International Journal of Psychophysiology 166 (2021) 9–18

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

# Interfering with fear memories by eye movement desensitization and reprocessing

Lena Jellestad [a], Thomas Zeffiro [a,b,c], Marco Piccirelli [d], Jolanda Malamud [a], Benedikt B. M. Klimke [a], Katrin Rauen [e], Michael Rufer [f], Scott P. Orr [g], Christoph Mueller-Pfeiffer [a,*]

[a] Department of Consultation- Liaison Psychiatry and Psychosomatic Medicine, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[b] Neurometrika, Potomac, MD, USA
[c] University of Maryland School of Medicine, Baltimore, MD, USA
[d] Department of Neuroradiology, Clinical Neuroscience Center, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[e] Department of Geriatric Psychiatry, Psychiatric Hospital Zurich & Institute for Regenerative Medicine, University of Zurich, Switzerland
[f] Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Zurich, Switzerland
[g] Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

ARTICLE INFO

*Keywords:*
Memory consolidation
Memory reconsolidation
Fear conditioning
Skin conductance
Posttraumatic stress disorder (PTSD)

ABSTRACT

*Objective:* Pharmacologic and behavioral interventions that block reconsolidation of reactivated fear memory have demonstrated only limited success in modifying stronger and long-standing fear memories. Given the efficacy of Eye Movement Desensitization and Reprocessing (EMDR) in treating PTSD, pursuit eye movements are a promising and novel intervention for studies of human memory reconsolidation. Here, we examined the efficacy of pursuit eye movements in interfering with reconsolidation of conditioned fear memories.

*Methods:* We conducted a 3-day differential Pavlovian fear conditioning procedure in healthy adults, using videos of biologically prepared stimuli (tarantulas), partly reinforced with electrical shocks while recording skin conductance response (SCR) as a measure of autonomic conditioned responses. Fear conditioning was performed on Day 1. On Day 2, 38 participants were randomized into groups performing pursuit eye movements either immediately after fear memory reactivation, when the fear memory was stable, or 10 min later, when the fear memory was assumed to be more labile. On Day 3, fear memory strength was assessed by SCR to both reactivated and nonreactivated fear memories.

*Results:* Strong differential conditioning to the spider stimuli were observed during both fear acquisition and fear memory reactivation. Reactivated fear memory conditioned responses of participants performing pursuit eye movements after a 10-min delay were significantly smaller in the reinstatement phase (0.16 μS; 95% CI [0.02, 0.31]).

*Conclusions:* Pursuit eye movements were effective in reducing fear-conditioned SCR in reinstatement. This result supports the theoretical proposition that EMDR can interfere with reactivated fear memory reconsolidation.

## 1. Introduction

Memory consolidation is a time-dependent stabilization process leading to permanent storage of newly acquired memories. Consolidation processes involve stabilization of changes in synaptic efficacy, which are dependent on neural production of new RNA and proteins (Kandel, 2004). Reactivation of a consolidated memory can return the memory to a labile state from which it must be restabilized in order to persist. This stabilization process has been termed "reconsolidation". Like consolidation, reconsolidation requires protein-dependent synaptic plasticity for renewed storage of the memory.

Manipulating these phenomena may be useful in clinical contexts. Various pharmacologic and behavioral interventions can modify or block the reconsolidation process in animals (Nader and Hardt, 2009). Based on animal and human reconsolidation studies it is believed that a window allowing destabilization of the fear memory trace lies between 10 min and 1 h after reactivation (Jones and Monfils, 2013). Although extinction can reduce, or even eliminate, conditioned fear, it typically does so by inhibiting the expression of fear memories, not by erasing them. As such, extinguished fear may relapse under various conditions

* Corresponding author at: University Hospital of Zurich, Department of Psychiatry and Psychotherapy, Culmannstrasse 8, 8091 Zurich, Switzerland.
*E-mail address:* christoph.mueller-pfeiffer@access.uzh.ch (C. Mueller-Pfeiffer).

https://doi.org/10.1016/j.ijpsycho.2021.04.006
Received 6 October 2020; Received in revised form 16 April 2021; Accepted 19 April 2021
Available online 24 April 2021

including renewal, i.e., encountering of the conditioned stimulus (CS) in a new context which can provoke fear recovery (Bouton, 2004; Maren et al., 2013; Vervliet et al., 2013), or reinstatement, i.e., encountering the US associated with a conditioned and extinguished stimulus in absence of the CS itself (Bouton, 2004; Bouton and Bolles, 1979; Westbrook et al., 2002). This return of conditioned and extinguished fear, hence, can rise major challenges to therapies employing extinction in e.g., anxiety disorders or posttraumatic stress disorder (PTSD). In contrast to extinction, reconsolidation blockade or interference is believed to erase, or at least diminish, fear memory traces (Pedreira and Romano, 2013).

In contrast to the hundreds of animal studies conducted in the last decade, only about a dozen studies have investigated reconsolidation of a reactivated fear-memory in healthy humans. These studies commonly employed designs involving Pavlovian differential fear conditioning on the first day, memory reactivation followed by a memory-weakening intervention on the second day, and memory strength testing on the third day. Inherently fear-irrelevant geometric stimuli are often used as conditioned stimuli (CS) and electric shocks or sound bursts are used as unconditioned stimuli (US). Potentiation of the eyeblink startle response and/or skin conductance response (SCR) often serve as measures of conditioned responses (CR).

Propranolol, a beta-adrenergic blocker, given prior to memory reactivation can eliminate subsequent startle fear responses in healthy individuals (Kindt et al., 2009; Sevenster et al., 2012, 2013; Soeter and Kindt, 2010, 2011). Also, propranolol administration prior to a traumatic memory reactivation sessions using written trauma narratives once a week for 6 consecutive weeks reduces symptom levels in PTSD patients more than placebo (Brunet et al., 2018). However, the effect of propanolol application in the latter study was measured using clinical parameters of PTSD symptoms rating. Conceivably, other factors in this study design may have contributed to PTSD symptom reduction.

In contrast, a behavioral approach for interfering with memory reconsolidation could involve extinction training, consisting of repeated presentations of unreinforced CS while a reactivated memory is still in a labile state (Schiller et al., 2010). Although this behavioral intervention yielded mixed results, some studies have shown associated abolition of SCRs (Oyarzún et al., 2012; Schiller et al., 2010; Steinfurth et al., 2014).

A difficulty associated with the most common procedures for testing reconsolidation blocking interventions for clinical applications is that fear memories resulting from traumatic experiences as in patients with PTSD are generally stronger and longer standing than laboratory fear memories induced in healthy individuals. PTSD may involve overly consolidated and persistently disturbing memories that will not fade (Keane et al., 1985). Fear memories established using naturalistic stimuli may result in memories that are better analogues to those resulting from pathological fear conditioning. Therefore, their use may result in more successful translation of the tested interventions to clinical treatment studies. Recently, we developed a novel experimental assay in which the relative strengths of various pharmacological and behavioral reconsolidation-based interventions can be compared (Spring et al., 2015). By incorporating several innovative design modifications into a differential Pavlovian fear conditioning design, we were able to create stronger fear memories in typical human participants. First, we enhanced CS ecological salience by not using still pictures (Kindt et al., 2009; Soeter and Kindt, 2010), but 12-s, high-definition video clips of crawling tarantulas. As already described by Seligman in his concept of biological preparedness (Seligman, 1971), it is precisely evolutionary sources of fear (e.g., dangerous animals) that favor the development of a strong fear activation and conditioning, even though nowadays contemporary hazards (e.g., motorcycles, cars) are much more likely to be a cause of potential trauma (Mineka and Öhman, 2002). Second, we limited our participant sample to candidates who fell within the upper half of the distribution of typical participants on a spider phobia questionnaire, for whom the CSs are likely to be especially salient. Third, in order for a participant who completed the initial acquisition phase of the experiment to proceed to the remaining phases, we required that they show strong evidence of conditioning to two different CS+ stimuli applying a stringent cut-off (Spring et al., 2015). Using the present experimental design, one-time pre-reactivation propranolol 10 min after fear memory reactivation failed to diminish conditioned strong fear memories (Spring et al., 2015). The same is true for extinction training performed 10 min after fear memory reactivation (Fricchione et al., 2016) that had no measurable reconsolidation-blocking effects on fear conditioned SCRs. One explanation for the failure of propranolol and extinction training to weaken fear memory in these studies is that these interventions may not have been powerful enough to affect the strong fear memories created with this novel procedure. These results motivated a search for alternative, more efficacious, interventions.

Eye Movement Desensitization and Reprocessing (EMDR) has proven to be effective in PTSD treatment (Bisson and Andrew, 2007), possibly by blocking memory reconsolidation (Oren and Solomon, 2012). Embedded in a standardized psychotherapy treatment protocol, desensitization and reprocessing of traumatic memories is effected by volitional triggering of a target memory, followed by pursuit eye movements repeated until a substantial reduction of subjective distress is achieved (Shapiro, 2001). A series of randomized-controlled trials conducted since the introduction of EMDR in 1989 reveals compelling evidence that EMDR is effective in treating PTSD with effect sizes for traumatic stress symptom reduction following treatment of −1.40 (standardized mean difference), which is similar to Prolonged Exposure and Cognitive Processing Therapy (Bisson and Andrew, 2007). In fear conditioning and extinction paradigms, prior research has demonstrated effects of EMDR (Rousseau et al., 2019) and bilateral alternating stimulation of the eyelid mimicking EMDR (Wurtz et al., 2016) in PTSD patients. In these studies, neutral visual images (Rousseau et al., 2019) and images of a Rorschach inkblot test (Wurtz et al., 2016) served as conditioned stimuli. Its effectiveness makes EMDR and its components a promising therapeutic candidate worthy of systematic testing of its ability to interfere with memory reconsolidation.

We tested pursuit eye movements, a core feature of EMDR, as a reconsolidation-based intervention for reducing the effects of fear conditioning memories during renewal and reinstatement in typical humans, using biologically prepared CSs in fear-sensitive subjects, incorporated in our novel differential Pavlovian fear conditioning design. For this, we performed pursuit eye movement after fear memory reactivation without delay (control condition) and with a 10-min delay (active condition) prior to fear memory testing during renewal and reinstatement. We hypothesized that during both, renewal and reinstatement, fear-conditioned SCRs in the active condition would be reduced by performing pursuit eye movements 10-min after reactivation - during the time when a reactivated fear memory is assumed to be in a labile state (Jones and Monfils, 2013).

## 2. Method

### 2.1. Participants

Participants were recruited from a pool of healthy participants identified from previous research studies and advertising. We included male and female participants between 18 and 60 years of age with manageable, non-phobic fear of spiders, as determined by scores above the mean (male: 8.06; female: 10.46) on the German-adapted Spider Phobia Questionnaire (SPQ) (Hamm, 2006) and the absence of specific spider phobia criteria from the Structured Clinical Interview for DSM-5 Axis I Disorders (SCID-I) (American Psychiatric Association, 2013). Prior to enrollment, participants were screened by email for the following exclusion criteria: 1) a current or past neurological or other medical condition affecting the brain, 2) current use of vasoactive or psychoactive medication, 3) current psychiatric disorders, 4) inability to follow the procedures of the study, e.g. due to language problems, 4)

pregnancy. Participants deemed to be eligible based on pre-screening information were scheduled for a diagnostic assessment for current psychiatric disorders using the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997).

Among the 155 participants enrolled, 107 (69%) were excluded prior to experimental procedures because they exhibited inadequate differential conditioning (see Stimuli), and 5 (3%) dropped out. Of the 43 remaining participants, five did not complete the procedure or had inadequate SC data quality, resulting in a final sample of 38 (Fig. 1). Sociodemographic data and mean SPQ scores are presented in Table 1. The study protocol was approved by the Institutional Review Board of the Canton of Zurich, Switzerland. All participants provided written informed consent according to the Helsinki Declaration.

**Table 1**
Demographic characteristics of the sample.

| Group | | | | | |
|---|---|---|---|---|---|
| Measure | Delay($N = 19$) | | No Delay ($N = 19$) | | $p$ |
| | Mean | SD | Mean | SD | |
| Age (years) | 24.47 | 5.62 | 23.05 | 5.08 | 0.419 |
| Education (years) | 15.05 | 2.82 | 15.53 | 4.18 | 0.685 |
| Spider Phobia Questionnaire | 16.40 | 3.97 | 18.71 | 4.68 | 0.379 |
| | N | % | N | % | $p$ |
| Female | 16 | 42.1 | 17 | 44.7 | 1.000 |

### 2.2. Approach for testing the persistence of the (latent) fear memory after the intervention

Traditionally, the persistence of the (latent) fear memory following extinction is demonstrated by experimental manipulations that succeed in reviving its expression. These manipulations include: 1) waiting a sufficient period of time for the conditioned response (CR) to reappear (spontaneous recovery) (Bouton, 1993; Pavlov, 1927; Rescorla, 2004); 2) presenting the CS in a context other than the context in which the CR was extinguished (renewal) (Bouton, 2004; Maren et al., 2013; Vervliet et al., 2013); 3) administering the US alone and then re-testing for the CR (reinstatement) (Bouton, 2004; Bouton and Bolles, 1979; Westbrook et al., 2002); and 4) showing that the CR to a previously conditioned and then extinguished CS is more readily re-acquired (savings) (Bouton, 2002). In contrast to extinction, a fear memory that has been reduced by blocking its reconsolidation typically does not show these four phenomena. Hence, renewal and reinstatement were used for testing whether pursuit eye movements during reconsolidation impacted the persistence of the fear conditioning memories. In contrast to our previous study (Spring et al., 2015), where reinstatement was tested in 2 trials after presenting the shock alone, reinstatement was here tested in 12 trials to increase statistical power for detecting potential group differences.

As previously (Spring et al., 2015), we used SCR for measuring CR. SCR is considered to be a very robust and direct measure of sympathetic activity (Wallin, 1981) with superior properties of reflecting PTSD associated fear, more than e.g., eye blink startle (Spring et al., 2015). As an objective parameter, SCR reflects fear response more reliable than e.g., subjective fear ratings.

### 2.3. Stimuli

In the differential Pavlovian fear conditioning design that we used, there was one non-reinforced stimulus (CS-) and two reinforced stimuli (CS + R, CS + N). Adequate differential fear conditioning was defined as a SCR difference between a CS+ and CS- >0.1 μS (Spring et al., 2015), which was tested in the psychophysiological laboratory prior to the experimental procedure. The aim of this screening procedure was to

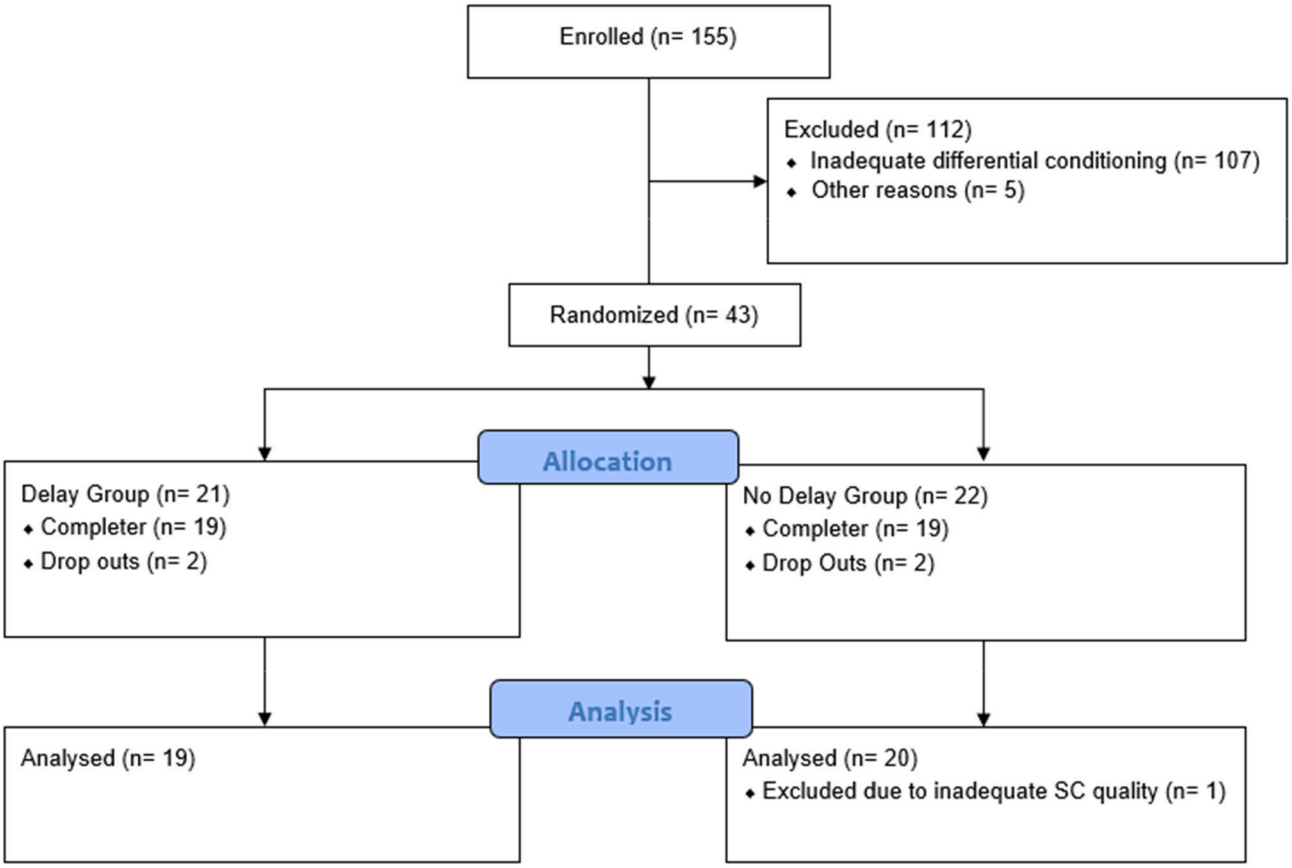


**Fig. 1.** Flow chart of study participants.

identify participants with high SC reactivity to biologically prepared fear-relevant stimuli before entering the experimental phase. The screening procedure used videos of spiders in natural outdoor contexts as the CSs, the experimental procedure used spider videos in indoor contexts. For the pre-experimental conditioning assessment, subjects were given instructions similar to those given on Day 1 of the experimental phase. See also supplemental information describing task procedures.

Stimuli in the experimental procedure were the same as previously used by Spring et al. (2015), comprising nine high-definition video clips (Virtually Better Inc., Decatur, GA) depicting one of three tarantulas shown in one of three contexts: kitchen, living room, and office (Fig. 2, top half). The use of the different contexts on Day 1 has less relevance for the current study than for those studies that were originally used to test mechanisms of extinction, i.e., inhibition of the original CS-US association (Pavlov, 1927) vs. unlearning of the original CS-US association (Rescorla and Wagner, 1972). Because our procedure follows that of previous reconsolidation work by Spring et al. (2015) and Fricchione et al. (2016), we chose to use the same conditioning paradigm for better comparability.

Two of the three tarantulas always served as a CS+, either the to-be-reactivated CS+ (CS + R) at Day 2 or the not-to-be-reactivated CS+ (CS + N). The third tarantula served as the CS−. The tarantula used to represent the CS−, CS + R, and CS + N was the same across participants. Video clips included 4 s of context alone with no tarantula, followed by 8 s of context plus tarantula. CS+ presentation was partly reinforced in acquisition (i.e., 63%). The CS- was never followed by shock. A 20-s interval between stimulus presentations consisted of a black screen. A

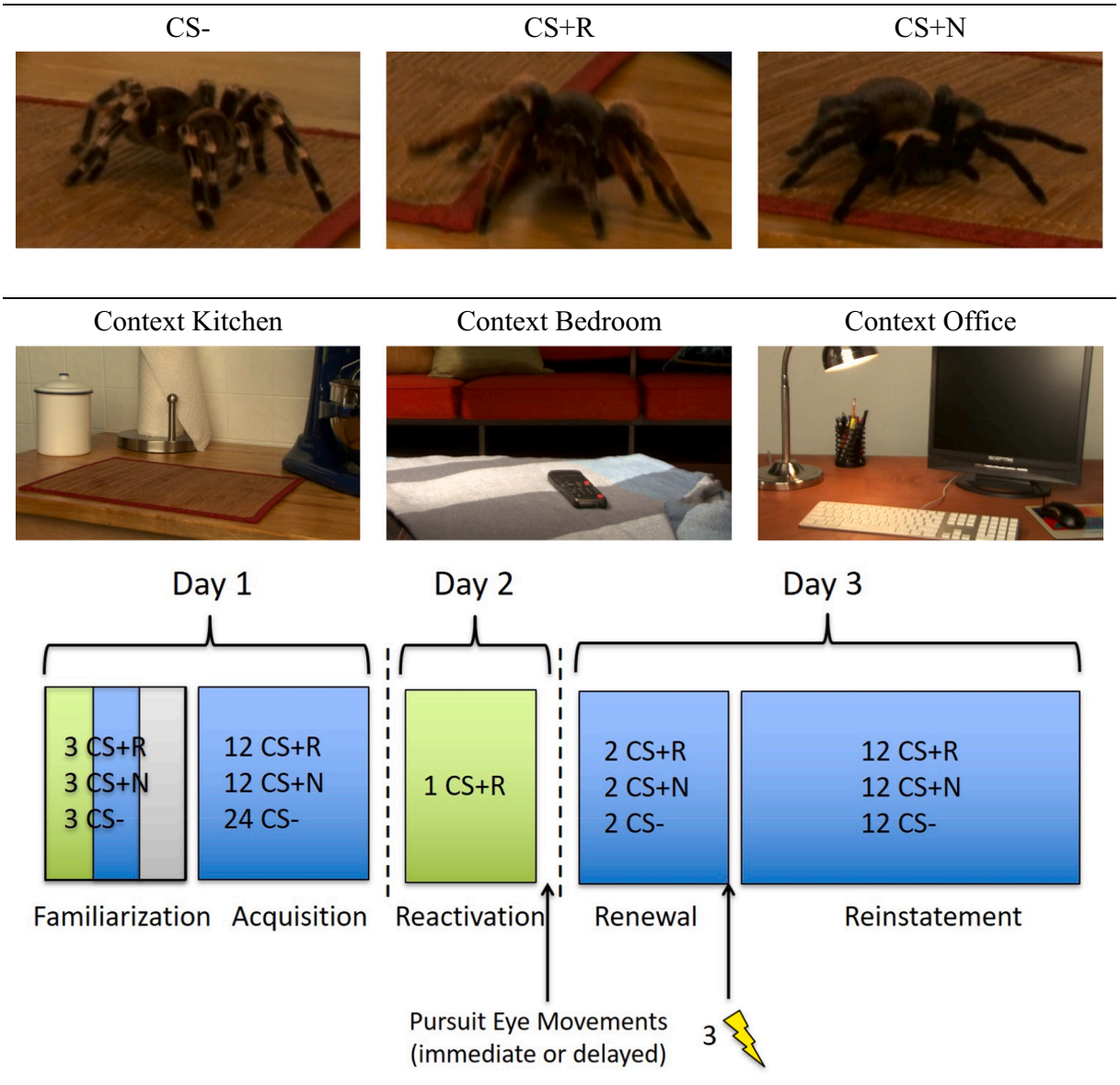


**Fig. 2.** Depiction of tarantula and context stimuli (top half) and three-session differential fear conditioning procedure (bottom half). Fear conditioning occurs on Day 1 using two different conditioning stimuli (CS+, with CS + R = CS+ reactivated; CS + N = CS+ not reactivated.). Trials were partly reinforced (i.e., 63% reinforcement, acquisition). One of the two CS + s (CS + R) was reactivated on Day 2, followed by ten 30 s sets of pursuit eye movements, either 0 or 10 min later. On Day 3, post-intervention reactivity to the conditioned stimuli was tested. Lightning bolts represent unsignalled presentations of the US alone. Shading colors represent the context in which the stimuli were presented: blue = kitchen, green = living room, grey = office. Video clips included 4 s of context alone with no tarantula, followed by 8 s of context plus tarantula. CS+ presentation was partly reinforced. The CS- was never followed by shock. A 20 s interval between stimulus presentations consisted of a black screen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

"highly annoying, but not painful" 0.5 s electrical shock was used as US, varying in intensity from 30 to 150 V according to the level set by each participant. Average level of intensity across participants was 80 V. The procedure was implemented using *E*-Prime Professional 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA).

### 2.4. Experimental phases

The experimental phases comprised a screening procedure, followed by the experimental procedure spanning three consecutive days (Fig. 2, bottom half). Experimental procedures were performed during fMRI with a 5-min baseline period to record physiological levels and a 10-min resting scan prior to the experimental procedures. fMRI results are not reported in this paper.

### 2.5. Fear conditioning screening procedure

Subjects who were eligible based on psychometric assessment performed a differential fear-conditioning procedure using video clips of spiders as conditioned stimuli. The procedure consisted of two sequential components: (1) three unreinforced presentations of each CS (habituation), followed by (2) eight presentations of each CS+, with five of the CS + R and CS + N presentations followed by shock (i.e., 63% reinforcement, acquisition). CS + R and CS + N were presented separately in blocks and interspersed pseudo-randomly with eight presentations of CS−. The order of presentation of CS + R and CS + N trial blocks was counterbalanced across subjects. Subjects who did not meet the defined cutoff for demonstrating a differential conditioned response (Spring et al., 2015) were withdrawn prior to Day 1. Subjects who met the cutoff were randomized to either the active or control conditions for the experimental procedure.

### 2.6. Day 1 (habituation, acquisition)

Day 1 comprised the same fear conditioning procedure as in the screening procedure except that 1) no context only stimuli were presented, and 2) 12 (instead of 8) trials of each CS were presented during acquisition with a 63% reinforcement rate. Day 1 CS presentations occurred in all three contexts during habituation, and in the kitchen context during acquisition.

### 2.7. Day 2 (intervention)

Day 2 consisted of a single, unreinforced presentation of the CS + R video clip, followed by no delay (control condition) or a 10-min delay (active condition) (Schiller et al., 2010). Other than the delay, which distinguished the two conditions, the eye movement intervention was the same in the two conditions. Specifically, it consisted of ten 30-s sets of pursuit eye movements that were separated by a fixation point presented for 20 s. The duration of the eye movement intervention was 6 min. For the pursuit eye movements, subjects were instructed to pursue a horizontally moving white dot (1 Hz) on a black background. Day 2 CS + R presentation took place within the living room context.

### 2.8. Day 3 (renewal and reinstatement phase)

Day 3 consisted of three sequential components: (1) two unreinforced presentations of each of the CS + R, CS + N, and CS− pseudo-randomly interspersed (renewal test), and (2) three unsignaled presentations of the US alone, followed by (3) twelve unreinforced presentations each of the CS + R, CS + N, and CS− pseudo-randomly interspersed (reinstatement test). Ordering of CS + R and CS + N presentations, within the full set of trials that included CS− presentations, was counterbalanced across subjects. All Day 3 CS presentations occurred in kitchen context.

### 2.9. Task procedures

Prior to the experiment, participants viewed still images of the three tarantulas serving as CSs, accompanied by these instructions: "During the experiment, it will be important that you are able to tell these spiders apart. To do this, try focusing on the legs. For this spider, note the alternating black and white stripe pattern. For this spider, note the orange highlights. For this spider, note that the legs are solid black." Participants were connected to the shock stimulator and SC recording electrodes and were instructed to lay still, keep their eyes open, and be attentive to the stimuli presented on the screen. After completing the experimental procedures, participants were debriefed.

### 2.10. Electrical shock deliverance and acquisition of physiological data

The US was delivered using a Biopac transcutaneous aversive finger stimulator (STMISOLA) through shock electrodes attached to the middle segments of the second and third fingers on the hand opposite to that on which the SC recording electrodes were attached. SC responses were recorded using a Biopac modular instrument system (Biopac Systems, Inc., Goleta, CA, USA) with an MRI-compatible electrodermal activity amplifier (EDA100C-MRI) using disposable radiotranslucent Biopac electrodes (EL509) filled with isotonic gel placed on the hypothenar surface of the subject's nondominant hand. The SC signal was sampled at 1000 Hz and digitized by an analog-to-digital converter (MP150). The analog amplifier low-pass cut-off frequency was 1 Hz for the EDA100C-MRI.

### 2.11. Data analysis

#### 2.11.1. Analysis of psychophysiological data

SCR for the CS interval was calculated for each trial by subtracting the mean SC during the 2 s prior to CS onset (context alone presentation) from the peak SC during the 8 s CS interval. These differences reflect changes in SC beyond those resulting from presentation of context alone. In the screening procedure, the SCR data were scored to determine whether a definable differential SCR was obtained for both the CS + N and CS + R during the acquisition phase. Averaging SCRs across respective CS+ and CS− trials, we calculated a difference score between the CS+ and CS− trials.

#### 2.11.2. Statistical methods

Differences in sociodemographics and SPQ scores between groups were tested using *t*-tests for dimensional variables and chi-square tests for nominal variables. For testing differences in SCRs to CS + R relative to CS + N between groups, we conducted a separate linear mixed model on SCRs during acquisition, renewal, and reinstatement with stimulus type (CS + R, CS + N), group (delay, non-delay) as fixed effects and subject as a random effect. To assess group differences in reactivation, we conducted a linear regression model on SCRs to CS + R with group as fixed effect. We calculated 95% CIs for estimates obtained from linear mixed models.

## 3. Results

### 3.1. Acquisition (Day 1) and reactivation (Day 2) of CS

CS + R (blue) and CS + N (red) were associated with larger SCRs (0.44, 95% CI [0.22, 0.67] and 0.28, 95% CI [0.01, 0.57] μS, respectively; Supplemental Table 1), compared to their respective CS- (green) trials during acquisition on Day 1, indicating successful fear conditioning (Fig. 3).

SCRs associated with CS + R and CS + N during acquisition were not significantly different (Table 2, Figs. 4 and 5), which suggests that the strength of fear conditioning was similar in both groups. On Day 2, SCR associated with the reactivated CS + R was on average 0.50 μS (95% CI

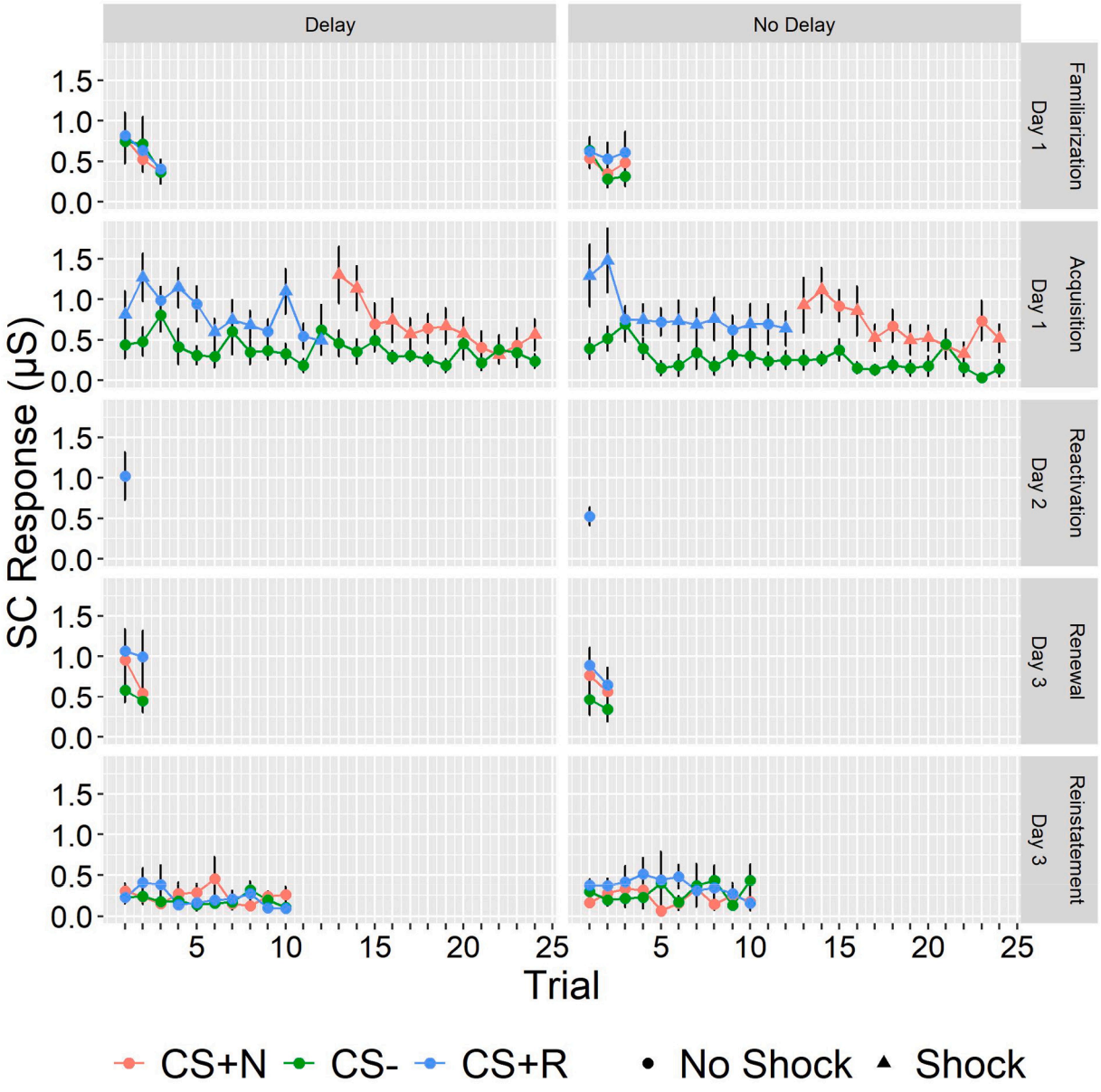


**Fig. 3.** Group mean skin conductance (SC) responses to CS + R (blue), CS + N (red), and CS- (green) trials during the familiarization and acquisition (Day 1), reactivation (Day 2), renewal and reinstatement (Day 3) phases. Bars represent standard errors. μS, microsiemens. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 2**
Results of mixed effect linear models of SCR to CS + R and CS + N (μS).

| Day | Test phase | Comparison | Estimate | *SE* | *df* | *F* | *95% CI* |
|---|---|---|---|---|---|---|---|
| | | CS + R vs. CS + N | 0.15 | 0.12 | 35 | 1.73 | −0.07, 0.38 |
| 1 | Acquisition | No delay vs. Delay | 0.01 | 0.25 | 35 | 0.00 | −0.48, 0.48 |
| | | CS + R vs. CS + N x No delay vs. Delay | −0.00 | 0.17 | 35 | 0.00 | −0.34, 0.32 |
| 2 | Reactivation | No delay vs. Delay | −0.50 | 0.32 | 33 | 2.41 | −1.04, 0.04 |
| | | CS + R vs. CS + N | 0.28 | 0.13 | 34 | 4.57 | 0.02, 0.54 |
| 3 | Renewal | No delay vs. Delay | −0.09 | 0.34 | 34 | 0.07 | −0.75, 0.57 |
| | | CS + R vs. CS + N x No Delay vs. Delay | −0.18 | 0.19 | 34 | 0.86 | −0.55, 0.20 |
| | | CS + R vs. CS + N | −0.02 | 0.05 | 34 | 0.10 | −0.11, 0.08 |
| 3 | Reinstatement | No delay vs. Delay | −0.03 | 0.09 | 34 | 0.10 | −0.21, 0.15 |
| | | CS + R vs. CS + N x No Delay vs. Delay | 0.16 | 0.07 | 34 | 5.08 | 0.02, 0.31 |

[−0.04, 1.04]) larger in the delay group compared to the non-delay group, which was, however, not statistically significant.

### 3.2. Renewal and reinstatement phase (Day 3)

During renewal on Day 3, SCRs to CR + R relative to CS + N did not differ between groups (−0.18 μS, 95% CI [−0.55, 0.20]). However,

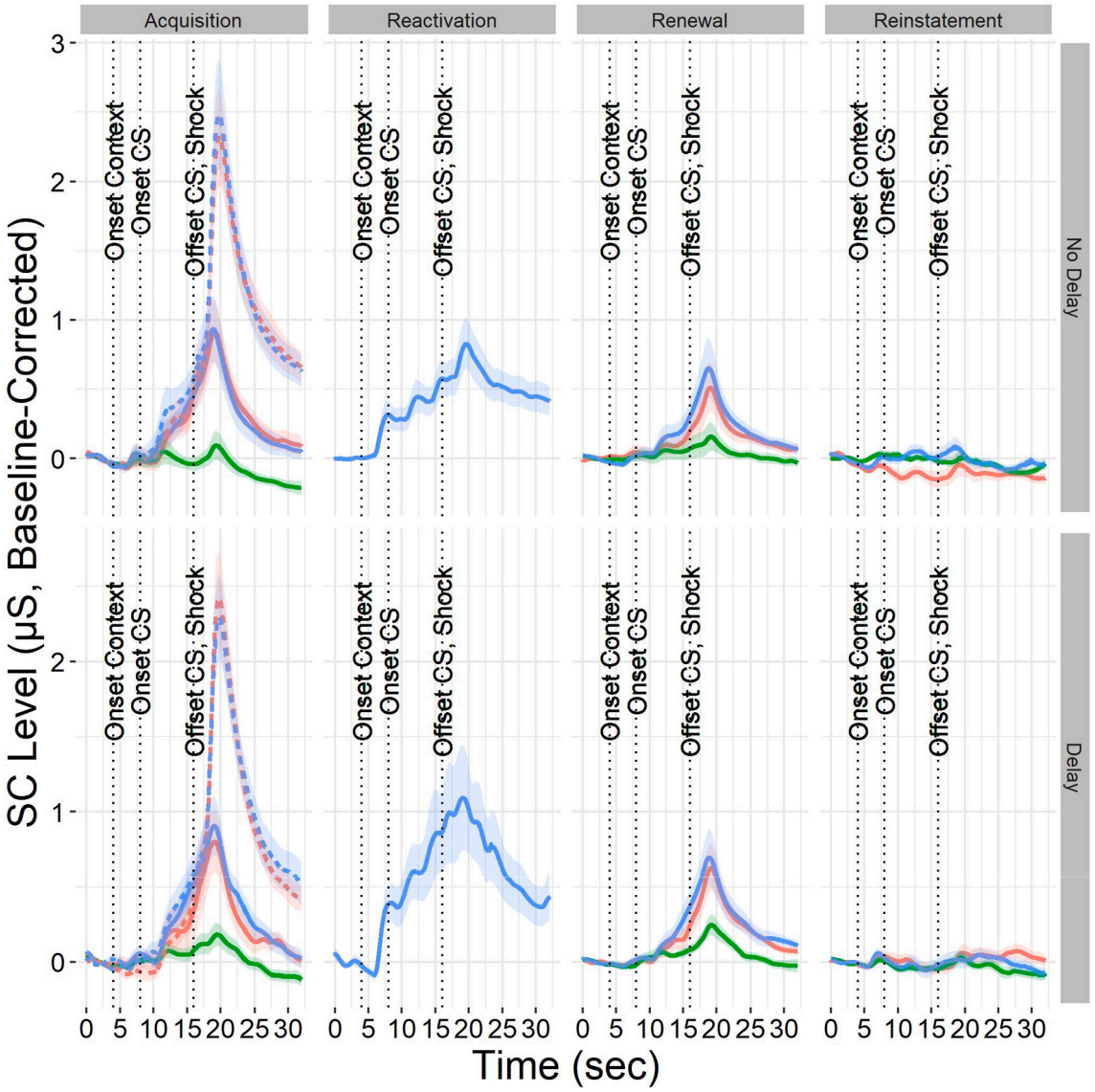


**Fig. 4.** Grand means for skin conductance (SC) time courses to CS + R (blue), CS + N (red), and CS- (green) trials which are paired (dotted line) and non-paired (solid line) with an electrical shock during acquisition (Day 1), reactivation (Day 2), renewal and reinstatement (Day 3). Ribbons represent standard errors. µS, microsiemens. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

when testing for CR effects after administering the US alone (reinstatement), we observed on average 0.16 µS (95% CI [0.02, 0.31]) smaller SCR to CS + R, compared to CS + N, in participants who performed eye movements with a 10-min delay, compared to participants with no delay (Table 2). As can be seen in Fig. 5 (Reinstatement), the significant interaction is driven by larger SCR to CS + R in the No Delay group of participants, compared to SCR to CS + R in the Delay group of participants and SCR to CS + N in both groups.

## 4. Discussion

### 4.1. Summary of results

We tested the potential efficacy of pursuit eye movement as a new candidate reconsolidation-blockade intervention in a differential fear conditioning paradigm (Spring et al., 2015). For this, the effect of pursuit eye movements performed with a 10-min delay after a conditioned fear stimulus (active condition) and without delay (control condition) was compared with regard to their memory reconsolidation blocking potential. Following previous studies using the same paradigm (Fricchione et al., 2016; Spring et al., 2015) video clips of crawling tarantula served as conditioned stimuli, SCR response as the index of conditioned fear. To induce stronger fear memory, this paradigm used biologically prepared CSs in fear-sensitive subjects and employed a stringent cut-off for measurable SCR response to two CS+ stimuli. In the following experimental procedures, they served to estimate memory reconsolidation blockage as reactivated (CS + R) and non-reactivated (CS + N) CS. After fear conditioning (Day 1), a single trial of CS + R was presented, followed by a 10 min delay (active condition) or no delay (control condition) before a subsequent set of pursuit eye movements (Day 2). The blockage of fear memory relapse was evaluated in renewal and reinstatement on Day 3.

We hypothesized that pursuit eye movements executed after a 10-min delay following fear memory reactivation, when the reactivated memory was in a labile state, would result in successful reduction of fear-conditioned SCRs in renewal and reinstatement. We observed that participants who performed eye movements 10 min, compared to immediately, after viewing the tarantula video clip on Day 2 (CSR + R), showed a smaller CS+ SCR when testing CS reinstatement on Day 3. This finding suggests that a brief session of pursuit eye movements is effective

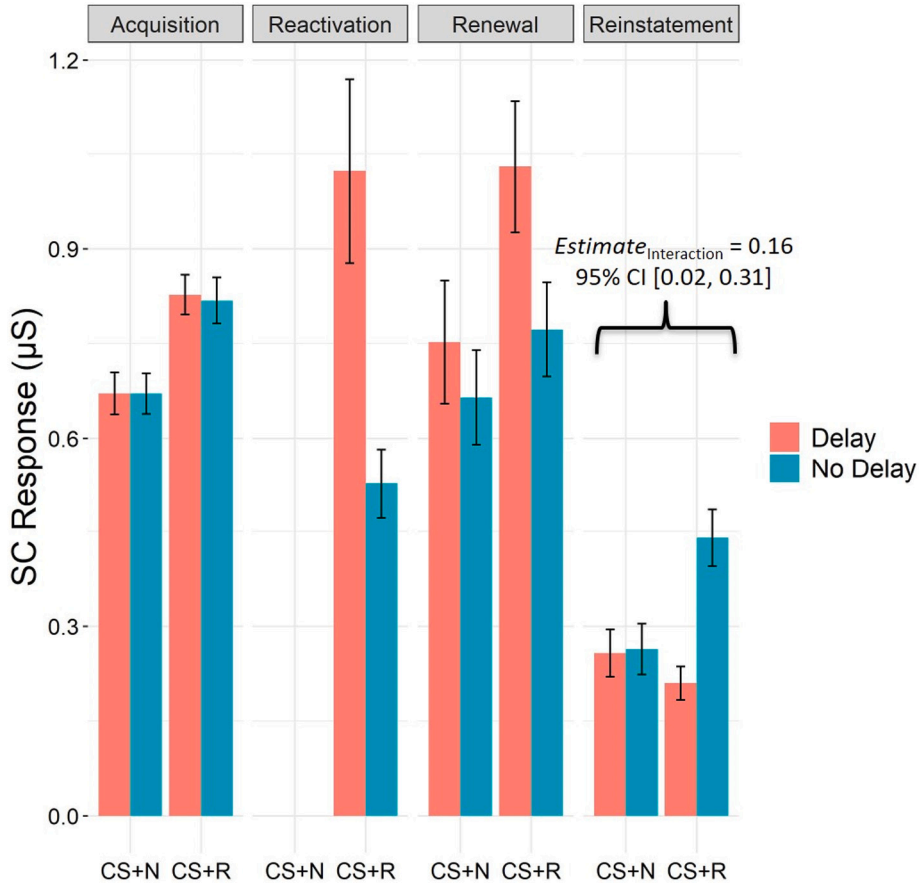


**Fig. 5.** Mean skin conductance (SC) responses to CS + R and CS + N during acquisition (Day 1), reactivation (Day 2), renewal, and reinstatement phases (Day 3) in subjects who performed pursuit eye movements after CS + R reactivation at Day 2 with either a 10 min delay or no delay. Error bars represent standard errors. µS, microsiemens.

in disrupting fear memory reconsolidation. Unexpectedly however, we saw no reduction of conditioned SCR in the renewal phase. We do not currently have a clear explanation for these discrepant results.

### 4.2. Relation to previous studies

The magnitude of mean SCRs was calculated in line with previous studies using spider stimuli (Milad et al., 2005; Orr et al., 2000). We observed that CS + N and CS + R during Day 1 acquisition were very similar to those observed in two previous studies employing similar methods (Fricchione et al., 2016; Spring et al., 2015). The same is true for the mean SCR magnitude seen during Day 2 reactivation of CS + R, supporting the validity of the fear conditioning and fear memory reactivation procedure used in our study.

Previous studies found no measurable reconsolidation blocking effect on fear-conditioned SCRs with propranolol given prior to CS + R reactivation (Spring et al., 2015) and extinction training performed 10 min after CS + R reactivation (Fricchione et al., 2016). The failure to reduce fear-conditioned SCR was seen both, in the renewal, as in the reinstatement and extinction phase. Regarding the latter, both studies first examined SCR across all CS presentations (reinstatement and extinction). Additionally, to avoid a potential attenuation of differences in SCR to the CSs by rapid extinction, only the first two CS presentations in the reinstatement phase were considered. In contrast to these previous studies, we observed a reduction of fear-conditioned SCR response when measuring reinstatement using data from all 12 CS presentations, when pursuit eye movements were performed 10 min after CS + R reactivation (active condition).

### 4.3. Possible neural mechanisms

Although the biological mechanisms underlying EMDR effects are not clear, one proposition is that pursuit eye movements block reconsolidation (Van den Hout and Engelhard, 2012), suggesting that engaging the fronto-parietal oculomotor orienting system interferes with the process of memory reconsolidation. There are a number of mechanisms through which eye movements could have their effects. First, the observation in healthy individuals that negative episodic memory is experienced less vividly with reactivation followed by pursuit eye movements suggests interaction between those systems (van den Hout et al., 2014). Second, an interaction with working memory and its limited resources in supporting cognitive processing has been postulated as a cause for the reduced emotional salience of memories associated with simultaneous task performance (van den Hout et al., 2014; van Veen et al., 2016). Third, other tasks associated with directed attention, including vertical (instead of pursuit) eye movements, auditory distraction, and manual drawing can also interfere with reconsolidation (Gunter & Bodner, 2008). Last, a neural model linking smooth pursuit eye movements and EMDR possibly underlying processes on memory reconsolidation has been recently postulated (Calancie et al., 2018).

From these lines of evidence, it is likely that pursuit eye movements may not have any unique therapeutic effects, as different effective variants of EMDR therapy utilize a range of distracting tasks. Nevertheless, performing tracking eye movements strongly engages neural systems that are largely co-extensive with those underlying attention and working memory processes and may thereby interfere with the reconsolidation of labile fear memories.

### 4.4. Application to PTSD

Since PTSD remains a treatment-refractory condition in more than one-third of cases (Bradley et al., 2005; Breslau et al., 1998), the efficiency of existing treatments, including EMDR, need to be improved. Our observation that pursuit eye movements only reduce fear-conditioned SCR when performed with a 10-min delay after reactivation when the memory is labile, but not immediately when the memory is more stable, suggests that pursuit eye movement may be effective by interrupting memory reconsolidation. This finding supports the theoretical proposition that pursuit eye movements as a core mechanism of effective EMDR treatment in PTSD involves interference with reactivated traumatic memory reconsolidation.

In future studies, the effect of pursuit eye movements on memory reconsolidation with an additional pharmacological agent such as the β-adrenergic blocker propranolol or mifepristone, could be worthwhile testing. One-time pre-reactivation propranolol failed to diminish conditioned strong fear memories using the present experimental procedure (Spring et al., 2015), yet, it has shown efficacy in other study designs using fear-conditioned startle fear response or self-rating of PTSD symptoms. Incorporated in the presented differential Pavlovian fear conditioning paradigm, combining a pre-reactivation attribution of propranolol with pursuit eye movement could have a synergistic effect on the blockade of memory reconsolidation and potentiate the observed effect. Moreover, the glucocorticoid antagonist mifepristone may reduce reconsolidation of reactivated fear memories by blocking the enhancing effect of glucocorticoids on reactivated memory reconsolidation (Meir Drexler et al., 2015) and its effect may even be potentiated by pursuit eye movements. To validate the effect of pursuit eye movements on memory reconsolidation and translate the paradigm into an adapted more clinical context, specific trauma-related stimuli could be used in a defined cohort of patients, e.g., patients with PTSD after car accident or trauma-exposed individuals without PTSD. Although SCR is recognized as a particularly appropriate index of fear in PTSD, it would also be worthwhile to complementary evaluate other fear indices in future studies using the same paradigm, e.g., a combination of objective indices like SCR response with subjective markers such as subjective fear rating as an essential marker of distress in the clinical context.

### 4.5. Limitations

The high exclusion rate in our study (72%) is noteworthy. Our exclusion rate is similar to our first study (70%) (Fricchione et al., 2016), and higher than our second study (42%) (Spring et al., 2015) which both used the same fear conditioning paradigm. However, it is not the purpose of this study to generalize the results to the entire population. Rather, we think that these results correspond more to individuals who are in need of clinical intervention, e.g., due to an aversive conditioning event as in PTSD, and who are likely to be more conditionable (Fricchione et al., 2016). Compared to other fear conditioning paradigms, the selected stimulus and screening procedure could have resulted in a generally higher exclusion rate. For instance, the chosen CS- could have been an aversive stimulus on its own for the fear-sensitive population of our study which resulted in lower differential fear-conditioning.

One consideration related to the fear stimuli used in this study is related to the use of video clips of actual tarantulas having different appearances and movements, which might explain the somewhat larger (although not significant) SCRs we observed to CS + R compared to CS + N stimuli during acquisition. Although using simulated tarantulas presented in a virtual environment would have allowed finer equalization of stimulus properties, the fear evoked by simulated tarantulas would likely have been lower. Another limitation is that we did not investigate the effects of eye movements without CS + R reactivation, or CS + R reactivation without eye movements, on fear memory strength. While it seems counterintuitive that isolated eye movements would have an influence on un-reactivated fearful memories, CS + R reactivation without accompanying shock might have initiated CS + R extinction and thereby reduced the conditioned response. Even so, this would not have influenced our main finding regarding delayed versus non-delayed eye movement effects. Finally, EMDR procedures involve many more elements than the pursuit eye movements tested as its core feature in our and prior studies (Wurtz et al., 2016). For instance, EMDR is applied by a therapist and also addresses cognitive distortions. Consequently, the conclusions that can be drawn from our results regarding biological mechanisms of EMDR are limited to those related to eye movement effects.

### 4.6. Conclusions

Taken together, we provide novel evidence that pursuit eye movements interfere with reactivated fear memory reconsolidation and thereby diminish the conditioned fear response. These results provide a promising starting point for systematic testing of ways to improve the reconsolidation blocking effect of eye movements in healthy participant or PTSD studies. The study represents a translational step between animal work and testing promising interventions in individuals with PTSD. The ultimate goal is to optimize existing treatment, such as EMDR, and develop novel treatments for PTSD based on the same, or similar, neural mechanisms.

## Declaration of competing interest

The authors reported no biomedical financial interests or potential conflicts of interest.

## Acknowledgment

The study was funded by the "Fonds für wissenschaftliche Zwecke im Interesse der Heilung von Geisteskrankheiten" of the Psychiatric University Hospital Zurich, Switzerland, EMDR Europe, and EMDR Switzerland.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpsycho.2021.04.006.

## References

American Psychiatric Association, 2013. The Diagnostic and Statistical Manual of Mental Disorders: DSM-5. American Psychiatric Publishing, Arlington, VA.
Bisson, J., Andrew, M., 2007. Psychological treatment of post-traumatic stress disorder (PTSD). Cochrane Database Syst. Rev. 1–103.
Bouton, M.E., 1993. Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. Psychol. Bull. 114, 80–99.
Bouton, M.E., 2002. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. Biol. Psychiatry 52, 976–986.
Bouton, M.E., 2004. Context and behavioral processes in extinction. Learn. Mem. 11, 485–494.
Bouton, M.E., Bolles, R.C., 1979. Role of conditioned contextual stimuli in reinstatement of extinguished fear. J. Exp. Psychol. Anim. Behav. Process. 5, 368–378.
Bradley, R., Greene, J., Russ, E., Dutra, L., Westen, D., 2005. A multidimensional meta-analysis of psychotherapy for PTSD. Am. J. Psychiatr. 162, 214–227.
Breslau, N., Kessler, R.C., Chilcoat, H.D., Schultz, L.R., Davis, G.C., Andreski, P., 1998. Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. Arch. Gen. Psychiatry 55, 626–632.
Brunet, A., Saumier, D., Liu, A., Streiner, D.L., Tremblay, J., Pitman, R.K., 2018. Reduction of PTSD symptoms with pre-reactivation propranolol therapy: a randomized controlled trial. Am. J. Psychiatr. 175, 427–433.
Calancie, O.G., Khalid-Khan, S., Booij, L., Munoz, D.P., 2018. Eye movement desensitization and reprocessing as a treatment for PTSD: current neurobiological theories and a new hypothesis. Ann. N. Y. Acad. Sci. 127–145.
Fricchione, J., Greenberg, M., Spring, J.D., Wood, N.E., Mueller-Pfeiffer, C., Milad, M.R., Pitman, R.K., Orr, S.P., 2016. Delayed extinction fails to reduce skin conductance reactivity to fear-conditioned stimuli. Psychophysiology 53, 1343–1351.
Gunter, R.W., Bodner, G.E., 2008. How eye movements affect unpleasant memories: Support for a working-memory account. Behav. Res. Ther. ISSN: 0005-7967 46 (8), 913–931. https://doi.org/10.1016/j.brat.2008.04.006.
Hamm, A., 2006. Spezifische Phobien. Hogrefe, Göttingen, Deutschland.

Jones, C.E., Monfils, M.H., 2013. Memory reconsolidation, in: Alberini, C.M. (Ed.), Using Reconsolidation and Extinction to Weaken Fear Memories in Animal Models, 1st ed. Academic Press, London, UK.
Kandel, E.R., 2004. The molecular biology of memory storage: a dialog between genes and synapses. Biosci. Rep. 24, 475–522.
Keane, T.M., Zimering, R.T., Caddell, J.M., 1985. A behavioral formulation of posttraumatic stress disorder in Vietnam veterans. Behav. Ther. 8, 9–12.
Kindt, M., Soeter, M., Vervliet, B., 2009. Beyond extinction: erasing human fear responses and preventing the return of fear. Nat. Neurosci. 12, 256–258.
Lecrubier, Y., Sheehan, D., Weiller, E., Amorim, P., Bonora, I., Sheehan, K., Janavs, J., Dunbar, G., 1997. The Mini International Neuropsychiatric Interview (MINI): a short diagnostic structured interview: reliability and validity according to the CIDI. Eur. Psychiatry 12, 224–231.
Maren, S., Phan, K.L., Liberzon, I., 2013. The contextual brain: implications for fear conditioning, extinction and psychopathology. Nat. Rev. Neurosci. 14, 417–428.
Meir Drexler, S., Merz, C.J., Hamacher-Dang, T.C., Tegenthoff, M., Wolf, O.T., 2015. Effects of cortisol on reconsolidation of reactivated fear memories. Neuropsychopharmacology 40, 3036–3043.
Milad, M.R., Orr, S.P., Pitman, R.K., Rauch, S.L., 2005. Context modulation of memory for fear extinction in humans. Psychophysiology 42, 456–464.
Mineka, S., Öhman, A., 2002. Phobias and preparedness: the selective, automatic, and encapsulated nature of fear. Biol. Psychiatry 52, 927–937.
Nader, K., Hardt, O., 2009. A single standard for memory: the case for reconsolidation. Nat. Rev. Neurosci. 10, 224–234.
Oren, E., Solomon, R., 2012. EMDR therapy: an overview of its development and mechanisms of action. Rev. Eur. Psychol. Appl. 62, 197–203.
Orr, S.P., Metzger, L.J., Lasko, N.B., Macklin, M.L., Peri, T., Pitman, R.K., 2000. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. J. Abnorm. Psychol. 109, 290–298.
Oyarzún, J.P., Lopez-Barroso, D., Fuentemilla, L., Cucurell, D., Pedraza, C., Rodriguez-Fornells, A., de Diego-Balaguer, R., 2012. Updating fearful memories with extinction training during reconsolidation: a human study using auditory aversive stimuli. PLoS One 7.
Pavlov, I.P., 1927. Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex. Oxford Univ. Press, Oxford, England.
Pedreira, M.A.E., Romano, A., 2013. Memory reconsolidation and extinction in invertebrates: evolutionarily conserved characteristics of memory reprocessing and restabilization, Memory Reconsolidation. Elsevier Inc., pp. 139–164
Rescorla, R.A., 2004. Spontaneous recovery. Learn. Mem. 11, 501–509.
Rescorla, R.A., Wagner, A., 1972. A Theory of Pavlovian Conditioning: Variations in the Effectiveness of Reinforcement and Nonreinforcement.
Rousseau, P.F., El Khoury-Malhame, M., Reynaud, E., Boukezzi, S., Cancel, A., Zendjidjian, X., Guyon, V., Samuelian, J.C., Guedj, E., Chaminade, T., Khalfa, S., 2019. Fear extinction learning improvement in PTSD after EMDR therapy: an fMRI study. Eur. J. Psychotraumatol. 10, 1568132.
Schiller, D., Monfils, M.H., Raio, C.M., Johnson, D.C., Ledoux, J.E., Phelps, E.A., 2010. Preventing the return of fear in humans using reconsolidation update mechanisms. Nature 463, 49–53.
Seligman, M.E.P., 1971. Phobias and preparedness. Behav. Ther. 2, 307–320.
Sevenster, D., Beckers, T., Kindt, M., 2012. Retrieval per se is not sufficient to trigger reconsolidation of human fear memory. Neurobiol. Learn. Mem. 97, 338–345.
Sevenster, D., Beckers, T., Kindt, M., 2013. Prediction error governs pharmacologically induced amnesia for learned fear. Science 339, 830–833.
Shapiro, F., 2001. Eye Movement Desensitization and Reprocessing (EMDR): Basic Principles, Protocols, and Procedures. The Guilford Press, New York.
Soeter, M., Kindt, M., 2010. Dissociating response systems: erasing fear from memory. Neurobiol. Learn. Mem. 94, 30–41.
Soeter, M., Kindt, M., 2011. Disrupting reconsolidation: pharmacological and behavioral manipulations. Learn. Mem. 18, 357–366.
Spring, J.D., Wood, N.E., Mueller-Pfeiffer, C., Milad, M.R., Pitman, R.K., Orr, S.P., 2015. Prereactivation propranolol fails to reduce skin conductance reactivity to prepared fear-conditioned stimuli. Psychophysiology 52, 407–415.
Steinfurth, E.C.K., Kanen, J.W., Raio, C.M., Clem, R.L., Huganir, R.L., Phelps, E.A., 2014. Young and old Pavlovian fear memories can be modified with extinction training during reconsolidation in humans. Learn. Mem. 21, 338–341.
Van den Hout, M.A., Engelhard, I.M., 2012. How does EMDR work? J. Exp. Psychol. 3, 724–738.
van den Hout, M.A., Eidhof, M.B., Verboom, J., Littel, M., Engelhard, I.M., 2014. Blurring of emotional and non-emotional memories by taxing working memory during recall. Cognit. Emot. 28, 717–727.
van Veen, S.C., Engelhard, I.M., van den Hout, M.A., 2016. The effects of eye movements on emotional memories: using an objective measure of cognitive load. Eur. J. Psychotraumatol. 7.
Vervliet, B., Baeyens, F., Van den Bergh, O., Hermans, D., 2013. Extinction, generalization, and return of fear: a critical review of renewal research in humans. Biol. Psychol. 92, 51–58.
Wallin, B.G., 1981. Sympathetic nerve activity underlying electrodermal and cardiovascular reactions in man. Psychophysiology 18, 470–476.
Westbrook, R.F., Iordanova, M., McNally, G., Richardson, R., Harris, J.A., 2002. Reinstatement of fear to an extinguished conditioned stimulus: two roles for context. J. Exp. Psychol. Anim. Behav. Process. 28, 97–110.
Wurtz, H., El-Khoury-Malhame, M., Wilhelm, F.H., Michael, T., Beetz, E.M., Roques, J., Reynaud, E., Courtin, J., Khalfa, S., Herry, C., 2016. Preventing long-lasting fear recovery using bilateral alternating sensory stimulation: a translational study. Neuroscience 321, 222–235.