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The effect of retrieval exposure duration on the reconsolidation and extinction of fear memory

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Abstract The retrieval-extinction paradigm based on memory reconsolidation shares significant similarities with the traditional extinction paradigm in terms of operational procedures. Minor adjustments in the retrieval phase may prevent memory from entering reconsolidation, thereby losing the effect of sustained suppression of fear relapse. Studies have found that the duration of retrieval exposure can regulate the memory entering different stages, and its mechanism is related to the prediction error induced by retrieval. This study modifies the retrieval-extinction paradigm based on the traditional extinction paradigm by controlling the number of retrieval trials to change the retrieval exposure duration. It aims to explore the regulatory role of retrieval exposure duration on memory reconsolidation and extinction, and attempts to elucidate its mechanism by quantifying prediction error. The results showed that single-retrieval extinction group triggers memory reconsolidation and updating, double-retrieval extinction group is ineffective (results consistent with traditional extinction group), and Quadruple-retrieval extinction group enhances extinction memory strength. The quantified prediction error results supported these process differences. These findings are conducive to further revealing the regulatory factors of human fear memory reconsolidation and extinction.

Keywords exposure duration, traditional extinction paradigm, retrieval extinction paradigm, prediction errors

1 Introduction

Fear memory has played a crucial role in species evolution, being a key factor in human survival. However, excessive and rigid fear can disrupt daily life and impact both mental and physical health, necessitating the attenuation and elimination of maladaptive memories. The formation of fear memory is based on Pavlovian classical conditioning, which is considered a typical experimental model for studying negative emotional memory (Kim & Richardson, 2010). When a neutral stimulus (conditioned stimulus, CS) is repeatedly paired with an aversive stimulus (unconditioned stimulus, US), the individual develops a conditioned fear response to the CS alone, similar to the response elicited by the US. This indicates the acquisition of a CS-US conditioned fear memory connection. After acquiring conditioned fear, if the CS is repeatedly presented without the US, the fear response to the CS will gradually diminish. This process is known as conditioned fear extinction, also referred to as the traditional extinction paradigm (Davis et al., 2003). However, both research and practice have shown that the original CS-US associative memory is not eliminated by extinction training. Traditional extinction training leads to the formation of new extinction memory that competes with the original fear memory. The outcome of this competition determines whether the fear response is expressed, with the dominant memory influencing the individual's behavior (Bouton, 2004). Despite significant progress in understanding the behavioral and neurobiological mechanisms of conditioned fear extinction, substantial evidence indicates that fear relapse occurs under various conditions, manifesting as spontaneous recovery, reinstatement, renewal, and rapid reacquisition (Myers & Davis, 2007). This presents a major challenge for clinical exposure therapy based on extinction training, which aims to reduce maladaptive responses caused by conditioned fear. Patients often experience fear relapse after undergoing exposure therapy.

In recent years, researchers have actively explored intervention methods targeting the original fear memory CS-US connection to avoid the problem of fear relapse observed with traditional extinction training. This led to the emergence of the memory reconsolidation intervention paradigm. Memory reconsolidation refers to the process by which previously consolidated long-term memory becomes temporarily destabilized under certain retrieval conditions and then restabilizes (Phelps & Hofmann, 2019). When fear memory becomes unstable, behavioral or pharmacological interventions during the restabilization process can modify or update the original fear memory (Lee et al., 2017; Nader et al., 2000). Numerous studies have shown that after an individual acquires conditioned fear, exposure to a conditioned stimulus (CS) related to the original context (retrieval cue) reactivates the original memory, making it unstable and entering the reconsolidation phase. During this time window (currently recognized as 6 hours), conducting traditional extinction training can effectively prevent fear relapse. This approach is known as the retrieval-extinction paradigm (Kredlow et al., 2016; Monfils et al., 2009; Schiller et al., 2010). As a non-invasive behavioral intervention, the retrieval-extinction paradigm is safer and more applicable to human subjects compared to other pharmacological and behavioral interventions based on the principle of memory reconsolidation.

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Its extinction effects are more enduring and less prone to relapse compared to the traditional extinction paradigm. Moreover, it closely aligns with the procedures used in current clinical exposure therapies, facilitating easier clinical translation.

Although the traditional extinction paradigm and the retrieval-extinction paradigm share significant operational similarities (both involve a certain amount of CS exposure without the US), their mechanisms and neurobiological foundations are different. The traditional extinction paradigm generates CS-noUS extinction memory that competes with the original fear memory, based on memory extinction. In contrast, the retrieval-extinction paradigm destabilizes the original memory through the retrieval operation, and the subsequent extinction training updates the unstable original CS-US connection to a safe CS-US connection, based on memory reconsolidation (Chen et al., 2021). Evidence from animal studies suggests that the effectiveness of the retrieval-extinction paradigm depends on changes in calcium-permeable AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole) receptors in the basolateral amygdala (BLA), whereas traditional extinction is not dependent on these changes (Clem & Huganir, 2010). Human functional magnetic resonance imaging (fMRI) data indicate that, compared to the traditional extinction group, the retrieval-extinction group shows reduced involvement of the ventromedial prefrontal cortex during the extinction training phase, weakened functional connectivity between the prefrontal cortex and the amygdala, and decreased amygdala activation (Schiller et al., 2013). This suggests that minor operational differences can lead to either memory reconsolidation or extinction. Numerous studies have shown that a key distinction between the two is that reconsolidation typically involves limited or brief exposure to the CS, while extinction involves prolonged exposure to the CS (Ferrara et al., 2023). In studies of contextual fear conditioning in mice, it was found that 3 minutes of exposure to a threatening environment induces a reconsolidation process, whereas 30 minutes of exposure induces extinction learning (Suzuki et al., 2004). On a neurochemical level, it was observed that, several days after acquiring conditioned fear to a tone, presenting four CSs induced a memory reconsolidation process marked by the internalization of AMPA receptors containing the GluA2 subunit, while presenting 40 CSs led to extinction learning and a reduction in the phosphorylation of CREB (a protein that regulates gene transcription) (Ferrara et al., 2021). However, human studies have rarely examined the regulation of memory reconsolidation and extinction by exposure duration.

Despite both memory reconsolidation and extinction being induced by CS exposure during the retrieval phase, their relationship is non-linear and controlled by "boundary conditions," which determine whether memory is activated into different processes. The boundary condition most studied is prediction error (PE) (Vaverkova et al., 2020). Cross-species studies on conditioned fear (crabs, rats, humans) have shown that both reconsolidation and extinction require prediction error during retrieval, meaning a discrepancy between previously acquired information and current information (Diaz-Mataix et al., 2013; Gershman et al., 2017; Pedreira et al., 2004). Research evidence from both foreign and our laboratories suggests that prediction error is a necessary but not sufficient condition for memory destabilization (Chen et al., 2018; Junjiao et al., 2019; Sevenster et al., 2013). Studies have found that reconsolidation demands a specific range of prediction errors: the extent of the prediction error must be significant enough to necessitate updating (appropriate PE triggers reconsolidation), but not so different as to warrant forming a new memory (excessive PE triggers extinction) (Chen et al., 2020; Exton-McGuinness et al., 2015). Therefore, quantifying the prediction error generated by the original memory during CS exposure can help elucidate how exposure duration regulates memory reconsolidation and extinction, supported by evidence from human and animal studies. For example, in human studies, researchers have demonstrated through increasing retrieval trials to alter prediction error amounts that different levels of prediction error can activate memory into different stages, defining the transition from retrieval to reconsolidation to extinction (Sevenster et al., 2014). Additionally, in rodent studies, altering the timing of shocks during retrieval exposure induced temporal prediction errors, and different exposure durations created trace dominance, showing that prediction error and trace dominance jointly mediate the transition from retrieval to reconsolidation to extinction (Alfei et al., 2015).

Most studies have found that the retrieval-extinction paradigm can inhibit fear relapse 24 hours later, with some studies even showing effects lasting over a year (Schiller et al., 2010). However, there is a small portion of negative evidence indicating no difference in fear elimination effects between the retrieval-extinction and traditional extinction paradigms (Chalkia et al., 2020; Zimmermann & Bach, 2020). In the conditioned fear model, the operational difference between the traditional extinction and retrieval-extinction paradigms is simply whether stimuli are presented continuously or in two stages: traditional extinction involves continuous CS presentation without the US, while retrieval-extinction involves presenting some trials, waiting a period (typically 10 minutes in human studies), and then presenting the remaining trials. Therefore, some scholars suggest that the reason for the negative findings in retrieval-extinction studies may be that the retrieval operation fails to destabilize the original memory, making retrieval-extinction equivalent to traditional extinction, both leading to new safety memory that coexists with the original fear memory, ultimately resulting in fear relapse after extinction (Zuccolo & Hunziker, 2019). According to reconsolidation theory, the key to the success of the retrieval-extinction paradigm is whether the retrieval phase can destabilize the memory, involving whether the CS exposure duration and the resulting prediction error meet the boundary conditions for destabilizing the original memory. In human conditioned fear models, exposure duration is expressed as the time or number of CS presentations. Research on CS presentation time has shown that when the retrieval phase involves 1-second or 4-second CS exposures, the retrieval-extinction paradigm shows superior fear response elimination compared to traditional extinction. When the retrieval phase involves 30-second or 3-minute CS exposures, the retrieval-extinction effect is the same as traditional extinction, indicating the memory did not enter the reconsolidation process (Hu et al., 2018). However, the regulation of fear memory towards reconsolidation or extinction by the number of CS presentations, and thus whether the retrieval-extinction effect surpasses traditional extinction, has not been clearly explored in human conditioned fear models.

In summary, the great clinical application potential of the retrieval-extinction paradigm lies in its ability to be directly

transformed from the traditional extinction paradigm by dividing it into a retrieval phase and an extinction phase with a certain interval in between. However, studies have found that if the retrieval phase does not destabilize the original memory but only involves retrieval (memory expression) or directly triggers extinction learning, the effects of retrieval-extinction and traditional extinction will be identical, making the entire retrieval-extinction process equivalent to traditional extinction. Therefore, from the perspective of clinical application of the retrieval-extinction paradigm, it is necessary to explore in the laboratory how to allocate retrieval trials (i.e., control retrieval exposure duration) to successfully transform the traditional extinction paradigm into the retrieval-extinction paradigm. Only by clarifying the effect of retrieval exposure duration on the fate of memory (reconsolidation or extinction) after retrieval can the traditional extinction paradigm be effectively transformed into the retrieval-extinction paradigm, leveraging the reconsolidation effect to inhibit fear relapse. To this end, this study modifies the retrieval-extinction paradigm based on the traditional extinction paradigm by controlling the number of retrieval trials to change the retrieval exposure duration. It aims to explore the regulatory role of retrieval exposure duration on memory reconsolidation and extinction and attempts to elucidate its mechanism by quantifying prediction error.

2 Methods

2.1 Participants

Participants were recruited from university students through volunteer sign-ups and recruitment posters, with the requirement that participants attend the experiment at the same time for four consecutive days. All participants were right-handed, had no history of physical or mental disorders, had normal or corrected-to-normal vision, normal hearing, and had no symptoms of nasal congestion or coughing recently. Additionally, they had not participated in similar emotional experiments within the past six months. The study was approved by the Ethics Committee of the School of Psychology at South China Normal University (Approval Number: SCNU-PSY-2022-131). All participants presented their ID cards before the experiment to ensure they were at least 18 years old and signed an informed consent form. The consent form informed participants of the test content (including skin conductance, questionnaire completion, and subjective assessment), explained the nature of the skin conductance experiment and the individualized evaluation of electric shocks, ensuring the voltage range was strictly controlled and would not harm the body. Participants were also informed that they could lower the shock value or terminate the experiment at any time if they felt uncomfortable. Confidentiality principles were explained, ensuring all data and information related to the participants would be strictly confidential. Participants were also asked to keep the experiment's content confidential and signed their names upon confirmation. Those who completed the four-day experiment received a certain amount of compensation, with additional rewards given based on their diligence.

The sample size was calculated using G*Power 3.1 software, setting the probability of Type I error $\alpha = 0.05$, test power $1 - \beta = 0.8$, and effect size $f = 0.25$, resulting in a required sample size of 80 participants. A total of 90 participants were recruited, with 87 valid participants, including 24 males (3 participants did not complete the experiment for personal reasons). The age range was 18 to 28 years ($M = 20.85$, $SD = 2.31$). Participants were randomly divided into four groups according to the experimental design: Group 1 was the traditional extinction group (Group E), Group 2 was the single-retrieval extinction group (Group R1), Group 3 was the double-retrieval extinction group (Group R2), and Group 4 was the quadruple-retrieval extinction group (Group R4). There were no significant differences among the four groups in terms of age, gender, trait anxiety level, depression level, or the intensity of the electric shocks, as shown in Table 1.

2.2 Experimental materials

Following previous studies (Chen et al., 2020, 2021), the conditioned stimuli in the experiment consisted of two images of single-colored, three-dimensional geometric shapes. One image depicted an orange cylinder, and the other depicted a purple cube, as shown in Figure 1. Both images had the same brightness, with a white background, and were presented in slideshow format (resolution 960×540) on a 16-inch LCD computer screen. Each image was displayed for 8 seconds. One of the conditioned stimuli was followed by an unconditioned stimulus (US, i.e., an electric shock) on 50% of the trials, termed CS+, while the other conditioned stimulus was not followed by the unconditioned stimulus, termed CS−. The assignment of the images to CS+ or CS− was counterbalanced across participants. The unconditioned stimulus was a constant voltage electric shock delivered to the participant's right wrist, intended to induce a fear response. The intensity of the electric shock was predetermined based on each participant's tolerance level, with each shock lasting 200 ms. Prior to the formal experiment, participants were exposed to the electric shock and asked to rate their discomfort on a scale of 0 to 9 (with 0 being "comfortable with no sensation" and 8 being "extremely uncomfortable but bearable," and 9 being "unbearable pain"). The

Table 1
Group information and questionnaire data of the participants

variables	Group				F or χ^2	p
	E (n = 23)	R1 (n = 23)	R2 (n = 21)	R4 (n = 20)		
Number of male (proportion)	6 (26.09%)	9 (39.13%)	5 (23.81%)	4 (20.00%)	2.29	0.515
Age	20.35 ± 4.24	21.43 ± 3.98	19.95 ± 4.16	21.70 ± 4.85	0.04	0.990
STAI-T	43.04 ± 8.98	42.87 ± 7.96	39.76 ± 8.29	43.00 ± 9.62	0.03	0.992
BDI	4.30 ± 0.90	5.52 ± 1.03	6.81 ± 1.42	6.95 ± 1.55	1.03	0.382
Shock intensity	54.96 ± 11.46	50.30 ± 9.34	55.38 ± 11.55	44.25 ± 9.89	0.23	0.877

Note. E: Traditional extinction group, R1: Single-retrieval extinction group, R2: Double-retrieval extinction group, R4: Quadruple-retrieval extinction group. STAI-T: State-Trait Anxiety Inventory, BDI: Beck Depression Inventory. $M \pm SD$.

Figure 1. Experimental material.

intensity corresponding to a rating of 8 was selected as the electric shock intensity for that participant for the entire experiment and remained constant throughout the study.

2.3 Measurement Indicators

2.3.1 Skin Conductance Response

Skin conductance response (SCR) was measured using the Biopac MP36 physiological data acquisition system at a sampling rate of 1000 Hz. Two electrodes were attached to the index and ring fingers of the left hand, and data were analyzed using the Biopac Student Lab 4.1 software.

For processing the SCR data during stimulus presentation: First, the skin conductance data were filtered using a low-pass filter (1 Hz) to eliminate noise interference. Second, the SCRs for all CS+ and CS− trials were analyzed by subtracting the average skin conductance level 1 s before the CS presentation from the maximum SCR within 7.8 s of the CS presentation (excluding the impact of the electric shock). This difference was used as the raw skin conductance response to the CS (Sevenster et al., 2013). All SCR data were then range-corrected, setting skin conductance values less than 0.02 μs to zero. Finally, all data were standardized using a square root transformation to reduce distribution skewness (Schiller et al., 2010).

2.3.2 Subjective Expectation Ratings and Prediction Error Quantification

This study adopted Thiele et al. (2021) method to collect participants' subjective expectation ratings of shock occurrence during the acquisition and retrieval-extinction phases. The size of the prediction error for each trial during the retrieval-extinction phase was calculated using a simplified Rescorla-Wagner model, which represents prediction error. The model is expressed in Equation (1).

$$V_{t+1} = V_t + \alpha^*(R - V_t) \tag{1}$$

V_t represents the expected value of the likelihood of the conditioned stimulus being followed by the unconditioned stimulus for trial t; α is the learning rate, set as a constant between 0 and 1, with different values for the fear acquisition and retrieval-extinction phases; R is the actual fear response value, which varies between reinforced (shock-present) and non-reinforced (shock-absent) trials; the prediction error for trial t equals $R - V_t$, indicating the discrepancy between the actual occurrence of the unconditioned stimulus and the prior expectation for that trial.

Subjective expectation ratings were collected by presenting a rating slider below the conditioned stimulus image during the first 6 s of the image presentation. The slider ranged from 0 to 100 (0 indicating "no chance of shock," 100 indicating "certain shock"), with an initial default value of 50. Higher scores indicated a higher likelihood of expecting a shock in that trial. Participants used a mouse to adjust the slider to the desired rating. The raw subjective expectation ratings were standardized to reduce individual differences and facilitate subsequent analysis and group comparison. Specifically, all participants' data were standardized as a whole, using the mean of the first CS+ and CS− ratings for each participant and the difference between the maximum and minimum values of all participants' ratings during the acquisition and retrieval-extinction phases (Thiele et al., 2021). The standardization and range correction steps are detailed in Equations (2) to (5).

$$V_t' = V_t - (V_{\text{first CS+}} - V_{\text{first CS−}}) / 2 \tag{2}$$

$$V_{\min} = \min(\min(V_t')) \tag{3}$$

$$V_{\max} = \max(\max(V_t')) \tag{4}$$

$$V_{\text{standardization}} = (V_t' - V_{\min}) / (V_{\max} - V_{\min}) \tag{5}$$

The actual fear response value R for each participant was calculated using standardized subjective ratings. There were two types of R values: for non-shock CS trials (CS− and non-shock CS+), the R value was the standardized expectation value corresponding to the last CS− trial during the acquisition phase; for shock CS+ trials, the R value was the standardized expectation value corresponding to the last CS+ trial during the acquisition phase divided by the reinforcement rate of 50%, as shown in Equation (6).

$$R = \begin{cases} R_{\text{no US}} = V_{\text{acq. last CS−}} \\ R_{\text{US}} = V_{\text{acq. last CS+}} / 0.5 \end{cases} \tag{6}$$

The mean standardized subjective ratings for the first CS+ and CS− trials during the acquisition phase were used as the initial expectation value V_0 for each participant. Starting from 0.01, a grid search was performed incrementally by 0.01 to find the learning rates α for the acquisition and retrieval-extinction phases that minimized the error between the fitted values and the actual values. The average α values for each group in each phase were used as the learning rates for that group and phase. Starting from V_0, the learning rate α and actual response value R were substituted into Equation (1) to obtain the fitted expected values V_t for each CS+ and CS− trial for each participant. According to the definition of prediction error in the simplified Rescorla-Wagner model, the prediction error for each CS trial during the retrieval-extinction phase was calculated as $R - V_t$.

2.4 Experimental Procedure

The experimental procedure was programmed and executed using E-Prime 3.0 software. The experiment was conducted over four days, comprising the following phases: Day 1 - Acquisition, Day 2 - Reactivation and Extinction, Day 3 - Spontaneous Recovery, and Day 4 - Reinstatement Test. Each day's session lasted approximately 30 minutes, with 24 h intervals between sessions. The types of stimuli, presentation times, and interstimulus intervals on Days 2, 3, and 4 were the same as on Day 1.

Day 1: Fear Acquisition Phase. Participants entered the laboratory, presented their ID cards to confirm their identity and age (at least 18 years old), and the experimenter explained the details of the experiment. After understanding the experiment, participants signed a joint informed consent form and completed the State Anxiety Inventory and Beck Depression Inventory. Following questionnaire completion, participants were fitted with the experimental apparatus, including skin conductance and shock devices. Before the formal experiment, participants' electric shock intensity was evaluated, with adjustable ranges from 10 to 60 V. Participants first practiced four trials to ensure they understood the experimental rules before starting the formal experiment. In the formal experiment, a red fixation point "+" was presented centrally for 2000 ms, followed by the CS+ and CS− stimulus images and the US subjec-

tive expectation rating slider in a pseudo-random sequence. Each CS stimulus image was presented for 8000 ms, with the rating slider appearing simultaneously but for 6000 ms. The electric shock for CS+ trials occurred 200 ms before the image disappeared and lasted for 200 ms. The acquisition phase included 12 CS+ and 12 CS− stimuli, with 6 CS+ stimuli paired with shocks (reinforcement rate 50%), and the 1st, 4th, 5th, 8th, 10th, and 11th CS+ stimuli unpaired with shocks (pseudo-random sequence). The first stimulus was always CS−, and the second was always a non-shocked CS+ to collect the initial expectation values for the CS. The intertrial interval (ITI) ranged from 8 to 10 s, with the screen displaying "please relax" to ensure participants' skin conductance levels returned to normal. After the experiment, participants were asked to report the association between the images and the shocks. The presentation flow of the experimental stimuli and shocks is shown in Figure 2.

Day 2: Reactivation and Extinction Phase. Before starting, participants were asked if they remembered the information from the first day and were informed that the same stimuli would be presented. Participants were re-fitted with the shock and Biopac MP36 devices, and the shock intensity was adjusted to the level rated as "8" on the first day. Participants in the experimental group with 0 retrieval trials (Group E) directly entered the extinction phase, where 12 CS+ and 12 CS− were randomly presented without shocks. Participants in the experimental group with 1 retrieval trial (Group R1) had one non-shocked CS+ trial, then rested for 10 min, during which they watched a 9 min neutral video, before entering the extinction phase. Participants in the experimental groups with 2 or 4 retrieval trials (Groups R2 and R4) had 2 or 4 non-shocked CS+ trials, respectively, then rested for 10 min before entering the extinction phase. During both the acquisition and retrieval-extinction phases, a subjective expectation rating slider was displayed at the bottom of the computer screen, allowing participants to rate their current level of fear at any time without receiving a shock.

Day 3: Spontaneous Recovery Test Phase. Participants entered the laboratory and were fitted with the equipment and connected to the devices. After the experiment started, a red fixation point "+" was presented on the screen for 2000 ms to capture participants' attention, followed by the random presentation of 12 CS+ and 12 CS− stimuli without shocks, measuring the recovery of fear memory. Participants were required to maintain full attention on the computer screen and rate the likelihood of shock association using the subjective expectation rating slider.

Day 4: Fear Memory Reinstatement Test Phase. Participants entered the laboratory and were fitted with the equipment and connected to the devices. After the experiment started, participants were presented with four consecutive unexpected shocks, each lasting 200 ms with a 1000 ms interval between shocks. Participants then rested for 5 min before the random presentation of 12 CS+ and 12 CS− stimuli without shocks, measuring the reinstatement of fear memory. Participants were again required to rate the likelihood of shock association. After the experiment, participants received compensation. The schedule and order of spontaneous recovery and reinstatement tests were based on previous studies (Sartor & Aston-Jones, 2014; Shumake & Monfils, 2015). The overall experimental procedure is shown in Figure 3.

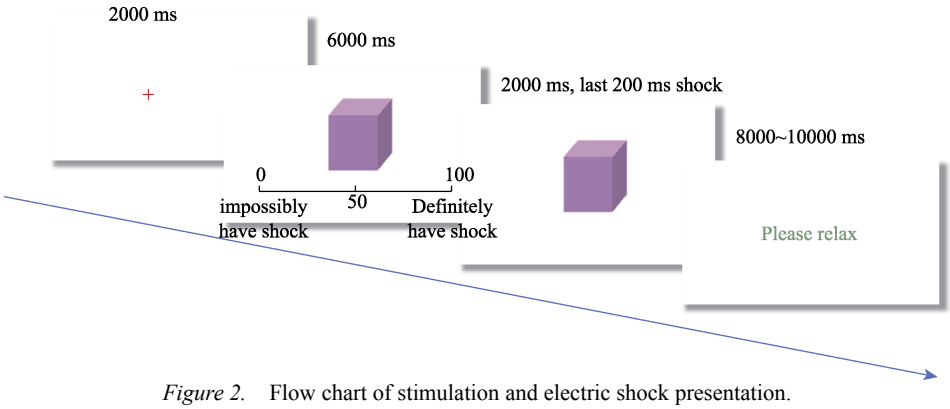

Figure 2. Flow chart of stimulation and electric shock presentation.

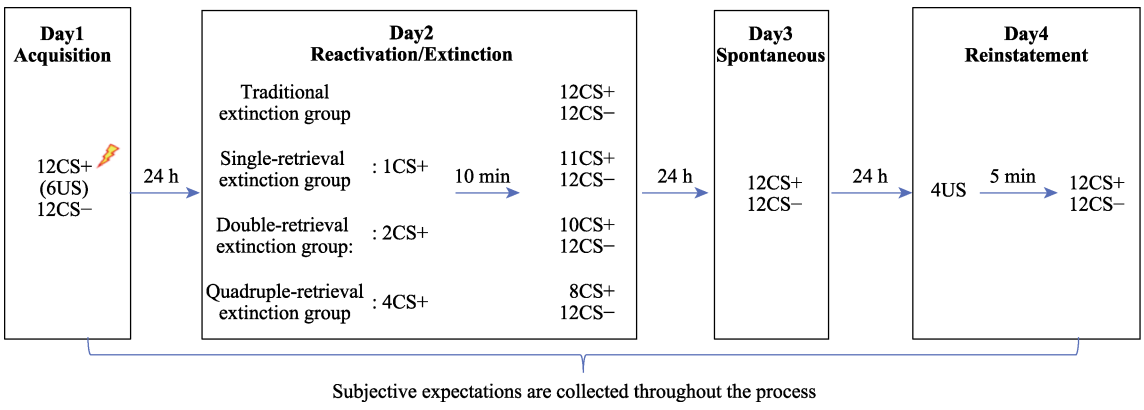

Figure 3. Overall experimental flow chart.

3 Experimental Results

3.1 Skin Conductance Response Analysis

The SCR data for the four groups during the fear acquisition, reactivation and extinction, spontaneous recovery test, and reinstatement test phases are shown in Figure 4.

Day 1: Acquisition Phase. A 2 (stimulus type: CS+, CS−) × 2 (phase: first half of acquisition trials, second half of acquisition trials) × 4 (group) multifactor repeated measures ANOVA was conducted on the acquisition phase of the four groups. The results showed a significant main effect of stimulus type, $F(1, 83) = 37.89$, $p < 0.001$, $\eta_p^2 = 0.31$; a significant main effect of phase, $F(1, 83) = 67.36$, $p < 0.001$, $\eta_p^2 = 0.45$; non-significant interaction effect between stimulus type and group, $F(3, 83) = 0.92$, $p = 0.435$; non-significant interaction effect between phase and group, $F(3, 83) = 0.43$, $p = 0.732$; non-significant interaction effect between stimulus type and phase, $F(1, 83) = 0.18$, $p = 0.675$; non-significant interaction effect between stimulus type, phase, and group, $F(3, 83) = 0.31$, $p = 0.817$; and non-significant between-group differences, $F(3, 83) = 1.10$, $p = 0.353$. These results indicate that there were no significant overall differences in fear responses to CS+ and CS− across the four groups. Paired-sample t-tests on the SCR of CS+ and CS− in the second half of the acquisition trials (trials 7-12) for each group revealed significant differences for Group E, $t(22) = 3.18$, $p = 0.004$, $d = 0.66$; Group R1, $t(22) = 2.04$, $p = 0.027$, $d = 0.42$; Group R2, $t(20) = 1.92$, $p = 0.035$, $d = 0.42$; and Group R4, $t(19) = 3.99$, $p < 0.001$, $d = 0.89$. These results indicate that all four groups successfully acquired the conditioned fear response to CS+.

Day 2: Extinction Phase. A 2 (stimulus type: CS+, CS−) × 2 (phase: first half of extinction trials, second half of extinction trials) × 4 (group) multifactor repeated measures ANOVA was conducted on the extinction phase of the four groups. The results showed a significant main effect of stimulus type, $F(1, 83) = 27.64$, $p < 0.001$, $\eta_p^2 = 0.25$; a significant main effect of phase, $F(1, 83) = 89.26$, $p < 0.001$, $\eta_p^2 = 0.52$; non-significant interaction effect between stimulus type and group, $F(3, 83) = 1.02$, $p = 0.390$; non-significant interaction effect between phase and group, $F(3, 83) = 0.30$, $p = 0.824$ $F(3, 83) = 0.30$, $p = 0.824$; significant interaction effect between stimulus type and phase,

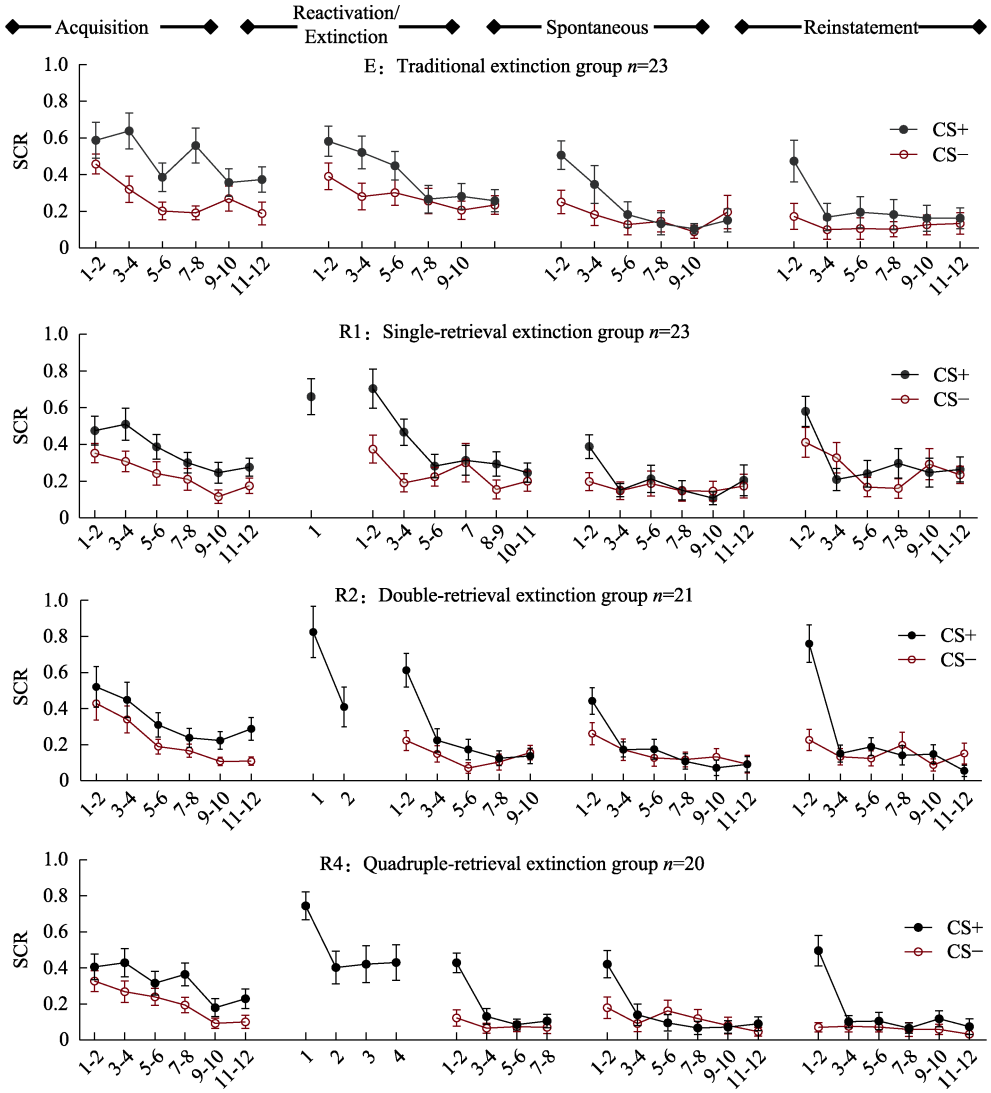

Figure 4. Four groups of participants in the fear memory acquisition, reactivation, extinction, spontaneous and reinstatement phase of the skin conductance response.

Note. E: The x axis represents the trials; Error bar stands for standard error.

$F(1, 83) = 15.02$, $p < 0.001$, $\eta_p^2 = 0.15$; non-significant interaction effect between stimulus type, phase, and group, $F(3, 83) = 0.26$, $p = 0.853$; and significant between-group differences, $F(3, 83) = 3.32$, $p = 0.024$, $\eta_p^2 = 0.11$. These results indicate significant changes in responses from the first to the second half of the extinction phase across the four groups. Because the extinction trials used for the ANOVA in each group were different (Groups R1, R2, and R4's extinction trials excluded the retrieval trials of CS− in order to use an equal number of CS+ and CS− for analysis, as shown in Figure 5), this can explain the between-group differences in overall SCR. Since the results of spontaneous recovery and the preceding extinction phase are related, paired-sample t-tests were conducted on the SCR of the last trial of CS+ and CS− in the extinction phase for each group to verify successful extinction. The results showed no significant differences for Group E, $t(22) = 0.97$, $p = 0.345$; Group R1, $t(22) = 1.71$, $p = 0.101$; Group R2, $t(20) = 0.39$, $p = 0.699$; and Group R4, $t(19) = 0.89$, $p = 0.387$, indicating that all four groups successfully completed fear extinction.

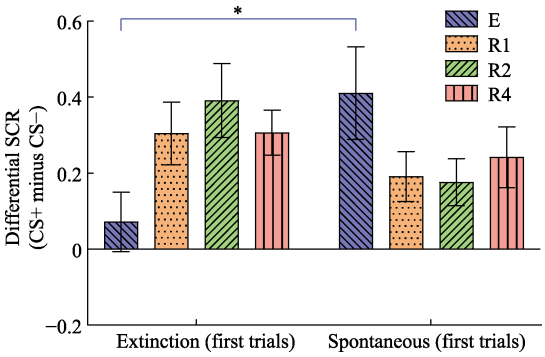

Figure 5. Comparison of extinction after retrieval in each group
Note. E: Traditional extinction group, R1: Single-retrieval extinction group, R2: Double-retrieval extinction group, R4: Quadruple-retrieval extinction group. $*p < 0.05$.

Post-retrieval Effect Analysis. Following previous studies, the mean differential skin conductance response (mdSCR) was used, calculated as the difference in SCR between CS+ and CS− (Chen et al., 2020; Schiller et al., 2010). To further explore the extinction effect brought by brief retrieval, a 4 (group) × 2 (first extinction trial, first spontaneous recovery trial) two-factor repeated measures ANOVA was conducted. The results showed no significant main effect of trial, $F(1, 83) = 0.05$, $p = 0.830$; no significant main effect of group, $F(3, 83) = 0.12$, $p = 0.95$; but a significant interaction effect between trial and group, $F(3, 83) = 4.85$, $p = 0.004$, $\eta_p^2 = 0.15$. These results indicate significant differences in subsequent extinction effects due to different retrieval exposure durations. Simple effect analysis revealed significant differences for Group E, $t(22) = -2.47$, $p = 0.022$, $d = 0.30$; non-significant differences for Group R1, $t(22) = 1.08$, $p = 0.290$; Group R2, $t(20) = 2.03$, $p = 0.056$; and Group R4, $t(19) = 0.74$, $p = 0.471$. These results indicate that brief retrieval can affect subsequent extinction effects, as Group E, which had no retrieval process and proceeded directly to extinction, showed significant differences compared to the other three groups.

Spontaneous Recovery Effect Analysis. Following previous studies, the change in mdSCR from the last extinction trial on Day 2 to the first spontaneous recovery trial on Day 3 was used as the index for spontaneous recovery (Chen et al., 2020; Schiller et al., 2010). A 4 (group) × 2 (trial) two-factor repeated measures ANOVA was conducted on the two key trials of the four groups. The results showed a significant main effect of trial, $F(1, 83) = 18.31$, $p < 0.001$, $\eta_p^2 = 0.18$; no significant main effect of group, $F(3, 83) = 0.63$, $p = 0.596$; and no significant interaction effect between trial and group, $F(3, 83) = 0.37$, $p = 0.778$, indicating a significant increase in the differential SCR from Day 2 to Day 3, suggesting a spontaneous recovery effect. To better detect the size of the spontaneous recovery effect in each group, key trial mdSCR changes were compared within groups. Paired-sample t-tests on the mdSCR of the last extinction trial and the first spontaneous recovery trial revealed significant differences for Group E, $t(22) = -2.70$, $p = 0.013$, $d = -0.56$; non-significant differences for Group R1, $t(22) = -1.47$, $p = 0.155$; significant differences for Group R2, $t(20) = -3.01$, $p = 0.007$, $d = -0.66$; and non-significant differences for Group R4, $t(19) = -2.09$, $p = 0.050$. These results indicate significant spontaneous recovery effects for Groups E and R2, reflected in a significant increase in mdSCR from the last extinction trial to the first spontaneous recovery trial, while Groups R1 and R4 did not show significant increases, indicating no significant spontaneous recovery effect. Additionally, comparisons of the mdSCR of the first spontaneous recovery trial among the four groups showed no significant differences between any two groups. Overall, these results suggest that compared to Groups E and R2, Groups R1 and R4 can weaken the degree of spontaneous recovery of the original fear memory. The spontaneous recovery results for the four groups are shown in Figure 6.

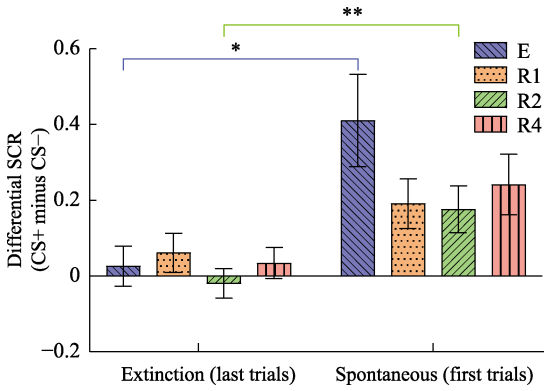

Figure 6. Comparison of spontaneous recovery of fear memory in each group.
Note. E: Traditional extinction group, R1: Single-retrieval extinction group, R2: Double-retrieval extinction group, R4: Quadruple-retrieval extinction group. Spontaneous recovery index = spontaneous recovery of the first trial of SCR value − extinction of the last trial of SCR value (Schiller et al., 2010). $*p < 0.05$, $**p < 0.01$

Fear Reinstatement Effect Analysis. Following previous studies, the change in mdSCR from the last spontaneous recovery trial on Day 3 to the first reinstatement trial on Day 4 was used as the index for fear reinstatement (Chen et al., 2020; Schiller et al., 2010). A 4 (group) × 2 (trial) two-factor repeated measures ANOVA was conducted on the two key trials of the four groups. The results showed a significant main effect of trial, $F(1, 83) = 34.87$, $p < 0.001$, $\eta_p^2 = 0.30$; non-significant main effect of group, $F(3, 83) = 1.72$, $p = 0.169$; and non-significant interaction effect between trial and group, $F(3, 83) = 2.03$, $p = 0.116$, indicating a significant increase in the differential SCR from Day 3 to Day 4, suggesting a fear rein-

statement effect. To better detect the size of the fear reinstatement effect in each group, key trial mdSCR changes were compared within groups. Paired-sample t-tests on the mdSCR of the last spontaneous recovery trial and the first reinstatement trial revealed significant differences for Group E, $t(22) = -2.48$, $p = 0.021$, $d = -0.52$; non-significant differences for Group R1, $t(22) = -1.07$, $p = 0.296$; significant differences for Group R2, $t(20) = -4.95$, $p < 0.001$, $d = -1.08$; and significant differences for Group R4, $t(19) = -4.46$, $p < 0.001$, $d = -0.99$. These results indicate significant fear reinstatement effects for Groups E, R2, and R4, reflected in a significant increase in mdSCR from the last spontaneous recovery trial to the first reinstatement trial, while Group R1 did not show a significant increase, indicating no significant reinstatement effect. Additionally, comparisons of the mdSCR of the first reinstatement trial among the four groups showed that Group R1 was significantly lower than Group R2, $t(20) = -2.74$, $p = 0.013$, $d = -0.60$, and significantly lower than Group R4, $t(19) = -2.14$, $p = 0.046$, $d = -0.48$. No other significant differences were found between any other pairs of groups. Overall, these results suggest that compared to Group R1, Groups E, R2, and R4 do not weaken the degree of fear response after US reinstatement, as shown in Figure 7.

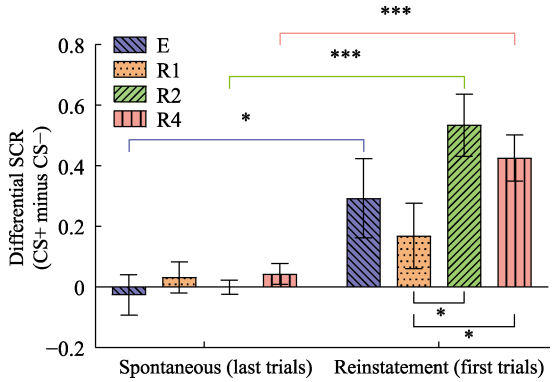

Figure 7. Comparison of reinstatement test of fear memory in each group.

Note. E: Traditional extinction group, R1: Single-retrieval extinction group, R2: Double-retrieval extinction group, R4: Quadruple-retrieval extinction group. Fear reinstatement index = reinstatement of the first trial of SCR value – spontaneous recovery of the first trial of SCR value (Schiller et al., 2010). $*p < 0.05$, $***p < 0.001$

3.2 Analysis of US Subjective Expectation Ratings and Prediction Error Quantification

The subjective expectation rating data for the US were imported into MATLAB 2022a, and the expected value V for each trial was calculated using the model. This allowed for the determination of the prediction error for each trial during the acquisition and retrieval-extinction phases (i.e., $R - V_t$). The subjective and fitted expected values for each trial for the four groups during the fear acquisition and retrieval-extinction phases are shown in Figure 8.

Since this study focuses on the differences in US expected values and prediction errors for CS+ trials among the four groups during the retrieval-extinction phase on the second day, only CS+ trials from the second day were statistically analyzed. A 12 (trials on the second day) × 4 (groups) two-factor repeated measures ANOVA was conducted on the US subjective expectation values for CS+ during the retrieval-extinction phase. The results showed a significant main effect of trials, $F(11, 869) = 56.65$, $p < 0.001$, $\eta_p^2 = 0.42$; no significant between-group differences, $F(3, 79) = 0.49$, $p = 0.690$; and no significant interaction effect between trials and groups, $F(33, 869) = 0.87$, $p = 0.674$. These results indicate significant changes in responses throughout the extinction phase for all four groups, but no significant differences between the groups.

The specific model-fitting parameters for each group are shown in Table 2. The prediction error curves for all trials on the second day, fitted according to the model, are shown in Figure 9.

A 12 (trials on the second day) × 4 (groups) two-factor repeated measures ANOVA was conducted on the PE values for CS+ on the second day. The results showed a significant main effect of trials, $F(11, 869) = 1176.79$, $p < 0.001$, $\eta_p^2 = 0.94$; significant between-group differences, $F(3, 79) = 15.49$, $p < 0.001$, $\eta_p^2 = 0.37$; and a significant interaction effect between trials and groups, $F(33, 869) = 5.10$, $p < 0.001$, $\eta_p^2 = 0.16$. These results indicate significant changes in responses over time on the second day and significant differences between the groups. Further analysis revealed that the change in PE values for Group R1 on the second day was significantly greater than that for the other three groups. The order of the PE values on the second day from smallest to largest was R1 < R4 < R2 < E. Combining the SCR results, Groups R1 and R4 showed better inhibition of spontaneous recovery in the spontaneous recovery test, while only Group R1 showed better inhibition of fear reinstatement in the reinstatement test. This follows a certain order of PE values for the four groups. Overall, the combined results of SCR and prediction error quantification suggest that the smaller the average PE value for the trials on the second day (see Table 2), the better the extinction effects on the third and fourth days.

4 Discussion

This study collected skin conductance response and subjective expectation ratings, combined with the simplified Rescorla-Wagner reinforcement learning model to fit the prediction error quantification curve. Based on the experimental design that transitions from the traditional extinction paradigm to the retrieval-extinction paradigm, extinction training was divided into retrieval and extinction phases according to the number of retrieval trials, resulting in four different retrieval exposure durations: traditional extinction, single-retrieval extinction, double-retrieval extinction, and quadruple-retrieval extinction. This study compared the effectiveness of conditioned fear memory extinction under these four conditions. The results showed that under the premise of equal levels of acquisition and extinction of fear memory among the four groups, the spontaneous recovery test revealed that the single-retrieval extinction group and the quadruple-retrieval extinction group did not exhibit significant spontaneous recovery effects, indicating a certain inhibitory effect on fear spontaneous recovery. In contrast, the traditional extinction group and the double-retrieval extinction group exhibited significant spontaneous recovery effects. In the fear reinstatement test, only the single-retrieval extinction group showed some inhibition of fear reinstatement, whereas the other three groups exhibited significant fear reinstatement effects. Furthermore, the subjective expectation and PE quantification results for CS+ trials on the second day for the four groups indicated that there were no significant between-group differences in the subjective expectation

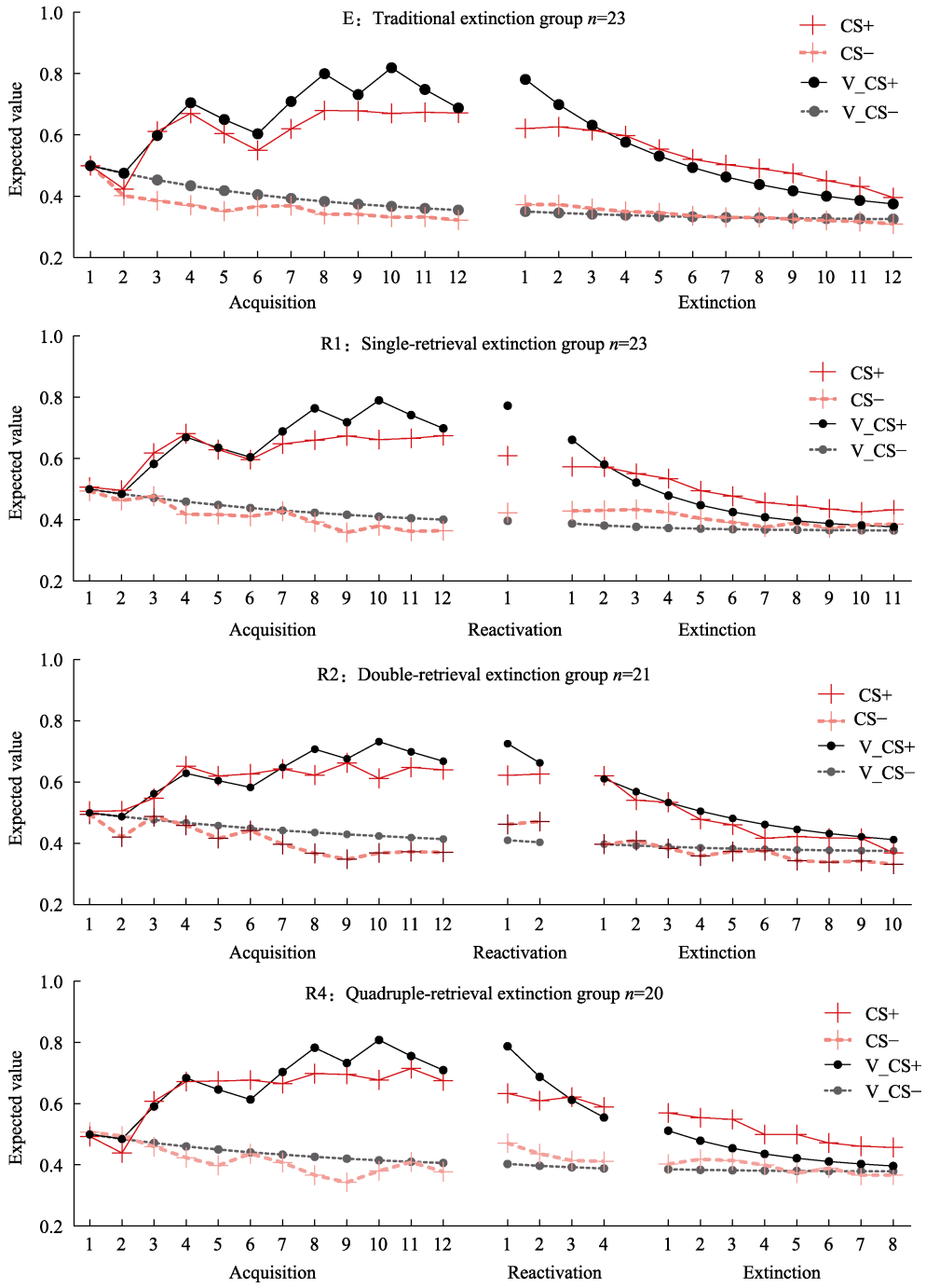

Figure 8. The subjective expected value and the fitting expected value of the acquisition and retrieval-extinction phase in each group.
Note. The red dotted line is the expected value of the subject's subjective assessment, and the black solid line is the expected value of the reinforcement learning model fit. The color map is available in electronic version

Table 2.
The model fits the main parameters

Group	α	model error	average PE
E	0.18	0.14	0.19
R1	0.27	0.12	0.12
R2	0.18	0.09	0.15
R4	0.24	0.14	0.14

Note. E: Traditional extinction group, R1: Single-retrieval extinction group, R2: Double-retrieval extinction group, R4: Quadruple-retrieval extinction group. α is the learning rate in day2, model error is the model fitting error, and average PE is the mean of the absolute values of prediction error in day2 calculated by the model.

of whether CS+ was accompanied by a shock. However, the PE quantification revealed that the single-retrieval extinction group exhibited the greatest change in PE for CS+ trials on the second day, with the overall smallest PE value.

4.1 The Impact of Retrieval Trial Quantity on the Transformation from Traditional Extinction Paradigm to Retrieval-Extinction Paradigm

In this study, although the number of CS presentations on the second day was the same for all four groups (12 CS+ and 12 CS−), the different allocation of trials to the retrieval phase resulted in varying effects on conditioned fear memory extinction. This indicates that, in the process of transforming the

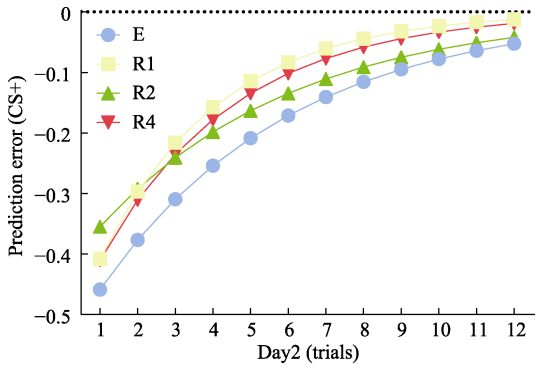

Figure 9. The prediction error value generated by 12 trials on the second day of the four groups of participants.
Note. E: Traditional extinction group, R1: Single-retrieval extinction group, R2: Double-retrieval extinction group, R4: Quadruple-retrieval extinction group.

traditional extinction paradigm into the retrieval-extinction paradigm, the number of retrieval trials is crucial for successful transformation (i.e., preventing fear relapse), in addition to requiring a time interval between retrieval and extinction trials. In this experiment, the successful transformation from the traditional extinction paradigm to the retrieval-extinction paradigm was observed in the single-retrieval extinction group, which inhibited fear relapse on the third and fourth days. In contrast, the double-retrieval extinction group and the quadruple-retrieval extinction group failed to inhibit fear relapse, showing no superior effect in fear extinction compared to the traditional extinction group. Presently studies demonstrating that the retrieval-extinction effect is superior to traditional extinction generally include the following exposure duration parameters: 1-3 CS retrieval trials in cued fear conditioning and 2-4 minutes of contextual exposure in contextual fear conditioning. Exposure durations shorter or longer than these parameters may lead to the loss of the fear extinction advantage of the retrieval-extinction paradigm (Raskin & Monfils, 2023). However, most of these studies are based on rodent models of conditioned fear, and research in human conditioned fear models is still relatively scarce. This study obtained results similar to those from rodent research in human, indicating that simply dividing phases is not sufficient to transform the traditional extinction paradigm into the retrieval-extinction paradigm. The retrieval exposure duration affects the effectiveness of the retrieval-extinction paradigm, with appropriate retrieval exposure duration (one CS retrieval trial in this experiment) being necessary for successful transformation.

The reason for this phenomenon is that the retrieval-extinction paradigm, which effectively inhibits fear relapse, is based on reconsolidation theory, whereas the traditional extinction paradigm is based on extinction learning. The mechanisms involved are different. Research has found that initial CS presentations in both traditional extinction and retrieval-extinction processes activate the prefrontal cortex and amygdala. However, as CS presentations continue, their neural activation patterns diverge. The traditional extinction paradigm continues to engage the prefrontal cortex, whereas the retrieval-extinction paradigm does not (Cahill & Milton, 2019). While both paradigms continue to activate the amygdala, the retrieval-extinction paradigm activates the same neuronal cell clusters that were active during fear acquisition (Khalaf et al., 2018). Additionally, studies have found that in the lateral amygdala (LA), AMPA receptors containing the GluR1 subunit are phosphorylated after a single CS presentation in the retrieval-extinction group, but are dephosphorylated during the second CS presentation one hour later, leading to a reduction in AMPA receptor-mediated transmission in the LA, weakening the CS-US connection. This change is not observed in the traditional extinction group (Clem & Huganir, 2010; Monfils et al., 2009). Many animal studies using immunohistochemistry to compare the differences in the location, type, and number of active neurons during retrieval-extinction and traditional extinction indicate that the two paradigms initially exhibit similar activation patterns but diverge as the process progresses (Khalaf & Graff, 2019; Lee et al., 2015; Tedesco et al., 2014). Therefore, the process of transforming the traditional extinction paradigm into the retrieval-extinction paradigm involves a mechanism shift, with retrieval exposure duration playing a critical regulatory role as a behavioral variable in this series of complex cellular and molecular mechanism changes.

4.2 Reconsolidation Update and Extinction Learning Enhancement as Two Mechanisms for Fear Memory Elimination

Previous studies using the classic three-day paradigm (with various fear relapse tests on the third day) have not been able to effectively compare the intervention effects of different fear elimination paradigms on conditioned fear responses. This is because the close proximity of the second and third days may result in inconsistent outcomes between spontaneous recovery and fear reinstatement tests, making it difficult to interpret and qualitatively determine the occurrence of fear relapse (Haaker et al., 2014; Lonsdorf et al., 2017). To evaluate the impact of different exposure durations on the fear elimination effect of the retrieval-extinction paradigm, this study adopted a four-day experimental paradigm. Tests were conducted over two days: the spontaneous recovery test was performed 24 hours after the retrieval-extinction phase, followed by the fear reinstatement test another 24 hours later. SCR analysis results indicated that in the single-retrieval extinction group, there were no significant spontaneous recovery or fear reinstatement effects in the key trials on both the third and fourth days, indicating a strong inhibitory effect on fear relapse. In contrast, the quadruple-retrieval extinction group exhibited a fear reinstatement effect only in the key trials on the fourth day, with no significant spontaneous recovery effect on the third day, indicating a weaker inhibitory effect on fear relapse. Combining previous research with our experimental results, we propose two main pathways for eliminating conditioned fear responses in conditioned fear models: reconsolidation update and extinction learning enhancement (Vaverkova et al., 2020).

Clinical exposure therapy based on the traditional extinction paradigm is prone to relapse. Therefore, researchers have explored many variations of the traditional extinction paradigm (including the retrieval-extinction paradigm) to improve and inhibit fear relapse phenomena (such as spontaneous recovery, reinstatement, and renewal). Besides the retrieval-extinction paradigm, which is based on a fundamentally different fear elimination mechanism from the traditional extinction paradigm, there are other variations that enhance the extinction learning-based extinction memory strength, increasing its competitive advantage over the original memory and effectively inhibiting short-term fear relapse. Examples include gradual extinction, vicarious extinction, and deepened extinc-

tion (Golkar et al., 2013; Leung et al., 2012; Shiban et al., 2015). Some scholars believe that only retrieval-extinction paradigms that meet specific boundary conditions are based on reconsolidation update, while other retrieval-extinction studies may also be based on extinction learning enhancement. If fear relapse tests are limited, misjudgments may occur (Monfils & Holmes, 2018). Researchers in rodent conditioned fear models have formed two experimental groups by swapping the number of retrieval and extinction trials. They found that both groups successfully eliminated fear responses in long-term memory tests (24 hours after intervention), but showed differences in short-term memory tests (3.25 hours after intervention). If based on reconsolidation update, fear responses would appear in short-term memory tests; if based on extinction learning enhancement, they would not, as the inhibitory effect of forming extinction memory manifests immediately. Similar results have been found in human conditioned fear models (Chen et al., 2021; Ponnusamy et al., 2016). Therefore, although both the single-retrieval extinction group and the quadruple-retrieval extinction group could inhibit spontaneous recovery, they may involve different mechanisms. Based on the test results on the last two days, it can be inferred that the single-retrieval extinction group is based on reconsolidation update, affecting the original memory trace. The absence of spontaneous recovery on the third day indicates that the original memory has been updated to a safe memory, hence no fear reinstatement effect on the fourth day. The quadruple-retrieval extinction group is based on extinction learning enhancement, forming a competitive extinction memory trace that competes with the original fear memory. On the third day, the extinction memory is dominant, but over time, the original fear memory outcompetes the extinction memory on the fourth day, leading to fear relapse. Due to the use of only SCR indicators, this study can only speculate on the mechanisms of fear elimination, and further verification with cognitive neuroscience indicators is needed.

4.3 Prediction Error Mediated Transition of Memory from Reconsolidation to Extinction Due to Exposure Duration

After acquiring Pavlovian associative memory, re-exposure to the CS will sequentially undergo several retrieval-dependent memory processes: solo retrieval (memory expression), reconsolidation, "limbo" (a state between reconsolidation and extinction), and extinction. The fate of the memory will shift with increased exposure duration (de Oliveira Alvares & Do-Monte, 2021; Kida, 2023). Rodent studies on conditioned fear have shown that brief CS exposure leads to memory reconsolidation, while longer CS exposure triggers extinction, indicating that the fate of the memory post-retrieval depends on the exposure duration. Fear memory interrupts the reconsolidation process and triggers extinction learning as the retrieval duration increases (Bustos et al., 2009; Suzuki et al., 2004). Research has found that extracellular signal-regulated kinase (ERK) phosphorylation in the hippocampus, amygdala, and medial prefrontal cortex increases transiently during the transition from reconsolidation to extinction. In this transitional process, ERK acts as a molecular switch to abolish reconsolidation and initiate extinction learning (Fukushima et al., 2021; Merlo et al., 2018). However, the exposure duration that determines whether memory enters reconsolidation or triggers extinction learning can vary with different experimental settings. We can only ascertain that longer retrieval exposure durations are more likely to result in extinction learning, making it challenging to define specific exposure duration parameters suitable for memory reconsolidation. To clarify the regulatory role of retrieval exposure duration on memory reconsolidation and extinction, further exploration of the changes induced by CS exposure is needed.

The consolidation, reconsolidation, and extinction of Pavlovian associative memory are all based on error-driven learning theory. Prediction error, the difference between the predicted and actual occurrence of the CS-US association, is essential for all retrieval-dependent memory processes (Vaverkova et al., 2020). Therefore, the amount of prediction error induced during the retrieval phase may be the underlying mechanism through which exposure duration regulates memory reconsolidation and extinction. The quantification results of PE induced by CS+ trials on the second day for each group in this study revealed that although the number of trials was the same, the PE induced by fixed-order trials varied between groups. Additionally, the overall change in PE across 12 trials differed between groups. The single-retrieval extinction group showed a significantly greater change in PE on the second day compared to the other three groups. Overall, the PE values from smallest to largest were R1 < R4 < R2 < E, corresponding to the ranking of fear elimination effectiveness across the four groups. This indicates that triggering memory reconsolidation during the retrieval phase is reflected by the accelerated reduction in PE values. The overall PE values induced by the intervention trials can predict the effectiveness of fear elimination, with lower PE values indicating better outcomes. Furthermore, additional analysis of the PE differences induced by retrieval trials among the three retrieval-extinction groups showed that the PE value induced by one retrieval trial in Group R1 was 0.41, the total PE value induced by two retrieval trials in Group R2 was 0.65 (mean 0.32), and the total PE value induced by four retrieval trials in Group R4 was 1.13 (mean 0.28). This demonstrates that we cannot simply rely on the total PE value of all retrieval trials or the PE value of the last retrieval trial to determine the fate of the memory. The determination of whether memory enters reconsolidation or extinction based on the size of the prediction error during the retrieval phase cannot be achieved through simple summation. Given the different exposure durations, it is likely that the prediction errors of all retrieval trials are integrated in a certain functional relationship. More complex computational models will be required for fitting and verification in the future.

4.4 Summary and Prospects

This study set up four different quantities of retrieval trials (0, 1, 2, 4) to represent different CS exposure durations. Combined with previous research and the results of this study, it can be confirmed that the quantity of retrieval trials is most directly related to the fate of the memory after retrieval. The underlying mechanism is related to the pattern of PE changes induced by the trials. It is worth noting that the relationship between the prediction error induced by retrieval exposure duration and the retrieval-extinction effect in this study is only speculative. In future studies, appropriate statistical methods could be used to directly correlate the two, thereby obtaining a predictive role of retrieval-induced prediction error on the retrieval-extinction effect. Additionally, due to the relatively simple data measurement and PE quantification methods used in this study, the exact exposure duration and the prediction error parameters

generated from the transition of memory from reconsolidation to extinction after retrieval cannot yet be fully parameterized. Although different cellular and molecular markers represent reconsolidation and extinction in animal studies, they only provide insight into the mechanisms of retrieval-dependent memory reconsolidation and extinction. These markers cannot be used in human studies and are even more challenging to translate clinically (Raskin & Monfils, 2023). Future research needs to delve deeper into identifying observable, real-time, non-invasive specific neural markers in human studies that determine the reconsolidation and extinction processes of memory. This will help explore the reasons for many negative results in reconsolidation intervention studies (whether the retrieval operation failed to destabilize the memory) and assist in designing new, more reliable clinical treatment methods for maladaptive emotional memories (such as post-traumatic stress disorder, phobias, and drug addiction).

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