



Peritraumatic unconditioned and conditioned responding explains sex differences in intrusions after analogue trauma



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ABSTRACT

Higher prevalence of posttraumatic stress disorder (PTSD) in women than men may be explained by sex differences in fear learning processes. Initial evidence points to elevated unconditioned and conditioned fear responding as well as to elevated state anxiety in women as potential peritraumatic mechanisms. Using the “conditioned-intrusion-paradigm”, which combines differential fear conditioning with the trauma-film paradigm, neutral sounds were presented as predictors of the occurrence (CS+) or non-occurrence (CS-) of highly aversive films. Intrusions were elicited by these sounds in the laboratory after conditioning and naturalistic intrusions were assessed in daily-life on subsequent days. Compared to men ($n = 62$), women ($n = 60$) reported more intrusions and associated distress following analogue trauma. Sex differences in intrusive symptoms were mediated by a) higher unconditioned trauma responding, b) slowed extinction of differential CS valence ratings, and c) elevated state anxiety increase across conditioning in women. Secondary analyses revealed that state anxiety was the strongest mediator, followed by slowed extinction learning. Mediation models were unrelated to sex differences in trait anxiety or depressive symptoms. Thus, associative (extinction learning) and non-associative (state anxiety, trauma responding) mechanisms contribute to sex differences in intrusive symptoms after analogue trauma and might add to the heightened vulnerability to PTSD in women.

Traumatic events are defined as “*exposure to actual or threatened death, serious injury or sexual violence*” (DSM-5; American Psychiatric Association, 2013, p.271). While experienced by most people at least once during their lifetime, only a few suffer from long term consequences such as posttraumatic stress disorder (PTSD). Women are twice as likely as men to develop PTSD after trauma and also experience more severe and persistent symptoms. The underlying mechanisms causing these sex differences are mostly unknown (e.g., Breslau et al., 1998; Olff, Langeland, Draijer, & Gersons, 2007; Tolin & Foa, 2006). Due to the well documented role of associative learning in the aetiology of PTSD (Pittig, Treanor, LeBeau, & Craske, 2018), the present study examined whether sex differences in peritraumatic unconditioned and conditioned fearful responding can explain this elevated risk for PTSD in women.

Although various risk factors have been associated with PTSD, most of them cannot account for sex differences (Breslau, 2009). Interpretability of clinical findings is mostly restricted by reliance on

retrospective measurement of peritraumatic risk factors (e.g., McNally, 2003), rendering them liable to biases due to current level of distress (e.g., Roemer, Litz, Orsillo, Ehlich, & Friedman, 1998; Wessely et al., 2003) and sex differences in reporting of negative autobiographical memories (Ros & Latorre, 2010). In contrast to clinical studies, experimental analogue studies allow for real-time assessment of potential risk-mediating variables. Analog trauma can be induced by aversive film clips: the *trauma film paradigm* has now been well validated for this purpose (James et al., 2016; Lapsa & Alden, 2008). Subsequent to such film-viewing, participants are instructed to report their involuntary recollections of the aversive clips during the following days. These so-called ‘intrusions’ are an analogue to one of the hallmark symptoms of PTSD, the involuntary re-experiencing of trauma memories (American Psychiatric Association, 2013; Conway, 2001). In line with clinical findings of higher PTSD symptomatology in women compared to men, more analogue intrusions and more intrusion-related distress in women compared to men have been reported (Kamboj et al., 2014; Wessel,

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Overwijk, Verwoerd, & de Vrieze, 2008 [study 2]; though, not invariantly, see; Clark, Mackay, & Holmes, 2015). To our knowledge, like clinical studies, no analogue study has yet investigated mechanisms linking sex differences in intrusive memories with sex differences in peritraumatic processes.

During the trauma film paradigm, experiencing aversive film clips as highly negative has been related to increased frequency of analogue intrusions (Clark et al., 2015; Olatunji & Fan, 2015; Ripley, Clapp, & Beck, 2017). In terms of sex differences, mounting evidence suggests that women are more responsive to emotionally negative pictures and films than men (e.g., Bradley, Codispoti, Sabatinelli, & Lang, 2001; Wilhelm et al., 2017), or – more generally – perceive trauma sequences as more threatening (Olf et al., 2007). Yet, this claim has not been tested in the responding to the trauma film paradigm and has not been linked to sex differences in intrusive memories.

Intrusions likely develop through *associative learning* mechanisms and can therefore be construed as conditioned emotional reactions to trauma cues (conditioned stimuli, CS+) that positively predict an aversive event (unconditioned stimulus, UCS; Ehlers & Clark, 2000; Foa, Zinbarg, & Rothbaum, 1992; Mineka & Oehlberg, 2008). Slowed extinction learning and the resulting persistence of fear responses has been characterized as one of the core mechanisms relating to PTSD development (e.g., Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Lommen, Engelhard, Sijbrandij, van den Hout, & Hermans, 2013; see Rothbaum & Davis, 2003 for a review). According to Orr et al. (2000), PTSD patients are more ‘conditionable’ in that their conditioned responding to the CS + exceeds CS- (CS that predicts the non-occurrence of an aversive event) during both acquisition and extinction. Slowed extinction of evaluative conditioning (i.e., differential valence ratings between CS+ and CS-) has been particularly related to PTSD development and maintenance, as it has been linked to return of fear (Hermans et al., 2005; Rachman, 1989) and avoidance behaviour (De Houwer, Thomas, & Baeyens, 2001). In accord, Wegerer, Blechert, Kerschbaum, and Wilhelm (2013) showed that slowed extinction of evaluative conditioning was related to elevated intrusions during the days following an analogue trauma in women. Findings for sex differences in fear acquisition and extinction learning are mixed (e.g., Inslicht et al., 2013; Milad et al., 2006; Shvil et al., 2014). The role of predictive cues (CSs) – and hence associative mechanisms – has not yet been examined as potential mediator explaining sex differences in relation to subsequent intrusions.

In addition, context-related anxious states are considered crucial for PTSD development and maintenance. Appraisals of the world as ‘a dangerous place’ illustrate such contextual anxiety and have been shown to predict PTSD development (Ehlers & Clark, 2000). Women report more anxiety immediately following trauma than men and this peritraumatic difference has been proposed to explain later sex differences in intrusion frequency (see Olf et al., 2007 for a review). Similarly, state anxiety increase following analogue trauma has been linked to increased intrusions (e.g., Davis & Clark, 1998; Holz, Lass-Hennemann, & Michael, 2017; Lapsa & Alden, 2008) but the presence of sex differences in this potential risk factor is unclear. State anxiety increase is non-associative, just like trauma film responses, but less closely tied to specific cues and thus less focal or prediction based.

In sum, the present study investigated sex differences in associative (evaluative extinction learning) and non-associative (responses to trauma films, state anxiety increase) processes as possible peritraumatic mediators for elevated analogue intrusions in women. Besides state anxiety increase, both, increased unconditioned responses to traumatic events (UCR, i.e., reactions to aversive film clips) and persistent conditioned trauma responding (CR) should strengthen emotional memory consolidation and therefore, increase subsequent intrusive memory recall (Brewin & Holmes, 2003). These three potential mechanisms were assessed during a modified version of the “conditioned-intrusion paradigm” (Wegerer, Blechert, & Wilhelm, 2013; Wegerer et al., 2013; Wegerer, Kerschbaum, Blechert, & Wilhelm, 2014) that combined

differential fear conditioning with the trauma film paradigm, two experimental analogues for PTSD development. Intrusions were measured in two ways. First, through a laboratory based ‘memory triggering task’ that examined to what degree intrusions could be triggered by near threshold presentations of the conditioned sound clips (CSs; Wegerer et al., 2013; see Lau Zhu, Holmes, & Porcheret, 2018 for a review). Second, intrusions were assessed in a more ecologically valid way (in the sense of PTSD re-experiencing symptomatology) through ambulatory reports during the following three days.

We hypothesized that women would report more analogue trauma intrusions for both assessment modes and that these sex differences would be mediated by 1) a heightened evaluative UCR (emotional response to films, measured by valence ratings), 2) slowed evaluative extinction learning (measured by differential CS-valence ratings at the end of the extinction phase), and 3) elevated state anxiety increase from pre- to post-conditioning. Secondary analyses assessed the strength of each mediator, including all three mediators in a multivariate mediation model; due to lack of previous research, we had no specific a-priori hypotheses which predictor would be strongest. Exploratory analyses also assessed the potential role of differential acquisition learning, specific effects of the CS- (inspired by fear generalization accounts of PTSD, e.g., Grillon & Morgan, 1999), and of electrodermal and expectancy-based extinction learning. Trait anxiety, depressive symptoms, and violent movie consumption served as control variables.

1. Method

1.1. Participants

A total of 66 healthy women and 78 healthy men aged 18–35 years were recruited at the University of Salzburg, Austria, and participated in exchange for course credit or 25 Euro. Exclusion criteria were self-report of psychotropic medication, psychosis, substance abuse/dependency, bipolar disorder, serious medical conditions, or history of traumatic head injury. Twenty-two participants were excluded due to premature study termination (3 women, 4 men), failure to follow study instructions (0 women, 2 men) alcohol consumption (0 women, 1 man), or failure to consistently attend to the videos (2 women, 1 man), missing questionnaire data (0 women, 5 men) or technical problems (1 woman, 3 men). Thus, 60 women and 62 men entered the final analyses. The study was approved by the local ethics committee and participants gave their informed consent and were informed they could withdraw from participation at any time. Some of the data of the female participants, validating the present paradigm, has been published elsewhere (Wegerer et al., 2013). In addition, effects of hormonal status were examined in a subsample of female participants ($n = 37$; Wegerer et al., 2014). The present sample represents a sample of young women and men in a university context (with 16 women taking oral contraceptives and 44 women being naturally cycling). Recruitment started with women, followed by partly overlapping recruitment of both sexes and finally, recruitment of men only to achieve an N of about 60 cases with valid data per group. Experimenters were of the same sex as the study participant. Experimental procedures were highly standardized including standard operating procedures and were consistently supervised to assure homogeneity of testing conditions across time.

1.2. Apparatus and physiological recordings

Stimulus presentation and behavioural data acquisition were controlled by E-Prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Acoustic stimuli were presented via shielded earphones at a constant volume. Skin conductance (SC) was measured using Ag/AgCl electrodes filled with isotonic electrode paste (Boucsein et al., 2012); electrodes were placed on the middle phalanx of the index and middle fingers of the non-dominant hand. 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 skin conductance data analysis (Blechert, Peyk, Liedlgruber, & Wilhelm, 2016; Wilhelm & Peyk, 2005).

1.3. Materials and procedure

After signing the consent form, participants completed the Trait-Anxiety Inventory (STAI, German version by Laux, Glanzmann, Schaffner, & Spielberger, 1981), the Centre for Epidemiologic Studies Depression Scale (CESD; Radloff, 1977; Allgemeine Depressionsskala, ADS-L; German version by Hautzinger & Bailer, 1993) and a question assessing habitual consumption of TV and film footage/video games depicting severe violence. Next, SC electrodes were attached and participants sat quietly for 2.5min for adaptation.

To prevent habituation over repeated presentations, the trauma film paradigm consisted of several aversive video clips. In the present study, three film scenes depicting severe interpersonal violence were extracted from commercial movies to be used as unconditional stimuli (UCS), each of 25s duration (“Antichrist”, 2009, by Lars von Trier; “Hostel”, 2005, by Eli Roth, both films depicting a man being tortured; “Scar”, 2007, by Jed Weintrob, depicting a man bleeding out on the bathroom floor; maximum sound pressure level, SPL, 89.2 dB). Two neutral sounds (typewriter and clock ticking) represented conditional stimuli (CS), lasting 5s each (SPL 67.8 dB). During acquisition, one sound type was followed by one of the aversive film scenes (CS+) and the other sound type was not followed by any film clip (CS-), with sound type to condition assignment counterbalanced across participants. Film scenes were comparable on negative valence and arousal and also sound types were matched on valence and arousal (see Wegerer et al., 2013 for details).

1.3.1. Fear conditioning task

The fear conditioning task consisted of habituation, acquisition, and extinction phases. During all phases, trials were pseudo randomized, with no more than two stimuli of the same type (CS+ or CS-) presented consecutively. Inter-trial intervals (i.e., end of CS+/film or CS- to beginning of next CS) varied between 12 and 20s.

1.3.2. Habituation phase

Prior to habituation, participants were informed that no aversive film clips would be presented during that phase. CS+ and CS- sounds were each presented six times.

1.3.3. Acquisition

Similar to other studies (e.g., Blechert et al., 2007; Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007), participants were informed that from now on, one of two sounds might be followed by an aversive film scene, whereas the other sound would not be followed by a film clip (i.e., partially instructed conditioning, enhancing recognition of contingencies of CS+ and CS-). Six CS- sounds were presented without the film, and eight CS+ sounds were presented with 75% reinforcement rate (each film clip was presented two times in pseudorandom order); during film presentation, the CS+ sound continued at a lowered volume.

1.3.4. Extinction phase

CS+ and CS- sounds were presented six times each without the film. This phase was followed by a 30min break.

1.3.5. Ratings

Participants rated valence and UCS-expectancy of the CS+ and CS- at the end of habituation and in the middle and end of acquisition and extinction. Ratings were assessed on a visual analogue scale (“How did you experience the sound during its last presentation?” ranging from

“very pleasant” to “very unpleasant”, 0–100; “How much did you expect the sound to be followed by an aversive film clip during its last presentation?” ranging from “not at all” to “certain”, 0–100).

Participants rated the valence of each film clip at the end of fear conditioning (while showing reminder pictures from the clip: “How did you experience this film clip?” ranging from “very pleasant” to “very unpleasant”, 0–100; *unconditioned response*, UCR). Contingency awareness was also assessed at the end of conditioning (“Do you think this sound was followed by an aversive film clip?” “yes” or “no”). Furthermore, participants completed the state-version of the STAI before the acquisition and after the extinction phase (*state anxiety increase*).

1.3.6. Memory triggering task

Three almost identical soundscapes of 3min duration were presented, each preceded by a 20s silent period. The basic soundscape (SPL 75.8 dB) featured people talking with neither content nor language identifiable, as may occur at a marketplace or shopping mall. In the CS+ condition, 7-s CS+ sounds were superimposed on the soundscape audio track six times (two per minute, at an SPL that made them just about distinguishable from the basic soundscape, SPL 78.6 dB). In the other conditions, either the CS- sound or no sound was superimposed. The order of conditions was counterbalanced across participants. Since the current research question focused on intrusions triggered by stimuli that were previously associated with analogue trauma, the CS+ condition was of prime interest (see Wegerer et al., 2013, for more information about the other conditions). By superimposing subtle sound cues that were still perceptible, intrusions elicited by CS sound cues could be assessed in a controlled but semi-naturalistic context. Participants were instructed that they would be presented with a background soundscape via headphones, and they could let their mind wander freely.

At the end of each soundscape, participants completed a customized version of the Intrusion Memory Questionnaire (IMQ; Ehring, Fuchs, & Kläsener, 2009; Zetsche, Ehring, & Ehlers, 2009). They were informed “We are interested in memories about the violent film clips which can involve images or thoughts about things that have been shown, as well as thoughts or feelings that you had while watching the film clips. Please do not report memories that you recalled deliberately, but only memories that came up spontaneously”. Subsequently, participants noted the total number of intrusions during this soundscape as well as the overall distress associated with those intrusions (ranging from “0 = not distressing at all” and “100 = extremely distressing”).

1.3.7. Ambulatory assessment of intrusive memories

Participants completed a customized online version of the IMQ shortly before going to bed on the day of the experiment and the two subsequent days, with the URL to the questionnaire website being sent out via e-mail. Once-a-day assessment was chosen to keep participant burden and reactivity low (Rattel et al., 2018; Wilhelm & Grossman, 2010). Definition of intrusive memories was identical to the memory triggering task. In addition, participants were instructed to include intrusive memories related to the CS sounds.

1.4. Data reduction and statistical analyses

As clinical research shows that intrusions perceived as distressing are those primarily linked to persistent PTSD (e.g., Steil & Ehlers, 2000), we were not interested in the mere frequency of intrusions, but the frequency of intrusions weighted for their distress. Thus, *intrusion load* was calculated as the product of total intrusion frequency and their average distress.

Unconditioned trauma response (UCR) was operationalized by mean valence ratings for the aversive film clips, as well as by skin conductance responses (SCR) to the aversive film clips. For SCR, mean baseline skin conductance level (SCL, –2 to 0 s relative to CS onset)

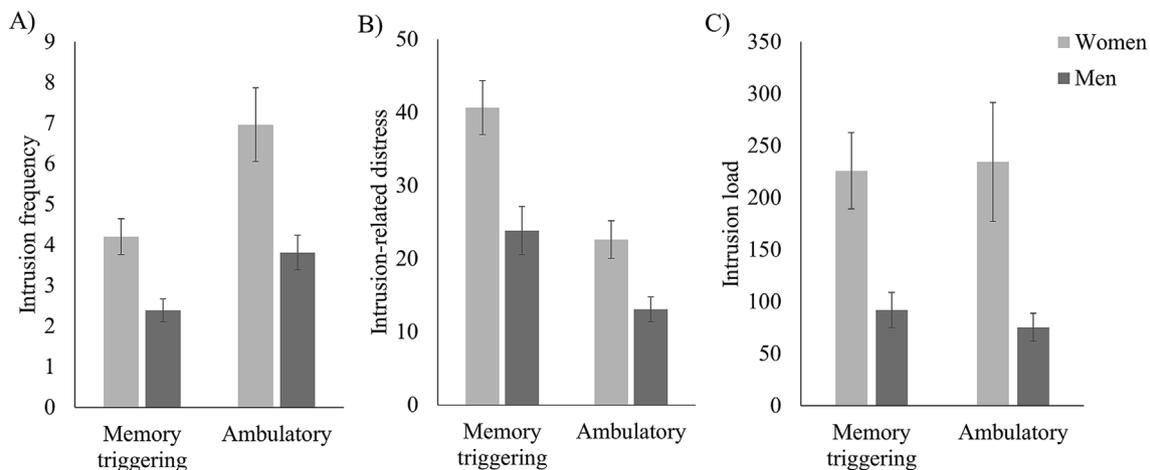


Fig. 1. Means (and standard errors) for intrusion frequency (A), intrusion-related distress (B), and intrusion load (C) following laboratory memory triggering and ambulatory, electronic diary daily-life assessment, for women and men.

was subtracted from the maximum SCL during the 25 film clips, considering only the first presentation of each film clip. Average individual UCR was calculated by normalizing UCRs for each film using the natural logarithm of $1 + \text{UCR}$ and averaging UCRs over all films. One male participant was excluded due to missing SC data.

Evaluative extinction learning was operationalized by differential valence ratings at the end of the extinction phase. Secondary analyses further investigated evaluative fear acquisition at the end of the acquisition phase, as well as UCS-expectancy ratings and SCRs for these times. For fear acquisition and extinction indices, CS+ and CS- end of habituation values served as individual pre-conditioning baselines. Baseline values were subtracted from acquisition and extinction values, respectively. A differential score was calculated by subtracting the “baseline-referenced” CS- values from the “baseline-referenced” CS+ values (see Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011; Wegerer et al., 2013). Higher scores on this index represent stronger and more persistent responding to CS+ relative to CS- (Orr et al., 2000). For conditioned SCRs, average pre-CS baseline SCL (–2 to 0 s relative to CS onset) was subtracted from maximum CS SCL (0–6 s relative to CS onset), and data were normalized using the natural logarithm of $1 + \text{SCR}$.

A state anxiety difference score (state anxiety increase) was computed by subtracting pre-conditioning from post-conditioning anxiety levels.

1.4.1. Statistical analyses

T-tests were calculated to check for sex differences in participant characteristics. Intrusion frequency data were checked for potential univariate outliers using box plots. One score was more than three standard deviations above the mean and was changed to one unit larger than the next most extreme score in the distribution (Tabachnick & Fidell, 1996). To check for sex differences in intrusion frequency, intrusion-related distress, and intrusion load, non-parametric Mann-Whitney U-tests were used, due to violation of the normality assumption.

To evaluate an indirect effect of sex on intrusion load through differences in evaluative UCR, evaluative extinction learning, and state anxiety increase, mediation analyses were computed using MPlus (Muthén & Muthén, 1998–2011), which allows for dichotomous predictors; unstandardized estimates are reported; Bayesian statistics were used, as this type of analysis does not rely on data distribution assumptions. Single mediation models were followed by parallel multiple mediation models (secondary analyses), thereby controlling for all other mediators and their collinearities in the model. Indirect effects were evaluated with 95% bias-corrected confidence intervals based on 5000 samples and Sobel tests. Furthermore, to give a standardized effect size for the indirect effect, a StdY standardization was chosen

because sex was binary (Muthén, Muthén, & Asparouhov, 2016), dividing the indirect effect by the standard deviation of the dependent variable. In line with Cohen (1992), we interpret 0.2 to 0.3 as a small effect size, ≥ 0.5 as medium and ≥ 0.8 as large. For parallel multiple mediations, the total indirect effect is the indirect effect for all mediators in the model added together. We additionally checked for collinearities between mediators using Pearson correlations.

Exploratory analyses investigated an indirect effect of sex on intrusion load by examining 1) differences in electrodermal UCR, 2) evaluative acquisition learning, 3) conditioned SCRs, 4) UCS-expectancy ratings, and 5) separate CS+ and CS- effects during evaluative acquisition and extinction learning.

Control analyses investigated to what degree mediation by evaluative extinction learning was secondary to mediation by acquisition learning; parallel multiple mediation models including both predictors were computed. Furthermore, we checked for trait anxiety, depressive symptoms, and violent movie consumption as potential confounders in the mediation models.

All analyses focused on end of acquisition and extinction ratings or, for SCR, on the second halves of these phases, since this provides sufficient learning trials for acquisition and extinction effects to unfold. The pattern of results for valence ratings half-way during acquisition and extinction was similar but findings were less pronounced (see Supplements).

2. Results

2.1. Primary Analyses

2.1.1. Sex differences in intrusion frequency, intrusion-related distress, and intrusion load

Women reported more intrusions (memory triggering: $U = 2469.50$, $z = 3.15$, $p = .002$, $r = 0.29$; ambulatory: $U = 2386.00$, $z = 2.71$, $p = .007$, $r = 0.25$), more distress (memory triggering: $U = 2472.00$, $z = 3.18$, $p = .001$, $r = 0.29$; ambulatory: $U = 2395.50$, $z = 2.77$, $p = .006$, $r = 0.25$) and thus, had higher intrusion load than men (memory triggering: $U = 2544.50$, $z = 3.54$, $p < .001$, $r = 0.32$; ambulatory: $U = 2417.00$, $z = 2.88$, $p = .004$, $r = 0.26$) (see Fig. 1). For the following analyses, intrusion load was the primary outcome variable (see Supplements for intrusion frequency and intrusion-related distress).

2.1.2. Sex differences in intrusion load mediated by evaluative UCR

Women rated films more negatively ($M = 87.34$, $SD = 11.24$) than men ($M = 78.90$, $SD = 13.88$; $b = 7.96$, $p < .001$); evaluating films as

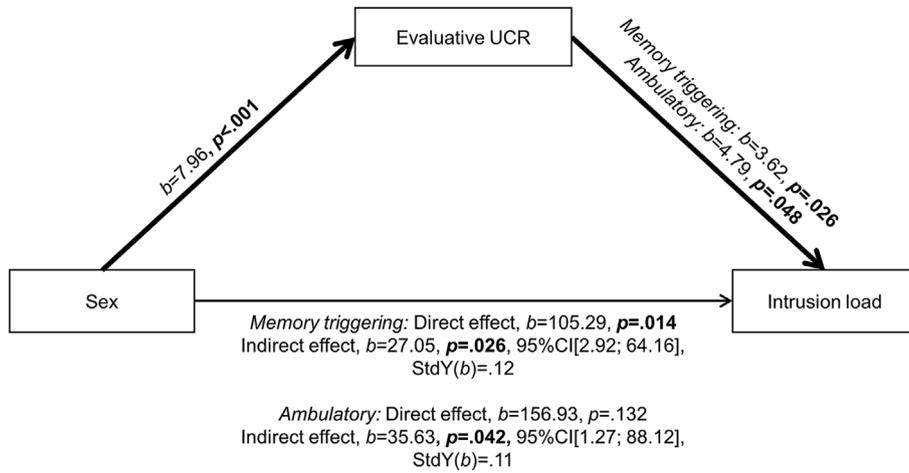


Fig. 2. Results of mediation analysis: Sex as a predictor of intrusion load, mediated by evaluative UCR (unconditioned trauma response, i.e., trauma film valence rating), both for intrusion load assessed by laboratory memory triggering task and ambulatory daily-life intrusions.

more negative, in turn, predicted intrusion load, posing the question whether the elevated intrusion load in women was (partially) mediated through their evaluative UCR. Mediation analyses confirmed that this was the case (see Fig. 2).

Evaluative UCR did not mediate the relationship between sex and frequency of intrusions ($ps > .290$); however, being female increased memory triggering and ambulatory intrusion-related distress indirectly via evaluative UCR ($ps \leq .002$; see Supplements).

2.1.3. Sex differences in intrusion load mediated by reduced evaluative extinction learning

Women displayed slower evaluative extinction learning ($M = 21.03$, $SD = 30.30$) than men ($M = 10.76$, $SD = 21.33$; $b = 10.22$, $p = .034$) and extinction learning predicted intrusion load, posing the question whether the elevated intrusion load in women was (partially) mediated through their slowed extinction learning. Mediation analyses confirmed that this was the case (see Fig. 3). Evaluative extinction learning also mediated the relationship between sex and frequency of intrusions ($ps \leq .036$) and intrusion-related distress ($ps \leq .043$; see Supplements).

2.1.4. Sex differences in intrusion load mediated by state anxiety increase

Women displayed a stronger state anxiety increase ($M = 15.13$, $SD = 8.71$) than men ($M = 8.14$, $SD = 10.05$; $b = 7.00$, $p < .001$) from pre- to post-conditioning and state anxiety increase predicted

intrusion load, posing the question whether the elevated intrusion load in women was (partially) mediated through their stronger state anxiety increase. Mediation analyses confirmed that this was the case (see Fig. 4). Note that women and men did not differ in their pre-conditioning state anxiety levels (women: $M = 34.84$, $SD = 5.58$, men: $M = 34.52$, $SD = 6.08$, $p = .761$).

State anxiety increase also mediated the relationship between sex and frequency of intrusions, as well as intrusion-related distress ($ps \leq .002$; see Supplements).

2.2. Secondary analyses

2.2.1. Parallel multiple mediation for memory triggering and ambulatory intrusion load

All three significant mediators, i.e., evaluative UCR, evaluative extinction learning, and state anxiety increase, were included in a parallel multiple mediation model, thereby controlling for the respective other mediators. Results revealed that only state anxiety increase and evaluative extinction learning remained significant mediators for both memory triggering and ambulatory intrusion load, but evaluative UCR did not. The total indirect effect (sum of all indirect effects) was significant for both memory triggering and ambulatory intrusion load and revealed a small to medium effect size (memory triggering: StdY (b) = 0.40; ambulatory: StdY(b) = 0.34; see Fig. 5).

Using intrusion frequency or intrusion-related distress as outcome,

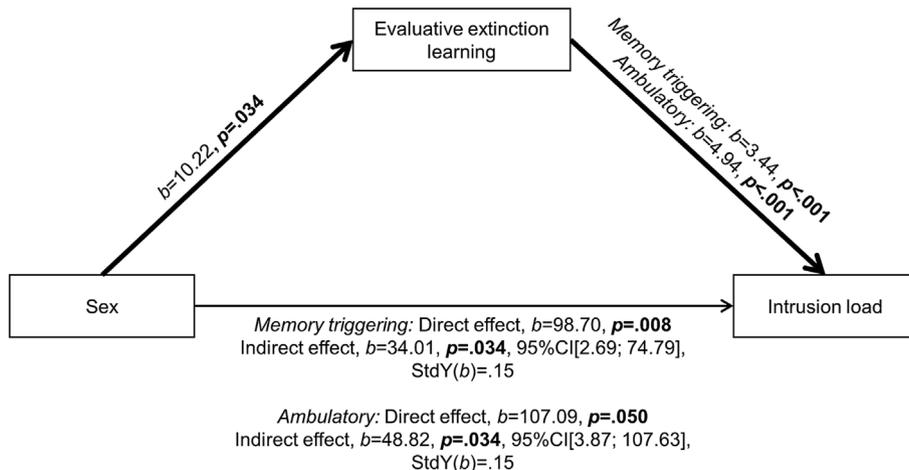


Fig. 3. Results of mediation analysis: Sex as a predictor of intrusion load, mediated by evaluative extinction learning, both for intrusion load assessed by laboratory memory triggering task and ambulatory daily-life intrusions.

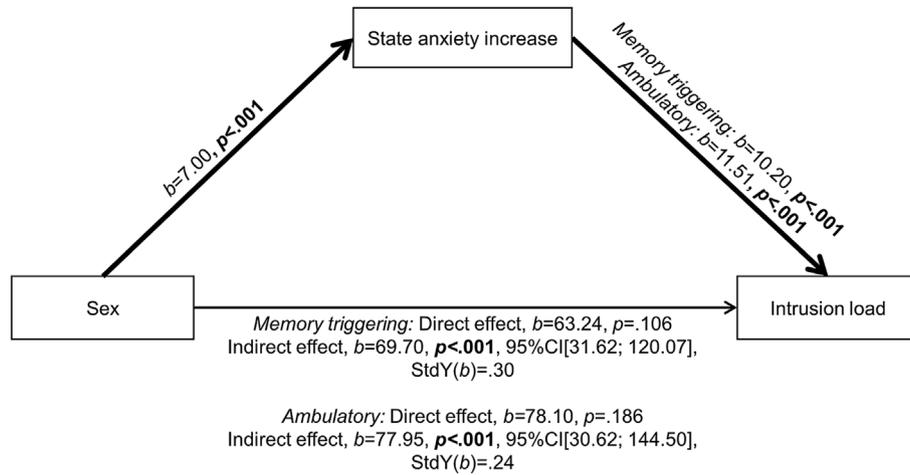


Fig. 4. Results of mediation analysis: Sex as a predictor of intrusion load, mediated by state anxiety increase, both for intrusion load assessed by laboratory memory triggering task and ambulatory daily-life intrusions.

state anxiety increase was a significant mediator for these outcomes ($ps \leq .004$). Evaluative extinction learning was a significant mediator for intrusion frequency measured during memory triggering and ambulatorily ($ps \leq .042$) and for intrusion-related distress measured ambulatorily ($p = .046$); though, not for intrusion-related distress measured during memory triggering ($p = .136$). Evaluative UCR neither increased intrusion frequency (during memory triggering and ambulatorily, $ps \geq .182$), nor intrusion-related distress during memory triggering ($p = .076$); though, evaluative UCR did predict intrusion-related distress measured ambulatorily ($p = .044$) (see Supplements).

Pearson correlations revealed that evaluative UCR correlated $r = 0.475, p < .001$ with state anxiety increase and $r = 0.172, p = .058$ with evaluative extinction learning. Evaluative extinction learning correlated $r = 0.227, p = .012$ with state anxiety increase. Thus, mediators showed small to medium correlations with each other, probably explaining the mostly non-significant results for evaluative UCR in the combined models.

2.2.2. Sex differences in intrusion load not mediated by electrodermal UCR

The SCR was very reliable in response to films; both women and men displayed significant electrodermal UCR. However, no sex differences were found for electrodermal UCR (women: $M = 0.61 \mu S, SD = 0.30$, men: $M = 0.64 \mu S, SD = 0.30, b = 0.06, p = .304$) and electrodermal UCR did not predict intrusion load (memory triggering: $b = 66.21, p = .346$; ambulatory: $b = 82.14, p = .418$); thus, no significant indirect effect was found (memory triggering: $b = 2.18, p = .552, CI[-6.71; 19.82], StdY(b) < 0.01$; ambulatory: $b = 2.46, p = .604, CI[-10.35; 26.68], StdY(b) < 0.01$).

2.2.3. Sex differences in intrusion load mediated by evaluative acquisition learning

Women displayed stronger fear acquisition ($M = 42.08, SD = 37.46$) than men ($M = 23.27, SD = 30.19; b = 18.74, p = .002$), with fear acquisition being linked to higher intrusion load both during memory triggering ($b = 1.72, p = .004$) and ambulatory assessment ($b = 2.13, p = .014$). Thus, higher intrusion load in women was

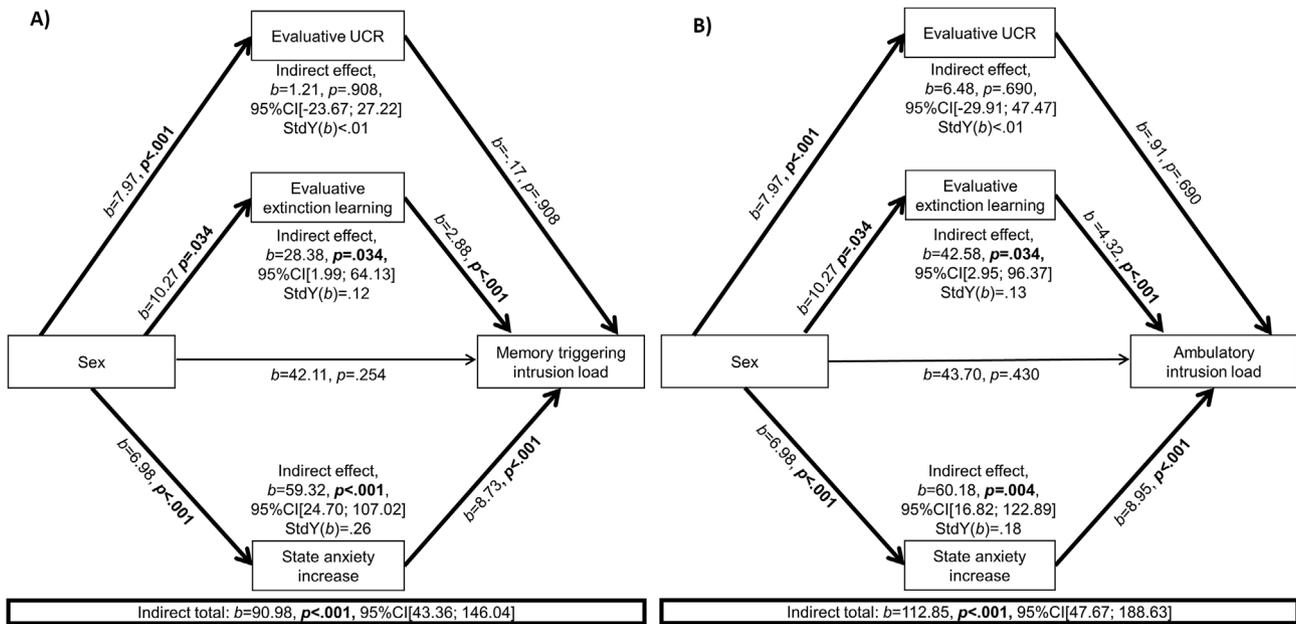


Fig. 5. Results of multiple mediation analysis: Sex as a predictor of intrusion load, mediated by evaluative UCR (unconditioned trauma response, i.e., trauma film valence rating), evaluative extinction learning, and state anxiety increase, both for intrusion load assessed by laboratory memory triggering task (A) and ambulatory daily-life intrusions (B).

mediated by their stronger fear acquisition (memory triggering: $b = 30.75$, $p = .006$, $CI[6.58; 67.96]$, $StdY(b) = 0.13$; ambulatory: $b = 37.60$, $p = .016$, $CI[5.35; 88.61]$, $StdY(b) = 0.11$).

2.2.4. Slowed evaluative extinction learning, not increased acquisition learning, mediated sex differences in intrusion load

Multiple mediation models including evaluative UCR, evaluative extinction learning, and state anxiety increase were computed that controlled for evaluative acquisition learning. Increased acquisition learning in women no longer explained sex differences in intrusion load ($ps \geq .574$) and the pattern of findings for extinction learning did not change ($ps \leq .034$).

2.2.5. Sex differences in intrusion load not mediated by conditioned SCRs

2.2.5.1. Acquisition. Women ($M = 0.06 \mu S$, $SD = 0.13$) and men ($M = 0.10 \mu S$, $SD = 0.25$) did not differ in differential SCR ($b = -0.04$, $p = .298$) and differential SCR did not predict intrusion load (memory triggering: $b = 55.57$, $p = .584$; ambulatory: $b = 234.67$, $p = .112$); thus, no significant indirect effect was found (memory triggering: $b = -1.02$, $p = .710$, $CI[-16.11; 8.41]$, $StdY(b) < -0.01$; ambulatory: $b = -6.85$, $p = .389$, $CI[-36.61; 3.34]$, $StdY(b) = -0.02$).

2.2.5.2. Extinction. Women ($M = 0.03 \mu S$, $SD = 0.12$) and men ($M = 0.01 \mu S$, $SD = 0.17$) displayed differential fear acquisition and extinction as indexed by SCR. However, sex did not predict differences in differential SCR ($b = 0.02$, $p = .288$) and differential SCR did not predict intrusion load (memory triggering: $b = 19.89$, $p = .886$; ambulatory: $b = -19.27$, $p = .920$); thus, no significant indirect effect was found (memory triggering: $b = 0.09$, $p = .940$, $CI[-9.04; 10.91]$, $StdY(b) < 0.01$; ambulatory: $b = -0.06$, $p = .968$, $CI[-15.10; 13.66]$, $StdY(b) < -0.01$).

2.2.6. Sex differences in intrusion load not mediated by differential UCS-expectancy ratings

2.2.6.1. Acquisition. Women did not display stronger differential UCS-expectancy during acquisition ($M = 57.07$, $SD = 47.31$) than men ($M = 57.11$, $SD = 52.43$; $b = -0.15$, $p = .986$) and UCS-expectancy was not linked to higher intrusion load during memory triggering ($b = -0.14$, $p = .726$) or ambulatory assessment ($b = -0.56$, $p = .318$). Thus, no indirect effect was found (memory triggering: ($b < 0.01$, $p = .994$, $CI[-8.43; 8.75]$, $StdY(b) < 0.01$; ambulatory: $b = 0.02$, $p = .990$, $CI[-16.29; 16.76]$, $StdY(b) < 0.01$).

2.2.6.2. Extinction. Women did not display stronger differential UCS-expectancy during extinction ($M = 26.07$, $SD = 40.79$) than men ($M = 27.06$, $SD = 50.64$; $b = -1.09$, $p = .888$) and UCS-expectancy was not linked to higher intrusion load during memory triggering ($b = 0.67$, $p = .124$) or ambulatory assessment ($b = 0.18$, $p = .774$). Thus, no indirect effect was found (memory triggering: ($b = -0.31$, $p = .914$, $CI[-15.42; 13.43]$, $StdY(b) < -0.01$; ambulatory: $b = -0.04$, $p = .972$, $CI[-12.47; 11.95]$, $StdY(b) < -0.01$).

2.2.7. Mediating role of evaluative acquisition and extinction learning: separate effects of CS+ and CS-

2.2.7.1. Acquisition. Women rated the CS + more negatively during acquisition ($M = 32.66$, $SD = 25.52$) than men ($M = 20.99$, $SD = 22.86$; $b = 11.61$, $p = .010$) and higher CS + ratings were linked to higher intrusion load during memory triggering ($b = 3.11$, $p < .001$) and ambulatory assessment ($b = 4.23$, $p < .001$). Thus, sex differences in intrusion load were mediated by CS + ratings during acquisition (memory triggering: $b = 34.71$, $p = .010$, $CI[7.51; 73.99]$, $StdY(b) = 0.15$; ambulatory: $b = 46.94$, $p = .010$, $CI[9.65; 102.12]$, $StdY(b) = 0.14$). No sex differences were found in the CS- ratings during acquisition, CS- ratings were not related to intrusion load, and no mediating relationship was found (all $ps \geq .152$).

2.2.7.2. Extinction. Women rated the CS + somewhat more negatively during extinction ($M = 16.04$, $SD = 24.72$) than men ($M = 8.37$, $SD = 20.38$), though, this was not statistically significant ($b = 7.62$, $p = .066$). Higher CS + ratings were linked to higher intrusion load during memory triggering ($b = 4.01$, $p < .001$) as well as ambulatory assessment ($b = 5.40$, $p < .001$). Overall, sex differences in intrusion load were marginally not mediated by CS + ratings during extinction (memory triggering: $b = 29.62$, $p = .066$, $CI[-2.06; 69.56]$, $StdY(b) = 0.13$; ambulatory: $b = 39.59$, $p = .066$, $CI[-2.76; 102.12]$, $StdY(b) = 0.12$). No sex differences were found in the CS- ratings during extinction, CS- ratings were not related to intrusion load, and no mediating relationship was found (all $ps \geq .330$).

2.2.8. Control analyses

2.2.8.1. No Sex Difference in Contingency awareness. There was no difference in contingency awareness between women and men at the end of the experiment ($ps \geq .702$). 95% of women and 93.5% of men correctly identified the CS+ to be predictive of an aversive film clip; 83.3% of women and 80.6% of men correctly rated the CS- to be predictive of omission of an aversive film clip. Objective diary compliance was very high, as all participants completed all three ambulatory IMQ questionnaires.

2.2.8.2. Sex differences in intrusion load not mediated by violent movie consumption, depression, or trait anxiety. Men ($M = 3.42$, $SD = 1.90$) reported more violent movie consumption than women ($M = 2.35$, $SD = 1.44$; $b = -1.07$, $p < .001$). However, violent movie consumption did not predict intrusion load (memory triggering: $b = -1.52$, $p = .902$; ambulatory: $b = -29.12$, $p = .096$). Therefore, no significant indirect effect was found (memory triggering: $b = 1.45$, $p = .902$, $CI[-25.42; 29.52]$, $StdY(b) = 0.01$; ambulatory: $b = 29.18$, $p = .096$, $CI[-5.17; 78.51]$, $StdY(b) = 0.09$). For symptoms of depression (women: $M = 12.72$, $SD = 7.57$; men: $M = 12.40$, $SD = 8.49$) and trait anxiety (women: $M = 38.22$, $SD = 9.70$; men: $M = 38.40$, $SD = 9.65$), no sex differences were found ($ps > .80$). Neither depression nor trait anxiety were linked to intrusion load ($ps > .230$) and no mediating relationship was found ($ps > .80$). Including either violent movie consumption, depression, or trait anxiety in the multiple mediation models did not decrease the indirect effects of the other mediators.

3. Discussion

Using the conditioned-intrusion paradigm, an experimental analogue of intrusion formation in PTSD, the current study examined sex differences in conditioning processes as potential mechanisms explaining heightened PTSD prevalence in women. First, women showed increased responding to the trauma analogue on a number of indices of associative learning (evaluative extinction and acquisition) and non-associative processes (evaluative UCR, state anxiety increase) compared to men. As expected, women reported more intrusions and more intrusion-related distress subsequent to the viewing of aversive films; this was well captured in the index “intrusion load”, which weighs intrusions by their distress intensity. Women's higher intrusion load was mediated by their increased evaluative UCR, slowed evaluative extinction learning, and stronger state anxiety increase. Including all three mediators in one statistical model, state anxiety increase was the strongest mediator, followed by evaluative extinction learning.

3.1. Stronger trauma film response (evaluative UCR) in women mediates sex differences in intrusive symptoms

Women rated the film clips as more negatively than men and this mediated their increased intrusion scores. Those findings are in line with clinical research that linked peritraumatic distress (e.g., “I felt afraid for my safety”) to subsequent PTSD development, with women

reporting more peritraumatic distress than men (Brunet et al., 2001; Ozer, Best, Lipsey, & Weiss, 2003 for a review). Findings are also in line with the cognitive model by Ehlers and Clark (2000), postulating that appraising trauma as particularly negative plays a central role in later intrusive memory formation. Closer examination of the intrusion scores, both for laboratory and ambulatory intrusion assessment, revealed that negative trauma valence ratings were not only linked to intrusion load, but also and particularly to the intrusion distress, with no relationship being found with intrusion frequency. This could imply that although stronger experiential reactions to trauma do not necessarily increase the mere frequency of intrusions, they do intensify the severity of related distress. Unlike rating data, electrodermal UCR was not linked to any intrusion score.

3.2. Stronger evaluative acquisition and slowed extinction learning in women mediates sex differences in intrusive symptoms

Women displayed slower evaluative extinction learning than men and this mediated their increased intrusion scores. In line with a review that linked failed extinction in standard conditioning tasks to PTSD, our results extend this to a novel PTSD analogue and, importantly, provide experimental support for reduced extinction learning being an important peritraumatic risk factor explaining women's heightened risk for PTSD development (see Rothbaum & Davis, 2003). Heightened evaluative learning in women vs. men was already apparent at the end of acquisition, which also explained women's elevated intrusion load. Effect sizes for the mediating role of evaluative fear acquisition vs. extinction (with regard to sex differences in intrusive memories) were only marginally smaller, in line with research linking PTSD to both faster fear acquisition and slower fear extinction (e.g., Blechert et al., 2007; Orr et al., 2000). When including both acquisition and extinction learning in the multiple mediation, thus controlling for increased acquisition learning when looking at the effects of slowed extinction learning on intrusion load, only increased extinction learning stayed significant. Therefore, increased intrusion load in women was best explained by women's slowed evaluative extinction learning, and only secondarily by their stronger acquisition learning. This may imply that subsequent to trauma women may particularly benefit from prolonged extinction training compared to men and future studies have yet to test this claim.

Similar to heightened differential responding in PTSD (Orr et al., 2000), women responded more to the CS + than men during acquisition (and only marginally during extinction) while no sex differences were found for the CS-. Although some researchers propose fear generalization (which may manifest as increased responding also to the CS-, despite its safety signal properties) as a mechanism explaining PTSD development and maintenance (e.g., Grillon & Morgan, 1999; Lissek, 2012), the present study linked heightened responding to the CS +, i.e. threat responding, to intrusive memories only.

Differential electrodermal responding and UCS-expectancy ratings were not linked to intrusions (neither during acquisition, nor extinction) and no sex differences were found. This may be explained by two different types of fear learning mechanisms (Blechert, Michael, Williams, Purkis, & Wilhelm, 2008): evaluative (valence) conditioning, being more implicit and less cognitive, is the change in experienced valence of a previously neutral CS due to repeated pairings with the UCS (e.g., De Houwer et al., 2001; Hofmann, De Houwer, Perugini, Baeyens, & Crombez, 2010). In comparison, expectancy learning, typically measured by UCS-expectancy ratings, represents rather explicit learning of a predictive relationship between CS and UCS due to repeated pairings. Electrodermal responding has often been related to such explicit conditioning (e.g., Weike, Schupp, & Hamm, 2007) but can, depending on the experimental context, also be implicit, as it has been shown to track conditioned responses to stimuli presented outside of awareness (e.g., Esteves, Parra, Dimberg, & Öhman, 1994). Slower evaluative extinction learning may particularly relate to PTSD

development and maintenance, as it has been linked to return of fear (Hermans et al., 2005; Rachman, 1989) and avoidance behaviour (De Houwer et al., 2001). Evaluating situations and stimuli associated with the UCS negatively may elicit negative mood, which, in turn, could make intrusive memories more likely (Ehlers, Mauchnik, & Handley, 2012). The present findings imply that both women and men learned the predictive relationship between the CS + und UCS; however, women experienced the CS + as more aversive during acquisition and displayed slowed differential evaluative extinction learning, which explained their elevated intrusion scores.

3.3. State anxiety increase: strongest mediator for sex differences in intrusive symptoms

Parallel multiple mediation revealed that if all three mediators were included in one statistical model, state anxiety increase was the strongest mediator of sex differences in intrusions (load, frequency, and distress), followed by evaluative extinction learning. Evaluative UCR was a significant mediator for daily-life intrusion-related distress only. These findings can be explained by the relatively low correlations between both evaluative UCR and extinction learning with state anxiety increase, indicating that state anxiety increase captured an additional aspect. Thus, although the change in state anxiety from immediately before to immediately after the 30-min conditioning procedure was likely somewhat determined by the net sum of evaluative UCRs and the efficiency of evaluative extinction learning, there must have been an additional process leading to increased anxiety. We propose that anxiety increase following our distressing trauma analogue could constitute the inability to swiftly regulate anxiety back to normal levels. Compared to men, women may have been less able to achieve this downregulation and thus their memory consolidation processes may have been less adaptive. Their more persistent anxiety may have interfered with subsequent information processing necessary for efficient and structured storage of information into episodic memory, which could explain their elevated intrusive memory recall (Brewin, Gregory, Lipton, & Burgess, 2010; Ehlers & Clark, 2000; Van der Kolk, 1998).

3.4. No effect of trait anxiety and depressive symptoms on sex differences in intrusive symptoms

The present study found no sex differences in trait anxiety and neither did women and men differ in their state-anxiety levels before conditioning. Thus, heightened anxiety following the distressing analogue trauma procedure in women was not explained by higher trait anxiety levels but rather represented an elevated sensitivity to react anxiously to the presented film stimuli and/or slowed anxiety downregulation at the end of the procedure. Present findings highlight the importance of real-time (compared to retrospective) assessment in order to disentangle trait from state anxiety factors in the aetiology of PTSD symptoms.

Furthermore, sex differences in intrusions were not explained by trait differences between men and women in depressive symptoms, which have been shown to sometimes differ between sexes (e.g., Altemus, Sarvaiya, & Epperson, 2014). This is particularly relevant since both anxiety and depression symptoms could increase fear conditioning (e.g., Lonsdorf & Merz, 2017; Nissen et al., 2010) and influence memory processes relevant for episodic memory consolidation and recall (e.g., Airaksinen, Larsson, & Forsell, 2005; Airaksinen, Larsson, Lundberg, & Forsell, 2004). Thus, our results are in line with the meta-analysis by Breslau (2009) that showed that trait anxiety and depressive symptoms were not linked to sex differences in intrusions in a clinical sample.

3.5. No effect of violent movie consumption and diary adherence on sex differences in intrusive symptoms

Men reported more violent movie consumption than women, which is a socio-culturally expected difference between male and female samples and cannot be stratified without making samples unrepresentative for their sexes. While some research links increased violent movie consumption to “emotional blunting” (e.g., Griffiths & Shuckford, 1989), movie consumption did not explain sex differences in evaluative UCR, evaluative extinction learning, and state anxiety increase in the current study. Importantly, movie consumption was not related to intrusive memories and did not mediate sex differences.

In line with the meta-analysis by Chung and Breslau (2008), no sex differences in intrusion reporting adherence in daily life were found; both women and men had very high objective compliance (100% completed questionnaires). Although generally consistent with laboratory intrusion assessment, the present results cannot rule out that sex differences in daily-life intrusions were partly explained by sex differences in memory recall for emotional events: research has shown that women can access emotional memory faster and more easily than men (e.g., Cahill, Uncapher, Kilpatrick, Alkire, & Turner, 2004; Ros & Latorre, 2010), which could explain why women recalled more intrusions at the end-of-day assessment, compared to men. Although Rattel et al. (2018) did not find any differences in intrusion frequency or distress between event-based (in the moment) and end-of-day assessment in a female sample, future studies may consider assessing intrusions event-based when investigating sex differences.

3.6. Consistent findings for triggered and daily-life intrusions

By using a memory triggering task after conditioning, analogue studies can mimic daily life situations in which trauma victims might experience reminder cues and related intrusive memories in a controlled experimental setting. Most of the present study's findings were consistent for both memory triggering and daily life intrusions, cross-validating these quite different approaches. Using these two types of intrusive memory assessment showed that women reported more cued intrusions and intrusion related distress right after trauma films (during early stages of memory consolidation), with this fear memory potentially manifesting as spontaneous intrusions during subsequent days. This could imply that early fear memory inhibition or consolidation interference in women could ameliorate later re-experiencing symptom manifestation.

3.7. Limitations and future directions

When considering the present findings, some limitations should be considered. Miedl, Wegerer, Kerschbaum, Blechert, and Wilhelm (2018) showed that in women low levels of estradiol as well as oral contraceptive use are associated with elevated neural fear network responding to trauma films, with initial evidence also pointing to a relationship with long-term intrusions (see also Merz, Kinner, & Wolf, 2018). Thus, as the present study did not control for menstrual cycle phase or oral contraceptive use, we cannot be sure if the here demonstrated peritraumatic risk factors will generalize to all gonadal hormone status subgroups of women (different cycle phases, oral contraceptive use). Second, we cannot exclude that women responded differently than men due to more frequent previous traumatic experiences. Childhood adversity, which is more prevalent and/or intense in women than men, has been linked to many (psycho-)pathological processes and may thus influence current results (e.g., see Rattel et al., in press; Schury & Kolassa, 2012). Although we did not assess childhood adversity, we think that sexes did not differ much on this, since the psychopathological dimensions of depressive symptoms and trait anxiety that are strongly related to childhood adversity did not differ. Relatedly, it may be noted that increased responding to distressing films in women vs.

men may imply increased environmental responsiveness in women and thus, may be adaptive (particularly with regard to an evolutionary survival perspective; see Wilhelm et al., 2017). Third, although aversive films bear more ecological validity than traditional UCS (such as electric shock), they can only partially approximate the aversiveness, self-relevance, and complexity of real-life trauma. Furthermore, although the validity of the trauma film approach for linking analogue intrusion findings to intrusions found in PTSD has been suggested to be high (James et al., 2016), intrusions elicited by aversive films do, of course, not possess the intensity and chronicity of PTSD intrusions, which restricts generalizability.

Future prospective studies should investigate if enhanced evaluative UCR, evaluative extinction learning, and state anxiety increase in women compared to men during experimental analogue trauma can predict later PTSD development after real-life trauma in a high-risk population. This would clarify if the here described peritraumatic risk factors assessed during analogue trauma are in fact pre-traumatic risk factors in the prediction of PTSD development after real-life trauma. This would extend research by Lommen et al. (2013), who linked fear extinction deficits (with regard to an electric shock) to later PTSD development in soldiers.

4. Conclusion

The present findings further underline the importance of associative (evaluative acquisition and extinction learning) and non-associative (state anxiety and to a lesser extent unconditioned trauma responding) mechanisms in PTSD development. Importantly, the present findings provide novel insights regarding the higher propensity of women for PTSD after trauma: Women experienced analogue trauma as more aversive, displayed stronger evaluative acquisition and slowed extinction learning, and displayed higher anxiety levels following conditioning (relative to before); those sex differences explained to a large extent why women reported more analogue intrusions and associated distress than men. As elevated anxiety following trauma was a particularly robust predictor for intrusive memories in women vs. men, future studies should investigate if reducing anxiety levels in women immediately after analogue trauma can offset sex differences in intrusions. This may also provide insights into designing early focal prevention measures after real-life trauma.

Conflicts of 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.2019.01.009>.

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