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Stress Selectively Affects the Reactivated Components of a Declarative Memory

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When long-term memories are reactivated, they can reenter a transient plastic state in which they are vulnerable to interference or physiological manipulations. The present study attempted to directly affect reactivated memories through a stress manipulation, and compared the effects of stress on reactivated and nonreactivated components of a declarative memory in a within-subject design. We presented image pairs that consisted of an image of an animal and an image of an unrelated object. Participants were instructed to memorize the object images. Forty-eight hours later, we presented half of the animal images again in an unrelated task to indirectly reactivate the associated object images. Immediately after reactivation, participants were exposed to cold pressor stress or a warm water control condition. Forty-eight hours later, we assessed memory for the object images with a free recall test. Reactivation boosted memory performance in the control condition, such that reactivated items were better recalled than nonreactivated items. This memory-enhancing effect of reactivation was completely abolished by cold pressor stress. Importantly, stress selectively impacted only the reactivated items while leaving memory for the nonreactivated items unaffected. The present study shows that it is possible to selectively reactivate and modulate specific parts of a declarative memory.

Keywords: memory reactivation, memory reconsolidation, stress

Reactivation of long-term memories triggers a state of transient instability in which memories are particularly vulnerable to disruptions and modifications. This instability gradually ceases as memories become restabilized or reconsolidated (Przybyslawski & Sara, 1997; Nader, Schafe & LeDoux, 2000). Reconsolidation has been extensively studied in animals, most commonly in fear conditioning paradigms (for a review, Besnard, Caboche, & Laroche, 2012), but a growing body of evidence suggests that reconsolidation extends to human procedural, fear, and episodic memories (for recent reviews, see Agren, in press; Hupbach, Gomez, & Nadel, 2013). Usually, reconsolidation studies are carried out in three-session paradigms, such that encoding, reactivation, and retrieval occur in separate sessions. While the first and third sessions are identical for all participants, the critical manipulations occur during the second session. Here, memory is either reactivated by representing parts of the original learning episode (reactivation condition) or memory is not reactivated (control condition), and then a potentially memory-modifying treatment is applied. Effects on reconsolidation processes are revealed in the final retrieval session: reconsolidation was affected if the treatment altered memory in the reactivation but not in the control condition, and if reactivation without treatment did not affect the reactivated memory in the same way as reactivation that was followed by the treatment.

Invasive postreactivation treatments, such as the intracranial injection of protein-synthesis inhibitors are common in animals, although effects of behavioral interventions have been demonstrated as well (e.g., Monfils, Cowansage, Klann, & LeDoux, 2009). In humans, postreactivation treatments range from oral administration of propanolol (e.g., Kindt, Soeter, & Vervliet, 2009), and ketamine (Corlett et al., 2013), to behavioral interventions such as extinction training (e.g., Agren et al., 2012; Schiller et al., 2010), and learning of new material (e.g., Hupbach, Gomez, Hardt, & Nadel, 2007). Moreover, reactivated memories in both animals and humans appear to be sensitive to stress manipulations (for a recent review, see Akirav & Maroun, 2013). In humans, stress has been found to *negatively* affect the reconsolidation of autobiographical memories (Schwabe & Wolf, 2010), object memories (Dongaonkar, Hupbach, Gomez, & Nadel, 2013), and drug-related memories in abstinent heroin addicts (Zhao, Zhang, Shi, Epstein, & Lu, 2009; for a similar result in rats, see X. Y. Wang, Zhao, Ghitza, Li, & Lu, 2008). In contrast, Coccoz, Maldonado, and Delorenzi (2011) report *enhancing* effects of a mild stressor on reconsolidation of memories for pairs of nonsense syllables. This divergence mimics the reported impairing effects of both glucocorticoid receptor agonists and antagonists on memory consolidation and reconsolidation in animal studies (cf., Akirav & Maroun, 2013), and might be attributable to a variety of factors. These include differences in the content and strength of the original memory (S. H. Wang, de Oliveira, & Nader, 2009) as well as differences in the severity of the induced stress, and the timing of the stress manipulation (Schwabe & Wolf, 2013).

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Despite the differences in the specific direction of influence (i.e., impairment vs. enhancement), prior studies clearly demonstrate that stress can affect the reconsolidation of memories. In humans, stress/reconsolidation studies have targeted declarative memories, that is, memories that can be consciously recalled (e.g., Squire, 2004). In most prior studies, memory was reactivated as a whole, that is, the reminder was intended to reactivate the entire prior learning episode. This was accomplished by having participants re-experience parts of the original learning event, such as the spatial context or sound stimuli (Coccoz et al., 2011; Dongaonkar et al., 2013), or by asking people to recall the original memory (Schwabe & Wolf, 2010; Zhao et al., 2009) before the stress manipulation. The present study extends these findings by asking whether it is possible to selectively reactivate *specific* components or parts of a declarative memory, and then affect only those components by stress without causing modifications of the nonreactivated parts. Thus, instead of reactivating the prior encoding episode as a whole (including all items that were part of the originally encoded set), we implemented a reactivation procedure that targeted only specific items. Recently, Kroes et al. (2014) provided evidence for selective reconsolidation in declarative memory. Patients with unipolar depression were presented with two different emotionally aversive slide-show stories. After one week, one of the stories was reactivated (by presenting parts of the first slide) and immediately after, patients received electroconvulsive shock therapy (ECT). When tested for story recall one day later, memory for the reactivated story was impaired, both in comparison with the nonreactivated story and in comparison with a control group of patients that had not received ECT after reactivation. Similar to the study by Kroes et al., our study used a within-subject design to compare treatments (in our case stress) effects on reactivated and nonreactivated memories. However, the selectivity of our reactivation procedure went beyond Kroes et al.'s study in that we targeted individual items, instead of an entire story. The question of whether it is possible to affect only specific components of a memory is not only of theoretical importance, it also has implications for clinical and educational practice. For instance, certain aspects of a memory might be especially troubling for an individual, and therefore, it might be desired to selectively weaken those parts while leaving other parts of the memory intact.

Memory reactivation is not an all-or-none phenomenon, and the extent of reactivation has implications for the vulnerability of memories to change (Forcato, Argibay, Pedreira, & Maldonado, 2009; Detre, Natarajan, Gershman, & Norman, 2013). For instance, moderate levels of reactivation lead to forgetting in the think/no-think paradigm (Detre et al., 2013), and trigger reconsolidation of episodic memories (Hupbach et al., 2007, 2008). In contrast, stronger reactivation methods (e.g., explicit retrieval) cause memory strengthening, which counteracts forgetting (Detre et al., 2013) as well as memory change (Potts & Shanks, 2012; Hupbach, 2014, but see Schwabe & Wolf, 2010). Therefore, in the present study we did *not* ask participants to recall parts of the original memory during the reactivation phase. Instead, we attempted to *indirectly* reactivate specific items that were part of a previously learned list.

Current Study

The current study asked whether it is possible to selectively reactivate certain components of a declarative memory, and then affect the reconsolidation of these components with a stress manipulation. Our reactivation procedure capitalized on statistical learning of regularities in item presentation orders. Turk-Browne, Scholl, Johnson, and Chun (2010) have shown that such regularities are acquired quickly and without conscious awareness, and that they guide the implicit anticipation of future events. In our study, we presented participants with alternating images of animals and objects. At least initially unbeknownst to the participants, we set up predictive temporal regularities in the presentation of the animal and object images, such that a particular object image (e.g., puzzle) was always preceded by a particular animal image (e.g., horse[1]). At the same time, there was no temporal predictability between object and animal images. The animal image that followed a particular object image was randomly chosen (e.g., puzzle was sometimes followed by a bear, and sometimes followed by a moose, etc.). In the reactivation phase, we presented a subset of the animal images without their associated object images in an unrelated task. We expected the animal images to reactivate the associated object images (cf. Turk-Browne et al., 2010). After reactivation, we subjected participants to cold pressor stress (CPS) or a warm water control treatment. To induce CPS, participants were asked to submerge their nondominant arm in ice-cold water, which causes a painful stimulation. This experience is associated with increased activity of the noradrenergic system and the HPA axis, which in turn promote a rise in cortisol levels (Lovallo, 1975). Importantly, and in extension to prior studies, for each participant we reactivated only a subset of the items and predicted that CPS would only affect the reactivated subset but not the nonreactivated subset. Based on prior human studies (Schwabe & Wolf, 2010; Zhao et al., 2009; Dongaonkar et al., 2013; but see Coccoz et al., 2011), we expected stress to *negatively* affect the reconsolidation of the reactivated items.

Method

Design and Participants

The study was reviewed and approved by Lehigh University's Institutional Review Board, and all participants provided written informed consent before the start of the experiment. Participants were male undergraduate and graduate students from Lehigh University and were recruited through online advertisements. Participants received monetary compensation for their participation. The sample consisted of 60 healthy male participants between the ages of 18 and 30. Data from two participants were excluded because recall performance in Session 3 was 2.5 standard deviations above the mean of the entire sample. Thus, the final sample consisted of 58 participants. The study followed a 2×2 mixed factorial design, with Condition (CPS vs. warm water control) as the between-subjects factor and Reactivation (reactivated vs. not) as the within-subject factor. Participants were randomly assigned to the CPS

[1] We refer to animal–object images that were presented in temporal succession as pairs, although they were never shown at the same time.

versus warm water control condition. Saliva samples were taken from 16 participants in the warm water control condition and from 16 in the CPS condition to confirm that CPS was effective in elevating cortisol levels. Despite taking saliva samples, no other procedural changes were made for these subjects. In all of the reported analyses, we used Saliva Sampling (yes vs. no) as a control factor to assess whether taking saliva samples by itself affected performance.

Materials

Study material. The study material consisted of two lists of 10 animal and 10 object images each. Animal images (e.g., penguin, rabbit, moose) and object images (everyday objects, e.g., pot, crayon, bandage) were presented as colored photographs. Photographs were found through Internet image searches. All items were intended to be neutral and nonarousing. Stable animal-object pairs were created, such that a particular object (e.g., pot) was always presented after the same animal (e.g., penguin). Both lists were presented in Session 1. In Session 2, the animal images from one of the two lists were presented again to reactivate the associated object images. Across participants, it was counterbalanced which of the two lists was presented in Session 2.

Salivary sampling and biochemical analysis. Saliva was collected for 32 participants ($n = 16$ in the CPS, $n = 16$ in the control condition) using oral cotton swabs (Salimetrics) which participants placed under their tongue for 2 min, after which the experimenter immediately placed it into a storage tube. Samples were stored at −20°C immediately after collection and until analysis. An independent commercial testing site, Salimetrics, analyzed salivary cortisol concentrations using immunoassays. Each sample was analyzed twice, and the average of the two levels for each sample was used as a dependent measure in statistical analyses. Participants were instructed to abstain from eating, physical exercise, soft drinks, and caffeine for at least one hour before saliva sampling. A total of 4 samples were taken in Session 2 (see Figure 1 for time points of saliva sampling). Sample 1 was taken upon arrival, immediately before memory reactivation. Sample 2 was taken immediately after the reactivation task. Sample 3 was taken immediately after the CPS/control treatment. Sample 4 was taken exactly 25 minutes after the onset of the stress versus control treatment. We chose a 25-minute delay because previous studies have shown that cortisol peaks at 20 to 30 min after the onset of CPS (e.g., Schoofs, Wolf, & Smeets, 2009; Schwabe, Haddad, & Schachinger, 2008). During the waiting time after the CPS/control treatment and final saliva sampling, participants sat quietly and read magazines.

Procedure

The study consisted of three separate sessions, which took place on Monday, Wednesday, and Friday of the same week, between 8:00 a.m. and 12:00 p.m. For each participant, the individual time of testing on each day was held constant across the 3 days. The experimental procedure is illustrated in Figure 1.

In *Session 1*, participants were presented with two lists of animal and object images. Always one image was presented at a time with animal and object images alternating. Images were presented for 3 seconds with an interstimulus interval of 1 second (fixation cross). A particular object always followed a particular animal (stable

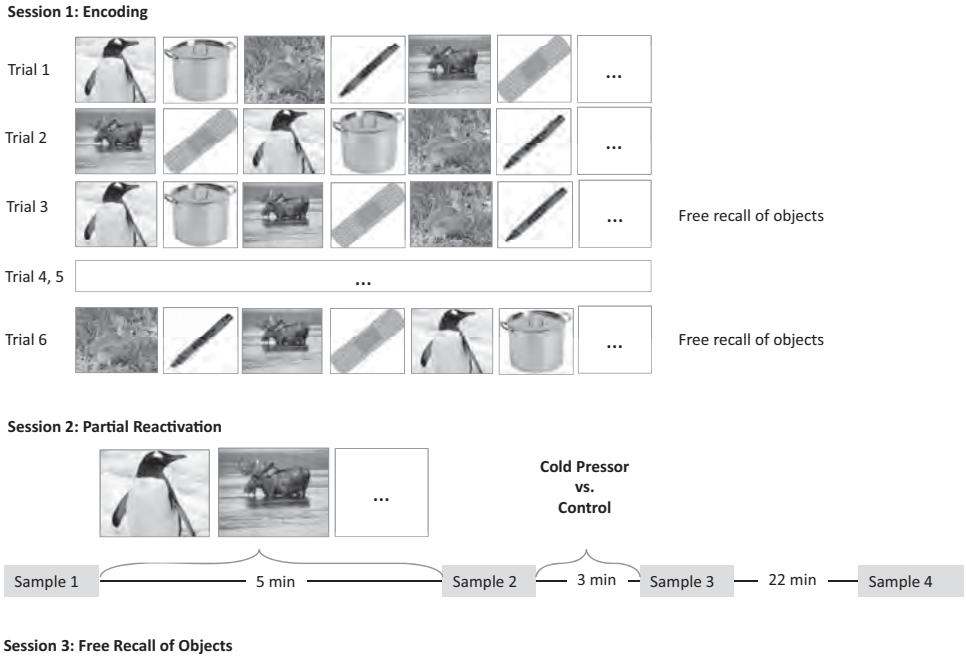

Figure 1. Overview of the experimental procedure. In Session 1, participants encoded animal and object images. In Session 2, half of the animal images were presented again to reactivate the associated object images, and then the stress versus control treatment was applied. Saliva samples were taken from a subset of the participants in each group. In Session 3, participants were asked to freely recall the objects from Session 1.

animal-object pairs). The presentation order of these pairs was random. Participants were not informed about the stability in animal–object pairing. They were instructed to pay attention to all images, but to memorize the objects only for a later memory test. Pairs were presented for six consecutive trials, and in each trial, the order of presentation was newly randomized. After three trials and again after all six trials, participants were asked to recall as many objects as they could.

In *Session 2* participants were presented with the animal images of one of the lists in random order. Each image was presented for 3 seconds and participants were asked to indicate whether the depicted animal lives on land, water, or both by clicking on one of the corresponding response buttons that appeared directly below the image on the computer screen. Then, participants were exposed to CPS or the warm water treatment. Participants submerged their nondominant arm, including the elbow, into a bucket filled with ice water (0–2°C) or warm water (35–37°C). Participants were asked to keep their arm in the water for 3 minutes, but were explicitly told that they could remove their arm from the water bath if the pain became too uncomfortable. The experimenter closely watched the participants, and recorded the exact time of submersion. Two participants in the CPS group removed their arm prematurely (resulting in submersion times of 90 seconds, and 107 seconds). All other participants kept their arm in the water for 3 minutes.

In *Session 3* participants were asked to write down on a piece of paper as many objects as they could freely recall from the Monday session.

Results

Session 1: Object Learning

To assess potential differences in object learning performances between the different conditions, we analyzed the number of objects recalled in the second (and final) recall trial in Session 1 with a 2 (Condition: CPS vs. control) × 2 (Saliva Sampling: yes vs. no) × 2 (Reactivation: yes vs. no) mixed Analysis of Variance (ANOVA). No main effects or interactions were significant ($F \leq 2.35$, $p \geq .13$), showing that learning was comparable across conditions.

Session 2: Cortisol Analysis

Saliva samples were taken from 32 participants ($n = 16$ for CPS, $n = 16$ for control) at four different time points (arrival, immediately after reactivation, immediately after CPS/stress, and 25 minutes after CPS/stress onset; see Figure 1). Mean salivary cortisol concentrations in the CPS versus control condition are displayed in Figure 2. Data from two participants (one in the CPS, one in the control condition) were excluded from analysis, because cortisol could not be detected in at least one of their samples.

Cortisol concentrations were analyzed with a 2 (Condition: CPS vs. control) × 4 (time points) mixed ANOVA. Because the sphericity assumption was violated, we report Greenhouse-Geisser corrected values. Only the interaction between Condition and Time was significant, $F(3, 46.79) = 9.82$, $MSE = .033$, $p = .001$. Simple effect analyses showed that cortisol concentrations did not differ between the conditions at time points 1 to 3 (Fs < 1), but

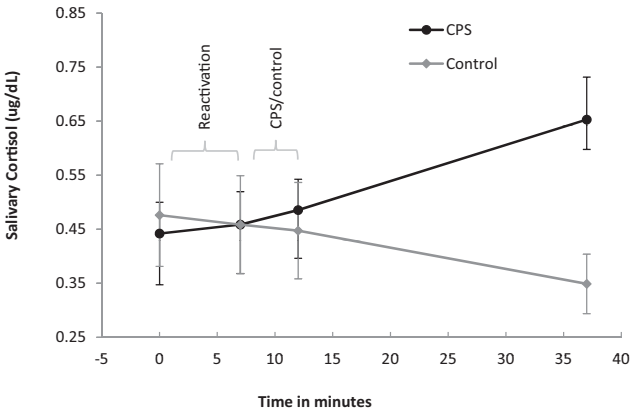

Figure 2. Mean salivary cortisol levels in the stress and control group in Session 2 before and after memory reactivation, and immediately before and 25 minutes after the CPS versus warm water treatment. Error bars represent *SEM*s.

that the CPS in comparison with the warm water control group showed significantly higher levels of cortisol at time point 4, $F(1, 28) = 8.77$, $MSE = .08$, $p = .006$. Thus, as predicted, CPS induced a significant physiological stress response.

Session 3: Object Recall

Final memory performance was calculated by dividing the number of items recalled in Session 3 by the number of items recalled at the end of Session 1. These proportions were calculated separately for reactivated and nonreactivated items (e.g., if three reactivated objects were recalled in Session 3, and six to-be-reactivated objects had been recalled after encoding in Session 1, the proportion of recalled reactivated objects would be .5). Mean performances in the CPS group and warm water control group are displayed in Figure 3.

A 2 (Condition: CPS vs. control) × 2 (Saliva Sampling: yes vs. no) × 2 (Reactivation: yes vs. no) mixed ANOVA revealed a marginally significant effect of Saliva Sampling, $F(1, 54) = 3.61$, $MSE = .068$, $p = .063$, which shows that the group without sampling ($M = .67$, $SD = .26$) remembered overall slightly more objects than the group in which samples were taken ($M = .58$, $SD = .27$). Importantly, this factor did not interact with Condition, Reactivation, or the Condition × Reactivation interaction, and thus taking samples did not selectively affect memory performance in any particular condition. As predicted, the ANOVA revealed a significant interaction between Condition and Reactivation, $F(1, 54) = 7.03$, $MSE = .067$, $p = .011$ (all other effects, $F \leq 1.74$, $p \geq .19$). Simple effects analyses showed that in the control group, reactivated objects were better remembered than nonreactivated objects, $F(1, 56) = 5.68$, $MSE = .07$, $p = .021$. In contrast, no such difference was observed in the CPS group, $F(1, 56) = 1.89$, $MSE = .06$, $p = .175$. Additionally, participants in the control group recalled significantly more reactivated items than participants in the CPS group, $F(1, 54) = 9.68$, $MSE = .05$, $p = .003$. The two groups did not differ in recall of nonreactivated items ($F < 1$).

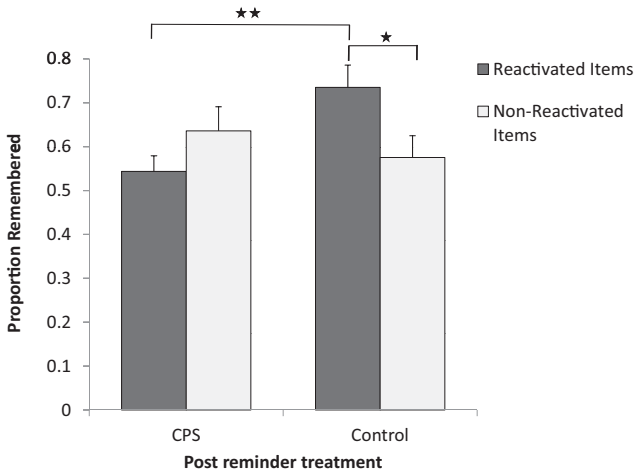

Figure 3. Proportions of objects recalled in Session 3 in the stress and control group. Proportions were calculated as the number of objects recalled in Session 3 in relation to the number of objects recalled at the end of the first session. For each participant, half of the objects had been reactivated, and half had not been reactivated in Session 2. Error bars represent *SEM*s.

Discussion

The present study shows that it is possible to selectively reactivate specific parts of a memory, and then to affect the reconsolidation of these reactivated, but not the nonreactivated parts with a postreminder stress manipulation. Whereas most previous studies have attempted to reactivate learning episodes as a whole (e.g., Chan & LaPaglia, 2013; Forcato et al., 2007; Hupbach et al., 2007), we targeted specific parts of the memory with our reactivation procedure (see also Kroes et al., 2014). That selective reactivation was successful is corroborated by two findings: (a) Reactivated objects were better recalled than nonreactivated objects in the control group, and (b) stress selectively affected memory for the reactivated objects without affecting memory for the nonreactivated objects. That final recall in the control group benefited from reactivation was not predicted but extends research on the testing effect (Roediger & Karpicke, 2006) because it shows that not only direct testing, but also indirect reactivation can strengthen memories (see also Kroes et al., 2014; Wichert, Wolf, & Schwabe, 2011). It also aligns with recent fMRI studies showing that spontaneous reactivation after encoding enhances later memory retrieval (Detre et al., 2013; Staresina, Alink, Kriegeskorte, & Henson, 2013). The level of "indirectness" of the reactivation in our study remains uncertain. Based on a study by Turk-Browne et al. (2010), we had expected that the presentation of the animal images in Session 2 would implicitly (i.e., without conscious awareness) reactivate the object images. In Turk-Browne et al.'s study, participants responded faster to items that consistently followed the presentation of some other stimuli in comparison with items that were presented with random predecessors. Importantly, participants indicated that they were not aware of the regularities in the stream of presented images, evidencing that faster responding was a result of implicit processes. In our study, we did not ask participants whether they had become aware of the stable animal–object pairings. However, because we did not include a condition in which object images were preceded by randomly selected animal images, it can be assumed that most participants had noticed the temporal contiguity of animal–object pairings by the end of Session 1. Thus, although we did not ask participants to overtly recall the associated objects when the animal images were presented in isolation in Session 2, the associated objects might have come to mind spontaneously, rendering reactivation more explicit than originally intended.

Another important finding of the present study is that stress completely eliminated the memory-enhancing effect of reactivation: Whereas the control group recalled more reactivated than nonreactivated objects, the stress group recalled slightly fewer reactivated than nonreactivated items. Additionally, the stress group recalled significantly fewer reactivated objects than the control group, but no such difference emerged for the recall of nonreactivated objects. This shows that stress selectively affected the reactivated components of the memory, while leaving the nonreactivated parts unaffected. Memory impairment was apparent when comparing performance for reactivated items in the stress relative to the control group, but not when comparing performance for reactivated and nonreactivated within the stress group. This finding is explained by the fact that reactivation enhanced memory in the control group, which we had not predicted. Presumably, memory enhancing (reactivation) and memory impairing (stress) effects canceled each other out, resulting in comparable memory performance for reactivated and nonreactivated items in the stress group.

A variety of factors determines whether stress impairs or enhances memory, such as whether the stress response is severe and accompanied by activity of the noradrenergic system (e.g., Cahill, Gorski, & Le, 2003; Segal & Cahill, 2009), or whether the content of the memory is neutral or emotionally charged (e.g., Smeets, Otgaar, Candel, & Wolf, 2008). Additionally, stress differently affects the various memory phases. Stress (hormones) commonly enhances the initial storage of an experience (consolidation; e.g., Andreano & Cahill, 2006; Beckner, Tucker, Delville, & Mohr, 2006; Preuss & Wolf, 2009). Specifically, information that is directly related or presented in close proximity to a stressful experience is especially well retained (cf. Schwabe & Wolf, 2013). This has been linked to catecholamine and nongenomic glucocorticoid effects on various brain regions that mobilize attentional resources and shift the cognitive system into a 'memory formation mode.' The subsequent delayed nongenomic glucocorticoid actions are assumed to instigate a 'memory storage mode' to ensure the long-term consolidation of stress-related information. The stress-induced focus on acquiring new information might in turn limit the cognitive resources available for retrieval and restabilization of reactivated "old" information (for a detailed description of this model, see Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012). This could explain why stress often impairs retrieval (see review by Het, Ramlow, & Wolf, 2005; but see Hupbach & Fieman, 2012) and reconsolidation (present study; Schwabe & Wolf, 2010; Zhao et al., 2009; Dongaonkar et al., 2013; but see Coccoz et al., 2011).

We restricted our study to men, because stress has been shown to affect memory processes differently in men and women (e.g., Andreano & Cahill, 2006; McCullough & Yonelinas, 2013; Hupbach & Fieman, 2012; Schoofs et al., 2009), which has been attributed to the interaction of stress with sex hormones (for a

review, see Andreano & Cahill, 2009). Future studies assessing stress effects on reconsolidation in women will have to control for variations in hormonal levels across the menstrual cycle and the use of hormonal birth control methods to account for the modulatory effect of sex hormones on the interaction between stress and memory.

Our study shows that it is possible to selectively reactivate specific components of a declarative memory, and then affect those components with stress. That type of selectivity has been observed for reconsolidation of human fear conditioning. Schiller et al. (2010) conditioned fear to two different stimuli (colored squares, e.g., red and blue), by repeatedly pairing the presentation of these stimuli with a mild shock to the wrist. After a delay, one of the squares (e.g., red) was presented again as a reminder, reactivating the red square-shock association or fear memory. Extinction training for both stimuli followed this reactivation procedure: Red and blue squares were repeatedly presented without shocks, resulting in extinction of fear responses to both stimuli. However, extinction was long lasting only for the red square, that is, the stimulus that had been reactivated prior to extinction training. In contrast, fear was easily reinstated to the blue square, that is, the nonreactivated stimulus. Thus, extinction training within the reconsolidation window resulted in a lasting change of the fear memory for the reactivated stimulus only, while leaving fear memory for the nonreactivated stimulus intact. Our study suggests that selective memory alteration through reconsolidation is also possible for declarative memories. In our study, we selectively reactivated specific objects and impaired their reconsolidation with a stress manipulation. It would be interesting to extend this finding in two ways: by asking whether it is possible to selectively reactivate and subsequently alter specific characteristics of individual items in declarative memory (e.g., object, scene or person attributes), and by testing the effects of behavioral interference (e.g., new learning, such as replacing old attributes with new ones) on selectively reactivated memory components. These studies could have important implications for understanding the specificity of memory change that can result from reconsolidation, and in turn could inform educational and clinical practice.

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