

# Positive and neutral updating reconsolidate aversive episodic memories via different routes

Jingyi Wang<sup>a,\*</sup>, Boxuan Chen<sup>a,1</sup>, Manqi Sha<sup>a</sup>, Yiran Gu<sup>b</sup>, Haitao Wu<sup>c,d</sup>, Cecilia Forcato<sup>e</sup>, Shaozheng Qin<sup>a,d,\*</sup>

<sup>a</sup> State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Faculty of Psychology at Beijing Normal University, Beijing, China

<sup>b</sup> Shanghai Key Laboratory of Brain Functional Genomics (Ministry of Education), Institute of Brain Functional Genomics, School of Life Science, NYU-ECNU Institute of Brain and Cognitive Science, East China Normal University, Shanghai, China

<sup>c</sup> Department of Neurobiology, Beijing Institute of Basic Medical Sciences, Beijing, China

<sup>d</sup> Chinese Institute for Brain Research, Beijing, China

<sup>e</sup> Laboratorio de Sueño y Memoria, Depto. De Ciencias de la Vida, Instituto Tecnológico de Buenos Aires (ITBA), Av. Madero 399, (1106) Capital Federal, Buenos Aires, Argentina

## ARTICLE INFO

### Keywords:

Episodic memory  
Updating  
Emotion  
Reconsolidation  
False memory

## ABSTRACT

Aversive memories are long-lasting and prone to burden our emotional wellbeing and mental health. Yet, how to remedy the maladaptive effects of aversive memories remains elusive. Using memory reactivation and emotional updating manipulations, we investigated how positive and neutral emotion may update aversive memories for reconsolidation in humans. We found that positive updating after reactivation was equivalent to neutral updating in impairing true memories of a previous aversive event after a 12-hour wakeful delay, but induced more false memory. Moreover, additional 12-hour delay with overnight sleep did not further enlarge true memory differences, but attenuated the effect of reactivation and updating on false memory. Interestingly, the neutral rather than the positive updating reduced the emotional arousal of the aversive memory 24 h later. Our findings could serve as a reference for real-world therapeutic applications regarding how positive and neutral updating may reshape aversive memories, especially when taking wake- and sleep-filled reconsolidation into account.

## 1. Introduction

Emotional episodic memory constitutes our individual lives. While joyful moments sparkle our memory bank with happiness, there are also incidents of aversive and distressing events, even traumatic. Once the aversive memories become maladaptive, they could burden our emotional wellbeing and mental health. For example, the sudden outburst of the global COVID-19 pandemic has infected over 200 million people and led to more than four million deaths till the publication of this work. The part-for-ever caused by this pandemic has become traumatic memories of millions of people worldwide (Rajkumar, 2020). Scientists have warned that overloaded traumatic episodic memory could lead to severe mental disorders like post-traumatic stress disorder (PTSD) and major depression even in the post-pandemic time (Carmassi

et al., 2020; Kathirvel, 2020; Xiao, Luo, & Xiao, 2020). Appropriate and efficient interventions for maladaptive memory to prevent the development of severe mental illnesses are in need. There are pieces of evidence showing pharmacological manipulations like adrenergic receptor antagonist (Loneragan, Brunet, Olivera-Figueroa, & Pitman, 2013; Soeter & Kindt, 2015), and electroconvulsive therapy (ECT) might interfere with aversive memories (Kroes et al., 2014; Misanin, Miller, & Lewis, 1968). However, these methods are limited for applications due to their invasive nature. Hence, patient-friendly and non-invasive approaches, like behavioral modifications, are under the urgent need for real-world applications.

Convincing evidence has proved that after memory retrieval, the consolidated memories can be rendered into a labile state; a *reconsolidation* process is then involved to stabilize it into the brain again (Nader

\* Corresponding authors at: State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Faculty of Psychology at Beijing Normal University, Beijing, China.

E-mail addresses: [research@jingyi.de](mailto:research@jingyi.de) (J. Wang), [szqin@bnu.edu.cn](mailto:szqin@bnu.edu.cn) (S. Qin).

<sup>1</sup> J. W. and B. C. contributed equally to this work.

<https://doi.org/10.1016/j.nlm.2021.107500>

Received 18 January 2021; Received in revised form 1 June 2021; Accepted 5 August 2021

Available online 10 August 2021

1074-7427/© 2021 Elsevier Inc. All rights reserved.

& Hardt, 2009). Once a memory is destabilized, it becomes susceptible to new information, leading to the existence of a time window for memory updating (Phelps & Hofmann, 2019). The discovery of memory malleability has generated broad interest to remedy symptoms linking to aversive memories in clinical populations (i.e., PTSD). Emerging evidence has suggested that introducing new learning shortly after memory reactivation can incorporate new information into the already labialized original memory, a process known as memory updating (Lee, Nader, & Schiller, 2017). Among conventional memory updating approaches, counter-conditioning that involves replacing an expected salient outcome with a new outcome of the opposite valence (Keller, Hennings, & Dunsmoor, 2020) has been proved with promising outcomes for appetitive-to-aversive applications. For instance, introducing aversive feelings shortly after memory reactivation had significantly reduced addictive behavior for food (Olshavsky et al., 2013), alcohol (Das, Lawn, & Kamboj, 2015), and cocaine (Goltseker, Bolotin, & Barak, 2017). In contrast, aversive-to-appetitive counter-conditioning studies reported inconsistent findings. On the one hand, utilizing behavioral and optogenetic techniques, researchers had successfully remedied depressive-like or aversive behavior in rodents, by artificially triggering positive memory engrams in the hippocampus during the reactivation of negative experiences (Ramirez et al., 2015; Redondo et al., 2014). On the other hand, findings from the aversive-to-appetitive counter-conditioning paradigm in humans were inconsistent. While many studies have shown a better effect for aversive-to-positive updating than aversive-to-neutral updating or extinction (Eifert, Craill, Carey, & O'Connor, 1988; Newall, Watson, Grant, & Richardson, 2017; Reynolds, Field, & Askew, 2018), there are also studies showing that counter-conditioning is not better than the traditional extinction protocol in some aspects (de Jong, Vorage, & van den Hout, 2000; Meulders, Karsdorp, Claes, & Vlaeyen, 2015). The counter-conditioning could even prone to renew the negative memory (Holmes, Leung, & Westbrook, 2016). Hence, although with promising real-world application potentials, the experimental boundary of counter-conditioning updating remains to be explored.

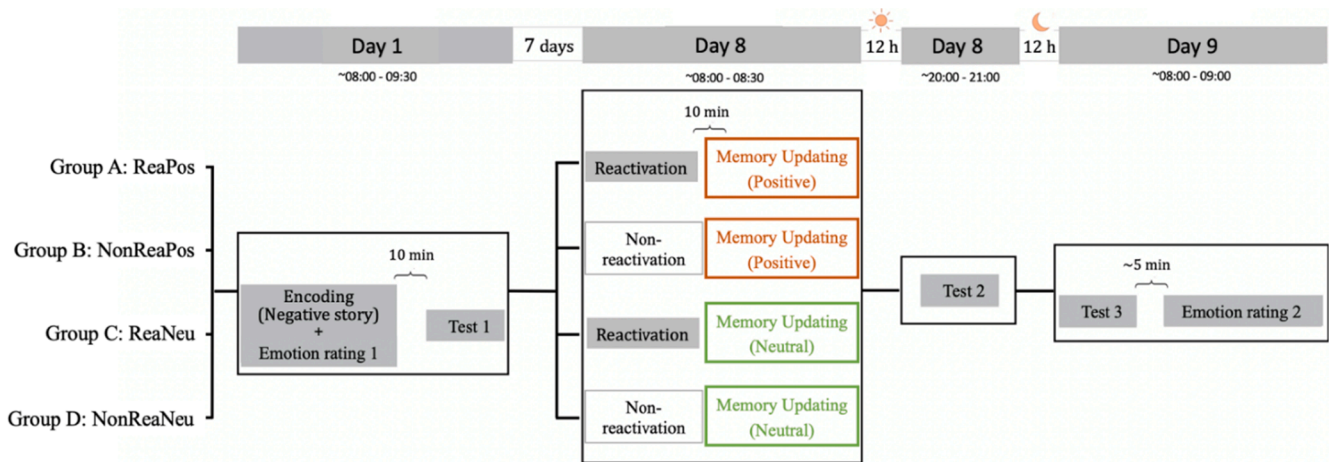
Episodic memory for an emotional event consists of multiple aspects of composited contents, including episodic details on what, where, and when such event occurred (Tulving, 1993), as well as the emotional significance of how we feel about that experience (Christianson, 1992; Dolan, Lane, Chua, & Fletcher, 2000; Liu et al., 2016). The recall of episodic memory includes the information that one truly experienced (i.e., true memory), and some fictitious yet plausible information that did not experience (i.e., distorted or false memory) (Guarnieri, Bueno, & Tudesco, 2019; Loftus, 1979). The fuzzy-trace theory (FTT) had proposed that the specific and detailed traits of the episodes are stored in a literal memory system, the recalling of which would generate true memory. In contrast, the gist and central theme of the episodes are stored in the essence memory system, generating false memory (Brainerd & Reyna, 2002, 2005). Besides the memory contents, the subjective emotional feeling is a vital component of emotional episodic memory, and it is also a crucial indicator to evaluate therapeutic modifications (Lane, Ryan, Nadel, & Greenberg, 2015). Ample studies have successfully reduced the individual's negative feelings (e.g., fear) through memory updating operations (Sandkühler & Lee, 2013; Soeter & Kindt, 2015). However, to our knowledge, there is no study yet to investigate how updating with positive emotion reshapes previously acquired aversive memories with either impaired or distorted outcomes, and even less is known how this procedure alters the emotional arousal of original memory representation.

Memory reconsolidation involves protein synthesis processes, requiring a period of hours, days or even longer to complete (Nader, Schafe, & LeDoux, 2000). Some studies suggested that the reconsolidation window lasts at least six hours during wakefulness (Björkstrand et al., 2016). Meanwhile, it is also reported that sleep supports memory reconsolidation (Klinzing, Rasch, Born, & Diekelmann, 2016; Walker, Brakefield, Hobson, & Stickgold, 2003), probably by speeding up or

shortening the reconsolidation window (Moyano, Diekelmann, Pedreira, & Forcato, 2019). This indicates that both sleep and wakefulness play an essential role in memory reconsolidation. In the context of emotional episodic memory, sleep is crucial to consolidate newly encoded episodic events for both true (Weber, Wang, Born, & Inostroza, 2014) and false memories (Payne et al., 2009). Importantly, when combining the modulation of emotion, sleep seems to consolidate these two kinds of memory in different ways (McKeon, Pace-Schott, & Spencer, 2012). Reconsolidation works as a follow-up step after memory retrieval rather than encoding, and it naturally involves both wake and sleep. Hence, it is critical to understand how sleep, after the wake reconsolidation, supports reconsolidation for both the true and false memory of episodic events that have been emotionally modified. To our knowledge, this has not been well studied.

Here we attempted to bridge the gaps mentioned above by raising the following questions: First, whether new information introduced shortly after reactivation can alter existing aversive memory under the reconsolidation procedure? Second, whether introducing interference with positive emotion can impair previous negative memory better than updating with neutral one? And third, how the effects of positive and neutral updating on aversive memory evolve over 12-hour wakefulness and 24-hour interval with a night of sleep? We set up a between-subject factorial experiment to address these critical questions, including the independent variables of reactivation and positive/neutral updating procedures. Participants encoded an aversive story presented as picture slides with auditory narratives on the Day 1 morning, with an immediate recall test as the baseline assessment of memory (Fig. 1). Seven days later (on the morning of Day 8), participants returned to the lab in morning and were assigned into four experimental groups with either memory reactivation combining with positive or neutral updating or just updating manipulations (Group A: ReaPos, B: ReaNeu, C: NonReaPos, and D: NonReaNeu; see Methods). For the reactivation, prediction errors (or surprise) are thought to initiate destabilization of memory traces (Extón-McGuinness, Lee, & Reichelt, 2015; Sinclair & Barense, 2018). Hence we instructed participants to perform a memory retrieval session, but surprisingly interrupted the retrieval after the first cue slide was presented (see *Methods*), a way that had been used for successful memory destabilization (Forcato et al., 2007). All participants were tested 12 h later in the evening of the same day for their memory of the original aversive story. Finally, after a night of sleep (on the morning of Day 9), all participants returned to the lab in the morning for a final test on memory, emotional valence, and arousal of the negative story.

With this design, we hypothesized that (1) an impairment of memory for the original negative (or aversive) story on Day-8 only appears in the groups that received both memory reactivation and updating; (2) Since the strength of the updating material differs the degree of impairment for the old memory, i.e., stronger new learning after reactivation leads to better memory updating, we would expect that the group with positive emotion updating should impair the negative memory more than the neutral group. Moreover, (3) a recent study in starlings showed that sleep promoted the reconsolidation of old memory once it has been reactivated, and this effect was notably more substantial when new interferences existed after the reactivation (Brawn, Nusbaum, & Margo-liash, 2018). Hence, we hypothesize that after 24-hour interval involving sleep could favor the recovery of the negative memory, especially in the positive group (as a stronger updating manipulation than the neutral updating) with memory reactivation. Apart from memory impairment, an early study suggested that after reactivation, the destabilized memory turns to be more susceptible to interference, intermixing with new information (Hupbach, Gomez, Hardt, & Nadel, 2007). Thus, we further hypothesized that (4) comparing with non-reactivation groups, memory performance from reactivation groups should have more false memory after the updating stories. Finally, we hypothesized that the emotional components of the updating material should also be integrated into the negative memory after reactivation, leading to a significant reduction of the negative feeling of the aversive



**Fig. 1. Experimental design.** Participants were assigned to one of the four groups. On the morning of Day 1, participants from all groups watched a negative story presented as picture slides with auditory narratives. Participants were asked to rate their emotional valence and arousal for each slide and the whole story (Emotion rating 1). Ten minutes after the encoding, the participants orally recalled the content of the just-viewed story (Test 1). On the morning of Day 8, participants from Group A and C were told to recall the negative story but were interrupted by the experimenter with the purpose to produce memory reactivation. Participants of Group B and D did not experience the memory reactivation process. Ten minutes later, participants in groups A and B watched a positive story, while groups C and D watched a neutral story. Twelve hours later in the evening, all the participants recalled the negative story again (Test 2). After a night of sleep, all of them recalled the negative memory on the morning of Day 9 (Test 3). Five minutes later, all participants scored their emotional valence and arousal of the original negative story again (Emotion rating 2). Notes: ReaPos, Reactivation + Positive updating; ReaNeu, Reactivation + Neutral updating; NonReaPos, Non-Reactivation + Positive updating; NonReaNeu, Non-Reactivation + Neutral updating.

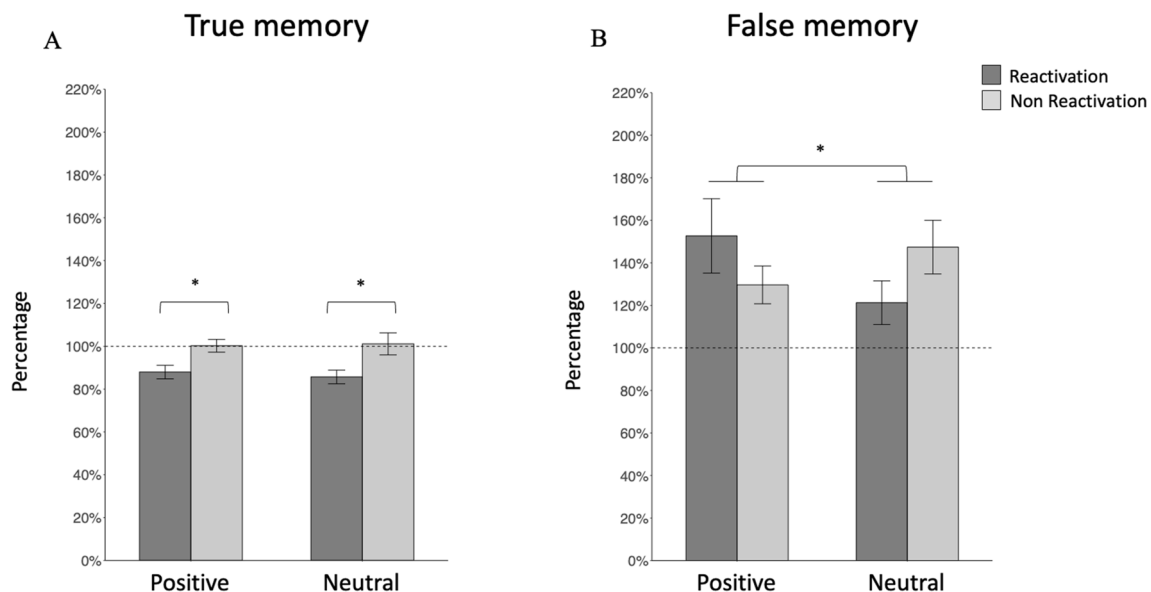
memory for subjects who received a positive updating.

## 2. Results

### 2.1. Memory updating effect of the negative story after 12-hour wakefulness on Day 8

First of all, ten minutes after the initial encoding on Day 1, there were no significant differences for neither true memory (all  $F_{(1, 76)} < 2.385$ , all  $p > 0.127$ ), nor false memory (all  $F_{(1, 76)} < 2.428$ , all  $p > 0.123$ ),

indicating comparable baseline performances across four experimental groups. We then conducted two separate 2 (Reactivation: Reactivated vs. non-Reactivated)  $\times$  2 (Updating: Positive vs. Neutral) between-subjects ANCOVAs for true and false memory percentage (relative to Day1) on Day 8, accounting the baseline performance (Day 1) as a covariate variable (see Methods). For true memory, this analysis revealed a strong main effect on Reactivation ( $F_{(1, 75)} = 12.453$ ,  $p < 0.001$ , partial  $\eta^2 = 0.142$ ), indicating the reactivated groups remembered less true information of the negative story on Day 8 than Day1 (Fig. 2A). However, neither significant interaction effect for Reactivation  $\times$  Updating



**Fig. 2. The updating effect of true and false memory after 12 h wake reconsolidation on Day 8.** Performance is indicated as the percentage of recalled correct (A) or incorrect (B) information on Day 8 with their corresponding performance on Day 1 set to 100%. Asterisks represent p-values from post hoc simple effect analysis and interaction effect of ANOVA in Fig. 2A and 2B, respectively. Percentage for correct (A) information per group: ReaPos group:  $88.0\% \pm 3.2\%$ . NonReaPos group:  $100.2\% \pm 3.0\%$ . ReaNeu group:  $85.7\% \pm 3.2\%$ . NonReaNeu group:  $101.1\% \pm 5.2\%$ . Percentage for incorrect (B) information per group: ReaPos group:  $152.7\% \pm 78.2\%$ . NonReaPos group:  $129.6\% \pm 39.7\%$ . ReaNeu group:  $121.3\% \pm 45.9\%$ . NonReaNeu group:  $147.4\% \pm 56.4\%$ . Data are mean  $\pm$  S.E.M. Rea: reactivation. \*:  $p < 0.05$ .

nor main effect of Updating were observed (all  $F_{(1, 75)} \leq 0.321$ , all  $p \geq 0.573$ ). This indicated that the true memory performance of the negative story in the reactivated groups is significantly worse than the non-reactivated groups, independent of whether they were updated with positive or neutral emotion. On the contrary, the percentage of false memory changes on Day 8 relative to Day 1 showed a significant interaction effect ( $F_{(1, 75)} = 4.389$ ,  $p = 0.040$ , partial  $\eta^2 = 0.055$ ) (Fig. 2B).

## 2.2. Memory updating effect of the negative story after 24-hour interval including sleep

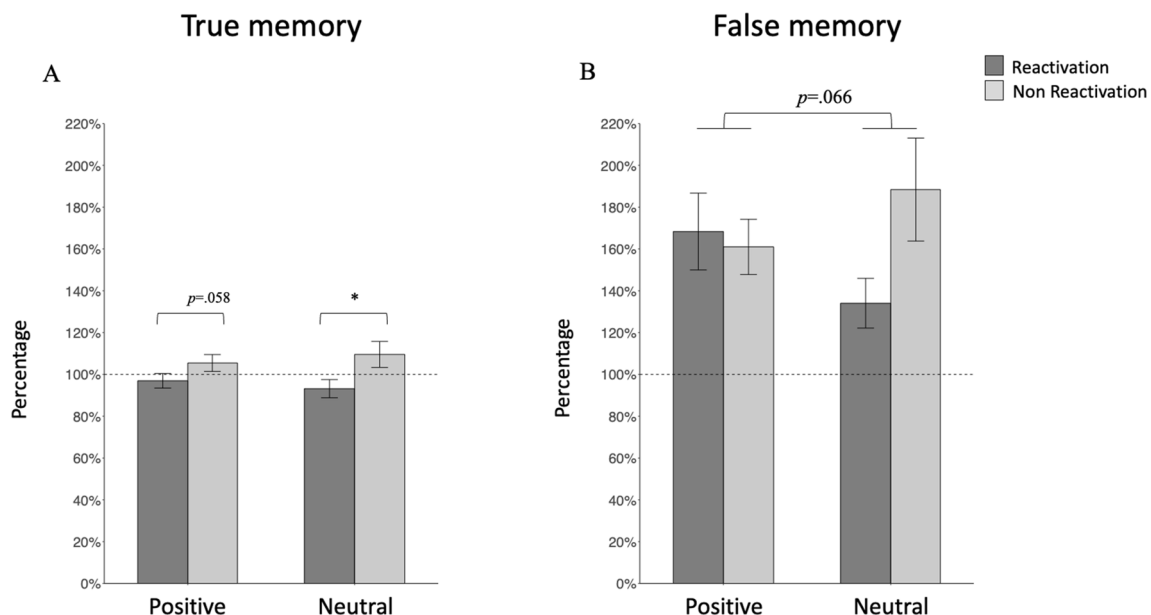
Next, we further investigated the updating effects on the negative memory after a 24-hour interval, as a typical reconsolidation window. Again, we conducted a 2 (Reactivation: Reactivated vs. non-Reactivated)  $\times$  2 (Updating: Positive vs. Neutral) between-subjects ANOVA on memory performance of Day 9 relative to Day 1. It also revealed a significant main effect of Reactivation for true memory ( $F_{(1, 75)} = 6.311$ ,  $p = 0.014$ , partial  $\eta^2 = 0.078$ ). Similar to the effect on Day 8, we observed significantly less true memory on Day 9 relative to Day 1 for the reactivation than the non-activation groups regardless of positive and neutral updating conditions (Fig. 3A). A parallel 2-by-2 ANOVA revealed a trending significant interaction effect, with a smaller effect size than Day 8 ( $F_{(1, 75)} = 3.477$ ,  $p = 0.066$ , partial  $\eta^2 = 0.044$ ) of false memory (Fig. 3B).

For further investigation about the different changes between the true memory and false memory going through a night of sleep, we conducted a 2 (Reactivation: Reactivated vs. non-Reactivated, between-subject factor)  $\times$  2 (Updating: Positive vs. Neutral, between-subject factor)  $\times$  2 (Sleep: pre-sleep vs. post-sleep, within-subject factor) repeated measures of ANCOVA on true and false memory performance of Day 8 and Day 9 relative to the memory on Day 1 (i.e., Day 8/Day 1 and Day 9/Day 1), with the baseline on Day 1 as a covariate variable. After a night of sleep, we observed a general significant increase for both true ( $F_{(1, 75)} = 8.702$ ,  $p = 0.004$ , partial  $\eta^2 = 0.104$ ) and false memory ( $F_{(1, 75)} = 16.404$ ,  $p < 0.001$ , partial  $\eta^2 = 0.179$ ). While there was no any significant interaction effect for the change of true memory across sleep (all  $F_{(1, 75)} < 1.247$ , all  $p > 0.268$ ), the change of false memory showed a

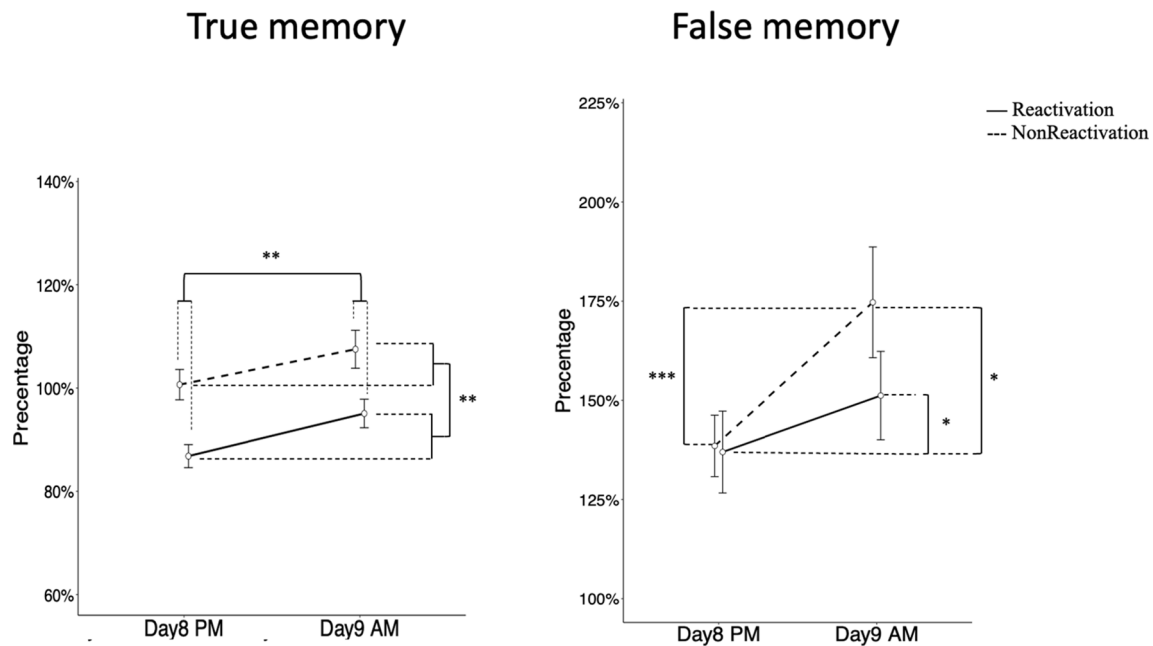
significant interaction effect between Sleep and Reactivation ( $F_{(1, 75)} = 5.763$ ,  $p = 0.019$ , partial  $\eta^2 = 0.071$ , Fig. 4). Post-hoc tests for simple effect revealed that this significant difference was mainly driven by the difference between pre- & post-sleep within the non-reactivated groups ( $t_{(75)} = -5.86$ ,  $p < 0.001$ ), pre- & post-sleep within the reactivated groups ( $t_{(75)} = -2.435$ ,  $p = 0.017$ ) and pre- & post-sleep between the non-reactivated and the reactivated groups ( $t_{(75)} = -2.073$ ,  $p = 0.042$ ). In order to reveal the interaction effect between sleep and reactivation of the false memory performance on Day 9 relative to Day 8, the present study built a further 2 (Reactivation: Reactivated vs. non-Reactivated, between-subject factor)  $\times$  2 (Updating: Positive vs. Neutral, between-subject factor) ANCOVA on the percentage of Day 9 relative to Day 8, with Day 1 as a covariate factor. This model revealed a trending main effect on Reactivation ( $F_{(1, 75)} = 3.822$ ,  $p = 0.054$ , partial  $\eta^2 = 0.048$ , Fig. 5), with the reactivated groups increased less false memory than the non-reactivated groups. These results indicate that true memory of the negative story rises evenly and slightly in all four groups after a night of sleep. However, memory reactivation prohibited false memory to increase more over 24-hour interval involving overnight sleep. This change after one-night of sleep blurred the interaction effect between reactivation and updating of false memory.

## 2.3. Neutral, rather than positive updating, altered emotional arousal of the negative story after reconsolidation

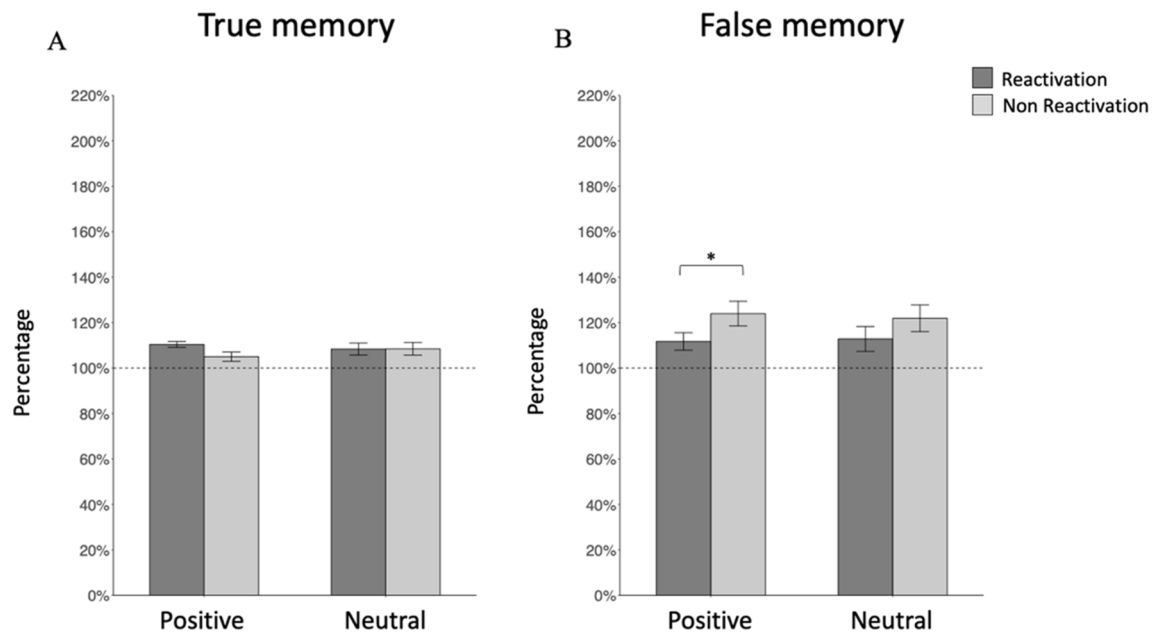
Besides the changes in true and false memory, we also investigated whether introducing an opposite emotion after memory reactivation can alter the original aversive memory's emotional feelings. Unlike memory that is based on original encoded information with multiple tests on Day 8 and Day 9, the feeling of an event is caused mainly by the perception of the current events (Schachter & Singer, 1962). Hence we only obtained the emotional valence and arousal subjecting to the ratings on Day 9, rather than the changes over time. A 2-by-2 ANOVA with Reactivation and Updating as between-subject factors revealed that the subjective rating of valence for the negative story was not different between experimental groups, neither on Day 1 nor on Day 9 (all  $F_{(1, 76)} < 1.548$ , all  $p > 0.217$ ). However, the ratings of arousal on Day 9 showed a



**Fig. 3.** Memory performance for true and false memory at Test 3 after 24-h delay including sleep on Day 9. Performance is indicated as percentage of recalled correct (A) or incorrect (B) information on Day 9 with their corresponding performance on Day 1 set to 100%. Percentage for correct (A) information per group: ReaPos group:  $97.0\% \pm 15.6\%$ . NonReaPos group:  $105.5\% \pm 18.0\%$ . ReaNeu group:  $93.2\% \pm 19.4\%$ . NonReaNeu group:  $109.6\% \pm 27.8\%$ . Percentage for incorrect (B) information per group: ReaPos group:  $168.3\% \pm 82.2\%$ . NonReaPos group:  $161.0\% \pm 59.0\%$ . ReaNeu group:  $134.1\% \pm 53.2\%$ . NonReaNeu group:  $188.4\% \pm 110.1\%$ . Data are mean  $\pm$  S.E.M. \*:  $p < 0.05$ .



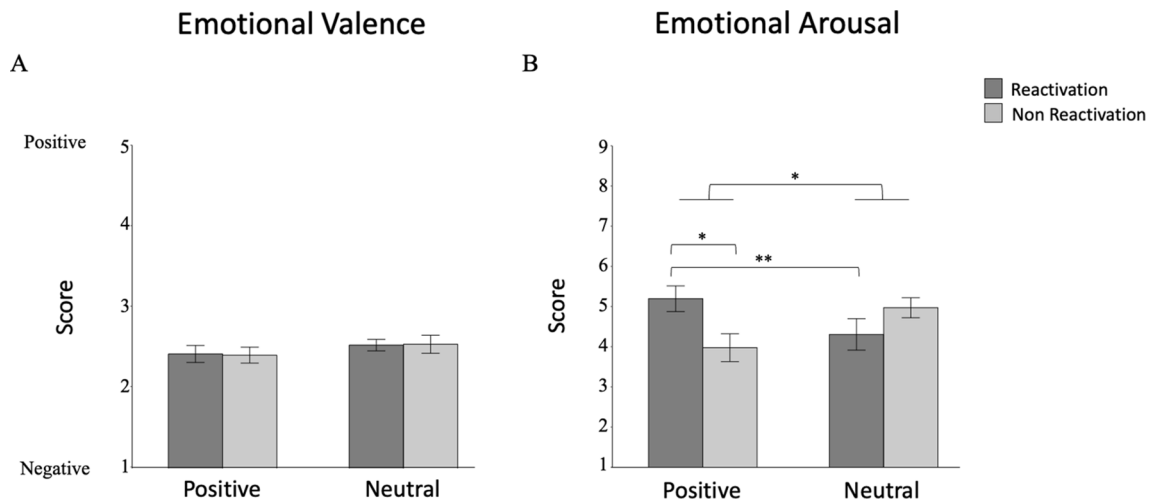
**Fig. 4.** The overnight changes on the updating effect of true and false memory, collapsing the updating emotion types. Performance is indicated as the percentage of recalled correct (A) or incorrect (B) information before and after sleep with their corresponding performance on Day 1 set to 100%. Percentage for correct information per group: Rea&Day8: 86.8%  $\pm$  14.1%. NonRea&Day8: 100.7%  $\pm$  18.6%. Rea&Day9: 95.1%  $\pm$  17.5%. NonRea&Day9: 107.5%  $\pm$  23.2%. Percentage for incorrect information per group: ReaDay8: 137.0%  $\pm$  11.1%. NonReaDay8: 138.5%  $\pm$  14.0%. ReaDay9: 151.2%  $\pm$  11.1%. NonReaDay9: 174.7%  $\pm$  13.4%. Data are mean  $\pm$  S.E.M. \*:  $p < 0.05$ , \*\*:  $p < 0.01$ .



**Fig. 5.** Performance changes of true and false memory over a night of sleep after 12-hour wake reconsolidation. Performance is indicated as percentage of recalled correct (A) or incorrect (B) information on the morning of Day 9 with their corresponding performance on the evening of Day 8 set to 100%. Percentage for correct (A) information per group: ReaPos group: 110.4%  $\pm$  5.7%. NonReaPos group: 105.0%  $\pm$  9.2%. ReaNeu group: 108.4%  $\pm$  11.9%. NonReaNeu group: 108.5%  $\pm$  12.4%. Percentage for incorrect (B) information per group: ReaPos group: 111.7%  $\pm$  17.2%. NonReaPos group: 124.0%  $\pm$  24.3%. ReaNeu group: 112.8%  $\pm$  24.6%. NonReaNeu group: 121.9%  $\pm$  26.2%. Data are mean  $\pm$  S.E.M. \*:  $p < 0.05$ .

significant interaction effect ( $F_{(1, 76)} = 8.11$ ,  $p = 0.006$ , partial  $\eta^2 = 0.096$ ), with higher scores for the positive reactivated than positive non-reactivated groups and neutral reactivated groups (Fig. 6). To note, although we did not observe any significant difference for the arousal on Day1 (all  $F_{(1, 76)} < 2.463$ , all  $p > 0.143$ ), it was strongly correlated with the arousal on Day 9 ( $r = 0.644$ ,  $p < 0.001$ , Spearman's rank correlation coefficient), suggesting some consistencies of the rating across the whole

experiment. Hence, we introduced the arousal rating on Day 1 as a covariate variable, and the interaction we previously observed on Day 9 still held true (interaction effect:  $F_{(1, 75)} = 6.840$ ,  $p = 0.011$ , partial  $\eta^2 = 0.084$ ). Post hoc analysis for simple main effect on the interaction effect revealed that this significant difference was mainly driven by the difference between the reactivated groups with positive vs. neutral updating ( $t_{(75)} = 2.665$ ,  $p = 0.009$ ), and the difference between the two



**Fig. 6. Subjective ratings of emotional valence (A) and arousal (B) on Day 9.** The Y-axis is the emotional valence (larger values indicated more positive valence) and arousal (larger values indicated higher arousal) score on Day 9. Valence score per group: ReaPos group:  $2.405 \pm 0.106$ . NonReaPos group:  $2.390 \pm 0.099$ . ReaNeu group:  $2.515 \pm 0.072$ . NonReaNeu group:  $2.525 \pm 0.112$ . Arousal score per group: ReaPos group:  $5.195 \pm 1.428$ . NonReaPos group:  $4.132 \pm 1.426$ . ReaNeu group:  $4.589 \pm 1.599$ . NonReaNeu group:  $4.928 \pm 1.126$ . Data are mean  $\pm$  S.E.M. \*:  $p < 0.05$ , \*\*:  $p < 0.01$ .

positive updating groups ( $t_{(75)} = -2.44$ ,  $p = 0.017$ ).

It is worth to note that none of the control measures describing participants' general emotional state (subjectively rated anxiety, depression, and general stress level) showed any significant differences across the whole experimental procedure for the four experimental groups (all  $F_{(1, 76)} < 1.706$ , all  $p > 0.174$ ). Meanwhile, participants were also comparable among groups in empathy ( $F_{(1, 76)} = 1.003$ ,  $p = 0.397$ ), and the PVT scores (all  $F_{(1, 76)} < 0.523$ , all  $p > 0.200$ ), suggesting the changes of the episodic memory is unlikely due to the differences from the sense of substitution and tiredness of each participant.

### 3. Discussion

In the present study, we investigated how positive and neutral updating after memory reactivation reshape previously acquired aversive episodic memory after reconsolidation over 12-hour wakeful and additional 12-hour sleep delays. As expected, memories from the reactivated groups were reduced on Day 8 compared with non-reactivation groups, suggesting that memory reactivation rendered original memory susceptible to new information. The updating effect was detectable after a 12-hour wakeful window followed reactivation. However, following memory reactivation, introducing positive emotion did not impair the memory of the learned initially negative story more than the ones updated with neutral information but induced more false memory, similar as it was observed in the neutral updating without reactivation. Moreover, one-night sleep did not seem to alter the reconsolidation outcomes for true memory within the 12-hour wake period followed reactivation, whereas it blurred the reconsolidation effect on false memory. Finally, the neutral rather than the positive updating after memory reactivation, surprisingly, reduced emotional arousal of the negative story 24 h later. In contrast, the valence of the negative story was not affected by the reactivation  $\times$  updating operations, being comparable among four groups.

#### 3.1. Updating of aversive memories after 12-hour wake intervals

Episodic memory of the negative story was impaired only in the groups with memory reactivation (relative to non-reactivation) on Day 8, regardless of positive and neutral updating, indicating that our reactivation manipulation (i.e., arbitrarily interrupting the retrieval process to elicit prediction error) was successful to destabilize the original memory trace (Kindt, Soeter, & Vervliet, 2009). This pattern of

results is in line with previous studies on declarative memory reconsolidation in humans (Forcato, Argibay, Pedreira, & Maldonado, 2009; Forcato et al., 2007; Hupbach et al., 2007). Memory reactivation was believed as an efficient way to render memories malleable. In the context of memory reconsolidation, memory reactivation is usually effectively induced by prediction errors, a mismatch of the expected outcome with a surprising outcome. It has been suggested that phasic activity of midbrain dopamine neurons (particularly in the ventral tegmental area, VTA) is considered to represent the prediction error that drives learning (Reichelt, Exton-McGuinness, & Lee, 2013; Sinclair & Barense, 2019), subsequently trigger destabilization of existing memory traces, and thus drives new learning (Exton-McGuinness et al., 2015). Another recent study that has also extended the prediction error engagement in episodic memory reconsolidation. By violating the action-outcome of video clips to generate the feeling of surprise (i.e., prediction error), this study showed that the memories that have been surprisingly interrupted were more susceptible to subsequent interference from a new set of semantically related videos, and the more surprising the subject rated, the more intrusion were induced (Sinclair & Barense, 2018). Our present study supports this research, showing that memory updating, most likely via introducing a prediction error, is a prerequisite to interrupt previously acquired aversive episodic memory.

After memory reactivation, updating with positive memory did not alter true memory (i.e., the accurate episodic details) of the negative story when is compared with the neutral updating. Instead, it generated more false memory (i.e., fictitious episodic details) after 12 h. A potential explanation of the different outcomes between true and false memory on Day 8 could be referred to the *affect-as-information theory* by Schwarz Norbert, which suggested that an individual's affective state may influence their style of information processing (Schwarz, 1990). According to this theory, when one is in a bad mood, his or her reasoning tends to be "low degree of originality, creativity, and playfulness", thus is more likely to recall the literal (i.e., verbatim) memory. On the contrary, when in positive states, one tends to believe the current environment "is safe, hence tends to use heuristics in information processing". In such situations, one is more likely to adopt gist-based memory recall strategies, which is known to generate false memory (Guerin, Robbins, Gilmore, & Schacter, 2012; Koutstaal & Schacter, 1997; Parker & Dagnall, 2007; Schacter, Guerin, & Jacques, 2011). In the present study, the valence of updating stories was significantly differentiated between neutral and positive, indicating that the participants can well distinguish the two types of emotion. Therefore, during

the updating session, either positive or neutral emotion was integrated into the already reactivated negative memory. According to the *affect-as-information* theory, we suspect that participants in the positive groups could “feel safe about the environment”, and thus used more gist-based processing for memory retrieval, which resulted in generating more false memory (Schwarz, 1990). On the contrary, since true memory of detailed information in an experienced event are more sensitive to negative rather than positive (and neutral) mood (Schwarz, 1990), this may explain why we did not observe any differences between positive and neutral updating.

### 3.2. Updating of aversive memories after 24-hour intervals, including both wake and sleep

Reconsolidation is a long-lasting process, including wake and sleep (Dudai, 2012). Our present study speculated that the longer delay after reactivation and updating, including sleep, could transform true and false memory in different mechanisms. Indeed, we observed although both true and false memory increased in general after a night of sleep, likely due to the testing effect, the two kinds of memory were transformed with different outcomes after sleep.

For true memory, reactivation disturbed the original negative memories already after a 12-hour wakeful delay (i.e., in the Day 8 evening), which effect did not further evolve during sleep. Sleep is well known to promote true memories through systems consolidation (see review (Rasch & Born, 2013)). But reconsolidation is not the same procedure as the original consolidation, but has a shorter time window (Debiec, LeDoux, & Nader, 2002; Phelps & Hofmann, 2019). Hence, a period of wakefulness could already be sufficient to complete the reconsolidation procedure (Björkstrand et al., 2016). Paying attention to the delay filled with wake and sleep progressively, our study refined the reconsolidation process into steps and inspired that 12 h of wakefulness per se seems to be sufficient to reconstruct true memory from reactivation and updating. But to note, lacking direct comparisons with immediate sleep after the updating, we cannot conclude whether true memory reconsolidation is time- or state- (wake vs. sleep) dependent.

Unlike true memory, we observed that sleep affected false memory after the 12-hour wake reconsolidation, i.e., false memory in the reactivated groups with both positive and neutral updating increased less over sleep than the non-reactivated groups. In another words, sleep seems to hinder the production of more false memory after memory reactivation, which process is independent from the updating emotion type. A previous study had shown similar finding that in consolidation, sleep reduces false memory by improving recollection of studied details and avoiding false details, and enabling more efficient and accurate retrieval (Fenn, Gallo, Margoliash, Roediger, & Nusbaum, 2009). In line with this study, our results provided further evidence in reconsolidation, showing that the late 12-hour delay of sleep might rescue the original memory in the way of promoting true memory as previous studies have shown (Klinzing et al., 2016), and meanwhile preventing the generation of more false memory, once the old memory was reactivated. For both true and false memory, our data did not reveal any effect on positive or neutral emotional updating over sleep. We suspect that it could result from the induced positive emotion naturally decayed with time (Davidson, 1998), the intervention of updating in our study might no longer sustain after the 12-hour daytime interval.

In a word, both true memory and false memory evolved across the delay with wakefulness and sleep after reactivation, but through distinct patterns, likely involving complicated reconsolidating mechanisms of different memory types. We speculate that sleep could play a role in memory reconsolidation, via preserving less false memory. To note, since we cannot wholly exclude the intermixed testing effect, and did not set a control group filled with wakefulness, this speculation needs further exploration.

### 3.3. Positive updating increases emotional arousal of aversive memory after 24-hour interval, including sleep

Apart from investigating memory alternation after memory updating, we were also interested in altering the emotional significance of the aversive memory by inserting positive emotion after memory reactivation. Our data showed, on Day 9, emotional arousal of the negative story had shown significant interaction effect, i.e., introducing neutral rather than positive emotion right after memory reactivation reduced the emotional arousal of the aversive memory 24 h later, while the valence of the aversive memory did not differ from each other among four groups. This result was seemingly counterintuitive at the first sight. However, there are also evidence from many studies showing that after incomplete reminders, the omission of expected stimuli (i.e., extinction) is more effective than introducing opposite valences (Claes, Karos, Meulders, Crombez, & Vlaeyen, 2014; Das et al., 2015; Goltseker et al., 2017; Holmes et al., 2016; Hon, Das, & Kamboj, 2016). In fact, omitting emotional stimulation to distinct the aversive feeling has been utilized in clinical psychotherapies to treat specific phobia, according to the *Systematic Desensitization* therapy that was developed by Joseph Wolpe (Wolpe, 1990). A typical protocol of this therapy involves a gradual exposure of the fearful stimulate, an immediate unfilled relaxation process (analogous to the neutral updating without receiving further emotional stimuli), and then an even stronger stimuli with further relaxations. Although not measuring the exact neural mechanisms, we are bold to propose a possible explanation that is based on solid neuroscience literatures from the related topics: Omitting expected aversive stimuli can lead to a rewarding result that is mediated by a prediction error signal in the mesocorticolimbic dopaminergic system (Kalisch, Gerlicher, & Duvanci, 2019; McNally, Johansen, & Blair, 2011). As a result, dopamine could accumulate in multiple brain regions, including the areas that are important for emotional memory like the amygdala (Bissière, Humeau, & Lüthi, 2003; Correia, McGrath, Lee, Graybiel, & Goossens, 2016; Marowsky, Yanagawa, Obata, & Vogt, 2005) and the hippocampus (Broussard et al., 2016; Chen et al., 2019; Ramirez et al., 2015). To note, when prediction error was generated (in our case is the abruptness of the negative story presentation) was also the time when the negative memory was reactivated. Hence, the relatively high levels of catecholamines including dopamine in the brain could likely increase the emotional aspect of the reactivated memory (Luo et al., 2018). It is known that dopamine accompanying with norepinephrine is also released during emotional processing (Badgaiyan, Fischman, & Alpert, 2009; Arnsten, 2009; Liu et al., 2016), therefore introducing positive emotion might maintain the high release of dopamine, thus possibly strengthening the emotional aspect of the negative memory. On the contrary, neutral updating materials would not trigger more dopamine release (analogous to the aforementioned relaxation process in the *Systematic Desensitization* therapy), hence could benefit a quick reduction of dopamine in memory reactivation brain regions. These are our preliminary hypotheses as possible explanations on our results, but lacking neurological data in our study, we would expect future studies to fully examine these assumptions. But to be clear, we do not assume that it was purely the valence difference of the updating material that determined the emotional arousal on Day 9 morning, because the arousal related neuromodulators (e.g., norepinephrine) also naturally fluctuate during sleep (Mitchell & Weinshenker, 2010). This might co-work on the modulation of the emotional arousal of the reactivated memory. Hence, we cannot conclude whether the observed arousal pattern could already appear in the evening of Day 8, or sleep might normalize it back to the current pattern. However, since all experimental groups underwent a normal nocturnal sleep, we would speculate the valence of the updating materials should at least participate the modifications of emotional arousal of the negative story on Day 9.

Our study also provided evidence that the emotional valence rating, unlike the emotional arousal result, did not show any significant difference on Day 9. This was not surprising because emotional valence and

arousal are supported by different brain regions. As it was shown in an fMRI study, the detection of valence was mainly supported by prefrontal-hippocampal networks, whereas the emotional arousal mainly depends on amygdala-hippocampal networks (Kensinger & Corkin, 2004). Hence, it seems that valence evaluation reflects the semantic knowledge of emotion types, while arousal truly reflects emotional responses (Kensinger & Corkin, 2003; Lang et al., 1993; Russell, 1980). Besides, it is understandable that one is unlikely to perceive it as either neutral or positive when facing a story about injury and illness because our knowledge of emotion types determined so.

There are several limitations in our present study. First, although consistent with most behavioral studies on reconsolidation (Kroes, Dunsmoor, Lin, Evans, & Phelps, 2017; Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013; Schiller et al., 2010; Steinfurth et al., 2014; Walker, Brakefield, Hobson, & Stickgold, 2003), our sample size in each group is relatively moderate, which is particularly relevant when interpreting the marginally significant effects of false memory. In addition, calculating the percentage of memory change has its strength for data normalization, but is also limited for its low power in statistics. We would be cautious that the false memory results could be sensitive for the change of sample size and calculations, due to its small-to-moderate effect size. However, we feel responsible to report these results because inducing false memory can be a double-edged sword, while reflecting a reconstructive nature of the reactivated memory for future modification, false memory could be unwanted for testify contexts. Hence, our data may inform that any opportunities that might introduce false memory should be well considered before any memory manipulations. Finally, our study shows that it was the voluntary memories (e.g., the facts of the original memory) were changed after our updating procedures. However, it is also important to target involuntary memories like those intrusive experiences for PTSD patients (Visser, Lau-Zhu, Henson, & Holmes, 2018). We admit that having the measures of involuntary memories would be critical for clinical applications. Yet, our study provides also valuable evidence to bring cautions in therapeutic applications, particularly for those situations that the factual memories are still critical for court settings. Future studies examine both voluntary (including both true and false memory) and involuntary memory, as well as subjective and objective measures of emotion should provide a full overview reference for real-world applications.

#### 4. Conclusions

Our study provides novel evidence into the pros and cons of combining memory reactivation and emotional updating for different aspects of consolidated aversive memory. Our findings suggest that the memory reactivation approach can significantly impair true memory of the aversive story, and such effect maintained over a 24-hour interval. On the contrary, false memory that represents the degree of memory distortion could be augmented when the counter emotion (i.e., positive) was attached right after the old memory is reactivated only during the first 12-hour wake interval, but a night of sleep seems to attenuate this effect. Moreover, updating with opposite emotion after memory reactivation could hinder the reduction of emotional arousal for the aversive feelings, which is usually unwanted.

Our results could be relevant for the development of memory intervention strategies in real-world applications: the exact therapeutic methods should be carefully evaluated and tailored to each individual's situation. For example, the reactivation along with neutral updating strategy could be considered when reducing the subjective feeling of the previous aversive memory is more urgent, and the reactivation + positive updating strategy could be preferred when reconstructing the original memory to introduce more positive outcomes. However, for the latter case, how to prevent the weakening effect from sleep should be carefully investigated by future studies.

#### 5. Methods and materials

##### 5.1. Participants

In total, ninety young adults took part of this study, but ten of them did not complete the full experiments due to their personal issues and technical failures. In the end, eighty right-handed young adults (mean age  $\pm$  S.E.M.,  $21 \pm 0.255$  years ranged from 18 to 27, 65 females) with normal or corrected-to-normal vision participated in this study. The sample size was not pre-determined by power analysis, which is a limitation of this study, but was from empirical studies with similar designs in the field, showing the reproducibility of these effects on memory with similar sample size (Schiller et al., 2010; Schiller et al., 2013; Walker, et al., 2003; Kroes et al., 2017; Steinfurth et al., 2014). Participants followed a regular daily work-rest schedule and reported no sleep-related problems during the last two months. All participants reported a good quality of 7–9 h sleep (mean  $\pm$  S.E.M,  $7.16 \pm 0.078$ ) during the night after the Day 8 Recall. Informed written consent was obtained from all participants before the experiment, and the Institutional Review Board approved the study protocol for human subjects at Beijing Normal University. Participants were assigned into four experimental groups, with twenty subjects in each group. We have controlled the gender bias, resulting in 13 males and 7 females in each experimental group. There was also no significant difference in age across all four groups.

All participants reported not to nap habitually, nor have any sleep disorders (e.g., sleep apnea, irregular sleep, and insomnia), and did not take any medication at the experimental appointments. None of the participants claimed to have known neurological and psychiatric disorders (such as attention deficit hyperactivity disorder, anxiety, and depression). Participants had an age-appropriate sleep-wake rhythm (7–9 h night/day), and they were not on any night shifts during the whole experimental procedure. Participants were instructed to keep a regular sleep schedule, abstain from caffeine- and alcohol-containing drinks on the experiments' days.

##### 5.2. Experimental procedure

The whole experiment took nine days in total, with a 7-day interval after the initiate encoding. On Day1, the encoding session started around 8 a.m.-10 a.m. Participants encoded one negative story consisted of 11 episodic slides with paired audio narratives, analog to previous studies (Cahill, Prins, Weber, & McGaugh, 1994; Kroes et al., 2014) (Fig. 1). Participants were not instructed to remember anything. Instead, they were told to watch the slides carefully and meanwhile, pay attention to the auditory narratives. Especially, the participants were asked to put themselves "into the story to experience what is happening on the screen", to increase their motivation to explore the whole story. After encoding, participants took a 10-min rest. After the 10-min rest, participants were asked to recall the encoded negative story slide-by-slide at their own pace, with the instruction *Please describe the No. X slide as detailed as possible*. After this immediate recall session, participants left the lab and did not know what they would have to do when returning to the lab after one week.

We asked all the participants to come back to the lab again for delayed recall seven days later. We designed to update the old memory seven days later because previous studies showed that the longer time the memory develops, the more susceptible it is to new information (Scully, Napper, & Hupbach, 2017). Participants in the reactivation groups were instructed to recall the learned negative story slide-by-slide seven days before (see **Memory Reactivation**), while the other two Non-reactivation groups were told to watch a new story (see **Episodic Stories**). The instruction of this phase was the same as encoding the negative story, i.e., they should put themselves "into the story to experience what is happening on the screen". All participants were asked not to nap during the daytime and then came back to the lab 12 h later (around 21:00 of the same day) for the Delayed Recall I. The delayed

recalls were the same as the Immediate Recall session. Afterward, participants were allowed to go home. They were instructed to keep their natural sleep schedule, and they should return to the lab the next morning.

About 12 h later, at about 9 a.m., participants returned to the lab for Delayed Recall Session II, which was also the same as the other two recalls. At the end of the experiment, participants were told to score the valence and arousal of the negative story again using the same procedure as the encoding.

### 5.3. Episodic stories

During the initial encoding session, participants were shown a negative story with 11 slides on the PC screen, accompanied by an auditory narrative forming an episode (See Fig. 7 as an illustration). Pictures of all slides were searched from the internet with free copyrights. All images were 27 cm high, 20 cm wide, with  $1280 \times 1024$  Pixels. A pre-recorded male voice read the narrative of the negative story, which volume was controlled to 50 dB for the whole presentation. The negative story outline was about “I” observing a severe traffic accident, in which a young boy injured his leg seriously, and he has been sent to a hospital for a stressful operation and leaves severe sequelae eventually. The negative story was the same for all experimental groups.

During the updating session, participants learned a new story (either positive or neutral) identical in structure and scene to the negative story they saw in the encoding session. Of note, to guarantee that it is the emotion rather than the complication of the visual contents, the updating stories used the same images for visual cues, but we played different emotional narratives (positive or neutral) to describe the episodes of the presented slides (Fig. 8). While the neutral story was in plain and unadorned words describing neutral events on the pictures, the positive story talked about “me” visiting a city and have experienced and observed a series of exciting and funny events (Fig. 8). Both the positive and neutral narratives were from reading from a female voice, the volume of which is also controlled to 50 dB.

We validated the emotional valence of three episodic stories used in this study. The subjective rating of the negative story’s valence and

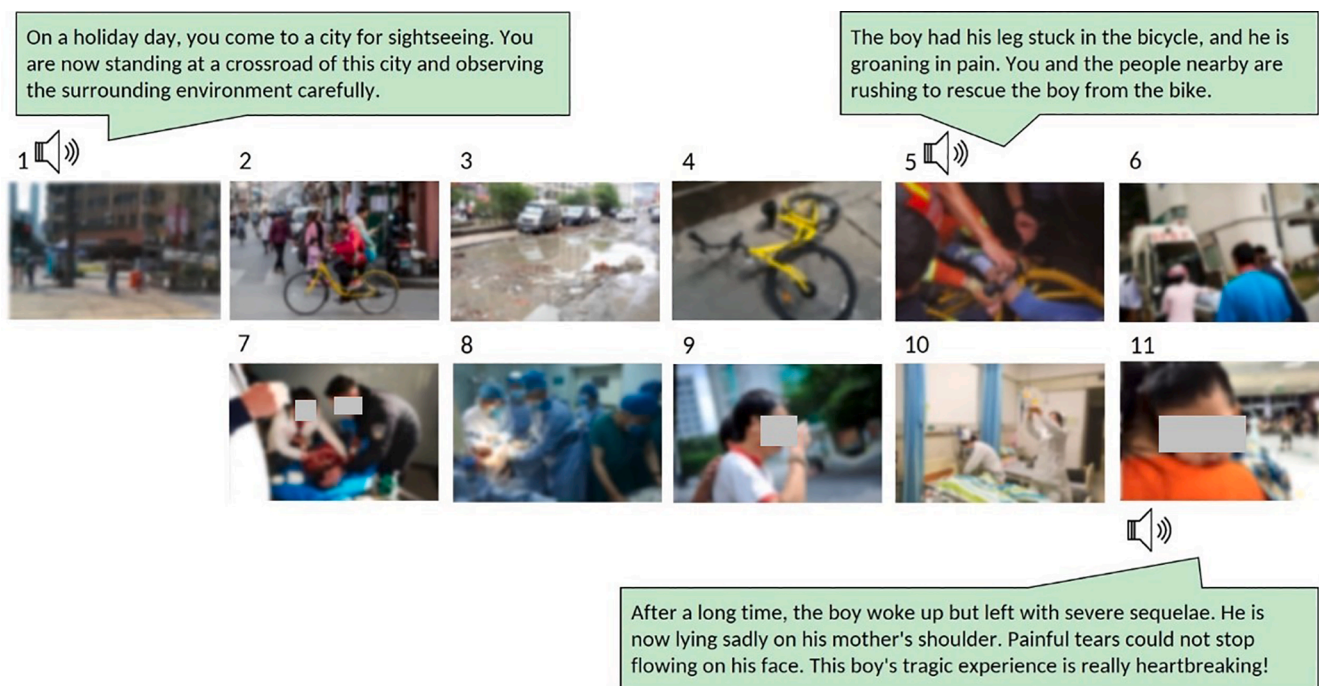
arousal for all participants were  $2.190 \pm 0.046$  and  $5.540 \pm 0.178$ , respectively. There were no significant differences across four groups (all  $p > 0.75$ ). The valence of the positive ( $3.790 \pm 0.082$ ) and neutral story ( $3.380 \pm 0.052$ ) was significantly different from each other ( $p < 0.001$ , Mann-Whitney’s test). The arousal of the positive and neutral stories was  $4.655 \pm 0.259$  and  $4.166 \pm 0.259$ , respectively. However, the arousal of the two stories did not reach significant level ( $t_{(78)} = -1.330$ ,  $p = 0.187$ ).

### 5.4. Memory reactivation

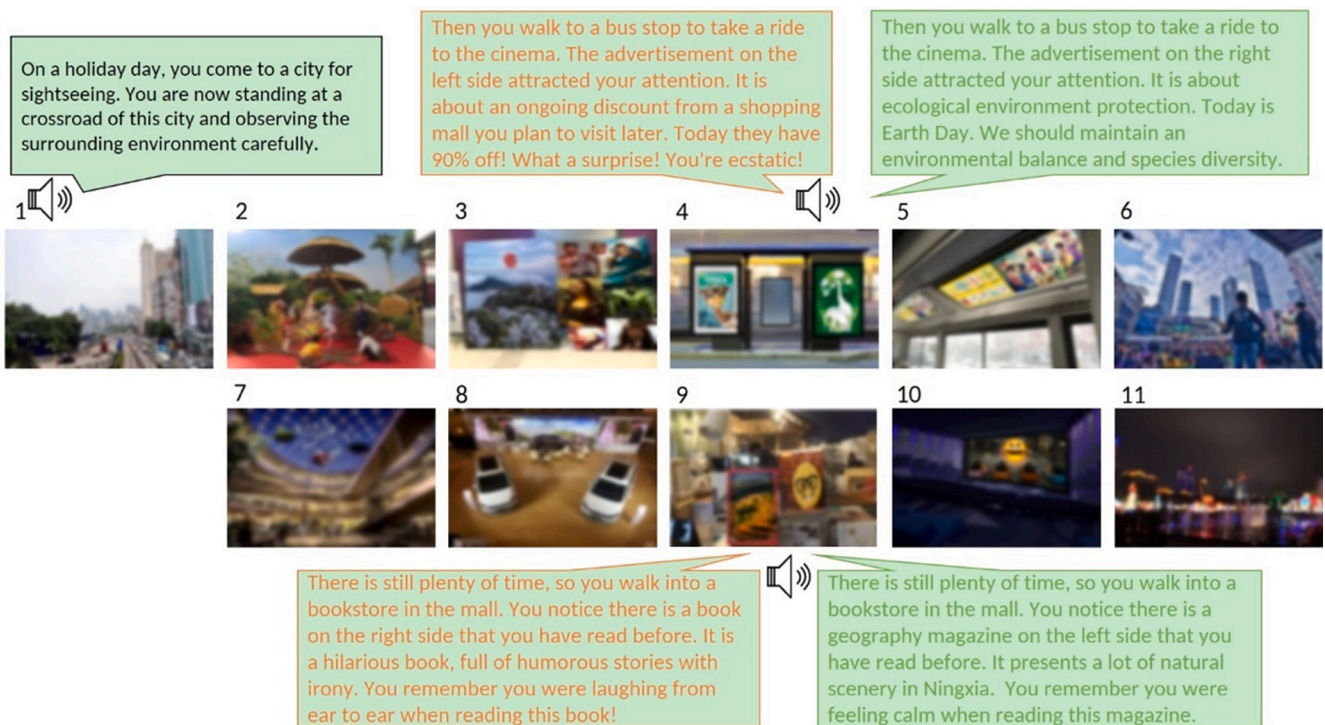
Memory reactivation operations were adopted from previous studies that show successful memory labilizations (Forcato, Fernandez, & Pedreira, 2014). In particular, we introduced a prediction error that has been suggested to be critical for memory labilizations (Sinclair & Barense, 2019). Hence, for the participants of the reactivation groups, the reactivation session started by showing a partially masked first slide of the negative story. Participants were asked to answer three forced-choice questions related to the masked content. Once participants chose their answer, the corresponding mask was then removed to see the real picture as feedback. The reactivation score was calculated as the number of correctly answered questions by multiple choice. After the three questions, an unexpected black screen was suddenly presented, and the experimenter pretended to be surprised about the error and took the device away for solutions. The participants were instructed to relax for a few minutes without any distractions, like looking at their phones. Ten minutes later, the experimenter informed the participant with regret that the program was not fixable. Therefore the recall session had to be canceled, and the procedure continued to the next session, which was to watch a new story. The new story (either positive or neutral for different updating groups) consisted of another 11 slides was presented in the same way as the encoding of the negative story.

### 5.5. Recall memory test

Three free recall tests were conducted 10 min after encoding of the first day, 12 h after the updating – the evening of the eighth day, and the



**Fig. 7. The Encoding Story.** All participants were presented with an emotionally negative story consisting of 11 slides on PC, with auditory narratives of each slide from a middle-aged male voice. The whole story lasted about six minutes.



**Fig. 8. The Updating Stories.** Participants in Positive and Neutral groups were presented with either a positive or a neutral story, respectively. All participants viewed the same pictures but with different auditory narratives (except the first slide). Both stories consisted of 11 slides, and each slide was accompanied by an auditory narrative from a young female voice. Orange: the positive narrative example, Green: the neutral narrative example. Each story lasts about six minutes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

morning of the ninth day. Before the recall test, participants need to recall according to a suggested framework, including the location, characters, events in the story, and the shape, clothes, and actions of the characters. The participants did not receive any feedback during the whole process of free recall. To ensure all related memories are reported, if the participants ended their recall within 3 min, they are encouraged by the experimenter to describe more, such as “Please describe the detail in this slide as much as you can” and “Is there anything else you can recall?” If participants reported nothing more, the experimenter continued to ask the next slide. This procedure continued until all eleven slides were recalled.

Each day's memory performance was first scored by two independent student raters for each slide according to each participant's oral report on correct (as True Memory) or incorrect information (as False Memory) of the negative episodic story. The raters were blind to our study design, hypotheses, and experimental details. They were only trained with the same criteria for consistent ratings. The final memory score was calculated as the sum of all slides, without the first slide that has been used for memory reactivation (i.e., the sum of slides 2 to 10). True memory was scored as any correct description of the corresponding slide. If the description was accurate (e.g., the boy was wearing a red jacket), this information was scored as 2 (i.e., one score for the “boy” and one score for the “red jacket”). If the description was not accurate but also not wrong (e.g., “there are many doctors perform surgery on children,” instead of “there are six doctors perform surgery on children”), this information was then scored as 0.5. False memory was scored according to any false information that the participant recalled about the corresponding image, including the incorrect details (e.g., wrong colors of someone's cloth, wrong location of an object, and et al.), and created information that was not presented on the slides. In the end, the inter-rater reliability of the two raters were convincing: True memory: Spearman's  $\rho = 0.863$ ,  $p < 0.001$ , and False memory: Spearman's  $\rho = 0.889$ ,  $p < 0.001$ .

### 5.6. Emotion self-assessment test

For each story presentation, i.e., the encoding of the negative story on Day1, the positive/neutral updating stories on Day8, and the final recall of the negative story on Day9, participants rated their subjective feeling of the slides on valence and arousal. The rating system was adopted from a standard emotion assessment instrument: The Self-Assessment Manikin and the Semantic Differential (Audrain & McAndrews, 2020). The Self-Assessment Manikin is a non-verbal picture-oriented questionnaire measuring emotional response associated with a person's affective reaction to a wide variety of stimuli (Bradley & Lang, 1994). The SAM includes single-item scales of three central features of human emotional response: valence/pleasure of the response (from positive to negative), perceived arousal (from high to low levels), and perceptions of dominance/control (from low to high levels) (Bynion & Feldner, 2017; Lang, Greenwald, Bradley, & Hamm, 1993). In the present study, the measure of dominance was omitted in the task. Participants were told to understand their feelings as much as possible, and then to score their real valence and emotional arousal level, for 5 points scoring (1 = very negative, 2 = relatively negative, 3 = neutral, 4 = relatively positive, 5 = very positive) and 9 points scoring (the higher the score is, the stronger the arousal level), respectively. To note, the emotion ratings on both Day 1 and Day 9 were calculated as the mean of 10 slides (excluding the cue slide) to avoid any unexplainable influence from the slide that has been viewed extra in the reactivated groups.

### 5.7. Statistical analyses

To track how later memory is updated (or changed) from their original form, both true and false memory were scored as the memory percentage of later recall relative to their baselines (e.g., Day 8/ Day 1, and Day 9/ Day 1). In addition, due to the design of a self-paced, unrestricted free recall, memory performance across individuals has

relatively wide ranges (True Memory score range: 27–232.5; False Memory score range: 4–135). To mitigate the potential masking for between-group difference by a large within-group variance, which would not be completely avoid by fraction calculation (Vickers, 2001), we accounted the individual baseline performances on Day 1 as covariates in the following ANCOVA models.

Statistics for testing group differences of both true and false memory performance on Day 8 and Day 9, subjective emotion rating, and control measures were all submitted to a 2 (Reactivation: Reactivated vs. Non-Reactivated)  $\times$  2 (Updating: Positive vs. Neutral) ANCOVA, with the corresponding performance at Test 1 on Day 1 as covariate variables. True and false memory differentiations over a night of sleep were submitted to a 2 (Reactivation)  $\times$  2 (Updating)  $\times$  2 (sleep: before vs. after sleep) repeated measures of ANCOVA, with the true and false memory performance on Day 1 as covariate variables.

When a significant interaction effect or main effect was found, *post hoc* tests followed significant ANCOVA effects, including Student's *t*-test, if variances were unequal, or Welch's *t*-test with an approximation for the degrees of freedom.

Values of group descriptive statistics were presented as Means  $\pm$  Standard Error, unless stated otherwise. Effect sizes for ANOVAs are partial eta squared, referred to as partial  $\eta^2$ . We used an alpha level of 0.05 for all statistical tests. P values are two-tailed, unless stated otherwise.

#### Author contributions

S.Q., J.W. and C.F. conceived the experiment. B.C. performed data collection. B.C., J.W., and M.S. performed data analysis. J.W. drafted the manuscript, with B.C. & M.S. drafted the methods and results. All authors wrote the manuscript, contributed to data discussion and interpretation.

#### CRediT authorship contribution statement

**Jingyi Wang:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Boxuan Chen:** Software, Formal analysis, Investigation, Data curation, Writing – review & editing, Visualization, Project administration. **Manqi Sha:** Validation, Writing – review & editing, Visualization. **Yiran Gu:** Writing – review & editing. **Haitao Wu:** Conceptualization, Funding acquisition. **Cecilia Forcato:** Conceptualization, Writing – review & editing. **Shaosheng Qin:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Acknowledgements

This work was supported by the Natural Science Foundation of China (32130045, 31522028, 81571056), the Open Research Fund of the State Key Laboratory of Cognitive Neuroscience and Learning (CNLZD1503), and the Major Project of National Social Science Foundation (19ZDA363). J.W. was supported by the International Postdoc Exchange Program in China (the Introduce Talent Program), and the Special fund (2018 T110060) from China Postdoctoral Science Foundation Grant.

We thank Ruiyi Chen and Liping Zhuang for their assistance in pilot experiments. We also appreciate that Dr. Marijn Kroes and Frederik D. Weber had provided valuable suggestions for the study design and the manuscript, respectively.

#### References

- Arnsten, A. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*, 10, 410–422. <https://doi.org/10.1038/nrn2648>.
- Audrain, S., & McAndrews, M. P. (2020). Schemas provide a scaffold for neocortical integration at the cost of memory specificity over time. *bioRxiv*.
- Badgaiyan, R. D., Fischman, A. J., & Alpert, N. M. (2009). Dopamine release during human emotional processing. *Neuroimage*, 47(4), 2041–2045.
- Bissière, S., Humeau, Y., & Lüthi, A. (2003). Dopamine gates LTP induction in lateral amygdala by suppressing feedforward inhibition. *Nat Neurosci*, 6(6), 587–592.
- Björkstrand, J., Agren, T., Åhs, F., Frick, A., Larsson, E.-M., Hjorth, O., ... Fredrikson, M. (2016). Disrupting Reconsolidation Attenuates Long-Term Fear Memory in the Human Amygdala and Facilitates Approach Behavior. *Current Biology*, 26(19), 2690–2695.
- Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: The self-assessment manikin and the semantic differential. *Journal of behavior therapy and experimental psychiatry*, 25(1), 49–59.
- Brainerd, C. J., & Reyna, V. F. (2002). Fuzzy-trace theory and false memory. *Current Directions in Psychological Science*, 11(5), 164–169.
- Brainerd, C. J., & Reyna, V. F. (Bradley & Lang) (2005). *The science of false memory* (Vol. 38). Oxford University Press.
- Brawn, T. P., Nusbaum, H. C., & Margoliash, D. (2018). Sleep-dependent reconsolidation after memory destabilization in starlings. *Nat Commun*, 9(1), 3093.
- Broussard, J. I., Yang, K., Levine, A. T., Tsetsenis, T., Jensen, D., Cao, F., ... Dani, J. A. (2016). Dopamine Regulates Aversive Contextual Learning and Associated In Vivo Synaptic Plasticity in the Hippocampus. *Cell Rep*, 14(8), 1930–1939.
- Bynion, T.-M., & Feldner, M. T. (2017). Self-assessment manikin. *Encyclopedia of personality and individual differences*, 1–3.
- Cahill, L., Prins, B., Weber, M., & McGaugh, J. L. (1994). Beta-adrenergic activation and memory for emotional events. *Nature*, 371(6499), 702–704.
- Carmassi, C., Foghi, C., Dell'Oste, V., Cordone, A., Bertelloni, C. A., Bui, E., & Dell'Osso, L. (2020). PTSD symptoms in healthcare workers facing the three coronavirus outbreaks: What can we expect after the COVID-19 pandemic. *Psychiatry research*, 113312.
- Chen, B. K., Murawski, N. J., Cincotta, C., McKissick, O., Finkelstein, A., Hamidi, A. B., ... Ramirez, S. (2019). Artificially Enhancing and Suppressing Hippocampus-Mediated Memories. *Curr Biol*, 29(11), 1885–1894 e1884.
- Christianson, S.-Å. (1992). Emotional stress and eyewitness memory: A critical review. *Psychological bulletin*, 112(2), 284.
- Claes, N., Karos, K., Meulders, A., Crombez, G., & Vlaeyen, J. W. S. (2014). Competing Goals Attenuate Avoidance Behavior in the Context of Pain. *The Journal of Pain*, 15(11), 1120–1129.
- Correia, S. S., McGrath, A. G., Lee, A., Graybiel, A. M., & Goossens, K. A. (2016). Amygdala-ventral striatum circuit activation decreases long-term fear. *eLife*, 5, Article e12669.
- Das, R. K., Lawn, W., & Kamboj, S. K. (2015). Rewriting the valuation and salience of alcohol-related stimuli via memory reconsolidation. *Transl Psychiatry*, 5, Article e645.
- Davidson, R. J. (1998). Affective style and affective disorders: Perspectives from affective neuroscience. *Cognition & Emotion*, 12(3), 307–330.
- de Jong, P. J., Vorage, I., & van den Hout, M. A. (2000). Counterconditioning in the treatment of spider phobia: Effects on disgust, fear and valence. *Behaviour Research and Therapy*, 38(11), 1055–1069.
- Debiec, J., LeDoux, J. E., & Nader, K. (2002). Cellular and systems reconsolidation in the hippocampus. *Neuron*, 36(3), 527–538.
- Dolan, R. J., Lane, R., Chua, P., & Fletcher, P. (2000). Dissociable temporal lobe activations during emotional episodic memory retrieval. *NeuroImage*, 11(3), 203–209.
- Dudai, Y. (2012). The Restless Engram: Consolidations Never End. *Annual Review of Neuroscience*, 35(35), 227–247.
- Eifert, G. H., Craill, L., Carey, E., & O'Connor, C. (1988). Affect modification through evaluative conditioning with music. *Behaviour Research and Therapy*, 26(4), 321–330.
- Exton-McGuinness, M. T. J., Lee, J. L. C., & Reichelt, A. C. (2015). Updating memories—The role of prediction errors in memory reconsolidation. *Behav Brain Res*, 278, 375–384.
- Fenn, K. M., Gallo, D. A., Margoliash, D., Roediger, H. L., & Nusbaum, H. C. (2009). Reduced false memory after sleep. *Learning & memory*, 16(9), 509–513.
- Forcato, C., Argibay, P. F., Pedreira, M. E., & Maldonado, H. (2009). Human reconsolidation does not always occur when a memory is retrieved: The relevance of the reminder structure. *Neurobiol Learn Mem*, 91(1), 50–57.
- Forcato, C., Burgos, V. L., Argibay, P. F., Molina, V. A., Pedreira, M. E., & Maldonado, H. (2007). Reconsolidation of declarative memory in humans. *Learning & Memory*, 14(4), 295–303.
- Forcato, C., Fernandez, R. S., & Pedreira, M. E. (2014). Strengthening a consolidated memory: The key role of the reconsolidation process. *J Physiol Paris*, 108(4–6), 323–333.
- Goltseker, K., Bolotin, L., & Barak, S. (2017). Counterconditioning During Reconsolidation Prevents Relapse of Cocaine Memories. *Neuropsychopharmacology*, 42(3), 716–726.
- Guarnieri, R. V., Bueno, O. F. A., & Tudesco, I. d. S. S. (2019). *True and False Memories: Neuropsychological and Neuropharmacological Approaches*. In Eat, Learn, Remember: IntechOpen.

- Guerin, S. A., Robbins, C. A., Gilmore, A. W., & Schacter, D. L. (2012). Retrieval failure contributes to gist-based false recognition. *Journal of Memory and Language*, 66(1), 68–78.
- Holmes, N. M., Leung, H. T., & Westbrook, R. F. (2016). Counterconditioned fear responses exhibit greater renewal than extinguished fear responses. *Learning & memory (Cold Spring Harbor, NY)*, 23(4), 141–150.
- Hon, T., Das, R. K., & Kamboj, S. K. (2016). The effects of cognitive reappraisal following retrieval-procedures designed to destabilize alcohol memories in high-risk drinkers. *Psychopharmacology*, 233(5), 851–861.
- Hupbach, A., Gomez, R., Hardt, O., & Nadel, L. (2007). Reconsolidation of episodic memories: A subtle reminder triggers integration of new information. *Learning & memory*, 14(1–2), 47–53.
- Kalisch, R., Gerlicher, A. M. V., & Duvarci, S. (2019). A Dopaminergic Basis for Fear Extinction. *Trends Cogn Sci*, 23(4), 274–277.
- Kathirvel, N. (2020). Post COVID-19 pandemic mental health challenges. *Asian Journal of Psychiatry*.
- Keller, N. E., Hennings, A. C., & Dunsmoor, J. E. (2020). Behavioral and neural processes in counter-conditioning: Past and future directions. *Behaviour Research and Therapy*, 125, Article 103532.
- Kensinger, E. A., & Corkin, S. (2003). Memory enhancement for emotional words: Are emotional words more vividly remembered than neutral words? *Memory & Cognition*, 31(8), 1169–1180.
- Kensinger, E. A., & Corkin, S. (2004). Two routes to emotional memory: Distinct neural processes for valence and arousal. *Proc Natl Acad Sci U S A*, 101(9), 3310.
- Kindt, M., Soeter, M., & Vervliet, B. (2009). Beyond extinction: Erasing human fear responses and preventing the return of fear. *Nature neuroscience*, 12(3), 256.
- Klinzing, J. G., Rasch, B., Born, J., & Diekelmann, S. (2016). Sleep's role in the reconsolidation of declarative memories. *Neurobiol Learn Mem*, 136, 166–173.
- Koutstaal, W., & Schacter, D. L. (1997). Gist-based false recognition of pictures in older and younger adults. *Journal of Memory and Language*, 37(4), 555–583.
- Kroes, M. C., Dunsmoor, J. E., Lin, Q., Evans, M., & Phelps, E. A. (2017). A reminder before extinction strengthens episodic memory via reconsolidation but fails to disrupt generalized threat responses. *Scientific reports*, 7(1), 1–14.
- Kroes, M. C., Tendolkar, I., van Wingen, G. A., van Waarde, J. A., Strange, B. A., & Fernandez, G. (2014). An electroconvulsive therapy procedure impairs reconsolidation of episodic memories in humans. *Nat Neurosci*, 17(2), 204–206.
- Lane, R. D., Ryan, L., Nadel, L., & Greenberg, L. (2015). Memory reconsolidation, emotional arousal, and the process of change in psychotherapy: New insights from brain science. In *Behavioral and brain sciences* (p. 38).
- Lang, P. J., Greenwald, M. K., Bradley, M. M., & Hamm, A. O. (1993). Looking at pictures: Affective, facial, visceral, and behavioral reactions. *Psychophysiology*, 30(3), 261–273.
- Lee, J. L. C., Nader, K., & Schiller, D. (2017). An Update on Memory Reconsolidation Updating. *Trends Cogn Sci*, 21(7), 531–545.
- Liu, Y., Lin, W., Liu, C., Luo, Y., Wu, J., Bayley, P. J., & Qin, S. (2016). Memory consolidation reconfigures neural pathways involved in the suppression of emotional memories. *Nature Communications*, 7, 13375. <https://doi.org/10.1038/ncomms13375>.
- Loftus, E. F. (1979). The malleability of human memory: Information introduced after we view an incident can transform memory. *American Scientist*, 67(3), 312–320.
- Lonergan, M. H., Brunet, A., Olivera-Figueroa, L. A., & Pitman, R. K. (2013). Chapter 12 - Disrupting Consolidation and Reconsolidation of Human Emotional Memory with Propranolol: A Meta-Analysis. An earlier version of this work was presented at the 12th European Conference on Traumatic Stress in Vienna, June 2011. In C. M. Alberini (Ed.), *Memory Reconsolidation* (pp. 249–272). San Diego: Academic Press.
- Luo, R., Uematsu, A., Weitemier, A., Aquili, L., Koivumaa, J., McHugh, T. J., & Johansen, J. P. (2018). A dopaminergic switch for fear to safety transitions. *Nat Commun*, 9(1), 2483.
- Marowsky, A., Yanagawa, Y., Obata, K., & Vogt, K. E. (2005). A Specialized Subclass of Interneurons Mediates Dopaminergic Facilitation of Amygdala Function. *Neuron*, 48(6), 1025–1037.
- McKeon, S., Pace-Schott, E. F., & Spencer, R. M. (2012). Interaction of sleep and emotional content on the production of false memories. *PLoS One*, 7(11), Article e49353.
- McNally, G. P., Johansen, J. P., & Blair, H. T. (2011). Placing prediction into the fear circuit. *Trends Neurosci*, 34(6), 283–292.
- Meulders, A., Karsdorp, P. A., Claes, N., & Vlaeyen, J. W. S. (2015). Comparing Counterconditioning and Extinction as Methods to Reduce Fear of Movement-Related Pain. *The Journal of Pain*, 16(12), 1353–1365.
- Misanin, J. R., Miller, R. R., & Lewis, D. J. (1968). Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science*, 160(3827), 554–555.
- Mitchell, H. A., & Weinschenker, D. (2010). Good night and good luck: Norepinephrine in sleep pharmacology. *Biochem Pharmacol*, 79(6), 801–809.
- Moyano, M. D., Diekelmann, S., Pedreira, M. E., & Forcato, C. (2019). Sleep accelerates re-stabilization of human declarative memories. *Neurobiol Learn Mem*, 162, 1–8.
- Nader, K., & Hardt, O. (2009). A single standard for memory: The case for reconsolidation. *Nat Rev Neurosci*, 10(3), 224–234.
- Nader, K., Schafe, G. E., & Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature*, 406(6797), 722–726.
- Newall, C., Watson, T., Grant, K.-A., & Richardson, R. (2017). The relative effectiveness of extinction and counter-conditioning in diminishing children's fear. *Behaviour Research and Therapy*, 95, 42–49.
- Olshavsky, M. E., Song, B. J., Powell, D. J., Jones, C. E., Monfils, M. H., & Lee, H. J. (2013). Updating appetitive memory during reconsolidation window: Critical role of cue-directed behavior and amygdala central nucleus. *Front Behav Neurosci*, 7, 186.
- Parker, A., & Dagnall, N. (2007). Effects of bilateral eye movements on gist based false recognition in the DRM paradigm. *Brain and Cognition*, 63(3), 221–225.
- Payne, J. D., Schacter, D. L., Propper, R. E., Huang, L.-W., Wamsley, E. J., Tucker, M. A., ... Stickgold, R. (2009). The role of sleep in false memory formation. *Neurobiology of learning and memory*, 92(3), 327–334.
- Phelps, E. A., & Hofmann, S. G. (2019). Memory editing from science fiction to clinical practice. *Nature*, 572(7767), 43–50.
- Rajkumar, R. (2020). Post-traumatic stress in the wake of the COVID-19 pandemic: A scoping review [version 1; peer review: Awaiting peer review]. *F1000Res*, 9(675). <https://doi.org/10.12688/f1000research.24513.1>.
- Ramirez, S., Liu, X., MacDonald, C. J., Moffa, A., Zhou, J., Redondo, R. L., & Tonegawa, S. (2015). Activating positive memory engrams suppresses depression-like behaviour. *Nature*, 522(7556), 335–339.
- Rasch, B., & Born, J. (2013). About Sleep's Role in Memory. *Physiological Reviews*, 93(2), 681–766. <https://doi.org/10.1152/physrev.00032.2012>.
- Redondo, R. L., Kim, J., Arons, A. L., Ramirez, S., Liu, X., & Tonegawa, S. (2014). Bidirectional switch of the valence associated with a hippocampal contextual memory engram. *Nature*, 513, 426.
- Reichelt, A. C., Exton-McGuinness, M. T., & Lee, J. L. (2013). Ventral tegmental dopamine dysregulation prevents appetitive memory destabilization. *J Neurosci*, 33(35), 14205–14210.
- Reynolds, G., Field, A. P., & Askew, C. (2018). Reductions in Children's Vicariously Learnt Avoidance and Heart Rate Responses Using Positive Modeling. *Journal of Clinical Child & Adolescent Psychology*, 47(4), 555–568.
- Russell, J. A. (1980). A circumplex model of affect. *Journal of personality and social psychology*, 39(6), 1161.
- Sandkühler, J., & Lee, J. (2013). How to erase memory traces of pain and fear. *Trends Neurosci*, 36(6), 343–352.
- Schachter, S., & Singer, J. (1962). Cognitive, social, and physiological determinants of emotional state. *Psychological review*, 69(5), 379.
- Schacter, D. L., Guerin, S. A., & Jacques, P. L. S. (2011). Memory distortion: An adaptive perspective. *Trends in cognitive sciences*, 15(10), 467–474.
- Schiller, D., Kanen, J. W., LeDoux, J. E., Monfils, M.-H., & Phelps, E. A. (2013). Extinction during reconsolidation of threat memory diminishes prefrontal cortex involvement. *Proceedings of the National Academy of Sciences*, 110(50), 20040–20045.
- Schiller, D., Monfils, M.-H., Raio, C. M., Johnson, D. C., LeDoux, J. E., & Phelps, E. A. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature*, 463(7277), 49–53.
- Schwarz, N. (1990). *Feelings as information: Informational and motivational functions of affective states*. The Guilford Press.
- Scully, I. D., Napper, L. E., & Hupbach, A. (2017). Does reactivation trigger episodic memory change? A meta-analysis. *Neurobiol Learn Mem*, 142, 99–107.
- Sinclair, A. H., & Barense, M. D. (2018). Surprise and destabilize: Prediction error influences episodic memory reconsolidation. *Learning & memory*, 25(8), 369–381.
- Sinclair, A. H., & Barense, M. D. (2019). Prediction error and memory reactivation: How incomplete reminders drive reconsolidation. *Trends in neurosciences*, 42(10), 727–739.
- Steinforth, E. C., Kanen, J. W., Raio, C. M., Clem, R. L., Haganir, R. L., & Phelps, E. A. (2014). Young and old Pavlovian fear memories can be modified with extinction training during reconsolidation in humans. *Learning & memory*, 21(7), 338–341.
- Soeter, M., & Kindt, M. (2015). An Abrupt Transformation of Phobic Behavior After a Post-Retrieval Amnesic Agent. *Biol Psychiatry*, 78(12), 880–886.
- Tulving, E. (1993). *What is an episodic memory?*
- Vickers, A. J. (2001). The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: A simulation study. *BMC medical research methodology*, 1(1), 1–4.
- Visser, R. M., Lau-Zhu, A., Henson, R. N., & Holmes, E. A. (2018). Multiple memory systems, multiple time points: How science can inform treatment to control the expression of unwanted emotional memories. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 373(1742), 20170209.
- Walker, M. P., Brakefield, T., Hobson, J. A., & Stickgold, R. (2003). Dissociable stages of human memory consolidation and reconsolidation. *Nature*, 425(6958), 616–620.
- Weber, F. D., Wang, J. Y., Born, J., & Inostroza, M. (2014). Sleep benefits in parallel implicit and explicit measures of episodic memory. *Learn Mem*, 21(4), 190–198.
- Wolpe, J. (1990). *The practice of behavior therapy*. Pergamon Press.
- Xiao, S., Luo, D., & Xiao, Y. (2020). Survivors of COVID-19 are at high risk of post-traumatic stress disorder. *Global Health Research and Policy*, 5(1), 1–3.