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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