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Sensation seeking and neuroticism in fear conditioning and extinction: The role of avoidance behaviour

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ABSTRACT

Maladaptive avoidance behaviour, a key symptom of anxiety-related disorders, prevents extinction learning and maintains anxiety. Individual personality traits likely influence avoidance propensity: high sensation-seeking may decrease avoidance, thereby increasing extinction, and neuroticism may have the reverse effect. However, research on this is scarce. Using a naturalistic conditioned avoidance paradigm, 163 women underwent differential fear acquisition to a conditioned stimulus (CSplus). Next, during extinction, participants could either choose a risky shortcut, anticipating shock signalled by CSplus, or a time-consuming avoidance option (lengthy detour). Across participants, increased skin conductance (SCR) acquisition learning predicted subsequent instrumental avoidance. Avoidance, in turn, predicted elevated post-extinction SCR and shock-expectancy, i.e., 'protection-from-extinction'. Mediation analyses revealed that sensation seeking decreased protection-fromextinction—both for shock-expectancy and SCR—via attenuating avoidance. Neither sensation seeking nor neuroticism were related to acquisition learning and neuroticism was neither related to avoidance nor extinction. Transcranial direct current stimulation administered before extinction did not influence present results. Results highlight the important role of elevated avoidance propensity in fear maintenance. Results moreover provide evidence for reduced sensation-seeking and increased acquisition learning to be avoidance-driving mechanisms. Since approach-avoidance conflicts are faced by anxiety patients on a daily basis, strengthening sensationseeking-congruent attitudes and approach behaviours may optimize individualized treatment.

1. Introduction

Excessive avoidance of relatively safe cues and situations is a key symptom of anxiety, posttraumatic stress (PTSD), and obsessive-compulsive disorders (APA, 2013). Persistent maladaptive avoidance behaviours prevent disconfirming experiences and maintain anxiety (Foa & Kozak, 1986; Lovibond, Davis, & O'Flaherty, 2000). The associated impairment in daily functioning is often related to long-term costs, such as social isolation or professional detriments (e.g., Ansseau et al., 2008; Domènech-Abella, Mundó, Haro, & Rubio-Valera, 2019). Although avoidance behaviour has long been recognized as a major driving mechanism in the development of anxiety-related disorders, it has become again a major research focus (c.f. special issue by Beckers & Craske, 2017; review by Dymond, 2019; LeDoux, Moscarello, Sears, &

Campese, 2017). Very little research has yet investigated the role of individual trait differences in avoidance propensity.

Experimentally, behavioural avoidance can be studied by conditioned avoidance paradigms (Krypotos, Vervliet, & Engelhard, 2018). Those paradigms assess the role of avoidance behaviour during extinction (i.e., the formation of a second, competing memory trace) of clinically relevant fear and anxiety responses (LeDoux & Pine, 2016; Lovibond, Mitchell, Minard, Brady, & Menzies, 2009; Rattel, Miedl, Blechert, & Wilhelm, 2017). At first, during Pavlovian fear/threat conditioning, an initially neutral stimulus is paired with an aversive unconditioned stimulus (US, typically an electric shock). This turns the neutral stimulus into a conditioned stimulus (CSplus) that will subsequently elicit fear and threat responses (e.g., increased US-expectancy and skin conductance response, SCR) in the absence of the US.

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Following, during the *instrumental phase*, performing an instrumental avoidance behaviour upon the CSplus cancels the US (following theoretical propositions by Lovibond et al., 2009). During extinction, the CSplus is no longer followed by the US and therefore, the threat responses should gradually decline. However, if avoidance behaviour to the CSplus persists, the CSplus-US relationship is not weakened because threat-beliefs are maintained (Lovibond, 2006; Lovibond, Saunders, Weidemann, & Mitchell, 2008). Thus, avoidance interferes with extinction learning, which has been termed *protection-from-extinction effect* (see Lovibond et al., 2009; Rattel et al., 2017).

As *Pavlovian fear conditioning* and *instrumental learning* (operant conditioning) seem to jointly influence the development and maintenance of anxiety-related disorders (Bouton, 2007; Mowrer, 1960) increased acquisition learning may well be related to increased avoidance. In line with this assumption, Pittig, Schulz, Craske, and Alpers (2014) linked increased physiological (SCR) acquisition learning to increased avoidance in a gambling task in healthy participants. One aim of the present study was to replicate those findings in a more ecologically valid, free-choice avoidance paradigm.

Personality traits may influence acquisition learning as well. Importantly, they may influence avoidance behaviours and as a consequence, extinction learning (Lonsdorf & Merz, 2017; Servatius, 2016), though, they have not been sufficiently addressed in avoidance research (see reviews by Krypotos et al., 2018; Lonsdorf & Merz, 2017). Sensation seeking (SS) is a trait disposition to pursue excitement, novelty, and intense sensations (Zuckerman, 2014) that has been shown to be related to decreased anxiety in non-clinical populations (Vries, Vries, & Feij, 2009). In terms of fear acquisition, low SS has been linked to increased SCR to predictable threat cues (Lissek et al., 2005).

In terms of approach vs. avoidance behaviour, approach behaviour to intense, novel, and often dangerous situations is assumed to be characteristic for high SS (Zuckerman, 1994). In line with this claim, an experimental study using an elevated plus-maze experiment linked high SS to approach compared to avoidance behaviour in healthy participants (Biedermann et al., 2017). To our knowledge, no conditioned avoidance paradigm has yet investigated the influence of SS on fear acquisition, avoidance behaviour, and extinction learning.

In addition to sensation seeking, neuroticism, a trait disposition to experience more negative feelings such as anxiety, worry, and fear (Clark, Watson, & Mineka, 1994), may be related to increased avoidance behavior. Neuroticism has been found to be a predisposing factor for clinical anxiety as well as depressive symptoms (e.g., Jorm et al., 2000; Watson, Gamez, & Simms, 2005) and high neuroticism has been linked to more depressive symptoms and distress following adverse life events (e.g., Creed, Muller, & Machin, 2001; Gallant & Connell, 2003; Millar, Purushotham, McLatchie, George, & Murray, 2005). Moreover, neuroticism has been associated with an avoidant coping style (Bolger, 1990; McCrae & Costa, 1986). In experimental studies, neuroticism has been linked to higher anxiety responses during threat anticipation (Drabant et al., 2011) and greater skin conductance responding to aversive pictures (Norris, Larsen, & Cacioppo, 2007). However, the role of neuroticism in fear acquisition and extinction is controversial, with most studies finding no significant relationship (see review by Lonsdorf & Merz, 2017). With regard to avoidance, Lommen, Engelhard, and van den Hout (2010) linked high neuroticism to more frequent avoidance during extinction (though only in trials with longer latencies) in a stimulus generalization paradigm using electric shock (see Arnaudova, Krypotos, Effting, Kindt, & Beckers, 2017 for a partial replication). To our knowledge, no conditioned avoidance paradigm has yet investigated the influence of neuroticism on avoidance behaviour and subsequent extinction learning.

First, the present study set out to replicate and extend previous findings using procedural improvements and a larger sample size (Rattel et al., 2017). Like our previous study, we used a more naturalistic free-choice conditioned-avoidance paradigm, operationalizing self-relevant avoidance costs using a timely detour (compared to often

used monetary gains). We wanted to replicate our previously found protection-from-extinction effect, extending these findings by psychophysiological indicators of fear. Second, in line with findings by Pittig et al. (2014), we expected that individuals with more pronounced acquisition learning would show increased instrumental avoidance responses, resulting in increased protection-from-extinction. Third, we wanted to investigate the role of individual differences on acquisition learning, free-choice avoidance behaviour, and extinction learning. We expected high SS to predict decreased avoidance and high neuroticism to predict increased avoidance. Moreover, we expected high SS to decrease protection-from-extinction and secondary analyses investigated whether either acquisition learning or instrumental avoidance mediated this relationship; an opposite pattern was expected for neuroticism. Due to lack of past studies, the predicted effect of SS on acquisition learning was of exploratory nature. Due to inconsistencies and non-significant findings in the literature, the predicted effect of neuroticism on acquisition and extinction learning was also of exploratory nature.

2. Method

2.1. Participants

One-hundred and seventy-nine healthy women participated in the study. Recruitment was limited to women only, as 1) anxiety-related disorders are particularly prevalent in women (McLean, Asnaani, Litz, & Hofmann, 2011) and 2) past research suggests substantial sex differences in fear conditioning (Craske, 2003; Rattel et al., 2019a). Exclusion criteria were self-reports of psychotropic medication, psychosis, substance abuse/dependency, bipolar disorder, serious medical conditions, history of traumatic head injury, or metal head implants. Sixteen participants were excluded: early termination, 6; technical problems, 4; non-compliance, 1; no avoidance during avoidance acquisition, 1; insufficient US-aversiveness rating (unpleasantness \leq 4 & painfulness \leq 2), 4. Thus, 163 participants were included in the analyses (*mean age* = 21.2, SD = 2.4). The study was approved by the local ethics committee. Participants gave informed consent and were informed that they could terminate participation at any time.

For our primary analyses (i.e., our simple effects), we conducted power analyses using GPower (Faul, Erdfelder, Lang, & Buchner, 2007), testing for simple linear regression effects (two-tailed). Based on our previous study (Rattel et al., 2017), we expected a medium to large effect size for the effect of avoidance on protection-from-extinction ($r \approx$ 0.43; $R^2 \approx 0.18$); based on an alpha level of p < .05, with a power of .80, a minimum sample size of 42 participants was required. Further, for individual difference effects on acquisition learning, avoidance and protection-from-extinction, we expected small (r = 0.10) to medium (r= 0.30) effect sizes (Cohen, 1992; see review by; Lonsdorf & Merz, 2017); based on a small to medium effect size ($r \approx 0.22$; $R^2 \approx 0.05$)) for an alpha level of p < .05, with a power of .80, a minimum sample size of 152 participants was required. Note that we are not aware of any similar study testing individual difference effects on avoidance and protection-from extinction, thus, no informative a-priori effect sizes were available.

2.2. Apparatus

Participants were seated on a chair placed 60 cm in front of a full-HD monitor. Stimulus presentation and behavioral data acquisition were controlled by E-Prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA, USA). An electric stimulator (Lucius & Bear GmbH, Geretsried, Germany) delivered the US via two Ag/AgCl electrodes placed at the inner side of the index and middle fingers of the left hand. Acoustic stimuli were presented via shielded headphones at a constant volume. Two saline-soaked surface sponge electrodes (39 cm²) were placed on the positions F3 (cathodal) and F4 (anodal), to apply a weak (1 mA) direct current to the scalp later during the experiment (transcranial

direct current stimulation, tDCS, DC-Stimulator, neuroConn GmbH, Ilmenau, Germany). Note that we report the tDCS null-findings in the Supplements. Importantly, when statistically controlling for tDCS effects, none of the present findings changed substantially and the pattern of significant findings remained exactly the same.

Skin conductance (SC) was measured using Ag/AgCl electrodes filled with isotonic electrode paste (TD-246, Med Associates, Inc., St. Albans, Vermont); electrodes were placed on the palm of the non-dominant hand (Boucsein et al., 2012). Recording of SC data was performed with a sampling rate of 1000 Hz using the software Polybench 1.22 (TMSi, Twente Medical Systems International, EJ Oldenzaal, Netherlands), a Porti 32-channels-amplifier (TMSi), and an SC-amplifier (Becker Meditec, Karlsruhe, Germany). ANSLAB 2.6 was used for filtering (16-Hz low-pass), data editing (contact artifacts appearing as irregular spikes), and data reduction (Blechert, Peyk, Liedlgruber, & Wilhelm, 2016).

For SC data, twenty-seven participants had to be excluded due to technical difficulties (N=16) or insufficient data quality that could not be edited (mainly due to electrode contact artifacts from excessive hand movement; N=11), resulting in N=136 for SCR analyses.

2.3. Materials and procedure

At the beginning of the session, participants filled out trait questionnaires.

Sensation seeking. Sensation seeking (SS) was assessed using the German version (Beauducel, Strobel, & Brocke, 2003) of the sensation seeking scale by Zuckerman (1994). This scale includes four subscales (10 items each): thrill and adventure seeking, experience seeking, disinhibition, and boredom susceptibility. Summing all subscales gives an overall SS-score. Items are dichotomous; thus, one point is allocated to each SS response item, with zero implicating low SS. Internal consistency is good ($\alpha = 0.83-0.86$; Zuckerman & Aluja, 2015), with sufficient internal consistency in the present study ($\alpha = 0.75$).

Neuroticism. The revised NEO Personality Inventory (NEO-PI-R; German version: Ostendorf & Angleitner, 2004; English version: Costa & Mccrae, 2010) was used to measure neuroticism (subscales: anxiety, angry hostility, depression, self-consciousness, impulsiveness, vulnerability). It is a 48-item self-report measure, to which individuals respond on a 5-point Likert-type scale ranging from 0 (*strongly disagree*) to 4 (*strongly agree*). In adults, internal consistency for this neuroticism scale is good ($\alpha = 0.86$), with a well replicated factor structure (McCrae & Costa, 2007). In the present study, we found high internal consistency ($\alpha = 0.91$).

Procedure. Following questionnaire assessment, electrodes for shock application and skin conductance response were attached. Subsequently, electric shock intensity was determined individually, adjusting pulse train presentations (duration 625 msec: 125 times 2msec stimulation + 3msec pause) to a mA-level participants described as 'unpleasant and demanding some effort to tolerate, but not painful' (on a scale ranging from 1 "not unpleasant/painful at all" to 9 "very unpleasant/ painful"; see (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Rattel et al., 2017). Shock intensity was adjusted until participants reached either a pain threshold of 4-6 and/or an aversiveness threshold of 6-8. Participants were not informed about this underlying threshold as we believe that this information could have biased their ratings. Few participants (N = 4) perceived shock as neither painful nor unpleasant even after several adjustments in shock sensitivity and had thus to be excluded from analyses. To potentiate its effects, each electric pulse train was accompanied by a 1sec presentation of a mildly aversive 90 dB square wave tone; the combination of the electric shock and square-wave tone served as US throughout the experiment. Geometric yellow shapes (triangle, circle, or square, 5.5 cm diameter) served as CSs (counterbalanced).

Ratings were assessed on visual analogue scales. US-expectancy after CS-presentation was rated trial-wise throughout the experiment ("How much do you expect this figure to be followed by shock?", 0%–100%). In

trials without choice option, participants rated the accessible route only (e.g., Fig. 1A, B, C, F); in all other trials (two accessible routes), participants rated each route separately (e.g., Fig. 1 D, E).

In line with Rattel et al. (2017), participants were informed about the existence of a relationship between the shape of the geometric figures and the occurrence of shock and instructed to pay attention to it (see Supplements for exact instructions). As depicted in Fig. 1, routes (R) varying in length and duration (two short routes, R1 and R2, and one long route, R3) led a manikin to a house; accessibility of different routes depended on the phase of the experiment. Participants were further informed that shock could only occur on R1 and that all other paths were safe. After explaining the setup, participants were instructed to lead the manikin to its house. Participants were told that they could leave as soon as the experiment was finished; they were informed that the duration of the experiment depended on their choices of routes.

Task. Number of trials and experimental phases were identical to the design of Rattel et al. (2017). Within each phase, trials were pseudo-randomized (not more than two CSs of the same type in sequence). All trials started with a picture of one of the three CSs in the center of the screen, accompanied by a map depicting the different routes as well as their accessibility (symbolized by a red barrier; see Fig. 1); this lasted for 4sec. Following, participants rated US-expectancy for the respective route.

In trials without choice option, the manikin automatically started to walk to the house (see Fig. 1 A, B, C, F); in all other trials (e.g., see Fig. 1 D, E), participants could choose a route by button press. After the rating, the manikin walked on; having covered two-thirds of R1 (after 4sec), the shock-tone US was administered. No US was administered on R2 and R3 irrespective of the concurrently presented CS (the manikin walked a distance equivalent to two-thirds of R1), as well as during CSminus and CSplus2 trials during extinction and test phase, and thus, the manikin merely paused for a moment. As soon as the manikin reached the house, the screen turned black, and a central fixation cross was displayed for 8.5–14.5sec (inter-trial interval).

Acquisition phase. As exemplified in Fig. 1 (A, B, C), a circle and a square represented the CSplus1 and the CSplus2, predicting the US. A triangle predicted US absence, serving as a safety signal (CSminus, shape-CS type assignment was counterbalanced across participants). During the acquisition phase, only R1 was accessible. CSplus1 and CSplus2 were each shown two times (100% US reinforcement) and the CSminus four times.

Avoidance-acquisition phase. Participants had the option to avoid the US without any associated costs during this experimental phase (see R2 in Fig. 1D), in order for them to become acquainted with the possibility of avoidance. This phase consisted of six CSplus1 trials with avoidance option (R1 and R2 open), where participants could actively choose either one of the two routes via mouse click. Moreover, one CSplus1 trial, one CSplus2 trial, and two CSminus trials were presented without avoidance option (only R1 open, CSplus trials reinforced by the US). Participants were informed that shock could only occur on R1.

Extinction phase. Immediately before extinction, participants were randomly assigned to tDCS (n=79) or sham (n=84). The tDCS group was stimulated for 600sec with 1 mA current intensity, the sham group was stimulated for 15sec. During the stimulation phase, four neutral/slightly positive (but low arousing) film clips were presented without sound (total duration of 10min; see Wilhelm et al., 2017 for details).

Following the mild-tDCS phase, the extinction phase started immediately, with six CSplus2 trials with avoidance option (see R3 on Fig. 1E), as well as two CSminus and two CSplus1 trials without avoidance option (only R1 open; see Fig. 1A, C). Thus, participants could avoid between zero to six times.

The walking duration for R1 and R2 was kept constant at 4.5sec. The walking duration for R3 was set to 41sec based on the study by Rattel et al. (2017), demonstrating that around 50% of participants tend to avoid at this detour duration; a 50/50 split was intended to study individual differences. As no US was administered for CSplus2 during

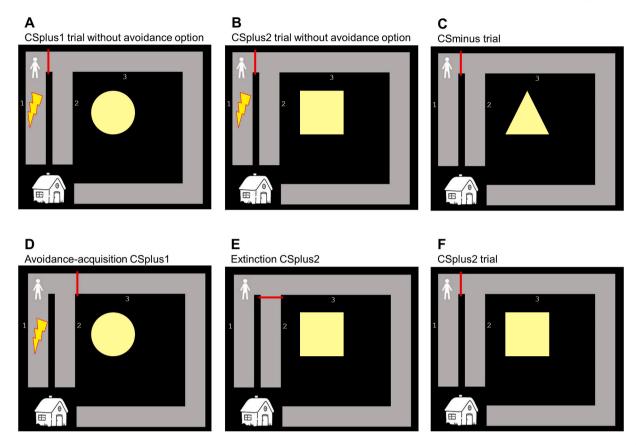


Fig. 1. Participants were instructed to repeatedly walk the manikin to its house. The red barrier signalled routes that were closed. Numbers (1, 2, 3) indicate different routes that could be chosen by button press. Different geometric figures displayed in the centre of the screen symbolized the respective CS (CSplus1, CSplus2, CSminus). The yellow flash on route 1 is only for illustration purposes and was not shown to participants. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

extinction, participants selecting the shortcut (see R1 on Fig. 1E) did not receive a US during these trials.

Test phase (i.e. measuring protection-from-extinction effect). Immediately after the extinction phase, one CSminus, one CSplus1, and one CSplus2 trial were presented without avoidance option (same instructions as during acquisition). The US was only presented during the CSplus1 trial. No US was presented during CSplus2; thus, this trial was always scheduled last, avoiding any influence on the CSplus1 and the CSminus trial.

2.4. Data reduction and statistical analyses

For SCR quantification, average pre-CS baseline SCL (-2 to 0sec relative to CS onset) was subtracted from maximum CS SCL 0-4sec following the US-expectancy rating(s). Following US-expectancy rating (s), the manikin started walking on the selected route for 4sec (while the CS was still displayed), before it shortly stopped and shock was administered on R1. Note that in this paradigm, the interval immediately following CS onset was before the US-expectancy rating(s); therefore, this interval was not suited, as participants felt safe up to the point of finishing the rating response(s). Due to the rating task-related prolonged CS presentation interval and a log-linear downward drift of SCL often occurring in trials associated with low US-expectancy, pre-CS baseline sometimes was higher than maximum CS SCL in the 0-4sec following US-expectancy ratings, resulting in negative values. These were included in the statistical analysis since otherwise a major proportion of data would have been lost for the low-US expectancy trials, resulting in biased results. Inspection of SCR characteristics indicated a normally distributed continuum of SCR values from slightly negative to positive values, suggesting a valid mapping of sympathetic efferent discharge due to fearful activation. SCR values were not scaled or transformed before statistical analysis.

Manipulation Check. Repeated measure ANOVAs checked for successful fear acquisition (CS-Type: CSplus1, CSplus2, CSminus) and avoidance acquisition (CS-Type: CSplus1 with vs. without avoidance option) using SPSS; the last CS-trial of each phase was used.

Simple Effects. Regression analyses were used to check for simple effects of acquisition learning on avoidance, avoidance on protection-from-extinction, and SS and neuroticism on acquisition learning, avoidance, and protection-from-extinction. In line with previous work by Pittig et al. (2014), acquisition learning was operationalized as differential CSplus2 vs. CSminus US-expectancy rating/SCR at the end of acquisition. In line with Lovibond et al. (2009) and Rattel et al. (2017), protection-from-extinction was operationalized as the differential CSplus2 vs. CSminus US-expectancy rating/SCR during test phase. Follow-up analyses investigated non-differential CSplus2 and CSminus ratings/SCRs (inspired by generalization accounts of PTSD, e.g., Grillon & Morgan, 1999).

Secondary Mediation Analyses. Simple regression analyses were followed by secondary analyses to further delineate underlying mechanisms. First, a mediation model investigating if acquisition learning increases protection-from-extinction indirectly via avoidance was computed. Second, integrating all previous findings in one statistical model, a serial mediation model (for SS only, as neuroticism did not reveal significant findings) was computed. This model tested for a serial indirect effect of SS on protection-from-extinction via acquisition learning and avoidance (see Figs. 4 and 5 for graphical display). The serial mediation model is based on three linear regression analyses. In the first regression analysis, the first mediator (acquisition learning) is predicted by the independent variable (SS). In the second regression

analysis, the second mediator (instrumental avoidance behaviour) is predicted by both the independent variable and the first mediator. In the third regression analysis, the outcome variable (protection-from-extinction) is predicted by the independent variable, the first mediator, and the second mediator.

MPlus was used for all simple regression and mediation analyses (Muthén, Muthén, & Asparouhov, 2017; Muthén & Muthén, 2011). For computation of simple effects and mediation analyses, Bayesian statistics were used using non-informative priors, as this type of analysis is not relying on data distribution assumptions (Muthen, Muthén, & Asparouhov, 2017; Muthén & Muthén (2011)). Note that the distribution of avoidance behavior was rather skewed, with a large proportion of participants avoiding all the time and many participants trying out avoidance once (see Supplements Figure S4 for a graphical display).

To obtain a standardized effect size for the indirect effect, a StdYX standardization was chosen (Muthén, Muthén, & Asparouhov, 2016), multiplying the indirect effect by the standard deviation of the independent variable divided by the standard deviation of the dependent variable. In line with Cohen (1992), we interpret 0.2 to 0.5 as a small, $\geq\!0.5$ as medium, and $\geq\!0.8$ as large effect size d. An alpha-level of $\alpha=0.05$ was chosen, with p-values below that level being judged as significant.

Note that the pattern of significance of results did not change if we controlled for tDCS (see review by Horvath, Forte, and Carter (2015) and Parkin, Bhandari, Glen, and Walsh (2019) on lack of evidence for cognitive effects from tDCS).

Bayes factors (*BF*; Depaoli & van de Schoot, 2017; Miočević, 2019; Yuan & MacKinnon, 2009) computed in JASP (2017) are reported for main results, allowing interpretations in favor of the H₀ (implying no group differences). *BF* quantify the relative evidence of the data supporting H₁ and H₀. IF a *BF* > 1, the data supports H₁ over H₀. If a *BF* < 1, the data supports H₀ over H₁. If a *BF* \approx 1, the experiment was not sensitive (Dienes, 2011). Moreover, Jeffreys (1961) suggested that a *BF*₁₀ < 1/3 could be interpreted as substantial relative evidence of the data supporting H₀ over H₁; a *BF*₁₀ > 1/3 and < 3 as no evidence to speak of, and a *BF*₁₀ > 3 as substantial relative evidence of the data supporting H₁ over H₀. Though, as pointed out by Jeffreys "the evidence is continuous and there are no thresholds as such in Bayesian theory" (p.277).

We chose a default Cauchy prior distribution with scale of 0.354, as implemented in JASP (Ly, Verhagen, & Wagenmakers, 2016).

Exploratory Analyses. For our simple effects, the different subscales (facets) within the neuroticism scale were examined (anxiety, angry hostility, depression, self-consciousness, impulsiveness, vulnerability).

3. Results

The US was rated as sufficiently unpleasant (M = 6.71, SD = 0.88; scale 1–9) and mildly painful (M = 4.71, SD = 1.23; scale 1–9).

Manipulation Check (see Fig. 2a & b for mean US-expectancy ratings and SCR in the course of conditioning).

US-expectancy ratings. A main effect for CS-Type was found (F(1,162) = 1354.11, p < .001, $\eta_p^2 = 0.89$); compared to the CSminus (M = 7.07, SD = 18.57), participants rated the CSplus1 to be more likely followed by the US (M = 88.64, SD = 17.44; F(1,162) = 1591.82, p < .001, $\eta_p^2 = 0.91$), as was the CSplus2 (M = 90.06, SD = 16.89; F(1,162) = 1540.55, p < .001, $\eta_p^2 = 0.91$).

SCR. A main effect for CS-Type was found $(F(1,135) = 71.26, p < .001, \eta_p^2 = 0.35)$; compared to the CSminus (M = -0.025, SD = 0.074), participants showed higher SCR to the CSplus1 $(M = 0.101, SD = 0.132; F(1,135) = 100.29, p < .001, \eta_p^2 = 0.43)$, as well as to the CSplus2 $(M = 0.064, SD = 0.112; F(1,135) = 74.89, p < .001, \eta_p^2 = 0.36)$.

3.1. Avoidance acquisition

US-expectancy ratings. Participants successfully learned that the CSplus1 with avoidance option (M = 7.55, SD = 20.32) was not followed

by the US, compared to the CSplus1 without avoidance option (M = 95.02, SD = 12.51; F(1,162) = 1916.05, p < .001, $y_p^2 = 0.92$).

SCR. Participants showed higher SCR to the CSplus1 without avoidance option (M=0.066, SD=0.125) compared to the CSplus1 with avoidance option (M=-0.004, SD=0.057; F(1,140)=41.74, p<0.01, $y_p^2=0.23$).

3.2. Simple effects: influence of acquisition learning on avoidance

US-expectancy acquisition learning was not related to avoidance (b=0.010, p=.152, 95% CI[-0.004; 0.023], $R^2=0.012$, $BF_{10}=0.44$). However, there was some evidence that increased differential *SCR* was related to increased avoidance (b=4.11, p=.010, 95% CI[0.94; 7.30], $R^2=0.046$, $BF_{10}=3.71$).

Subsequent analyses showed that this effect may in part be explained by increased *SCR* CSplus (b=3.30, p=.070, 95% CI[-0.27; 6.90], $R^2=0.024$, $BF_{10}=0.85$) and not *SCR* CSminus (b=-4.04, p=.146, 95% CI [-9.53; 1.43], $R^2=0.016$, $BF_{10}=0.50$).

3.3. Simple effects: influence of avoidance on protection-from-extinction

The more participants avoided, the higher was their protection-from-extinction *US-expectancy* rating (b=10.16, p<.001, 95% CI[7.90; 12.43], $R^2=0.33$, $BF_{10}>999$) as well as differential *SCR* (b=0.014, p=.004, 95% CI[0.001; 0.024], $R^2=0.058$, $BF_{10}=8.31$) during test phase.²

Follow up analyses showed that this effect was due to increased *US-expectancy* CSplus ($b=10.67,\ p<.001,\ 95\%$ CI[8.63; 12.73], $R^2=0.039,\ BF_{10}>999$) and *SCR* CSplus ($b=0.013,\ p=.010,\ 95\%$ CI[0.003; 0.023], $R^2=0.048,\ BF_{10}=4.24$); not due to *US-expectancy* CSminus ($b=0.51,\ p=.414,\ 95\%$ CI[-0.74; 1.76], $R^2=0.005,\ BF_{10}=0.23$) nor *SCR* CSminus ($b=-0.001,\ p=.634,\ 95\%$ CI[-0.007; 0.004], $R^2=0.004,\ BF_{10}=0.20$).

3.4. Secondary Mediation Analyses: acquisition learning explains protection-from extinction via avoidance

As depicted in Fig. 3, stronger *SCR* acquisiton learning was linked to more avoidance, which in turn was linked to more SCR protection-from-extinction. Thus, avoidance (partially) mediated to relationship between SCR acquisition learning and SCR protection from extinction.

As *US-expectancy* acquisition learning was not related to avoidance, no indirect effect of avoidance behaviour between US-expectancy acquisiton learning and US-expectancy protection-from-extinction was found (b = .10, p = .154, 95% CI[-0.04; 0.24], StdYX = 0.06).

3.5. Influence of individual trait differences on acquisition learning, avoidance, and protection-from-extinction

SS and neuroticism scores were not significantly correlated (r=-0.041, p=.600, $BF_{10}=0.11$), neither were SS and the neuroticism subscales anxiety (r=-0.173, p=.028, $BF_{10}=1.09$, indicating no evidence to speak of), angry hostility (r=-0.004., p=.961, $BF_{10}=0.10$), depression (r=-0.046, p=.562, $BF_{10}=0.12$), self-consciousness (r=-0.179, p=.022, $BF_{10}=1.30$, indicating no evidence to speak of), and vulnerability (r=-0.032, p=.686, $BF_{10}=0.11$). Only impulsiveness was significantly correlated with sensation seeking (r=0.317, p<.001, $BF_{10}=457$).

Influence of SS and neuroticism on acquisition learning. SS (M = 19.97, SD = 5.39; scale 0–40, range 1–31) was neither related to US-expectancy (b = 0.30, p = .454, 95% CI[-0.48; 1.07], R^2 <0.01, BF_{10} =

¹ Note that BFs changed depending on prior, see Supplements Table S1.

 $^{^{2}\,}$ Note that findings were not influenced by choice of prior, see Supplements Table S2.

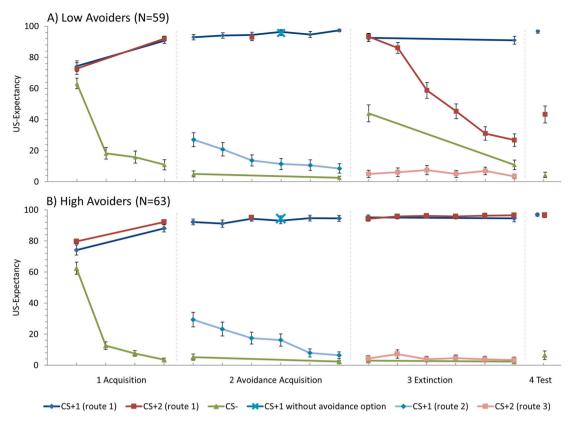


Fig. 2a. Mean US-expectancy ratings in the course of conditioning and extinction for A) participants choosing the avoidance option (R3) throughout all six extinction trials (i.e., high avoiders) and B) participants choosing the shortcut R1 five to six times throughout the six extinction trials (i.e., low avoiders). US-expectancy was rated trial-wise; in trials without choice option, participants rated the accessible route only; in all other trials (two accessible routes), participants rated each route separately (i.e., the CS+1 during avoidance acquisition and the CS+2 during extinction). Bars represent standard errors (SE). Note that 41 participants were not included in this graphical display of the course of conditioning because they did not show a consistent avoidance pattern (see Figure S4 in the Supplements); however, all participants were included in the statistical analysis.

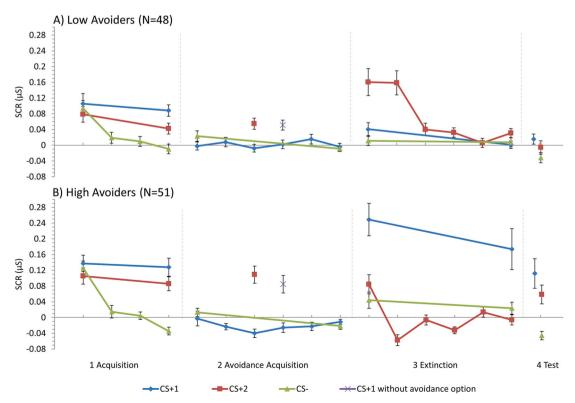


Fig. 2b. Mean SCR in the course of conditioning and extinction. For details see Fig. 2a.

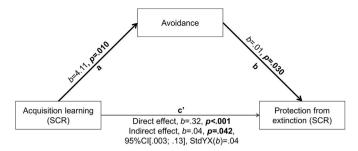


Fig. 3. Mediation model in which acquisition learning (SCR) was used for predicting protection-from-extinction (SCR) via avoidance. Numbers represent beta values.

Alpha level: ***p < .001, **p < .01.

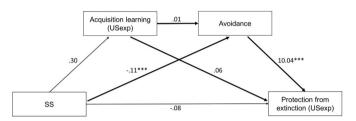


Fig. 4. Serial mediation model in which SS was used for predicting protection-from-extinction (USexp = US-expectancy) via acquisition learning (USexp; first mediator) and avoidance (second mediator). Numbers represent beta values. Alpha level: ***p < .001, **p < .01.

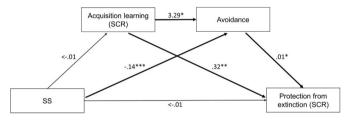


Fig. 5. Serial mediation model in which SS was used for predicting protection-from-extinction (SCR) via acquisition learning (SCR; first mediator) and avoidance (second mediator). Numbers represent beta values. Alpha level: ***p < .001, **p < .01, *p < .05.

0.22) nor to SCR acquisition learning (b=-0.003, p=.102, 95% CI [-0.007; 0.001], $R^2=0.019$, $BF_{10}=0.22$). Neuroticism (M=87.27, SD=21.32; scale 0–192, range 28–136) was neither related to US-expectancy (b=-0.15, p=.126, 95% CI[-0.35; 0.04], $R^2=0.01$, $BF_{10}=0.51$) nor SCR (b<0.000, p=.676, 95% CI[-0.001; 0.001], $R^2=0.004$, $BF_{10}=0.19$). None of the neuroticism subscales showed a significant relationship with either US-expectancy ($ps\ge.098$; $BFs_{10}\le0.62$) or SCR acquisition learning ($ps\ge.344$; $BFs_{10}\le0.27$).

Simple Effects: Influence of SS and neuroticism on avoidance behaviour. SS was related to decreased avoidance (b=-0.11, p=.002, 95% CI[-0.18; -0.05], $R^2=0.062$, $BF_{10}=24.53$), whereas neuroticism was not related to avoidance (b=-0.007, p=.392, 95% CI[-0.025; 0.010], $R^2=0.005$, $BF_{10}=0.24$). None of the neuroticism subscales showed a significant relationship with avoidance $(ps \ge .070; BFs_{10} \le 0.74)$.

Simple Effects: Influence of SS and neuroticism on protection-from-extinction. SS was neither related to decreased US-expectancy protection-from-extinction (b=-1.17, p=.052, 95% CI[-2.35; 0.01], $R^2=0.02$, $BF_{10}=0.96$) nor to differential SCR (b=-0.003, p=.186, 95% CI[-0.007; 0.001], $R^2=0.013$, $BF_{10}=0.41$). Neuroticism was neither related to US-expectancy (b=0.11, p=.458, 95% CI[-0.19; 0.42], $R^2<0.01$, $BF_{10}=0.22$), nor SCR protection-from-extinction (b=0.12)

= 0.001, p = .576, 95% CI[-0.001; 0.001], R^2 = 0.004, BF_{10} = 0.21). Except for the subscale impulsivity (p = .020), with a BF pointing to no evidence to speak of (BF_{10} = 2.29), none of the other neuroticism subscales showed a significant relationship with either *US-expectancy* ($ps \ge .058$, $BF_{310} \le 0.91$) or *SCR* acquisition learning ($ps \ge .164$, $BF_{10} < .45$).

3.6. Secondary analyses: serial mediation - influence of SS on protection-from-extinction mediated by acquisition learning (first mediator) and avoidance (second mediator).³

US-expectancy (see Fig. 4). An indirect effect of SS on protection-from-extinction via avoidance was found (b=-1.13, p<.001, 95% CI[-1.90; -0.46], StdYX=0.15). SS decreased protection-from-extinction indirectly via decreasing avoidance. No indirect effect of SS on protection-from-extinction via acquisiton learning was found (b<0.01, p=.750, 95% CI[-0.08; 0.16], StdYX<0.01). No serial indirect effect of SS on protection-from-extinction via acquisition learning and avoidance was found (b=0.02, p=.518, 95% CI[-0.06; 0.17], StdYX<0.01).

SCR (*see Fig. 5*). A small indirect effect of SS on protection-from-extinction SCR via avoidance was found (b = -0.001, p = .046, 95% CI[-0.003; 0.000], StdYX = -0.04). SS decreased protection-from-extinction SCR indirectly via decreasing avoidance. No indirect effect of SS on protection-from-extinction SCR via acquisition learning was found (b = -0.001, p = .106, 95% CI[-0.003; 0.000], StdYX = 0.04).

No serial indirect effect of SS on protection-from-extinction SCR via acquisition learning SCR and avoidance was found (b < -0.001, p = .166, 95% CI[< -0.001; < 0.001], StdYX = -0.04).

4. Discussion

The present study had three main aims. First, to replicate and extend previous findings with regard to acquisition learning and avoidance second with 2014), regard protection-from-extinction effect (Lovibond et al., 2009; Rattel et al., 2017). Third, to investigate the role of personality trait differences on acquisition learning, avoidance, and extinction learning in a naturalistic conditioned avoidance paradigm. Replicating past findings (Pittig et al., 2014), increased physiological SCR but not US-expectancy acquisition learning was linked to increased avoidance. Moreover, frequent instrumental avoidance behaviour was linked to protection-from-extinction (for both US-expectancy and SCR), i.e., a preservation of fear responses during test phase (Lovibond et al., 2009; Rattel et al., 2017). In terms of individual trait differences, high SS was linked to reduced avoidance, which in turn reduced post-extinction US-expectancy and SCR. Present findings highlight the key role of maladaptive avoidance behaviour in the maintenance of fear responses and emphasize the importance of taking into account inter-individual differences in conditioning and avoidance.

4.1. Replicating past findings

The present study not only replicated past findings linking increased physiological acquisition learning to avoidance, it furthermore showed that both acquisition learning and avoidance mutually influenced fear extinction (i.e., protection-from-extinction). Mediational analyses revealed that SCR acquisition learning increased SCR protection-from-extinction indirectly via increased avoidance (see Fig. 3); though, as avoidance only partially mediated this relationship, SCR acquisition learning remained a significant direct predictor of protection-from-extinction. Moreover, exploratory analyses revealed that increased

³ Note that neuroticism was not further investigated in our secondary analyses, as we did neither find a relationship between neuroticism and acquisition learning nor avoidance.

responding to the CSplus, and not to the CSminus, during fear acquisition and extinction explained this relationship. Deficient stimulus discrimination or fear generalization have been proposed as mechanisms explaining the development of anxiety-related disorders, reflected in fear responses to harmless stimuli or situations (e.g., Dunsmoor & Paz, 2015; Grillon & Morgan, 1999). However, in the present study, increased avoidance was linked to fear responding (CSplus) only and not to the safe CSminus. In summary, on the one hand, present findings support the idea of Pavlovian conditioning and instrumental avoidance behaviour being two factors mutually contributing to the development of anxiety-related disorders (Lovibond, 2006; Mowrer, 1960). On the other hand, they make clear that increased physiological acquisition learning is related to protection-from-extinction beyond its effects on avoidance.

The present study found no effect of US-expectancy acquisition learning on avoidance and subsequent fear extinction. According to Lovibond's expectancy model (2006) acquisition learning and postextinction fear (i.e., protection-from-extinction) are linked by an individual's outcome expectancy. In the present study, during test phase, no avoidance option was available, similar to the acquisition phase. Participants may have thus expected shock, causing a return of fear directly influenced by their acquisition learning (see Fig. 2a & b). However, as the expectancy model solely focuses on expectancy learning and thereby giving less weight to more implicit emotional processes that may also be indicated by our physiological index of fear learning, it cannot fully explain the present findings. Better in line with present findings, a recent review by LeDoux et al. (2017) proposed that "subjective fear is not what causes avoidance to be acquired and sustained". According to these authors, avoidance may thus be primarily motivated and reinforced by nonconscious processes rather than conscious fear reduction (Anderson & Phelps, 2002; Feinstein et al., 2013). Therefore, present findings underline that subjective fear is not just the mere expression of a cognitive expectation but often represented in sympathetic autonomic preparatory activity.

Avoidance itself is not inherently maladaptive (Hofmann & Hay, 2018). However, it becomes maladaptive when it is excessive and persists in the absence of threat (i.e., during extinction). Maladaptive avoidance preserves threat beliefs, thereby impeding fear extinction, and is often related to long-term costs. Anxiety patients often face an approach-avoidance decision-making conflict similar to decision-making conflict faced by our participants during the extinction phase (Aupperle & Paulus, 2010; Stein & Paulus, 2009): their decision to avoid entails a trade-off between a positive short-term outcome (evade threat-path; clinical equivalent, e.g., avoidance of social situation that may induce fear) and a costly negative long-term outcome (longer time-expenditure; clinical equivalent, e.g., missed job opportunities in social anxiety). During exposure treatment and long-term maintenance of therapy gains in daily life of patients it is thus crucial to prevent avoidance responses in order to successfully decrease anxiety (e.g., Salkovskis, Clark, Hackmann, Wells, & Gelder, 1999). Our avoidance paradigm provides a relatively naturalistic laboratory analogue for investigating mechanisms underlying avoidance behaviour and the protection-from-extinction-effect in the development, maintenance, and relapse of anxiety-related disorders. As has been pointed out recently (Servatius, 2016), extinguishing avoidance behaviour is likely even more difficult than extinguishing fear. Thus, understanding why some people are more likely to avoid than others can potentially help to find targets for individualized prevention and treatment plans.

4.2. Effects of individual trait differences on avoidance and extinction

In line with previous reviews emphasizing the importance – and at the same time lack – of literature on individual trait differences in conditioning research (Krypotos et al., 2018; Lonsdorf & Merz, 2017), the present study investigated effects of SS and neuroticism on avoidance and fear extinction. We found that high SS went along with reduced

protection-from-extinction (SCR and US-expectancy) indirectly via decreased instrumental avoidance. SS was not related to acquisition learning, possibly explaining the lack of previous publications on this. Neuroticism was neither related to fear acquisition, avoidance, nor protection-from-extinction. Findings for neuroticism revealed Bayes factors below 1/3, implying that the null model (no effect of neuroticism) is more probable than H_1 .

Present findings of decreased avoidance in high SS were supported by a large Bayes factor and are in line with the study by Biedermann et al. (2017) that linked SS to approach compared to avoidance behaviour in an elevated plus-maze. Those findings also fit with claims by Zuckerman (1994), proposing approach behaviour to intense, novel, and often dangerous situations in high SS. Thus, in terms of an approach-avoidance conflict faced during extinction in our study, high SS individuals resolved this conflict in congruence with their risk propensity and more likely chose approach than avoidance behaviour. This implies that individual differences in SS may change how the trade-off between positive short-term and negative long-term outcomes is weighted. Besides not caring much about the risk of receiving shocks on the short path, high sensation-seekers may have perceived the detour as particularly boring and thus more costly, making approach behaviour more likely as approach behaviour increases with increasing costs (Rattel et al., 2017). Present results highlight that fostering person's approach motivation, e.g. by learning to adopt more sensation-seeking behaviours, may decrease avoidance, as has been previously shown in studies using competing rewards (Bublatzky, Alpers, & Pittig, 2017; Schlund et al., 2016).

No relationship between neuroticism and avoidance was found in the present study, with a Bayes factor supporting H₀, i.e. the absence of an effect of neuroticism. Moreover, the neuroticism sum score as well as all subscales, except for the impulsivity subscale, were not related to SS, in line with previous findings (Panitz et al., 2018). Impulsivity was correlated with SS and we found some evidence that increased impulsivity decreased protection-from-extinction; though, we did not find a relationship between impulsivity and avoidance. Therefore, the impulsivity subscale of neuroticism may overlap with some personality facets measured by SS (like the subscale disinhibition); however, they do not fully tap into the same underlying construct (Steinberg et al., 2008; Whiteside & Lynam, 2001). Note that none of the other neuroticism subscales showed a relationship with either acqusition learning, avoidance, or protection-from-extinction. These null-findings are in line with previous studies that mostly failed to link neuroticism to either increased acquisition or slowed extinction learning (see review by Lonsdorf & Merz, 2017). In contrast, Lommen et al. (2010) linked high neuroticism to more frequent button press avoidance during extinction, if avoidance decision latency was long enough (5sec but not 1sec) using a generalization paradigm. Compared to Lommen et al. (2010), the current study's procedure was optimized to rather naturalistically model free-choice avoidance decisions incorporating costs (contrasting mere button press) in anxious patients, possibly explaining diverging results; in addition, the present study used larger sample size (N = 163)compared to Lommen and colleagues (N = 55). In summary, although neuroticism has been proposed as a risk factor for clinical anxiety (Jorm et al., 2000; Watson et al., 2005), the present study could not link neuroticism to fear acquisition, avoidance, or extinction.

4.3. Strengths and limitations of the present study

Strengths. The present study extended our past findings (Rattel e al., 2017), with a larger sample size and assessing SCR. Thereby, we could replicate our findings showing that avoidance behaviour in a free-choice avoidance paradigm prevents extinction as evidenced by increased US-expectancy and SCR. Moreover, we replicated and extended findings by Pittig et al. (2014) showing that increased SCR acquisition learning resulted in more instrumental avoidance in a more naturalistic, free-choice avoidance paradigm. Thereby, we assessed fear expression

on three different levels, namely cognitive (US-expectancy ratings), behavioural (avoidance), and physiological (SCR; Bradley & Lang, 2000; Wilhelm et al., 2017) in a relatively large sample.

In terms of individual differences, the present study was the first to investigate how SS and neuroticism affect avoidance and, in turn, protection-from-extinction. We used continuous trait measurements in the statistical analyses, compared to previous studies often using median split (e.g. Lissek et al., 2005; see review by; Lonsdorf & Merz, 2017). We examined both negative and positive affect-related traits, as opposed to the typical focus on negative traits in the fear conditioning literature. Both appetitive and aversive systems play a role in internalizing pathology (Bijttebier, Beck, Claes, & Vandereycken, 2009) and may have transdiagnostic importance.

We believe that the present study's experimental design entails more ecological and face validity than most of the previous study designs using button-press (see review by Krypotos et al., 2018 for discusion). By using a time-consuming detour, we introduced avoidance costs (time expenditure) that are self-relevant to our student population (Mischel, Grusec, & Masters, 1969; Wilson et al., 2014). As avoidance responses in anxiety-related disorders may also result in a larger expenditure of time (i.e., time-consuming detours when avoiding elevators, bridges, or tunnels), we believe that a lengthy detour is a suitable analogue for naturalistic avoidance costs.

Limitations and Concerns. We also want to name some of the present study's limitations and stress some concerns that could possibly explain the null findings regarding neuroticism. First of all, SS and neuroticism reside on different hierarchy levels in terms of how personality is organized (John, Naumann, & Soto, 2008, pp. 114–158). Whereas SS is a rather narrowly defined construct, neuroticism covers a broad range of personality facets. To resolve this issue, future studies may consider using the extraversion trait from the NEO-PI-R (instead of or in addition to SS) and conduct parallel analyses to the neuroticism trait. In addition, although the present study's sample size was large, it might have still not been sufficient to find significant (possibly rather small) effects for neuroticism (see Schönbrodt & Perugini, 2013 for recommendations on sample size).

Moreover, we tested women only, who were primarily Caucasian students (with about 50% psychology undergraduates). This may restrict generalizability to other populations, particularly to men, as past research suggests sex differences in fear conditioning (Craske, 2003; Rattel et al., 2019b); Rattel et al. showed increased acquisition and slowed extinction learning in women compared to men, which explained increased PTSD-like symptomatology in women. Therefore, present findings may not generalize to men, with the here found links between acquisition learning, avoidance, and protection-from-extinction possibly being one mechanism explaining the higher propensity towards anxiety-related disorders in women than men (McLean et al., 2011).

We furthermore want to note that it has been proposed that fear generalization paradigms (see review by Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015) as well as the use of partial reinforcement may be more sensitive to individual differences by creating a less "strong situation" resulting in more inter-individual variance in task response during fear acquisition (Lissek, Pine, & Grillon, 2006; Lonsdorf et al., 2017). The present study did, however, entail an ambiguous extinction context, which may well be suited to study individual differences. Supplementary analyses indicated reasonable variance in task response at end of acquisition and during the protection-from-extinction test (see Supplements, Figure S2 & S3).

In addition, the questionnaires assessing individual differences were filled out right before the experimental session, which may have increased anxiety levels in our sample; thus, future studies should assess these data at least one day before the experimental session. Moreover, although the present study's avoidance costs have better face validity than most previous designs, the present study may lack other criteria of external validity (see Vervliet & Raes, 2013); thus, findings should be generalized and interpreted with caution.

Moreover, we want to note that BF can change depending on the prior chosen (see Supplements for sensitivity analyses on particularly relevant results). Exploratory analyses revealed that interpretation of relative evidence for acquisition learning predicting avoidance depended on the prior chosen (in line with our non-significant p-values); though, findings for avoidance increasing protection-from-extinction did not depend on the chosen prior (all BFs indicated relative evidence for H₁). Lastly, we want to note that, although significant, some of the observed effect sizes are small and this should be kept in mind when interpreting the clinical relevance of some of the findings.

4.4. Future directions

We believe that future research should further investigate the assumption that avoidance behavior is primarily regulated by implicit processes (LeDoux & Pine, 2016), using a conditioned avoidance paradigm assessing neural responses in, e.g., areas of the saliency network, besides SCR, and US-expectancy. Moreover, likely additional, clinically relevant individual trait differences such as early adversity (e.g., Rattel et al., 2019a; Remmes et al., 2016) may govern avoidance decisions and explain further variance in fear extinction. In addition, although sex differences exist in fear conditioning (Lonsdorf & Merz, 2017; Rattel et al., 2019b), no study has yet investigated sex differences in avoidance. In summary, research on individual trait differences in fear extinction, particularly with respect to the important mechanism of avoidance, is still in its infancy. Fostering sensation seeking-congruent attitudes and behaviours in anxious patients lacking them may help them reduce their avoidance-propensity in the long-term and increase treatment success (e.g., Watkins, Sprang, & Rothbaum, 2018).

5. Conclusion

Present findings highlight the important role of maladaptive instrumental avoidance behaviour in the maintenance of fear responses. They propose that individual trait differences in SS are linked to post-extinction fear responses via avoidance behaviour; high sensation seekers may be less likely to develop and maintain anxiety-related disorders following aversive experiences, as they are more likely to choose approach behaviours and overcome conditioned fear responses. Studying inter-individual differences can provide missing links in the current understanding of what may have driven fear acquisition, avoidance behaviour, and deficient fear extinction in patients with anxiety-related disorders during the development and maintenance of the disorder; ultimately, this will help to individualize treatment plans and thereby increase treatment success (Hayes et al., 2019).

CRediT authorship contribution statement

Julina A. Rattel: Conceptualization, Methodology, Formal analysis, Writing - original draft. Stephan F. Miedl: Conceptualization, Methodology, Software, Visualization. Michael Liedlgruber: Software, Data curation, Formal analysis, Visualization. Jens Blechert: Conceptualization. Esther Seidl: Conceptualization, Data curation. Frank H. Wilhelm: Conceptualization, Methodology, Supervision, Writing - review & editing.

Declaration of competing interest

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2020.103761.

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