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Pavlovian threat conditioning can generate intrusive memories that persist over time

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Abstract:	Although Pavlovian threat conditioning has proven to be a useful translational model for the development of anxiety disorders, it remains unknown if this procedure can generate intrusive memories – a symptom of many anxiety-related disorders, and whether intrusions persist over time. Social support has been related to better adjustment after trauma however, experimental evidence regarding its effect on the development of anxiety-related symptoms is sparse. We had two aims: to test whether threat conditioning generates intrusive memories, and whether different social support interactions impacted expression of emotional memories. Non-clinical participants (n=81) underwent threat conditioning to neutral stimuli. Participants were then assigned to a supportive, unsupportive, or no social interaction group, and asked to report intrusive memories for seven days. As predicted, threat conditioning can generate intrusions, with greater number of intrusions of CS+ (M=2.35, SD=3.09) than CS- (M=1.39, SD=2.17). Contrary to predictions, compared to no social interaction, supportive social interaction did not reduce, and unsupportive interaction did not increase skin conductance of learned threat or number of intrusions. Unsupportive interaction resulted in a relative difference in number of intrusions to CS+ vs CS-, suggesting that unsupportive interaction might have increased image-based threat memories. Intrusions were still measurable one year after conditioning (one-year follow-up; n=54), when individuals with higher trait anxiety and greater number of previous trauma experiences reported more intrusions. Our findings show that threat conditioning can create long-lasting intrusions, offering a novel experimental psychopathology model of intrusive memories with implications for both research on learning and clinical applications.

Covering letter

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Dear Professor Craske,

We are pleased to submit an original research article for publication in *Journal of Behavior Research and Therapy*, entitled "Pavlovian threat conditioning can generate intrusive memories persisting over time" for consideration.

Our paper presents the first study examining whether the standard Pavlovian threat conditioning using neutral images (e.g. image of a clock) as conditioned stimuli (CS) and electrical stimulations as aversive stimuli, can generate intrusive memories of the CS and whether these intrusive memories persist over time. This work further validates the emerging body of evidence showing the contribution of conditioning processes in the development of intrusive memories (Franke et al., 2021; Miedl et al., 2020; Wegerer et al., 2013). We also investigated the potential modulating effect of social support (active social support, low social support and no social interaction) after acquisition of learned threat on autonomic responses (skin conductance) during threat conditioning and number of intrusive memories of the stimuli during the following seven days.

Across a lab experiment and a one-year follow-up survey, we demonstrate that threat conditioning indeed generates intrusive memories of the CS and that they persist over time. Social support did not influence autonomic indices of threat learning or number of intrusions, but low social support lead to a significantly larger difference between the number of CS+ and CS- intrusions.

These findings reveal that through threat conditioning, benign stimuli can become long-lasting intrusions, supporting the use of Pavlovian threat conditioning paradigms to explore both the exposure and the (short and longer-term) outcome of an aversive event in terms of core phenomenology characterizing clinical anxiety disorders. This represents a step forwards both for experimental psychology use of the Pavlovian threat conditioning and for clinical psychology tools to study intrusive memories that are so prevalent in psychopathology but as yet little understood.

Our manuscript has not been published and is not under consideration for publication elsewhere. We include in our submission a supplemental material document, as well as the link to our OSF page containing key data and relevant material and documents, which are available to reviewer upon request. Potentially relevant conflicts of interest are disclosed at the end of the manuscript. This study was approved by Regional Ethical Review Board in Stockholm. All of the authors listed here have agreed to submission of the manuscript in this form. Lisa Espinosa will be serving as the corresponding author for this manuscript.

We recommend the following potential reviewers, who have no conflicts of interest: Prof. Frank H. Wilhelm from University of Salzburg (Frank.Wilhelm@plus.ac.at), expert in experimental work investigating threat conditioning and development of intrusive memories; Dr. James Bisby from University College London (j.bisby@ucl.ac.uk), expert in neuroscience and intrusive memories; Prof. Sunjeev Kamboj from University College London (sunjeev.kamboj@ucl.ac.uk), expert in clinical psychology and intrusive memories; Dr. Andre Pittig from University of Würzburg (andre.pittig@uni-wuerzburg.de), who has expertise in threat conditioning, experimental psychopathology and translation into psychotherapeutic interventions; Dr. Melanie Wegerer from University of Vienna (melanie.wegerer@univie.ac.at), expert in research on threat conditioning and intrusive memories. We have no non-preferred reviewers.

On behalf of the co-authors, we would like to thank you for your consideration. We appreciate your time and look forward to your response.

Sincerely,

Lisa Espinosa, PhD student　　Prof. Emily A. Holmes　　Prof. Andreas Olsson

Pavlovian threat conditioning can generate intrusive memories that persist over time

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Acknowledgments:

We are grateful to Ella James, who shared the protocol and gave training in using the intrusive memory diary; Lina Hansson and Vanja Zenlander for the help with data collection; Paola Romano, who provided assistance in coding the diary; Armita Golkar, who provided statistical advice for the analyses of the return of threat data. Thomas Ågren and Amy Walsh for their feedback on the final draft of the manuscript.

This research was supported by the Knut and Alice Wallenberg Foundation (KAW 495 2014.0237), from KI Development (KID) grant (2-3591/2014) and a Consolidator Grant (2018-00877) from the Swedish Research Council (Vetenskapsrådet) to AO. EAH reports grants from the Swedish Research Council (2017-00957), The Lupina Foundation, and The Oak Foundation (OCAY-18-442), during the conduct of the study. NB reports a grant by the Swedish Research Council (Vetenskapsrådet, 2017-06146).

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Dear Professor Craske

Re: Pavlovian threat conditioning can generate intrusive memories that persist over time

Authors: Lisa Espinosa, Michael B. Bonsall, Nina Becker, Emily A. Holmes & Andreas Olsson

Ref number BRAT-D-21-00627

Thank you very much for your decision to accept our manuscript for publication in *Behaviour Research and Therapy* pending some final revisions. We thank you for the opportunity to make final improvements to our manuscript and hope that you find it ready for publication.

We have addressed the concerns raised by Reviewer #2 (all changes are to be found in each of our responses to the Reviewer's comments and highlighted in yellow in the Revised Manuscript).

Lisa Espinosa,

on behalf of co-authors Dr Nina Becker, Prof Michael Bonsall, Prof Emily A. Holmes and Prof Andreas Olsson

REPLY TO REVIEWERS' COMMENTS

Reviewer #1:
The author's responses to the previous round of critiques are comprehensive and the manuscript is now even clearer for readers. Their inclusion of additional limitations and caveats based on comments from myself and the other reviewer provide important insight into how to interpret the results and the outcome is a useful addition to the literature.
RESPONSE: We thank the Reviewer for their constructive feedback, which notably helped improve the clarity of our manuscript.

Reviewer #2:
Thank you to the authors for your responses and for considering my feedback. I have a few comments below and recommend publication pending these minor revisions.
RESPONSE: We are grateful for the Reviewer's constructive feedback. These changes have improved the quality of this manuscript and we are very thankful for that.

1. In the abstract, the authors state, "As predicted, threat conditioning can generate intrusions (M=3.75, SD=4.18), with more intrusions of CS+ than CS-." However, no units are provided for the M and SD. If you'd like to keep the numbers, please include the unit of measurement. Also, as a reader, I'd be more interested in the M and SD separately for the CS+ and CS-, so if you keep the numbers, I suggest you provide them for the CS+ and CS- separately.
RESPONSE: Thank you for this comment, we have added the following information to improve clarity to the abstract, see p.2 of the Revised Manuscript:

"As predicted, threat conditioning can generate intrusions, with greater number of intrusions of CS+ (*M*=2.35, *SD*=3.09) than CS- (*M*=1.39, *SD*=2.17)."

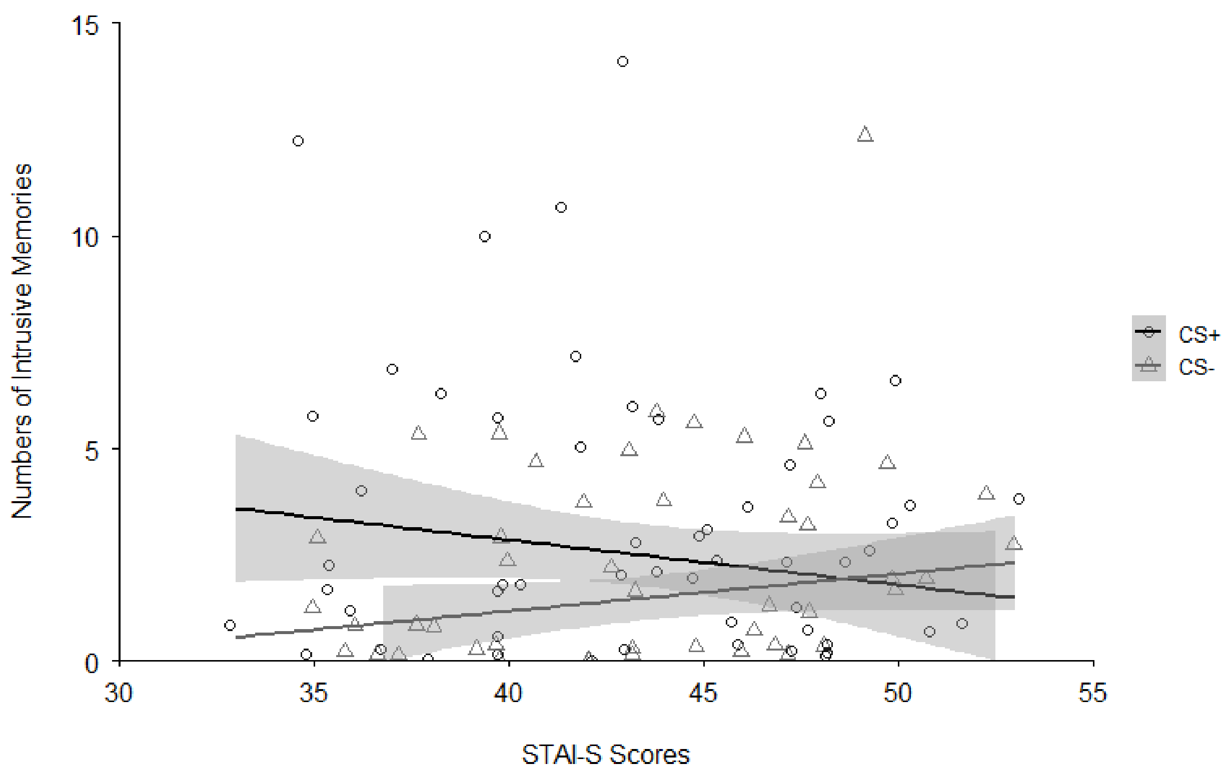
2. The authors state, "A significant interactions between CS-type and STAIS score on the number of intrusive memories (X2(1) = 9.52, p < .05, b = .00, SE = .00, t = 3.02, 95% CI [7.43, 3.52]). No such significant interaction was found between CS-type and STAIS score on the number of intrusive memories (X2(1) = .44, p = .05, b = .00, SE = .00, t = -.65, 95% CI [-1.42, 7.17])." It seems like the two sentences are verbally describing the same analysis: "interactions between CS-type and STAIS score on the number of intrusive memories... interaction was found between CS-type and STAIS score on the number of intrusive memories." Was the latter sentence supposed to be STAIT? Also, the stats seem strange: "(X2(1) = .44, p = .05, b = .00, SE = .00, t = -.65, 95% CI [-1.42, 7.17])." How do p = .05, b = 0, and SE = 0? The confidence interval also doesn't seem to match. Additionally, this is a generally interesting finding that higher STAIS was associated with greater CS- intrusive memories. This relates to the literature showing increased fear of safety signals in clinically anxious vs non-anxious individuals (e.g., Lissek, et al., 2007; Duits, et al., 2015).

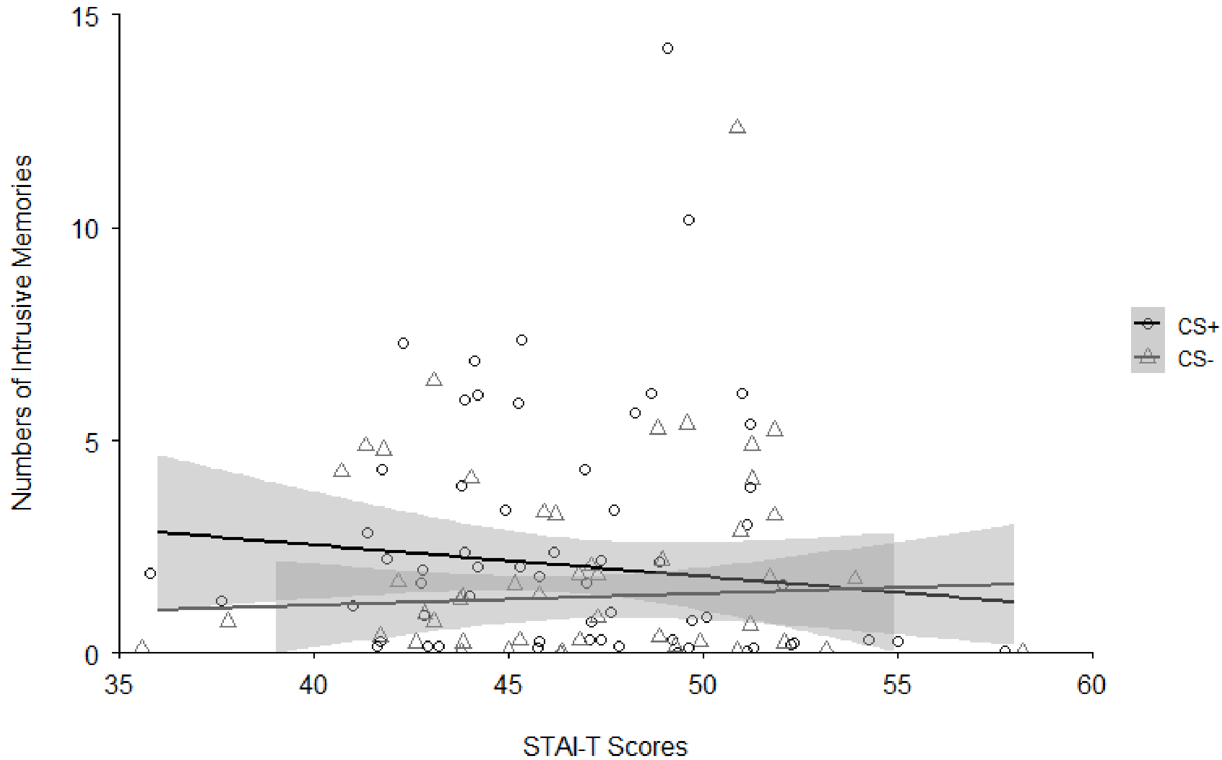
RESPONSE: We thank the Reviewer for noticing 1) the two sentences described the same analysis. The second sentence was supposed to describe the result for STAI-T (and not STAI-S). It is now changed, see response below. 2) the peculiarity in the statistical results for the CS and STAI-T interaction. These results were in fact incorrect. We now entered the correct centered variables and the accurate results of the model requested by the Reviewer i.e. the main effects of CS, STAIS, STAIT and their interactions, show significant interactions between CS and STAI-S ***as well as*** CS and STAIT. The text was modified as followed (Revised Manuscript p.29):

"Significant interactions were found between CS-type and STAIS score ($X^2(1) = 20.62$, $p < .001$, $b = .05$, $SE = .01$, $t = 4.45$, 95% CI [.03, .08]) and CS-type and STAIT ($X^2(1) = 8.23$, $p < .01$, $b = .02$, $SE = .01$, $t = 2.81$, 95% CI [.01, .04]) on the number of intrusive memories. This suggests that both higher state and trait anxiety scores were linked to a greater number of intrusive memories for CS- compared to CS+ (Figure S4a and S5 in the online supplementary materials). [...]"

We also added the literature suggested by the Reviewer in our Discussions, see response to comment #4 below.

3. Figure S4: the authors show the individual datapoints. I see that there are overlapping datapoints (which was made apparent to me by the gray circles with black borders, since the CS+ is white circles with black borders and the CS- is gray circles without borders; e.g., coordinate (40, 2)). I then tried counting the number of visible datapoints but didn't reach the n = 54. This leads me to three suggestions: 1) can you please modify the datapoints to have transparency? This will allow us to see the approximate density of datapoints on a given spot.
2) Can you make the X-axis border thinner? It's difficult to see the 0-value datapoints.
3) Can you use different shapes for CS+ vs CS- (e.g., circles vs triangles)? I provide these suggestions to improve the visibility of the authors' data, but the authors can modify this however they prefer.
RESPONSE: We thank the Reviewer for their suggestions. We have modified Figure S4 by using different shapes for each CS, modifying the thickness of the axis and jittering the data points to avoid overlapping of datapoints.
Due to the significant interaction between STAIT and CS-type on number of intrusive memories reported above, we added a Figure S5. See Figure S4 and S5 in revised Suppl. Mat. and here:





4. **Did you include a discussion of the STAIS and STAIT results in the Discussion section? I see you retained your previous discussion regarding STAIT. How about the STAIS CS- effect? I see Figure S4, but I don't see a discussion of STAIS in the Supplemental Materials, either.**

RESPONSE: We thank the Reviewer for this comment. Based on the final results described above, we have adapted and developed both the Lab Experiment Discussion and the General Discussion to discuss the effect found between our measures of anxiety and greater number of intrusive memories of CS-, see as followed:

Section 4. Discussion Lab Experiment, Revised Manuscript p. 33

"Our results showed that both higher state and trait anxiety were related to a greater number of intrusive memories of the CS-. This result supports previous findings in the conditioning literature showing an increased threat response to CS- in clinically anxious compared to non-anxious individuals (Druits et al., 2015). One interpretation is that such enhancement of threat response to CS- is related to an impaired inhibition of threat response to safety cues (Jovanovic et al 2013) and/or a greater tendency to generalize conditioned threat response (Craske et al., 2012; Lissek & Grillon, 2010), which could explain the greater number of CS- intrusive memories in more anxious individuals in our sample."

General Discussion, Section *8.1. Threat Conditioning Generates Persistent Intrusive Memories*, Revised Manuscript p. 47

"Our results also indicated that, anxiety, which is associated with sensitivity to traumatic stress reactions (Clark et al., 2015; Laposa & Alden, 2008), was found to be linked to a greater number of intrusive memories of the CS-. This suggests that, similarly to the enhanced psychophysiological threat responses to CS- observed in anxious individuals, these individuals display a generalized imaged-based threat response to the safe stimulus and/or an impaired ability to inhibit image-based threat response to the safety cue.

Highlights

- Pavlovian threat conditioning can generate intrusive memories of neutral stimuli, with more CS+ than CS- intrusions.
- Individuals with higher anxiety and greater number of previous trauma experiences reported more intrusive memories, up to one year after conditioning.
- Receiving low social support after acquisition of threat increases image-based conditioned threat memories.
- Results support the translational potential of threat conditioning paradigms to clinical developments.

Pavlovian threat conditioning can generate intrusive memories that persist over time

Lisa Espinosa, Michael B. Bonsall, Nina Becker , Emily A. Holmes, Andreas Olsson

Declaration of competing interest:

EAH receives book royalties from Oxford University Press and Guilford Press and occasional personal fees from clinical workshops and conference keynotes.

CRediT authorship contribution statement:

Lisa Espinosa: Conceptualization, Data curation, Methodology, Formal analysis, Visualization, Writing – original draft. **Michael B. Bonsall:** Formal analysis, Supervision, Writing – review & editing. **Nina Becker:** Methodology, Visualization, Writing – review & editing. **Emily A. Holmes:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Andreas Olsson:** Conceptualization, Funding acquisition, Methodology, Supervision, Project administration, Writing – review & editing.

Pavlovian threat conditioning can generate intrusive memories that persist over time

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Abstract

Although Pavlovian threat conditioning has proven to be a useful translational model for the development of anxiety disorders, it remains unknown if this procedure can generate intrusive memories – a symptom of many anxiety-related disorders, and whether intrusions persist over time. Social support has been related to better adjustment after trauma however, experimental evidence regarding its effect on the development of anxiety-related symptoms is sparse. We had two aims: to test whether threat conditioning generates intrusive memories, and whether different social support interactions impacted expression of emotional memories. Non-clinical participants (n=81) underwent threat conditioning to neutral stimuli. Participants were then assigned to a supportive, unsupportive, or no social interaction group, and asked to report intrusive memories for seven days. As predicted, threat conditioning can generate intrusions, with greater number of intrusions of CS+ (*M*=2.35, *SD*=3.09) than CS- (*M*=1.39, *SD*=2.17). Contrary to predictions, compared to no social interaction, supportive social interaction did not reduce, and unsupportive interaction did not increase skin conductance of learned threat or number of intrusions. Unsupportive interaction resulted in a relative difference in number of intrusions to CS+ vs CS-, suggesting that unsupportive interaction might have increased image-based threat memories. Intrusions were still measurable one year after conditioning (one-year follow-up; n=54), when individuals with higher trait anxiety and greater number of previous trauma experiences reported more intrusions. Our findings show that threat conditioning can create long-lasting intrusions, offering a novel experimental psychopathology model of intrusive memories with implications for both research on learning and clinical applications.

Keywords: Pavlovian Conditioning, Intrusive Memories, Skin Conductance, Social Support, Trauma

Pavlovian threat conditioning can generate intrusive memories that persist over time

1. Introduction

An estimated 70% of the world population has experienced or witnessed a traumatic event in their lifetime (Benjet et al., 2016). While we have some effective evidence based treatments, given the scale of trauma exposure there is clearly an imperative to develop simple experimental procedures to understand how specific mechanisms modulate particular symptoms (Holmes et al., 2018) after trauma including post-traumatic stress disorder (PTSD) and anxiety (Holmes et al., 2014; Iyadurai et al., 2019). One commonly used experimental analogue of a stressful event is the Pavlovian threat conditioning paradigm (Craske, Hermans & Vansteenwegen, 2006; Haaker et al., 2019; Milad & Quirk, 2012). This paradigm has been used to investigate the basic processes underlying (maladaptive) associative learning, which are considered important components in the etiology of anxiety disorders and PTSD (Duits et al., 2015; Lissek & van Meurs, 2014; Pittig et al., 2018). Using standard Pavlovian threat conditioning, researchers have examined the engagement of both the non-declarative and declarative aspect of threat memories (for a review, see (for a review, see Dunsmoor & Kroes, 2019). Psychophysiological measures, such as skin conductance, fear potentiated startle and pupil size are the most common indices of implicit non-declarative fear memory processes (Bach et al., 2020) while self-reported CS–US contingency (Boddez et al., 2013) and recognition memory test (Dunsmoor, Niv, et al., 2015) have also been used to examine the declarative aspect of threat memories. To our knowledge, however, Pavlovian threat conditioning has not yet been modeled to investigate the involuntarily occurrence and image-based aspect of certain threat memories, or more specifically, intrusive mental images of previously neutral stimuli. To our knowledge, however, this paradigm has not yet been modelled to investigate the involuntarily occurrence and image-based aspect of certain threat memories, or more specifically, *intrusive mental images* of previously neutral stimuli.

Here we used a Pavlovian threat conditioning paradigm as an experimental model to study how learning and memory of an analogue stressful event may lead to intrusive memories, defined as recurrent, involuntary, and intrusive recollections of an event (DSM-5; American Psychiatric Association, 2013, p.282). We asked whether threat conditioning could be used to generate intrusive memories of neutral conditioned stimuli, and whether these memories would persist over time. Next, we asked whether different social support interactions after an aversive experience could modulate the expressions of the emotional memory generated by Pavlovian threat conditioning. Social support is considered a protective factor that can moderate outcome of traumatic experiences (*Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. [*DSM-5*]; American Psychiatric Association, 2013, p.277), but experimental evidence of the effect of social support on the development and potential persistence of symptoms, such as those characterizing PTSD, is sparse. We reasoned that experimentally manipulating social support following threat conditioning could inform us about how post-trauma social support regulates emotional responses to negative experiences.

Studies investigating basic mechanisms linking memory disruption and intrusive memories in non-clinical participants have been crucial in better understanding the development of intrusive memories (for a review, see Bisby et al., 2020; Bisby & Burgess, 2017). The current study could therefore further help developing approaches that target specific mechanisms and fuel treatment research (Holmes et al., 2018). Overall, this study attempts to bridge the experimental and well-controlled benefits of threat conditioning with a clinical research approach.

1.1 Pavlovian Threat (“Fear”) Conditioning as an Experimental Model for a Stressful Event

In humans, differential Pavlovian threat conditioning consists of repeatedly pairing a neutral conditioned stimulus (CS+) with a naturally aversive unconditioned stimulus (US), such as an electric shock, whereas another conditioned stimulus (CS-) is never paired with the US. As a result of its association with the US, the CS+ gains emotional significance and produces a conditioned response (CR), such an elevated autonomic arousal measured through skin conductance. Following conditioning, an extinction procedure, during which the CS are presented in the absence of the US, leads to the diminishing of the conditioned response.

There is growing evidence about the role of associative learning in the development and maintenance of symptoms of anxiety-related disorders and PTSD, supporting the use of the threat conditioning paradigm as an experimental framework for memory processes underlying trauma memories (Fani et al., 2015; Milad & Quirk, 2012; Pittig et al., 2018; Visser et al., 2018; Zuj & Norrholm, 2019). In particular, laboratory experiments using threat conditioning have enabled research to target the mechanisms underlying the development, regulation and relapse of threat responses with greater precision than clinical settings would allow (Carpenter et al., 2019). The identification of specific key neural, molecular and genetic factors involved in threat conditioning has helped the development of hypotheses-driven studies translated to clinical applications (A. Holmes & Singewald, 2013).

Wegerer and colleagues (2013) developed a conditioned-intrusion paradigm to investigate the link between conditioning and intrusive memories in a laboratory setting. This paradigm paired neutral sounds (conditioned stimuli, CS) with aversive film clips, serving as unconditioned stimuli (US). When presented during a neutral soundscape, the sound previously associated with the aversive versus neutral films led to more intrusive memories (images or thoughts) (Streb et al., 2017; Wegerer et al., 2013). A more recent study using a similar paradigm (Franke et al., 2021) showed that participants reported intrusive memories (visual, auditory, thought and/or feelings) of both US (aversive films) and CS (neutral faces). Using complex and naturalistic stimuli, these results support the role of conditioned associations in the development of intrusive memories after a stressful experience.

In the current study, we were interested in examining the development of intrusive memories of previously neutral stimuli following a standard Pavlovian conditioning paradigm, using electrical stimulations as US. This procedure allowed us to control for pre-existing aversions towards specific stimuli containing representations of, for example, blood, violence and injuries. Intrusive memories can develop not only of overtly traumatic moments but also to fragments of scenes (e.g. knocking at neighbors door) or objects (e.g. broken glass), and even seemingly neutral objects (e.g. green curtains or a pair of shoes; Grey & Holmes, 2008; Holmes et al., 2005), Albeit less naturalistic, the simple, and well-controlled nature of the

Pavlovian conditioning paradigm – here using neutral visual cues such as a clock or a zip - enhances generalizability of the results across learning situations. Accordingly, we examined whether standard Pavlovian threat conditioning can be used to generate intrusive memories of neutral CS that may persist over time.

1.2. Clinical and Experimental Approaches to Intrusive Memories

Intrusive memories after a traumatic event often become less frequent over time. Nevertheless, for some people they persist over time, and their recurrent and distressing form are symptoms of both Acute Stress Disorder (ASD) and PTSD (American Psychiatric Association [APA], 2013, pp. 271-286). Laboratory experiments using an analogue trauma experience have determined that pre-existing psychological vulnerabilities such as anxiety, depression and trauma history are associated with the increased likelihood to develop intrusive memories (Clark et al., 2015; Laposa & Alden, 2008).

Experiencing intrusive memories is one key symptom of psychopathology that can arise following stressful event such as trauma, raising the importance of targeting intrusive memories clinically in treatment. Previous work has developed cognitive imagery-competing task strategies as part of a short behavioral intervention to interfere with the development of intrusive memories in both experimental (Holmes et al., 2009, 2010) and clinical (Iyadurai et al., 2018; Kanstrup et al., 2021) settings. Such studies indicate that the frequency of intrusive memories can be reduced, while preserving the voluntary memory of the negative experience (Lau-Zhu, Henson, & Holmes, 2019). These results are consistent with the idea that trauma memory is composed of multiple systems (episodic and perceptual memory systems) that can be specifically targeted (Visser et al., 2018).

In the current study, our goal was to uncover whether *neutral stimuli* (similar to the ones commonly used in standard conditioning paradigms) can create intrusive memories through one session of Pavlovian threat conditioning, and whether these intrusive memories could persist. This would mean that in addition to investigate implicit, non-declarative aspects of threat memory, standard Pavlovian threat conditioning might also be used to investigate image-based, intrusive memories – i.e. another clinically important feature of threat memories.

Finally, we note that intrusive memories in clinical psychopathology can vary in emotional valence (from negative to positive), though for our work on intrusive memories the types of affective association related to the intrusive memories is not the central line of enquiry (Holmes et al., 2005; Iyadurai et al., 2019; Singh et al., 2020). The characterizing feature of intrusive memories is that they occur in the form of involuntary recollection, i.e. without being expected. Further, recent linguistic analysis of intrusive memories soon after trauma (both in the clinic and lab) indicates that intrusive memories primarily contain words related to space and sensory features, yet few words related to cognitions and emotions (Hoppe et al., 2022; Singh et al., 2022). Our interest in these features and in reducing the number of times intrusion reoccur (rather than say the cognitive or emotional content of such intrusions) has informed our current line of work.

1.3. Social Support as a Protective Factor

Social support, defined as positive social interactions in times of need, has been found to buffer the negative effect of stress on health (for a review, see Ditzen & Heinrichs, 2014). For instance, experimental work looking at the effect of social support during a cold pressor task reported that receiving verbal support from a confederate significantly decreased measures of blood pressure and heart rate compared to being alone or the mere presence of a confederate (Roberts et al., 2015).

Pavlovian threat conditioning has been used to assess the influence of social processes on the basic threat learning processes. For example, studies have shown that observing someone being calm when watching a neutral stimulus that was previously followed by a shock (vicarious safety learning) can facilitate extinction learning (Golkar et al., 2013; Olsson et al., 2020). Hornstein & Eisenberger (2018) examined how social support reminders can work as prepared safety stimuli, altering threat learning processes. For example, they showed that presenting the image of a support figure (compared to a neutral image or an image of a stranger) during threat acquisition, inhibited acquisition and enhanced extinction of learned threat (Hornstein et al., 2016; Hornstein & Eisenberger, 2017). These results suggest that the support reminders can impact underlying learning mechanisms, strengthening the idea that social support can similarly affect the consolidation of threat learning.

In real life, it might be less common to go through negative experiences in the presence of a calm person or while being reminded of a social support figure. Here, we aimed at modeling situations in which support interactions occur after the negative experience, such as interactions a patient might have with medical staff in the waiting room at the emergency department. In fact, trauma research has shown that lack of social support after real traumatic experiences is an important predictor of PTSD (Brewin et al., 2000; Bryant et al., 2017; Ozer et al., 2008) and low level of support, meaning negative reactions or the absence of supportive behavior by others, after a stressful event such as trauma, have been identified as being strongly related to development of PTSD symptoms (Wagner et al., 2016) and greater PTSD symptom severity (Ullman & Filipas, 2001).

Only few studies have however used experimental paradigms to explore how interpersonal interactions after a negative experience regulate the development of intrusive mental images. One study looked at social support given by one's partner (Woodward & Gayle Beck, 2017). After viewing a traumatic film, participants who received negative reactions from their romantic partner, such as sarcastic comments minimizing their experience or partners expressing negative affect, reported more intrusive memories of the films during the subsequent 72 hours as compared to those whose partners expressed positive responses, such as reassuring, comforting or validating comments. Another study looked at social support given by a stranger (Pruitt & Zoellner, 2008). After viewing a short footage of automobile accidents, participants who received no social support from a stranger (e.g. ignoring what happened or not providing tangible aid) reported having more intrusive thoughts during the following 48 hours than participants receiving positive (e.g. validating their experience or positive emotional support) or negative (e.g. invalidating, negative emotional support or disregard for the participant's concern) social support. How previous studies have defined supportive, unsupportive or no support varies from studies to studies, where the absence of support resembles more a negative interaction than not receiving support (as defined in Pruitt & Zoellner, 2008). Here we define supportive social interaction as the provision or exchange of emotional, informational or instrumental resources in response to someone's need of help (Cohen & McKay, 1984). We characterize unsupportive interaction as the opposite of supportive interaction, including aspects of social negativity (Brooks & Schetter, 2011) and social rejection (Eisenberger, 2011). Unsupportive social interactions after a stressful event, such as trauma, are, in fact, identified as being strongly related to greater PTSD symptom severity (Ullman & Filipas, 2001).

In the current study, our other goal was to experimentally test how social support interactions after a negative experience could modulate the expression of emotional memory. We aimed to examine whether a supportive or unsupportive social interaction with minimal verbal exchange (vs no social interaction) given by a stranger would impact expression of emotional memory measured by skin-conductance and number of intrusive memories. This type of interaction was chosen to model an interaction between strangers after a stressful experience (e.g. between a patient and medical staff in the waiting room at the emergency department). Other than the two studies mentioned above, no other experimental work has, to our knowledge, investigated the effect of simple in-person social support interaction on the expression of emotional memory.

1.4. Experiment Overview

The objective of our study was to determine whether a Pavlovian threat conditioning paradigm with pictures of neutral objects as CS and electrical stimulation as US, could generate intrusive memories of the CS during the subsequent seven days. This would further validate findings showing the contribution of conditioning processes in the development of intrusive memories (Franke et al., 2021; Miedl et al., 2020; Wegerer et al., 2013). We predicted that participants would report having more intrusive memories of the CS+ than the CS-.

To understand, more fully, the development of intrusive memories, we investigated whether the total number of intrusive memories of CS+ and CS- during the following week and whether having intrusive memories at all, would be driven by pre-existing vulnerabilities that have previously been associated with sensitivity to traumatic stress reactions (Clark et al., 2015; Laposa & Alden, 2008). We predicted that the development of intrusive memories would be influenced by inter-individual differences (i.e. higher state and trait anxiety scores, higher depressive mood score, greater number of previous traumatic experiences) and/or individuals' physiological expressions of threat conditioning.

Verifying our first objective was a necessary requirement to be able to evaluate our next aim, that is, whether different social support interactions (supportive social interaction , unsupportive social interaction or no social interaction) after acquisition of learned threat influenced the expression of the emotional memory measured by skin conductance responses (SCR; during extinction and during a reinstatement test procedure 7 days after conditioning), and number of intrusive memories of the CS during 7 days following conditioning. We predicted that, compared to the control condition (no social interaction), supportive social interaction would lead to (i) a stronger extinction of learned fear and (ii) a weaker return of fear a week later, and that unsupportive social interaction would lead to (i) a weaker extinction of learned fear and (ii) a stronger return of fear a week later. We also predicted that compared to the control condition (no social interaction), supportive social interaction would lead to a lower number of intrusive memories of the CS, and unsupportive social interaction would lead to a higher number of intrusive memories of the CS. We reason that social support interactions taking place directly after acquisition of threat would alter the expression of emotional memory by interfering with the underlying memory consolidation processes. Our manipulation thus extended previous studies demonstrating the effectiveness of interventions interfering with the consolidation of emotional memories, using for instance an imagery interfering task competing with cognitive resources soon after exposure to experimental trauma (Holmes et al., 2010; James et al., 2015; Lau-Zhu et al., 2019).

Finally, to examine whether intrusive memories may persist over time, we carried out a one-year follow-up survey comparing participants reporting intrusive memories only during the seven days after conditioning to participants reporting to have continued to experience intrusions during the year after conditioning. We predicted that having intrusive memories during the one year following conditioning would be related to a) pre-existing vulnerabilities (i.e. higher state and trait anxiety scores, higher depressive mood score, greater number of previous traumatic experiences) and higher CR during threat conditioning, b) better memory performance (free recall and recognition) of the picture stimuli used as CS, and c) free recall of which CS was followed by a shock during Pavlovian threat conditioning.

To test our predictions, we developed an experimental procedure consisting of a laboratory experiment (two sessions), as well as an associated one-year follow-up. At session 1 of the lab experiment (on Day 1), participants acquired conditioned threat responses to pictures of neutral objects, immediately followed by a social support interaction manipulation, which was followed by extinction of learned threat. During Day 1 to 7, participants then reported the occurrence of intrusive memories of the CS using an electronic intrusive memory diary outside the lab. At Session 2 (on Day 8): the recovery of the learned threat was measured in the laboratory setting through a standard reinstatement test procedure. Finally, the one-year follow-up test consisted of an electronic survey assessing whether intrusive memories would last beyond the seven days lab experiment, as well as tests of free recall and recognition memory of the CS.

2. Method Lab Experiment

2.1 Participants

Ninety-one participants (47 female) between the age of 18 and 40 (*M* = 26.60, *SD* = 5.66) were recruited via advertisement on the Karolinska Institutet Psychology division's recruitment website, and using advertisement posters at the University campus. Selection criteria were age between 18 and 40 and no reported psychiatric disorders. Sample size was determined based on estimated known effects of threat conditioning, extinction and interference of consolidation in healthy participants (Duits et al., 2015; Kindt & Soeter, 2013). Based on an estimated effect size of $d = .40$, a total of 28 participants per group ($n = 83$) were estimated as needed to obtain 90% power to detect a moderate effect of the interference of social support on the consolidation of threat response during extinction ($\alpha = .05$). Following guidelines for conservative exclusion criteria in threat conditioning (Lonsdorf et al., 2019), we excluded one participant classified as non-responder, and nine participants classified as 'non-learners'. 'Non-responder' exclusion was based on lack of general physiological responses and represented participants displaying a SCR response of ≤ 0 µS (microSiemens) to at least three of the four US trials (response to the shocks), as well as to the CS+ and CS- trials. To avoid sampling bias, 'non-learners' exclusion was based on two outcome measures, where we excluded participants with both an average differential (CS+ vs CS-) SCR response of ≤ 0 µS across the last 3 trials of acquisition and failing to report correct awareness of the CS+/US contingency. The final sample consisted of 81 participants (supportive social interaction, n = 27 (15 females); unsupportive social interaction, n = 30 (16 females, 1 unknown); no social interaction, n = 24 (13 females)), indicating a total exclusion rate of 11 %. Demographic information and baseline self-report measures of the excluded participants can be found in Table S1 in the online supplementary materials. Approval for this study was obtained by the Regional Ethical Review Board in Stockholm (Dnr: 2018/549-31/1).

2.2. Apparatus and Materials

2.2.1. Picture Stimuli

Eight pictures of neutral objects from the IAPS database (Lang, Bradley & Cuthbert, 2008) were selected as picture stimuli. As shown in Table 1, the pictures have previously been rated as being low arousal (*M* = 3.05, *SD* = 2.01), neutral valence (*M* = 5.00, *SD* = 1.32) and neutral dominance (*M* = 6.04, *SD* = 1.95) (Lang, Bradley & Cuthbert, 2008) and depicted a neutral object, for example a tray of buttons or a blue mug on a wooden table. Neutral and non-traumatic picture stimuli were purposely selected not to be intrinsically intrusive. For each participant, two of the eight pictures were randomly selected and used as conditioned stimuli (CS) in the threat conditioning paradigm (acquisition, extinction and reinstatement).

Table 1

Valence, Arousal and Dominance Ratings (n = 100) for IAPS Pictures Used as Conditioned Stimuli in Conditioning Paradigm

	Valence	**Arousal**	**Dominance**
Buttons	5.32 (1.19)	3.20 (2.15)	5.82 (2.02)
Zipper	4.97 (0.76)	3.32 (1.96)	6.28 (1.72)
Fork	5.27 (1.09)	2.32 (1.84)	7.04 (1,84)
Clock	4.81 (1.92)	4.20 (2.40)	4.90 (2.32)
Mug	4.92 (1.00)	3.01 (1.97)	6.53 (1.92)
Book	5.19 (1.45)	2.61 (2.05)	6.35 (2.03)
Umbrella	4.72 (1.69)	2.61 (1.76)	5.55 (2.01)
Training shoes	4.82 (1.46)	3.18 (1.88)	5.90 (1.75)
Mean	*5.00 (1.32)*	*3.06 (2.01)*	*6.04 (1.95)*

2.2.2. Threat Conditioning

Each CS was presented on a computer screen for six seconds, followed by an inter-trial interval (ITI) of 10 seconds. The threat conditioning paradigm was programed using PsychoPy (Peirce et al., 2019) and presented on a desktop screen. SCR were captured by Biopac EL507 EDA electrodes and a Biopac MP150 system at a sample rate of 250 Hz (Biopac System, Inc., Goleta, CA, USA). SCR were acquired and scored using the Biopac AcqKnowledge software and the electric stimulations were delivered by a STM200 Biopac Systems with a 100 ms DC-pulse.

2.2.3. Self-Reported Baseline Measures

We assessed individual differences in pre-existing vulnerabilities that might strengthen the development of intrusive memories such as anxiety with the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983); general use of mental imagery with the Spontaneous Use of Imagery Scale (SUIS; Nelis et al., 2014); and a self-report measure of depressive symptoms using the Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001). Number of previous traumatic experiences was calculated using the Traumatic Experience Questionnaire (TEQ; Crawford et al., 2008). We assessed individual differences that might impact the effect of our social support manipulation such as empathy using the Balanced Emotional Empathy Test (BEES; Mehrabian, 1996); and a measure of an individual’s tendency to recruit social resources to regulate their emotions using the Interpersonal Regulation Questionnaire (IRQ; Williams et al., 2018). For additional information, see the online supplementary materials (S1, supplementary Methods).

2.2.4. Intrusive Memory Diary

Intrusive memories were defined to the participants as (sometimes clear, sometimes “fuzzy”) mental images of the pictures stimuli they saw during the experiment [acquisition and extinction], which might pop into their mind, without expecting them to, throughout daily life. This definition of intrusive memories has been used in previous associated studies (Holmes et al., 2010; Iyadurai et al., 2019; James, Lau-Zhu, Tickle, et al., 2016). We consider intrusiveness in terms of the involuntary, unwanted nature of the recollection (involuntary memory rather than deliberate memory retrieval).

The diary consisted of an electronic survey sent by email every morning, which participants could open and answer from a computer and/or a mobile phone. With the help of four reminders set on their mobile phone (morning, afternoon, evening and night), participants were told to report intrusive memories that appeared in their mind unexpected (i.e. involuntarily recalled), but not those which were deliberately recalled or triggered by the phone reminders. As they opened the diary, they were first asked to report how many intrusive memories they had during the specific time frame (during the night; get-up time to midday, midday to 5pm; 5pm to 11pm) and then to write one entry for each intrusive memory, even if they had the same intrusive memory several times. They were also asked to indicate '0' if no intrusive memories had occurred. Participants were asked to write a brief description (free report) of each intrusive memory (e.g. "a blurry blue mug on a brown table"), which was used to verify whether the intrusive memory was of one of the two picture stimuli (CS) each participant saw. Each participant's diary was discussed with the participant at the end of their participation when they returned to the lab at day 8, for possible clarifications of unclear entries. The brief descriptions of the intrusive memories were extracted from the diary and categorized by the experimenter into whether they matched or not with the CS+ and CS- that a given individual had seen (e.g. a clock, zipper, button, see Table 1).

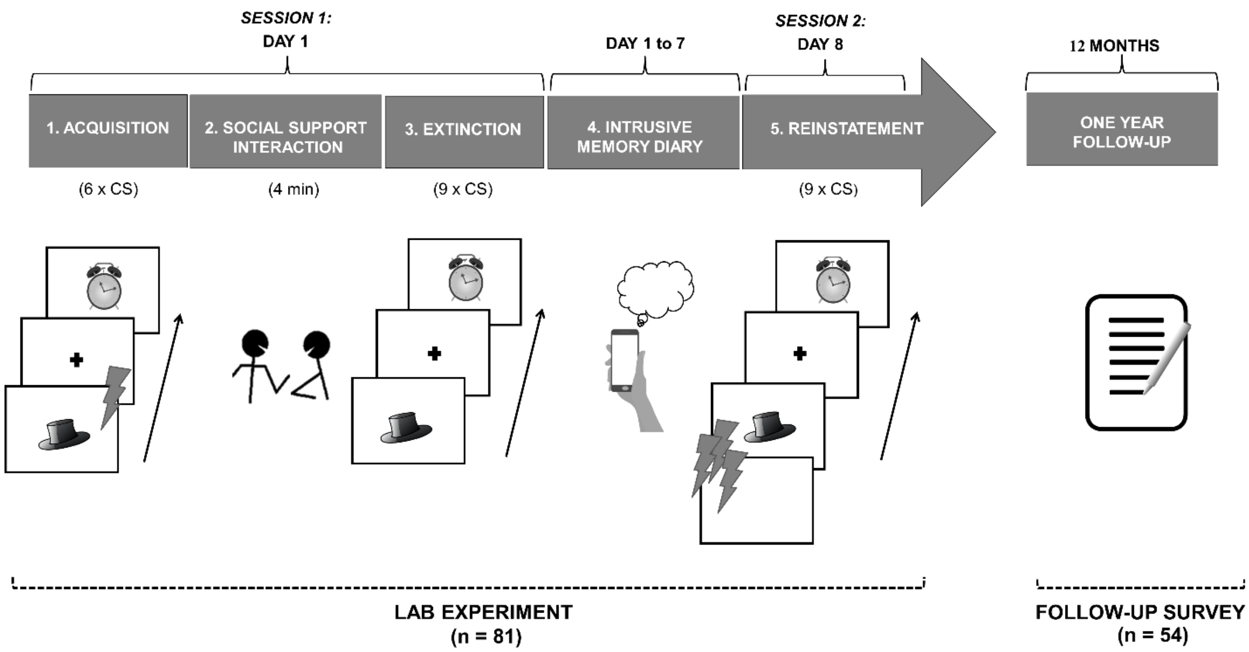
The instructions and the protocol for used of the intrusive memory diary were adapted for electronic format using Karolinska Institutet Survey and Report computer program (Artologik, version 23, Survey & Report, Artisan AB) based on earlier studies using a paper-based intrusive memory diary (Holmes et al., 2004; James et al., 2016).

2.3. Procedure

The study design consisted of a mixed design with three between-subjects conditions (types of social support; supportive social interaction, unsupportive social interaction and not social interaction) and two within-subjects conditions (conditioned stimuli; CS+ and CS-), which is described below and illustrated in Figure 1.

Figure 1

Schematic Overview of the Experimental Procedure Including Threat Conditioning and Intrusive Memory Monitoring.



Note. The experimental procedure consists of a two-session laboratory experiment taking place across eight days (Day 1 and Day 8) and a one-year follow-up survey. (1) During acquisition, participants saw two consecutive picture stimuli, six times each, each presentation separated by a grey screen with a cross (intertrial interval). One picture stimuli was followed by a shock (CS+) and one never followed by a shock (CS-). (2) The social support interaction takes place during a 3-4 minutes break, participants were randomized to experience a supportive social interaction, unsupportive social interaction or no social interaction. (3) During extinction, participants see the same two picture stimuli, nine times each, without receiving any shocks. (4) Participants answered the electronic intrusive memory diary during seven days. (5) Participants came back to the lab and were presented with a grey screen and three unexpected electric stimulations, followed by nine presentations of the two picture stimuli, without receiving any shocks. Finally, the one-year follow-up electronic survey was sent via email, 12 months after their participation.

2.3.1. Day 1

Session 1 was divided into three phases: threat acquisition, social support interaction and threat extinction. To measure SCR two electrodes were attached to the participant's fingers of their left hand and one shock-electrode to their right lower arm. The intensity of the electrical stimulations was calibrated for each participant to a level that was uncomfortable but not painful for them, using an ascending staircase procedure. At the start of the experiment, the participant was instructed both verbally and on the computer screen to focus on the presented pictures. No information was provided regarding the picture stimuli-shock contingency.

***Threat Acquisition*.** Two picture stimuli were shown six times each. To establish acquisition of threat conditioning, one of the two picture stimuli was randomly selected to be the CS+ (picture stimuli reinforced with a shock during four out of the six presentations) and the other one to be the CS- (never reinforced). At the end of the presentation, the participant was informed on the computer screen that there would be a break.

Social Support Interaction. Social support was operationalized as two social support conditions (supportive social interaction vs negative social support) providing two qualitatively distinct social interactions aimed to induce positive and negatively valenced social experience, respectively. A third neutral condition was used as control group (no social interaction). These interactions (duration 3-4 min, M = 3.61, SD = 0.36) consisted of minimal verbal exchange and designed to provide informational (provision of information that can be used to guide and advice), instrumental (provision of concrete aid through material goods or physical assistance) and emotional support (verbal and nonverbal communication of empathy and care) (Hogan et al., 2002). We chose an in-person interaction with a stranger as opposed to an interaction with a social support figure or a support reminder, as we were primarily interested in testing an interaction similar to the one occurring between strangers after a traumatic experience (e.g. between a patient and medical staff in the waiting room at the emergency department). In fact, the objective of using a social support interaction with minimal verbal exchange was to aid the development of a supportive interaction given by laypeople, immediately after a negative experience, such as a trauma.

Immediately after acquisition, a second experimenter, who had not yet interacted with the participant, entered the room where the participant sat and administered one of three social interactions with the aim to provide a positive, negative or neutral (control) social interactive experiences (random assignment).

In the supportive social interaction condition, the participant was given social support, which consisted of (1) *informational support* by being informed about what was going on during the break and how long the break would last; (2) *instrumental support* by being offered a glass of water, being informed that the door of the experimental room would be left open to let fresh air into the room during the break, and at the end of the break, being informed about the possibility of pressing a button to continue the experiment when they felt ready; (3) *emotional support* by asking them if they felt alright while having a hand on their shoulder; keeping eye contact with them and smiling to them; asking them if they felt good to continue the experiment. This condition aimed to induce a positive state.

In the unsupportive social interaction condition, the participant was given unsupportive social interaction and aimed to induce a negative state. This interaction consisted of (1) the second experimenter not providing the participant any information about what was happening during the break; did not answer any questions the participant might have; the participant was informed that the time they would spend in the room was unclear; (2) a dirty glass of water not intended for the participant was put next to them by the second experimenter without explanation; (3) the door of the room was left open without any explanation, the second experimenter walked in and out the room several times without talking directly to them or having eye contact.

Finally, in the neutral control condition (no social interaction – NSI), the participant received, by the second experimenter, a commercial furniture catalogue to read, which was taken back at the end of the four minute break. Allowing experimenter entering the room without having social interaction with the participant provided an experimental design control for the presence of someone in the supportive social interaction and unsupportive social interaction conditions. The furniture catalogue was meant to equalize the level of distraction between the conditions during the break, whilst controlling for the neutral and low arousing content (furniture). There was no difference between the three conditions in the average duration of the interactions (supportive social interaction, $M = 3.61$, $SD = .34$); unsupportive social interaction, $M = 3.73$, $SD = .38$ and no social interaction , $M = 3.63$, $SD = .32$) ($F(2, 80) = .76$, $p = .46$, $\eta_p^2 = .02$). A link to video illustrations of the three experimental condition interactions can be found in the online supplementary materials.

Threat Extinction. After the short break, extinction of learned threat consisted of nine non-reinforced presentation of the two pictures serving as CS.

Manipulation Checks And Self-Reported Baseline Measures. Once the electrodes had been removed, the participant was asked to answer two manipulation checks: First, questions about contingency awareness between the CS and the US. Then, questions about their perception of support received during the break to determine whether participants in the different social support conditions perceived our social support manipulation differently (i.e. perceived support manipulation check, details found in the online supplementary materials). Finally, the participant answered a set of self-reported baseline questionnaires and was given the instructions on how to use the intrusive memory diary.

2.3.2. Day 1 to 7

The participant completed the online daily intrusive memory diary containing four parts (night, morning, afternoon and evening). The participant was asked to report the number of intrusive memories of the picture stimuli (CS) they have had during a specific time frame (during the night; get-up time to midday, midday to 5pm; 5pm to 11pm).

2.3.3. Day 8

At session 2, the participant returned to the same experimental room as session 1 and was informed that the settings of the experiment would be the same. They were asked to pay attention to the pictures shown on the computer screen.

2.3.4. Reinstatement

Reinstatement of learned threat consisted of a presentation of a grey screen and three unexpected electric stimulations. Following this, the two CS (presented during acquisition and extinction) were presented nine times without shock reinforcement. Importantly, because the reinstatement phase took place seven days after the extinction phase, our procedure could not exclude the potential impact of spontaneous recovery (Norrholm et al., 2006).

As part of the debriefing, the participant was asked for possible clarifications of unclear entries in their intrusive memories diary and was debriefed on the nature of the study. The participant was then reminded that they will be contacted 12 months later for a follow-up with questions regarding their participation in this study and was finally thanked and reimbursed for their time with two cinema vouchers.

2.4. Statistical Analysis

SCR data during threat conditioning, reinstatement and intrusive memory data were checked for possible univariate outliers within each social support condition on each of the main outcome measures. One outlier (for the supportive social interaction condition on intrusive memories) was identified as having > 3 *SD* from the mean of its group. Following previous studies using measure of intrusive memory (Holmes et al., 2004; Lau-Zhu et al., 2019), the outlier was changed to one unit larger than the next most extreme score in the distribution (Tabachnick & Fidell, 2007). All analyses used a significant alpha threshold of 0.05 and include measures of effect size. The Benjamini-Hochberg procedure was used to control for multiple comparisons and the false discovery rate was set to 5% (Benjamini & Hochberg, 1995). Non-parametric tests were used if assumptions of normality were violated. Statistical analysis were performed in R version 3.6.0 (R Core Team, 2019) and IMB SPSS version 24 (IBM Corp., 2016).

2.4.1. Threat Conditioning

To establish acquisition, extinction and reinstatement of threat response to the CS, the SCR were measured for the presentation of each CS as the base-to-peak amplitude of the largest response in a time window between 0.5 seconds to 4.5 seconds following stimulus onset. All SCR with an amplitude below 0.02μS, or with absence of any SCR within the time window mentioned above, were set to 0 (Dunsmoor, Murty, et al., 2015; Golkar et al., 2012). Raw SCR data from acquisition, extinction and reinstatement were separately squared root transformed to normalize the distribution and were analyzed separately. Identification of non-learners and non-responders for exclusion was done based on these squared-transformed SCR data.

Assessment of acquisition and extinction of threat conditioning was carried out using linear mixed effects models (LMEMs, 'nlme' package of R software ; Pinheiro, Bates, DebRoy & Sarkar, 2020). This model allowed us to analyze the data by dealing with the non-independence due to the repeated measure design (Bauer & Curtin, 2017) and takes into account both the variation explained by the independent variables (fixed effects) and the variation introduced by random sampling associated participants (random effects). To assess acquisition of learned threat, we modelled the main effects of CS-type, Trials and Condition and their interactions as fixed effects. CS-type included two levels (CS+ and CS-), Trials included six levels (trials 1 to 6) and Condition included three levels (supportive social interaction, unsupportive social interaction and no social interaction). As random effects we included intercepts for subjects, as well as by-subject slopes. A similar model was used to assess extinction of learned threat with main effects of CS-type, Trials and Condition and their interactions as fixed effects, and random intercepts and slopes for subjects. Confidence intervals were calculated for each effect as measure of effect size. Reinstatement of threat at Day 8 was defined as the increase in SCR from the end of extinction at Day 1 (extinction block 3) to the beginning of reinstatement at Day 8, right after three unannounced shocks (reinstatement block 1) (Haaker et al., 2014). Assessment of reinstatement of learned threat achieved using a repeated measure GLM of the SCR with CS-type and Trials (mean of last three trials of extinction and mean of first three trials of reinstatement) as within-subjects factors and Condition and number of intrusive memories for CS+, and for CS-, as between-subject factors.

2.4.2. Intrusive Memories

Our main outcome was the total number of intrusive memories summed across the seven day diary period (Holmes, Brewin, & Hennessy, 2004; Holmes et al., 2009; James et al., 2016; Lau-Zhu, Henson, & Holmes, 2019), also analyzed for each of the two picture stimuli (CS+ and CS-) separately. That is, intrusive memories included in the analyses consisted of those containing the two pictures stimuli (CS) that the participant saw during threat conditioning at Day 1 and later intruded spontaneously (involuntarily) in the form of mental images.

To test the hypothesis that a neutral picture followed by a shock (CS+) would generate more intrusive memories than the picture never followed by a shock (CS-), we used linear mixed effects models (LMEMs, Pinheiro et al., 2020). We modelled CS-type as fixed effect with intercepts for subjects as a random effect. This analysis in essence consists of a t-test that takes into account random variation between individuals.

Further, to explore potential covariates that might explain number of CS+ and CS- intrusive memories, we added one covariate at a time as fixed effect and its interaction with CS-type to the previous model.

Finally, to test the hypothesis that, compared to no social interaction, supportive social interaction would lead to a lower number of intrusive memories and unsupportive social interaction would lead to a higher number of intrusive memories, we carried out two statistical procedures using linear mixed effects models (LMEMs) on the count data (i.e. including only participants who reported having at least one intrusive memory, $n = 56$). First, we tested whether adding social support conditions to the simplest model containing CS-type only improved model fit (i.e. how well the model explains the variance in our data). Next, due to our study design, we tested a nested model, that is, a model where CS-type is nested within the social support conditions. More specifically, this is a model where the variance of social support condition on intrusive memories is considered within the variance of the nested factor (CS). Both steps are reported and compared. The model with the best model fit is further explained. We also modelled subjects as random effect and calculated confidence intervals as a measure of effect size.

3. Results Lab Experiment

3.1. Demographics and Social Support Manipulation Check

Individuals in the three social support conditions did not differ with regard to the baseline self-report measures (Table 2). The manipulation checks indicated that the social support manipulation was successful, with a significant difference in perceived support between the support conditions ($F(2, 80) = 57.12$, $p < .00$, $\eta_p^2 = .59$). Multiple comparisons showed that, as predicted, compared to controls (NSI; $M = 5.07$, $SD = .96$), individuals in the supportive social interaction reported a significantly higher level of perceived support ($M = 7.05$, $SD = .88$, $p < .001$), and individuals in the unsupportive social interaction reported significantly lower perceived support ($M = 4.22$, $SD = 1.15$, $p < .01$).

Table 2

Baseline Self-report Measures, Split by Social Support Interaction Conditions (n = 81)

	Supportive social interaction (n = 27)		Unsupportive social interaction (n = 30)		No social interaction (n = 24)		Between groups differences: Test values[a]	p-values	Effect Sizes[b]
	Mean	SD	Mean	SD	Mean	SD	F	*p*	η_p^2
Demographic characteristics									
Age	26.96	6.51	28.07	6.12	24.50	4.18	2.64	.07	.06
Gender (*male/female*)	12/15		13/16[1]		11/13		1.75[c]	.78	.78[d]
Ethnicity (*Caucasian/non-Caucasian*)	16/10 [2]		13/17		15/8[2]		3.06[c]	.21	.19[d]
Individual differences									
BEES	14.00	39.47	11.96	43.35	13.79	37.14	.02	.98	.00
IRQ	79.03	15.29	78.14	16.83	76.81	13.18	.12	.88	.00
Negative tendency	16.03	4.75	15.06	5.99	13.83	4.86	1.08	.34	.02
Negative efficacy	21.85	4.84	21.17	4.21	21.52	4.57	.15	.86	.00
Positive tendency	19.74	5.29	20.60	5.82	21.16	3.84	.03	.96	.01
Positive efficacy	21.48	4.30	21.33	4.42	19.86	4.54	.21	.80	.00
SUIS	36.77	6.18	38.96	8.27	38.85	7.10	.76	.47	.02
Anxiety measures									
STAI-S	44.24	4.98	42.96	4.86	43.61	5.21	.42	.65	.01
STAI-T	46.04	3.35	48.11	4.79	47.29	4.93	1.34	.26	.03
PHQ-9	5.91	4.01	8.25	6.12	7.31	3.38	1.55	.22	.04
Traumatic experience history									
TEQ	1.84	1.87	2.10	2.04	2.60	2.06	.92	.40	.02
Social Support manipulation check									
Perceived Support Scale Score	7.05	.88	4.22	1.15	5.07	.96	57.12	.00**	.59

Note. BEES = Balanced Emotional Empathy Test; IRQ = Interpersonal Regulation Questionnaire; SUIS = Spontaneous use of imagery scale; STAI-S = State-Trait anxiety inventory – State; STAI-T = State-Trait anxiety inventory – Trait; PHQ-9 = Patient

Health Questionnaire; TEQ = Traumatic Experience Questionnaire. [1] One gender unknown, [2] One unknown ethnicity. [a] One-way ANOVA, between groups comparisons, [b] Partial Eta-Squared, [c] Pearson Chi-square, [d] Cramer's V. **p* < .05. ***p* < .01.

3.2. Assessment of Acquisition of Learned Threat

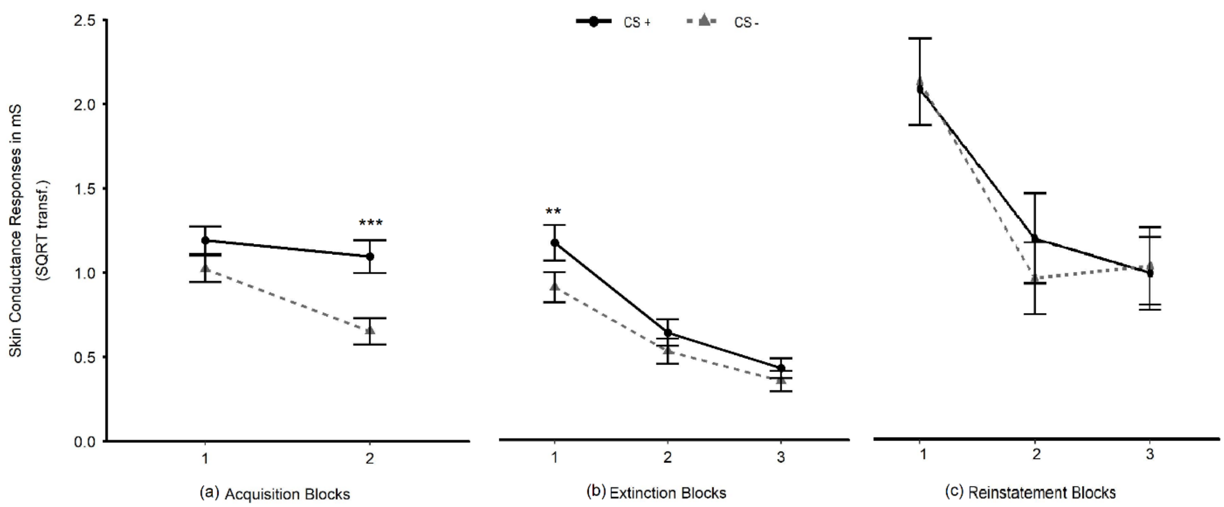
Analysis of SCR during threat acquisition using LMEMs indicated a change in SCR to the CS+ versus the CS- over time. This is illustrated by a significant effect of CS-type ($X^2(1) = 40.73$, $p < .0001$, $b = .03$, $SE = .13$, $t = .25$, 95% CI [-.22, .29]), of Trials ($X^2(1) = 24.30$, $p < .0001$, $b = .05$, $SE = .05$, $t = 1.01$, 95% CI [-.04, -.15]), and an interaction CS-type*Trials ($X^2(1) = 17.16$, $p < .0001$, $b = -.11$, $SE = .02$, $t = 4.12$, 95% CI [-.17, -.06]). This interaction, illustrated in Figure 2a, verified that learning occurred. As expected, there were no significant main effects of Condition ($p = .24$), nor were there Condition*CS-type ($p = .57$) and Condition*Trial interactions ($p = .08$), indicating that learning was equal across all conditions (Figure S3a).

3.3. Effect of Social Support on Threat Extinction

Analysis of SCR during the threat extinction showed a significant effect of CS-type ($X^2(1) = 17.57$, $p < .001$, $b = -.32$, $SE = .09$, $t = 3.38$, 95% CI [-.51, -.13]), of Trials ($X^2(1) = 194.90$, $p < .001$, $b = -.16$, $SE = .02$, $t = 6.32$, 95% CI [-.21, -.11]), but not an interaction between CS-type*Trials type ($p = .08$). Figure 2b suggests that the difference between CS+ and CS- was stronger during the first block (first three trials) of extinction and decreased over time. Contrary to prediction, there was no significant effect of Condition ($p = .57$), nor were there interactions between Condition and CS-type ($p = .35$) or Condition and Trials ($p = .43$) (Figure S3b). This implies that different social support interactions did not have differential effects on participants' physiological responses to the presentation of the CS during extinction.

Figure 2

Block by Block SCR for CS+ and CS- during (a) Acquisition, (b) Extinction and (c) Reinstatement of Threat



Note. A block consists of the mean of three trials. (a) Indicates a learned threat response illustrated by a stronger SCR for CS+ than CS- at block 2. (b) Indicates an extinction of threat response illustrated by a stronger SCR for CS+ than CS- at block 1 and a non-significant difference in SCR between CS+ and CS- at block 2 and 3. (c) Indicates a return of threat for both CS, illustrated by the increase of SCR between the block 3 of extinction and the block 1 of reinstatement. No significant differences between the social support interaction conditions were found in neither of the experimental phases. Figures showing the trial by trial SCR for each threat conditioning part and for each support condition separately are found in Figure S1 to S3 in the online supplementary materials. Error bars represent $\pm$ 1 SEM. ** p < .01, *** p < .001.

3.4. Intrusive Memory Diary

Across all conditions, 78% of the participants sent back their electronic diary at the end of each day. The other 22% verbally informed the experimenter (at day 8), that in the days they did not send their diary, they did not have any intrusive memories. These empty entries were replaced by 0. There was no difference in compliance (i.e. of sending back the diary at the end of each day) between the Conditions (supportive social interaction = 73%, unsupportive social interaction = 80% and no social interaction = 80%).

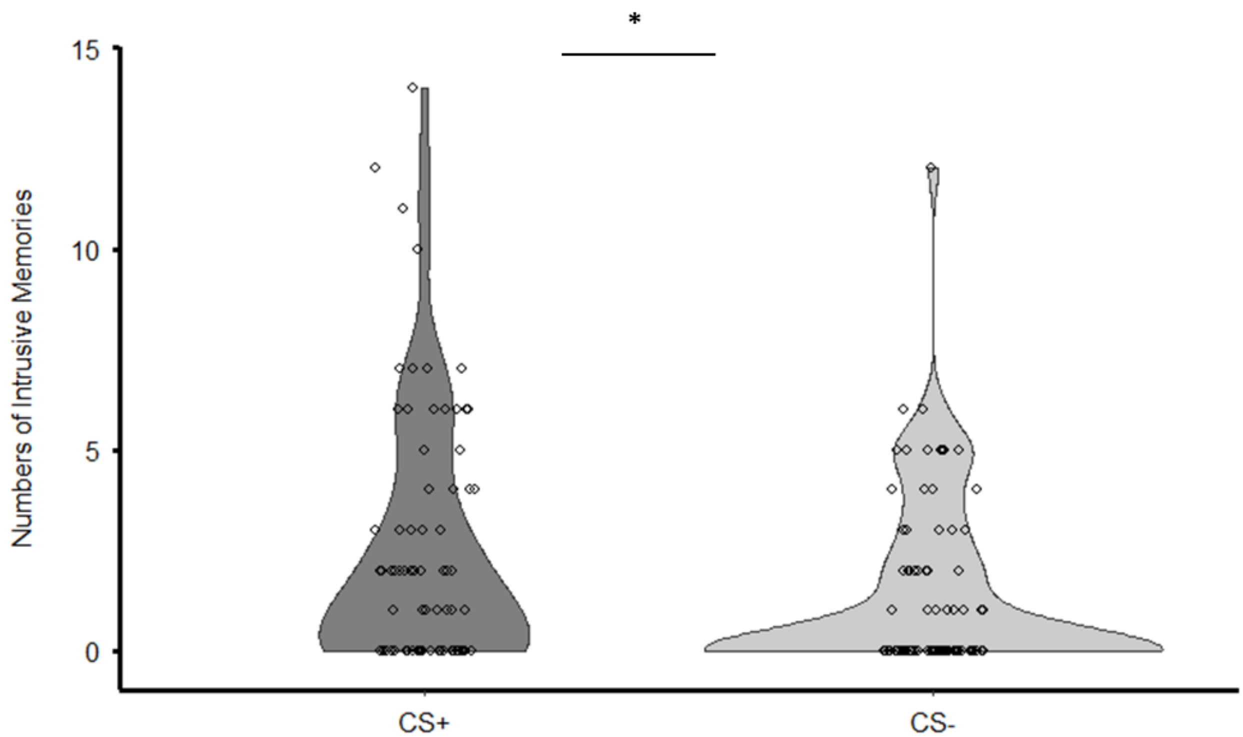
Examples of the intrusive memories of the picture stimuli as written in the diaries are “part of a clock”, “A very vague image of the zipper” and “the tray of buttons”. A total of 85% of intrusive memories were successfully matched by the experimenter to the two picture stimuli each participant saw, indicating that a majority of the intrusive memories reported came from the threat conditioning paradigm session. Other intrusive memories than of the two picture stimuli were not included in the analyses. Overall, around 70% of the participants reported experiencing at least one intrusive memory of the picture stimuli, with a mean number of 3.75 intrusive memories (*SD* = 4.18; range = 0-16).

3.5. Threat Conditioning Generates Intrusive Memories

Critically and as predicted, overall, participants reported 69 % more intrusive memories of CS+ (*M* = 2.35, *SD* = 3.09) than CS- (*M* = 1.39, *SD* = 2.17) ($X^2(1) = 6.35$, $p < .05$, $b = -.96$, $SE = .38$, $t = 2.50$, 95% CI [-1.72, -.20]), as illustrated in Figure 3.

Figure 3

Violin Plot of Number of Intrusive Memories for the CS+ and the CS- Reported over Seven Days in the Diary



Note. Significant difference between the total number of intrusive memories for CS+ and CS-, across conditions combined. The dots illustrate individual data points for CS+ and CS- intrusive memories. * $p < .05$.

3.6. Effects of Individual Differences on Total Number of Intrusive Memories

To examine whether potential pre-existing vulnerabilities such as state and trait anxiety, depressive mood and number of previous traumatic experiences could explain the total number of CS+ and CS- intrusive memories, we entered them in our model as covariates. Each covariate and its interaction with CS-type were entered as fixed effect into separate models and compared to the simplest model containing CS-type only.

Due to their low inter-correlation (r = .17) and low multicollinearity (VIF = < 10), STAIS and STAIT were added together to the simplest model. Significant interactions were found between CS-type and STAIS ($X^2(1) = 20.62$, $p < .001$, $b = .05$, $SE = .01$, $t = 4.45$, 95% CI [.03, .08]) and CS-type and STAIT ($X^2(1) = 8.23$, $p < .01$, $b = .02$, $SE = .01$, $t = 2.81$, 95% CI [.01, .04]) on the number of intrusive memories. This suggests that both higher state and trait anxiety scores were linked to a greater number of intrusive memories for CS- compared to CS+ (Figure S4a and S5 in the online supplementary materials). No significant contributions of any other baseline measures or SCR during threat conditioning were found to explain CS+ and CS- intrusive memories (all *ps* > .06).

3.7. Effects of Individual Differences on Having Intrusive Memory at all

To examine whether potential pre-existing vulnerabilities could explain the appearance of intrusive memories (i.e. whether participants reported having any intrusive memories or not), we split the sample into two groups. We looked at these pre-existing vulnerabilities on participants who had zero intrusive memories (n = 25) and participants who had at least one intrusive memory (n = 57). Please note that the following results did not survive correction for multiple comparisons. Mann-Whitney U test indicated that those with (at least one) intrusive memory had a greater number of reported trauma experiences in the past (TEQ score) (M = 2.49, SD = 2.10) compared to those with zero intrusive memories (M = 1.40, SD = 1.47), U = 471.00, z = -2.29, $p < .05$, r = .25. Participants with (at least one) intrusive memory had significantly lower trait anxiety (STAI-T score) (M = 46.28. SD = 4.61) compared to those with zero intrusive memories (M = 48.78, SD = 4.25), U = 406.50, z = -2.20, $p < .05$, r = 25.

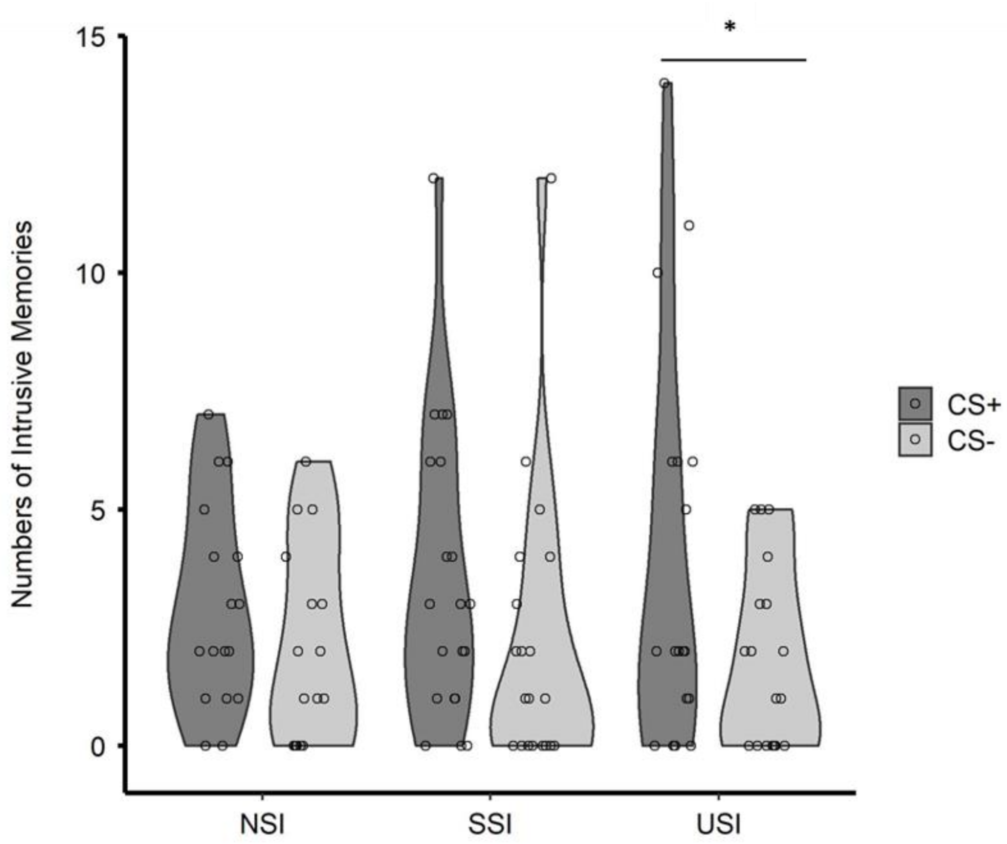
3.8. Effect of Social Support on Number of Intrusive Memories

To test the hypothesis that, compared to no social interaction, supportive social interaction would lead to a lower number of intrusive memories and unsupportive social interaction would lead to a higher number of intrusive memories, we carried out two statistical procedures using linear mixed effects models (LMEMs). First, the results from the LMEM showed that social support conditions alone did not improve model fit ($X^2(2) = .21$, $p = .89$) as compared to the simplest model (CS-type only). Simple group comparisons corroborated this, indicating that contrary to predictions there was no difference between conditions in total number of intrusive memories (no social interaction, *M* = 3.62, *SD* = 3.28; supportive social interaction, *M* = 4.29, *SD* = 4.33; unsupportive social interaction , *M* = 3.43, *SD* = 4.55; *p* = .71).

Next, we tested we tested a nested model where CS-type is nested within the social support conditions. LMEMs indicated that, compared to the simplest model, the nested model improved model fit ($X^2(3) = 8.13$, $p < .05$), meaning that it better explains the variance in our data. As illustrated in Figure 4, the effect of condition on intrusive memories depends on the kind of CS. Our results showed that there was no difference in number of intrusive memories between CS+ and CS- in the no social interaction condition (*b* = -.64, *SE* = .98, *t* = .65, *p* =.51, 95% CI [-2.56, 1.26]) and in the supportive social interaction condition (*b* = -1.42, *SE* = .88, *t* = 1.61, *p* =.11, 95% CI [-3.15, -.29]) but highlighted a difference between the number of intrusive memories for CS+ (*M* = 3.88, *SD* = 4.19) and CS- (*M* = 1.82, *SD* = 1.91) in the unsupportive social interaction condition (*b* = -.2.05, *SE* = 0.95, *t* = 2.15, *p* =.03, 95% CI [-.3.91, -.19]) suggesting that unsupportive social interaction led to stronger image-based conditioned threat memories. Follow-up analyses were run to examine the difference in number of intrusive memories for CS+ and CS- using differential scores (CS+ minus CS-) for each group. This showed that unsupportive interaction (M = 1.23, SD = 3.66) did not have a significantly higher CS differential score than active social support (M = 1.11, SD = 3.84, *p* = .99) or than no social interaction (M = .45, SD = 2.75, *p* = .69).

Figure 4

Violin Plot of Social Support Conditions and CS Indicating a Nested Effect on Intrusive Memories



Note. As compared to the control condition (no social interaction, NSI), supportive social interaction (SSI) did not differ in number of intrusive memories for CS+ and CS-. Unsupportive social interaction (USI), however, showed a significant difference between the number of intrusive memories for CS+ and CS-. The dots illustrate individual data points for CS+ and CS- intrusive memories. The dots illustrate individual data points for CS+ and CS- intrusive memories. * $p < .05$.

3.9. Effect of Social Support and Intrusive Memories on Reinstatement of Threat

Contrary to predictions, a repeated measure GLM showed a significant effect of Blocks ($F(1,40) = 14.63$, $p < .0001$, $\eta_p^2 = .26$), but not of CS-type ($p = .88$) or Condition ($p = .57$; Figure S3c). This suggests a non-differential reinstatement of threat response for both CS for all conditions (Figure 2c) and implies that reinstatement of learned threat did not occur. Adding number of intrusive memories as covariates showed no significant effects of CS+ (p = .59) and CS- (p = .59) intrusive memories on the return of threat response, and no significant interactions between number of intrusive memories, CS-type and Condition (all *ps* > .39).

4. Discussion Lab Experiment

We examine whether threat conditioning could be used to generate intrusive memories of neutral conditioned stimuli. As predicted and shown in Figure 3, across conditions, participants reported having significantly more intrusive memories of a neutral object (e.g. a blue mug) during the seven days following conditioning when previously paired with a shock compared to objects never followed by a shock. The greater number of intrusive memories to the CS+ versus CS- in this study provides further validation of the involvement of associative learning processes in the emergence of intrusive memories, and suggests that the encoding of conditioned threat responses also involves encoding mental images, which can become intrusive. Research has shown that brain activation at the time of encoding during trauma analogue (i.e. viewing of a traumatic film) can determine which moments of the film will later become intrusive (Bourne et al., 2013; Clark et al., 2016). Such work suggests that intrusive memories occur due to an improved encoding of particular moments that later become intrusive memory. We would therefore reason that through the learning paradigm, CS+ is better encoded and therefore results in more intrusive memories. Unfortunately, the current study cannot disentangle whether this improved encoding of the CS+ is due to the increased attention to CS+ compared to CS-, or due to the distress during the learning task due to the shocks. However, we suggest that the predictive function of CS+ to shocks might have improved visual encoding of CS+. Future work should further investigate the encoding of the imaged-based threat memory during threat conditioning, to shed light on the underlying mechanisms of how a neutral image can transform into an intrusive visual image. While the emotional features of the intrusive memories were not measured in the current study, future work could include measures capturing the emotions associated with the intrusive memories.

Our results showed that both higher state and trait anxiety were related to a greater number of intrusive memories of the CS-. This result supports previous findings in the conditioning literature showing an increased threat response to CS- in clinically anxious compared to non-anxious individuals (Duits et al., 2015). One interpretation is that such enhancement of threat response to CS- is related to an impaired inhibition of threat response to safety cues (Jovanovic et al., 2013) and/or a greater tendency to generalize conditioned threat response (Craske et al., 2012; Lissek & Grillon, 2010), which could explain the greater number of CS- intrusive memories in more anxious individuals in our sample.

Next, our lab experiment aimed to assess whether different social support interactions (supportive social interaction , unsupportive social interaction or no social interaction) after acquisition of learned threat influenced the expression of the emotional memory measured by skin conductance responses and number of intrusive memories of the CS during the seven days following conditioning. Contrary to our predictions, different social support interactions did not modulate participants' physiological responses (i.e. during extinction and reinstatement). Therefore, although our social support manipulation check indicated that the three groups perceived receiving different social support interactions (supportive social interaction> no social interaction > unsupportive social interaction), this difference did not translate into differences in physiological indices of learning, suggesting that the type of social support interactions operationalized in this study did not disrupt learned physiological arousal.

Further and contrary to our expectations, compared to no social interaction, supportive social interaction did not decrease and unsupportive social interaction did not increase the number of intrusive memories. However, results showed that unsupportive social interaction resulted in a larger CS+ and CS- difference in number of intrusive memories as compared to the no social support condition. This suggests the possibility that an actively unsupportive interaction can cause more involuntary image-based conditioned threat responses, possibly due to a stronger consolidation of visual threat memory following conditioning – though further investigation would be needed before any substantive conclusions on this can be made.

5. Method - One-Year Follow-Up

What is the impact of threat conditioning on the long-term expression of threat memories? Unpleasant stimuli (IAPS pictures) have been shown to be better recalled and more likely to generate intrusive memories up to a year after exposure (Bywaters et al., 2004) and subjective experience related to conditioning has been shown to be maintained up to a year after conditioning (Wiggert et al., 2017). Therefore, we carried out a one-year follow-up survey to examine whether intrusive memories of the CS might persist over time.

5.1 Participants

Fifty-nine of the 81 original participants (36 females) between the age of 18 and 40 years (*M* = 26.94, *SD* = 5.64) answered the one-year follow-up survey. In order to keep the same sample throughout, non-learner and non-responders from the lab experiment, were also excluded from the one-year follow-up sample. The final follow-up sample consisted of 54 participants (supportive social interaction, *n* = 18 (13 females); unsupportive social interaction, *n* = 19 (11 females, 1 unknown); no social interaction, *n* = 17 (11 females)).

5.2. Apparatus and Materials

All participants in the lab experiment were contacted by email 12 months after their participation by receiving the link to an online survey. The survey was created using Karolinska Institutet Survey and Report computer program (Artologik, version 23, Survey & Report, Artisan AB).

5.3. Follow-Up Survey

5.3.1. Free Recall

The first part of the survey investigated whether the picture associated with CS+ was better remembered than the picture associated with the CS-, and whether this potential effect would be related to the emotional value and vividness of the respective CS (Bywaters et al., 2004). Participants were asked to freely recall the picture stimuli they saw during the lab experiment previous year. For each picture stimulus they recalled, participants were then asked to report their vividness (1 = *Not vivid (I don't see the picture in my head)* to 7 = *Very vivid (I see the picture as vivid as actual vision)*), their valence (1 = *unpleasant/sad* to 9 = *feeling pleasant/happy*), their arousal level (1 = *Feeling calm/drowsy* to 9 = *Feeling alert/intense*), as well as their distress level of and emotional response to the picture stimulus (-10 = *Extremely negative* to +10 = *Extremely positive*).

5.3.2. Intrusive Memories

The second part of the survey investigated if participants had intrusive memories after their participation in the lab experiment. More specifically, participants were asked how many intrusive memories of each picture stimulus they had during the past year, how often they have had these intrusive memories (1 = *Never* to 6 = *Very frequently*) and how distressing those intrusive memories were (1 = *Not at all distressing* to 9 = *Very distressing*). Data on the exact content of these intrusive memories were not collected.

5.3.3. Recognition

The third part investigated if participants could correctly recognize the picture stimuli that served as the CS during the lab experiment. Participants were presented with eight images of objects (i.e., all images used in the Pavlovian threat conditioning paradigm) and asked to indicate whether they had seen each picture stimulus during the lab experiment or not. Further, they were asked to indicate the confidence level of their answer on a three-point scale (i.e., *not certain, quite certain, very certain*). To investigate if participants could correctly recall the CS+ they were further asked to indicate which of the presented picture stimuli was followed by a shock during the lab experiment.

5.3.4. Social Support

In the fourth part, participants answered a question about how much support they had received from the person who had entered the room during the break of the lab experiment (1 = *No support at all* to 9 = *Lots of support*). Demographic information (i.e., age and gender) was collected.

5.4. Statistical Analysis

Data were examined for potential univariate outliers on the number of intrusive memories at one-year follow-up and similar procedure for reducing the influence of outliers described earlier was used. One outlier was identified (in the supportive social interactioncondition) and was changed to one unit larger than the next most extreme score in the distribution (Tabachnick & Fidell, 2007). Due to unequal group sizes, non-parametric tests were performed. Mann-Whitney U tests were performed to compare the groups with regards to nominal and continuous dependent variables (i.e. SCR, STAI, PHQ-9 and TEQ) and chi-square tests were used for categorical dependent variables (i.e. performance in the free recall and recognition tasks) (or Fisher's exact test in case of small sample size). All analyses used a significant alpha threshold of 0.05 and include measures of effect size (rank-biserial for Mann-Whitney U tests and phi for chi-square tests). Statistical analyses were performed using IMB SPSS version 24 (IBM Corp., 2016).

To investigate potential predictors underlying why some individuals might continue to have intrusive memories during the following year, we split the sample into two groups. One group consisting of participants who continued to have intrusive memories (i.e. intrusive memories during both the seven-day lab experiment and at the one-year follow-up; n = 20) and another group of participants who did not (i.e. who only had intrusive memories during the seven-day lab experiment; n = 18). The remaining participants never had intrusive memories (n = 14). As we aimed to investigate why some might continue to have intrusive memories, two participants who did not have any intrusive memories during the seven-day lab experiment but reported having intrusive memories at one-year follow-up were excluded from the analyses. To identify potential predictors, the two groups were compared with regard to baseline self-reported measures (i.e., STAI, PHQ-9 and TEQ) and SCR during conditioning measured at Day 1 (mean CR during acquisition and mean CR during extinction). Next, to examine the relationship between the continuing having intrusive memories and memory performance, these two groups were compared on their performance on free recall and recognition of the picture stimuli.

In addition, similar analyses were undertaken comparing participants who reported never having intrusive memories (*n* = 14) with those who have had at least one intrusive memory at any point during the study (*n* = 36). These secondary analyses enabled us to determine if baseline self-reported measures, SCR and memory performance were linked to continuing having intrusive memories or simply the emergence of intrusive memories *per se*.

6. Results

6.1. Demographics

The one-year follow-up subsample did not significantly differ from the lab experiment sample in terms of age, gender, the distribution of the social support conditions and any of the baseline self-report measures (see Table S2 in online supplementary materials).

6.2. Intrusive Memories Reported at One-Year Follow-Up

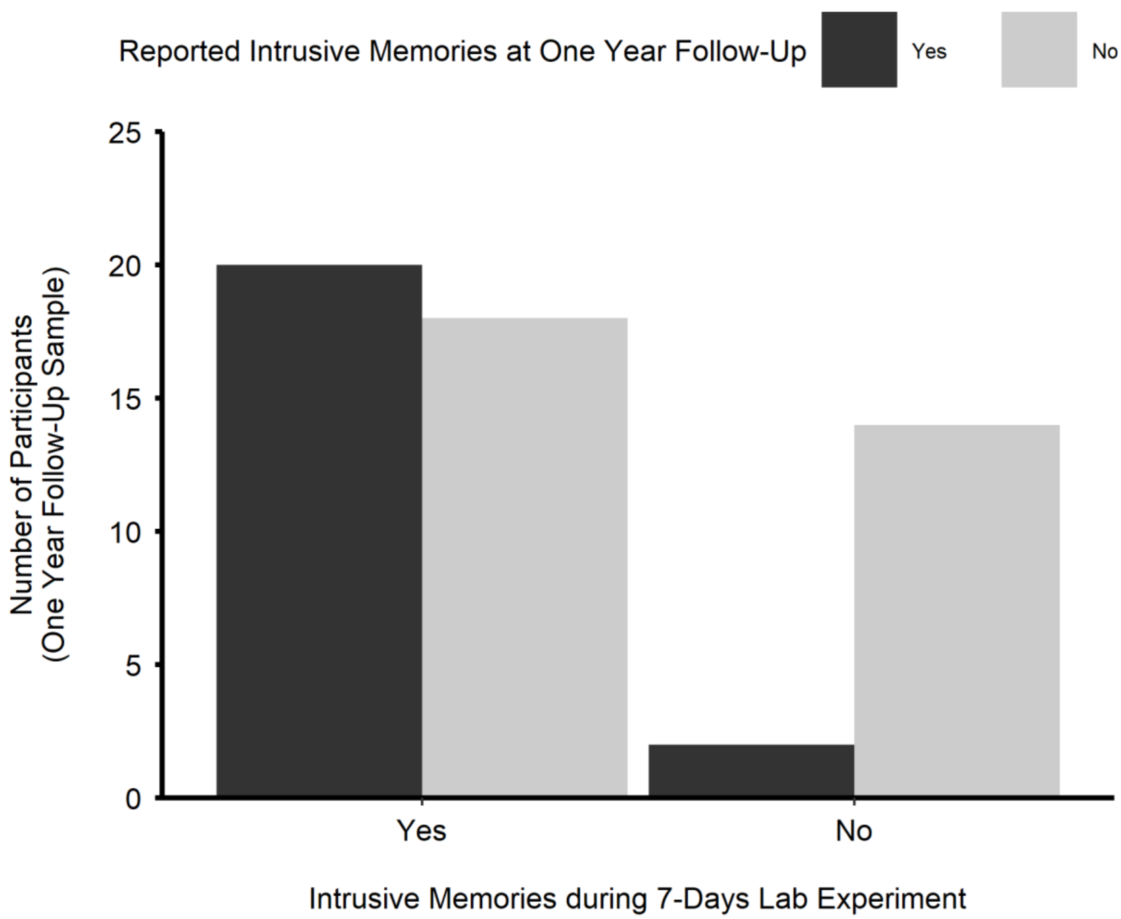
Overall, the mean number of intrusive memories during the following year was = 2.28 (*SD* = 4.76; range = 1 to 20), with numerically more intrusive memories for CS+ (*M* = 3.5, *SD* =4.72) than CS- (*M* = 2.40, *SD* = 4.62), although this difference was not statistically significant (t (19) = .73, p = .47, d = .23). Overall, intrusive memories were reported as having low distress level (*M* = 1.10, *SD* = .91, range .50 to 4.5) and low frequency (*M* = 1.32, *SD* = .61, range .50 to 2.5). Within those who reported intrusive memories at one-year follow-up, 50% reported intrusive memories of only the CS+, 25% of only the CS- and 25% of both stimuli.

Half of the participants who had intrusive memories during the lab experiment, reported, at the one-year follow-up, that they continued to have intrusive memories (*n* = 20), as illustrated in Figure 5. A chi-square test of independence indicated a significant relationship between having intrusive memories during the lab experiment and continuing to have intrusive memories (X^2 (1, N = 52) = 11.97, p <.01, *phi* = .48).

No significant relationship between the social support conditions (supportive social interaction, unsupportive social interaction and no social interaction) and continuing to have intrusive memories was found (X^2 (2, N = 38) = .38, p = .91).

Figure 5

Relationship Between Reporting Intrusive Memories During the Seven-Day Lab Experiment and Continuing Having Intrusive Memories (Reported at One-Year Follow-Up)



Note. Significant relationship between having intrusive memories during the seven-day lab experiment and continuing having intrusive memories, reported at one-year follow-up: 52.6% of the participants who had intrusive memories during the lab experiment continued to have intrusive memories (*n* = 20); 47.4% did not continue to have intrusive memories after the lab experiment (*n* = 18); 87.5% of the participants who did not have intrusive memories during the lab experiment reported at the one year follow-up that they did not have intrusive memories later on (*n* = 14); 12.5% (*n* = 2) who did not have intrusive memories during the lab experiment reported, at the one-year follow-up, having intrusive memories later on and were excluded in the analyses.

6.3. Predictors Underlying why Some Might Report, at One-Year Follow-Up, Having Continued Experiencing Intrusive Memories

To investigate why some might continue to have intrusive memories, we compared participants who reported having continued to experience intrusive memories versus those who did not. We investigated pre-existing vulnerabilities (self-reported measures reported at Day 1 of lab experiment), see Table 3. Two Mann-Whitney U tests of independence indicated that individuals who continued to have intrusive memories had significantly higher STAI-T scores (M = 47.37, SD = 3.13) than those who only had intrusive memories during the lab experiment (M = 43.66, SD = 3.49; U = 60.00, z = -2.90, p < .01, r = .48) as well as greater number of previous traumatic experiences (M = 2.78, SD = 1.68) than those who only had intrusive memories during the lab experiment (M = 1.58, SD = 1.87; U = 94.50, z = -2.16, p < .05, r = .35). The two groups did not significantly differ with regards to their CR during acquisition and extinction during Pavlovian threat conditioning (all ps > .19, see Table 3).

Table 3

Baseline Self-report Measures for One-Year Follow-Up Sample, Comparing Participants who Continued to Have Intrusive Memories (n = 20) to Those who did not (n = 18)

	Continued to have intrusive memories (n = 20)		Did not continue to have intrusive memories (n = 18)		Between groups differences: Test values	p-values	Effect Sizes
Social Support Conditions							
No social interaction	5		6				
Supportive social interaction	7		5		.48[c]	.78	.10[d]
Unsupportive social interaction	8		9				
	Mean	SD	Mean	SD			
Demographic characteristics							
Age	25.90	5.41	29.72	4.98	2.25[a]	.03*	.39[b]
Gender (*male/female*)	15/5		10/8[1]		1.59c	.20	.20[d]
Ethnicity (*Caucasian/non-Caucasian*)	7/12[2]		10/8		1.30[c]	.25	.18[d]
Anxiety measures							
STAI-S	44.50	5.24	41.17	5.73	112.00[a]	.07	.28[b]
STAI-T	47.35	3.13	43.66	3.49	60.00[a]	.00**	.48[b]
PHQ-9	7.00	4.45	5.00	3.65	105.50[a]	.18	.22[b]
Traumatic experience history							
TEQ	2.78	1.68	1.58	1.87	94.50[a]	.03*	.35[b]
SCR - threat conditioning							
CR Acquisition	.39	.43	.16	.73	151.00[a]	.39	.13[b]
CR Extinction	-.05	.39	.13	.47	135.00[a]	.18	.03[b]
Emotion ratings for recall							
Valence							
CS+	4.71	1.06	5.20	1.09	28.00[a]	.50	.12[b]
CS-	4.30	1.54	5.33	1.02	24.50[a]	.19	.04[b]
Arousal							
CS+	4.85	1.02	5.20	1.09	32.00[a]	.76	.14[b]

CS-	4.76	1.30	5.16	.98	30.50[a]	.41	.09[b]
Vividness							
CS+	4.50	1.09	4.00	.70	26.00[a]	.37	.06[b]
CS-	3.76	1.42	3.83	1.32	39.00[a]	1.00	.22[b]
Emotional response							
CS+	-.71	2.94	1.00	3.46	26.00[a]	.39	.07[b]
CS-	-.61	3.45	.83	2.56	28.50[a]	.35	.07[b]

Note. All measures were taken at Day 1 of the lab experiment. Continued to have intrusive memories = participants who reported having intrusive memories both during the seven-day lab experiment and during the following year. Did not continue to have intrusive memories = participants who only had intrusive memories during the seven-day lab experiment. STAI-S = State-Trait anxiety inventory – State; STAI-T = State-Trait anxiety inventory – Trait; PHQ-9 = Patient Health Questionnaire; TEQ = Traumatic Experience Questionnaire; CR Acquisition = Mean conditioned response during Acquisition; CR Extinction = Mean conditioned response during Extinction. [1] One gender unknown, [2] One unknown ethnicity. [a] Mann-Whitney U test, [b] Rank-Biserial, [c] Pearson Chi-square , [d] Phi, [e] Independent sample t-test, [f] Cohen's d. * $p < .05$. ** $p < .01$.

6.4. Relation Between Continuing to Have Intrusive Memories and Memory Performance

6.4.1. Free Recall of the Picture Stimuli

Overall, 82.7% of the participants who answered the one-year follow-up survey could correctly recall seeing at least one picture stimulus, of which 37.2% recalled only the CS + picture, 20.9% recalled only the CS- picture and 41.9% of the participants recalled both. There were no significant differences in free recall of only the CS+, only the CS- or both stimuli between participants who continued to have intrusive memories and those who did not (X^2 (2, N = 32) = 2.05, $p = .35$). As shown in Table 3, there were no significant differences in terms of valence, arousal, vividness or emotional response of the CS+ and CS- picture stimuli between these two groups (all *p values* > .19).

6.4.2. Recognition of Picture Stimuli

Overall, 96.2% of the participants could correctly recognize the at least one picture stimuli, 38% recognized only the CS + picture, 16% recognized only the CS- picture and 46% of the participants recognized both picture stimuli. There were no significant differences in how confident participants recognized the picture stimuli, between participants who continued to have intrusive memories and those who did not, i.e. *not certain* (X^2 (1, N = 7) = 2.10, p = .14), *quite certain* (X^2 (2, N = 7) = .19, p = .90), *very certain* (X^2 (2, N = 33) = 2.29, p = .31).

6.5. Relation Between Continuing to Have Intrusive Memories and Recognition of the CS+

Overall, 49% of participants correctly recognized which picture was followed by a shock (CS+) during the lab experiment, 19.6% incorrectly recognized CS- as the picture that was followed by a shock and 17.6% incorrectly recognized both pictures as being followed by a shock. There were no significant differences in correctly recognize which picture stimulus was followed by a shock between participants who reported, at the one year follow-up, continuing to have intrusive memories and those who did not (X^2 (3, N = 37) = 3.90, p = .29).

6.6. Emergence of Intrusive Memories versus Continuing to Have Intrusive Memories

Secondary analyses examined potential pre-existing vulnerabilities between participants who reported never having intrusive memories (i.e. neither during the seven-day lab experiment, nor at the one-year follow-up) with those who have had at least one intrusive memory (at any point). No significant differences were found between these two groups, i.e. STAI-S (U = 167.00, p = .19), STAI-T (U = 142.00, p = .06), PHQ-9 (U = 149.00, p = .31) and TEQ (U = 194.00, p = .20) or in SCR (CR acquisition, U = 263.50, p = .95; CR extinction, (U = 180.00, p = .07). Neither were there significant differences in terms of the emotional ratings of the picture stimuli (all *p values* > .10) nor in terms of free recall (X^2 (2, N = 43) = 3.93, p = .14) or recognition (all *p values* > .11) of the picture stimuli between these two groups. Finally, no significant differences in recognition of which picture stimulus was followed by a shock was found between these groups (X^2 (3, N = 51) = 2.84, p = .42).

7. Discussion - One-Year Follow-Up

In our one-year follow-up survey, we examined whether the intrusive memories generated by the threat conditioning paradigm persisted over a longer period of time, and investigated potential predictors underlying why some might continue to have intrusive memories. For that purpose, we compared participants who continued to have intrusive memories with those who did not.

As shown in Figure 5, half of the participants who had intrusions during the lab experiment, continued to have intrusions a year later. Although participants reported numerically more intrusions of CS+ compared to CS- at one-year, contrary to predictions, this difference was not significant. We found no effect of social support conditions on the persistence of intrusive memories. We refrain from interpreting this lack of effect due to the small sample sizes in each of the three conditions (no social interaction, N = 5; supportive social interaction, N = 7; unsupportive social interaction , N = 8).

As predicted, we found that continuing to have intrusive memories was related to particular pre-existing vulnerabilities: higher trait anxiety at baseline and greater number of previous traumatic experiences. These results support previous research showing that anxiety and prior exposure to trauma have been reported as pre-trauma factors associated with higher risk of developing PTSD symptoms (Ozer et al., 2008). Interestingly, these pre-existing vulnerabilities were not found in participants who, at the time of the one-year follow-up, had never experienced intrusive memories. This indicates that these predictors are most likely specifically related to continuing to have intrusive memories, rather than the emergence of intrusive memories. Contrary to predictions, there was no differences in state anxiety, depressive mood and in CR during threat conditioning between participants who continued to have intrusive memories and participants who did not.

Importantly, and contrary to our predictions, our one-year follow-up results showed no relationship between continuing to have intrusive memories and better memory performances (free recall and recognition) of the two picture stimuli or of the CS+. These findings are however consistent with the pattern of dissociation between intrusive memories and recognition performance found one week after exposure to experimental trauma (Lau-Zhu et al., 2019), and with the notion of multiple memory systems (Squire, 2004).

Importantly, due to the reduced sample size at one-year follow-up, these results must be interpreted with caution.

8. General Discussion

In the current study, we united the experimental and well-controlled benefits of Pavlovian threat conditioning with a clinical research approach to studying symptoms (intrusive memory diary) in addressing two key questions: Does threat conditioning generates intrusive memories that may persist? And, does social support modulate emotional responses?

8.1. Threat Conditioning Generates Persistent Intrusive Memories

As predicted, threat conditioning (with pictures of neutral objects and electrical stimulations) generated intrusive memories of the conditioned stimuli during the subsequent seven days, with more CS+ than CS- intrusive memories. Furthermore, our one-year follow-up indicated that these intrusive memories can persist over time.

An emerging body of evidence is now showing that associative processes contribute to the formation of intrusive memories (Franke et al., 2021; Miedl et al., 2020; Wegerer et al., 2013). Therefore, we reason that adding the measure of intrusive memories to a standard Pavlovian threat conditioning paradigm suggests one way that this paradigm can evolve, which would benefit clinical research in anxiety disorders and post-traumatic stress (both of which features intrusive mental images). Doing so may aid the translation from investigating basic mechanisms towards understanding processes involved in the phenomenology of psychopathology – such as the intrusive memories of an initially neutral object that springs to mind unbidden, and may cause distress.

Our results also indicated that, anxiety, which is associated with sensitivity to traumatic stress reactions (Clark et al., 2015; Laposa & Alden, 2008), was found to be linked to a greater number of intrusive memories of the CS-. This suggests that, similarly to the enhanced psychophysiological threat responses to CS- observed in anxious individuals, these individuals display a generalized imaged-based threat response to the safe stimulus and/or an impaired ability to inhibit image-based threat response to the safety cue. Moreover, our results showed that trait anxiety at baseline and greater number of previous traumatic experiences might explain why intrusive memories might persist over time. This informs us of possible risk factors that could help identify people after trauma who may be at risk for longer-term intrusive memories.

8.2. Experimental Manipulation of Social Support - Contrary to Predictions

During a negative experience, social support has been shown to buffer biological stress response (Ditzen & Heinrichs, 2014). However, whether a social interaction immediately after threat acquisition can alter the maintenance of stress response had, to our knowledge, not been tested. Contrary to our predictions, different social support did not influence participants' physiological responses (i.e. during extinction and reinstatement). Furthermore, compared to no social interaction, supportive social interaction did not decrease and unsupportive social interaction did not increase the number of intrusive memories of the CS. In this study, we used an in-person interaction with a stranger, i.e. the type of interaction that could take place directly after a stressful event such as a trauma, and did not see an effect of this social support manipulation. However, other studies which have examined the effect of the presentation of support figures (Hornstein et al., 2016) or attachment representations (Bryant & Foord, 2016) during an analogue for stressful event, have found a decrease in stress responses to negative stimuli. Therefore, this suggests the need for further research on the type of social support needed to disrupt memory consolidation.

Our results, suggest the possibility that unsupportive social interaction resulted in a relative difference between the number of CS+ and CS- intrusive memories, which suggests that an unsupportive social experience could enhance the consolidation of visual threat memory. Follow-up analyses using differential scores (CS+ minus CS-) however indicated that this difference was not significantly larger in the unsupportive social interaction group compared to the other two groups, meaning that this result must be interpreted with caution.

8.3. Research Implications

Clinicians and neuroscientists have long been interested in the translational potential of threat conditioning paradigms. Such paradigms have, however, rarely taken into account intrusive memories

(Fullana et al., 2019; Holmes et al., 2021; Visser et al., 2018), which are central symptoms of anxiety-related disorders or disorders after trauma such as PTSD (DSM-5; American Psychiatric Association, 2013). Indeed, the standard Pavlovian threat conditioning has been criticized and was (erroneously) assumed not likely to yield intrusive memories (James et al., 2016, p.107; Wegerer et al., 2013, p.2). Contrary to this, our findings suggest that this paradigm can indeed be used to investigate the intrusive image-based aspect of threat memories. Moreover, we demonstrate that the threat conditioning paradigm can produce both short and long-term intrusive memories.

An advantage of this model is the use of benign stimuli (e.g. a clock) that become intrusive through conditioning and the use of a mild aversive experience (uncomfortable but not painful electrical stimulations) while minimizing the influence of individual differences in pre-existing aversions and emotional learning history. This model therefore differs from the conditioned-intrusion paradigm (Franke et al., 2021; Wegerer et al., 2013) and the trauma film paradigm (James, Lau-Zhu, Clark, et al., 2016) that use intrinsically aversive stimuli (aversive film clips depicting interpersonal violence and blood) to generate intrusive memories in lab settings.

8.4. Clinical Implications

The current study offers a novel experimental psychopathology model of intrusive memories, which may particularly aid our understanding of previously neutral stimuli. By adding a measure of intrusive memories to a threat conditioning paradigm, these findings contribute to the development of an experimental approach linking experimental work to clinical developments (Holmes et al., 2018; Iyadurai et al., 2019; James et al., 2016).

Our results that a previously neutral object, such as a button can become intrusive, supports clinical findings demonstrating that images of neutral scenes or neutral objects, such as the light above the operating table (Horsch et al., 2017) or the rain falling onto the window of the car right before a car accident (Iyadurai et al., 2018) can later become intrusive when present during a real life traumatic event. A better understanding of the mechanisms underpinning the development of intrusive memories of neutral scenes or objects could improve the detection of specific images that might later become intrusive, and therefore aid the development interventions targeting specific hotspot scenes of the traumatic experience. Consequently, investigating how neutral stimuli become intrusive would also challenge at times the general misconception, that only aversive scenes can become intrusive. This would rather validate the lived experience of those who are experiencing intrusive memories whose content is benign per se but whose meaning and associated reactions feel aversive.

In our study, we are intrigued that unsupportive social interaction led to a stronger difference in number of CS+ and CS- intrusions. The negative impact of the unsupportive social interaction on adjustment after negative experience is consistent with the existing experimental and clinical literature, stating that unsupportive interactions can do further harm (Littleton, 2010; Zoellner et al., 1999). Brief intervention approaches, consisting of minimal verbal exchange, which can be delivered by lay people are needed to improve mental health worldwide (Holmes et al., 2018). While the form of social support developed in this study did not translate into beneficial effects, more experimental research targeting the modulating effect of social support interactions after a negative experience could help the development of delivery models improving post-trauma clinical care.

8.5. Methodological Limitations

Reinstatement of learned threat was used to investigate the effect of our social support manipulation on return of threat. Our results indicates an over-arousal response to the sudden presentation of the CSs after the three unexpected electric stimulations (Figure 2c). Due to the seven days following extinction, our results cannot distinguish the effect of spontaneous recovery from reinstatement. In fact, the non-differential return of threat might have been caused by the intrusion diary task taking place between conditioning and the reinstatement procedure. That is, by being asked to report potential intrusive memories of the CS, participants might have generalized the threat response to both CS. Future studies interested in the reinstatement of learned threat and using both Pavlovian conditioning and the intrusive memory diary, could include a control group where participants do not complete the intrusive memory diary, in order to identify whether reporting intrusive memories over a week leads to generalization of threat responses to both CS.

Additionally, it is possible that this over-arousal response is due to our specific reinstatement procedure, which was not preceded by a re-extinction procedure, i.e. presenting the CSs without reinforcement before the reinstatement procedure. The current design does not enable us to determine the cause of the non-differential responses that might be due to our reinstatement procedure, spontaneous recovery, the intrusive diary task or a combination of these. Future studies should include a re-extinction procedure (Haaker et al., 2014), which would aid the interpretation of the results.

Another consideration is our limited number of baseline measures, which did not cover the full range of potential factors influencing the emergence (or non-emergence) of intrusive memories or their maintenance over time. For instance, we reported that a greater number of previous traumatic experiences was associated with continuing to have intrusive memories. Our baseline measures did not however control for the possibility that individuals who had intrusions and a greater number of previous trauma, might have a better understanding of what an intrusive memory is, and could have led them to report more intrusive memories overall. The impact of past trauma in response to this experimental paradigm should be further investigated.

An additional consideration is the potential effect of the extinction procedure on intrusive memories. The current study looked at the effect of the social support interaction on extinction of learned threat, therefore we included an extinction procedure directly following acquisition of learned threat. However, extinction is known to weaken the CS-US association (Craske et al., 2018). The addition of second group of participants who underwent acquisition and social support interaction only would have informed us on the effect of extinction on intrusive memories formation (Franke et al., 2021).

Finally, a general consideration is the relative simplicity of the standard Pavlovian threat conditioning procedure as compared to the complexity of real world aversive experience. There is a tradeoff between complex paradigms mimicking the intricacy of our reality and simple, and well controlled, paradigms that can be generalized across situations. We hope that our experimental model will help to inform a wide range open questions in the clinic and beyond.

9. Conclusion

The Pavlovian threat conditioning has long proven to be a useful translational model for the development of anxiety disorders, and here we have demonstrated that this paradigm can generate intrusive memories of neutral images, which may persist over time, such as a clock or a button. Our results indicating that Pavlovian threat conditioning can generate intrusive memories brings new opportunities to unite the benefits of a well-controlled experimental conditioning paradigm with clinical research approach to studying psychopathological symptoms.

CRediT authorship contribution statement:

Lisa Espinosa: Conceptualization, Data curation, Methodology, Formal analysis, Visualization, Writing – original draft. **Michael B. Bonsall:** Formal analysis, Supervision, Writing – review & editing. **Nina Becker:** Methodology, Visualization, Writing – review & editing. **Emily A. Holmes:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Andreas Olsson:** Conceptualization, Funding acquisition, Methodology, Supervision, Project administration, Writing – review & editing.

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Open science practices:

Key data, instructions to experimenters and participants, statistical scripts, and relevant material presented in this article will be made publicly available via Open Science Framework upon request to reviews and accessible at https://osf.io/5nq8z/ (note that training to use such methods from the primary authors is advised). This study was not pre-registered.

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Pavlovian threat conditioning can generate intrusive memories that persist over time

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Abstract

Although Pavlovian threat conditioning has proven to be a useful translational model for the development of anxiety disorders, it remains unknown if this procedure can generate intrusive memories – a symptom of many anxiety-related disorders, and whether intrusions persist over time. Social support has been related to better adjustment after trauma however, experimental evidence regarding its effect on the development of anxiety-related symptoms is sparse. We had two aims: to test whether threat conditioning generates intrusive memories, and whether different social support interactions impacted expression of emotional memories. Non-clinical participants (n=81) underwent threat conditioning to neutral stimuli. Participants were then assigned to a supportive, unsupportive, or no social interaction group, and asked to report intrusive memories for seven days. As predicted, threat conditioning can generate intrusions, with greater number of intrusions of CS+ (*M*=2.35, *SD*=3.09) than CS- (*M*=1.39, *SD*=2.17). Contrary to predictions, compared to no social interaction, supportive social interaction did not reduce, and unsupportive interaction did not increase skin conductance of learned threat or number of intrusions. Unsupportive interaction resulted in a relative difference in number of intrusions to CS+ vs CS-, suggesting that unsupportive interaction might have increased image-based threat memories. Intrusions were still measurable one year after conditioning (one-year follow-up; n=54), when individuals with higher trait anxiety and greater number of previous trauma experiences reported more intrusions. Our findings show that threat conditioning can create long-lasting intrusions, offering a novel experimental psychopathology model of intrusive memories with implications for both research on learning and clinical applications.

Keywords: Pavlovian Conditioning, Intrusive Memories, Skin Conductance, Social Support, Trauma

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1. Introduction

An estimated 70% of the world population has experienced or witnessed a traumatic event in their lifetime (Benjet et al., 2016). While we have some effective evidence based treatments, given the scale of trauma exposure there is clearly an imperative to develop simple experimental procedures to understand how specific mechanisms modulate particular symptoms (Holmes et al., 2018) after trauma including post-traumatic stress disorder (PTSD) and anxiety (Holmes et al., 2014; Iyadurai et al., 2019). One commonly used experimental analogue of a stressful event is the Pavlovian threat conditioning paradigm (Craske, Hermans & Vansteenwegen, 2006; Haaker et al., 2019; Milad & Quirk, 2012). This paradigm has been used to investigate the basic processes underlying (maladaptive) associative learning, which are considered important components in the etiology of anxiety disorders and PTSD (Duits et al., 2015; Lissek & van Meurs, 2014; Pittig et al., 2018). Using standard Pavlovian threat conditioning, researchers have examined the engagement of both the non-declarative and declarative aspect of threat memories (for a review, see (for a review, see Dunsmoor & Kroes, 2019). Psychophysiological measures, such as skin conductance, fear potentiated startle and pupil size are the most common indices of implicit non-declarative fear memory processes (Bach et al., 2020) while self-reported CS–US contingency (Boddez et al., 2013) and recognition memory test (Dunsmoor, Niv, et al., 2015) have also been used to examine the declarative aspect of threat memories. To our knowledge, however, Pavlovian threat conditioning has not yet been modeled to investigate the involuntarily occurrence and image-based aspect of certain threat memories, or more specifically, intrusive mental images of previously neutral stimuli. To our knowledge, however, this paradigm has not yet been modelled to investigate the involuntarily occurrence and image-based aspect of certain threat memories, or more specifically, *intrusive mental images* of previously neutral stimuli.

Here we used a Pavlovian threat conditioning paradigm as an experimental model to study how learning and memory of an analogue stressful event may lead to intrusive memories, defined as recurrent, involuntary, and intrusive recollections of an event (DSM-5; American Psychiatric Association, 2013, p.282). We asked whether threat conditioning could be used to generate intrusive memories of neutral conditioned stimuli, and whether these memories would persist over time. Next, we asked whether different social support interactions after an aversive experience could modulate the expressions of the emotional memory generated by Pavlovian threat conditioning. Social support is considered a protective factor that can moderate outcome of traumatic experiences (*Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. [*DSM-5*]; American Psychiatric Association, 2013, p.277), but experimental evidence of the effect of social support on the development and potential persistence of symptoms, such as those characterizing PTSD, is sparse. We reasoned that experimentally manipulating social support following threat conditioning could inform us about how post-trauma social support regulates emotional responses to negative experiences.

Studies investigating basic mechanisms linking memory disruption and intrusive memories in non-clinical participants have been crucial in better understanding the development of intrusive memories (for a review, see Bisby et al., 2020; Bisby & Burgess, 2017). The current study could therefore further help developing approaches that target specific mechanisms and fuel treatment research (Holmes et al., 2018). Overall, this study attempts to bridge the experimental and well-controlled benefits of threat conditioning with a clinical research approach.

1.1 Pavlovian Threat (“Fear”) Conditioning as an Experimental Model for a Stressful Event

In humans, differential Pavlovian threat conditioning consists of repeatedly pairing a neutral conditioned stimulus (CS+) with a naturally aversive unconditioned stimulus (US), such as an electric shock, whereas another conditioned stimulus (CS-) is never paired with the US. As a result of its association with the US, the CS+ gains emotional significance and produces a conditioned response (CR), such an elevated autonomic arousal measured through skin conductance. Following conditioning, an extinction procedure, during which the CS are presented in the absence of the US, leads to the diminishing of the conditioned response.

There is growing evidence about the role of associative learning in the development and maintenance of symptoms of anxiety-related disorders and PTSD, supporting the use of the threat conditioning paradigm as an experimental framework for memory processes underlying trauma memories (Fani et al., 2015; Milad & Quirk, 2012; Pittig et al., 2018; Visser et al., 2018; Zuj & Norrholm, 2019). In particular, laboratory experiments using threat conditioning have enabled research to target the mechanisms underlying the development, regulation and relapse of threat responses with greater precision than clinical settings would allow (Carpenter et al., 2019). The identification of specific key neural, molecular and genetic factors involved in threat conditioning has helped the development of hypotheses-driven studies translated to clinical applications (A. Holmes & Singewald, 2013).

Wegerer and colleagues (2013) developed a conditioned-intrusion paradigm to investigate the link between conditioning and intrusive memories in a laboratory setting. This paradigm paired neutral sounds (conditioned stimuli, CS) with aversive film clips, serving as unconditioned stimuli (US). When presented during a neutral soundscape, the sound previously associated with the aversive versus neutral films led to more intrusive memories (images or thoughts) (Streb et al., 2017; Wegerer et al., 2013). A more recent study using a similar paradigm (Franke et al., 2021) showed that participants reported intrusive memories (visual, auditory, thought and/or feelings) of both US (aversive films) and CS (neutral faces). Using complex and naturalistic stimuli, these results support the role of conditioned associations in the development of intrusive memories after a stressful experience.

In the current study, we were interested in examining the development of intrusive memories of previously neutral stimuli following a standard Pavlovian conditioning paradigm, using electrical stimulations as US. This procedure allowed us to control for pre-existing aversions towards specific stimuli containing representations of, for example, blood, violence and injuries. Intrusive memories can develop not only of overtly traumatic moments but also to fragments of scenes (e.g. knocking at neighbors door) or objects (e.g. broken glass), and even seemingly neutral objects (e.g. green curtains or a pair of shoes; Grey & Holmes, 2008; Holmes et al., 2005), Albeit less naturalistic, the simple, and well-controlled nature of the

Pavlovian conditioning paradigm – here using neutral visual cues such as a clock or a zip - enhances generalizability of the results across learning situations. Accordingly, we examined whether standard Pavlovian threat conditioning can be used to generate intrusive memories of neutral CS that may persist over time.

1.2. Clinical and Experimental Approaches to Intrusive Memories

Intrusive memories after a traumatic event often become less frequent over time. Nevertheless, for some people they persist over time, and their recurrent and distressing form are symptoms of both Acute Stress Disorder (ASD) and PTSD (American Psychiatric Association [APA], 2013, pp. 271-286). Laboratory experiments using an analogue trauma experience have determined that pre-existing psychological vulnerabilities such as anxiety, depression and trauma history are associated with the increased likelihood to develop intrusive memories (Clark et al., 2015; Laposa & Alden, 2008).

Experiencing intrusive memories is one key symptom of psychopathology that can arise following stressful event such as trauma, raising the importance of targeting intrusive memories clinically in treatment. Previous work has developed cognitive imagery-competing task strategies as part of a short behavioral intervention to interfere with the development of intrusive memories in both experimental (Holmes et al., 2009, 2010) and clinical (Iyadurai et al., 2018; Kanstrup et al., 2021) settings. Such studies indicate that the frequency of intrusive memories can be reduced, while preserving the voluntary memory of the negative experience (Lau-Zhu, Henson, & Holmes, 2019). These results are consistent with the idea that trauma memory is composed of multiple systems (episodic and perceptual memory systems) that can be specifically targeted (Visser et al., 2018).

In the current study, our goal was to uncover whether *neutral stimuli* (similar to the ones commonly used in standard conditioning paradigms) can create intrusive memories through one session of Pavlovian threat conditioning, and whether these intrusive memories could persist. This would mean that in addition to investigate implicit, non-declarative aspects of threat memory, standard Pavlovian threat conditioning might also be used to investigate image-based, intrusive memories – i.e. another clinically important feature of threat memories.

Finally, we note that intrusive memories in clinical psychopathology can vary in emotional valence (from negative to positive), though for our work on intrusive memories the types of affective association related to the intrusive memories is not the central line of enquiry (Holmes et al., 2005; Iyadurai et al., 2019; Singh et al., 2020). The characterizing feature of intrusive memories is that they occur in the form of involuntary recollection, i.e. without being expected. Further, recent linguistic analysis of intrusive memories soon after trauma (both in the clinic and lab) indicates that intrusive memories primarily contain words related to space and sensory features, yet few words related to cognitions and emotions (Hoppe et al., 2022; Singh et al., 2022). Our interest in these features and in reducing the number of times intrusion reoccur (rather than say the cognitive or emotional content of such intrusions) has informed our current line of work.

1.3. Social Support as a Protective Factor

Social support, defined as positive social interactions in times of need, has been found to buffer the negative effect of stress on health (for a review, see Ditzen & Heinrichs, 2014). For instance, experimental work looking at the effect of social support during a cold pressor task reported that receiving verbal support from a confederate significantly decreased measures of blood pressure and heart rate compared to being alone or the mere presence of a confederate (Roberts et al., 2015).

Pavlovian threat conditioning has been used to assess the influence of social processes on the basic threat learning processes. For example, studies have shown that observing someone being calm when watching a neutral stimulus that was previously followed by a shock (vicarious safety learning) can facilitate extinction learning (Golkar et al., 2013; Olsson et al., 2020). Hornstein & Eisenberger (2018) examined how social support reminders can work as prepared safety stimuli, altering threat learning processes. For example, they showed that presenting the image of a support figure (compared to a neutral image or an image of a stranger) during threat acquisition, inhibited acquisition and enhanced extinction of learned threat (Hornstein et al., 2016; Hornstein & Eisenberger, 2017). These results suggest that the support reminders can impact underlying learning mechanisms, strengthening the idea that social support can similarly affect the consolidation of threat learning.

In real life, it might be less common to go through negative experiences in the presence of a calm person or while being reminded of a social support figure. Here, we aimed at modeling situations in which support interactions occur after the negative experience, such as interactions a patient might have with medical staff in the waiting room at the emergency department. In fact, trauma research has shown that lack of social support after real traumatic experiences is an important predictor of PTSD (Brewin et al., 2000; Bryant et al., 2017; Ozer et al., 2008) and low level of support, meaning negative reactions or the absence of supportive behavior by others, after a stressful event such as trauma, have been identified as being strongly related to development of PTSD symptoms (Wagner et al., 2016) and greater PTSD symptom severity (Ullman & Filipas, 2001).

Only few studies have however used experimental paradigms to explore how interpersonal interactions after a negative experience regulate the development of intrusive mental images. One study looked at social support given by one's partner (Woodward & Gayle Beck, 2017). After viewing a traumatic film, participants who received negative reactions from their romantic partner, such as sarcastic comments minimizing their experience or partners expressing negative affect, reported more intrusive memories of the films during the subsequent 72 hours as compared to those whose partners expressed positive responses, such as reassuring, comforting or validating comments. Another study looked at social support given by a stranger (Pruitt & Zoellner, 2008). After viewing a short footage of automobile accidents, participants who received no social support from a stranger (e.g. ignoring what happened or not providing tangible aid) reported having more intrusive thoughts during the following 48 hours than participants receiving positive (e.g. validating their experience or positive emotional support) or negative (e.g. invalidating, negative emotional support or disregard for the participant's concern) social support. How previous studies have defined supportive, unsupportive or no support varies from studies to studies, where the absence of support resembles more a negative interaction than not receiving support (as defined in Pruitt & Zoellner, 2008). Here we define supportive social interaction as the provision or exchange of emotional, informational or instrumental resources in response to someone's need of help (Cohen & McKay, 1984). We characterize unsupportive interaction as the opposite of supportive interaction, including aspects of social negativity (Brooks & Schetter, 2011) and social rejection (Eisenberger, 2011). Unsupportive social interactions after a stressful event, such as trauma, are, in fact, identified as being strongly related to greater PTSD symptom severity (Ullman & Filipas, 2001).

In the current study, our other goal was to experimentally test how social support interactions after a negative experience could modulate the expression of emotional memory. We aimed to examine whether a supportive or unsupportive social interaction with minimal verbal exchange (vs no social interaction) given by a stranger would impact expression of emotional memory measured by skin-conductance and number of intrusive memories. This type of interaction was chosen to model an interaction between strangers after a stressful experience (e.g. between a patient and medical staff in the waiting room at the emergency department). Other than the two studies mentioned above, no other experimental work has, to our knowledge, investigated the effect of simple in-person social support interaction on the expression of emotional memory.

1.4. Experiment Overview

The objective of our study was to determine whether a Pavlovian threat conditioning paradigm with pictures of neutral objects as CS and electrical stimulation as US, could generate intrusive memories of the CS during the subsequent seven days. This would further validate findings showing the contribution of conditioning processes in the development of intrusive memories (Franke et al., 2021; Miedl et al., 2020; Wegerer et al., 2013). We predicted that participants would report having more intrusive memories of the CS+ than the CS-.

To understand, more fully, the development of intrusive memories, we investigated whether the total number of intrusive memories of CS+ and CS- during the following week and whether having intrusive memories at all, would be driven by pre-existing vulnerabilities that have previously been associated with sensitivity to traumatic stress reactions (Clark et al., 2015; Laposa & Alden, 2008). We predicted that the development of intrusive memories would be influenced by inter-individual differences (i.e. higher state and trait anxiety scores, higher depressive mood score, greater number of previous traumatic experiences) and/or individuals' physiological expressions of threat conditioning.

Verifying our first objective was a necessary requirement to be able to evaluate our next aim, that is, whether different social support interactions (supportive social interaction , unsupportive social interaction or no social interaction) after acquisition of learned threat influenced the expression of the emotional memory measured by skin conductance responses (SCR; during extinction and during a reinstatement test procedure 7 days after conditioning), and number of intrusive memories of the CS during 7 days following conditioning. We predicted that, compared to the control condition (no social interaction), supportive social interaction would lead to (i) a stronger extinction of learned fear and (ii) a weaker return of fear a week later, and that unsupportive social interaction would lead to (i) a weaker extinction of learned fear and (ii) a stronger return of fear a week later. We also predicted that compared to the control condition (no social interaction), supportive social interaction would lead to a lower number of intrusive memories of the CS, and unsupportive social interaction would lead to a higher number of intrusive memories of the CS. We reason that social support interactions taking place directly after acquisition of threat would alter the expression of emotional memory by interfering with the underlying memory consolidation processes. Our manipulation thus extended previous studies demonstrating the effectiveness of interventions interfering with the consolidation of emotional memories, using for instance an imagery interfering task competing with cognitive resources soon after exposure to experimental trauma (Holmes et al., 2010; James et al., 2015; Lau-Zhu et al., 2019).

Finally, to examine whether intrusive memories may persist over time, we carried out a one-year follow-up survey comparing participants reporting intrusive memories only during the seven days after conditioning to participants reporting to have continued to experience intrusions during the year after conditioning. We predicted that having intrusive memories during the one year following conditioning would be related to a) pre-existing vulnerabilities (i.e. higher state and trait anxiety scores, higher depressive mood score, greater number of previous traumatic experiences) and higher CR during threat conditioning, b) better memory performance (free recall and recognition) of the picture stimuli used as CS, and c) free recall of which CS was followed by a shock during Pavlovian threat conditioning.

To test our predictions, we developed an experimental procedure consisting of a laboratory experiment (two sessions), as well as an associated one-year follow-up. At session 1 of the lab experiment (on Day 1), participants acquired conditioned threat responses to pictures of neutral objects, immediately followed by a social support interaction manipulation, which was followed by extinction of learned threat. During Day 1 to 7, participants then reported the occurrence of intrusive memories of the CS using an electronic intrusive memory diary outside the lab. At Session 2 (on Day 8): the recovery of the learned threat was measured in the laboratory setting through a standard reinstatement test procedure. Finally, the one-year follow-up test consisted of an electronic survey assessing whether intrusive memories would last beyond the seven days lab experiment, as well as tests of free recall and recognition memory of the CS.

2. Method Lab Experiment

2.1 Participants

Ninety-one participants (47 female) between the age of 18 and 40 (*M* = 26.60, *SD* = 5.66) were recruited via advertisement on the Karolinska Institutet Psychology division's recruitment website, and using advertisement posters at the University campus. Selection criteria were age between 18 and 40 and no reported psychiatric disorders. Sample size was determined based on estimated known effects of threat conditioning, extinction and interference of consolidation in healthy participants (Duits et al., 2015; Kindt & Soeter, 2013). Based on an estimated effect size of *d* = .40, a total of 28 participants per group (*n* = 83) were estimated as needed to obtain 90% power to detect a moderate effect of the interference of social support on the consolidation of threat response during extinction (α = .05). Following guidelines for conservative exclusion criteria in threat conditioning (Lonsdorf et al., 2019), we excluded one participant classified as non-responder, and nine participants classified as 'non-learners'. 'Non-responder' exclusion was based on lack of general physiological responses and represented participants displaying a SCR response of ≤ 0 μS (microSiemens) to at least three of the four US trials (response to the shocks), as well as to the CS+ and CS- trials. To avoid sampling bias, 'non-learners' exclusion was based on two outcome measures, where we excluded participants with both an average differential (CS+ vs CS-) SCR response of ≤ 0 μS across the last 3 trials of acquisition and failing to report correct awareness of the CS+/US contingency. The final sample consisted of 81 participants (supportive social interaction, n = 27 (15 females); unsupportive social interaction, n = 30 (16 females, 1 unknown); no social interaction, n = 24 (13 females)), indicating a total exclusion rate of 11 %. Demographic information and baseline self-report measures of the excluded participants can be found in Table S1 in the online supplementary materials. Approval for this study was obtained by the Regional Ethical Review Board in Stockholm (Dnr: 2018/549-31/1).

2.2. Apparatus and Materials

2.2.1. Picture Stimuli

Eight pictures of neutral objects from the IAPS database (Lang, Bradley & Cuthbert, 2008) were selected as picture stimuli. As shown in Table 1, the pictures have previously been rated as being low arousal (*M* = 3.05, *SD* = 2.01), neutral valence (*M* = 5.00, *SD* = 1.32) and neutral dominance (*M* = 6.04, *SD* = 1.95) (Lang, Bradley & Cuthbert, 2008) and depicted a neutral object, for example a tray of buttons or a blue mug on a wooden table. Neutral and non-traumatic picture stimuli were purposely selected not to be intrinsically intrusive. For each participant, two of the eight pictures were randomly selected and used as conditioned stimuli (CS) in the threat conditioning paradigm (acquisition, extinction and reinstatement).

Table 1

Valence, Arousal and Dominance Ratings (n = 100) for IAPS Pictures Used as Conditioned Stimuli in Conditioning Paradigm

	Valence	**Arousal**	**Dominance**
Buttons	5.32 (1.19)	3.20 (2.15)	5.82 (2.02)
Zipper	4.97 (0.76)	3.32 (1.96)	6.28 (1.72)
Fork	5.27 (1.09)	2.32 (1.84)	7.04 (1,84)
Clock	4.81 (1.92)	4.20 (2.40)	4.90 (2.32)
Mug	4.92 (1.00)	3.01 (1.97)	6.53 (1.92)
Book	5.19 (1.45)	2.61 (2.05)	6.35 (2.03)
Umbrella	4.72 (1.69)	2.61 (1.76)	5.55 (2.01)
Training shoes	4.82 (1.46)	3.18 (1.88)	5.90 (1.75)
Mean	*5.00 (1.32)*	*3.06 (2.01)*	*6.04 (1.95)*

2.2.2. Threat Conditioning

Each CS was presented on a computer screen for six seconds, followed by an inter-trial interval (ITI) of 10 seconds. The threat conditioning paradigm was programed using PsychoPy (Peirce et al., 2019) and presented on a desktop screen. SCR were captured by Biopac EL507 EDA electrodes and a Biopac MP150 system at a sample rate of 250 Hz (Biopac System, Inc., Goleta, CA, USA). SCR were acquired and scored using the Biopac AcqKnowledge software and the electric stimulations were delivered by a STM200 Biopac Systems with a 100 ms DC-pulse.

2.2.3. Self-Reported Baseline Measures

We assessed individual differences in pre-existing vulnerabilities that might strengthen the development of intrusive memories such as anxiety with the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983); general use of mental imagery with the Spontaneous Use of Imagery Scale (SUIS; Nelis et al., 2014); and a self-report measure of depressive symptoms using the Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001). Number of previous traumatic experiences was calculated using the Traumatic Experience Questionnaire (TEQ; Crawford et al., 2008). We assessed individual differences that might impact the effect of our social support manipulation such as empathy using the Balanced Emotional Empathy Test (BEES; Mehrabian, 1996); and a measure of an individual's tendency to recruit social resources to regulate their emotions using the Interpersonal Regulation Questionnaire (IRQ; Williams et al., 2018). For additional information, see the online supplementary materials (S1, supplementary Methods).

2.2.4. Intrusive Memory Diary

Intrusive memories were defined to the participants as (sometimes clear, sometimes "fuzzy") mental images of the pictures stimuli they saw during the experiment [acquisition and extinction], which might pop into their mind, without expecting them to, throughout daily life. This definition of intrusive memories has been used in previous associated studies (Holmes et al., 2010; Iyadurai et al., 2019; James, Lau-Zhu, Tickle, et al., 2016). We consider intrusiveness in terms of the involuntary, unwanted nature of the recollection (involuntary memory rather than deliberate memory retrieval).

The diary consisted of an electronic survey sent by email every morning, which participants could open and answer from a computer and/or a mobile phone. With the help of four reminders set on their mobile phone (morning, afternoon, evening and night), participants were told to report intrusive memories that appeared in their mind unexpected (i.e. involuntarily recalled), but not those which were deliberately recalled or triggered by the phone reminders. As they opened the diary, they were first asked to report how many intrusive memories they had during the specific time frame (during the night; get-up time to midday, midday to 5pm; 5pm to 11pm) and then to write one entry for each intrusive memory, even if they had the same intrusive memory several times. They were also asked to indicate ‘0’ if no intrusive memories had occurred. Participants were asked to write a brief description (free report) of each intrusive memory (e.g. “a blurry blue mug on a brown table”), which was used to verify whether the intrusive memory was of one of the two picture stimuli (CS) each participant saw. Each participant’s diary was discussed with the participant at the end of their participation when they returned to the lab at day 8, for possible clarifications of unclear entries. The brief descriptions of the intrusive memories were extracted from the diary and categorized by the experimenter into whether they matched or not with the CS+ and CS- that a given individual had seen (e.g. a clock, zipper, button, see Table 1).

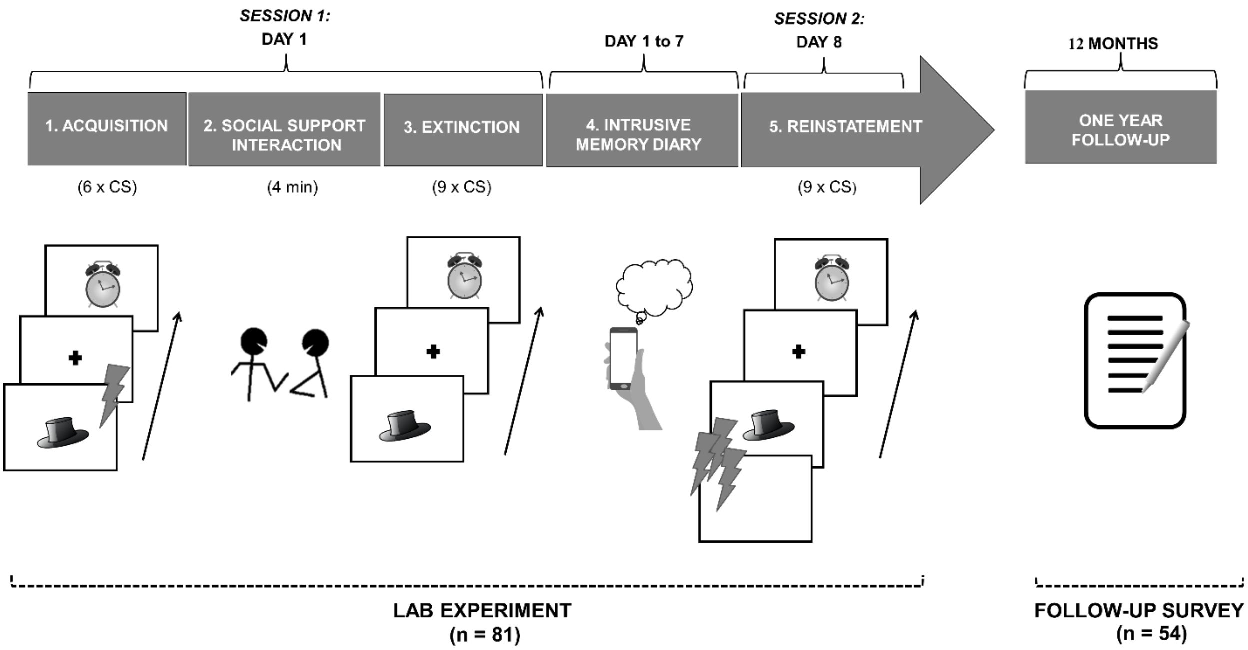
The instructions and the protocol for used of the intrusive memory diary were adapted for electronic format using Karolinska Institutet Survey and Report computer program (Artologik, version 23, Survey & Report, Artisan AB) based on earlier studies using a paper-based intrusive memory diary (Holmes et al., 2004; James et al., 2016).

2.3. Procedure

The study design consisted of a mixed design with three between-subjects conditions (types of social support; supportive social interaction, unsupportive social interaction and not social interaction) and two within-subjects conditions (conditioned stimuli; CS+ and CS-), which is described below and illustrated in Figure 1.

Figure 1

Schematic Overview of the Experimental Procedure Including Threat Conditioning and Intrusive Memory Monitoring.



Note. The experimental procedure consists of a two-session laboratory experiment taking place across eight days (Day 1 and Day 8) and a one-year follow-up survey. (1) During acquisition, participants saw two consecutive picture stimuli, six times each, each presentation separated by a grey screen with a cross (intertrial interval). One picture stimuli was followed by a shock (CS+) and one never followed by a shock (CS-). (2) The social support interaction takes place during a 3-4 minutes break, participants were randomized to experience a supportive social interaction, unsupportive social interaction or no social interaction. (3) During extinction, participants see the same two picture stimuli, nine times each, without receiving any shocks. (4) Participants answered the electronic intrusive memory diary during seven days. (5) Participants came back to the lab and were presented with a grey screen and three unexpected electric stimulations, followed by nine presentations of the two picture stimuli, without receiving any shocks. Finally, the one-year follow-up electronic survey was sent via email, 12 months after their participation.

2.3.1. Day 1

Session 1 was divided into three phases: threat acquisition, social support interaction and threat extinction. To measure SCR two electrodes were attached to the participant's fingers of their left hand and one shock-electrode to their right lower arm. The intensity of the electrical stimulations was calibrated for each participant to a level that was uncomfortable but not painful for them, using an ascending staircase procedure. At the start of the experiment, the participant was instructed both verbally and on the computer screen to focus on the presented pictures. No information was provided regarding the picture stimuli-shock contingency.

Threat Acquisition. Two picture stimuli were shown six times each. To establish acquisition of threat conditioning, one of the two picture stimuli was randomly selected to be the CS+ (picture stimuli reinforced with a shock during four out of the six presentations) and the other one to be the CS- (never reinforced). At the end of the presentation, the participant was informed on the computer screen that there would be a break.

Social Support Interaction. Social support was operationalized as two social support conditions (supportive social interaction vs negative social support) providing two qualitatively distinct social interactions aimed to induce positive and negatively valenced social experience, respectively. A third neutral condition was used as control group (no social interaction). These interactions (duration 3-4 min, $M = 3.61$, $SD = 0.36$) consisted of minimal verbal exchange and designed to provide informational (provision of information that can be used to guide and advice), instrumental (provision of concrete aid through material goods or physical assistance) and emotional support (verbal and nonverbal communication of empathy and care) (Hogan et al., 2002). We chose an in-person interaction with a stranger as opposed to an interaction with a social support figure or a support reminder, as we were primarily interested in testing an interaction similar to the one occurring between strangers after a traumatic experience (e.g. between a patient and medical staff in the waiting room at the emergency department). In fact, the objective of using a social support interaction with minimal verbal exchange was to aid the development of a supportive interaction given by laypeople, immediately after a negative experience, such as a trauma.

Immediately after acquisition, a second experimenter, who had not yet interacted with the participant, entered the room where the participant sat and administered one of three social interactions with the aim to provide a positive, negative or neutral (control) social interactive experiences (random assignment).

In the supportive social interaction condition, the participant was given social support, which consisted of (1) *informational support* by being informed about what was going on during the break and how long the break would last; (2) *instrumental support* by being offered a glass of water, being informed that the door of the experimental room would be left open to let fresh air into the room during the break, and at the end of the break, being informed about the possibility of pressing a button to continue the experiment when they felt ready; (3) *emotional support* by asking them if they felt alright while having a hand on their shoulder; keeping eye contact with them and smiling to them; asking them if they felt good to continue the experiment. This condition aimed to induce a positive state.

In the unsupportive social interaction condition, the participant was given unsupportive social interaction and aimed to induce a negative state. This interaction consisted of (1) the second experimenter not providing the participant any information about what was happening during the break; did not answer any questions the participant might have; the participant was informed that the time they would spend in the room was unclear; (2) a dirty glass of water not intended for the participant was put next to them by the second experimenter without explanation; (3) the door of the room was left open without any explanation, the second experimenter walked in and out the room several times without talking directly to them or having eye contact.

Finally, in the neutral control condition (no social interaction – NSI), the participant received, by the second experimenter, a commercial furniture catalogue to read, which was taken back at the end of the four minute break. Allowing experimenter entering the room without having social interaction with the participant provided an experimental design control for the presence of someone in the supportive social interaction and unsupportive social interaction conditions. The furniture catalogue was meant to equalize the level of distraction between the conditions during the break, whilst controlling for the neutral and low arousing content (furniture). There was no difference between the three conditions in the average duration of the interactions (supportive social interaction, M = 3.61, SD = .34); unsupportive social interaction, M = 3.73, SD = .38 and no social interaction , M = 3.63, SD = .32) ($F(2, 80) = .76$, $p = .46$, $\eta_p^2 = .02$). A link to video illustrations of the three experimental condition interactions can be found in the online supplementary materials.

Threat Extinction. After the short break, extinction of learned threat consisted of nine non-reinforced presentation of the two pictures serving as CS.

Manipulation Checks And Self-Reported Baseline Measures. Once the electrodes had been removed, the participant was asked to answer two manipulation checks: First, questions about contingency awareness between the CS and the US. Then, questions about their perception of support received during the break to determine whether participants in the different social support conditions perceived our social support manipulation differently (i.e. perceived support manipulation check, details found in the online supplementary materials). Finally, the participant answered a set of self-reported baseline questionnaires and was given the instructions on how to use the intrusive memory diary.

2.3.2. Day 1 to 7

The participant completed the online daily intrusive memory diary containing four parts (night, morning, afternoon and evening). The participant was asked to report the number of intrusive memories of the picture stimuli (CS) they have had during a specific time frame (during the night; get-up time to midday, midday to 5pm; 5pm to 11pm).

2.3.3. Day 8

At session 2, the participant returned to the same experimental room as session 1 and was informed that the settings of the experiment would be the same. They were asked to pay attention to the pictures shown on the computer screen.

2.3.4. Reinstatement

Reinstatement of learned threat consisted of a presentation of a grey screen and three unexpected electric stimulations. Following this, the two CS (presented during acquisition and extinction) were presented nine times without shock reinforcement. Importantly, because the reinstatement phase took place seven days after the extinction phase, our procedure could not exclude the potential impact of spontaneous recovery (Norrholm et al., 2006).

As part of the debriefing, the participant was asked for possible clarifications of unclear entries in their intrusive memories diary and was debriefed on the nature of the study. The participant was then reminded that they will be contacted 12 months later for a follow-up with questions regarding their participation in this study and was finally thanked and reimbursed for their time with two cinema vouchers.

2.4. Statistical Analysis

SCR data during threat conditioning, reinstatement and intrusive memory data were checked for possible univariate outliers within each social support condition on each of the main outcome measures. One outlier (for the supportive social interaction condition on intrusive memories) was identified as having > 3 *SD* from the mean of its group. Following previous studies using measure of intrusive memory (Holmes et al., 2004; Lau-Zhu et al., 2019), the outlier was changed to one unit larger than the next most extreme score in the distribution (Tabachnick & Fidell, 2007). All analyses used a significant alpha threshold of 0.05 and include measures of effect size. The Benjamini-Hochberg procedure was used to control for multiple comparisons and the false discovery rate was set to 5% (Benjamini & Hochberg, 1995). Non-parametric tests were used if assumptions of normality were violated. Statistical analysis were performed in R version 3.6.0 (R Core Team, 2019) and IMB SPSS version 24 (IBM Corp., 2016).

2.4.1. Threat Conditioning

To establish acquisition, extinction and reinstatement of threat response to the CS, the SCR were measured for the presentation of each CS as the base-to-peak amplitude of the largest response in a time window between 0.5 seconds to 4.5 seconds following stimulus onset. All SCR with an amplitude below 0.02µS, or with absence of any SCR within the time window mentioned above, were set to 0 (Dunsmoor, Murty, et al., 2015; Golkar et al., 2012). Raw SCR data from acquisition, extinction and reinstatement were separately squared root transformed to normalize the distribution and were analyzed separately. Identification of non-learners and non-responders for exclusion was done based on these squared-transformed SCR data.

Assessment of acquisition and extinction of threat conditioning was carried out using linear mixed effects models (LMEMs, 'nlme' package of R software ; Pinheiro, Bates, DebRoy & Sarkar, 2020). This model allowed us to analyze the data by dealing with the non-independence due to the repeated measure design (Bauer & Curtin, 2017) and takes into account both the variation explained by the independent variables (fixed effects) and the variation introduced by random sampling associated participants (random effects). To assess acquisition of learned threat, we modelled the main effects of CS-type, Trials and Condition and their interactions as fixed effects. CS-type included two levels (CS+ and CS-), Trials included six levels (trials 1 to 6) and Condition included three levels (supportive social interaction, unsupportive social interaction and no social interaction). As random effects we included intercepts for subjects, as well as by-subject slopes. A similar model was used to assess extinction of learned threat with main effects of CS-type, Trials and Condition and their interactions as fixed effects, and random intercepts and slopes for subjects. Confidence intervals were calculated for each effect as measure of effect size. Reinstatement of threat at Day 8 was defined as the increase in SCR from the end of extinction at Day 1 (extinction block 3) to the beginning of reinstatement at Day 8, right after three unannounced shocks (reinstatement block 1) (Haaker et al., 2014). Assessment of reinstatement of learned threat achieved using a repeated measure GLM of the SCR with CS-type and Trials (mean of last three trials of extinction and mean of first three trials of reinstatement) as within-subjects factors and Condition and number of intrusive memories for CS+, and for CS-, as between-subject factors.

2.4.2. Intrusive Memories

Our main outcome was the total number of intrusive memories summed across the seven day diary period (Holmes, Brewin, & Hennessy, 2004; Holmes et al., 2009; James et al., 2016; Lau-Zhu, Henson, & Holmes, 2019), also analyzed for each of the two picture stimuli (CS+ and CS-) separately. That is, intrusive memories included in the analyses consisted of those containing the two pictures stimuli (CS) that the participant saw during threat conditioning at Day 1 and later intruded spontaneously (involuntarily) in the form of mental images.

To test the hypothesis that a neutral picture followed by a shock (CS+) would generate more intrusive memories than the picture never followed by a shock (CS-), we used linear mixed effects models (LMEMs, Pinheiro et al., 2020). We modelled CS-type as fixed effect with intercepts for subjects as a random effect. This analysis in essence consists of a t-test that takes into account random variation between individuals.

Further, to explore potential covariates that might explain number of CS+ and CS- intrusive memories, we added one covariate at a time as fixed effect and its interaction with CS-type to the previous model.

Finally, to test the hypothesis that, compared to no social interaction, supportive social interaction would lead to a lower number of intrusive memories and unsupportive social interaction would lead to a higher number of intrusive memories, we carried out two statistical procedures using linear mixed effects models (LMEMs) on the count data (i.e. including only participants who reported having at least one intrusive memory, n = 56). First, we tested whether adding social support conditions to the simplest model containing CS-type only improved model fit (i.e. how well the model explains the variance in our data). Next, due to our study design, we tested a nested model, that is, a model where CS-type is nested within the social support conditions. More specifically, this is a model where the variance of social support condition on intrusive memories is considered within the variance of the nested factor (CS). Both steps are reported and compared. The model with the best model fit is further explained. We also modelled subjects as random effect and calculated confidence intervals as a measure of effect size.

3. Results Lab Experiment

3.1. Demographics and Social Support Manipulation Check

Individuals in the three social support conditions did not differ with regard to the baseline self-report measures (Table 2). The manipulation checks indicated that the social support manipulation was successful, with a significant difference in perceived support between the support conditions ($F(2, 80) = 57.12$, $p < .00$, $\eta_p^2 = .59$). Multiple comparisons showed that, as predicted, compared to controls (NSI; $M = 5.07$, $SD = .96$), individuals in the supportive social interaction reported a significantly higher level of perceived support ($M = 7.05$, $SD = .88$, $p < .001$), and individuals in the unsupportive social interaction reported significantly lower perceived support ($M = 4.22$, $SD = 1.15$, $p < .01$).

Table 2

Baseline Self-report Measures, Split by Social Support Interaction Conditions (n = 81)

	Supportive social interaction (n = 27)		Unsupportive social interaction (n = 30)		No social interaction (n = 24)		Between groups differences: Test values[a]	p-values	Effect Sizes[b]
	Mean	SD	Mean	SD	Mean	SD	F	*p*	η_p^2
Demographic characteristics									
Age	26.96	6.51	28.07	6.12	24.50	4.18	2.64	.07	.06
Gender (*male/female*)	12/15		13/16[1]		11/13		1.75[c]	.78	.78[d]
Ethnicity (*Caucasian/non-Caucasian*)	16/10 [2]		13/17		15/8[2]		3.06[c]	.21	.19[d]
Individual differences									
BEES	14.00	39.47	11.96	43.35	13.79	37.14	.02	.98	.00
IRQ	79.03	15.29	78.14	16.83	76.81	13.18	.12	.88	.00
Negative tendency	16.03	4.75	15.06	5.99	13.83	4.86	1.08	.34	.02
Negative efficacy	21.85	4.84	21.17	4.21	21.52	4.57	.15	.86	.00
Positive tendency	19.74	5.29	20.60	5.82	21.16	3.84	.03	.96	.01
Positive efficacy	21.48	4.30	21.33	4.42	19.86	4.54	.21	.80	.00
SUIS	36.77	6.18	38.96	8.27	38.85	7.10	.76	.47	.02
Anxiety measures									
STAI-S	44.24	4.98	42.96	4.86	43.61	5.21	.42	.65	.01
STAI-T	46.04	3.35	48.11	4.79	47.29	4.93	1.34	.26	.03
PHQ-9	5.91	4.01	8.25	6.12	7.31	3.38	1.55	.22	.04
Traumatic experience history									
TEQ	1.84	1.87	2.10	2.04	2.60	2.06	.92	.40	.02
Social Support manipulation check									
Perceived Support Scale Score	7.05	.88	4.22	1.15	5.07	.96	57.12	.00**	.59

Note. BEES = Balanced Emotional Empathy Test; IRQ = Interpersonal Regulation Questionnaire; SUIS = Spontaneous use of imagery scale; STAI-S = State-Trait anxiety inventory – State; STAI-T = State-Trait anxiety inventory – Trait; PHQ-9 = Patient

Health Questionnaire; TEQ = Traumatic Experience Questionnaire. [1] One gender unknown, [2] One unknown ethnicity. [a] One-way ANOVA, between groups comparisons, [b] Partial Eta-Squared, [c] Pearson Chi-square, [d] Cramer's V. *$p < .05$. **$p < .01$.

3.2. Assessment of Acquisition of Learned Threat

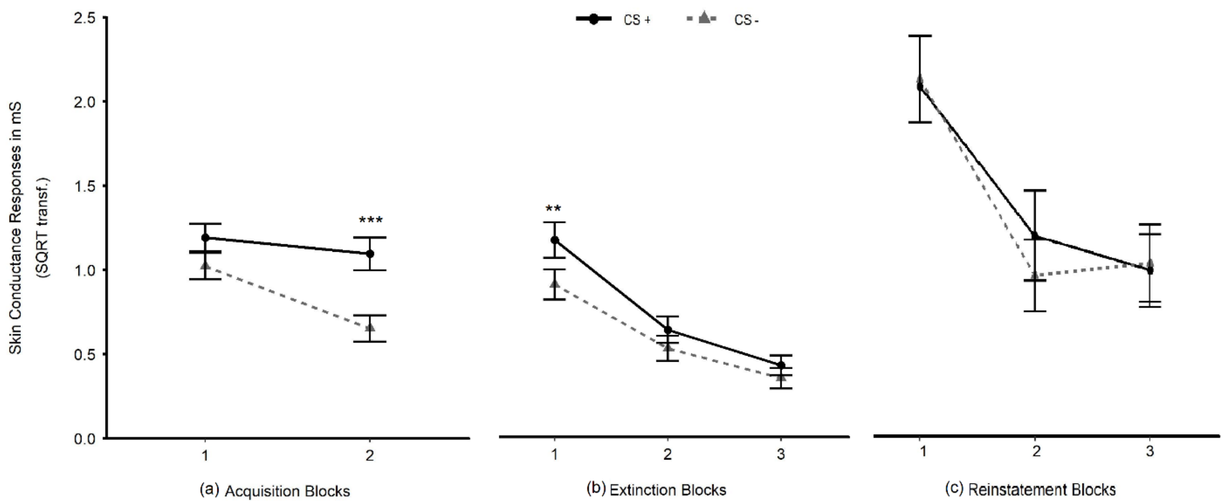
Analysis of SCR during threat acquisition using LMEMs indicated a change in SCR to the CS+ versus the CS- over time. This is illustrated by a significant effect of CS-type ($X^2(1) = 40.73$, $p < .0001$, $b = .03$, $SE = .13$, $t = .25$, 95% CI [-.22, .29]), of Trials ($X^2(1) = 24.30$, $p < .0001$, $b = .05$, $SE = .05$, $t = 1.01$, 95% CI [-.04, -.15]), and an interaction CS-type*Trials ($X^2(1) = 17.16$, $p < .0001$, $b = -.11$, $SE = .02$, $t = 4.12$, 95% CI [-.17, -.06]). This interaction, illustrated in Figure 2a, verified that learning occurred. As expected, there were no significant main effects of Condition ($p = .24$), nor were there Condition*CS-type ($p = .57$) and Condition*Trial interactions ($p = .08$), indicating that learning was equal across all conditions (Figure S3a).

3.3. Effect of Social Support on Threat Extinction

Analysis of SCR during the threat extinction showed a significant effect of CS-type ($X^2(1) = 17.57$, $p < .001$, $b = -.32$, $SE = .09$, $t = 3.38$, 95% CI [-.51, -.13]), of Trials ($X^2(1) = 194.90$, $p < .001$, $b = -.16$, $SE = .02$, $t = 6.32$, 95% CI [-.21, -.11]), but not an interaction between CS-type*Trials type ($p = .08$). Figure 2b suggests that the difference between CS+ and CS- was stronger during the first block (first three trials) of extinction and decreased over time. Contrary to prediction, there was no significant effect of Condition ($p = .57$), nor were there interactions between Condition and CS-type ($p = .35$) or Condition and Trials ($p = .43$) (Figure S3b). This implies that different social support interactions did not have differential effects on participants' physiological responses to the presentation of the CS during extinction.

Figure 2

Block by Block SCR for CS+ and CS- during (a) Acquisition, (b) Extinction and (c) Reinstatement of Threat



Note. A block consists of the mean of three trials. (a) Indicates a learned threat response illustrated by a stronger SCR for CS+ than CS- at block 2. (b) Indicates an extinction of threat response illustrated by a stronger SCR for CS+ than CS- at block 1 and a non-significant difference in SCR between CS+ and CS- at block 2 and 3. (c) Indicates a return of threat for both CS, illustrated by the increase of SCR between the block 3 of extinction and the block 1 of reinstatement. No significant differences between the social support interaction conditions were found in neither of the experimental phases. Figures showing the trial by trial SCR for each threat conditioning part and for each support condition separately are found in Figure S1 to S3 in the online supplementary materials. Error bars represent ± 1 SEM. ** $p < .01$, *** $p < .001$.

3.4. Intrusive Memory Diary

Across all conditions, 78% of the participants sent back their electronic diary at the end of each day. The other 22% verbally informed the experimenter (at day 8), that in the days they did not send their diary, they did not have any intrusive memories. These empty entries were replaced by 0. There was no difference in compliance (i.e. of sending back the diary at the end of each day) between the Conditions (supportive social interaction = 73%, unsupportive social interaction = 80% and no social interaction = 80%).

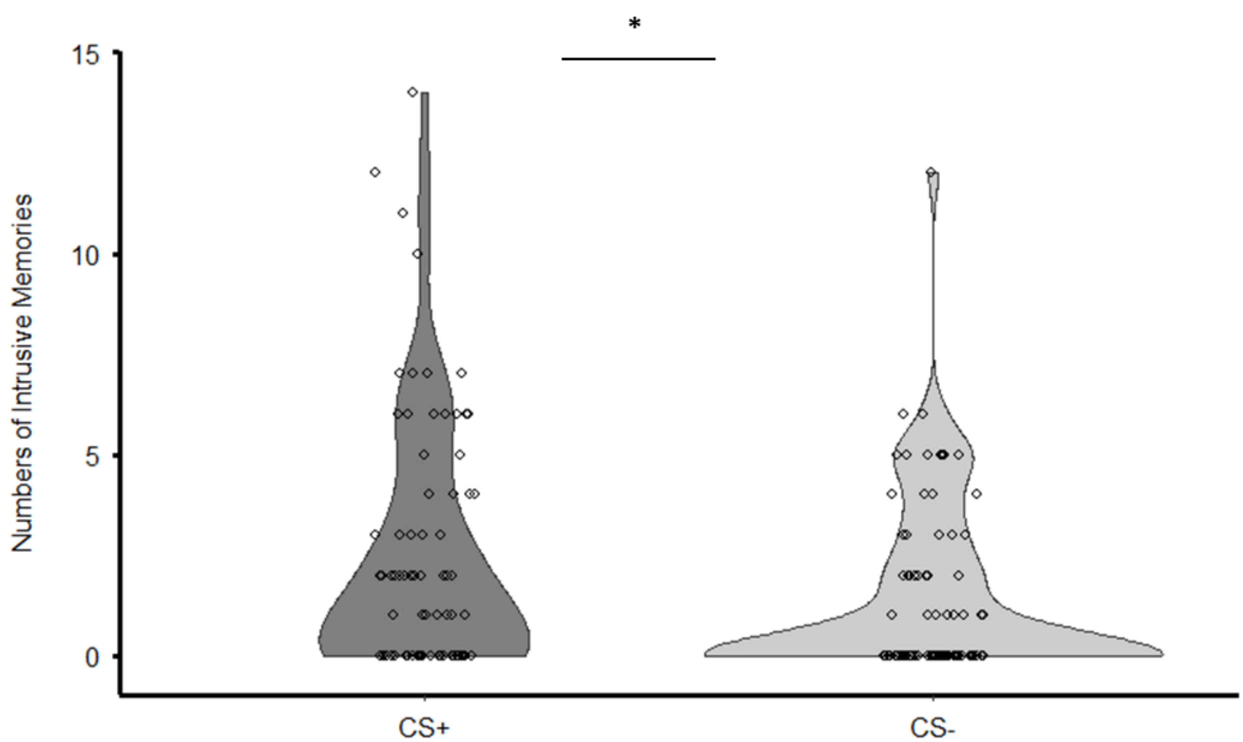
Examples of the intrusive memories of the picture stimuli as written in the diaries are “part of a clock”, “A very vague image of the zipper” and “the tray of buttons”. A total of 85% of intrusive memories were successfully matched by the experimenter to the two picture stimuli each participant saw, indicating that a majority of the intrusive memories reported came from the threat conditioning paradigm session. Other intrusive memories than of the two picture stimuli were not included in the analyses. Overall, around 70% of the participants reported experiencing at least one intrusive memory of the picture stimuli, with a mean number of 3.75 intrusive memories (*SD* = 4.18; range = 0-16).

3.5. Threat Conditioning Generates Intrusive Memories

Critically and as predicted, overall, participants reported 69 % more intrusive memories of CS+ (*M* = 2.35, *SD* = 3.09) than CS- (*M* = 1.39, *SD* = 2.17) ($X^2(1) = 6.35$, $p < .05$, $b = -.96$, $SE = .38$, $t = 2.50$, 95% CI [-1.72, -.20]), as illustrated in Figure 3.

Figure 3

Violin Plot of Number of Intrusive Memories for the CS+ and the CS- Reported over Seven Days in the Diary



Note. Significant difference between the total number of intrusive memories for CS+ and CS-, across conditions combined. The dots illustrate individual data points for CS+ and CS- intrusive memories. * $p < .05$.

3.6. Effects of Individual Differences on Total Number of Intrusive Memories

To examine whether potential pre-existing vulnerabilities such as state and trait anxiety, depressive mood and number of previous traumatic experiences could explain the total number of CS+ and CS- intrusive memories, we entered them in our model as covariates. Each covariate and its interaction with CS-type were entered as fixed effect into separate models and compared to the simplest model containing CS-type only.

Due to their low inter-correlation (*r* = .17) and low multicollinearity (VIF = < 10), STAIS and STAIT were added together to the simplest model. Significant interactions were found between CS-type and STAIS ($X^2(1) = 20.62$, $p < .001$, $b = .05$, $SE = .01$, $t = 4.45$, 95% CI [.03, .08]) and CS-type and STAIT ($X^2(1) = 8.23$, $p < .01$, $b = .02$, $SE = .01$, $t = 2.81$, 95% CI [.01, .04]) on the number of intrusive memories. This suggests that both higher state and trait anxiety scores were linked to a greater number of intrusive memories for CS- compared to CS+ (Figure S4a and S5 in the online supplementary materials). No significant contributions of any other baseline measures or SCR during threat conditioning were found to explain CS+ and CS- intrusive memories (all *ps* > .06).

3.7. Effects of Individual Differences on Having Intrusive Memory at all

To examine whether potential pre-existing vulnerabilities could explain the appearance of intrusive memories (i.e. whether participants reported having any intrusive memories or not), we split the sample into two groups. We looked at these pre-existing vulnerabilities on participants who had zero intrusive memories (*n* = 25) and participants who had at least one intrusive memory (*n* = 57). Please note that the following results did not survive correction for multiple comparisons. Mann-Whitney U test indicated that those with (at least one) intrusive memory had a greater number of reported trauma experiences in the past (TEQ score) (*M* = 2.49, *SD* = 2.10) compared to those with zero intrusive memories (*M* = 1.40, *SD* = 1.47), *U* = 471.00, *z* = -2.29, *p* < .05, *r* = .25. Participants with (at least one) intrusive memory had significantly lower trait anxiety (STAI-T score) (*M* = 46.28. *SD* = 4.61) compared to those with zero intrusive memories (*M* = 48.78, *SD* = 4.25), *U* = 406.50, *z* = -2.20, *p* < .05, *r* = 25.

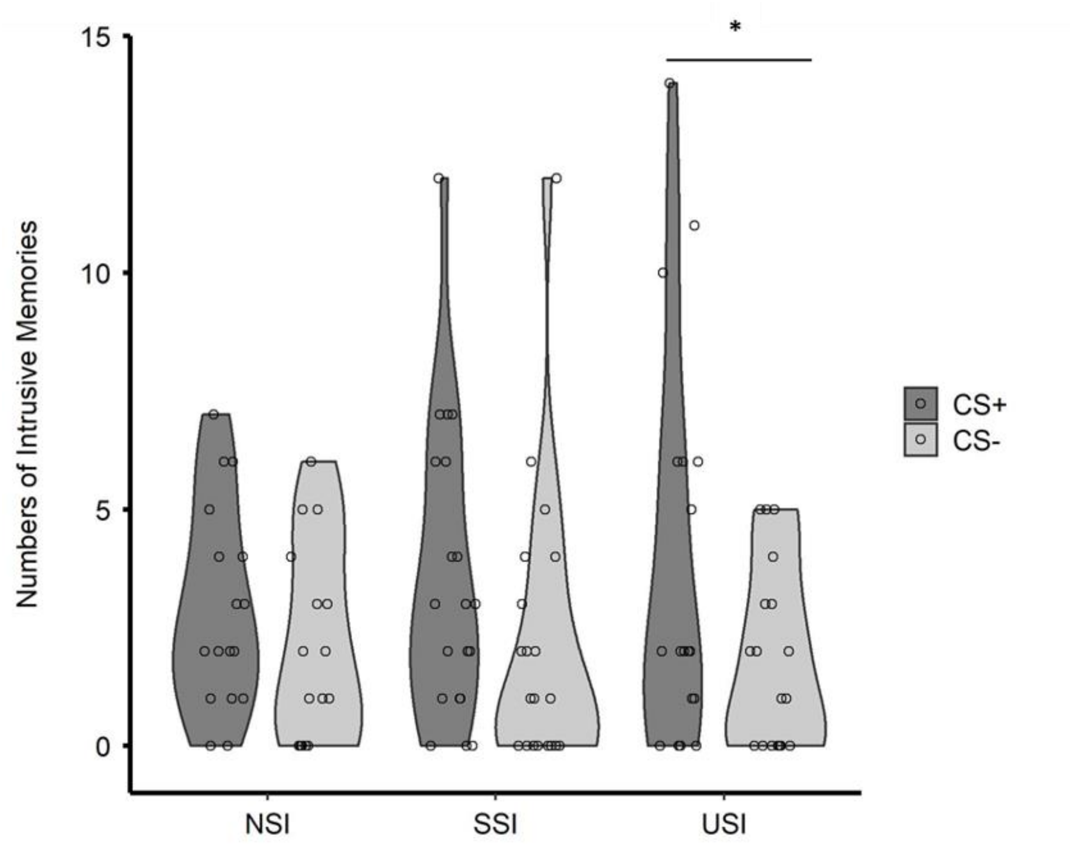
3.8. Effect of Social Support on Number of Intrusive Memories

To test the hypothesis that, compared to no social interaction, supportive social interaction would lead to a lower number of intrusive memories and unsupportive social interaction would lead to a higher number of intrusive memories, we carried out two statistical procedures using linear mixed effects models (LMEMs). First, the results from the LMEM showed that social support conditions alone did not improve model fit ($X^2(2) = .21$, $p = .89$) as compared to the simplest model (CS-type only). Simple group comparisons corroborated this, indicating that contrary to predictions there was no difference between conditions in total number of intrusive memories (no social interaction, *M* = 3.62, *SD* = 3.28; supportive social interaction, *M* = 4.29, *SD* = 4.33; unsupportive social interaction , *M* = 3.43, *SD* = 4.55; *p* = .71).

Next, we tested we tested a nested model where CS-type is nested within the social support conditions. LMEMs indicated that, compared to the simplest model, the nested model improved model fit ($X^2(3) = 8.13$, $p < .05$), meaning that it better explains the variance in our data. As illustrated in Figure 4, the effect of condition on intrusive memories depends on the kind of CS. Our results showed that there was no difference in number of intrusive memories between CS+ and CS- in the no social interaction condition (*b* = -.64, *SE* = .98, *t* = .65, *p* =.51, 95% CI [-2.56, 1.26]) and in the supportive social interaction condition (*b* = -1.42, *SE* = .88, *t* = 1.61, *p* =.11, 95% CI [-3.15, -.29]) but highlighted a difference between the number of intrusive memories for CS+ (*M* = 3.88, *SD* = 4.19) and CS- (*M* = 1.82, *SD* = 1.91) in the unsupportive social interaction condition (*b* = -.2.05, *SE* = 0.95, *t* = 2.15, *p* =.03, 95% CI [-.3.91, -.19]) suggesting that unsupportive social interaction led to stronger image-based conditioned threat memories. Follow-up analyses were run to examine the difference in number of intrusive memories for CS+ and CS- using differential scores (CS+ minus CS-) for each group. This showed that unsupportive interaction (M = 1.23, SD = 3.66) did not have a significantly higher CS differential score than active social support (M = 1.11, SD = 3.84, *p* = .99) or than no social interaction (M = .45, SD = 2.75, *p* = .69).

Figure 4

Violin Plot of Social Support Conditions and CS Indicating a Nested Effect on Intrusive Memories



Note. As compared to the control condition (no social interaction, NSI), supportive social interaction (SSI) did not differ in number of intrusive memories for CS+ and CS-. Unsupportive social interaction (USI), however, showed a significant difference between the number of intrusive memories for CS+ and CS-. The dots illustrate individual data points for CS+ and CS- intrusive memories. The dots illustrate individual data points for CS+ and CS- intrusive memories. * $p < .05$.

3.9. Effect of Social Support and Intrusive Memories on Reinstatement of Threat

Contrary to predictions, a repeated measure GLM showed a significant effect of Blocks ($F(1,40) = 14.63$, $p < .0001$, $\eta_p^2 = .26$), but not of CS-type ($p = .88$) or Condition ($p = .57$; Figure S3c). This suggests a non-differential reinstatement of threat response for both CS for all conditions (Figure 2c) and implies that reinstatement of learned threat did not occur. Adding number of intrusive memories as covariates showed no significant effects of CS+ ($p = .59$) and CS- ($p = .59$) intrusive memories on the return of threat response, and no significant interactions between number of intrusive memories, CS-type and Condition (all *ps* > .39).

4. Discussion Lab Experiment

We examine whether threat conditioning could be used to generate intrusive memories of neutral conditioned stimuli. As predicted and shown in Figure 3, across conditions, participants reported having significantly more intrusive memories of a neutral object (e.g. a blue mug) during the seven days following conditioning when previously paired with a shock compared to objects never followed by a shock. The greater number of intrusive memories to the CS+ versus CS- in this study provides further validation of the involvement of associative learning processes in the emergence of intrusive memories, and suggests that the encoding of conditioned threat responses also involves encoding mental images, which can become intrusive. Research has shown that brain activation at the time of encoding during trauma analogue (i.e. viewing of a traumatic film) can determine which moments of the film will later become intrusive (Bourne et al., 2013; Clark et al., 2016). Such work suggests that intrusive memories occur due to an improved encoding of particular moments that later become intrusive memory. We would therefore reason that through the learning paradigm, CS+ is better encoded and therefore results in more intrusive memories. Unfortunately, the current study cannot disentangle whether this improved encoding of the CS+ is due to the increased attention to CS+ compared to CS-, or due to the distress during the learning task due to the shocks. However, we suggest that the predictive function of CS+ to shocks might have improved visual encoding of CS+. Future work should further investigate the encoding of the imaged-based threat memory during threat conditioning, to shed light on the underlying mechanisms of how a neutral image can transform into an intrusive visual image. While the emotional features of the intrusive memories were not measured in the current study, future work could include measures capturing the emotions associated with the intrusive memories.

Our results showed that both higher state and trait anxiety were related to a greater number of intrusive memories of the CS-. This result supports previous findings in the conditioning literature showing an increased threat response to CS- in clinically anxious compared to non-anxious individuals (Duits et al., 2015). One interpretation is that such enhancement of threat response to CS- is related to an impaired inhibition of threat response to safety cues (Jovanovic et al., 2013) and/or a greater tendency to generalize conditioned threat response (Craske et al., 2012; Lissek & Grillon, 2010), which could explain the greater number of CS- intrusive memories in more anxious individuals in our sample.

Next, our lab experiment aimed to assess whether different social support interactions (supportive social interaction , unsupportive social interaction or no social interaction) after acquisition of learned threat influenced the expression of the emotional memory measured by skin conductance responses and number of intrusive memories of the CS during the seven days following conditioning. Contrary to our predictions, different social support interactions did not modulate participants' physiological responses (i.e. during extinction and reinstatement). Therefore, although our social support manipulation check indicated that the three groups perceived receiving different social support interactions (supportive social interaction> no social interaction > unsupportive social interaction), this difference did not translate into differences in physiological indices of learning, suggesting that the type of social support interactions operationalized in this study did not disrupt learned physiological arousal.

Further and contrary to our expectations, compared to no social interaction, supportive social interaction did not decrease and unsupportive social interaction did not increase the number of intrusive memories. However, results showed that unsupportive social interaction resulted in a larger CS+ and CS- difference in number of intrusive memories as compared to the no social support condition. This suggests the possibility that an actively unsupportive interaction can cause more involuntary image-based conditioned threat responses, possibly due to a stronger consolidation of visual threat memory following conditioning – though further investigation would be needed before any substantive conclusions on this can be made.

5. Method - One-Year Follow-Up

What is the impact of threat conditioning on the long-term expression of threat memories? Unpleasant stimuli (IAPS pictures) have been shown to be better recalled and more likely to generate intrusive memories up to a year after exposure (Bywaters et al., 2004) and subjective experience related to conditioning has been shown to be maintained up to a year after conditioning (Wiggert et al., 2017). Therefore, we carried out a one-year follow-up survey to examine whether intrusive memories of the CS might persist over time.

5.1 Participants

Fifty-nine of the 81 original participants (36 females) between the age of 18 and 40 years (*M* = 26.94, *SD* = 5.64) answered the one-year follow-up survey. In order to keep the same sample throughout, non-learner and non-responders from the lab experiment, were also excluded from the one-year follow-up sample. The final follow-up sample consisted of 54 participants (supportive social interaction, *n* = 18 (13 females); unsupportive social interaction, *n* = 19 (11 females, 1 unknown); no social interaction, *n* = 17 (11 females)).

5.2. Apparatus and Materials

All participants in the lab experiment were contacted by email 12 months after their participation by receiving the link to an online survey. The survey was created using Karolinska Institutet Survey and Report computer program (Artologik, version 23, Survey & Report, Artisan AB).

5.3. Follow-Up Survey

5.3.1. Free Recall

The first part of the survey investigated whether the picture associated with CS+ was better remembered than the picture associated with the CS-, and whether this potential effect would be related to the emotional value and vividness of the respective CS (Bywaters et al., 2004). Participants were asked to freely recall the picture stimuli they saw during the lab experiment previous year. For each picture stimulus they recalled, participants were then asked to report their vividness (1 = *Not vivid (I don't see the picture in my head)* to 7 = *Very vivid (I see the picture as vivid as actual vision)*), their valence (1 = *unpleasant/sad* to 9 = *feeling pleasant/happy*), their arousal level (1 = *Feeling calm/drowsy* to 9 = *Feeling alert/intense*), as well as their distress level of and emotional response to the picture stimulus (-10 = *Extremely negative* to +10 = *Extremely positive*).

5.3.2. Intrusive Memories

The second part of the survey investigated if participants had intrusive memories after their participation in the lab experiment. More specifically, participants were asked how many intrusive memories of each picture stimulus they had during the past year, how often they have had these intrusive memories (1 = *Never* to 6 = *Very frequently*) and how distressing those intrusive memories were (1 = *Not at all distressing* to 9 = *Very distressing*). Data on the exact content of these intrusive memories were not collected.

5.3.3. Recognition

The third part investigated if participants could correctly recognize the picture stimuli that served as the CS during the lab experiment. Participants were presented with eight images of objects (i.e., all images used in the Pavlovian threat conditioning paradigm) and asked to indicate whether they had seen each picture stimulus during the lab experiment or not. Further, they were asked to indicate the confidence level of their answer on a three-point scale (i.e., *not certain, quite certain, very certain*). To investigate if participants could correctly recall the CS+ they were further asked to indicate which of the presented picture stimuli was followed by a shock during the lab experiment.

5.3.4. Social Support

In the fourth part, participants answered a question about how much support they had received from the person who had entered the room during the break of the lab experiment (1 = *No support at all* to 9 = *Lots of support*). Demographic information (i.e., age and gender) was collected.

5.4. Statistical Analysis

Data were examined for potential univariate outliers on the number of intrusive memories at one-year follow-up and similar procedure for reducing the influence of outliers described earlier was used. One outlier was identified (in the supportive social interactioncondition) and was changed to one unit larger than the next most extreme score in the distribution (Tabachnick & Fidell, 2007). Due to unequal group sizes, non-parametric tests were performed. Mann-Whitney U tests were performed to compare the groups with regards to nominal and continuous dependent variables (i.e. SCR, STAI, PHQ-9 and TEQ) and chi-square tests were used for categorical dependent variables (i.e. performance in the free recall and recognition tasks) (or Fisher's exact test in case of small sample size). All analyses used a significant alpha threshold of 0.05 and include measures of effect size (rank-biserial for Mann-Whitney U tests and phi for chi-square tests). Statistical analyses were performed using IMB SPSS version 24 (IBM Corp., 2016).

To investigate potential predictors underlying why some individuals might continue to have intrusive memories during the following year, we split the sample into two groups. One group consisting of participants who continued to have intrusive memories (i.e. intrusive memories during both the seven-day lab experiment and at the one-year follow-up; n = 20) and another group of participants who did not (i.e. who only had intrusive memories during the seven-day lab experiment; n = 18). The remaining participants never had intrusive memories (n = 14). As we aimed to investigate why some might continue to have intrusive memories, two participants who did not have any intrusive memories during the seven-day lab experiment but reported having intrusive memories at one-year follow-up were excluded from the analyses. To identify potential predictors, the two groups were compared with regard to baseline self-reported measures (i.e., STAI, PHQ-9 and TEQ) and SCR during conditioning measured at Day 1 (mean CR during acquisition and mean CR during extinction). Next, to examine the relationship between the continuing having intrusive memories and memory performance, these two groups were compared on their performance on free recall and recognition of the picture stimuli.

In addition, similar analyses were undertaken comparing participants who reported never having intrusive memories (*n* = 14) with those who have had at least one intrusive memory at any point during the study (*n* = 36). These secondary analyses enabled us to determine if baseline self-reported measures, SCR and memory performance were linked to continuing having intrusive memories or simply the emergence of intrusive memories *per se*.

6. Results

6.1. Demographics

The one-year follow-up subsample did not significantly differ from the lab experiment sample in terms of age, gender, the distribution of the social support conditions and any of the baseline self-report measures (see Table S2 in online supplementary materials).

6.2. Intrusive Memories Reported at One-Year Follow-Up

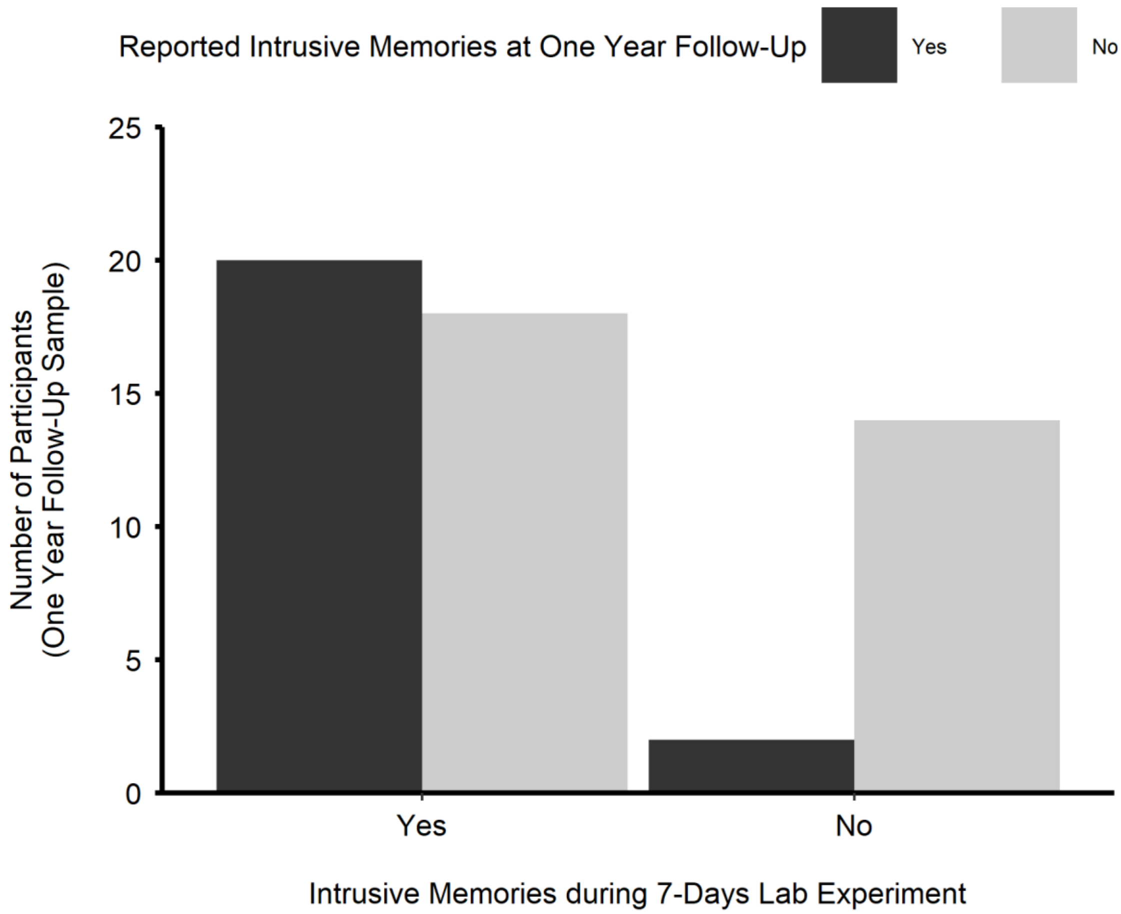
Overall, the mean number of intrusive memories during the following year was = 2.28 (*SD* = 4.76; range = 1 to 20), with numerically more intrusive memories for CS+ (*M* = 3.5, *SD* =4.72) than CS- (*M* = 2.40, *SD* = 4.62), although this difference was not statistically significant (t (19) = .73, p = .47, d = .23). Overall, intrusive memories were reported as having low distress level (*M* = 1.10, *SD* = .91, range .50 to 4.5) and low frequency (*M* = 1.32, *SD* = .61, range .50 to 2.5). Within those who reported intrusive memories at one-year follow-up, 50% reported intrusive memories of only the CS+, 25% of only the CS- and 25% of both stimuli.

Half of the participants who had intrusive memories during the lab experiment, reported, at the one-year follow-up, that they continued to have intrusive memories (*n* = 20), as illustrated in Figure 5. A chi-square test of independence indicated a significant relationship between having intrusive memories during the lab experiment and continuing to have intrusive memories (X^2 (1, N = 52) = 11.97, p <.01, *phi* = .48).

No significant relationship between the social support conditions (supportive social interaction, unsupportive social interaction and no social interaction) and continuing to have intrusive memories was found (X^2 (2, N = 38) = .38, p = .91).

Figure 5

Relationship Between Reporting Intrusive Memories During the Seven-Day Lab Experiment and Continuing Having Intrusive Memories (Reported at One-Year Follow-Up)



Note. Significant relationship between having intrusive memories during the seven-day lab experiment and continuing having intrusive memories, reported at one-year follow-up: 52.6% of the participants who had intrusive memories during the lab experiment continued to have intrusive memories (*n* = 20); 47.4% did not continue to have intrusive memories after the lab experiment (*n* = 18); 87.5% of the participants who did not have intrusive memories during the lab experiment reported at the one year follow-up that they did not have intrusive memories later on (*n* = 14); 12.5% (*n* = 2) who did not have intrusive memories during the lab experiment reported, at the one-year follow-up, having intrusive memories later on and were excluded in the analyses.

6.3. Predictors Underlying why Some Might Report, at One-Year Follow-Up, Having Continued Experiencing Intrusive Memories

To investigate why some might continue to have intrusive memories, we compared participants who reported having continued to experience intrusive memories versus those who did not. We investigated pre-existing vulnerabilities (self-reported measures reported at Day 1 of lab experiment), see Table 3. Two Mann-Whitney U tests of independence indicated that individuals who continued to have intrusive memories had significantly higher STAI-T scores (M = 47.37, SD = 3.13) than those who only had intrusive memories during the lab experiment (M = 43.66, SD = 3.49; U = 60.00, z = -2.90, $p < .01$, r = .48) as well as greater number of previous traumatic experiences (M = 2.78, SD = 1.68) than those who only had intrusive memories during the lab experiment (M = 1.58, SD = 1.87; U = 94.50, z = -2.16, $p < .05$, r = .35). The two groups did not significantly differ with regards to their CR during acquisition and extinction during Pavlovian threat conditioning (all $ps > .19$, see Table 3).

Table 3

Baseline Self-report Measures for One-Year Follow-Up Sample, Comparing Participants who Continued to Have Intrusive Memories (n = 20) to Those who did not (n = 18)

	Continued to have intrusive memories (n = 20)		Did not continue to have intrusive memories (n = 18)		Between groups differences		
					Test values	p-values	Effect Sizes
Social Support Conditions							
No social interaction	5		6				
Supportive social interaction	7		5		.48[c]	.78	.10[d]
Unsupportive social interaction	8		9				
	Mean	SD	Mean	SD			
Demographic characteristics							
Age	25.90	5.41	29.72	4.98	2.25[a]	.03*	.39[b]
Gender (*male/female*)	15/5		10/8[1]		1.59c	.20	.20[d]
Ethnicity (*Caucasian/non-Caucasian*)	7/12[2]		10/8		1.30[c]	.25	.18[d]
Anxiety measures							
STAI-S	44.50	5.24	41.17	5.73	112.00[a]	.07	.28[b]
STAI-T	47.35	3.13	43.66	3.49	60.00[a]	.00**	.48[b]
PHQ-9	7.00	4.45	5.00	3.65	105.50[a]	.18	.22[b]
Traumatic experience history							
TEQ	2.78	1.68	1.58	1.87	94.50[a]	.03*	.35[b]
SCR - threat conditioning							
CR Acquisition	.39	.43	.16	.73	151.00[a]	.39	.13[b]
CR Extinction	-.05	.39	.13	.47	135.00[a]	.18	.03[b]
Emotion ratings for recall							
Valence							
CS+	4.71	1.06	5.20	1.09	28.00[a]	.50	.12[b]
CS-	4.30	1.54	5.33	1.02	24.50[a]	.19	.04[b]
Arousal							
CS+	4.85	1.02	5.20	1.09	32.00[a]	.76	.14[b]

CS-	4.76	1.30	5.16	.98	30.50[a]	.41	.09[b]
Vividness							
CS+	4.50	1.09	4.00	.70	26.00[a]	.37	.06[b]
CS-	3.76	1.42	3.83	1.32	39.00[a]	1.00	.22[b]
Emotional response							
CS+	-.71	2.94	1.00	3.46	26.00[a]	.39	.07[b]
CS-	-.61	3.45	.83	2.56	28.50[a]	.35	.07[b]

Note. All measures were taken at Day 1 of the lab experiment. Continued to have intrusive memories = participants who reported having intrusive memories both during the seven-day lab experiment and during the following year. Did not continue to have intrusive memories = participants who only had intrusive memories during the seven-day lab experiment. STAI-S = State-Trait anxiety inventory – State; STAI-T = State-Trait anxiety inventory – Trait; PHQ-9 = Patient Health Questionnaire; TEQ = Traumatic Experience Questionnaire; CR Acquisition = Mean conditioned response during Acquisition; CR Extinction = Mean conditioned response during Extinction. [1] One gender unknown, [2] One unknown ethnicity. [a] Mann-Whitney U test, [b] Rank-Biserial, [c] Pearson Chi-square , [d] Phi, [e] Independent sample t-test, [f] Cohen's d. * $p < .05$. ** $p < .01$.

6.4. Relation Between Continuing to Have Intrusive Memories and Memory Performance

6.4.1. Free Recall of the Picture Stimuli

Overall, 82.7% of the participants who answered the one-year follow-up survey could correctly recall seeing at least one picture stimulus, of which 37.2% recalled only the CS + picture, 20.9% recalled only the CS- picture and 41.9% of the participants recalled both. There were no significant differences in free recall of only the CS+, only the CS- or both stimuli between participants who continued to have intrusive memories and those who did not (X^2 (2, N = 32) = 2.05, $p = .35$). As shown in Table 3, there were no significant differences in terms of valence, arousal, vividness or emotional response of the CS+ and CS- picture stimuli between these two groups (all *p values* > .19).

6.4.2. Recognition of Picture Stimuli

Overall, 96.2% of the participants could correctly recognize the at least one picture stimuli, 38% recognized only the CS + picture, 16% recognized only the CS- picture and 46% of the participants recognized both picture stimuli. There were no significant differences in how confident participants recognized the picture stimuli, between participants who continued to have intrusive memories and those who did not, i.e. *not certain* (X^2 (1, N = 7) = 2.10, p = .14), *quite certain* (X^2 (2, N = 7) = .19, p = .90), *very certain* (X^2 (2, N = 33) = 2.29, p = .31).

6.5. Relation Between Continuing to Have Intrusive Memories and Recognition of the CS+

Overall, 49% of participants correctly recognized which picture was followed by a shock (CS+) during the lab experiment, 19.6% incorrectly recognized CS- as the picture that was followed by a shock and 17.6% incorrectly recognized both pictures as being followed by a shock. There were no significant differences in correctly recognize which picture stimulus was followed by a shock between participants who reported, at the one year follow-up, continuing to have intrusive memories and those who did not (X^2 (3, N = 37) = 3.90, p = .29).

6.6. Emergence of Intrusive Memories versus Continuing to Have Intrusive Memories

Secondary analyses examined potential pre-existing vulnerabilities between participants who reported never having intrusive memories (i.e. neither during the seven-day lab experiment, nor at the one-year follow-up) with those who have had at least one intrusive memory (at any point). No significant differences were found between these two groups, i.e. STAI-S (U = 167.00, p = .19), STAI-T (U = 142.00, p = .06), PHQ-9 (U = 149.00, p = .31) and TEQ (U = 194.00, p = .20) or in SCR (CR acquisition, U = 263.50, p = .95; CR extinction, (U = 180.00, p = .07). Neither were there significant differences in terms of the emotional ratings of the picture stimuli (all *p values* > .10) nor in terms of free recall (X^2 (2, N = 43) = 3.93, p = .14) or recognition (all *p values* > .11) of the picture stimuli between these two groups. Finally, no significant differences in recognition of which picture stimulus was followed by a shock was found between these groups (X^2 (3, N = 51) = 2.84, p = .42).

7. Discussion - One-Year Follow-Up

In our one-year follow-up survey, we examined whether the intrusive memories generated by the threat conditioning paradigm persisted over a longer period of time, and investigated potential predictors underlying why some might continue to have intrusive memories. For that purpose, we compared participants who continued to have intrusive memories with those who did not.

As shown in Figure 5, half of the participants who had intrusions during the lab experiment, continued to have intrusions a year later. Although participants reported numerically more intrusions of CS+ compared to CS- at one-year, contrary to predictions, this difference was not significant. We found no effect of social support conditions on the persistence of intrusive memories. We refrain from interpreting this lack of effect due to the small sample sizes in each of the three conditions (no social interaction, N = 5; supportive social interaction, N = 7; unsupportive social interaction , N = 8).

As predicted, we found that continuing to have intrusive memories was related to particular pre-existing vulnerabilities: higher trait anxiety at baseline and greater number of previous traumatic experiences. These results support previous research showing that anxiety and prior exposure to trauma have been reported as pre-trauma factors associated with higher risk of developing PTSD symptoms (Ozer et al., 2008). Interestingly, these pre-existing vulnerabilities were not found in participants who, at the time of the one-year follow-up, had never experienced intrusive memories. This indicates that these predictors are most likely specifically related to continuing to have intrusive memories, rather than the emergence of intrusive memories. Contrary to predictions, there was no differences in state anxiety, depressive mood and in CR during threat conditioning between participants who continued to have intrusive memories and participants who did not.

Importantly, and contrary to our predictions, our one-year follow-up results showed no relationship between continuing to have intrusive memories and better memory performances (free recall and recognition) of the two picture stimuli or of the CS+. These findings are however consistent with the pattern of dissociation between intrusive memories and recognition performance found one week after exposure to experimental trauma (Lau-Zhu et al., 2019), and with the notion of multiple memory systems (Squire, 2004).

Importantly, due to the reduced sample size at one-year follow-up, these results must be interpreted with caution.

8. General Discussion

In the current study, we united the experimental and well-controlled benefits of Pavlovian threat conditioning with a clinical research approach to studying symptoms (intrusive memory diary) in addressing two key questions: Does threat conditioning generates intrusive memories that may persist? And, does social support modulate emotional responses?

8.1. Threat Conditioning Generates Persistent Intrusive Memories

As predicted, threat conditioning (with pictures of neutral objects and electrical stimulations) generated intrusive memories of the conditioned stimuli during the subsequent seven days, with more CS+ than CS- intrusive memories. Furthermore, our one-year follow-up indicated that these intrusive memories can persist over time.

An emerging body of evidence is now showing that associative processes contribute to the formation of intrusive memories (Franke et al., 2021; Miedl et al., 2020; Wegerer et al., 2013). Therefore, we reason that adding the measure of intrusive memories to a standard Pavlovian threat conditioning paradigm suggests one way that this paradigm can evolve, which would benefit clinical research in anxiety disorders and post-traumatic stress (both of which features intrusive mental images). Doing so may aid the translation from investigating basic mechanisms towards understanding processes involved in the phenomenology of psychopathology – such as the intrusive memories of an initially neutral object that springs to mind unbidden, and may cause distress.

Our results also indicated that, anxiety, which is associated with sensitivity to traumatic stress reactions (Clark et al., 2015; Laposa & Alden, 2008), was found to be linked to a greater number of intrusive memories of the CS-. This suggests that, similarly to the enhanced psychophysiological threat responses to CS- observed in anxious individuals, these individuals display a generalized imaged-based threat response to the safe stimulus and/or an impaired ability to inhibit image-based threat response to the safety cue. Moreover, our results showed that trait anxiety at baseline and greater number of previous traumatic experiences might explain why intrusive memories might persist over time. This informs us of possible risk factors that could help identify people after trauma who may be at risk for longer-term intrusive memories.

8.2. Experimental Manipulation of Social Support - Contrary to Predictions

During a negative experience, social support has been shown to buffer biological stress response (Ditzen & Heinrichs, 2014). However, whether a social interaction immediately after threat acquisition can alter the maintenance of stress response had, to our knowledge, not been tested. Contrary to our predictions, different social support did not influence participants' physiological responses (i.e. during extinction and reinstatement). Furthermore, compared to no social interaction, supportive social interaction did not decrease and unsupportive social interaction did not increase the number of intrusive memories of the CS. In this study, we used an in-person interaction with a stranger, i.e. the type of interaction that could take place directly after a stressful event such as a trauma, and did not see an effect of this social support manipulation. However, other studies which have examined the effect of the presentation of support figures (Hornstein et al., 2016) or attachment representations (Bryant & Foord, 2016) during an analogue for stressful event, have found a decrease in stress responses to negative stimuli. Therefore, this suggests the need for further research on the type of social support needed to disrupt memory consolidation.

Our results, suggest the possibility that unsupportive social interaction resulted in a relative difference between the number of CS+ and CS- intrusive memories, which suggests that an unsupportive social experience could enhance the consolidation of visual threat memory. Follow-up analyses using differential scores (CS+ minus CS-) however indicated that this difference was not significantly larger in the unsupportive social interaction group compared to the other two groups, meaning that this result must be interpreted with caution.

8.3. Research Implications

Clinicians and neuroscientists have long been interested in the translational potential of threat conditioning paradigms. Such paradigms have, however, rarely taken into account intrusive memories

(Fullana et al., 2019; Holmes et al., 2021; Visser et al., 2018), which are central symptoms of anxiety-related disorders or disorders after trauma such as PTSD (DSM-5; American Psychiatric Association, 2013). Indeed, the standard Pavlovian threat conditioning has been criticized and was (erroneously) assumed not likely to yield intrusive memories (James et al., 2016, p.107; Wegerer et al., 2013, p.2). Contrary to this, our findings suggest that this paradigm can indeed be used to investigate the intrusive image-based aspect of threat memories. Moreover, we demonstrate that the threat conditioning paradigm can produce both short and long-term intrusive memories.

An advantage of this model is the use of benign stimuli (e.g. a clock) that become intrusive through conditioning and the use of a mild aversive experience (uncomfortable but not painful electrical stimulations) while minimizing the influence of individual differences in pre-existing aversions and emotional learning history. This model therefore differs from the conditioned-intrusion paradigm (Franke et al., 2021; Wegerer et al., 2013) and the trauma film paradigm (James, Lau-Zhu, Clark, et al., 2016) that use intrinsically aversive stimuli (aversive film clips depicting interpersonal violence and blood) to generate intrusive memories in lab settings.

8.4. Clinical Implications

The current study offers a novel experimental psychopathology model of intrusive memories, which may particularly aid our understanding of previously neutral stimuli. By adding a measure of intrusive memories to a threat conditioning paradigm, these findings contribute to the development of an experimental approach linking experimental work to clinical developments (Holmes et al., 2018; Iyadurai et al., 2019; James et al., 2016).

Our results that a previously neutral object, such as a button can become intrusive, supports clinical findings demonstrating that images of neutral scenes or neutral objects, such as the light above the operating table (Horsch et al., 2017) or the rain falling onto the window of the car right before a car accident (Iyadurai et al., 2018) can later become intrusive when present during a real life traumatic event. A better understanding of the mechanisms underpinning the development of intrusive memories of neutral scenes or objects could improve the detection of specific images that might later become intrusive, and therefore aid the development interventions targeting specific hotspot scenes of the traumatic experience. Consequently, investigating how neutral stimuli become intrusive would also challenge at times the general misconception, that only aversive scenes can become intrusive. This would rather validate the lived experience of those who are experiencing intrusive memories whose content is benign per se but whose meaning and associated reactions feel aversive.

In our study, we are intrigued that unsupportive social interaction led to a stronger difference in number of CS+ and CS- intrusions. The negative impact of the unsupportive social interaction on adjustment after negative experience is consistent with the existing experimental and clinical literature, stating that unsupportive interactions can do further harm (Littleton, 2010; Zoellner et al., 1999). Brief intervention approaches, consisting of minimal verbal exchange, which can be delivered by lay people are needed to improve mental health worldwide (Holmes et al., 2018). While the form of social support developed in this study did not translate into beneficial effects, more experimental research targeting the modulating effect of social support interactions after a negative experience could help the development of delivery models improving post-trauma clinical care.

8.5. Methodological Limitations

Reinstatement of learned threat was used to investigate the effect of our social support manipulation on return of threat. Our results indicates an over-arousal response to the sudden presentation of the CSs after the three unexpected electric stimulations (Figure 2c). Due to the seven days following extinction, our results cannot distinguish the effect of spontaneous recovery from reinstatement. In fact, the non-differential return of threat might have been caused by the intrusion diary task taking place between conditioning and the reinstatement procedure. That is, by being asked to report potential intrusive memories of the CS, participants might have generalized the threat response to both CS. Future studies interested in the reinstatement of learned threat and using both Pavlovian conditioning and the intrusive memory diary, could include a control group where participants do not complete the intrusive memory diary, in order to identify whether reporting intrusive memories over a week leads to generalization of threat responses to both CS.

Additionally, it is possible that this over-arousal response is due to our specific reinstatement procedure, which was not preceded by a re-extinction procedure, i.e. presenting the CSs without reinforcement before the reinstatement procedure. The current design does not enable us to determine the cause of the non-differential responses that might be due to our reinstatement procedure, spontaneous recovery, the intrusive diary task or a combination of these. Future studies should include a re-extinction procedure (Haaker et al., 2014), which would aid the interpretation of the results.

Another consideration is our limited number of baseline measures, which did not cover the full range of potential factors influencing the emergence (or non-emergence) of intrusive memories or their maintenance over time. For instance, we reported that a greater number of previous traumatic experiences was associated with continuing to have intrusive memories. Our baseline measures did not however control for the possibility that individuals who had intrusions and a greater number of previous trauma, might have a better understanding of what an intrusive memory is, and could have led them to report more intrusive memories overall. The impact of past trauma in response to this experimental paradigm should be further investigated.

An additional consideration is the potential effect of the extinction procedure on intrusive memories. The current study looked at the effect of the social support interaction on extinction of learned threat, therefore we included an extinction procedure directly following acquisition of learned threat. However, extinction is known to weaken the CS-US association (Craske et al., 2018). The addition of second group of participants who underwent acquisition and social support interaction only would have informed us on the effect of extinction on intrusive memories formation (Franke et al., 2021).

Finally, a general consideration is the relative simplicity of the standard Pavlovian threat conditioning procedure as compared to the complexity of real world aversive experience. There is a tradeoff between complex paradigms mimicking the intricacy of our reality and simple, and well controlled, paradigms that can be generalized across situations. We hope that our experimental model will help to inform a wide range open questions in the clinic and beyond.

9. Conclusion

The Pavlovian threat conditioning has long proven to be a useful translational model for the development of anxiety disorders, and here we have demonstrated that this paradigm can generate intrusive memories of neutral images, which may persist over time, such as a clock or a button. Our results indicating that Pavlovian threat conditioning can generate intrusive memories brings new opportunities to unite the benefits of a well-controlled experimental conditioning paradigm with clinical research approach to studying psychopathological symptoms.

CRediT authorship contribution statement:

Lisa Espinosa: Conceptualization, Data curation, Methodology, Formal analysis, Visualization, Writing – original draft. **Michael B. Bonsall:** Formal analysis, Supervision, Writing – review & editing. **Nina Becker:** Methodology, Visualization, Writing – review & editing. **Emily A. Holmes:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Andreas Olsson:** Conceptualization, Funding acquisition, Methodology, Supervision, Project administration, Writing – review & editing.

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Open science practices:

Key data, instructions to experimenters and participants, statistical scripts, and relevant material presented in this article will be made publicly available via Open Science Framework upon request to reviews and accessible at https://osf.io/5nq8z/ (note that training to use such methods from the primary authors is advised). This study was not pre-registered.

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