetic autonomic responses to assess reactive responses to threat is further notable in considering the relationship between trait aggression and the likelihood of expressing proactive vs. reactive responses. Previous research has demonstrated that aggressive

animals exhibit higher plasma noradrenaline following social defeat and have higher resting blood pressure [23,33,34]. Likewise, aggression in humans is linked to cardiovascular disease risk, and it has been suggested that this reflects increased sympathetic autonomic activity [40,45]. Our results, however, suggest that heightened trait aggression is associated with more proactive and less reactive responses to threat, which is linked to lower sympathetic activity. It is possible this discrepancy stems from a lack of clarity regarding the assessment of tonic vs. phasic responses or the type of stressor used to assess sympathetic activity. Our paradigm assessed phasic sympathetic activity during avoidable threatening stimuli, and it is possible that the relationship observed here is primarily driven by heightened avoidance behavior in those with high trait aggression, leading to reduced sympathetic responses. As was true for the association between trait anxiety and factor scores on the first principal component representing threat responsiveness broadly, the associations between trait aggression and scores on the second principal component reflecting the trade-off between proactive and reactive responses was present only in men. Men exhibit higher levels of physical aggression than women [3], and this may reflect an increased disposition to manipulate the environment through proactive responses.

Our study is not without limitations. First, from a theoretical perspective, instrumental avoidance is a complex phenomenon as learning is thought to occur on trials when the aversive outcome is omitted and there is still debate over whether animals learn to avoid the shock or learn to approach safety [11,30]. Our study utilized instructed avoidance, in that participants were informed about experimental contingencies. However it is possible that other forms of learning took place. On trials during which participants failed to retract their finger and received a shock, the aversive stimulus was always preceded by the avoidance cue. Further, successful finger withdrawal always led to omission of the shock. As such, we cannot rule out the possibility that stimulus-stimulus or response-outcome learning occurred during our instructed avoidance paradigm.

Moreover, although the behavioral response itself (i.e., finger withdrawal) was acquired via instruction, evidence suggests that the facilitation of these responses during threat (i.e., increased accuracy and faster reaction times) only emerged in the second and third blocks of the experiment. Surprisingly, although previous research has demonstrated that freezing responses and SCRs to avoidance cues decrease after the instrumental response is acquired [15,57] we observed no such reduction in SCR over time. One potential explanation for this discrepancy is that aversive instrumental paradigms measure the learning of an avoidance response, while the AAST measures the performance of active avoidance. Future research, which is specifically designed to disentangle these interrelated processes, will be needed to address the learning and motivational mechanisms underlying the effects we observed with the AAST.

Second, the measurement of finger withdrawal as a proactive response to threat may limit the ability of our results to address how threat impacts more elaborate forms of proactive behavior. In order to mitigate threat exposure, humans at times engage in proactive responses that require sequential actions and fine motor skills, such as seeking safety behind a door by unlocking it with a key. Although our results demonstrate that withdrawal to auditory stimuli is enhanced during the shock condition, it is possible that threat would impair fine motor movements or the ability to engage in planned action sequences. Future research will be required to identify how specific features of the environment and action plans impact the dynamics between threat exposure and proactive responses to threat.

Third, although within the context of avoidance paradigms proactive responses terminate aversive outcomes while reactive responses do not, it is doubtful that proactive responses are more adaptive in all situations. Researchers have suggested that proactive responses are more adaptive in stable environments, while reactive responses are more adaptive in changing environments [51]. Notably, it has been suggested that effective active avoidance depends on accurate representations of CS-US contingencies [4], which may be lacking in unstable environments. As such, it would be premature to characterize either proactive or reactive responses as preferable in all situations.

Lastly, although prior work has reported links between heritable behavioral traits and active avoidance behavior in male but not female animals [7,39,53], it is unclear what may be driving the effects of sex on the AAST. We did not observe sex differences in factor scores associated with emotional responsiveness and coping style. However, sex interacted with trait personality, such that trait anxiety was positively related to general emotional responsiveness, while trait aggression was related to proactive vs. reactive coping style only in men. One potential explanation is that associations between trait anxiety and a given behavior depend on the congruence between the threatening situation and the facet of anxiety being measured [21]. For example, previous research has shown that a subcomponent of anxiety related to physical danger predicts increased state anxiety during parachute training, but not during a social evaluative situation [20]. The STAI-T assesses symptoms of anxiety (e.g., "I have disturbing thoughts" and "I feel nervous and restless") but not the source of that anxiety. It is possible that higher scores on the STAI-T in men map onto anxiety in response to situations and stimuli congruent with our paradigm (e.g., physical danger), while women do not. Additionally, male gender roles allow for the greater expression of aggressive behavior [49] and it is possible that as a consequence, the BPAQ physical subscale is a more effective indicator of aggression in men. Future studies with larger sample sizes and more refined personality instruments will be needed to unpack the mechanisms driving these effects.

These limitations notwithstanding, our results are the first to suggest that variability in coping style can be observed during instructed avoidance in human participants, and that trade-offs between proactive and reactive responses are associated with stable measures of trait personality in men. Variability in active avoidance behavior has been linked to susceptibility to stress [47], and researchers have suggested that proactive behaviors may aid those suffering from mood disorders in coping with threatening stimuli [36]. Our work can serve as a starting point for research investigating whether variability in active avoidance is related to risk for psychopathology and can inform future treatment strategies employing proactive responses to threat.

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