Effects of prediction error and acute stress on retrieval-extinction of fear memories of different intensities

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Abstract

Under the conditional fear memory reconsolidation model, prediction error has been established as a necessary prerequisite for inducing memory destabilization; however, its function in fear memories of differing intensities remains to be elucidated. Retrieval failure that may arise from high-intensity memories has not been adequately investigated to identify remedial strategies, and the role of stress in this phenomenon warrants exploration. The present study examined in human subjects the role of prediction error in fear memories of varying intensities and the impact of administering exogenous stress following retrieval on the extinction process. The results demonstrated that for weaker fear memories, extinction after a single prediction error retrieval significantly attenuated spontaneous fear recovery; conversely, for stronger fear memories, a single prediction error failed to trigger reconsolidation of fear memory, resulting in relapse of extinguished memories; moreover, under such conditions, application of exogenous acute stress after retrieval exacerbated fear recovery.

Full Text

Effects of Prediction Error and Acute Stress on Retrieval-Extinction of Fear Memories of Different Strengths

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Abstract

Under the reconsolidation model of conditioned fear memory, prediction error (PE) has been established as a necessary condition for triggering memory destabilization. However, its role across different memory strengths remains unclear. For high-intensity memories that may resist retrieval, few studies have explored potential solutions, while the role of stress in this process warrants investigation. This study examined the effects of PE on fear memories of varying intensities and the impact of post-retrieval exogenous stress on extinction in human participants. Results showed that for weaker fear memories, extinction following a single PE retrieval trial significantly suppressed spontaneous fear recovery. For stronger fear memories, however, a single PE failed to engage reconsolidation, leading to relapse of extinguished memories. Moreover, under these conditions, applying exogenous acute stress after retrieval further increased fear recovery.

Keywords: conditioned fear, retrieval-extinction, prediction error, acute stress, memory strength

1. Introduction

Memory is a dynamic process. When new information is present, existing memories may be updated or modified. This dynamic nature enhances individual adaptability while offering researchers the possibility to edit maladaptive memories (Hupbach et al., 2007; Phelps & Hofmann, 2019). Various clinical disorders —including phobias, anxiety disorders, post-traumatic stress disorder (PTSD), and addiction—are characterized by maladaptive memories. How to leverage memory plasticity to intervene in these memories and prevent relapse has become a central focus of research.

1.1 Retrieval-Extinction Paradigm for Fear Memory Elimination in Humans

Memory reconsolidation theory posits that after a memory is formed and stabilized, retrieval can render it labile again, requiring new protein synthesis for restabilization. Memory is thus a continuous process of retrieval and restorage, with the re-storage phase termed reconsolidation. Numerous studies have demonstrated the independence of this process (Alberini et al., 2006; Duvarci & Nader, 2004; Lee et al., 2006; Nader et al., 2000). Retrieval of a consolidated fear memory triggers two nearly opposing processes: reconsolidation and extinction. If retrieval cues meet certain conditions, the original fear memory becomes fully activated and destabilized. Interventions via pharmacological or

behavioral manipulations during this window can inhibit protein synthesis required for reconsolidation, preventing subsequent memory retrieval and suggesting that the memory may have been erased or persistently suppressed (Duvarci & Nader, 2004; Nader et al., 2000; Kindt et al., 2009; Monfils et al., 2009). In terms of behavioral interventions, Schiller et al. (2010) used the retrieval-extinction paradigm to demonstrate that extinction training after memory retrieval effectively eliminated fear memories and prevented their return. A typical retrieval-extinction paradigm spans three consecutive days: on Day 1, a conditioned stimulus (CS)-unconditioned stimulus (US) association is established using a classic fear conditioning model; 24 hours later, memory is activated using a single CS+ trial without the US, followed by extinction training after a 10-minute delay; on Day 3, the degree of fear recovery is tested (Schiller et al., 2010). In recent years, successful applications of this paradigm have spawned numerous variations and explorations of other behavioral interventions, including using US retrieval to reduce cue specificity (Liu et al., 2014; Yan et al., 2012), employing multi-cue compound stimuli (Li et al., 2017), using uncertain retrieval to trigger reconsolidation (Yang et al., 2019), and substituting traditional extinction with cognitive tasks (James et al., 2015), counterconditioning (Gera et al., 2019), vicarious extinction (Golkar et al., 2017), and imagined extinction (Agren et al., 2017). These approaches have been applied to eliminate fear memories as well as drug and alcohol addiction memories (Das et al., 2015; Goltseker et al., 2017; Luo et al., 2015).

1.2 Fear Memory Strength and Retrieval Prediction Error as Boundary Conditions for Reconsolidation

Not all memories enter a reconsolidation state upon retrieval; some may simply be recalled without returning to a labile state, a phenomenon termed "retrieval only" (Elsey & Kindt, 2017). Only when retrieval renders a memory unstable and susceptible to integration of new information can it be modified or deleted. The conditions enabling this unstable state are known as boundary conditions for memory reconsolidation. Current consensus identifies two main categories: retrieval-phase boundary conditions and memory-intrinsic characteristics (Li et al., 2017; D. Sevenster et al., 2018). Among retrieval boundary conditions, novelty information during retrieval is considered the driving force for memory updating. Research demonstrates that prediction error (PE)—the discrepancy between expected and actual outcomes (Rescorla & Wagner, 1972), or violation of expectation—is a key determinant of memory destabilization (Junjiao et al., 2019; Dieuwke Sevenster et al., 2013).

Sevenster et al. (2013) first reported using PE to trigger memory reconsolidation. Subsequent studies across different memory types and PE induction methods have confirmed PE' s crucial role in transitioning memory from stable to labile states via synaptic plasticity (Diaz-Mataix et al., 2013; Fernandez et al., 2016; Alyssa H. Sinclair & Barense, 2018). A major recent advancement is the shift from qualitative to quantitative investigation of PE. Kindt et al.'s research using

the β-adrenergic receptor blocker propranolol demonstrated that PE' s effect on triggering reconsolidation is not all-or-none but involves the degree of PE (D. Sevenster et al., 2014b). Our previous work translating this paradigm from pharmacological to behavioral intervention yielded consistent results (Chen et al., 2018). These findings underscore the universal role of PE across species, experimental settings, and intervention modalities.

Additionally, memory-intrinsic characteristics—including memory strength and age—are important boundary conditions. Studies show that strong, robust memory traces resist reconsolidation, rendering interventions ineffective (Eisenberg et al., 2003; M. J. Robinson & Franklin, 2010; Suzuki et al., 2004; Wang et al., 2009). Such memories require extended retrieval duration or increased retrieval trials to engage reconsolidation (Suzuki et al., 2004). Since clinical applications of reconsolidation interference must address the high intensity and stress associated with clinical emotional disorders, restoring sensitivity to retrieval operations for high-intensity fear memories represents a critical challenge for translating retrieval-extinction research to clinical practice. In summary, these two categories of boundary conditions interact to determine whether a memory can be destabilized and modified through reconsolidation interventions.

1.3 The Role of Stress in Memory Reconsolidation

1.3.1 Stress Can Amplify Prediction Error Signals Prediction error drives new learning, while stress also significantly impacts memory plasticity. A recent fMRI study investigated the relationship between PE signals in the ventral striatum and stress, finding that participants in threatening contexts exhibited significantly stronger negative PE neural signals compared to safe contexts, though no difference was observed for positive PE (O. J. Robinson et al., 2013). Researchers suggest that since PE is a key driver of stimulus-outcome associations, stress-induced increases in PE intensity may facilitate stimulus-threat associations over stimulus-reward associations, which has biological evolutionary significance.

1.3.2 Stress Can Enhance or Impair Memory Reconsolidation Stress exerts complex effects on memory reconsolidation, with outcomes varying according to stress task nature, stressor type, and timing of stress application, often yielding contradictory results (Akirav & Maroun, 2013). Studies using the glucocorticoid antagonist RU486 injected into the basolateral amygdala (BLA) after memory retrieval found impairment of both auditory fear memory and inhibitory avoidance memory, indicating that auditory fear memory reconsolidation requires glucocorticoids (Tronel & Alberini, 2007). Conversely, other research found that glucocorticoid receptor agonists can also impair fear memory reconsolidation. Cai et al. (2006) administered cortisol immediately after contextual fear memory activation, resulting in significantly reduced subsequent recall, though fear returned during reinstatement testing, suggesting cortisol can temporarily weaken fear memory after retrieval.

Another animal study demonstrated that stress hormone effects on activated memory depend on acquisition intensity. Rats were trained with either high-intensity fear (1.5 mA foot shock) or low-intensity fear (0.4 mA foot shock). Twenty-four hours later, their fear memory was activated by placing them in the original context for 90 seconds, followed immediately by cortisol or saline injection. Memory tests on Days 1, 7, and 14 post-retrieval showed that cortisol impaired retrieval of high-intensity fear memory but had no effect on low-intensity fear memory (Abrari et al., 2008).

Human studies reveal that timing of stress application is particularly critical for predicting its effects on memory consolidation or reconsolidation. Acute stress applied *before* rather than *after* memory retrieval disrupts conditioned fear memory reconsolidation and suppresses fear recovery without requiring additional extinction training. This suggests stress exerts a broad inhibitory effect on fear memory reconsolidation, similar to pharmacological interventions like propranolol (Meir Drexler & Wolf, 2017). However, opposite effects emerge when stress is applied *after* retrieval. Research on human conditioned fear found that administering cortisol after memory retrieval (or no retrieval) led to significant fear reinstatement on Day 3 only in the retrieval group, demonstrating that stress hormones promote memory reconsolidation (Drexler et al., 2015).

Thus, whether stress enhances or impairs memory reconsolidation cannot be generalized and depends on specific experimental parameters. Given stress' s multiple potential effects on memory plasticity and its relationship with PE, it is necessary to explore whether stress hormones combined with PE can overcome boundaries imposed by fear intensity.

1.4 Research Questions

In summary, current research lacks integration of fear characteristics (e.g., intensity) and retrieval boundaries (e.g., PE), limiting translation of retrieval-extinction paradigms from laboratory to clinic. First, there is a lack of experimental paradigms for establishing high-intensity fear memories in humans. Although clinical patients possess high-intensity fear memories, their diverse disorder types, courses, and etiologies complicate research design and interpretation. Second, few studies have validated the effectiveness of single PE retrieval for high-intensity memories. Most PE research uses low-intensity laboratory models without manipulating memory strength, limiting direct applicability to clinical disorders. Third, research is scarce on applying stress during retrieval of high-intensity fear memories. Stress hormone effects on memory reconsolidation vary by timing, yet few studies have explored post-retrieval stress effects or whether combining stress with PE can overcome intensity-related boundaries.

Therefore, this study aimed to: (1) establish different-intensity fear memories in humans based on animal research; (2) test whether single PE retrieval can destabilize high-intensity fear memories; and (3) examine how post-retrieval stress manipulation affects extinction. We hypothesized that single PE retrieval

would trigger reconsolidation for moderate-intensity fear memories but not for high-intensity memories. For high-intensity fear, post-retrieval stress would either facilitate reconsolidation (if it helps open the reconsolidation window) or, if it fails to destabilize memory, impair extinction memory retrieval and cause greater fear recovery due to stress-induced retrieval deficits.

2. Methods

2.1 Participants

Healthy participants aged 18–25 were recruited from South China Normal University. Exclusion criteria included medical or psychiatric problems and medications affecting the hypothalamic-pituitary-adrenal (HPA) axis. Beck Depression Inventory (BDI) scores were required to be <19. The study was approved by the Ethics Committee of the School of Psychology, South China Normal University (Approval No. 182). All participants provided written informed consent and received compensation upon completing all three experimental days. Participants were randomly assigned to three conditions: (1) G1: unpredictable US during acquisition, single PE retrieval without stress (“Unpredictable US_{No} Stress”); (2) G2: unpredictable US during acquisition, single PE retrieval with stress (“Unpredictable US_{Stress}”); (3) G3: predictable US during acquisition, single PE retrieval without stress (“Predictable US_{No} Stress”).

Seventy-seven participants were enrolled. Skin conductance response (SCR) and fear-potentiated startle (FPS) served as fear measures, collected in two phases. SCR data were collected from 50 participants, all included in analysis. FPS data were collected from 76 participants; 18 were excluded due to equipment failure or failure to acquire fear, leaving 59 valid FPS datasets (42 from Phase 1, 17 from Phase 2). The criterion for fear acquisition failure was negative Z-scores for FPS during the second half of Day 1 acquisition.

A total of 67 participants with valid SCR or FPS data were compared across groups on trait anxiety (STAI-T) and BDI. No significant group differences emerged (STAI-T: $F(2,64) = 1.35$, $p = 0.266$; BDI: $F(2,64) = 0.43$, $p = 0.655$). Participant distribution and scale scores are shown in Table 1 .

Table 1 Experimental Groups and Sample Sizes

Group	Condition	N (SCR)	N (FPS)	STAI-T	BDI
G1	Unpredictable US_{No} Stress	16	15	20.88$±1.54|6.94±4.53||G2|UnpredictableUS_{Stress}|	

Note: SECPT = Socially Evaluated Cold Pressor Test; PE = Prediction Error. Values are M±SD.

2.2 Experimental Materials

A single cue stimulus served as the experimental material. Two differently shaped and colored geometric figures were used as conditioned stimuli CS1 and CS2. One stimulus (CS+) was always paired with the US, while the other (CS−) was never paired. The US was a 200-ms, 50-pulse/second electric shock delivered by a DS2A-Mk.II constant voltage stimulator (Hertfordshire, UK). Shock intensity was individually calibrated before the experiment to be "extremely uncomfortable but not painful." Shocks were delivered via electrodes attached to the right wrist using conductive gel. To avoid material bias, CS+ assignment was counterbalanced across participants.

2.3 Measurements

2.3.1 Skin Conductance Response (SCR) SCR was recorded using a NEXUS-10 biofeedback system (BioTrace Medical, San Carlos, CA, USA) at 120 Hz. Electrodes were attached to the first and second phalanges of the left index and middle fingers. BioTrace+ software was used for offline analysis. SCR amplitude was calculated as the maximum response during the 5 s following CS onset (3 s in the unpredictable US condition) minus the mean response during the 1 s pre-CS baseline, then square-root transformed. This method is a standard SCR processing approach validated in multiple human studies for effectively measuring fear responses (Dieuwke Sevenster et al., 2013; Soeter & Kindt, 2011).

2.3.2 Fear-Potentiated Startle Response (FPS) The blink reflex is enhanced under aversive conditions, providing a measure of conditioned fear magnitude via electromyography (EMG) of the right orbicularis oculi muscle in response to loud noise (Davis & Michael, 2006). During each CS presentation (4300 ms post-CS onset), a 104 dB, 40 ms burst served as a probe stimulus; identical noises during inter-trial intervals (ITI) served as noise-alone (NA) trials. Two 7 mm Ag/AgCl electrodes with conductive gel were placed 1 cm below the pupil center and 1 cm below the outer canthus, with a ground electrode behind the ipsilateral ear (Blumenthal et al., 2005). Auditory stimuli were delivered via headphones. EMG signals were recorded using a domestic Xeye Human Startle Reflex system at 1000 Hz (low-pass 500 Hz, high-pass 10 Hz) for analysis.

FPS data were processed following Kindt et al.' s method, using peak amplitude in the 50–300 ms window post-probe (Kindt & Soeter, 2013; Soeter & Kindt, 2011). Trials with baseline activity >10 V were excluded due to pre-startle eye movements or poor electrode contact. Raw FPS data were Z-scored within each participant by day.

2.3.3 Blood Pressure and Heart Rate Variability (HRV) Blood pressure was measured using an OMRON 7320 electronic sphygmomanometer on the left upper arm, recording systolic and diastolic values. Heart rate was recorded in real-time via BioTrace finger sensors.

HRV reflects variation in consecutive heartbeat intervals. Short-term HRV analysis serves as a valid index of acute psychological stress in healthy adults (Castaldo et al., 2015). While cortisol is considered the "gold standard" for stress measurement, HRV is also an effective stress indicator used across multiple domains (Brugnera et al., 2017; Schubert et al., 2009; Wagner et al., 2015). Therefore, HRV served as the primary physiological stress measure. Frequency-domain analysis was employed, decomposing RR intervals into frequency components including high frequency (HF), low frequency (LF), and LF/HF ratio. HRV data were processed by marking four timepoints during blood pressure measurement (Figure 2 [Figure 2: see original paper]) and extracting 1-minute epochs (30 s pre-mark to 30 s post-mark).

2.4 Procedure

The experiment spanned three days, with participants attending at the same time each day. Single-blind control was implemented. On Day 1, participants were told the study comprised several unrelated tasks (mild shock testing, ice water challenge, questionnaires) conducted on separate days to avoid interference. Before the experiment, individualized shock intensity was determined via a 0–9 rating scale to identify the "extremely uncomfortable but not painful" level. Subjective measures included the Positive and Negative Affect Scale (PANAS) and a Subjective Feeling (SF) questionnaire assessing perceived stress. The overall procedure is illustrated in Figure 1 [Figure 1: see original paper]-A.

Figure 1 Experimental Procedure Schematic. (A) Overall experimental flowchart; (B) Fear strength manipulation during acquisition and retrieval phase illustration. *Note: Fear strength manipulation: On Day 1, two shocks (US) were delivered at unpredictable times during the second half of CS presentation to form CS-unpredictable US associations, expected to produce higher-intensity fear memory (G1, G2). Two shocks delivered at fixed times (4800 ms and 5800 ms) during CS presentation formed CS-predictable US associations, expected to produce lower-intensity fear memory (G3). PE manipulation: On Day 2, all groups received a single US at 5800 ms during retrieval, creating a PE in shock count (participants expected two shocks based on acquisition, but only received one).*

2.4.1 Day 1: Fear Acquisition A classic conditioning paradigm established fear associations, with CS+ presentations always paired with shock (100% reinforcement) and CS− presentations never paired. After acquisition, participants reported the CS-US contingency. Memory strength was manipulated by varying US predictability: predictable shock timing created weaker CS-predictable US associations, while unpredictable timing created stronger CS-unpredictable US associations (Figure 1-B) (Amadi et al., 2017). Each CS lasted 6000 ms. To avoid SCR interference, shocks occurred during the second half (last 3000 ms) of CS+ presentations, with two shocks per CS+. ITI varied randomly between 15–17 s. Based on Amadi et al. (2017), CS-unpredictable US associations produce

significantly greater amygdala-dependent fear responses than CS-predictable US associations, suggesting this manipulation creates relative intensity differences. Acquisition trial details and strength manipulation are shown in Figure 1-A and 1-B.

2.4.2 Day 2: Memory Retrieval and Extinction Twenty-four hours later, participants returned to the same laboratory. They were instructed to avoid eating or drinking (except water) for 2 hours prior. Before starting, participants recalled and reported the CS-US contingency from Day 1. Retrieval consisted of a single CS+ trial paired with only one US, creating a single PE via the discrepancy between the expected two shocks (from acquisition) and the actual one shock received (Figure 1-B).

For Group G2 (Unpredictable US_{Stress}), the experimenter immediately entered the room after retrieval and administered the Socially Evaluated Cold Pressor Test (SECPT) for 3 minutes. After SECPT, participants rested 7 minutes before extinction training, which comprised 10 CS+ and 11 CS− trials (Figure 1).

SECPT is a well-established exogenous stress induction method (Schwabe & Schachinger, 2018; Schwabe & Wolf, 2010) proven more effective than standard cold pressor tests. SECPT procedures: (1) immerse hand up to the wrist in ice water (0–4°C) for 3 minutes; (2) participants may withdraw if intolerable but are encouraged to persist, with withdrawal mandated at 3 minutes (Bos et al., 2014); (3) participants are video-recorded and monitored during immersion.

For Groups G1 (Unpredictable US_{No} Stress) and G3 (Predictable US_{No} Stress), participants performed a 3-minute warm water task (hand immersed in 35–37°C water) without monitoring or recording (Schwabe & Wolf, 2010), followed by 7 minutes rest and extinction training.

Physiological stress measures (HRV and blood pressure) were assessed at four timepoints: pre-task, mid-task, post-task, and end-of-experiment. Subjective stress was assessed post-SECPT/warm task via three questions: "To what extent do you feel stressed?" , "To what extent do you feel pain?" , and "To what extent do you feel unpleasant?" Participants rated current feelings on a 0–9 scale (0 = not at all, 9 = extremely) (Bos et al., 2014). Day 2 measurement timepoints are shown in Figure 2 [Figure 2: see original paper].

Figure 2 Measurement timepoints for physiological indices and questionnaires on Days 1 and 2. *Note: BDI = Beck Depression Inventory; STAI-T = Trait Anxiety Inventory; PANAS = Positive and Negative Affect Scale; BP = blood pressure; HR = heart rate; SF = subjective feeling. Numbers indicate measurement sequence.*

2.4.3 Day 3: Fear Recovery Test Twenty-four hours later, participants underwent fear recovery testing in the same context. After connecting all equipment with the shock device powered on, spontaneous recovery and reinstatement

were tested using an extinction sequence (8 CS+, 9 CS−). After a 1-minute rest, participants received 4 unsignaled shocks at acquisition intensity, followed by a 5-minute rest. Finally, reinstatement testing and final extinction were conducted using the same extinction sequence (Figure 1-A).

3. Results

3.1 Stress Manipulation Check

3.1.1 Physiological Indices: HRV and Blood Pressure Blood pressure, heart rate, and subjective measures were analyzed using all participants with valid SCR or FPS data. For HRV, after excluding extreme values ($±$3 SD), frequency-domain parameters were obtained (Table 2). During the stress task, Group G2 showed higher LF components than G1 and G3 (Figure 3 [Figure 3: see original paper]), though the ANOVA was not significant ($F(2, 42) = 2.29$, $p = 0.11$). However, pairwise comparisons (LSD) showed G2 > G3 ($p = 0.04$). LF is primarily associated with sympathetic activity and typically increases under stress. Thus, SECPT induced elevated acute stress in Group G2.

Figure 3 Comparison of low-frequency HRV components across groups during SECPT.

Table 2 HRV Frequency-Domain Parameters During Socially Evaluated Cold Pressor Test/Warm Water Task

Group	n	Pre	Mid	Post
Unpredictable US_{No} Stress	15	71.70$±40.66\|106.56±145.84\|125.57±109.65\|\|$UnpredictableUS_{Stress}$|20|44.83±		

Note: Pre = before immersion; Mid = during immersion (1.5 min); Post = immediately after immersion. LF = low frequency; HF = high frequency. Values are M±SD.

Blood pressure results revealed significant group differences in systolic (SBP) and diastolic (DBP) blood pressure during SECPT. SBP(mid) differed significantly across groups ($F(2,63) = 21.72$, $p < 0.001$, $^2 = 0.41$). Post-hoc tests showed G2 SBP(mid) was significantly higher than G1 ($t = 5.49$, $p < 0.001$, $d = 1.62$, 95% CI [14.06, 35.94]) and G3 ($t = 5.81$, $p < 0.001$, $d = 1.86$, 95% CI [13.54, 32.61]). DBP(mid) also differed significantly ($F(2,63) = 40.50$, $p < 0.001$, $^2 = 0.56$), with G2 DBP(mid) significantly higher than G1 ($t = 7.67$, $p < 0.001$, $d = 2.76$, 95% CI [16.13, 30.83]) and G3 ($t = 7.76$, $p < 0.001$, $d = 2.09$, 95% CI [14.31, 27.11]).

Paired t-tests across timepoints revealed that only Group G2 showed significant blood pressure increases from pre- to mid-task (SBP: $t(22) = -9.40$, $p < 0.001$, $d = -1.96$, 95% CI [-26.75, -17.08]; DBP: $t(22) = -12.14$, $p < 0.001$, $d = -2.53$,

95% CI [-30.75, -21.77]). Elevated blood pressure, combined with HRV results, confirms that SECPT effectively induced acute stress in Group G2.

3.1.2 Subjective Indices of Stress Subjective ratings of "stress," "pain," and "unpleasantness" showed significant group differences: stress ($F(2,63) = 3.42$, $p = 0.04$, $^2 = 0.10$), pain ($F(2,63) = 15.14$, $p < 0.001$, $^2 = 0.33$), and unpleasantness ($F(2,63) = 8.15$, $p < 0.001$, $^2 = 0.21$). Post-hoc tests indicated G2 reported significantly higher stress than G3 ($t = 2.41$, $p = 0.048$, $d = 0.67$), higher pain than both G1 ($t = 4.48$, $p < 0.001$, $d = 1.40$) and G3 ($t = 4.94$, $p < 0.001$, $d = 1.36$), and higher unpleasantness than G1 ($t = 2.82$, $p = 0.017$, $d = 0.82$) and G3 ($t = 3.88$, $p < 0.001$, $d = 1.08$). No differences emerged between G1 and G3, confirming that SECPT induced robust subjective stress.

3.2 SCR Results

3.2.1 Overall SCR Across Phases Figure 4 [Figure 4: see original paper] shows SCR for all groups during acquisition, retrieval, extinction, and test phases.

Figure 4 Skin conductance responses across experimental phases. *Note: Trials 1-6 = Day 1 acquisition; Trial 8 = Day 2 retrieval; Trials 10-19 = Day 2 extinction; Trials 21-28 = Day 3 spontaneous recovery test; Trials 30-37 = Day 3 reinstatement test. Error bars represent SEM. Lightning bolt symbols indicate shocks.*

3.2.2 Fear Acquisition A 2 (Stimulus Type) × 2 (Time: first half, second half) × 3 (Group) repeated-measures ANOVA revealed significant main effects of stimulus type ($F(1,47) = 12.81$, $p = 0.001$, $^2 = 0.21$) and trial ($F(1,47) = 13.00$, $p = 0.001$, $^2 = 0.21$), and a significant interaction ($F(1,47) = 23.19$, $p < 0.001$, $^2 = 0.33$). Paired t-tests for the second half of acquisition showed significantly higher SCR to CS+ than CS− ($t(49) = 5.06$, $p < 0.001$, $d = 0.72$), confirming successful fear acquisition across groups.

To assess fear intensity differences, SCR increase from the last CS+ trial on Day 1 to the first CS+ trial on Day 2 was compared across groups. A one-way ANOVA showed a marginally significant group effect ($F(2,47) = 2.43$, $p = 0.099$), with pairwise comparisons revealing significantly greater fear increase in G2 than G3 ($p = 0.033$, 95% CI [0.06, 1.32]). Despite limited sample size, this trend suggests the intensity manipulation was effective.

3.2.3 Fear Extinction A 2 (Stimulus Type) × 2 (Time: first half, second half) × 3 (Group) ANOVA during extinction showed significant main effects of stimulus type ($F(1,47) = 31.97$, $p < 0.001$, $^2 = 0.40$) and trial ($F(1,47) = 47.34$, $p < 0.001$, $^2 = 0.50$), and a significant interaction ($F(1,47) = 5.25$, $p = 0.026$, $^2 = 0.09$). Paired t-tests for the second half of extinction revealed no significant difference between CS+ and CS− SCR ($t(49) = 1.83$, $p > 0.05$, $d = 0.26$), indicating successful extinction across groups.

3.2.4 Fear Recovery Tests: Spontaneous Recovery and Reinstatement For spontaneous recovery, a 2 (Stimulus Type) × 2 (Trial: last extinction vs. first recovery) × 3 (Group) ANOVA revealed significant main effects of stimulus type ($F(1,47) = 14.00$, $p < 0.001$, $^2 = 0.22$) and trial ($F(1,47) = 29.11$, $p < 0.001$, $^2 = 0.34$), and a significant Trial × Group interaction ($F(2,47) = 4.47$, $p = 0.017$, $^2 = 0.11$).

Spontaneous recovery magnitude was calculated as SCR to the first recovery CS+ minus SCR to the last extinction CS+. A one-way ANOVA showed significant group differences ($F(2,47) = 5.14$, $p = 0.01$, $^2 = 0.18$). Post-hoc tests (Tukey) revealed G2 had significantly greater spontaneous recovery than G3 ($t = 3.17$, $p = 0.007$, $d = 1.03$). Within-group paired t-tests showed significant SCR increases from last extinction to first recovery in G1 ($t(15) = -3.06$, $p = 0.008$, $d = -0.77$) and G2 ($t(18) = -4.64$, $p < 0.001$, $d = -1.07$), but not in G3 ($t(14) = -0.81$, $p > 0.05$, $d = -0.21$). These results indicate spontaneous recovery in G1 and G2 but not G3 (Figure 5 [Figure 5: see original paper]-A left).

For reinstatement, a 2 (Stimulus Type) × 2 (Trial: last spontaneous recovery vs. first reinstatement) × 3 (Group) ANOVA showed a significant main effect of trial ($F(1,47) = 9.14$, $p = 0.004$, $^2 = 0.16$) but no other significant effects, suggesting similar reinstatement across groups (Figure 5-A right).

3.3 FPS Results

3.3.1 Overall FPS Across Phases Figure 6 [Figure 6: see original paper] shows FPS across experimental phases for all groups.

Figure 6 Fear-potentiated startle responses across experimental phases.

3.3.2 Fear Acquisition A 2 (Stimulus Type) × 2 (Time) × 3 (Group) ANOVA revealed significant main effects of stimulus type ($F(1,56) = 7.57$, $p = 0.008$, $^2 = 0.12$) and trial ($F(1,56) = 9.87$, $p = 0.003$, $^2 = 0.15$), and a significant interaction ($F(1,56) = 12.95$, $p = 0.001$, $^2 = 0.18$). Paired t-tests for the second half of acquisition showed significantly higher FPS to CS+ than CS− ($t = 4.05$, $p < 0.001$, $d = 0.53$), confirming successful fear acquisition.

3.3.3 Fear Extinction A 2 (Stimulus Type) × 2 (Time) × 3 (Group) ANOVA showed significant main effects of stimulus type ($F(1,56) = 48.07$, $p < 0.001$, $^2 = 0.45$) and trial ($F(1,56) = 56.57$, $p < 0.001$, $^2 = 0.48$), and a significant interaction ($F(1,56) = 16.76$, $p < 0.001$, $^2 = 0.23$). Paired t-tests for the second half of extinction revealed no significant differences between CS+ and CS− FPS in any group (all $p > 0.05$), indicating successful extinction.

3.3.4 Fear Recovery Tests: Spontaneous Recovery and Reinstatement For spontaneous recovery, a 2 (Stimulus Type) × 2 (Trial) × 3 (Group) ANOVA showed significant main effects of stimulus type ($F(1,56) = 26.63$, $p < 0.001$, $^2 = 0.31$) and trial ($F(1,56) = 88.26$, $p < 0.001$, $^2 = 0.60$), and a significant

interaction ($F(1,56) = 8.05$, $p = 0.006$, $^2 = 0.12$). No group differences in spontaneous recovery emerged on FPS, though G2 showed numerically highest recovery (Figure 5-B left).

For reinstatement, a 2 (Stimulus Type) × 2 (Trial) × 3 (Group) ANOVA revealed a marginally significant three-way interaction ($F(2,56) = 2.88$, $p = 0.06$), significant main effects of stimulus type ($F(1,56) = 17.51$, $p < 0.001$, $^2 = 0.22$) and trial ($F(1,56) = 26.17$, $p < 0.001$, $^2 = 0.32$), and a significant Stimulus Type × Group interaction ($F(2,56) = 3.90$, $p = 0.026$, $^2 = 0.10$). A one-way ANOVA on reinstatement magnitude (first reinstatement CS+ minus last spontaneous recovery CS+) was not significant ($F(2,56) = 2.10$, $p > 0.05$), but pairwise comparisons (LSD) showed G2 reinstatement was significantly higher than G3 ($p = 0.047$, 95% CI [0.02, 1.96]), suggesting stronger reinstatement in G2 (Figure 5-B right).

4. Discussion

This study manipulated fear intensity through different acquisition procedures in human participants and examined the effects of PE and post-retrieval stress on retrieval-extinction. Results showed that for CS-predictable US associations, single PE retrieval engaged reconsolidation and prevented spontaneous recovery. For CS-unpredictable US associations (stronger fear), single PE failed to trigger reconsolidation, resulting in fear relapse. Under these conditions, post-retrieval acute stress further increased fear recovery.

4.1 Fear Intensity as a Boundary Condition for Memory Destabilization

Laboratory paradigms for establishing strong human fear memories remain underdeveloped. This study adapted animal paradigms and found that SCR increase from Day 1 to Day 2 was significantly greater in G2 (unpredictable US) than G3 (predictable US), preliminary evidence that unpredictable US timing effectively manipulates fear intensity in humans. However, the limited US timing variability (3-second window) may have constrained the intensity difference. Future research should expand this range and combine additional methods to develop robust paradigms for simulating high-intensity fear memories.

SCR results showed significant group differences in fear recovery, with spontaneous recovery present in G1 and G2 but not G3, indicating that G1 and G2 failed to enter reconsolidation. This replicates previous findings that high-intensity fear memories resist both extinction and destabilization, rendering retrieval-extinction manipulations ineffective. Recent advances conceptualize reconsolidation as comprising two distinct temporal processes: destabilization and restabilization. Destabilization involves the transition from stable to labile states, where synaptic plasticity shifts from inactive to active. Known boundary conditions, including memory-intrinsic and retrieval-phase factors, affect destabilization but not restabilization. This highlights the importance of clarifying

which specific phase is targeted by behavioral or pharmacological interventions.

4.2 The Role of Prediction Error Depends on Memory Characteristics

The critical role of PE in opening the reconsolidation window shows cross-species and cross-memory-type consistency (A. H. Sinclair & Barense, 2019). Previous studies have used diverse PE induction methods, including CS+ without US, rule-based expectancy violations, incomplete CS retrieval, and temporal errors (Diaz-Mataix et al., 2013; Dieuwke Sevenster et al., 2013; Alyssa H. Sinclair & Barense, 2018). This study successfully used US count discrepancy (two shocks during acquisition vs. one during retrieval) to create PE, demonstrating flexibility in PE generation methods.

Crucially, PE is not a sufficient condition for reconsolidation but is modifiable. The G1 vs. G3 comparison shows that despite PE generation during retrieval, memory destabilization depends on memory-intrinsic characteristics. The only difference between conditions was acquisition procedure, yet G3 showed no spontaneous recovery while G1 did, indicating that acquisition-based intensity manipulation produced differential outcomes. Recent research suggests boundary conditions are not fixed but vary with memory characteristics (Zuccolo & Hunziker, 2019). PE' s variability manifests in two ways: First, the degree of PE determines memory updating (Chen et al., 2018; D. Sevenster et al., 2014b). Insufficient PE fails to motivate updating, while excessive PE is interpreted as a novel event, leading to new learning rather than memory modification—essentially traditional extinction (Milad et al., 2006). Only moderate PE drives updating without creating new associations. Second, PE requirements may vary with memory strength. This study found single PE effectively retrieved predictable-US fear (G3) but not unpredictable-US fear (G1), suggesting single PE is insufficient for high-intensity memories. Whether increasing PE could retrieve strong memories remains untested. These findings have important implications for PTSD treatment protocols.

4.3 Stress Has Different Effects Across Fear Memory Formation, Extinction, and Reconsolidation

Extensive research shows stress has divergent effects depending on memory phase and timing. During acquisition, stress levels can create boundary conditions resisting destabilization. During retrieval, this study found post-retrieval stress increased fear recovery compared to no-stress conditions, partially aligning with but also diverging from previous findings. Drexler et al. (2015) found cortisol after retrieval increased fear reinstatement in humans, but only when memory was retrieved, suggesting stress hormones enhance reconsolidation. The current study differs in that retrieval failed to open the reconsolidation window for high-intensity memories (G2), so results cannot be interpreted as enhanced reconsolidation. We propose two interpretations:

First, post-retrieval acute stress cannot compensate for failed retrieval due to

insufficient PE. While stress may amplify PE signals in the ventral striatum (O. J. Robinson et al., 2013), this effect does not salvage retrieval failures caused by inadequate PE magnitude.

Second, since stress was applied after retrieval, its effects depended on retrieval success. Successful retrieval would target reconsolidation; failed retrieval meant stress preceded extinction, thus affecting extinction learning. Prior research shows pre-extinction stress impairs extinction memory formation and retrieval (Raio et al., 2014), explaining why G2 showed maximal fear return on Day 3.

Furthermore, because G2 and G3 differed in both acquisition and retrieval procedures, G2' s greater spontaneous recovery and reinstatement likely resulted from combined effects of intensity differences and pre-extinction acute stress, making extinction more difficult and relapse more likely. This may partially explain why PTSD treatment is challenging—concurrent stress during memory activation may promote relapse post-intervention. This aligns with cognitive-behavioral therapy (CBT) findings recommending avoidance of additional stressors during treatment (Raio et al., 2013).

4.4 Differences Between Fear Measures and Recovery Indices

Using SCR and FPS revealed measure-specific patterns: reinstatement was significant on FPS (G2 > G3) but not SCR, while spontaneous recovery was significant on SCR (G2 > G3) but not FPS. This likely reflects the multifaceted nature of fear memory, which includes physiological arousal, defensive reflexes, subjective feelings, cognitive evaluation, and episodic memory (Phelps & Hofmann, 2019). Different measures tap different components. SCR is a broad index not specific to fear (D. Sevenster et al., 2012, 2014a) and reflects conscious CS-US contingency awareness and declarative memory components (Lovibond & Shanks, 2002; Weike et al., 2007). FPS directly indexes fear, correlates with amygdala activity, and measures implicit, subcortical fear corresponding to procedural memory (Davis & Michael, 2006; D. Sevenster et al., 2014a). These measures also differ in sensitivity to retrieval-extinction manipulations; propranolol's disruption of fear memory reconsolidation affects FPS but not SCR, highlighting that fear comprises multiple memory systems (Soeter & Kindt, 2012b). Inconsistent results across measures have been frequently reported (Soeter & Kindt, 2010, 2011, 2012a, 2012b; D. Sevenster et al., 2012), with some evidence suggesting SCR is more sensitive than FPS in retrieval-extinction studies (Zuccolo & Hunziker, 2019).

These differences suggest our three groups showed distinct recovery patterns across fear memory components: G2 exhibited greater unconscious fear recovery (reinstatement) and greater conscious/cognitive fear recovery (spontaneous recovery). This also highlights intrinsic differences between recovery types—spontaneous recovery reflects time-dependent relapse, while reinstatement reflects fear return after explicit negative stimulation. Other recovery forms like reacquisition and renewal may involve different mechanisms (Vervliet et al.,

2013). Future research should explore the distinct mechanisms underlying different recovery types and which components each measure best captures.

These findings have positive implications for clinical treatment of phobias and PTSD and for translating retrieval-extinction to clinical practice. Future work should develop safe methods for establishing high-intensity memories, further quantify PE effects, and explore multiple approaches—including stress hormones —for opening reconsolidation windows in high-intensity memories.

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Note: Figure translations are in progress. See original paper for figures.