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A novel method to trigger the reconsolidation of fear memory

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ABSTRACT

The procedure of memory reconsolidation provides an opportunity to improve some mental disorders caused by maladaptive memories, such as Posttraumatic Stress Disorder. Prediction error was considered a necessary condition for triggering memory reconsolidation. However, it is difficult to create a satisfying prediction error to successfully open memory reconsolidation in a clinical context. The purpose of this study was to explore a more practicable method to trigger memory reconsolidation. We used a successive 4-day fear-potentiated startle paradigm to compare the effect of uncertainty with prediction error during retrieval on preventing the return of fear. Bayes factor, combined with p value and effect size, was used as the main indicator of statistical inference. The results indicated that spontaneous recovery and reinstatement of fear were not observed in the uncertainty group, whereas return of fear was observed for the prediction error group. However, the direct comparison between the two groups did not yield statistically significant results, potentially reflecting a lack of statistical power. Nonetheless, these results suggest that uncertainty retrieval could be a better means to trigger memory reconsolidation than prediction error, making uncertainty a worthwhile factor to consider in future research on memory reconsolidation.

1. Introduction

Maladaptive memories are considered the main cause of some mental disorders, such as Posttraumatic Stress Disorder (PTSD); thus, they have become the main target in treatment (Visser, Lau-Zhu, Henson, & Holmes, 2018). Usually, these consolidated memories are stable and not susceptible to change. Therefore, directly modifying these original memories often leads to failure due to a high recurrence rate (Quirk et al., 2010). Fortunately, according to the memory reconsolidation theory, these consolidated memories can return a transient labile state upon retrieval, in which the reactivated memories become susceptible to change; thus, it provided an opportunity to modify those maladaptive memories through behavioural or pharmacological intervention (Kamboj & Das, 2017). The retrieval–extinction paradigm was developed based on the theory of memory reconsolidation and has been a focus of research for its advantage of preventing relapse (Schiller et al., 2010; Thompson & Lipp, 2017).

However, the retrieval–interference procedure did not always show its advantage over traditional extinction in laboratory and clinical situations (Culver, Stoyanova, & Craske, 2011). For instance, Klucken et al. used a within-subjects design to examine whether retrieval–extinction interference can permanently block the return of fear and unfortunately found its failure on preventing relapse (Klucken et al., 2016). Moreover, a study of pharmacological intervention aimed at disrupting reconsolidation of associative fear memory with propranolol unexpectedly found that propranolol before memory reactivation resulted in no improvement in the startle fear response (Bos, Beckers, & Kindt, 2014). The instability of the effect of the retrieval–interference procedure on preventing relapse has greatly hindered the translation from basic research to clinical practice.

A major cause of this instability may be the presence of unknown boundary conditions and their triggering of memory reconsolidation. The key to the success of retrieval–interference is to destabilize the consolidated memory by retrieval manipulation and make it enter memory reconsolidation. However, a brief retrieval manipulation by re-exposure to the previously reinforced conditioned stimulus cannot assure destabilization of the consolidated memory despite its capacity to reactivate or retrieve the initial memory (Faliagkas, Rao-Ruiz, & Kindt, 2018). Studies have demonstrated that prediction error (PE) is a necessary condition to trigger memory reconsolidation (Sevenster, Beckers, & Kindt, 2014).

PE is defined as a mismatch between expected and actual events and

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considered the impetus of memory updating (López et al., 2016). The notion that PE is a mandatory condition for initiating memory reconsolidation has been widely accepted (Alfei, Monti, Molina, Bueno, & Urcelay, 2015; Sevenster, Beckers, & Kindt, 2013). However, a classical study showed that retrieval with a single PE, but not without PE or with multiple PEs, can significantly attenuate the fear response (Sevenster, Beckers, & Kindt, 2014). Another study provided direct evidence that PE is not a sufficient condition under which the reconsolidation is likely to occur (Bos et al., 2014).

Additionally, it is difficult—to the point of impossible—to create a satisfactory PE to destabilize the consolidated memories in the real world. There are at least three reasons for this phenomenon: (a) it is difficult to find a specific retrieval cue that represents the crucial aspects of the maladaptive memory that needs to be changed in the clinical context (Visser et al., 2018); (b) it is difficult to manipulate the parameters of retrieval cue because of the ignorance of the acquisition history of the maladaptive memory; and (c) it is difficult to control the strength level of PE.

Some studies have indicated that a low PE cannot destabilize the strong memories and thus fails to trigger memory reconsolidation; by contrast, a high PE for relatively weak memories may lead to forming a new, separate memory. These factors have limited the application of retrieval–interference protocols in clinical settings. According to our review of the literature, there is no effective method to solve these problems. Under the circumstances, it is crucial to investigate an alternative or better means to substitute the role of PE to induce memory reconsolidation.

Fortunately, an excellent study was conducted by Radiske et al. and is of great enlightening significance to conquer these difficulties (Radiske et al., 2017). In their studies, rats were assigned to three groups: Control group, Open-field group, and Training box group. The first group was handled; the second group was allowed to explore an open-field arena; the third group was put into the training box for 5 min/d during the five days before all the rats experienced contextual fear conditioning in the training box days later, respectively. Only the third group learned the safe memory before they learned the fear memory for the training box.

The results indicated that the strong and weak fear memories could be erased permanently only in the third group when pharmacological interventions were given immediately after reactivation. In addition, the pharmacological interventions had no effect on the fear memories without reactivation, which further indicated that the fear-impairing effect depended on the memory reconsolidation process. Furthermore, and most notable, the pharmacological interventions immediately after reactivation could not improve the fear response when there was only a single pre-exposure before fear conditioning, which was thought to be the result of having not yet learned the safe memory of the training box.

Several similar studies have replicated these results. According to these findings, it is not difficult to surmise that only when the safe memory of the training box was acquired before fear conditioning could the manipulation of retrieval by re-exposure in the same training box effectively trigger the fear memory reconsolidation. However, the other two groups failed to trigger the reconsolidation of fear memory, even though the PE has theoretically occurred. Why did that phenomenon occur? The studies had supposed that the necessary condition of triggering the reconsolidation of fear memory may not be the PE, but was instead, the uncertainty of the consequences of avoidance caused by previously acquired conflicting information.

According to our review of the literature, no studies have tested this hypothesis. In this study, we used a fear-potentiated startle paradigm to examine the role of uncertainty during retrieval in preventing fear relapse, and we compared the impact of retrieval with PE versus uncertainty on the fear-impairing effect. Specifically, we used a 4-day procedure to achieve experimental purpose: pre-exposure on day 1 to form the positive memory of the conditioned stimulus before fear conditioning for the uncertainty retrieval group (Uncer-group), but not for PE retrieval group (PE-group); acquisition on day 2; retrieval–extinction on day 3; and spontaneous recovery test and reinstatement test on day 4.

In addition, to avoid the uncertainty being produced in the PE-group and to create a strong fear memory, we adopted a 100% reinforcement rate in the acquisition. We expected that uncertainty retrieval would result in more fear-impairing effect and less fear relapse than PE retrieval.

2. Materials and methods

2.1. Participants

Fifty-four participants (21 males) were recruited from South China Normal University through digital advertising, and 27 participants were in each group. Most participants were college students aged 18–24 years. Participants excluded if they said yes to having 1) any medical treatment in the past two weeks or 2) if they felt ANY noticeable physical or mental discomfort. In addition, the Beck Depression Inventory was used to measure depression levels and four participants with scores above 19 were excluded from study participation. All the participants had never participated in our previous similar studies. Before the subjects came to the laboratory, they were told to not use stimulant drinks or strenuous exercise 2 h before beginning the experiment and not until they completed all the experiments. We excluded these participants who did not acquire or extinguish fear conditioning according to the criteria of acquisition and extinction used by Li et al. and Hu et al. [mean conditioned stimulus (CS)− < CS+ in late acquisition, n = 7; and mean CS+ in early extinction ≮ mean CS+ in late extinction, n = 6] (Hu et al., 2018; Li et al., 2017). Due to technical problems, the data of one subject was invalidated. Hence, the data of 18 participants in each group was used for statistical analysis (Uncer-group: 20.462 ± 1.761 years old, 7 males; PE-group: 21.941 ± 7.146 years old, 7 males). These data exclusions did not change our key findings and conclusions.

All the participants were paid 100 RMB, and the monetary reward was received after they completed the experiments at the end of day 4. We obtained written informed consent from all the participants. The research was approved by the human research ethics committee for non-clinical faculties of School of Psychology, South China Normal University (Approval Number: 227).

2.2. Materials

2.2.1. Stimuli

Conditioned stimulus (CSs): We employed two images of fear-irrelevant stimuli (i.e. a yellow cylinder and brown cube) as the CS+ and CS-. The two images were counterbalanced within groups. The CS+ was paired with the unconditioned stimulus (US) on a 100% reinforcement schedule, and the CS- was never paired with the US.

Unconditioned stimulus: The US used in the Uncer-group on day 1 was a money reward. Each CS + trail was paired with a message on the computer screen centre that offered congratulations on the award of 10 RMB (US_p). A mild electric shock, determined individually to be 'uncomfortable but not painful', served as the US in the acquisition phase. A 100% reinforcement rate was observed in the two groups (US_n).

Startle stimulus: We used an acoustic startle pulse (108 dB, 40-ms) as the startle probe stimulus and NA (noise alone) trail. The CSs were presented for 6000-ms in a pseudo-randomised manner. The startle pulse was presented at 5000-ms of each CS, and the US_n was presented at 5800-ms, with a 200-ms duration. NA trails were presented without any stimulus. The onset of US_p began immediately after CS + on day 1. Inter-trial intervals (ITIs) randomly varied from 15-s to 18-s.

2.2.2. Apparatus and data collection

Skin Conductance Response (SCR): The data of SCR in this study

was collected using Spirit NeXus-10 (BioTrace Medical, San Carlos, CA, USA) and sampled at 120 Hz. Electrodes were attached to finger pulp of the forefinger and middle finger of the left hand. We analysed SCR waveforms offline using BioTrace + software for NeXus-10. The level of the SCR response to each CSs was calculated by taking the base-to-peak difference, determined by the first waveform in the 0.5–5.0-s window after stimulus onset. The SCRs less than 0.02 μs were scored as zero (Schiller et al., 2010). Next, we normalized the raw SCR data by square root transformation.

Fear-Potentiated Startle (FPS): We presented all experimental stimuli with the Xeye Human Startle system (Beijing Macroambition S& T Development Co., Ltd), which was also used to collect the data of acoustic startle response (ASR). ASR is sensitive to emotional valence and has become an excellent tool to study emotional processing. Specifically, an unpleasant stimulus could potentiate the startle response, and a positive stimulus would attenuate the startle response (Bradley, Codispoti, Cuthbert, & Lang, 2001). Fear-relevant stimuli, such as the CS+ in the fear conditioning, have been found to effect the potentiated startle reflex, which is the so-called FPS. As an effective physiological index, it has been widely used in aversive conditioning (Leer, Haesen, & Vervliet, 2018; Orcutt et al., 2016).

In this study, we collected the data of FPS by positioning two 5 mm Ag/AgCl electrodes filled with electrolyte gel approximately 1 cm under the pupil and lateral can thus, and we attached the ground electrode to the mastoid process behind the right ear. We began to collect the data of ASR at 1000-ms before the onset of the acoustic startle pulses. These data were automatically pre-processed by the Xeye Human Startle system. We redefined the data offline by the base-to-peak method to compute the ASR to each CSs and NA during the time window from 50-ms before startle probe stimuli onset to 250-ms after the stimuli offset. The raw ASR data was normalized by Z scores and then transformed into T scores.

2.3. Procedure

2.3.1. Preparation

At least 30 min before began the experiments, the experimenter arrived in the laboratory to adjust the indoor light and temperature of the laboratory to avoid their effects on fear conditioning (Yoshiike, Honma, Yamada, Kim, & Kuriyama, 2018). All subjects completed all the experiments in the same environment that comprised a mild light and a temperature of 26 °C. Next, we started the instrument ahead of time to ensure it was in a stable, working state.

As soon as the subjects arrived in the lab, we asked them to complete the Beck Depression Inventory-II (Beck, Steer, Ball, & Ranieri, 1996), a State version of the State-Trait Anxiety Inventory (Spielberger, 1970), and the Positive Affect and Negative Affect Scale (Tellegen, 1988). Next, we administered a breath-holding test to ensure that we could collect effective SCRs from each subject. Specially, each subject held his or her breath for 3-s to observe if there was any significant SCR (Atlas, Doll, Li, Daw, & Phelps, 2016). All the subjects passed the test.

Next, we evaluated the electric shocks' intensity level for each subject by the calibration procedure. After all subjects completed the aforementioned tasks on day 1, we told the PE-group that they had completed all the day-1 tasks and should return to the lab at the same time tomorrow (i.e. day 2), and we told the Uncer-group that they had to continue to complete the pre-exposure procedure.

2.3.2. Pre-exposure on day 1

The aim of pre-exposure was to learn a pleasant memory of CS + for the Uncer-group. The process began with a 60-s acclimation period where a 65-dB background noise was presented, with the background of 'Please relax' on the computer screen, which was also used as the background during ITIs. Ten startle probes were presented alone immediately after the acclimation period, which was called the habituation, to reduce initial startle reactivity.

The later procedure included four stimuli: CS+, CS-, US_p, and NA. The NA trials were used to measure the baseline startle reactivity across the phase. We used the block design, and each block included one CS+, one CS-, and one NA presented in a pseudo-randomised manner. There were three blocks in the present phase. Subjects were told that the background noise would play throughout the experiments. The subjects were subsequently told that two pictures would be presented on the computer screen, and that one of the pictures would be followed by a monetary reward, whereas the other picture would not be followed by a monetary reward. The subjects were then told that the monetary reward combined with experimental reward would be paid after they had completed all the experiments.

The only task the subjects were required to perform during this phase was to learn the association between the pictures and the monetary reward. Half of the subjects were asked to complete the Positive Affect and Negative Affect Scale again after the pre-exposure to examine whether the emotional state changed.

2.3.3. Acquisition on day 2

Day 2, 24 h after pre-exposure, we conducted the same fear conditioning for all subjects. To build a strong fear memory for both groups, we conducted a 100% reinforcement rate fear conditioning. This manipulation was also used to avoid the possible uncertainty during the retrieval phase in the PE-group. Each CS+ was paired with a mild electric shock, and the CS- was never paired with electric shock. The fear acquisition phase included six blocks. Subjects were told that the background noise would play throughout the experiments. The subjects were subsequently told that two pictures would be presented on the computer screen, and that one of the pictures would be followed by an electric shock, whereas the other picture would not be followed by an electric shock. The only task subjects were required to perform during this phase was to learn the association between the pictures and electric shock.

2.3.4. Retrieval–extinction on day 3

Day 3, 24 h after acquisition, we reactivated the consolidated fear memory by re-exposure to the reinforced CS during the acquisition phase (i.e. CS+) without the US paired.

For the Uncer-group, we defined the retrieval as uncertainty retrieval because the retrieval simultaneously reactivated two memories of CS + acquired by the pre-exposure phase and acquisition phase; thus, which memory would be presented followed by the retrieval was uncertain. To examine and quantify the level of uncertainty, we asked all the subjects to report immediately after seeing a picture, based on their previous learning experience, whether electric shock or monetary reward was more likely to follow; next, the subjects reported the corresponding quantity on a scale from 0 (*absolutely uncertainty*) to 4 (*absolutely certainty*). We defined the level of uncertainty as the absolute value of the difference between the number size reported by the subjects and 4.

For the PE-group, we defined the retrieval as PE retrieval because there was only one memory of CS + for this group, and we used a 100% reinforcement rate scheme. These two aspects led to a definite expectation that CS+ was bound to follow electric shock. A PE thus occurred when there was no electric shock presented.

Additionally, 10-m after retrieval, extinction occurred immediately after the acclimation period and habituation phase. The extinction procedure included eight blocks consisting of CS+, CS-, and NA. All the stimuli were presented without reinforcement.

2.3.5. Tests on day 4

Day 4, 24 h after extinction, we conducted tests of spontaneous recovery by using a re-extinction procedure. Similar to the aforementioned sessions, the test began with the acclimation period and habituation phase, followed by a re-extinction procedure consisting of six blocks. Re-extinction ended with four electric shocks without

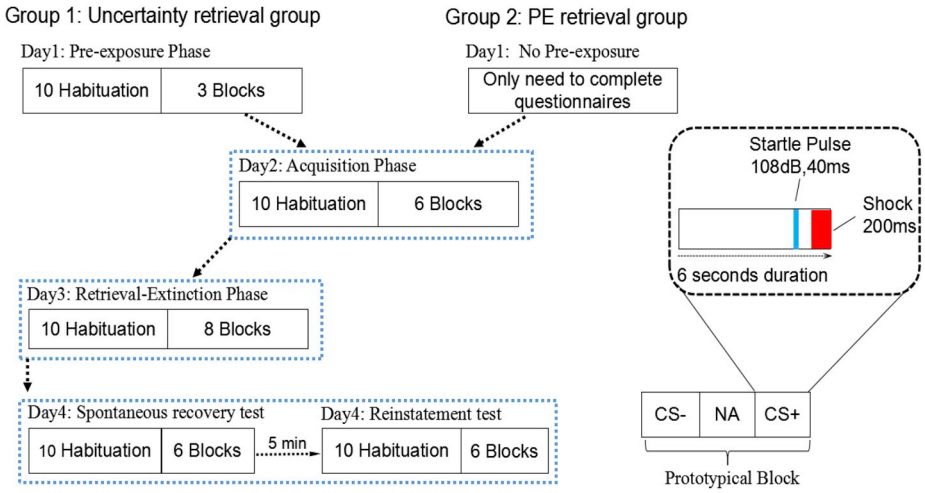

Fig. 1. Schematic of the fear potentiated startle procedure and illustrating a prototypical trial block and trial. CS+ was always paired with unconditioned stimulus that was money reward, presented immediately after CS + offset on the first day. and electric shock, presented at the last 200 ms of CS + onset in the acquisition phase. Habituation and NA were startle pulse alone.

conditioned stimuli; 5-m after that, all the subjects started the reinstatement test, consisting of six blocks. Complete experimental procedures and the timeline are illustrated in Fig. 1.

2.4. Data analysis

Notably, null hypothesis significance testing (NHST), the dominant method used for statistical inference in science (Wasserstein & Lazar, 2016), has often been misunderstood and misused, leading to false positive and unreproducible findings (Hu, Kong, Wagenmakers, Ly, & Peng, 2018). To address this problem, some researchers have suggested that a better method might be to substitute the Bayes factor for p values (Dienes & Mclatchie, 2017; Wagenmakers et al., 2018).

Compared with NHST, the Bayes factor has many advantages (Wagenmakers, Marsman, et al., 2018). For example, it provides evidence for the null hypothesis and can quantify the evidence for the H0 and the H1. Additionally, the Bayes factor allows us to monitor the evidence as the data accumulate and does not depend on sampling plans (Hu et al., 2018). Based on the aforementioned considerations, we adopted the Bayes factor as a dominant method for statistical inference with JASP 0.8.6.0 in this study (Marsman & Wagenmakers, 2017). Although some researchers have lost faith in p values, we also provided the p value and the effect size in this study to provide more useful information.

3. Results

3.1. Psychometric data

No evidence was observed for group differences in Beck depression ($BF = 0.610$, $t_{(34)} = 1.286$, $P = 0.207$, *Cohen's d* $= 0.429$), state anxiety ($BF = 0.611$, $t_{(34)} = 1.287$, $P = 0.207$, *Cohen's d* $= 0.429$), positive affect ($BF = 0.896$, $t_{(34)} = -1.633$, $P = 0.112$, *Cohen's d* $= -0.544$), and negative affect ($BF = 0.516$, $t_{(34)} = 1.102$, $P = 0.278$, *Cohen's d* $= 0.367$) before the subjects participated in our experiments by independent samples *t*-test. To examine the effect of pre-exposure on the emotional state, we compared the emotional state before and after pre-exposure by paired samples *t*-test in the Uncer-group. The results showed that the pre-exposure had no significant effect on the emotional state (positive affect: $BF = 0.471$, $t_{(12)} = 1.123$, $P = 0.283$, *Cohen's d* $= 0.312$; negative affect: $BF = 0.314$, $t_{(12)} = -0.528$, $P = 0.607$, *Cohen's d* $= -0.146$). (Fig. 2).

3.2. SCR

3.2.1. Acquisition of conditioned fear memory

To test that each group had learned the same intensity of fear memory, we performed a mixed ANOVA with factors of group (Uncer-group vs PE-group) × phase (early and late of acquisition session) × stimulus type (CS+, CS-). The results revealed a significant main effect of phase ($BF = 155.176$; $F_{(1,34)} = 30.448$, $P < 0.001$,

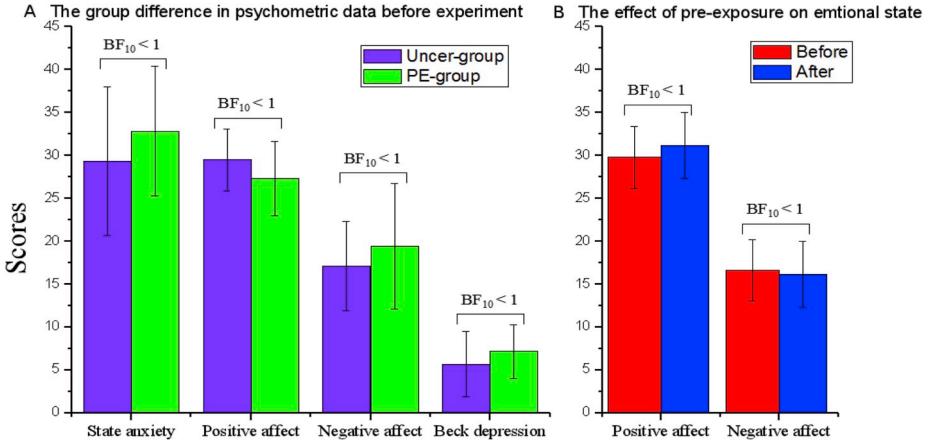

Fig. 2. Psychometric data analysis. **A**. There were no evidences for group differences in Beck depression, state anxiety, positive affect, and negative affect before experiments. **B**. The pre-exposure had no significant effect on the emotional state. Error bars represent standard errors.

Table 1
Descriptive statistics and independent samples *t*-test of the uncertainty for both groups.

	N	Mean	SD	95% CI	*t*	*df*	*p*	*BF*
Uncer-group	18	1.844	1.486	(1.18, 2.59)	5.043	34	< 0.001	1100.390
PE-group	18	0.056	0.236	(0, 0.18)				

$\eta^2 = 0.422$) and stimulus type ($BF = 1.328e+11$; $F_{(1,34)} = 45.320$, $P < 0.001$, $\eta^2 = 0.568$). Although a significant interaction between phase × group was revealed by NHST ($F_{(1,34)} = 7.782$, $P = 0.009$, $\eta^2 = 0.108$), the result of the Bayes factor provided weak evidence for it ($BF = 1.125$). Follow-up t tests showed significantly higher SCR to CS + than to CS- in both groups during all phases (early phase of acquisition: Uncer-group, $BF = 5.349$, $t_{(17)} = 2.905$, $P = 0.010$, *Cohen's* $d = 0.685$; PE-group, $BF = 89.671$, $t_{(17)} = 4.430$, $P < 0.001$, *Cohen's* $d = 1.044$; late phase of acquisition: Uncer-group, $BF = 642.566$, $t_{(17)} = 5.493$, $P < 0.001$, *Cohen's* $d = 1.295$; PE-group, $BF = 4281.808$, $t_{(17)} = 6.565$, $P < 0.001$, *Cohen's* $d = 1.547$). These results indicated that participants have successfully learned the fear memory.

The ANOVA also showed a non-significant main effect of group ($BF = 0.478$; $F_{(1,34)} = 0.134$, $P = 0.716$, $\eta^2 = 0.004$) and a non-significant interaction effect of group × stimulus type ($BF = 0.381$; $F_{(1,34)} = 0.421$, $P = 0.521$, $\eta^2 = 0.005$), phase × stimulus type ($BF = 0.779$; $F_{(1,34)} = 0.991$, $P = 0.327$, $\eta^2 = 0.027$) and group × stimulus type × phase ($BF = 0.240$; $F_{(1,34)} = 2.390$, $P = 0.131$, $\eta^2 = 0.064$), which indicated that all the subjects learned the equivalent fear memory.

3.2.2. Validity test on the manipulation of uncertainty retrieval

An independent samples T test was conducted to examine the validity of the manipulation of uncertainty retrieval and showed the level of uncertainty in the Uncer-group was significantly higher than in the PE-group ($BF = 1100.390$; $t_{(34)} = 5.043$, $P < 0.001$, *Cohen's* $d = 1.681$). The result confirmed the manipulation of retrieval successfully reactivated two memories of CS+ in the Uncer-group and thus produced an uncertain state. It also reactivated only one memory and a strong US expectancy for CS+ in the PE-group and produced a PE (Table 1.).

3.2.3. Extinction of conditioned fear memory

A mixed ANOVA with factors of group (Uncer-group vs PE-group) × phase (early and late extinction session) × stimulus type (CS +, CS-) was conducted to assure the extinction of fear memory in both groups. Fear memory was successfully eliminated, and the evidence is the significant main effect of phase ($BF = 2.759e+9$; $F_{(1,34)} = 49.062$, $P < 0.001$, $\eta^2 = 0.591$) and non-significant main effect of stimulus type ($BF = 0.560$; $F_{(1,34)} = 6.127$, $P = 0.018$, $\eta^2 = 0.153$). Due to the inconsistent results of the main effect of stimulus type provided by NHST and the Bayes factor, we performed a paired samples *t*-test on stimulus type in both groups during all phases, and the results showed no differential responding to CSs during all phases (early phase of extinction: Uncer-group, $BF = 0.497$, $t_{(17)} = 1.292$, $P = 0.214$, *Cohen's* $d = 0.304$; PE-group, $BF = 0.372$, $t_{(17)} = 0.985$, $P = 0.338$, *Cohen's* $d = 0.232$; late phase of extinction: Uncer-group, $BF = 0.564$, $t_{(17)} = 1.406$, $P = 0.178$, *Cohen's* $d = 0.331$; PE-group, $BF = 0.337$, $t_{(17)} = 0.860$, $P = 0.402$, *Cohen's* $d = 0.203$). A Paired Samples T test on phase showed a significant reduction in fear response to both CS+ (Uncer-group, $BF = 549.019$, $t_{(17)} = 5.406$, $P < 0.001$, *Cohen's* $d = 1.274$; PE-group, $BF = 5.893$, $t_{(17)} = 2.960$, $P = 0.009$, *Cohen's* $d = 0.698$) and CS- (Uncer-group, $BF = 23.328$, $t_{(17)} = 3.713$, $P = 0.002$, *Cohen's* $d = 0.875$; PE-group, $BF = 31.450$, $t_{(17)} = 3.873$, $P = 0.001$, *Cohen's* $d = 0.913$) (see Fig. 3).

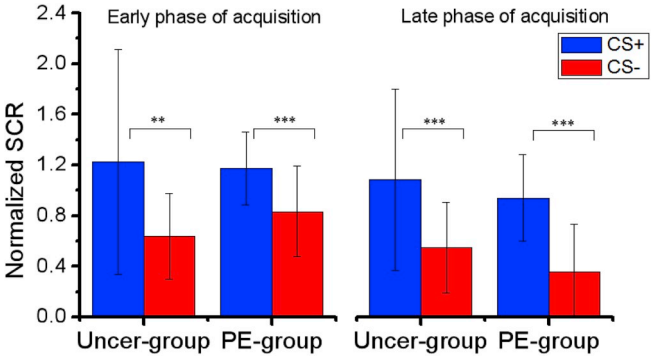

Fig. 3. Both groups have successfully acquired equivalent fear memory. Note: ** indicate a moderate evidence for HI ($BF_{10} > 3$), *** indicate a strong evidence for HI ($BF_{10} > 10$). Error bars represent standard errors (similarly hereinafter).

The results of the non-significant main effect of group ($BF = 0.317$; $F_{(1,34)} = 1.269$, $P = 0.268$, *partial* $\eta^2 = 0.036$) and non-significant interaction effect of group × phase ($BF = 0.225$; $F_{(1,34)} = 5.499e-5$, $P = 0.994$, $\eta^2 = 0.000$), group × stimulus type ($BF = 0.135$; $F_{(1,34)} = 0.005$, $P = 0.944$, $\eta^2 = 0.000$), phase × stimulus type ($BF = 0.293$; $F_{(1,34)} = 5.299e-4$, $P = 0.982$, $\eta^2 = 0.000$) and group × phase × stimulus type ($BF = 0.012$; $F_{(1,34)} = 0.052$, $P = 0.822$, $\eta^2 = 0.002$) indicated that both groups learned an equivalent extinction memory (Fig. 4.).

3.2.4. Spontaneous recovery of conditioned fear memory

We tested the spontaneous recovery of fear memory by re-extinction procedure and observed a significantly higher SCR to CS+ in the early phase of re-extinction compared with the late phase of extinction would be considered as fear memory recovery. Thus, we conducted a paired samples *t*-test in both groups. There was non-significant spontaneous recovery in the Uncer-group ($BF = 0.850$, $t_{(17)} = 1.739$, $P = 0.100$, *Cohen's* $d = 0.410$), but moderate spontaneous recovery in the PE-group ($BF = 2.908$, $t_{(17)} = 2.550$, $P = 0.021$, *Cohen's* $d = 0.601$). A direct comparison of the BFs indicated that the evidence for spontaneous recovery in the PE-group was 3.42 times stronger than the evidence for spontaneous recovery in the Uncer-group.

We also compared the fear response to CS- during the early phase of re-extinction and during the late phase of extinction. There was no evidence for phase differences in both groups (Uncer-group: $BF = 0.306$, $t_{(17)} = 0.721$, $P = 0.481$, *Cohen's* $d = 0.170$; PE-group: $BF = 0.248$, $t_{(17)} = -0.206$, $P = 0.839$, *Cohen's* $d = -0.049$). These results showed that there was no significant fear response to CS+ and CS- in the Uncer-group compared with the late phase of extinction; however, an evident fear response to CS + but not to CS- occurred during the early phase of re-extinction in the PE-group.

To compare the spontaneous recovery in two groups directly, we performed a repeated measures ANOVA with group × phase (late extinction and early re-extinction) × stimulus type (CS + vs CS-), which yielded a significant main effect of phase ($BF = 5.473$; $F(1,34) = 5.635$, $P = 0.023$, $\eta^2 = 0.142$) and stimulus type ($BF = 313.473$; $F(1,34) = 15.007$, $P < 0.001$, $\eta^2 = 0.306$), and an interaction effect of stimulus type × phase ($BF = 5.005$; $F(1,34) = 8.585$, $P = 0.006$, $\eta^2 = 0.202$). However, we observed neither significant inter-group differences ($BF = 0.339$; $F(1,34) = 1.493$, $P = 0.230$, $\eta^2 = 0.042$) nor the interaction effect of group × phase ($BF = 0.222$; $F(1,34) = 0.010$, $P = 0.921$, $\eta^2 = 0.000$).

Furthermore, the fear-impairing effect of retrieval–extinction procedure could also be reflected by comparing it with the initial fear memory (Hu et al., 2018). Thus, we contrasted the fear response to the CSs during the early phase of re-extinction and the late phase of acquisition by ANOVA with group × phase (late acquisition and early re-

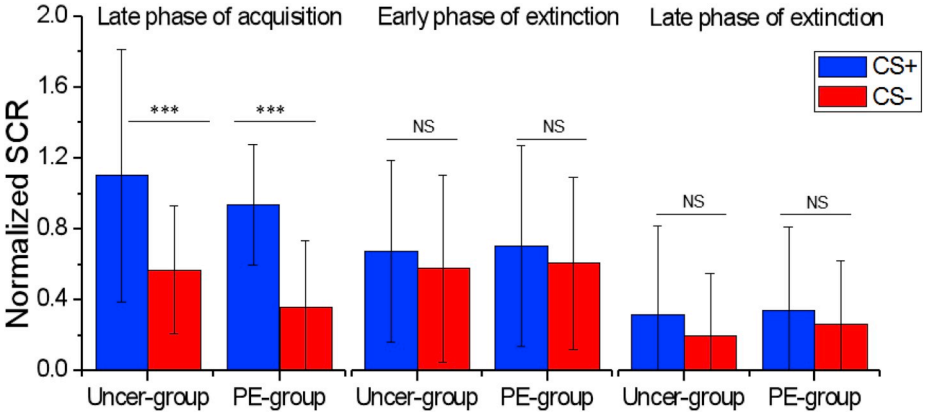

Fig. 4. Successful extinction in both groups. Compared with the late phase of acquistion, both groups showed significant reduction in SCR to CS+ during the late phase of extinction. There was no different responding to CS+ and CS- in the late phase of extinction.

extinction) × stimulus type (CS + vs CS-), which yielded a significant main effect of phase (BF = 59657.905; $F_{(1,34)}$ = 17.100, P < 0.001, η^2 = 0.131) and stimulus type (BF = 8.807e +6; $F_{(1,34)}$ = 80.594, P < 0.001, η^2 = 0.701), and the interaction effect of stimulus type × phase (BF = 2.051; $F_{(1,34)}$ = 5.129, P = 0.030, η^2 = 0.131).

Follow-up t tests further provided strong evidence for the fear-impairing effect in the Uncer-group because we observed a significant reduction in fear response to CS+ (BF = 8.090, $t_{(17)}$ = 3.137, P = 0.006, *Cohen's* d = 0.739) and CS- (BF = 45.894, $t_{(17)}$ = 4.074, P < 0.001, *Cohen's* d = 0.960). Additionally, follow-up t tests also provided relatively weak evidence for the fear-impairing effect in the PE-group by a certain amount of reduction in fear response to CS+ (BF = 1.820, $t_{(17)}$ = 2.261, P = 0.037, *Cohen's* d = 0.533) but non-significant improvement of the fear response to the CS- (BF = 0.363, $t_{(17)}$ = 0.957, P = 0.352, *Cohen's* d = 0.225).

These results together indicated that the Uncer-group and PE-group could produce a fear-impairing effect, but the effect of uncertainty retrieval on deleting fear memory may be better than the effect of PE retrieval because only the Uncer-group did not show a significant spontaneous recovery of fear memory (Fig. 5A.).

3.2.5. Reinstatement of conditioned fear memory

We examined the fear response to CS+ 5 min after four USs without CSs. We used the different SCR to CS + between the early phase of reinstatement and the late phase of re-extinction as the index of reinstatement. Thus, we conducted a paired samples t-test in both groups. The results indicated no evidence for remarkable return of fear response to CS+ in the Uncer-group (BF = 0.244, $t_{(17)}$ = 0.088, P = 0.931, *Cohen's* d = 0.021). However, there was anecdotal evidence for significant reinstatement of fear memory in the PE-group (BF = 2.125, $t_{(17)}$ = 2.358, P = 0.031, *Cohen's* d = 0.556). In addition, the paired samples t-test found no evidence for phase difference on fear response to CS- in both groups (Uncer-group: BF = 0.451, $t_{(17)}$ = 1.197, P = 0.248, *Cohen's* d = 0.282; PE-group: BF = 0.342, $t_{(17)}$ = 0.880, P = 0.391, *Cohen's* d = 0.207). Thus, these results indicated that only the Uncer-group could effectively prevent relapse.

Additionally, to compare the reinstatement in the two groups directly, we performed a repeated measures ANOVA with group × phase (late re-extinction and early reinstatement) × stimulus type (CS + vs CS-), which yielded a significant main effect of phase (BF = 1.229; F(1,34) = 4.462, P = 0.042, partial η^2 = 0.116) and stimulus type (BF = 214.342; F(1,34) = 15.829, P < 0.001, η^2 = 0.318). We found that the main effect of the group reached a significant margin (BF = 0.860; F(1,34) = 3.638, P = 0.065, η^2 = 0.097), and no evidence for significant interaction effect of group × phase (BF = 0.798; F(1,34) = 2.710, P = 0.109, η^2 = 0.074) was observed.

Similarly, we also assessed the fear-impairing effect in this phase by comparing the SCR to CS+ in the late phase of acquisition and in the early phase of reinstatement with the paired samples t-test. The results showed that a meaningful improvement on fear response to CSs occurred only in the Uncer-group (CS+: BF = 1801.739, $t_{(17)}$ = 6.068, P < 0.001, *Cohen's* d = 1.430; CS-: BF = 258.218, $t_{(17)}$ = 4.996, P < 0.001, *Cohen's* d = 1.178). By contrast, there was unremarkable improvement in the PE-group compared with the initial fear memory (CS+: BF = 0.586, $t_{(17)}$ = 1.440, P = 0.168, *Cohen's* d = 0.339; CS-: BF = 0.315, $t_{(17)}$ = 0.765, P = 0.455, *Cohen's* d = 0.180).

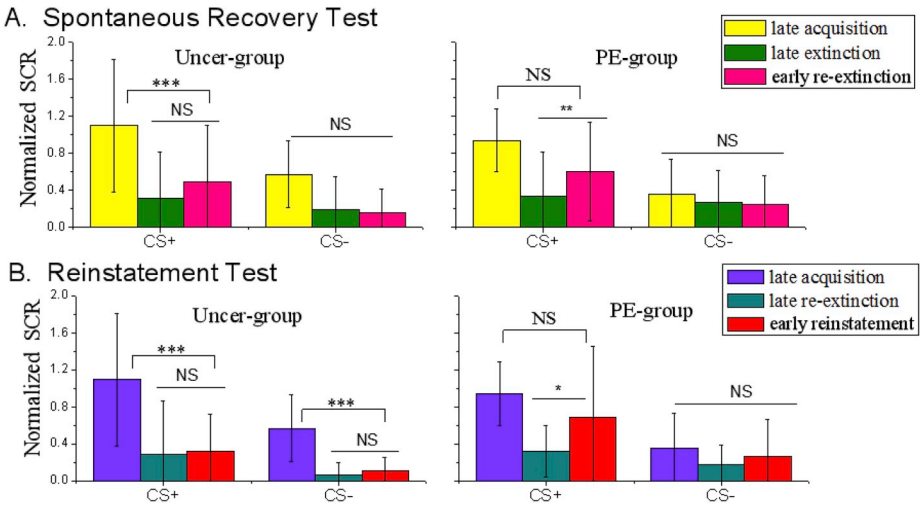

Fig. 5. Fear relapse test. A: Spontaneous recovery tests showed a significant fear-imparing effect and non-significant spontaneous recovery in the Uncer-group, while the contrary results showed in the PE-group. B: Reinstatement tests indicated a significant fear-imparing effect and non-significant reinstatement in the Uncer-group, and the contrary results in the PE-group.

These results confirmed a robust fear-impairing effect of post-retrieval extinction in the Uncer-group. Additionally, deleting fear memory in the PE-group was an evident failure (Fig. 5B.).

3.3. FPS

3.3.1. Acquisition and extinction of conditioned fear memory

FPS was defined as the potentiation of the magnitude of startle to the acoustic probe in the presence of CSs relative to the magnitude of the startle to NA (Glover et al., 2011; Jovanovic et al., 2009). The value of FPS was calculated by subtracting the mean value of startle responses to NA from those to CSs.

A mixed ANOVA with factors of group (Uncer-group vs PE-group) × phase (early and late of acquisition session) × stimulus type (CS+, CS-) was conducted to assess the acquisition of fear memory. The results showed a significant main effect of stimulus type (BF = 1.707e +6; $F_{(1,34)}$ = 37.801, P < 0.001, η^2 = 0.506); a non-significant main effect of group (BF = 0.293; $F_{(1,34)}$ = 0.008, P = 0.931, η^2 = 0.000); and non-significant interaction effect of group × stimulus type (BF = 0.647; $F_{(1,34)}$ = 2.972, P = 0.094, η^2 = 0.040), phase × stimulus type (BF = 1.464; $F_{(1,34)}$ = 5.362, P = 0.027, η^2 = 0.136), and group × stimulus type × phase (BF = 0.140; $F_{(1,34)}$ = 0.075, P = 0.786, η^2 = 0.002). Follow-up *t tests* showed significantly higher FPS to CS + than to CS- during all phases in the Uncer-group (early phase of acquisition: BF = 232.843, $t_{(17)}$ = 4.941, P < 0.001, *Cohen's d* = 1.165; late phase of acquisition: BF = 402.978, $t_{(17)}$ = 5.237, P < 0.001, *Cohen's d* = 1.234), but only during the late phase of acquisition in the PE-group (early phase of acquisition: BF = 0.353, $t_{(17)}$ = 0.923, P = 0.369, *Cohen's d* = 0.218; late phase of acquisition: BF = 41.112, $t_{(17)}$ = 4.016, P < 0.001, *Cohen's d* = 0.946). These results indicated that the Uncer-group learned fear memory faster than the PE-group but finally, both successfully learned fear memory.

Similarly, the repeated measures ANOVA with factors of group × phase (early and late of extinction session) × stimulus type was used to test the extinction of fear memory and found only a significant main effect of phase (BF = 4.260e +8; $F_{(1,34)}$ = 43.163, P < 0.001, η^2 = 0.549) and stimulus type (BF = 4.690; $F_{(1,34)}$ = 8.209, P = 0.007, η^2 = 0.190). Follow-up *t tests* revealed weak evidence for differential response to CSs during the early phase of extinction (BF = 1.483, $t_{(17)}$ = 2.128, P = 0.048, *Cohen's d* = 0.502), but no evidence for it during the late phase (BF = 0.969, $t_{(17)}$ = 1.835, P = 0.084, *Cohen's d* = 0.433) in the Uncer-group, and no evidence for differential responding to CSs during all phases in the PE-group (early phase of extinction: BF = 0.670, $t_{(17)}$ = 1.553, P = 0.139, *Cohen's d* = 0.366; late phase of extinction: BF = 0.289, $t_{(17)}$ = 0.624, P = 0.541, *Cohen's d* = 0.147). To ensure that both groups learned an equivalent extinction memory, we compared the FPS to CSs during the late phase of extinction between two groups by independent samples *t*-test. The result revealed no difference in FPS to CS+ (BF = 0.373, $t_{(17)}$ = 0.613, P = 0.544, *Cohen's d* = 0.204) and CS- (BF = 0.325, $t_{(17)}$ = −0.162, P = 0.872, *Cohen's d* = −0.054) between the groups during the late phase of extinction. These results confirmed that the two groups have finally succeeded to equivalently eliminate the fear response to CSs.

3.3.2. Spontaneous recovery of conditioned fear memory

We compared the FPS to CSs during the early phase of re-extinction and the late phase of extinction to assess the spontaneous recovery in both groups. For the FPS to CS+, no evidence was observed for spontaneous recovery in both groups by non-significant main effect of phase (BF = 0.306; $F_{(1,34)}$ = 1.193, P = 0.282, η^2 = 0.033), group (BF = 0.449; $F_{(1,34)}$ = 1.451, P = 0.237, η^2 = 0.041), and the interaction effect of phase × group (BF = 0.179; $F_{(1,34)}$ = 0.577, P = 0.453, η^2 = 0.016). The FPS to CS- between two phases showed an unremarkable difference by non-significant main effect of phase BF = 0.257; $F_{(1,34)}$ = 0.826, P = 0.370, η^2 = 0.024), group (BF = 0.231; $F_{(1,34)}$ = 0.017, P = 0.897, η^2 = 0.000) and the interaction effect of phase × group (BF = 0.079; $F_{(1,34)}$ = 0.012, P = 0.914, η^2 = 0.000). These results indicated that spontaneous recovery did not occur in either group.

3.3.3. Reinstatement of conditioned fear memory

We compared the FPS to CSs during the early phase of the reinstatement session and the late phase of re-extinction to assess the reinstatement of fear memory in both groups. For the FPS to CS+, there was no evidence for spontaneous recovery in both groups by non-significant main effect of phase (BF = 0.319; $F_{(1,34)}$ = 1.261, P = 0.269, η^2 = 0.035), group (BF = 0.299; $F_{(1,34)}$ = 0.713, P = 0.404, η^2 = 0.021), and the interaction effect of phase × group (BF = 0.130; $F_{(1,34)}$ = 0.392, P = 0.535, η^2 = 0.011). By contrast, there was strong evidence for phase difference in the FPS to CS- by a significant main effect of phase (BF = 57.911; $F_{(1,34)}$ = 10.909, P = 0.002, η^2 = 0.242), but a non-significant main effect of group (BF = 0.323; $F_{(1,34)}$ = 0.785, P = 0.382, η^2 = 0.023) and interaction effect of phase × group (BF = 0.352; $F_{(1,34)}$ = 0.131, P = 0.719, η^2 = 0.003). Follow-up *t tests* revealed an unremarkable difference between the FPS to CS during the early phase of reinstatement session and in the late phase of re-extinction in the Uncer-group. The FPS to CS- during the early phase of the reinstatement session was significantly higher than those during the late phase of re-extinction. This result indicated that a possible fear generalisation occurred in the PE-group (Fig. 6).

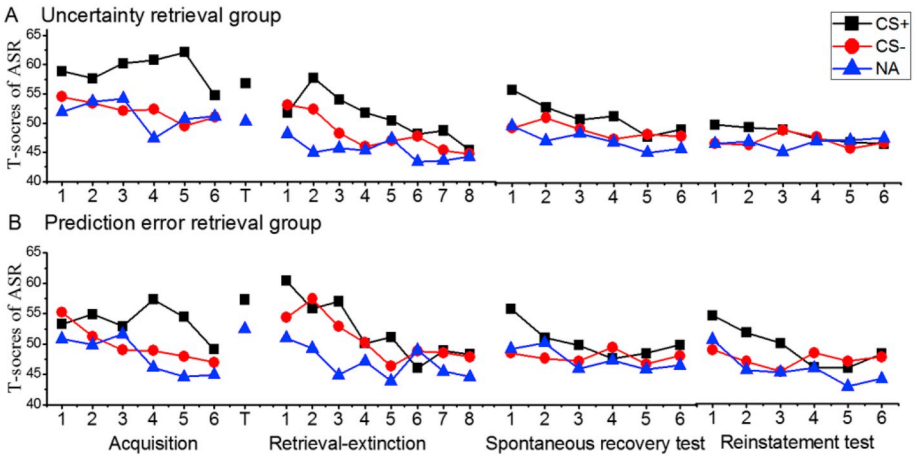

Fig. 6. T-transformed acoustic startle response (ASRs) to the CS+ and CS- trials during acquisition, reactivation, extinction and spontaneous recovery test and reinstatement test in each group.

4. Discussion

The purpose of this study was to test whether there was an alternative or a better means to open the reconsolidation window of fear memory than PE retrieval. The results indicates that the extinction after retrieval with uncertainty, compared with PE, had a potential advantage on the ability to prevent relapse and the fear-impairing effect. However, when we compared between groups, we did not find the advantage of uncertainty retrieval in the ability to prevent relapse. In addition, this advantage is only reflected in the SCR level. These results preliminarily verified the assumption by Radiske et al. in humans for the first time (Radiske et al., 2017). Overall, our study presents suggestive but not decisive evidence that uncertainty retrieval could be a better means to trigger memory reconsolidation than prediction error, making uncertainty a worthwhile factor to consider in future research on memory reconsolidation.

It should be noted that we defined the successful intervention according to two main indicators, which is consistent with our clinical intervention goals. Firstly, there must be a significant fear-impairing effect after intervention (i.e. significant difference between late acquisition and early re-extinction); Secondly, there is no significant recurrence (i.e. no significant difference between late extinction and early re-extinction).

Firstly, we found that only the extinction after uncertainty retrieval produced a robust fear-impairing effect on the strong fear memory. There are three possible explanations for this advantage on the fear-impairing effects. One explanation is that the positive memory acquired during the pre-exposure can serve as an improvement in the ability of emotion regulation, which can further modulate the duration and intensity of emotional responding (Vanderlind, Stanton, Weinbrecht, Velkoff, & Joormann, 2017). This emotion regulation may work by producing positive emotions, enhancing the cognitive resources, and thus increasing the capacity of the down-regulation of negative emotions (Contractor et al., 2018; Fredrickson, 2001). Therefore, the fear-impairing effect caused by uncertainty retrieval may have roots in the effect of the positive effect induced by pre-exposure. However, pre-exposure had no remarkable effect on the emotional state in the current study. In addition, the fear memory during the early and late phases of acquisition in the Uncer-group was slightly stronger than in the PE-group, and these results provide a strong evidence that deprecates the possibility that the fear-impairing effects are rooted in the down-regulation of positive affect.

An argument is that the fear-impairing effects may result from double PEs produced by uncertainty retrieval. Indeed, the CS+ was linked with two memories and neither presented during retrieval, which seems to generate double PEs; but in practice, this view is untenable. On the one hand, according to the definition of PE, it would be produced only when a certain and specific prediction of the memory mismatch with the reality. However, the most important characteristic for uncertainty retrieval is not the expectation of one of two memories, but the conflicting information, which would lead to an uncertain state but not PE. On the other hand, according to the dominant trace principle, two competing memories would weaken each other (Wimber, Alink, Charest, Kriegeskorte, & Anderson, 2015). In this case, individuals would not have strong expectations for either of these memories. Therefore, it would be a relatively weak one even if the PE occurred. Notably, a stronger prediction error have failed to generate a significant fear-impairing effect in the PE-group. Hence, the fear-impairing effect in the Uncer-group was unlikely caused by the PE.

Secondly, we found that only the extinction after uncertainty retrieval could effectively prevent fear relapse. This finding is inconsistent with most the literature, which found that PE retrieval can trigger the reconsolidation of fear memory and the intervention during this process can effectively prevent the fear relapse. One possible reason for this result is that we adopted excessive reinforcement learning, leading to the formation of a strong fear memory. The strength of memory was considered a crucial boundary condition for triggering memory reconsolidation (Kwak, Choi, Bakes, Lee, & Kaang, 2012). Specifically, a stronger fear memory would be more resistant to destabilization by PE retrieval. Thus, the PE-group may not destabilize the initial fear memory and could not enter the memory reconsolidation process. The extinction session of the PE-group formed only a new memory, which competed with the original fear memory and left the initial fear memory intact. Therefore, the retrieval–extinction of the PE-group had no remarkable improvement on the cognitive level of fear memory and showed significant recovery of fear.

However, we did not observe significant inter-group differences in the ability to prevent relapse, when we directly compared the effects of the two interventions. This non-significant effect may be due to the relatively small sample size in this study. Although no significant differences were found in direct inter-group comparisons (non-significant inter-group effects and interactions), separate *t-test* results provided—at least—a qualitative difference between the effects of the two interventions: success or failure.

Based on the aforementioned considerations, we speculate that the uncertainty, not the PE, is the necessary condition for triggering memory reconsolidation. The greatest significance of memory reconsolidation is to help people adapt to a new environment. Only when the initial memory system cannot manage the current situation, would it open its window and allow new information in to update itself. The uncertainty, caused by previously acquired conflicting information or new situations, is the main target for memory reconsolidation to overcome. To solve the uncertainty, the memory system must incorporate new information, which provides an opportunity to modify the maladaptive memories. The PE can produce an uncertainty when the initial memory is weak, but not when the memory is strong. Thus, PE retrieval can often successfully facilitate the elimination of the fear response in a laboratory scenario but fails to prevent fear relapse in the clinical context.

Uncertainty retrieval has some advantages over PE retrieval in clinical application. We can create a robust uncertainty during retrieval on the basis of previously acquired conflicting information without strictly controlling the acquisition history of initial fear memory. In addition, uncertainty retrieval can effectively open the memory reconsolidation window despite the strength of the initial fear memory. Thus, the uncertainty retrieval will greatly facilitate the transformation from basic research to clinical practice.

Our results provide promising evidence to support the great significance of uncertainty in the memory updating. However, this study has some limitations worthy of consideration in the further research. Firstly, we did not completely separate the effect of PE and uncertainty on memory updating. Although we can deduce the unique function of uncertainty from the results, it is necessary to manipulate uncertainty more accurately to verify its role in memory renewal. Secondly, we set up only two groups to preliminarily investigate the role of uncertainty retrieval in opening the reconsolidation of fear memory, so an additional no-reminder control condition is recommend to determine the role of uncertainty in reconsolidation-related mechanism. In addition, a larger sample is recommended in future research.

5. Conclusions

This study indicated that uncertainty during retrieval can enhance the fear-impairing effect of an extinction procedure. Additionally, uncertainty retrieval effectively prevented fear relapse, whereas the PE retrieval did not. These results provided a possibility that uncertainty retrieval could be a better method to trigger memory reconsolidation.

Conflicts of interest

None.

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