



Measuring extinction learning across the lifespan – Adaptation of an optimized paradigm to closely match exposure treatment procedures

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ABSTRACT

Here, we tested the feasibility of a new paradigm developed to investigate the mechanisms of exposure-therapy. The protocol was previously developed for the use with adults and optimized to closely model the mechanisms underlying exposure, i.e. extinction learning. We adapted this paradigm for the use with children, and tested its feasibility in children and adult participants. We used an aversive acoustic unconditioned stimulus (US), picture-based rating scales and a child-oriented instruction/practice procedure. Results indicate robust fear acquisition, extinction and reinstatement on a self-report (US-expectancy) and on a physiological (startle reflex) level. We found evidence for the paradigms sensitivity to age and anxiety-dependent individual differences in fear-learning and extinction. We conclude that the present paradigm is capable of modeling the key mechanisms of exposure-therapy, that is extinction-learning, and can be accomplished with children, adolescents and adults, rendering it promising to bridge the gap between experimental protocols and treatment across the lifespan.

1. Introduction

Extinction learning is thought to be a core mechanism underlying the reduction of pathological fear during exposure therapy in both children and adults (In-Albon & Schneider, 2006; McGuire, Lewin, & Storch, 2014; Milad & Quirk, 2012; Vervliet, Craske, & Hermans, 2013; Waters & Pine, 2016). In this regard, laboratory-based models of extinction learning are a promising experimental treatment model to improve exposure (e.g., Anderson & Insel, 2006; Pittig, Van Den Berg, & Vervliet, 2016). They facilitate our understanding of basic learning mechanisms relevant to exposure therapy, and thus have a translational potential to improve treatments that focus on extinction learning.

However, despite promising attempts (e.g., Raeder et al., 2019; Zlomuzica, Preusser, Schneider, & Margraf, 2015; for a review of recent approaches see Lipp, Waters, Luck, Ryan, & Craske, 2020), the translation of these findings from bench to bedside remains a yet unresolved challenge (Richter, Pittig, Hollandt, & Lueken, 2017). Recently, it has been argued that this might be in part due to a methodological gap between experimental protocols and treatment procedures (Hollandt et al., 2020). To bridge this gap, the same authors presented an optimized paradigm for use in adult research, aimed at improving the match

between experimental extinction training and exposure-based treatment.

In brief, the paradigm has been optimized in several ways (see Hollandt et al., 2020 for more details):

- (1) The paradigm allows fear memory consolidation. That is, participants acquire the fear response on day one, while extinction learning is accomplished 24 h later on day two, after fear memory consolidation. Indeed, the delay between fear-acquisition and extinction training has been shown to influence the time course and endpoint of fear extinction (Lonsdorf et al., 2017). Moreover, allowing for fear memory consolidation before extinction learning is ecologically more valid and clinically relevant, because it more closely models the generally highly consolidated fear memory in pathological anxiety (Lonsdorf et al., 2017). Thus, the employment of delayed extinction protocols has been recommended (Lonsdorf et al., 2017).
- (2) Participants are informed about CS-US contingencies prior to fear acquisition to facilitate fear acquisition and to assure comparable levels of fear across participants. Non-instructed fear acquisition results in large individual differences in the acquisition of

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conditioned fear (Lonsdorf & Merz, 2017), hampering the interpretation of results from post-acquisition phases. Thus, instructed fear procedures are recommended, when more uniform fear learning is desired and post-acquisition phases (i.e., the extinction phases within the present study) are targeted (Lonsdorf, et al., 2017).

- (3) Prior to each trial, participants are informed about the upcoming stimulus (either a CS+ or a CS-), and a US contingency rating (i.e., risk assessment) is taken resembling the assessment of central concerns towards the feared stimulus prior to exposure in exposure-based treatment protocols. Such a procedure thus enables the assessment of risk-overestimation, a critical feature in pathological anxiety (Lonsdorf et al., 2017).
- (4) A return of fear test (i.e., reinstatement procedure) is included. Return of fear after successful extinction models relapse after successful exposure-based treatment and is thus suited to assess inhibitory memory recall, a central process for symptom relapse after successful treatment (Haaker, Golkar, Hermans, & Lonsdorf, 2014). Thus, the reliable assessment of return of fear is crucial to enhance the ecological validity of extinction learning procedures in terms of its clinical relevance.
- (5) Finally, a medium CS-US contingency rate was used to assure reliable fear acquisition and considerable variance in extinction learning (for details see, Lonsdorf et al., 2017).

Despite the importance of childhood anxiety disorders for mental health and/ or illness over the life span (Kessler et al. 2005; Kossowsky et al. 2013), remarkably little basic and mechanistic treatment research exists in the field (Seehagen, Margraf, & Schneider, 2014). Within the scope of the present study, we aimed at adapting the above described novel extinction learning protocol for the use with children and adolescents to gain a protocol which can be used across the lifespan. Adapting the current paradigm for the use with children might help to bridge the gap between experimental psychopathology research considering adults and children and might thus enhance translational research over the lifespan. It might further help to foster standardization among the methodologically diverse paradigms currently used in developmental fear conditioning research (for a comprehensive overview see Ryan et al., 2019).

The suggested protocol (see Hollandt et al., 2020, for details) was designed for adult participants, and thus does not match the methodological requirements of experimental fear conditioning and extinction procedures in children and adolescents (i.e., the usage of an aversive electrical shock as US, language-based rating scales, probability-based assessment of expectancy ratings etc.). However, an experimental paradigm which (1) closely models the key ingredients of exposure-based treatments and (2) is applicable for adults, adolescents and children would be highly beneficial, as it would allow to assess the mechanisms underlying exposure-based treatments across the entire lifespan. Indeed, research so far has found both similarities and differences between adult and childhood anxiety disorders, as well as for their treatments. Like for adults, anxiety disorders are among the most prevalent mental disorders in children and adolescents (Cartwright-Hatton, McNicol, & Doubleday, 2006; Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015; Schneider & Seehagen, 2014), and exposure-based cognitive behavior therapy (CBT) is the treatment of choice for childhood anxiety disorders with comparable relapse and non-response rates as for adults (Ale, McCarthy, Rothschild, & Whiteside, 2015; Davis, May, & Whiting, 2011; In-Albon & Schneider, 2006; Reynolds et al., 2012; Taylor, Abramowitz, & McKay, 2012).

Seen from the developmental perspective, contrary to the fully developed adult brain, the neuronal extinction network undergoes substantial development during childhood and adolescence (e.g., Konrad et al., 2020). For example, extinction learning in general has been found to be superior in children and adults as compared to adolescents (Ganella, Drummond, Ganella, Whittle, & Kim, 2018; Pattwell et al.,

2012; Water et al., 2017), most likely due to developmental restructuring of the extinction network during adolescence (Pattwell et al., 2012). Notably, there are also findings not supporting deficient extinction learning in adolescents (Den, Graham, Newall, & Richardson, 2015; Shechner et al., 2015). Interestingly, although extinction might to be impaired during adolescence, meta-analytic data show larger effect sizes for exposure-based CBT in adolescents as compared to children at younger ages (Reynolds, Wilson, Austin & Hooper, 2012).

To date, despite the above-mentioned evidence, it is still an open question whether developmental differences in the extinction network also differentially affect the course of anxiety disorders or the outcome of exposure-based treatments. Very few studies have yet examined these mechanisms within childhood anxiety disorders (for an overview see Dvir, Horovitz, Aderka, & Shechner, 2019; Jovanovic, Nylocks, & Gamwell, 2013), or their association with the outcome of exposure-based treatments (Waters & Pine, 2016), and to the best of our knowledge only a handful of studies to date compared extinction learning across different age groups, yielding mixed findings (Den, Graham, Newall, & Richardson, 2015; Jovanovic et al., 2014; Pattwell et al., 2012; Waters, Theresiana, Neumann, & Craske, 2017).

In sum, these findings highlight the need for cross-sectional and longitudinal studies covering the entire lifespan to understand the interplay of developmental trajectories of the extinction network with the mechanisms underlying the outcome of exposure-based treatments. Knowledge about these mechanisms is a prerequisite to enhance exposure-based treatments for children, adolescents, and adults. However, to successfully accomplish cross-sectional studies across the lifespan it is essential to assure that the paradigms used (1) show high correspondence between experimental extinction training and exposure-based treatment procedures, and (2) the mechanisms under observation (i.e., fear conditioning, extinction learning, etc.) are operationalized accordingly in children, adolescents and adults.

1.1. Aim of the current study

The aim of the present study was to test the feasibility of an experimental protocol, which, as accurately as possible, depicts the underlying processes of exposure-based treatments – that is extinction learning – and can be applied across the life span. For this purpose, a recently established paradigm (Hollandt et al., 2020), with improved construct and predictive validity for exposure-based treatments in adults (see above), was adapted for the use with children and adolescents. For the current study, the paradigm was modified to correspond with the requirements for the use with children and adolescents. An aversive acoustic US replaced the electroshock US used in adult studies, picture-based rating scales were developed for the assessment of self-report online ratings and a comprehensive instruction and practice procedure was established to enable also young children to accomplish online expectancy ratings. To test for the feasibility of the paradigm, we recruited a sample of children and adolescents (8–16 years) and adults in a cross-sectional design. Our main aim was to test, (1) whether the paradigm reliably assesses fear conditioning, extinction, as well as reinstatement within children, adolescents and adults (research question 1) and to (2) test its sensitivity for age-dependent individual differences (research question 2). In a set of exploratory analyses, we (3) tested the paradigms sensitivity to effects of trait-anxiety (research question 3).

2. Methods

2.1. Participants

A total of $N = 42$ participants were recruited for the present study. Adults were undergraduate students receiving course credit for participation. Children were recruited via web-based and word-of-mouth advertising. Overall, participants ranged in age from 8 to 39 years

(overall $M = 17.02$, $SD = 8.86$; children $M = 11.08$, $SD = 2.19$, range 8–16; adults $M = 26.69$, $SD = 6.77$, range 19–39). The sex distribution (children $n = 26$, male $n = 13$; adults $n = 16$, male $n = 4$) between the two groups did not differ significantly, $\chi^2_{df1} = 2.57$, $p = .11$.

All participants gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki, the German Federal Data Protection Act and the GCP-guideline. The study was approved by the ethics committee of the University of Bochum. The study was pre-registered at the German Clinical Trials Register (German CTR ID DRKS00009709). Of the 42 participants, two had to be excluded from the startle-analysis analyses because of startle non-response (non-response > 40% of startle probes) and startle-data of four participants were lost due to technical problems during data acquisition. Thus, for the startle-data, only $N = 36$ participants could be analyzed ($N = 22$ female, age $M = 18.1$, $SD = 8.9$).

2.2. Questionnaires

To assess trait anxiety, the trait form of the State Trait Anxiety Inventory was used. The adult (STAI-T) (Laux, Glanzmann, Schaffner, & Spielberger, 1981) and child versions (STAI-C) (Spielberger, 1973) both consist of 20 items, each assessing relatively stable individual differences in anxiety proneness on a four-point rating scale. Internal consistency was $\alpha = 0.87$ for the adult version and $\alpha = 0.80$ for the child version. The mean STAI score for the current sample was $M = 28.94$ ($SD = 4.50$). Children and adults did not differ significantly in the anxiety severity sum score, $t(39) = -1.03$, $p = .31$.

The participants current mood was assessed on two rating scales asking the participant to indicate how they feel (Valence Scale: 0 = very negative – 100 = very positive) and how aroused they are (Arousal Scale: 0 = very calm – 100 = very aroused) at that moment. All participants indicated a neutral mood state on both days (day1: valence: $M = 54.95$, $SD = 26.30$, arousal: $M = 51.63$, $SD = 25.03$; day2: valence: $M = 57.69$, $SD = 30.66$, arousal: $M = 39.45$, $SD = 32.69$).

In addition, an expectancy rating was assessed with a rating scale ranging from 0% to 100%. To make sure that children and adults fully understand the rating scale, they were comprehensively instructed on how to give US expectancy ratings, using three example questions on printed slides¹. For these example questions, the answer was either on the extreme points or right in the middle of the scale to allow children to easily grasp the concept of the scale (“If I drop an egg on the floor, how likely is it that the egg will break?”, “When I toss a coin, how likely is it that tails will be up?” and “If I drop a shoe on the floor, how likely is it that the shoe will break?”). Participants were asked to point with their finger on the correct answer on the slides. If they were giving a wrong answer, participants were asked for their explanation of the answer and if it was not plausible, the scale was explained again in different words until the participant understood the rating scale.

2.3. Fear-conditioning paradigm

The current paradigm closely resembles a previously established paradigm optimized to reliably assess mechanisms of exposure treatment (Hollandt et al., 2020). Methodological recommendations by Lonsdorf et al. (2017) are taken into account for the terminology, design, methods and analyses of the fear-conditioning paradigm. Moreover, full attention was given to an age-appropriate preparation of the entire paradigm and procedures. Therefore, the instructions and materials were fundamentally revised and adapted in this respect (for comprehensive information about methodological issues in psychophysiological studies with children please refer to Wilhelm, Schneider, & Friedman, 2006).

In brief, the paradigm consists of pre-conditioning, acquisition and extinction phases and a reinstatement test and was split over two days (day 1: pre-conditioning, acquisition; day 2 after a 24-hour delay: extinction, reinstatement). The aversive US was a female scream taken

from the International Affective Digitized Sounds Database (IADS; Bradley & Lang, 2007) with a duration of 3 s and an intensity of 80 dB presented binaurally through headphones (DT 770 M, Beyerdynamics GmbH, Germany). It has been successfully used as US in previous conditioning tasks (Britton et al., 2013; Haddad, Bilderbeck, James, & Lau, 2015; Lau et al., 2008). Two pictures of male faces depicting a neutral facial expression shaded in blue or yellow were taken from the Karolinska Directed Emotional Faces database (KDEF; Lundqvist, Flykt, & Ohman, 1998) to serve as CS+ and CS-, respectively. To ensure that the pictures were perceived as neutral by the children, 15 children rated how they feel while perceiving the respective face on a valence rating scale ranging from 0 (very negative) to 100 (very positive) beforehand. Children indeed rated both pictures as neutral ($M_1 = 56.13$, $SD_1 = 19.09$; $M_2 = 57.13$, $SD_2 = 23.02$) and there was no significant difference between the two pictures, $t(14) = -0.21$, $p = .84$.

The use of either picture as CS+ or CS- was counterbalanced across participants. During each trial, the picture was presented for 6 s with an intertrial interval (ITI) of 10–14 s. Prior to the beginning of each trial (for all CS+ and CS- presentations), participants were instructed to rate the probability of US occurrence (minimum response duration 2 s). Therefore, the presentation of the upcoming CS was preceded by a smaller version of the respective picture CS accompanied by a visual analogue scale optimized for the use with children, asking the participant to rate on a scale from 0 to 100 how much they think that the upcoming bigger picture will be followed by a scream-US. After participants accomplished this expectancy rating, the actual trial began after a delay of 3 s (see Fig. 1 for an example conditioning trial).

During the pre-conditioning phase on day 1, participants viewed the CS+ and CS- in absence of the US (two trials each). The acquisition phase involved 10 trials each of the CS+ and CS-. On 60% of the trials, and upon disappearance of the CS+ (after 6 s), the US was immediately presented accompanied by a black screen for 3 s. In trials without UCS, only a black screen was presented.

On day 2, the extinction training phase started with one re-acquisition trial (CS+ with US). The following extinction training phase was subdivided into three blocks of 10 trials of CS+ and 10 trials of CS- presentations each, presented in absence of the US. Prior to the last block, a reinstatement including three US presentations without any CS occurred. During each experimental phase (i.e., pre-conditioning, acquisition, extinction), CS+ and CS- were delivered in pseudo-randomized order with the exception, that no more than two CS+ or CS- in consecution. In total, two different orders were used and half of the participants have been allocated to each of the two different orders.

2.4. Psychophysiological recordings and apparatus

The startle eye-blink response was recorded from the orbicularis oculi muscle using two Ag/AgCl electrodes (inner diameter: 5 mm, outer diameter: 20 mm) with hypertonic electrode cream placed beneath the left eye according to published guidelines (Fridlund & Cacioppo, 1986). Psychophysiological data were recorded using a Coulbourn amplifier system using a sampling rate of 1000 Hz and digitized with 12 bit. A 50 ms blast of white noise (95 dB/A) with instantaneous rise time was used to elicit the startle-reflex. Startle probes were presented within 8 presentations of the CS+ and CS- in the conditioning and the three blocks of extinction. To assure that the same number of probes are presented during the ITIs and the CS-presentations 16 probes were presented within the ITIs.

2.5. Procedure

Upon arriving at the laboratory (day 1 and 2), participants were asked to indicate how they are feeling at the moment. In addition, on day 1, participants filled out the STAI. On the first day, participants are shown around the laboratory and the general setup and procedure is explained to them. They are given the possibility to ask questions and

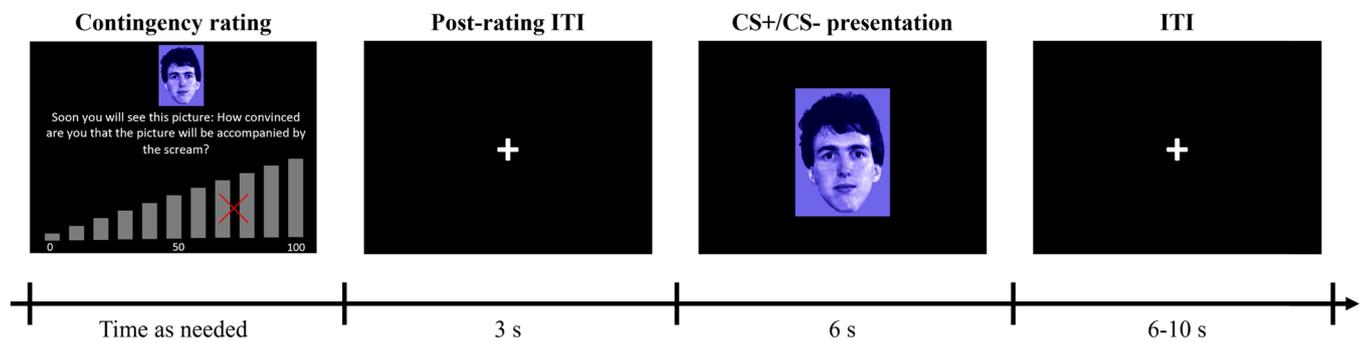


Fig. 1. Example of a single fear conditioning trial. The first slide announced the next stimulus and asked for the US expectancy rating. It was followed by a post-rating ITI. The next CS was presented and in 60% of the trials during conditioning in case of a CS+ presentation, the US accompanied the CS+. The CS presentation was followed by an ITI. Startle probes were presented during 8 presentations of the CS+ and CS- in the conditioning and the three blocks of extinction, 16 probes were presented during the ITIs. CS conditioned stimulus; US unconditioned stimulus; ITI intertrial interval. Adapted from [Hollandt et al. \(2020\)](#)².

are made aware of their right to discontinue the tasks at any time (without any consequences). Then, participants were instructed that they occasionally would be asked to do some self-report ratings during the experiment (i.e., US expectancy ratings). All rating scales and instructions were identical for children and adults. After participants had signaled full understanding of the rating scales, they practiced the ratings in three example trials on the computer. All ratings were given by mouse-click. In case the participant signaled no comprehensive understanding of the rating scales, the practice trials were accomplished again then accompanied by exemplifying questions, like “where would you have to click if you believe that the next picture is (not) accompanied by a scream?”.

Prior to the beginning of the first pre-conditioning phase, all participants received 6 startle probes to induce startle habituation (Presented with an interstimulus interval varying randomly between 3 and 5 s) and one US presentation for familiarization. Participants also gave an arousal (“how aroused did you feel when you were listening to the scream?”; range: 0 =not at all aroused, 100 =extremely aroused) and valence rating (“how did you feel when you were listening to the scream?”; range: 0 =extremely negative, 100 =extremely positive) in response to the US. For each phase, the instructions are depicted on the computer screen. All rating scales were language-free and have been previously developed to enhance validity of children’s self-reported emotional responses (for details see [Wilhelm et al., 2006](#)).

Prior to the beginning of the pre-conditioning phase, participants were explicitly instructed that no US would be given during this phase. Prior to the acquisition phase, participants were instructed that during this phase the US might be presented during the presentation of the CS+ but not during the CS-. Upon ending of the acquisition phase, electrodes were removed, and the participants were released.

On day 2, the experiment continued in the same room as on day 1. The second session took part at least 12 h (always including the night to assure consolidation during sleep) and always less than 24 h after the first session on day one. Prior to the beginning of the first extinction phase, participants again received again 6 startle probes to induce habituation. In addition, one CS+ was presented accompanied with a US for fear memory re-activation. Participants were instructed that during this phase some US presentations might be presented. However, no information was given about CS-US contingencies. The first and second extinction block were presented in consecution. Prior to the last 20 trials, and after a short break, participants received three presentations of the US to induce reinstatement. After the experiment had ended, electrodes were removed and participants were thanked for participation and received a compensation (i.e., adults: course credit; children: stuffed animal, toy, or a chocolate bar).

2.6. Data reduction

Startle data were analyzed offline using Brain Vision Analyzer Version 2.1. Raw-EMG data were notch (50 Hz) and bandpass-filtered (28–499 Hz, 24db/oct), rectified and smoothed using a 10 ms moving average. The response magnitude was calculated as the difference between the peak EMG response, 30–150 ms after the startle-probe, and the startle baseline, 20 ms before startle onset. Startle responses beginning prior to 30 ms after startle probe onset were excluded (1.40%). Non-responses (amplitudes < 2 *maximum during baseline; see [Grillon & Davis, 1995](#)) were scored as zero (11.31%). Missing values were replaced by that person’s average response to the respective CS (i.e. CS+ or CS-) within the respective experimental phase. The individual values were then z-standardized. For each experimental phase (i.e., pre-conditioning, acquisition, early extinction, intermediate extinction, late extinction/ post reinstatement) mean startle magnitudes were then calculated. To assess startle magnitude potentiation and to control for startle response habituation (see also [Lonsdorf et al., 2017](#)) we then calculated startle-response-potential-scores. This was done by subtracting the mean startle magnitudes obtained during the ITI from that respective experimental phase (mean ITI startle response) from the mean magnitudes during CS+ and CS- presentations (i.e., mean CS+ - mean ITI, mean CS- - mean ITI) obtained during the same experimental phase.

Analogous to the startle data, mean US expectancy ratings were calculated for each CS within each of the five experimental phases. To test for reinstatement effects on expectancy ratings and startle magnitudes, data from the last trial prior to reinstatement (i.e., last trial of intermediate extinction phase) and the first trial after reinstatement (i.e., first trial of late extinction/ post reinstatement phase) were subjected to analyses for each CS (i.e., CS+, CS-).

2.7. Statistical analyses

Analysis of general feasibility and age-dependent differences in fear conditioning and extinction (research question 1 and 2). Repeated measures analyses of variance (ANOVA) were conducted to test the fear acquisition, extinction and reinstatement effects on startle eye blink magnitudes and contingency ratings. To test for conditioning and extinction, mixed model ANOVAs including the within-individual independent variables CS (CS+, CS-) and experimental phase (pre-conditioning, acquisition, early extinction, intermediate extinction, extinction after reinstatement) and the between subject independent variable group (children, adults) were calculated. To assess reinstatement, mixed model ANOVAs were calculated including the within-individual independent variables CS (CS+, CS-) and time (last trial prior to reinstatement, first trial after reinstatement), as well as the between subject

independent variable age group (children, adults).

For significant effects, where appropriate, corrected degrees of freedom and epsilon (ϵ) were calculated and reported according to published recommendations (Girden, 1992). Significant main effects and interactions were then followed-up with standard post hoc means comparisons with Bonferroni correction for multiple testing. In addition, partial eta squared (η^2_p) effect sizes as well as achieved power ($1-\beta$) are reported and the alpha level was set to .05.

Exploratory analyses of trait anxiety effects (research question 3). Previous meta-analyses have shown distinct differences between anxious and healthy individuals in the outcome of fear conditioning experiments (for meta-analytical data in children see: Dvir et al., 2019, for meta-analytical data in adults: Duits et al., 2015). Thus, to gather first evidence of the current paradigm's sensitivity to those differential effects of anxiety on fear conditioning and extinction, mixed model ANCOVAs including the within-individual independent variables CS (CS+, CS-) and experimental phase (pre-conditioning, acquisition, early extinction, intermediate extinction, extinction after reinstatement) and the continuous covariate trait anxiety were calculated. Within the results section, we only report main effects and interactions including the independent variable trait anxiety (i.e., main effect trait anxiety, interactions Trait Anxiety x CS, Trait Anxiety x Experimental Phase, Trait Anxiety x CS x Experimental Phase) because the main effects and interactions including the independent variable CS and experimental phase are already given in the results section describing the general feasibility analysis (see above).

For significant effects, where appropriate, corrected degrees of freedom and epsilon (ϵ) were calculated and reported according to published recommendations (Girden, 1992). Due to the comparably small sample size, significant main effects and interactions were then followed-up with Spearman correlations. In addition, partial eta squared effect sizes (η^2_p) as well as achieved power ($1-\beta$) are reported and the alpha level was set to .05.

2.8. Control for possible differences in fear learning on fear extinction

In addition to the main analyses, we controlled for possible effects of the amount of fear acquisition on explicit extinction learning as displayed by US expectancy ratings (i.e., being an experimental representation of the process of expectancy violation during exposure therapy, US expectancy ratings are supposed to be highly relevant for the translation of experimental data to the therapeutic context). Therefore, we correlated US expectancy ratings at the end of extinction (i.e., last extinction trial), with expectancy ratings at the end of acquisition (i.e., last acquisition trial on day one) and at the beginning of extinction (i.e., first extinction trial on day two). If extinction learning is independent of the amount of fear acquisition, these associations should be weak (see Hollandt et al., 2020 for details). Finally, we assessed whether changes in US expectancy during extinction represent the extinction learning process. Therefore, we correlated US expectancy ratings at the end of extinction (i.e., last extinction trial), with the change in expectancy ratings from the first to the last trial of extinction (see Hollandt et al., 2020). For all analyses Spearman correlation coefficients were calculated.

3. Results

3.1. General feasibility and age-dependent differences in fear conditioning and extinction

US expectancy ratings. The repeated measures ANOVA indicated overall larger US expectancy ratings for CS+ trials as compared to CS- trials, as shown by a significant main effect for CS, $F(1, 39) = 171.39$, $p < .001$, $\eta^2_p = .815$, $1-\beta = 1$, as well as larger expectancy ratings for children as compared to adults (main effect for age group), $F(1, 39) = 11.54$, $p = .002$, $\eta^2_p = .228$, $1-\beta = 0.91$. Furthermore the ANOVA

revealed a significant main effect for experimental phase, $F(4156) = 17.01$, $p < .001$, $\eta^2_p = .304$, $1-\beta = 1$ ($\epsilon = 0.54$), and significant interactions for CS x Age Group, $F(1, 39) = 11.29$, $p = .002$, $\eta^2_p = .225$, $1-\beta = 0.91$, CS x Experimental Phase, $F(4156) = 65.18$, $p < .001$, $\eta^2_p = .626$, $1-\beta = 1$ ($\epsilon = 0.67$). The interaction Experimental Phase x Age Group did not reach significance, $F(4, 156) = 1.02$, $p = .38$.

Importantly, we also found a significant interaction for CS x Experimental Phase x Age Group, $F(4156) = 7.37$, $p < .001$, $\eta^2_p = .159$, $1-\beta = 0.98$ ($\epsilon = 0.67$). Post-hoc tests revealed that children displayed higher US expectancy than adults towards the CS+ in the early, $M_{Diff} = 20.99$; $CI-95 [10.28-31.69]$, $p < .001$, intermediate, $M_{Diff} = 24.52$; $CI-95 [7.80-41.23]$, $p = .005$, and extinction after reinstatement, $M_{Diff} = 30.61$; $CI-95 [18.19-43.04]$, $p < .001$, phases. No differences between children and adults were found for US expectancy ratings in CS+ trials (see Fig. 2) in the pre-conditioning, $M_{Diff} = 6.71$; $CI-95 [-0.35-19.79]$, $p = .39$, and acquisition phase, $M_{Diff} = 9.72$; $CI-95 [-8.83-22.25]$, $p = .06$. For CS- trials, analyses revealed higher US-expectancy ratings for children as compared to adults in the pre-conditioning phase, $M_{Diff} = 17.26$; $CI-95 [2.49-32.03]$, $p = .023$, but not in the other experimental phases (i.e., acquisition; early extinction; intermediate extinction; extinction after reinstatement, all $p > .13$).

Children alone gave higher US expectancy ratings to the CS+ trials during the acquisition as compared to the pre-conditioning phase, $M_{Diff} = 36.92$; $CI-95 [22.09-51.75]$, $p < .001$. While CS+ expectancy ratings did not differ between acquisition and early extinction, $M_{Diff} = 3.76$; $CI-95 [-6.88-15.48]$, $p = 1.00$, they were significantly smaller during intermediate extinction than during early extinction, $M_{Diff} = -25.91$; $CI-95 [-37.64 - 14.19]$, $p < .001$ expectancy ratings did not differ between intermediate extinction and extinction after reinstatement, $M_{Diff} = 0.76$; $CI-95 [-10.50 - 12.02]$, $p = 1.00$. Complementing these findings, direct comparison for CS+ and CS- trials revealed that the children's US expectancy ratings to CS- trials and CS+ trials did not differ during pre-acquisition, $M_{Diff} = 7.8$; $CI-95 [-0.44 - 16.04]$, $p = .06$, but were higher towards CS+ trials as compared to CS- trials during all remaining phases (i.e. acquisition, early extinction, intermediate extinction, extinction after reinstatement, all $p < .001$). Adults alone showed a slightly different pattern of results. While they also gave higher US expectancy ratings to CS+ trials during acquisition than during pre-conditioning, $M_{Diff} = 33.91$; $CI-95 [15.38 - 52.45]$, $p < .001$, their US expectancy ratings to the CS+ decreased from acquisition to early extinction, $M_{Diff} = -15.57$; $CI-95 [-29.55 - 1.59]$, $p = .020$, and from early to intermediate extinction, $M_{Diff} = -29.44$; $CI-95 [-44.10 - 14.78]$, $p < .001$. Like for children, expectancy ratings to the CS+ did not differ between intermediate extinction and extinction after reinstatement, $M_{Diff} = 5.34$; $CI-95 [-19.42 - 8.74]$, $p < .001$. Comparing CS+ and CS- trials in adults revealed comparable US expectancy ratings to CS- trials and CS+ trials during pre-acquisition, $M_{Diff} = 2.75$; $CI-95 [-7.55 - 13.05]$, $p = .59$, higher US expectancy ratings to CS+ trials as compared to CS- trials during acquisition, $M_{Diff} = 53.24$; $CI-95 [43.29 - 63.18]$, $p < .001$, early extinction, $M_{Diff} = 29.64$; $CI-95 [18.62 - 40.67]$, $p < .001$, but comparable expectancy ratings during intermediate extinction, $M_{Diff} = 4.24$; $CI-95 [-6.23 - 14.72]$, $p = .42$ and extinction after reinstatement, $M_{Diff} = 2.53$; $CI-95 [-10.76 - 5.69]$, $p = .54$.

Startle-reflex. Mixed-model ANOVA revealed a significant interaction for CS x Experimental Phase, $F(4136) = 4.37$, $p = .027$, $\eta^2_p = .114$, $1-\beta = 0.67$ ($\epsilon = 0.38$) (see Table 1). However, the main effects for CS, $F(1, 34) = 1.09$, $p = .30$, experimental phase, $F(4, 136) = 2.05$, $p = .16$, and age group, $F(1, 34) = 0.04$, $p = .85$, as well as the interactions for CS x Age Group, $F(1, 34) = 0.55$, $p = .46$, Experimental Phase x Age Group, $F(4, 136) = 0.03$, $p = .90$, and CS x Experimental Phase x Age Group, $F(4, 136) = 0.61$, $p = .51$, did not reach significance. Table 2.

Post-hoc analyses for the CS x Experimental Phase interaction did not show a significant difference between CS+ and CS- in startle magnitudes in the pre-conditioning phase, $M_{Diff} = 0.30$; $CI-95 [-0.72 - 0.12]$, $p = .16$. Startle magnitudes were higher towards the CS+ than towards

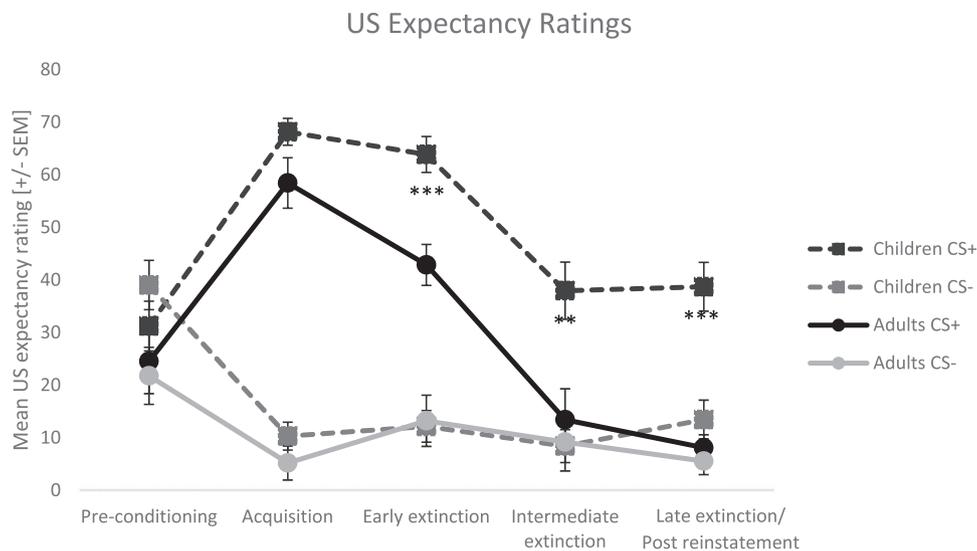


Fig. 2. Mean (+/- SEM) US expectancy ratings (range 0–100) for children (dashed lines) and adults (solid lines) during pre-conditioning, acquisition and the three extinction phases. *** $p < .001$, ** $p < .01$.

Table 1

Mean startle reflex magnitudes (z-scores) towards CS+ and CS- presentations during the pre-conditioning, acquisition and the three extinction phases.

	CS+		CS-	
	M	SD	M	SD
Pre-conditioning	0.36	1.75	0.63	1.60
Acquisition	0.31	0.36	0.07	0.30
Early extinction	0.34	0.43	0.12	0.30
Intermediate extinction	0.11	0.21	0.01	0.20
Extinction after reinstatement	0.06	0.27	0.04	0.18

Table 2

Mean US expectancy ratings (range 0–100) and mean startle reflex magnitudes (z-scores) during the last trial prior to the reinstatement test and during the first trial after reinstatement.

		CS+		CS-	
		M	SD	M	SD
US expectancy ratings	Prior to reinstatement	27.34	32.00	10.80	24.93
	After reinstatement	46.85	29.90	10.90	18.54
Startle reflex	Prior to reinstatement	-0.04	0.73	-0.32	0.59
	After reinstatement	0.27	0.54	0.17	0.63

the CS- in the acquisition, $M_{Diff} = 0.25$; $CI-95$ [0.11 – 0.38], $p < .001$, early extinction, $M_{Diff} = 0.20$; $CI-95$ [0.05–0.25], $p = .010$, and intermediate extinction phases, $M_{Diff} = 0.11$; $CI-95$ [0.04 – 0.18], $p = .003$. Importantly, startle responses to the CS+ and the CS- did not differ in the extinction after reinstatement phase, $M_{Diff} = 0.01$; $CI-95$ [– 0.07 – 0.09], $p = .87$. For the CS+ alone, startle magnitudes did not differ between pre-conditioning and acquisition, $M_{Diff} = 0.02$; $CI-95$ [– 0.90 – 0.94], $p = 1.00$, as well as between acquisition and early extinction, $M_{Diff} = 0.02$; $CI-95$ [– 0.28 – 0.24], $p = 1.00$. Startle magnitudes to the CS+ were smaller in intermediate than in early extinction, $M_{Diff} = -0.22$; $CI-95$ [– 0.43 – 0.02], $p = .026$. There was no significant difference between intermediate and extinction after reinstatement, $M_{Diff} = 0.06$; $CI-95$ [– 0.09 – 0.21], $p = 1.00$. Startle magnitudes towards the CS- did not differ between any of the experimental phases (all $p > .10$).

3.2. General Feasibility and Age-dependent Differences in Reinstatement

US expectancy ratings. The repeated measures ANOVA revealed significant main effects for CS, $F(1, 39) = 36.26$, $p < .001$, $\eta^2_p = .482$, $1-\beta = 1$, time, $F(1, 39) = 6.74$, $p = .013$, $\eta^2_p = .147$, $1-\beta = 0.72$, and age group, $F(1, 39) = 7.41$, $p = .010$, $\eta^2_p = .160$, $1-\beta = 0.76$, as well as significant interaction effects between CS x Age Group, $F(1, 39) = 6.72$, $p = .013$, $\eta^2_p = .147$, $1-\beta = 0.72$, and CS x Time, $F(1, 39) = 13.79$, $p = .001$, $\eta^2_p = .261$, $1-\beta = 0.95$. The interactions between Time x Age Group, $F(1, 39) = 0.38$, $p = .54$, and CS x Time x Age Group, $F(1, 39) = 3.14$, $p = .08$, did not reach significance.

Post-hoc analyses showed that the expectancy ratings towards the CS+ were significantly larger in the first extinction trial after reinstatement trial than in the last intermediate extinction trial, $M_{Diff} = 18.10$; $CI-95$ [– 8.75 – 27.46], $p < .001$. No significant differences were found for the CS-, $M_{Diff} = 0.53$; $CI-95$ [– 7.45 – 8.51], $p = .89$.

Startle reflex. For the startle magnitudes, the repeated measures ANOVA revealed larger startle-magnitudes towards the CS+ than towards the CS-, as indicated by a significant main effect of CS, $F(1, 34) = 4.14$, $p = .050$, $\eta^2_p = .108$, $1-\beta = 0.51$. Furthermore, startle responses were larger after reinstatement than prior to reinstatement, as indicated by a significant main effect for time, $F(1, 34) = 10.77$, $p = .002$, $\eta^2_p = .240$, $1-\beta = 0.89$. The main effect of age group, $F(1, 34) = 0.35$, $p = .56$, and the interactions CS x Age Group, $F(1, 34) = 0.07$, $p = .79$, Time x Age Group, $F(1, 34) = 3.08$, $p = .09$, CS x Time, $F(1, 34) = 3.17$, $p = .08$, and CS x Time x Age Group, $F(1, 34) = 2.78$, $p = .11$, were not significant.

3.3. Exploratory analyses of trait anxiety effects

ANCOVA results revealed that trait anxiety differentially influenced US expectancy ratings during the five experimental phases, $F(4, 152) = 4.81$, $p = .006$, $\eta^2_p = .112$, $1-\beta = 0.85$ ($e = 0.62$) (interaction Experimental Phase x Trait Anxiety). Follow-up correlational analyses indicate that higher trait anxiety was significantly associated with higher US expectancy ratings during the pre-conditioning, $r_s(40) = 0.318$, $p = .046$, and the acquisition phase, $r_s(40) = 0.348$, $p = .028$, but not during the extinction phases (all $p > .20$). There were no other significant main effects or interactions including trait anxiety for US expectancy ratings or the startle reflex.

3.4. Control for possible influences of differences in fear learning on fear extinction

We found that greater decline in US expectancy ratings during the extinction process (i.e., between the first and the last extinction trial) was related to lower US expectancy at the end of extinction (i.e., during the last extinction trial), $r_s(41) = -0.69, p < .001$. In contrast, US expectancy ratings during the last extinction trial were neither significantly associated with US expectancy ratings at the end of acquisition on day 1 (i.e., last acquisition trial), $r_s(41) = -0.04, p = .79$, nor with US expectancy ratings at the beginning of extinction (i.e., first extinction trial) on day 2, $r_s(41) = -0.09, p = .56$.

4. Discussion

The aim of the present study was to adapt and test for the applicability of a novel fear extinction protocol for the use with children and adolescents. The protocol has been developed previously to improve the correspondence between experimental extinction training and exposure-based treatment (Hollandt et al., 2020). To match ethical and age-dependent requirements for the use with children, the aversive electroshock US was replaced by an aversive sound, the language-based rating scales were replaced by picture-based, and non-verbal scales and a comprehensive instruction/ practice procedure were developed.

Supporting the general feasibility and age-appropriate adaption of the current protocol, the experimental procedures were highly accepted by children and adults and no child prematurely terminated the paradigm. Moreover, confirming previous reports on fear conditioning/extinction comparing adults and children (Den, Graham, Newall, & Richardson, 2015; Pattwell et al., 2012; Schiele et al., 2016), we found robust fear conditioning (on day 1), as well as decreasing responses indicating fear extinction (on day 2). Additionally, we found a return of the conditioned fear response after US reinstatement after initial fear extinction learning in both children and adults, suggesting the paradigms feasibility to assess return of fear. Supporting response coherence, fear acquisition, fear extinction and reinstatement were present both on the self-report (i.e., using US expectancy ratings), as well as on the physiological level (i.e., using the fear potentiated startle reflex) (see Mauss, McCarter, Levenson, Wilhelm, & Gross, 2005 for a comprehensive discussion on emotion response coherence). Thus, using age-appropriate, ethically sound methods, the current data clearly support the capability of the current protocol to assess conditioning and extinction on basis of both US-expectancy ratings and the fear potentiated startle-reflex even in children as young as age 8.

In detail, during the acquisition phase on day 1, both children and adults displayed higher US expectancy ratings and startle reflex magnitudes towards the presentation of the CS+ than towards the presentation of the CS-. Importantly, this effect was not explained by pre-conditioning differences between the CS+ and CS- indicating de novo fear learning during fear acquisition. On day 2, US expectancy ratings and the startle reflex magnitudes towards the CS+ gradually decreased for both groups indicating successful extinction learning in adults and children. Thereby, final extinction performance (i.e., US expectancy ratings during the last CS+ trial of late extinction) on day 2 was largely independent of individual differences in fear learning as indicated by non-significant and low correlations between US expectancy ratings at the end of the extinction process (i.e., last trial of late extinction phase) with US-expectancy ratings at the end of fear acquisition on day 1 (i.e., during the last trial of acquisition) and the beginning of extinction on day 2 (i.e., first trial of extinction). In contrast, independent of the participants' age, final extinction performance was related to the change in US expectancy ratings from the first to the last trial of extinction. This replicates and extends previous findings (see Hollandt et al., 2020) in adults, indicates the successful adaption of the current paradigm; and supports the paradigms capability to specifically monitor the process of extinction in adults and children independent from fear acquisition

capacity.

The assessment of US expectancy ratings prior to the presentation of the CSs during the entire course of extinction is one particular strength of the current paradigm (cf. Hollandt et al., 2020). The overall correspondence in US-expectancy ratings between adults and children supports the effectiveness of the age-appropriate instruction procedure and vivid presentation of the ratings scales. The successful administration of US-expectancy ratings enables the monitoring of key aspects of exposure treatment for anxiety disorders. Typically, prior to exposure, the therapist assesses the patients' expectations towards the upcoming exposure session. In a typical case, the patient will report adverse expectations concerning the exposure to the feared stimulus, being violated within the exposure session (expectancy violation, see for example Pittig et al., 2016 for a comprehensive discussion). This expectancy violation is supposed to be one major trajectory for the treatment response in exposure-based treatments. The adaptation of the current paradigm for the use with children enables to explore functional aspects of exposure-based treatments in adults and children using one single experimental setup. This renders the current paradigm especially useful to investigate the boundary conditions of exposure treatment over the entire lifespan (for an overview see Craske, Hermans, & Vervliet, 2018; Scheveneels, Boddez, Vervliet, & Hermans, 2016).

Besides US expectancy ratings, the current paradigm proved feasible to modulate the startle reflex, a subcortical defensive reflex indicating an individuals' defensive motivational state. It has been well validated that the amplitude of the eyeblink startle reflex varies with emotional valence of the background stimulus viewed simultaneously (for a comprehensive overview see Bradley, Codispoti, Cuthbert, & Lang, 2001). For example, the startle reflex is potentiated when viewing pictures with negative content (e.g., Vrana, Spence, & Lang, 1988) reflecting the activation of the defensive system to protect the organism from threat (Lang, 1995). The current data show that during fear acquisition on day 1, we found robust potentiation of the startle reflex towards CS+ presentations as compared to the CS-. Paralleling these results, the startle response towards the CS+ increased from the pre-conditioning to the fear acquisition phase, indicating an increase in defensive activation during the perception of the CS+. On day 2, startle reflexes towards the CS+ decreased from early to intermediate extinction indicating a decrease in defensive activation towards the CS+ during the course of extinction putatively reflecting inhibitory learning. Importantly, the current reduction in startle-response magnitudes cannot be attributed to mere habituation effects. In detail, mean startle responses to the startle probes during the interstimulus intervals which have been evenly distributed over each of the experimental phases (and thus cover response habituation) were subtracted from the response-magnitudes recorded in response to the CS+ and CS- presentations within the respective experimental phases. Thus, this approach enables to effectively remove the habituation effects from startle-responses to the CS and has been recommended in fear conditioning research (Lonsdorf et al., 2017).

Although we found evidence for extinction on the self-report and physiological level, extinction was more pronounced for US expectancy ratings than the startle-reflex. In addition, unlike for US expectancy ratings, we did not find a significant interaction including age group for the startle-reflex data. In general, emotional reactions could be measured on different response levels (i.e., self-report, physiological or behavioral responses), which do not necessarily show coherent response patterns, or do not converge at all (for a comprehensive discussion on this issue see Mauss et al. 2005). For example, some authors propose different processes underlying affective and expectancy learning respectively (i.e. the dual process model of fear learning, see Hamm and Vaitl, 1996). This is why current recommendations include multiple response measurements in fear conditioning studies (see Lonsdorf et al., 2017). Thus, the different result patterns may have emerged due to different learning processes, leading to low response coherence.

In demonstrating inhibitory learning in both adults and children, our

results extend previous reports supporting the capability of the current paradigm to model inhibitory learning both on the self-report and physiological level (Hollandt et al., 2020). Moreover, in their initial report, Hollandt et al. (2020) provided evidence for the current paradigms capability of triggering distinct brain activation patterns resembling brain activity during inhibitory learning as reported previously (i. e., prefrontal cortex and hippocampus, see Knight, Smith, Cheng, Stein, & Helmstetter, 2004; Lindner et al. 2015; Milad et al. 2007). This opens important windows for future research. Not much is known about brain patterns involved in extinction learning in children. In providing tools for the direct comparison of brain activation during extinction learning between adults and children the current paradigm thus offers the opportunity to close this gap and to further our understanding of the underlying behavioral, physiological and neural mechanisms associated with normative and pathological fear learning across development (Shechner, Hong, Britton, Pine, & Fox, 2014).

Interestingly, we found initial evidence for differential fear extinction between children and adults. Children, in comparison to adults, displayed significantly less pronounced extinction with respect to US expectancy towards the CS+ . In brief, in comparison to adults who displayed a decline in US expectancy from acquisition to intermediate extinction and also complete extinction (i.e. no significant differences between the CS+ and the CS- in last two extinction phases), US expectancy ratings for children showed a decline between early and intermediate extinction only, and incomplete extinction (significantly larger US expectancy ratings towards the CS+ during all extinction phases). Moreover, US expectancy ratings differed significantly from adults throughout extinction. Thus, from the current data, it could be concluded that, although generally present, extinction was initiated later and did not reach the same final performance than in adults. Comparative research on infant and adult fear learning and fear extinction in humans is still sparse. So far, to our knowledge, only very few studies compared extinction learning between adults, children and adolescents (Den, Graham, Newall, & Richardson, 2015; Pattwell et al., 2012; Waters, Theresiana, Neumann, & Craske, 2017). One study found less extinction learning as measured with the skin conductance response (a marker of sympathetic activation) in adolescents in comparison to adults and younger children (Pattwell et al., 2012), while the other did not find any differences in extinction performance between adults and adolescents (Den et al., 2015). Another study compared fear conditioning between pre-adolescent children and adults. This study did not assess extinction but reported more pronounced fear generalization in children as compared to adults on the self-report level, an effect probably based on neural structures also involved in extinction learning (Schiele et al., 2016), and largely in line with findings from Waters et al. (2017) reporting less safety learning in children as compared to adolescents and adults. However, the current sample comprised of children aged 8–17, but the sample was too small to comprehensively explore differences between children and adolescents. Both animal and human literature (Konrad et al., 2020, for comprehensive discussion in Baker, Den, Graham, & Richardson, 2014) suggest a window of vulnerability for less extinction learning during the course of ontogenesis, probably based on non-linear maturation of relevant brain areas (i.e., amygdala, hippocampus and prefrontal cortex). Clearly, further research is needed to determine if less extinction performance found in the present study is based on pre-adolescent or adolescent children. The current paradigm has proved suitable for assessing extinction learning in both adults and children, offering the opportunity to address these important developmental research questions in future research.

Finally, in line with the initial study by Hollandt et al. (2020) preliminary analysis including trait anxiety shows higher expectancy ratings in high anxious individuals regardless of the participants' age. However, previous meta-analytical work supports robust differences in fear learning and extinction between anxiety disorder patients (meta-analysis in adults: Duits et al., 2015; meta-analysis in children: Dvir et al., 2019), as assessed with various different fear conditioning/

extinction paradigms. Thus, the current findings and previous literature suggest that the paradigm is promising for assessing individual differences in fear learning also in a clinical context.

4.1. Limitations

A limitation of our study was the relatively small sample size. For example, we cannot entirely rule out that the missing interaction including age group from our startle data analysis may be due to insufficient test power. Although we initially performed a power analysis to gather the required N, several participants had to be excluded from the startle analysis. Thus we cannot entirely rule out the possibility that the non-significant interaction including age group within the startle data may have resulted from missing overall test power.

In the same vein, the current sample may have been too small for comprehensive analysis of the trait anxiety effects, thus, the current results should be considered preliminary and the analysis are exploratory.

Another limitation might be, that we did not include skin conductance as a dependent variable. The skin conductance response is probably the most common measure for the quantification of fear condition/ extinction. However, both the startle reflex, as well as the skin conductance response are well suited to assess the outcome of such paradigms and a multitude of research in fear conditioning/ extinction assessed startle responses as an outcome measure (for a comprehensive overview see Lonsdorf et al., 2017). Nonetheless, future studies should include the skin conductance response to further improve comparability of results between studies.

Finally, another limitation could be, that we collapsed outcome measures over the entire experimental phases and did not calculate trial-by-trial learning curves. However, we used an instructed fear paradigm (i.e. all participants were aware of the contingencies between the CSs and the UCS prior to fear-acquisition). This approach results in a different acquisition process as compared to non-instructed fear conditioning and as such comparison of learning curves to those from non-instructed paradigms should be done with caution. Being in accord with current guidelines (Lonsdorf, et al., 2017) for the extinction phases, the current approach resulted in three consecutive values enabling us to monitor extinction as a process with the current paradigm. Nonetheless, future studies should consider reporting learning curves to gather more fine-grained analysis of the differential effects of extinction between adults and children.

4.2. Conclusion

In sum, the current data renders the current paradigms usefulness for investigating the longitudinal development of extinction learning to enhance our understanding of the complex processes involved in the etiology of anxiety disorders. Moreover, the data further underscore the paradigms potential as an experimental treatment model for exposure-based anxiety treatments over the lifespan. The most common treatment methods for anxiety disorders in children and adults share exposure therapy as a core ingredient (In-Albon & Schneider, 2006; Kaczurkin & Foa, 2015). The underlying process of fear extinction in the laboratory putatively resembles the complex inhibitory learning process elicited during exposure therapy. Supporting and extending previous research (Hollandt et al., 2020), the current results suggest the capability of the current paradigm to assess individual differences in extinction learning in both adults and children. Because the current paradigm is optimized in several ways to ideally model the key mechanisms in extinction learning during exposure-based treatments for children and adults, it seems ideally suited to bridge the gap between experimental psychopathology and treatment process across the lifespan.

Disclosures

The authors have no conflict of interest to declare.

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Declarations of interest

None.

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