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Stress, aggression, and the balance of approach and avoidance

Susanne Vogel*, Lars Schwabe

Department of Cognitive Psychology, Institute of Psychology, University of Hamburg, Von-Melle-Park 5, 20146, Hamburg, Germany

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ABSTRACT

Stress is a well-established risk factor for many mental disorders including anxiety disorders or substance abuse. A hallmark of these disorders is an imbalance between behavioral approach and avoidance in situations with approach-avoidance conflicts and unclear outcomes. However, if and how stress affects human behavior in approach-avoidance conflicts is largely unknown. To investigate the effects of stress on approach-avoidance behavior, 80 participants underwent a stress or control manipulation before performing an approach-avoidance conflict task. Stress markedly increased behavioral inhibition when threats were distant and accelerated responses when threats were close; suggesting that stress amplifies the importance of threat distance. However, participants high in trait aggression showed increased approach behavior, particularly when stressed. These findings indicate that stress generally leads to enhanced avoidance, but induces approach in individuals prone to aggression, with important implications for stress-related psychopathologies.

1. Introduction

Approaching positive stimuli and avoiding negative, potentially dangerous stimuli is a natural and evolutionary highly conserved behavioral tendency in humans and other animals (Chen and Bargh, 1999; Lewin, 1935). Many situations, however, contain both positive and negative stimuli with uncertainty about the resulting outcome, inducing conflicts between approach and avoidance (Lewin, 1935; Miller, 1944). For instance, you may have mixed feelings about taking a timesaving shortcut through the dark park at night rather than walking the much longer but brightly illuminated road. A disturbance of the delicate balance between approach and avoidance is a hallmark of several mental disorders. For example, anxiety disorders and trauma-related disorders are characterized and maintained by excessive avoidance even for non-threatening stimuli (Forbes et al., 2014; Gray and McNaughton, 2000). In contrast, patients suffering from substance use disorder or excessive aggression show markedly increased approach to stimuli that are potentially dangerous or harmful (von Borries et al., 2012; Wiers et al., 2014). Despite the high potential relevance for basic science and the clinic, factors modulating human behavior in approach-avoidance conflicts are largely unknown.

In healthy individuals, conflicts between approach and avoidance are tracked and resolved by the anterior hippocampus and the anterior or ventromedial prefrontal cortex (PFC; Bach et al., 2014; Volman et al., 2011). The amygdala, in contrast, plays a key role in mediating avoidance behavior in approach-avoidance conflicts (Korn et al., 2017). Stress not only plays a critical role in the development and maintenance of many of the aforementioned mental disorders (e.g., Shin and Liberzon, 2010), it also has a major impact on these brain regions involved in approach-avoidance conflicts (McEwen et al., 2016). Stress can be understood as the ‘perception of uncontrollability and/or unpredictability that is expressed in a physiological and behavioral response’ (Koolhaas et al., 2011, p. 1292), for instance by showing feelings of distress accompanied by activation of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal axis (HPA), resulting in the release of cortisol. Preliminary evidence in rodents, human infants, and patients with social anxiety disorder suggests that individuals with higher release of the stress hormone cortisol display increased avoidance (Buss et al., 2003; Cavigelli et al., 2007; Roelofs et al., 2009). However, to date it is unclear if and how stress affects behavior in situations with approach-avoidance conflicts, when the appropriate response is unclear and there is uncertainty about the outcome.

When studying the impact of stress on approach-avoidance conflicts, it is important to note that the behavior displayed in these situations heavily depends on threat distance (Blanchard and Blanchard, 1990; Miller, 1944) and threat level (e.g., Khemka et al., 2017). For instance, when threats are distant, the behavioral response is characterized by attentive freezing and behavioral inhibition, i.e., passive avoidance. However, with decreasing threat distance, flight becomes more likely, which is referred to as active avoidance (Löw et al., 2015; McNaughton and Corr, 2004; Wendt et al., 2017). Moreover, it has been

* Corresponding author. Present address: MSH Medical School Hamburg, Am Kaiserkai 1, 20457, Hamburg, Germany.
E-mail addresses: Susanne.vogel@medicalschool-hamburg.de (S. Vogel), schwabe@uni-hamburg.de (L. Schwabe).

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suggested that there are considerable individual differences in approach-avoidance behavior that might be driven by personality traits such as anxiety, harm avoidance, or related traits associated with avoidance (e.g., Cloninger, 1987) or aggression and novelty seeking related to more approach (Cloninger, 1987; Haller et al., 2014). Thus, we aimed to investigate the effects of acute stress, trait aggression, and anxiety on behavior in approach-avoidance conflicts, depending on threat distance and threat level.

To investigate the effect of acute stress on human behavior in approach-avoidance conflicts, 80 healthy individuals underwent either a stress induction procedure (Trier Social Stress Test, TSST, Kirschbaum et al., 1993) or a non-stressful control manipulation. Afterwards, participants completed a recently developed computerized approach-avoidance conflict task (Bach et al., 2014) in which they moved a player to collect monetary tokens (approach motivation). Importantly, they were under threat of virtual predators who could awake and chase them to steal the points collected in that trial (avoidance motivation). Critically, this task allowed us to assess the effects of stress depending on threat level (manipulated by using two predators with different wake-up probabilities) and threat distance (manipulated by varying the starting locations of player and predator). Based on preliminary evidence involving cortisol in avoidance behavior (Buss et al., 2003; Roelofs et al., 2009), we hypothesized that stress might increase avoidance in approach-avoidance conflicts, possibly depending on threat distance and threat level, and that this effect may be moderated by trait anxiety and aggression.

2. Material and methods

2.1. Participants

Eighty healthy individuals with normal or corrected-to-normal vision and normal body weight (19 ≤ body mass index, BMI ≤ 29) completed this experiment (40 men, 40 women, mean age 25.0 years, SD: 3.79 years). Three additional participants (all female) stopped participation before or during stress induction and were replaced to obtain the a-priori planned sample size of n = 80. The intended sample size was chosen in accordance with previous studies on stress effects on human behavior (e.g., Vogel and Schwabe, 2016; Wirkner et al., 2013) and studies employing the approach-avoidance conflict task (Bach et al., 2014), while also having adequate power of approximately 80% to find a medium-sized correlation (r = .30) with personality traits (Faul et al., 2009).

Individuals with current medication intake or any past or current medical condition potentially affecting stress reactivity were excluded from participation during a telephone screening. We also excluded smokers and women using hormonal contraceptives as both smoking and hormonal contraceptives affect cortisol release (Kirschbaum et al., 1999; Rohleder and Kirschbaum, 2006). Furthermore, women were not tested during their menses. The study protocol was approved by the institutional review board of the University of Hamburg (Vogel II, 08 2015). All participants provided written informed consent and received monetary compensation for participation (16.50 €, approximately 20 USD).

We used a mixed design with the between subjects factor treatment (stress/control) and the within subjects factors initial threat distance, threat level, and task block (see 2.3) to investigate the impact of stress on behavior in approach-avoidance conflicts depending on threat distance and threat level. Participants were pseudo-randomly assigned to the stress or control group while balancing for gender and ensuring that all participants in the stress group were naïve to the stress protocol. The resulting groups did not differ in age ($p =$ .815), BMI ($p =$ .139), trait anxiety ($p =$ .950), depressive symptoms ($p =$ .434), or self-reported aggression (all scales $p \geq$ .065, Table S1).

2.2. Experimental procedure

All participants were tested between 12:30 and 19:30 to control for the diurnal rhythm of the stress hormone cortisol. Participants were instructed not to do sports, eat, or drink anything but water for two hours before testing.

Upon their arrival at the laboratory, participants' vital signs (blood pressure, heart rate) were assessed using a Dinamap system (Critikon) and they provided a baseline saliva sample (see 2.4). They also answered a German mood questionnaire assessing subjective mood (elevated vs. low), wakefulness, and restlessness (MDBF; Steyer et al., 1994). Next, they filled in questionnaires assessing state and trait anxiety (German version of the Spielberger State-Trait Anxiety Inventory; Laux et al., 1981), self-reported physical and verbal aggression, anger, and distrust (German aggression questionnaire; Werner and von Collani, 2014), and depressive symptoms (German version of Beck Depression Inventory; Hautzinger et al., 1994). Participants were then brought to a separate room to undergo either the TSST (Kirschbaum et al., 1993) or a non-stressful control procedure of comparable duration. The TSST is a standardized stress induction protocol for humans, leading to robust subjective, autonomous, and endocrine stress responses. It combines unpredictability and socio-evaluative threat with a cognitive task and has been shown to result in reliable stress responses in most participants (Dickerson and Kemeny, 2004). In brief, the TSST simulated a job interview and encompassed a 3-minute preparation phase, a 5-minute public speech about the participant's aptitude for his/her favorite job, and a 5-minute difficult mental-arithmetic task (counting backwards from 2043 in steps of 17). Throughout the TSST, participants were videotaped and evaluated by two neutral, non-reinforcing committee members in white laboratory coats. Participants in the control condition were not evaluated or videotaped and spoke about a topic of their choice, followed by an easy arithmetic task (counting forwards in steps of 10). In participants of both groups, vital signs were assessed once at the beginning of the mental arithmetic task to assess the immediate treatment effect on autonomic reactivity.

After the stress induction or control procedure, participants were guided back to the laboratory and their vital signs and subjective mood were assessed again. Participants also provided a saliva sample and rated the difficulty, unpleasantness, and stressfulness of the stress induction/control procedure on three scales from 0 ('not at all') to 100 ('very much'). They were then instructed about the approach-avoidance task and started the task approximately ten minutes after the offset of the TSST/control procedure. Another saliva sample was taken after the first block of the task, approximately ten minutes after task onset. After task completion, participants provided another vital signs assessment, mood rating, and saliva sample, and were debriefed about the study procedures.

2.3. Approach-Avoidance conflict task

To assess the effect of stress on behavior in approach-avoidance conflicts depending on threat distance and level, we adapted a task from Bach et al. (2014), programmed using Pygame 1.9.2 for Python 3.2.5. This computerized task is based on animal paradigms and allows the assessment of human behavior in approach-avoidance conflicts (Bach et al., 2014; Korn et al., 2017). Moreover, approach-avoidance conflicts in this task have been related to activity in the anterior hippocampus, amygdala and the vmPFC (Bach et al., 2014; Khemka et al., 2017; Korn et al., 2017) which are known to be sensitive to stress (McEwen et al., 2016).

On each trial, participants, shown as green triangle (Fig. 1), navigated in a 24 × 16 grid presented on a standard computer monitor. Participants were instructed to collect as many tokens (yellow diamonds) as possible and that the number of tokens collected would relate to monetary rewards (in fact, all participants received a bonus of € 1.50 on top of the € 15 mentioned initially on the informed consent).

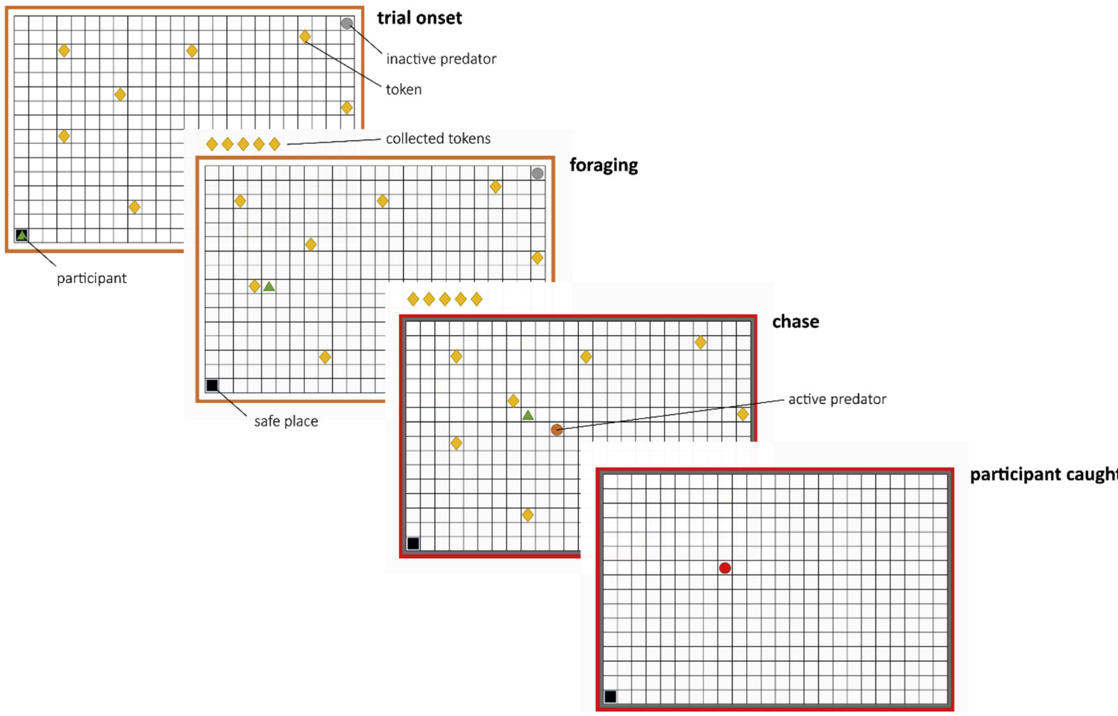

Fig. 1. Task setup, adapted from (Bach et al., 2014). Participants (green triangle) were instructed to collect as many tokens (yellow diamonds) as possible. The presence of a latent threat was indicated by a 'sleeping' predator (grey circle) and a colored frame. There were two possible predators (orange and purple) with different wake up probabilities (60% and 20%), resulting in high and low threat, respectively. In 50% of the trials, participants started in the same location as the predator ('active' condition), in the other trials, participants started in the 'safe place' far from the predator, indicated by a black square ('passive' condition). In the foraging phase, participants tried to collect as many tokens as possible. Collected tokens were displayed on top of the screen. If the predator woke up, it took on its true color and chased the participant at high speed. If the participant was caught, all tokens from that trial were lost. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Although previous studies used a performance-dependent reward based on ten randomly drawn trials (Bach et al., 2014, 2018; Korn et al., 2017), this difference was not apparent to the participants and is thus unlikely to have impacted their behavior during the task. A grey circle depicted the presence of an inactive threat, which started either in the same position as the participant (short distance to threat, 50% of trials) or in the opposite corner (long distance to threat). Trials, in which the predator is initially close engage active avoidance at first to escape the threatening position (thus termed 'active avoidance'), and passive avoidance later on to stay away from the predator (Bach et al., 2014). In contrast, trials with (initially) long distance to threat involve mainly passive avoidance to stay away from threat (thus termed 'passive avoidance').

Threat level was manipulated by using two differently colored predators, which were either highly dangerous (high threat, 60% wake-up probability, 50% of trials) or less dangerous (low threat, 20% wake-up probability). The identity of the predator (orange or purple) was shown by the colored outer frame of the grid; the relationship between predator color and threat level was randomized across participants and not instructed explicitly. Whereas some previous studies employed three threat levels (Bach et al., 2014; Khemka et al., 2017; Korn et al., 2017), we decided to use only low and high threat as behavior was often comparable for low and medium levels of threat in previous studies.

To collect tokens, participants moved using the arrow keys and increased speed by continuous pressing to reach the maximum speed of eight blocks/s. If the player moved over a token, the token disappeared from the grid, was added to the row above the grid, and replaced by a new token in the grid. Independent of token collection, every two seconds one of the tokens randomly changed position. The predator could awake 6, 7.5, 9, 10.5, 12, 13.5, or 15 s after trial onset. These wake-up times were counterbalanced such that the average time (and its SD) to collect tokens before the predator woke up or the trial ended (in case the predator did not wake up) were of equal duration across both predators. If the predator woke up, the outer frame turned red, the predator took on its true color, and chased the participant with a speed of 20 blocks/s. If the participant was caught, the green triangle disappeared, the predator turned red, all tokens disappeared, and all tokens collected in that trial were lost (avoidance motivation). To avoid the predator, participants could enter a 'safe place' (black square) which was always opposite to the starting position of the predator. However, as the predator moved at least 2.5 times faster, escape was only possible if participants were close to the safe place when the predator awoke. Previous studies showed that participants adaptively retract to the safe quadrant and collect tokens in the proximity of the safe place as time-in-trial increases to avoid losing the tokens collected thus far (Bach et al., 2014, 2018; Korn et al., 2017).

Three and a half seconds after the predator awoke, the trial ended independently of whether the participant was caught or not. If the predator did not awake, trial duration was 6, 7.5, 9, 10.5, 12, 13.5, or 15 s. After a short inter-trial-interval of 0.5 s showing a white fixation cross on a black background, the next trial started. The task was presented in four blocks of 40 trials each (20 per predator), separated by self-paced breaks in which the total number of collected tokens was displayed. After task completion, participants were asked to estimate wake-up probabilities for both predators in a questionnaire.

2.4. Saliva sampling

Over the course of the experiment, each participant provided four saliva samples using Salivettes® (Sarstedt) to assess cortisol concentrations. At the end of the experiment, samples were frozen and stored at −18 °C (−0.4 °F). After study completion, all samples were thawed and the fraction of free cortisol was assessed using a commercially available

Table 1
Subjective mood ratings and evaluation of the stress induction/control procedures in both groups.

	control group			stress group		
	start of experiment	after control treatment	end of experiment	start of experiment	after stress induction	end of experiment
subjective mood	34.1 [32.68, 35.57]	34.0** [32.54, 35.41]	33.4 [31.81, 34.99]	33.8 [32.51, 34.99]	30.7 [28.67, 32.73]	34.0 [32.62, 35.43]
calmness	32.5 [30.75, 34.20]	32.4** [30.68, 34.17]	33.2 [31.57, 34.78]	32.9 [31.42, 34.38]	28.3 [26.22, 30.38]	32.2 [30.44, 34.01]
wakefulness	31.3 [29.68, 32.82]	30.6 [28.76, 32.34]	28.8 [26.76, 30.74]	30.4 [28.70, 32.10]	30.6 [28.57, 32.58]	28.0 [26.01, 30.04]
evaluation of treatment	difficult	unpleasant	stressful	difficult	unpleasant	stressful
	24.3*** [18.65, 29.85]	30.8*** [22.17, 39.33]	27.3*** [20.73, 33.77]	66.3 [59.78, 72.72]	66.0 [57.78, 74.22]	61.0 [54.10, 67.90]

Note. Values represent mean [95% CI], higher values represent elevated mood, more calmness, and more wakefulness.
*** $p < .001$ compared to stress group.
** $p < .01$ compared to stress group.

chemiluminescence immunoassay (IBL, Tecan Group, Switzerland). All intra- and inter-assay coefficients of variance were < 8%, respectively. One sample (stress group, third sample) did not contain sufficient saliva and was replaced using linear regression over all participants.

2.5. Statistical analysis

To test for successful stress induction in the stress group, subjective and physiological data (heart rate, blood pressure, cortisol levels) were analyzed using repeated measures analyses of variance (rmANOVAs) with the between-subjects factor treatment and the within-subject factor time. Holmes-Bonferroni correction was applied to correct for 10 variables assessing stress reactivity. Please note that uncorrected *p*-values are reported. T-tests were used as post-hoc tests and to investigate group differences in control variables (e.g., age or BMI) and the ratings of the TSST/control manipulation.

RmANOVAs with the within-subject factors threat level (low vs. high), initial threat distance (active vs. passive condition), and block, and the between-subjects factor treatment were used to investigate the effect of stress on approach and avoidance behavior indicated by the dependent variables time to approach (foraging latency prior to predator awakening), percentage of failed avoidance per block (participant caught), and sum of tokens collected per non-caught trial. Holmes-Bonferroni correction was used to correct for three measures of task performance. Note that previous studies using this paradigm also investigated seven outcome variables over time-in-trial (e.g. proportion of presence in the safe quadrant, Bach et al., 2014, 2018; Korn et al., 2017). We focused on three summary measures per trial, which were introduced in recent studies (Bach et al., 2018; Korn et al., 2017). For completeness, the analyses concerning outcome variables over time-in-trial are reported in the supplement.

Another rmANOVA with the factors threat level and treatment investigated possible stress effects on predator awareness (indicated wake-up probabilities). To test exploratively whether cortisol reactivity was associated with task performance variables, we calculated the baseline-to-peak difference in cortisol reactivity, as this measure most closely relates to cortisol reactivity (Miller et al., 2018). Pearson product-moment correlations were used to assess the relationship between cortisol reactivity and approach-avoidance behavior.

To assess the influence of personality traits (anxiety and aggression) on the number of tokens collected, we calculated Pearson correlation coefficients, followed by Z tests to investigate potential group differences in correlations. To assess formally whether stress and personality traits interacted to alter behavior in approach-avoidance conflicts while also controlling for potential confounders (e.g., age, gender, average walking speed), we implemented linear regression models to predict the total number of tokens collected. Walking speed was assessed in blocks/s averaged across the whole trial. We implemented a stepwise approach with first adding (again, stepwise) participants' age, sex, and average walking speed. In the next step, all predictors of interest were included, i.e., treatment group, trait anxiety, physical aggression, verbal aggression, anger, distrust, all mean-centered, and the interaction of these five variables with treatment group. We also added depressive symptom scores as predictor to exclude that the influence of trait anxiety might be driven by heightened levels of depressive symptomatology.

All analyses were conducted using IBM SPSS Statistics 24 (IBM, NY). The alpha level (before multiple comparison correction) was set to 0.05 for all analyses (two-tailed), and Greenhouse-Geisser correction was used to correct for violations of sphericity (corrected df reported).

3. Results

3.1. Successful stress induction prior to the approach-avoidance conflict task

As expected, the TSST resulted in a pronounced subjective, physiological, and endocrine stress response. Subjectively, the TSST was experienced as significantly more difficult, unpleasant, and stressful than the control procedure (all $p < .001$, Table 1). Moreover, stress decreased positive mood (time × treatment $F(1.9, 149.2) = 8.39$, $p < .001$, $\eta_P^2 = .097$, Table 1) and increased restlessness (time × treatment $F(1.9, 148.1) = 8.57$, $p < .001$, $\eta_P^2 = .099$) leading to lower mood ($p = .009$) and higher restlessness ($p = .003$) in the stress group compared to the control group directly after the TSST but not prior to treatment or at the end of the experiment (all $p \geq .40$). In line with previous studies from our lab using the TSST (Vogel et al., 2018; Vogel and Schwabe, 2016), stress did not affect self-reported wakefulness (all $p \geq .50$).

Moreover, the stress group showed a marked increase in blood pressure (BP) and heart rate (HR), indicating an activation of the ANS (systolic BP: time × treatment $F(2.9, 224.8) = 42.28$, $p < .001$, $\eta_P^2 = .352$, treatment $F(1, 78) = 19.15$, $p < .001$, $\eta_P^2 = .197$; diastolic BP: time × treatment $F(2.5, 193.5) = 69.77$, $p < .001$, $\eta_P^2 = .472$, treatment $F(1, 78) = 27.24$, $p < .001$, $\eta_P^2 = .259$, HR: time × treatment $F(1.8, 140.2) = 32.49$, $p < .001$, $\eta_P^2 = .294$, treatment $F(1, 78) = 7.53$, $p = .008$, $\eta_P^2 = .088$, Fig. 2A–C). Whereas treatment groups did not differ before the TSST/control procedure (systolic BP: $p = .223$, diastolic: $p = .078$, heart rate: $p = .444$), the stress group showed elevated BP and HR compared to the control group during the TSST (all $p < .001$) and directly thereafter (BP both $p < .001$, HR $p = .020$). At the end of the experiment, the stress group still showed elevated systolic BP ($p = .048$), while diastolic BP and HR had already returned to levels comparable to the control group ($p = .297$ and $p = .078$, respectively). Finally, a profound activation of the HPA axis in response to the TSST was indicated by elevated cortisol levels in the stress group compared to the control group (time × treatment $F(1.4, 111.8) = 10.23$, $p < .001$, $\eta_P^2 = .116$, treatment $F(1, 78) = 10.84$, $p = .001$, $\eta_P^2 = .122$, Fig. 2D). Accordingly, the stress group showed increased cortisol levels directly after the TSST ($p = .023$), prior to the approach-avoidance conflict task ($p < .001$), and after task completion ($p = .001$), whereas groups did not differ at the

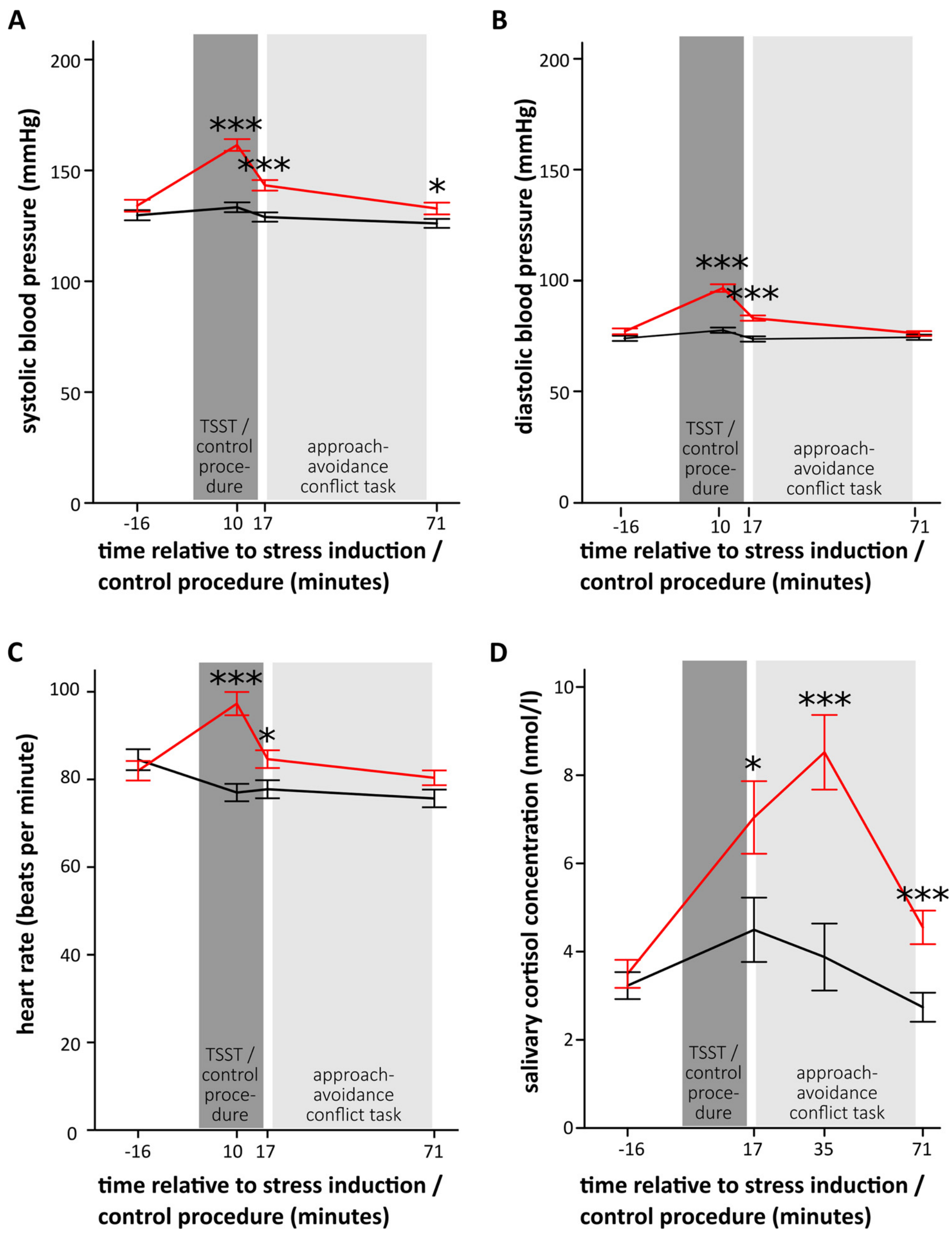

Fig. 2. Results of the stress induction using the Trier Social Stress Test (TSST). Individuals in the stress group (red line) showed elevated diastolic blood pressure (A), systolic blood pressure (B), and heart rate (C). (D) Additionally, the TSST resulted in heightened cortisol levels during the approach-avoidance conflict task in the stress group. Data show mean ± 1 SEM, *** $p \leq .001$, ** $p \leq .01$, * $p \leq .05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

beginning of the experiment ($p = .548$).

3.2. Approaching rewards and avoiding threats depends on threat level

Participants in both groups successfully learned to differentiate between high- and low-threat predators as reflected in higher self-reported predator wake up probabilities for the high threat compared to the low threat (mean estimated wake-up probability 59.68% vs. 42.05%, $F(1,78) = 25.20$, $p < .001$, $\eta_P^2 = .244$). These ratings were independent of treatment (all $p \geq .70$). Moreover, stress did not affect average walking speed ($t(78) = -1.010$, $p = .316$), thus excluding that potential group differences can be explained by stress-induced differences in mere motor control.

Task performance data also confirmed that participants learned to perform the task: the percentage of trials with failed avoidance (participant caught by predator in trials in which the predator woke up) decreased significantly over the four task blocks ($F(2.6, 206.4) = 27.80$, $p < .001$, $\eta_P^2 = .263$, Fig. 3A), independent of threat level, threat distance, and treatment (all $p \geq .09$). Moreover, successful approach responses increased over blocks such that participants were able to collect and keep more tokens over the course of the task (sum tokens collected, block $F(2.7, 208.7) = 36.42$, $p < .001$, $\eta_P^2 = .318$). As expected, participants showed more approach behavior and collected more tokens in low threat trials compared to high threat trials ($F(1, 78) = 291.63$, $p < .001$, $\eta_P^2 = .789$), although the difference between threat levels decreased over blocks (threat level × block $F(2.9, 223.3) = 7.01$, $p < .001$, $\eta_P^2 = .082$).

3.3. Stress amplifies the importance of threat distance for avoidance behaviors

Importantly, behavior in approach-avoidance conflicts was

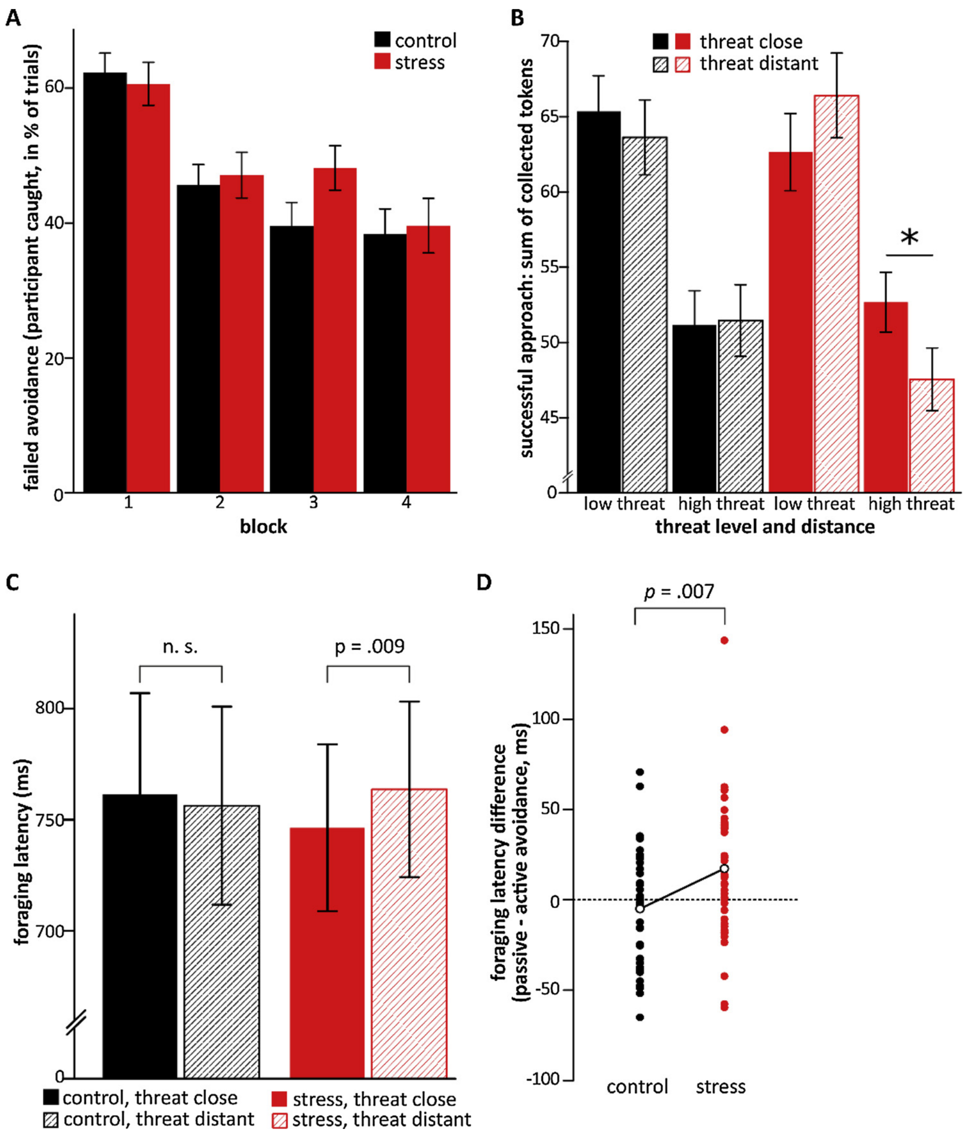

Fig. 3. Stress effects on task performance and foraging latency. A Percentage of failed avoidance (getting caught by the predator) over blocks across groups. B Total token collection depending on threat distance, threat level, and experimental group (red bars: stress group, black bars: control group). C Foraging latencies were modulated by initial threat distance and experimental group. D Individual difference scores (passive avoidance - active avoidance) of foraging latencies displayed per group. A–C Data show mean ± 1 SEM, (D) Data show individual means, empty circles show group averages, *** $p \leq .001$, ** $p \leq .01$, * $p \leq .05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

significantly affected by the stress manipulation (threat distance × treatment $F(1,78) = 7.81$, $p = .007$, $\eta_P^2 = .091$, Fig. 3C and D). In particular, foraging latencies in the stress group were modulated by initial threat distance, resulting in longer foraging latencies when initial threat distance was long (passive condition) compared to when threat distance was short (active avoidance; $p = .009$). In contrast, control participants showed no such difference in foraging latencies depending on threat distance ($p = .318$). Explorative analyses revealed no interaction between treatment and gender (all $p \geq .080$), although men responded faster in general ($F(1,76) = 28.11$, $p < .001$, $\eta_P^2 = .270$).

Together, these results suggest that stress led to an increased importance of threat distance, resulting in strengthened active avoidance as indicated by accelerated responding when threats were close, and/or increased passive avoidance as indicated by more inhibition when threats were distant.

The number of tokens collected as a measure of approach was also affected by treatment and initial threat distance at trend-level, as indicated by a treatment × threat distance × threat level interaction ($F(1,78) = 4.06$, $p = .047$, $\eta_P^2 = .050$, Fig. 3B), which was nominally significant but did not survive Holmes-Bonferroni correction (corrected $\alpha = .025$). Whereas participants in the control group did not show threat distance related differences in the number of tokens collected at any level of threat (low threat: $p = .401$, high threat: $p = .884$), stressed participants collected specifically fewer tokens and were thus presumably more inhibited when highly threatening predators were distant compared to when they were close and the participants had to flee quickly ($t(39) = 2.62$, $p = .013$ $d = .398$) while no difference was found for the low threat level ($p = .151$). Importantly, this effect was not merely driven by the stress-induced response time differences reported above, as the inclusion of the foraging latency difference score as a covariate in the current analysis on did not alter the results (treatment × threat distance × threat level interaction: $F(1,77) = 4.22$, $p = .043$, $\eta_P^2 = .052$). Moreover, although the sum of tokens collected might be biased as there are less successful trials under high-level threat (on average 57) as compared to low-level threat (on average 72), the number of trials in which the participant was caught did not differ between active and passive condition (all $p \geq .130$) and so does not drive this finding.

To further investigate this finding, we again calculated difference scores subtracting the number of tokens collected in the passive condition (threat distant) from the number of tokens collected in the active condition (threat close), again resulting in larger values with increasing inhibition during passive avoidance. Whereas the control group showed no difference between low and high threat levels ($p = .561$), the stress group showed higher difference scores, thus more inhibition, for high threat compared to low threat ($t(39) = -2.12$, $p = .040$, $d = .62$). Moreover, there was a trend for the stress group to show more behavioral inhibition at high threat levels than the control group ($t(78) =$

-1.972, $p = .052$, $d = .441$). To summarize, stress led to increased avoidance in the passive high threat condition, i.e., when a dangerous predator is prominent, but distant.

Explorative analyses revealed no interaction between treatment and gender (all p ≥ .190), although men, in general, collected more tokens ($F(1,76) = 36.91, p < .001, \eta_P^2 = .327$). Interindividual differences in cortisol reactivity were not associated with the total number of tokens collected ($p = .142$) or the percentage of failed avoidance ($p = .328$). However, participants with higher cortisol reactivity responded faster across groups (average RT: r −.275, $p = .014$, active condition: $r = -.280$, $p = .012$, passive: $r = -.274$, $p = .014$) and in the stress group alone (average RT: r −.341, $p = .031$, active condition: $r = -.338$, $p = .033$, passive: $r = -.363$, $p = .021$), but not in the control group (all $p > .10$). Note, however, that this effect was independent of threat distance.

3.4. Stress has opposite effects in anxious and aggressive individuals

Supporting the validity of the approach-avoidance task, participants with higher scores in trait anxiety (r = −.330, p = .003) and distrust ($r = -.227$, $p = .043$) collected on average fewer tokens than less anxious and distrustful individuals (Fig. 4A and B), suggesting stronger avoidance in these individuals. Importantly, these associations were not driven by momentary differences in state anxiety as these correlations remained when accounting for state anxiety ($r_p = -.358$, $p < .001$ and $r_p = -.226$, $p = .045$, respectively). In contrast, participants with higher levels of self-reported physical aggression tended to collect more tokens ($r = .220$, $p = .050$, Fig. 4C), indicating enhanced approach in individuals prone to physical aggression. Verbal aggression and anger were not related to the number of tokens collected ($p = .636$ and $p = .205$, respectively). Importantly, the reported associations were not merely due to the fact that anxious individuals were caught less and aggressive individuals were caught more frequently (correlations between percentage of caught trials and trait anxiety: $p = .148$, physical aggression: $p = .526$, distrust: $p = .978$).

Next, we tested whether the relationships between trait aggression or anxiety and approach-avoidance behavior were affected by our stress manipulation. The associations involving anxiety and distrust were highly significant in the control group (anxiety: $r = -.575$, $p < .001$, distrust: $r = -.466$, $p = .002$, Fig. 4), but absent in the stress group ($p = .989$ and $p = .895$, respectively) with striking group differences in correlations (anxiety: $Z = -2.83$, $p = .005$, distrust: $Z = -2.27$, $p = .023$). In contrast, the relationship between physical aggression and collected tokens was specific for the stress group ($r = .468$, $p = .002$) and absent in the control group ($p = .930$, significant group difference: $Z = 2.12$, $p = .034$).

To formally test whether stress and personality traits interacted to shape behavior in approach-avoidance conflicts, we implemented linear regression models to predict the total number of tokens collected. First, control variables, i.e. the participants' age, sex, and average walking speed (which was, as expected, highly correlated with the number of tokens collected, $r = .629$, $p < .001$) were added in a stepwise fashion. In the next block, all predictors of interest were included (again stepwise), i.e., treatment group, trait anxiety, physical aggression, verbal aggression, anger, distrust, the five interaction terms of these personality dimensions with treatment group, and depressive symptoms. We found that trait anxiety predicted fewer collected tokens (β = −.368, $p < .001$, final model in Table 2) above and beyond the influence of average walking speed (β = .422, $p < .001$), gender (β = .214, $p = .027$), and age ($p = .274$, whole model: $R^2 = .639$, adjusted $R^2 = .604$, $F(7,72) = 18.237$, $p < .001$). Moreover, we found that the influence of trait anxiety and physical aggression depended on treatment group (trait anxiety × treatment: β = .216, $p = .019$, physical aggression × treatment: β = .310, $p < .001$) in line with the correlations reported above. In contrast, distrust was not included in the final model, most likely due to the high intercorrelation with trait anxiety ($r = .519$, $p < .001$). Finally, also verbal aggression interacted with treatment group to affect the number of collected tokens (β = −.164, $p = .039$) such that the association was more positive in the control

Table 2
Multiple regression analysis predicting the total number of tokens collected.

Predictors	β	t	p	VIF	tolerance
(Constant)		4.313	< .001***		
average walking speed	.422	4.492	< .001***	1.762	0.568
gender[a]	.214	2.260	.027*	1.794	0.558
age	−.090	−1.103	.274	1.314	0.761
physical aggression[b] × treatment[c]	.310	3.866	< .001***	1.286	0.777
trait anxiety[b]	−.368	−3.875	< .001***	1.804	0.554
trait anxiety[b] × treatment[c]	.216	2.395	.019*	1.629	0.614
verbal aggression[b] × treatment[c]	−.164	−2.106	.039*	1.218	0.821

Note: Predictors are shown in the order of being included in the stepwise regression model. $R^2 = .639$, adjusted $R^2 = .604$, $F(7,72) = 18.237$, $p < .001$. [a] 0 = female, 1 = male; [b] mean centered; [c] 0 = control, 1 = stress. Note that average walking speed, gender and age were added stepwise as control variables in a first block and the remaining variables were added stepwise thereafter, resulting in the final non-significant effect of age. Variance inflation factor (VIF) and tolerance are indicators of multicollinearity. Typically, VIF values above 4 or 5 and tolerance below .2 are considered to be indicators that the regression model may be unduly biased by multicollinearity (Hair et al., 2012).
*** $p < .001$.
* $p < .05$.

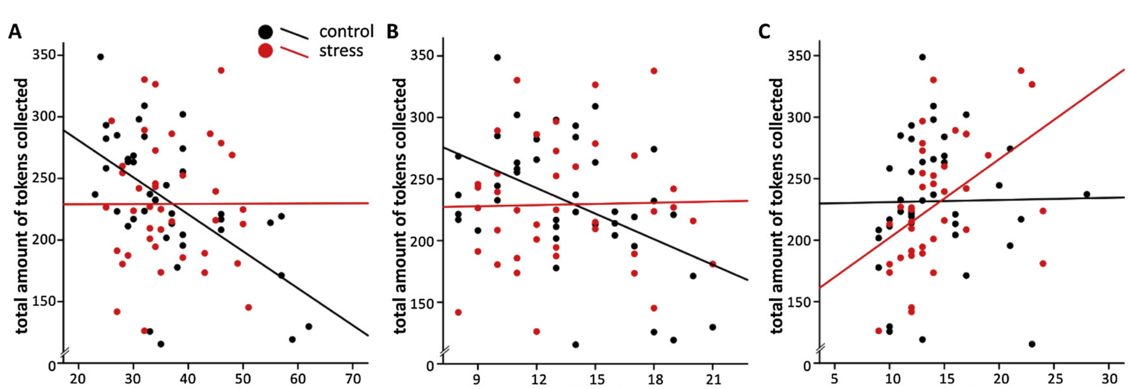

Fig. 4. Stress interacts with trait anxiety and trait aggression to affect approach behavior. Correlations between the total amount of collected tokens and individual trait anxiety (A), distrust (B), and physical aggression (C) are shown per group (stress group: red, control group: black). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

group. Together, the final model explained 60.4% of variance in approach and avoidance behavior which is a large effect according to Cohen (1992).

4. Discussion

An altered balance between approach and avoidance is key to several mental disorders (e.g., anxiety disorders or substance abuse) and its modification critical in the therapeutic process (Hofmann, 2007). Although stress is a main risk factor for these disorders, if and how stress affects behavior in situations with conflicts between the tendencies to approach and avoid is currently unknown. In this study, we demonstrate that stress generally increases the importance of threat distance in avoidance, but that the precise behavioral outcome is dependent on threat level and, importantly, interindividual differences in anxiety and aggression.

In detail, stressed participants showed increased behavioral inhibition when predators were distant as revealed by longer response latencies and fewer collected tokens compared the active avoidance condition, especially during high threat. Behavioral inhibition, i.e. the interruption of ongoing actions, has been shown to be adaptive and cost-minimizing in humans, scaling linearly with threat probability and magnitude (Bach, 2015; Khemka et al., 2017). However, excessive behavioral inhibition can be maladaptive which explains the strong association with trait anxiety, a potent risk factor for anxiety disorders (Bach, 2015). Interestingly, behavioral inhibition in a very similar paradigm is controlled by the amygdala and can be reduced by anxiolytic drugs like benzodiazepines (Korn et al., 2017) or the gamma-Aminobutyric acid (GABA) analogue pregabalin (Bach et al., 2018). Studies investigating freezing under threat, a form of behavioral inhibition, also point towards a critical role of the amygdala and its connection to the periaqueductal grey (PAG) in behavioral inhibition (Roelofs, 2017). Given that stress, via noradrenergic activation, rapidly increases amygdala functioning and connectivity (e. g., Hermans et al., 2011), stress may boost behavioral inhibition when threats are distant by promoting this amygdala-PAG pathway. This might also explain why we did not find a relationship between approach-avoidance behaviors and cortisol reactivity. Previous findings suggested that cortisol reactivity is associated with increased avoidance (Roelofs et al., 2009), but the role of cortisol in situations with approach-avoidance conflicts without a clearly correct response remains unclear. It is thus possible that other neuromodulators like noradrenalin are involved in the effects of stress on behavior in approach-avoidance conflicts.

In addition to enhanced behavioral inhibition when threats are distant, our results demonstrate that stress increases active avoidance when a predator is close, as evidenced by response acceleration compared to when threats are distant. In contrast to behavioral inhibition, which is accompanied by a potentiation of the startle reflex, active avoidance is accompanied by startle inhibition and heart rate acceleration (Wendt et al., 2017). Despite seemingly opposite effects to behavioral inhibition, also active avoidance involves the amygdala and the PAG (Wendt et al., 2017). Together, our findings suggest that stress amplifies avoidance behaviors, but that the precise behavioral outcome depends heavily on threat distance, resulting in either behavioral inhibition or acceleration. This is in line with previous models (Blanchard and Blanchard, 1990; McNaughton and Corr, 2004) suggesting that defensive behaviors vary considerably with threat distance. Although these behaviors seem apparently different, they might subserve the same purpose, putting the individual's safety first.

However, the amygdala-PAG pathway is likely not the sole circuit involved in avoidance behaviors. For instance, previous studies using related paradigms showed that the anterior hippocampus tracks current threat level (Bach et al., 2014) and that hippocampal activity is related to foraging latencies (Khemka et al., 2017). Moreover, a study by Wendt et al. suggested that the mPFC is a key structure for switching between active and passive avoidance. Interestingly, hippocampal-mPFC coupling increases with threat level (Khemka et al., 2017) and the anterior / ventromedial PFC has also been implicated in the resolution of approach-avoidance conflicts using indirect joystick tasks (Volman et al., 2011). Given that stress and major stress mediators, such as glucocorticoids and noradrenaline, are known to affect hippocampal and prefrontal functions (McEwen et al., 2016), future studies might delineate in more detail whether stress also affects the set point when behavioral inhibition switches to active avoidance (and vice versa), which might involve the hippocampus and the medial PFC.

Beyond these general effects of stress, our study revealed that the effects of stress on approach-avoidance conflicts depend strongly on interindividual differences in trait anxiety and aggression. Interestingly, stress amplified approach behaviors in individuals with higher levels of self-reported physical aggression. This finding is in line with previous reports on psychopaths who approach threatening stimuli faster than controls, which was associated with self-reported instrumental aggression (von Borries et al., 2012). Our findings suggest that this phenomenon might be exacerbated by acute stress. However, it would be very interesting to investigate whether the stress-induced approach behavior we saw in aggressive individuals may also be reflected in individuals prone to substance abuse. For instance, a previous study showed that stress increases impulsivity in a community based sample and that this effect mediated stress-induced alcohol consumption (Hamilton et al., 2013). Thus, the effect of stress on (excessive) approach may be mediated by heightened impulsivity. It should be noted, though, that approach in our task was adaptive and aggression was not correlated with the percentage of being caught. Future studies could test whether stress also increases approach in aggressive individuals when this approach behavior is maladaptive and comes with costs.

Beyond aggression, we also found that the avoidance-enhancing effect of trait anxiety (and the related trait distrust) depends on the current state of the individual. More precisely, trait anxiety was associated with more avoidance in the control condition, but acute stress abolished interindividual differences due to trait anxiety. This finding that stress overrides individual differences due to trait anxiety is in line with a previous finding from our group investigating the effects of stress and personality on learning by instruction (Vogel and Schwabe, 2018). Together, both studies demonstrate that acute stress can override or exacerbate the influence of personality differences on behavior, and that personality traits in turn strongly moderate the effects of acute stress, possibly explaining some of the large interindividual variability in responding to stress. However, we did not investigate effects of long-term stress experience. Recent studies demonstrated that repeated stress exposure during puberty leads to both stronger aggressive approach and heightened anxiety-like behavior in rats, accompanied, for instance, by differences in basal brain activity (Walker and Sandi, 2018; Walker et al., 2017). Thus, the experience of repeated stress during critical time windows might bias individuals to both heightened aggression and anxiety, which might affect stress-related changes in behavior.

In the current study, we employed a recently developed task that allowed to assess human behavior in situations with approach-avoidance conflicts where there is no clearly correct response (Bach et al., 2014). This is in contrast to more indirect assessments of approach and avoidance behaviors like joystick tasks, which require participants to push or pull a joystick in response to positive and negative stimuli, where reaction time differences for these responses are interpreted as avoidance or approach tendencies. Notably, it has been shown that tasks in which a player is moved to approach stimuli and avoid threats have higher reliability and criterion-validity than joystick tasks (Krieglmeyer and Deutsch, 2010). Moreover, there is a clearly defined correct response in joystick tasks, which is less the case in the conflict task used in the present study, and might bear less resemblance with approach-avoidance conflicts in everyday life. Despite these strong advantages of the task used here, a possible limitation is that we cannot clearly dissociate effects as being driven solely by approach or avoidance motivation, similarly to many rodent approach-avoidance conflict paradigms. Thus, longer latencies to approach can be driven by higher avoidance and/or reduced approach motivation. Whereas we could demonstrate clear effects of stress on the balance between approach and avoidance using this paradigm, different tasks could inform about stress-induced changes on approach and avoidance, separately. Similarly, sex effects may be more apparent when investigating approach and avoidance independently or using a different task design (e.g., Sheynin et al., 2014).

5. Conclusions

To summarize, we found that acute stress boosts the importance of threat distance in approach-avoidance conflicts, but that the precise behavioral outcomes depend strongly on individual differences in trait aggression and anxiety. A better understanding of how stress affects approach and avoidance in healthy individuals may have important implications for our understanding of how stress-related mental disorders develop and may lead to novel avenues to treat these disorders or prevent relapse. Our findings also provide novel insights into the striking interindividual variability in response to stress and highlight the important influences of stress, trait anxiety, and trait aggression on a fundamental aspect of human behavior, the balance between approaching positive and avoiding negative stimuli.

Author statement

Susanne Vogel: Conceptualization, Investigation, Formal Analysis, Visualization, Writing- Original draft. Lars Schwabe: Conceptualization, Writing- Reviewing and Editing.

Declarations of interest

None.

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