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Decontextualized fear memories? Stronger conditioned fear responses during extinction learning and extinction recall in a safe context predict the development of long-term analog intrusions

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Abstract

Background. Difficulties in the context-dependent modulation of conditioned fear are known for posttraumatic stress disorder and may explain the occurrence of intrusive memories in safe contexts. The current study therefore investigated if reduced context-dependent modulation of conditioned fear and its underlying neural circuitry constitute risk factors for the development of analog intrusions in response to an experimental trauma.

Methods. Eighty-five healthy women participated in the trauma film paradigm to investigate the development of analog intrusions as well as explicit memory for an experimental trauma after one week and three months, respectively. Before, participants underwent a context-dependent fear conditioning paradigm during functional magnetic resonance imaging with fear acquisition in context A and extinction training in context B on a first day, as well as extinction recall in context B and fear renewal in a novel context C one day later. Skin conductance responses (SCRs) and blood oxygen level dependent responses were main outcome measures.

Results. In addition to stronger fear acquisition in context A, stronger conditioned fear responses in the safe context B, as indicated by stronger conditioned SCRs or stronger activation of fear expressing regions during extinction learning and recall, predicted the development of long-term analog intrusions.

Conclusions. Stronger fear responses in safe and danger contexts were risk factors for the development of long-term analog intrusions and point to decontextualized fear memories and difficulties in the context-dependent modulation of conditioned fear. Altered fear conditioning processes and reduced storage of contextual information may cause the occurrence of fear independent of context.

Introduction

Intrusions are a core symptom of posttraumatic stress disorder (PTSD) (American Psychiatric Association [APA], 2013). They consist of unwanted and involuntary recollections and impressions of a traumatic event and cause feelings and reactions as if the traumatic situation happens again, although a person is in a safe context (Ehlers, Hackmann, & Michael, 2004; Hackmann, Ehlers, Speckens, & Clark, 2004).

Theoretical models of PTSD (Brewin & Holmes, 2003; Brewin, Gregory, Lipton, & Burgess, 2010; Ehlers & Clark, 2000; Liberzon & Abelson, 2016) assume fear conditioning and reduced processing and storage of contextual information in the autobiographical memory during and after a traumatic event as relevant processes for the development of intrusions, which are conceptualized as conditioned fear responses (Franke et al., 2021). These processes may explain why PTSD patients are easily triggered by conditioned cues and show conditioned fear responses in safe contexts, which is also demonstrated in context-dependent fear conditioning studies: PTSD patients showed a stronger return of conditioned fear in a safe extinction context (reduced extinction recall), but also a missing up-regulation of conditioned fear (reduced fear renewal) when a dangerous context was presented (Garfinkel et al., 2014; Milad et al., 2009). These results indicate deficits in the contextual modulation of fear because of problems in identifying the context as a safety or danger signal. On the neural level, especially the hippocampus, the ventromedial prefrontal cortex (vmPFC) and the dorsal anterior cingulate cortex (dACC) are crucial brain regions for the context-dependent modulation of conditioned fear expression via the amygdala (Bouton, Westbrook, Corcoran, & Maren, 2006; Hermann,

Stark, Milad, & Merz, 2016; Kalisch et al., 2006; Maren, Phan, & Liberzon, 2013). Up to now, it is unclear, if difficulties in the contextual modulation of conditioned fear and underlying neural mechanisms constitute risk factors for the development of PTSD symptoms or rather are the result of traumatic stress or the disorder itself.

Besides longitudinal studies with high risk populations, the trauma film paradigm (TFP) is a valid experimental trauma model to efficiently investigate risk factors for (analog) intrusion development in healthy samples (Holmes & Bourne, 2008; James et al., 2016). In the context of the TFP, healthy participants are exposed to film scenes with stressful or traumatic content. The exposure to the film (analog trauma) elicits intrusive symptoms, which are defined as analog intrusions (James et al., 2016; Weidmann, Conradi, Groger, Fehm, & Fydrich, 2009). They are similar in their characteristics to intrusive memories reported by PTSD patients (Holmes, 2003; Holmes & Bourne, 2008). Although watching 'traumatic' film scenes might not be comparable to experiencing a real traumatic event regarding the intensity of elicited emotional responses, the underlying cognitive information-processing mechanism (e.g. reduced contextualization) are considered to be the same (Holmes, 2003; Holmes & Bourne, 2008; Holmes, Brewin, & Hennessy, 2004; Steel, Fowler, & Holmes, 2005). The TFP is therefore suitable for investigating the development and modulation of posttraumatic stress symptoms and underlying mechanism in a healthy population (Holmes & Bourne, 2008; James et al., 2016). In our study, we were interested in measuring the development of analog intrusions, but also in assessing explicit memory aspects of the analog trauma, since the relationship between involuntary and explicit 'trauma' memories is still unclear (James et al., 2016). People who experienced e.g. sexual violence recall some details about the perpetrator (e.g. 'perpetrator's eyes'), which become conditioned cues signaling danger (Ehlers et al., 2002; Hackmann et al., 2004) and therefore might be better retrieved, while contextual information about the situation seems hardly stored and retrievable (Michael, Ehlers, Halligan, & Clark, 2005). Aspects of the trauma memory (e.g. contextual integration) can also be measured retrospectively in traumatized PTSD populations (Ehring, Kleim, & Ehlers, 2011), but explicit memory contents are difficult to compare when the trauma is not identical across participants. The TFP has the advantage that an analog trauma is standardized across participants, which facilitates the study of explicit memory aspects.

A recent study by Miedl et al. (2020) combined the trauma film with a fear conditioning paradigm by using the aversive film clips as unconditioned stimuli. They showed that stronger activation of the insula and dACC during late extinction learning predicted the development of analog intrusions within the following days. These results validate previous findings (Rattel et al., 2019) which demonstrated that fear acquisition and especially extinction learning were both linked to analog intrusion development. Further prospective fear conditioning studies also found evidence for deficits in extinction learning as a risk factor for PTSD (Guthrie & Bryant, 2006; Lommen, Engelhard, Sijbrandij, van den Hout, & Hermans, 2013; Orr et al., 2012). Besides fear conditioning, dysfunctional context processing is assumed as an additional relevant etiological factor in PTSD (Brewin et al., 2010; Brewin & Holmes, 2003; Ehlers & Clark, 2000; Liberzon & Abelson, 2016), which is however not taken into account in prospective fear conditioning studies with analog samples and PTSD patients so far. Results of cross-sectional studies with PTSD patients (Garfinkel et al., 2014; Milad et al., 2009) using a context-dependent fear conditioning paradigm as in the current study showed consistent evidence for dACC-related extinction deficits, which is also in accordance with the above-mentioned prospective study by Miedl et al. (2020) despite their differences in design and sample characteristics. Moreover, the dACC is a region which is consistently and robustly found to be involved in human fear conditioning (Fullana et al., 2016). In contrast to some others regions of the fear and extinction network, there is also some evidence that hyperactivation of the dACC seem to be a predisposing risk factor for the development of PTSD (Admon, Milad, & Hendler, 2013). The dACC is further regarded as a core region for the detection of intrusions (Crespo-García, Wang, Jiang, Anderson, & Lei, 2022).

This functional magnetic resonance imaging (fMRI) study aims to expand previous findings by investigating the relevance of context-dependent fear conditioning processes including extinction learning, but also delayed extinction recall and fear renewal for the development of analog intrusions in a healthy female sample. Therefore, participants completed a two-day context-dependent differential fear conditioning paradigm during functional magnetic resonance imaging (fMRI) with fear acquisition in context A and extinction training in context B on a first day, as well as extinction recall in the safe extinction context B and fear renewal in a novel context C one day later (see online Supplement). Skin conductance responses (SCRs) and blood oxygen level dependent responses served as main outcome measures. After the conduction of the fear conditioning paradigm, participants underwent the TFP, where they were exposed to film scenes of physical and sexual violence. Extending previous research, we assessed not only short-term analog intrusions (within one week), but also long-term intrusions (after three months) in response to the film. Moreover, we also measured explicit film memory for different content categories (context, perpetrator and victim) by questionnaire.

In addition to stronger conditioned fear responses during fear acquisition in context A, we hypothesized that difficulties in the context-dependent modulation of conditioned fear predict the development of analog intrusions. Difficulties in the context-dependent modulation of fear should be reflected in stronger conditioned fear responses during extinction learning and recall in the safe extinction context B as well as in reduced conditioned fear responses during fear renewal (missing fear renewal) in a novel context C. Stronger conditioned fear responses should be indicated by stronger conditioned SCRs and by activation in brain regions of the fear network (especially stronger activation of the dACC). With regard to the TFP, we also hypothesized that stronger analog intrusions are associated with reduced explicit context memory and a better memory for the perpetrator (which might represent a conditioned cue predicting danger).

Methods and materials

Sample and study procedure

A sample of 94 physically and mentally healthy female students with a mean age of $M = 23.24$ years (s.d. = 2.746, range: 18–31 years) was recruited via mailing lists at the local university and included in the study after screening for study in- and exclusion criteria comprising a structured clinical interview for mental disorders (see online Supplement A). This study was part of a larger project with six study days (see online Supplement B and Supplementary Fig. S1), investigating the relevance of fear

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Table 1. Characteristics and differences between women with (INT) and without (NO-INT) long-term analog intrusions

	INT ($n = 35$) M (s.d.)	NO-INT ($n = 30$) M (s.d.)	Test statistic (two-sided)
Age in years	23.57 (2.893)	22.33 (2.040)	$t(63) = 1.962$, $p = 0.054$
Relationship (yes/no)	0.60 (0.497)	0.53 (0.507)	$\chi^2(1) = 0.293$, $p = 0.588$
Usage of contraceptives (yes/no)	0.34 (0.482)	0.53 (0.507)	$\chi^2(1) = -2.390$, $p = 0.122$
Beck Depression Inventory-II (sum)	3.11 (3.579)	1.73 (3.140)	$t(63) = 1.640$, $p = 0.106$
Global Severity Index of the Symptom Checklist-90-R (sum)	0.18 (0.163)	0.12 (0.124)	$t(63) = 1.541$, $p = 0.128$
State-Trait-Anxiety Inventory (sum)	35.37 (8.303)	33.07 (6.787)	$t(63) = 1.212$, $p = 0.230$
Weeks between study day 6 and online survey	12.84 (0.587)	12.85 (0.889)	$t(63) = -0.059$, $p = 0.953$

conditioning, pattern separation, and emotion regulation for the development of analog intrusions. Data for the current study comprise the diagnostic session (day 1), the context-dependent fear conditioning paradigm (day 4 and 5), the TFP (day 5) with the assessment of analog intrusions, and explicit film memory after one week (day 6) as well as approximately three months after the TFP via an online survey. Six participants dropped out before the completion of the fear conditioning paradigm on study day 4; 14 participants were excluded from fMRI analyses (e.g. due to technical problems or excessive head movements during scanning, see online Supplement C). Three participants did not attend study day 6 for the assessment of short-term intrusions in reaction to the TFP; 1 participant was excluded due to a missing value for short-term intrusions. Regarding long-term intrusions, 65 participants responded to the 3-months-follow-up questionnaires. Therefore, the final sample regarding the prediction of short-term/long-term analog intrusions from neural correlates of context-dependent fear conditioning processes consisted of 70/56 women, respectively. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethical review board. Participants gave written informed consent and received 10 Euros/h or course credits for participation.

Trauma film paradigm

During the TFP, participants viewed film clips with a total length of 11:18 min from the movie 'Irreversible' by Gaspar Noé (2002) showing physical and sexual violence. The film clips were successfully used in previous studies to induce analog intrusions (Holz, Lass-Hennemann, & Michael, 2017; Nixon, Cain, Nehmy, & Seymour, 2009; Weidmann et al., 2009). Prior to film viewing, participants were instructed to watch various film scenes within the next 11 min, to concentrate and to watch each scene completely as well as to avoid distracting themselves from the film. Furthermore, they should imagine being a witness of the scene. The audio was played via headphones and individually adjusted beforehand using a neutral audio clip. The Positive and Negative Affect Schedule (PANAS; Krohne, Egloff, Kohlmann, & Tausch, 1996) was conducted immediately before and after the trauma film as a mood manipulation check, in addition to several post-hoc film ratings (see online Supplement D). Analog intrusions and explicit film memory were measured by questionnaires and different tasks (see below and online Supplement D).

Short- and long-term analog intrusions

We used an adapted German version of the intrusion subscale of the Impact of Event Scale-Revised (IES-R; Maercker & Schützwohl, 1998) rather than the number of intrusions as the main outcome measure for short- and long-term analog intrusions, in order to investigate more sustained and potentially clinically relevant intrusion symptoms (see online Supplement D). Higher IES-R scores reflect stronger analog intrusions.

Short-term analog intrusions (assessed one week after the TFP on study day 6) referred to a period of one week following the analog trauma. As indicated by sum scores of the intrusion scale of the IES-R, three participants reported none, all others reported short-term analog intrusions within one week ($M = 8.82$, s.d. = 6.221, range: 0–26).

Long-term analog intrusions were assessed three months after study day 6 ($M = 12.84$ weeks, s.d. = 0.736) via an online-survey. During this 3-months follow-up assessment, participants retrospectively rated for the last 4 weeks (preceding the 3-months follow-up assessment) whether they had intrusive memories. The distribution of long-term analog intrusions was not well suited for applying a correlative method. The median for long-term analog intrusions (intrusion scale of the IES-R) was $Md = 1.00$, indicating a low occurrence of long-term analog intrusions in the whole sample. Therefore, the data were further analyzed by splitting the participants into two groups. After three months, nearly half of the participants ($n = 30$) reported no analog intrusions in the last 4 weeks and were post-hoc classified as the NO-INT (no intrusions) group. The other participants ($n = 35$) reported the experience of long-term analog intrusions (intrusion scale of the IES-R: $M = 4.43$, s.d. = 4.279, range: 1–20) and were post-hoc classified as the INT (intrusion) group. Both groups did not significantly differ in clinical variables, nor relationship status, but the NO-INT group tended to be slightly younger (see Table 1). Therefore, we entered age as a covariate in the analyses when investigating group differences. As shown in Table 1, groups did also not significantly differ in the use of hormonal contraceptives. We evaluated group differences regarding the use of hormonal contraceptives, in order to exclude that group effects in fear conditioning might be the result of the intake of contraceptives influencing sex hormones, which affect fear conditioning processes (Merz, Kinner, & Wolf, 2018; Peyrot, Brouillard, Morand-Beaulieu, & Marin, 2020).

Explicit film memory for context, perpetrator, and victim information

In order to measure the explicit film memory after one week and after three months, we developed a recognition memory questionnaire (see online Supplement E) including ten statements for each content category (context, perpetrator, victim), which should be

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classified as true or false. A sum score (number of correctly classified statements) was calculated for each category. We used correlational analyses according to Pearson (two-sided) to analyze the a priori hypothesized associations between short-term intrusions and explicit film memory. We further conducted univariate analyses of covariance (two-sided) including age as a covariate to assess the a priori hypothesized differences in explicit film memory between the INT and NO-INT group after one week and after three months, using SPSS 27 (IBM Corporation, Armonk, NY, USA).

Context-dependent fear conditioning paradigm

Experimental design

Participants completed a 2-day context-dependent differential fear conditioning paradigm (Hermann et al., 2016; Milad et al., 2007; Milad, Orr, Pitman, & Rauch, 2005) during fMRI, see online Supplementary Fig. S2 and Supplement C for more details. In short, the paradigm consisted of fear acquisition in context A and immediate extinction training in context B on one day. After approximately 24 h, retrieval testing in the extinction context B ('extinction recall') and in the novel context C ('fear renewal') took place. Pictures of different rooms (e.g. office room) served as contexts A, B and C. The lamplight colors (blue, yellow) of a desk lamp presented in each room were used as reinforced conditioned (CS+) or non-reinforced (CS−) stimuli. Electrical stimulation applied via electrodes positioned at the right middle and forefinger served as the unconditioned stimulus (UCS). Fear acquisition included 8 trials per CS type, extinction training 16 trials per CS type. Retrieval testing one day later in the safe context ('extinction recall') and in a novel context ('fear renewal') consisted of 8 trials per CS type. Each trial contained the presentation of a picture of a room (context) with a turned-off desk lamp for 3s, which was followed by the same picture with a turned-on desk lamp, which lit up blue or yellow (CS) for 6s (and was followed by a 500 ms UCS application in 5 out of 8 CS+ trials during fear acquisition).

FMRI data acquisition and analyses

Brain images were acquired with a 3-Tesla whole-body tomograph (Siemens Prisma) with a 64-channel head coil. A T2*-weighted gradient echo-planar imaging sequence (EPI, see online Supplement C) was used for assessing blood oxygen level dependent responses during all experimental phases. For preprocessing and first-level analyses as well as details regarding second-level analyses, see online Supplement C. The CS+ and CS− were contrasted for fear acquisition and for early (first 8 CS+/CS− trials) and late (last 8 CS+/CS− trials) extinction training phase. For retrieval testing in the safe and novel contexts, CS+ and CS− were contrasted for the first 4 CS+/CS− trials of each phase (early extinction/ early fear renewal). Data of 14 participants had to be excluded from fMRI analyses due to technical problems or strong movement (see online Supplement C).

For the analyses of main effects (CS+ minus CS−, $n = 74$) of the fear conditioning paradigm, see online Supplement C. Multiple regression analyses were performed during second-level analyses implemented in SPM12 (r7771) to analyze the relevance of neural activation in our regions of interests (ROI) during context-dependent fear conditioning for the development of short-term analog intrusions ($n = 70$). For the prediction of long-term analog intrusions, differences between the INT and NO-INT group in neural responses (CS+ minus CS−) in our ROIs (covariate of no interest: age) were analyzed ($n = 56$). We defined the dACC (bilaterally) as our primary ROI, as we had strong evidence for its involvement in fear conditioning processes and for its relevance for PTSD (symptom development). We conducted FWE (family-wise error) small volume correction for our primary ROI (dACC). We defined amygdala, insula, vmPFC and hippocampus as secondary ROIs. We conducted FWE small volume correction inside one mask with all secondary ROIs. For all ROI analyses, we used F tests to investigate effects in both directions for all experimental phases. For more information about ROI analyses and masks, see online Supplement C and Supplementary Fig. S5. Peak voxels surviving $p < 0.05$ (FWE, random field theory) were considered significant either for the whole brain or ROIs (small volume correction).

Skin conductance responses and analyses

SCRs were measured with Ag/AgCl electrodes filled with isotonic (0.05 M NaCl) electrolyte paste placed on the hypothenar of the left hand. Data were preprocessed and analyzed via 'trough-to-peak' analyses (Pineles, Orr, & Orr, 2009), which are described in more detail in the online Supplement. Conditioned responses were conceptualized as larger responses to the CS+ compared with CS−. SCR data were analyzed for each experimental phase in parallel to the fMRI data. Statistical analyses were conducted in SPSS 27 (IBM Corporation, Armonk, NY, USA) using non-parametric procedures due to a lack of normality of SCR data. Data of 15 participants were excluded from SCR data analyses (see online Supplement C for details).

For main effect analyses ($n = 59$), we conducted Wilcoxon-tests (see online Supplement C). In order to examine the predictive value of context-dependent fear conditioning for the development of short-term intrusions, correlational analyses according to Spearman's rho (two-sided) were performed ($n = 56$). Wilcoxon-tests (two-sided) were done to investigate group differences (INT *v.* NO-INT group) in conditioned SCRs (CS+ minus CS−) for each experimental phase ($n = 44$; $n = 22$ for each group).

Post hoc ratings

After the fear conditioning paradigm, post-hoc ratings were conducted outside the scanner to measure context recognition and UCS expectancy for the extinction context and the novel context (see online Supplement C for details).

Results

Trauma film paradigm

Mood manipulation check

Participants reported stronger negative affect after ($M = 23.58$, S.D. = 6.898) compared to before ($M = 10.75$, S.D. = 1.164) film viewing ($t(85) = 17.098$, $p < 0.001$), indicating successful induction of negative affect by the trauma film. The post-hoc film ratings also indicated high levels of concentration, stress, arousal and low positive valence during film watching (see online Supplementary Table S1).

Analog intrusions and explicit film memory

The film successfully induced intrusive symptoms as shown in Fig. 1a and online Supplementary Fig. S3. Stronger short-term intrusions predicted the development of long-term intrusions after three months: The INT group ($M = 10.66$, S.D. = 6.394) reported stronger short-term analog intrusions than the NO-INT group ($M = 6.41$, S.D. = 5.068), $t(62) = 2.897$, $p = 0.005$).

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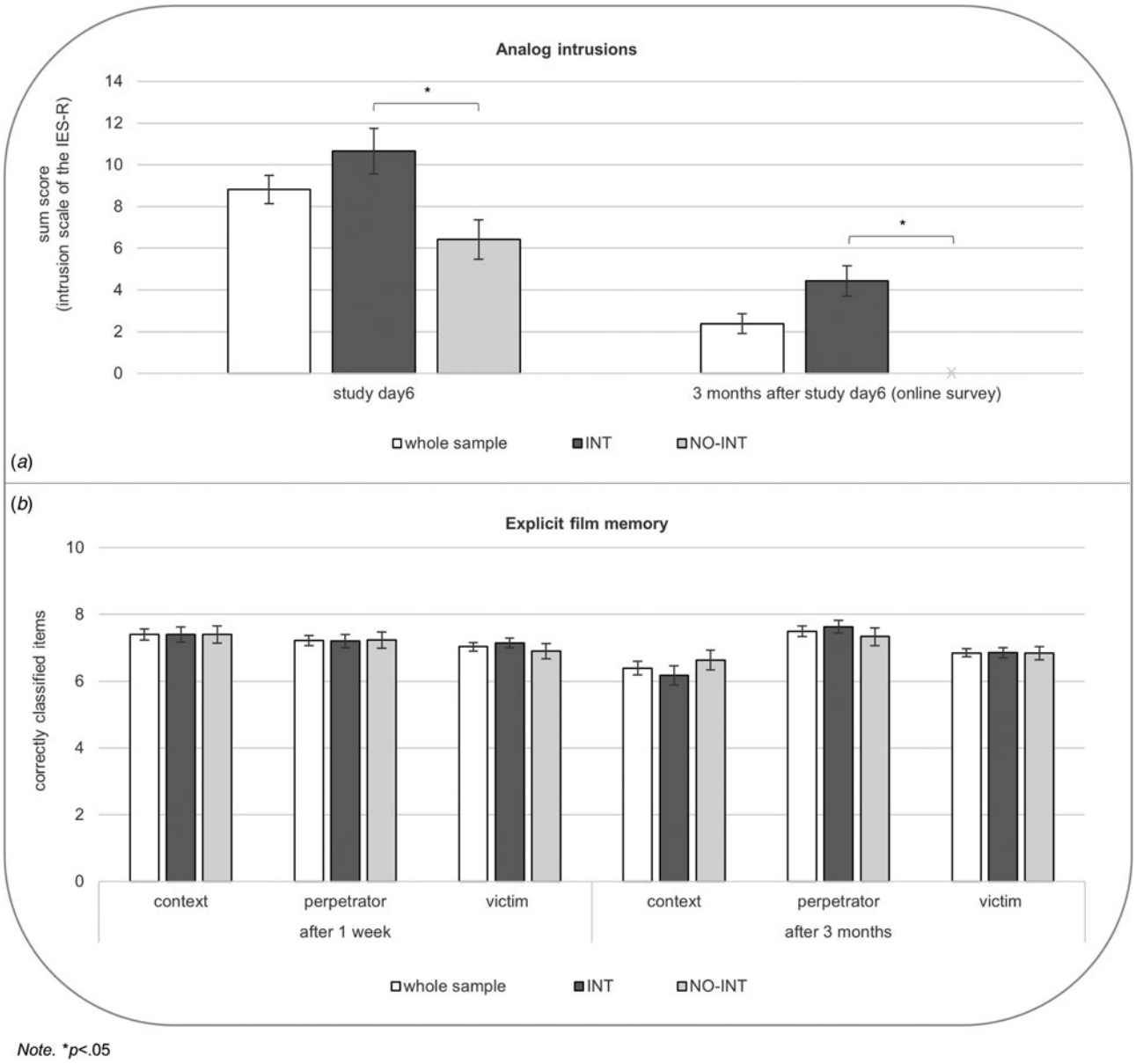

Fig. 1. Trauma film paradigm: analog intrusions and explicit film memory. (a) Analog intrusions [intrusion scale of the Impact of Event Scale-Revised (IES-R)] in response to the trauma film within one week (measured at study day 6) and after three months (measured via online survey) for the whole sample and for each group (INT: women with long-term intrusions; NO-INT: women without long-term intrusions). Error bars depict standard errors of the mean. (b) Explicit film memory (correctly classified items) for context, perpetrator, and victim information one week and three months after the trauma film paradigm for the whole sample and for women with (INT) and women without (NO-INT) long-term intrusions in response to an experimental trauma. Error bars depict standard errors of the mean.

Regarding explicit film memory in the whole sample (Fig. 1b), memory recognition scores for perpetrator, context, and victim information did not significantly differ after one week ($F_{(2,168)} = 2.190$, $p = 0.115$), but after three months ($F_{(2,128)} = 11.650$, $p < 0.001$). The recognition memory was better for perpetrator in comparison to victim ($t(64) = 3.152$, $p = 0.002$) and in comparison to context information ($t(64) = 4.571$, $p < 0.001$). Information about the victim was also better retrieved than context information (see Fig. 1b), but this difference was not statistically significant, ($t(64) = 1.905$, $p = 0.061$).

With regard to our hypotheses, there was no significant association of short-term analog intrusions with the explicit recognition memory for context, perpetrator, and victim information (see online Supplementary Table S2). Regarding long-term intrusions, groups did not significantly differ in memory scores for context, perpetrator, or victim information after one week and after three months (see online Supplementary Table S2 and Fig. 1b).

Context-dependent fear conditioning and its predictive value for short- and long-term analog intrusions

Analyses of main effects of the fear conditioning paradigm are described and presented in the online Supplement C and Supplementary Table S3.

Short-term analog intrusions and context-dependent fear conditioning

ROI and whole brain analyses (all $p > 0.05$) showed no significant correlations between short-term analog intrusions and neural

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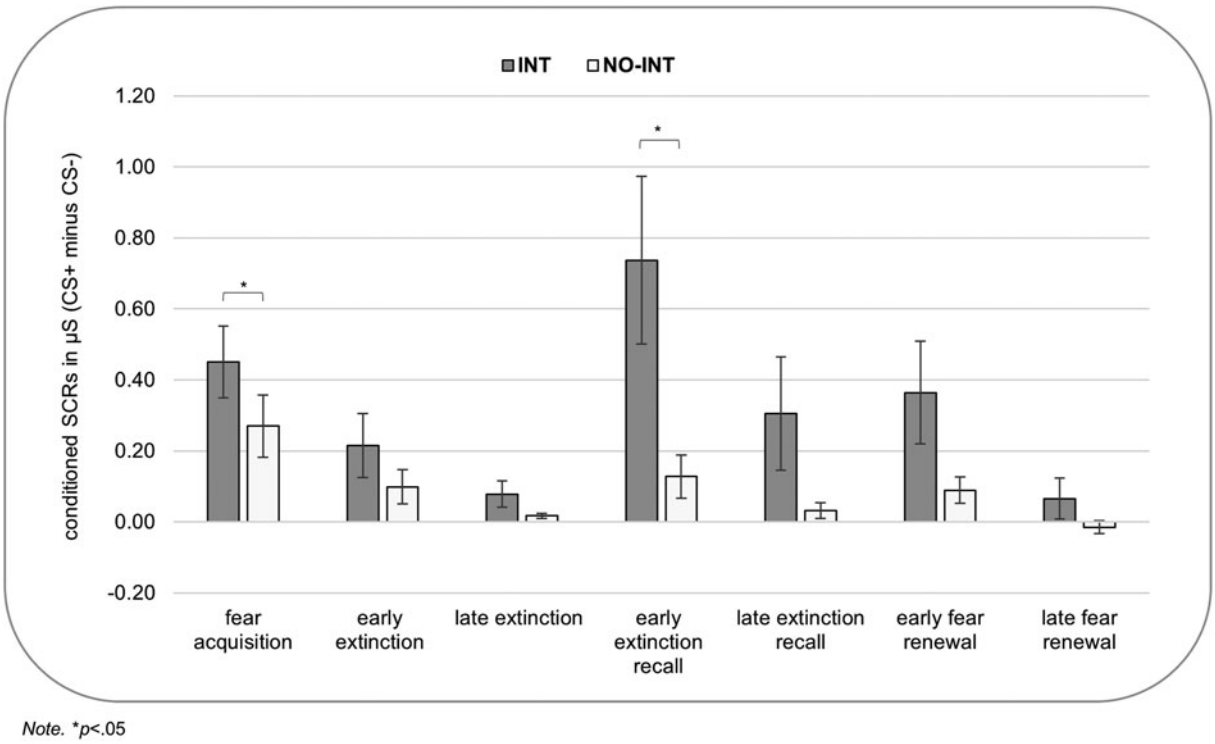

Fig. 2. Conditioned (CS+ minus CS−) skin conductance responses (SCRs) during fear acquisition in context A, (early/late) extinction learning in context B, (early/late) extinction recall in context B and (early/late) fear renewal in context C for women with (INT) and women without (NO-INT) long-term intrusions in response to an experimental trauma. Error bars depict standard errors of the mean.

responses (CS+ minus CS−) during all experimental phases. Moreover, there were no significant correlations between short-term analog intrusions and differential conditioned SCRs during fear acquisition ($r_s = 0.062$, $p = 0.648$), early extinction ($r_s = -0.077$, $p = 0.575$), or late extinction ($r_s = -0.069$, $p = 0.612$) as well as during early extinction recall ($r_s = -0.014$, $p = 0.921$) or early fear renewal ($r_s = -0.132$, $p = 0.334$).

Long-term analog intrusions and context-dependent fear conditioning

In comparison to the NO-INT group, the INT group demonstrated stronger activation of the dACC ($F = 21.11$, $p_{fwecorr} = 0.024$, MNI: $x = 14$, $y = 12$, $z = 34$) during fear acquisition. The INT group also showed stronger SCRs for CS+ compared with CS− ($z = 2.277$, $p = 0.023$; see Fig. 2). There was no group difference for responses towards the UCS after CS+ compared with the omission response after CS− ($z = 1.338$, $p = 0.181$) during the fear acquisition phase.

During early extinction, the INT group showed stronger activation of the right amygdala ($F = 46.55$, $p_{fwecorr} < 0.001$, MNI: $x = 20$, $y = -4$, $z = -12$) and the left vmPFC ($F = 26.38$, $p_{fwecorr} = 0.012$, MNI: $x = -6$, $y = 44$, $z = -6$) for CS+ compared with CS−, but not significantly stronger conditioned SCRs ($z = 1.495$, $p = 0.135$) than the NO-INT group (see Fig. 2 and 3). During late extinction, when context B should be acquired as a safety context, the INT group showed increased conditioned SCRs ($z = 1.800$, $p = 0.072$) than the NO-INT group (see Fig. 2); however, this difference was not statistically significant. There were also no significant group differences in neural activation towards CS+ compared to CS− (all ROI and whole brain analyses: $p > 0.05$).

During early extinction recall in context B, when context B should signal safety, the INT compared to the NO-INT group showed stronger conditioned SCRs ($z = 2.616$, $p = 0.009$) (see Fig. 2). Further SCR analyses revealed a stronger return of fear from late extinction training to early extinction recall for the INT than the NO-INT group ($z = 2.475$, $p = 0.013$). Within-group analyses revealed a significant return of fear on the SCR level only in the INT group ($z = 3.622$, $p < 0.001$), but not in the NO-INT group ($z = 1.758$, $p = 0.079$). On the neural level, the INT group also showed stronger activation of the dACC for the CS+ compared with the CS− than the NO-INT group, but this group difference was not statistically significant ($F = 17.46$, $p_{fwecorr} = 0.073$, MNI: $x = 0$, $y = 26$, $z = 24$).

Regarding fear renewal in context C, analyses revealed no significant group differences in neural activation (ROI and whole brain analyses, all $p > 0.05$). We could observe stronger conditioned SCRs for the INT than the NO-INT group (see Fig. 2), but this group difference was not significant ($z = 1.748$, $p = 0.080$). Further analyses regarding a stronger return of fear from late extinction recall in context B to early fear renewal in context C also revealed no group differences ($z = 0.455$, $p = 0.649$) on SCR level. Within-group analyses, however, indicated a significant return of conditioned SCRs for the NO-INT group ($z = 2.134$, $p = 0.033$), but not for the INT group ($z = 0.327$, $p = 0.744$).

Groups did not differ in UCS expectancy for context B ($F_{(1,52)} = 2.677$, $p = 0.108$, controlled for age) nor context C ($F_{(1,51)} = 0.025$, $p = 0.874$, controlled for age), as indicated by post-hoc ratings.

Discussion

As a main finding of our study, long-term analog intrusions in response to an experimental trauma were not only predicted by

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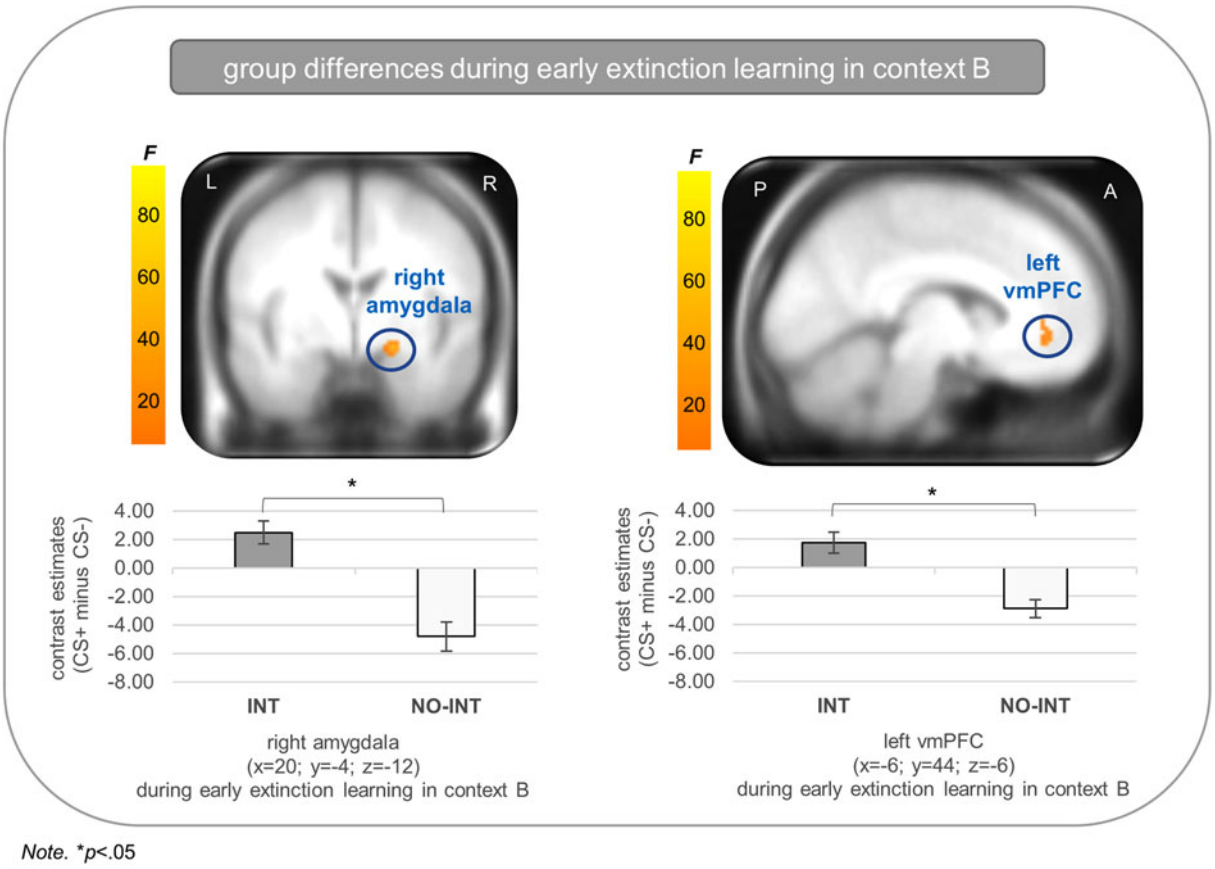

Fig. 3. Stronger activation for CS+ minus CS− in the right amygdala and the left ventromedial prefrontal cortex (vmPFC) during early extinction learning in context B in the INT (INT, women with long-term analog intrusions) compared to the NO-INT (NO-INT, women without long-term analog intrusions) group. Neural activations were superimposed on the MNI305 T1 template. All coordinates (*x*, *y*, *z*) are given in MNI space. The color bar depicts *F* values. A, anterior; *P*, posterior; L, Left; R, Right. Error bars depict standard errors of the mean.

stronger conditioned SCRs in the danger context during fear acquisition, but also in the safe context during extinction recall. Stronger conditioned fear expression, as indicated by stronger SCRs, in danger and safe contexts in women with long-term analog intrusions point to decontextualized fear memories and difficulties in the context-dependent modulation of conditioned fear to be risk factors for the development of analog intrusions. Neural findings support this interpretation, as stronger activation in fear expressing regions (e.g. amygdala, dACC) during fear acquisition in context A and during extinction learning in the safe context predicted the development of long-term analog intrusions. These findings are mainly in line with a meta-analysis, reporting increased fear expression on the neural level during fear acquisition, but also during extinction learning and extinction recall in PTSD patients (Suarez-Jimenez et al., 2019).

Stronger conditioned fear responses in a safe context during extinction learning and recall, as indicated by SCR or neural data, might be due to difficulties in using the context as a safety signal (Jovanovic, Kazama, Bachevalier, & Davis, 2012; Rougemont-Bücking et al., 2011; Sangha, Diehl, Bergstrom, & Drew, 2020). Deficits in using context information for fear modulation are proposed to be etiologically relevant risk factors for PTSD and may explain why patients with PTSD show conditioned fear responses in form of intrusions in safe contexts (Brewin & Holmes, 2003; Ehlers & Clark, 2000; Liberzon & Abelson, 2016). Considering the neural findings, stronger conditioned fear responses in the safe context in the INT compared to the NO-INT group were reflected in increased activation of the amygdala and the vmPFC during extinction learning. The amygdala is a brain region relevant for fear expression (Cheng, Knight, Smith, & Helmstetter, 2006), while the vmPFC is thought to have a modifying influence on the amygdala (Andrewes & Jenkins, 2019; Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2015). Hyperactivity of fear expressing brain regions like the amygdala might enhance the vulnerability for increased fear acquisition and fear retrieval in safe contexts. Neural findings mainly fit the findings of previous context-dependent fear conditioning studies with PTSD patients who showed stronger amygdala activation during early extinction in context B and increased dACC activation, but also hypoactivation of vmPFC and hippocampus, during extinction recall in context B (Garfinkel et al., 2014; Milad et al., 2009). Furthermore, our results of stronger fear responses in safe contexts also point to extinction difficulties as a risk factor for analog intrusions and validates previous findings (Miedl et al., 2020).

Regarding fear renewal in context C, there was no significant group difference in the return of fear, when a novel, potentially dangerous context was presented. However, in within-group analyses the INT group did not show an increase of differential conditioned SCRs from late extinction recall to early fear renewal, indicating reduced or missing fear renewal processes. A significant up-regulation of fear (from late extinction recall to early

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fear renewal) was only found on SCR level within the NO-INT group, reflecting successful context-dependent fear modulation. Reduced fear renewal was previously shown for PTSD patients and might result from problems in identifying a contextual change or in using the context for fear modulation (Garfinkel et al., 2014). Successful fear renewal is linked to stronger hippocampal activation and connectivity with structures of the fear and extinction network (Hermann et al., 2016). Difficulties in fear renewal might rather be associated with dysfunctions in specific brain areas (e.g. hippocampus, vmPFC) as a consequence of traumatic stress and resulting PTSD symptoms than a predisposing factor for the development of PTSD (Admon et al., 2013; Stark et al., 2015) or might be related to other symptoms of PTSD, as PTSD is characterized by multiple symptom clusters (American Psychiatric Association [APA], 2013).

With regard to the TFP, we were able to show that long-term analog intrusions, which rather resemble pathological intrusions known for PTSD, were predicted by short-term intrusions, which are common and not pathological *per se* after a(n) (experimental) trauma (Ehlers & Steil, 1995). This might explain why we did not find significant associations between short-term analog intrusions and electrodermal and neural indicators of context-dependent fear conditioning processes. In addition to analog intrusions, explicit memory scores regarding the trauma film were measured. Scores did not differ in the whole sample after one week, but three months after the TFP. The findings suggest that context information is forgotten more quickly over time or stored less deeply compared to information about the perpetrator in the whole sample. Against our expectations, neither context nor perpetrator information were predictive for the development of short-term nor long-term analog intrusions. Deficits in the storage and retrieval of contextual information of the traumatic situation might therefore be no predisposing factors for the development of (analog) intrusions. However, our results and the interpretation of them are limited as they depend on the quality of the questionnaire, which was newly developed in the context of the current study and has not yet been validated. In general, studying different memory aspects in response to an experimental trauma might help to improve prevention and treatment of memory dysfunctions in PTSD (Al Abed et al., 2020; Desmedt, 2021).

The current study has several limitations: the findings were based on a healthy female sample and cannot be generalized to other genders or clinical populations. Regarding the TFP, the questionnaire for explicit film memory was developed for this study and used for the first time. Furthermore, analyses of main effects of the context-dependent fear conditioning paradigm (see online Supplement C) revealed a significant recall of conditioned fear in the novel, but also in the safe extinction context, which reflects a missing extinction recall in the whole sample. Return of fear in a safe context can be a result of immediate extinction training after fear acquisition, promoting a stronger return of fear (Merz, Hamacher-Dang, & Wolf, 2016).

In sum, the findings of our study indicate that increased conditioned fear responses during extinction learning and recall in a safe context (but also during fear acquisition) are significant predictors for the development of long-term intrusions in response to an experimental trauma. Stronger conditioned fear expression in safe contexts was indicated by stronger SCRs or stronger activation in fear expressing brain regions (e.g. amygdala). Hyperactivation of fear expressing regions is regarded as a risk factor for PTSD (Admon et al., 2013; Stark et al., 2015) and may contribute to decontextualized fear memories and extinction deficits, which are considered as etiologically relevant factors for the development of posttraumatic stress symptoms (Ehlers & Clark, 2000; Liberzon & Abelson, 2016; Miedl et al., 2020). Reduced fear renewal, however, was no significant predictor of intrusion development. Findings of reduced fear renewal in PTSD (Garfinkel et al., 2014) might therefore rather be a consequence of traumatic stress and resulting PTSD symptoms than a precondition of the disorder or might be related to other symptoms of PTSD than intrusions.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723001125

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Authors' contributions. **Marie K. Neudert:** Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Writing – Original Draft, Visualization. **Axel Schäfer:** Software, Formal Analysis, Writing – Review & Editing. **Raphaela I. Zehtner:** Conceptualization, Investigation, Writing – Review & Editing. **Susanne Fricke:** Investigation, Writing – Review & Editing. **Rosa J. Seinsche:** Investigation, Writing – Review & Editing. **Rudolf Stark:** Writing – Review & Editing, Supervision. **Andrea Hermann:** Conceptualization, Methodology, Writing – Review & Editing, Project Administration, Supervision.

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Conflict of interest. The authors declare no conflict of interest.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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