EFFECTS OF PSYCHOSOCIAL STRESS ON EPISODIC MEMORY UPDATING

by

Bhaktee Dongaonkar

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As members of the Dissertation Committee, we certify that we have read the dissertation prepared by Bhaktee Dongaonkar entitled Effects of Psychosocial Stress on Episodic Memory Updating and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy

Lynn Nadel

Date: 8/6/2012

Rebecca Gomez

Date: 8/6/2012

W. Jake Jacobs

Date: 8/6/2012

Lee Ryan

Date: 8/6/2012

Date:

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copies of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Dissertation Director: Lynn Nadel

Date: 8/6/2012

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SIGNED: Bhaktee Dongaonkar

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ABSTRACT

The malleable nature of human memory has been the focus of considerable research in recent years. Memory is no longer viewed as permanent and non-modifiable. When a consolidated memory is reactivated it becomes labile and modifiable again. Recently, updating of reactivated memory has been demonstrated, manifesting as the addition of new but relevant information. New, similar, information that is acquired in a separate learning episode is embedded within the original memory. We were interested in exploring the effects of psychosocial stress on this episodic memory updating. Individuals were stressed prior to reactivation of the original memory (Experiment 1) or prior to the onset of reconsolidation of the original memory (Experiment 2). Based on prior research, we hypothesized that in both experiments stress would impair memory updating. In Experiment 1, stress reduced memory updating, but this effect did not achieve statistical significance. In Experiment 2, stress impaired the consolidation of an 'updated' memory. These findings not only corroborate stress-induced impairments of memory but also shed light on the possible consequences of impaired memory updating. We discuss the relevance of these experimental results in the context of problem solving.

1. INTRODUCTION

1.1. Physiology of Stress

The term '*stress*', i.e. distress, evolved partly from Old French '*destresse*' (*constraint*) and partly from Latin '*districtus*' (*to hinder*). Although the word 'stress' is used in engineering fields to describe physical strain, psychological stress is related to homeostatic conditions of our brain. Psychological stress is characterized by a feeling of uncontrollability over a situation, as a result of which it is perceived as aversive and is accompanied by heightened arousal (Kim & Diamond, 2002). In response to stress, the hypothalamus secretes Corticotropin Releasing Hormone (CRH), which then stimulates secretion of Adrenocorticotrophic Hormone (ACTH). ACTH in turn stimulates the adrenal medulla, atop the kidneys, to release epinephrine/adrenaline (a catecholamine). ACTH also stimulates the adrenal cortex (a layer surrounding the adrenal medulla) to secrete glucocorticoids (cortisol in humans). While cortisol easily enters the brain, epinephrine cannot cross the blood-brain barrier. It enters indirectly by stimulating the release of norepinephrine via the Locus Coeruleus (LC) in the brain stem.

Under acute stress conditions, cortisol directs metabolic activity towards overcoming the stressor. Under chronic stress conditions, physiological changes vary depending on the duration and intensity of a stressor. Since most laboratory experiments have studied acute stress effects, I will focus here on the physiological changes caused by acute stress. Cortisol binds to two types of receptors in the brain – mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). MRs have high affinity for cortisol

and become saturated at low to medium levels of cortisol. GRs have a low affinity for cortisol and are only activated at medium to high levels of cortisol, after MR saturation. MR and GR activation modify ongoing neuronal activity in ways that may alter learning and memory in different brain regions.

Catecholamines, norepinephrine and dopamine accompany glucocorticoids in response to stress (Arnsten, 2009; Roozendaal, 2006). Physiologically, under stress, epinephrine and norepinephrine increase arousal, heart rate, sweating, and blood pressure. In addition, norepinephrine increases overall activity in many regions across the brain, especially those involved in learning and memory (Aston-Jones & Cohen, 2005; Gray & Johnston, 1987). Norepinephrine and cortisol innervate many brain regions causing other related hormones to be released, including dopamine, and as a result can alter a wide range of behaviors. Dopamine also regulates learning and memory, in some cases reducing activity in neurons for non-preferred inputs (Arnsten, 2009). Dopamine is important for conveying novelty, motivation, and reward signals to other brain regions involved in learning and memory. Neurons in many brain regions that are influenced by norepinephrine and dopamine do not function optimally if either is absent. Depending on the levels of cortisol, norepinephrine, and dopamine, performance may be enhanced or impaired on various tasks. Although these three neurotransmitters alter activity in many regions of the brain, I am going to focus mainly on those brain regions that are crucial for learning and memory and are most relevant to the experiments in this dissertation. I will first discuss the stages of memory processing and brain areas involved in these processes, followed by some discussion of the effects of stress on those regions.

1.2. Stages of Memory Processing

Acquisition or encoding initiates an active memory trace that is later transformed into a permanent trace suitable for long-term access. This process of transforming an active trace into long-term memory is known as consolidation (Lechner, Squire, & Byrne, 1999; McGaugh, 2000; Müller & Pilzecker, 1900). Consolidation involves molecular cascades in the postsynaptic cell that trigger intracellular processes (RNA and protein synthesis), which in turn lead to structural changes that protect the memory whilst transforming it into long term form (Davis & Squire, 1984; Flexner, Flexner, De La Haba, & Roberts, 1965). Before consolidation, the memory representation is prone to interference such that new information presented immediately after the first learning may interfere with the initial learning (Lechner, Squire, & Byrne, 1999; McGaugh, 1966, 2000; Müller & Pilzecker, 1900). The process of consolidation protects old learning from being distorted by new learning.

Initially, the sensory information comprising an episode is bound together with contextual information to yield an integrated episodic memory representation. The hippocampus, a structure in the medial temporal lobe, forms a memory representation that links to sub-representations across different brain areas to form a coherent episode of learning. For an initial period of hours to days to months this memory representation is dependent primarily on the hippocampus for retrieval. Over time, through repeated retrievals, and associations to other information networks, the memory becomes integrated with information already learned and stored outside the hippocampus, in

multimodal association cortices. However, the hippocampus is needed to resurrect contextual information each time an episodic memory is retrieved.

When a memory is reactivated it is destabilized, allowing changes to be made to the existing memory representation. Protein-degradation is essential to reactivate or destabilize a memory representation, which can be considered as the reverse of consolidation (Alberini, Milekic, & Tronel, 2006; Kaang & Choi, 2011; Kaang, Lee, & Kim, 2009; Lee, 2008). Unless reactivated, a memory representation cannot be updated or changed. A reactivated memory can be weakened (Zhao et al., 2009) or destroyed (Nader, 2000) by experimental manipulations. In contrast, reactivation accompanied by increased attention or arousal (Sara, 2000a, b) or additional exposure to the same materials (Lee, 2008) may strengthen a memory trace. Finally, new information may be incorporated into the reactivated memory trace, yielding updating rather than interference (Hupbach et al., 2008; Lee, 2009, 2010). Following reactivation, the memory trace undergoes re-consolidation to stabilize the memory representation again. Wang and Morris (2010) reviewed reconsolidation research and concluded that memory reconsolidation can only update a memory when incremental learning takes place or something new related to the reactivated memory is detected. The protein synthesis associated with reconsolidation is observed under these conditions only and not during reactivation without the encoding of new information or learning (Wang & Morris, 2010). However, Miyashita and colleagues (2008) show that irrespective of changes in training, learning occurs every time a memory is reactivated, as seen by the presence of arc transcription induction, a cellular process that signifies plasticity. This suggests that

memory representations are fine tuned by every reactivation. All the above makes clear that the conditions bringing about reconsolidation are not fully understood at present. Regardless of this uncertainty, there is consensus that a modified memory representation will reconsolidate.

Memory reactivation engages a network of brain regions, including the prefrontal cortex (PFC), striatum, hippocampus and parieto-temporal regions (Cabeza & Nyberg, 2000a, b; Chan, 2009; Cohen et al., 1997; Nyberg et al., 1999, 2000), which serve to reinstate memory representation. The PFC directs the integration of new learning into existing representations via its projections to the parieto-temporal regions (Bechtereva et al., 2004; Bledowski, Rahm, & Rowe, 2009; Blumenfeld & Ranganath, 2007; Dietrich, 2004; O'Reilly & Rudy, 2001). These brain regions also coordinate to form associative inferences within reactivated memory networks (Henke, Weber, Kneifel, Wieser, & Buck, 1999; Kuhl, Shah, DuBrow, & Wagner, 2010; Schacter, Alpert, Savage, Rauch, Albert, 1996) from different learning episodes (Zeithamova & Preston, 2010; Zeithamova, Schlichting, & Preston, 2012). Overall the frontal cortex and parieto-temporal areas are important for flexible thinking and re-organizing information (Runco, 2007).

1.3. Effects of Stress on Memory-Related Brain Regions

The PFC and the hippocampus are among the main orchestrators of memory. I focus on the effects of stress on these two regions since they are particularly important

for memory encoding and retrieval processes and are both highly susceptible to stress, given the abundance of norepinephrine, glucocorticoids, and dopamine receptors found in these areas.

The hippocampal response to stress follows an inverted U-shaped function, under regulation by glucocorticoids (MRs and GRs) and norepinephrine. The hippocampus has a high density of both MRs and GRs (Joëls & de Kloet, 1990, 1991). At low levels of glucocorticoids, MRs are activated but not saturated, and the hippocampus performs poorly. At intermediate levels, MRs are saturated and GRs slowly become activated. This condition is optimal for hippocampal function. At high levels of cortisol the GRs begin to saturate and hippocampal performance deteriorates, with gradual deactivation of neural activity (Joëls & de Kloet, 1990, 1991; Joëls, 2006; Sandi, 2011). Effects of GR activation are not immediate. Genomic mechanisms introduce a lag of 20-30 minutes before glucocorticoids can impair hippocampal functions via GR activation. During that time, after an initial increase in performance, hippocampal functions are slowly impaired (Joëls & de Kloet, 1990; 1991; Kim & Diamond, 2002). Similarly, norepinephrine regulation of hippocampus follows an inverted U-shaped function (Ashton – Jones & Cohen, 2005).

Dopamine is important specifically for late-phase long-term potentiation (late - LTP) in the hippocampus. In other words, the presence of dopamine determines whether a learned event should be incorporated into long-term memory (Lisman, Grace, and Duzel, 2011). However, whether increase of dopamine is beneficial or not remains poorly

understood. It has been suggested that dopamine effects follow an inverted U-shape, just as glucocorticoids (Lisman, Grace, and Duzel, 2011).

The function of PFC is also modulated in an inverted U-shaped fashion, by these various neuro-modulators. Note that the effects of glucocorticoids in the PFC are not direct. Rather, glucocorticoids trigger the release of a series of catecholamines (norepinephrine and dopamine) in the PFC via the amygdala (a small area neighboring the hippocampus in the medial temporal lobe that is important for processing emotion) and its projections to the basal ganglia (a mid-brain region). Dopamine producing neurons in the basal ganglia project to, and modulate the processing of, the PFC (Kehagia, Murray, & Robbins, 2010). On perceiving stress, the amygdala elicits activity in the hypothalamus to set off the cycle of glucocorticoid release as discussed in Section 1.1. As a consequence, increased norepinephrine levels enhance activity in the PFC (Arnsten, 2000; Birnbaum, Podell, & Arnsten, 2000; Roozendaal, McReynolds, McGaugh, 2004) and in the amygdala, which in turn stimulates the basal ganglia to release more dopamine in the PFC (Arnsten, 2009). PFC is sensitive to norepinephrine and dopamine and requires both for optimal performance (Mizoguchi, 2004). PFC function is enhanced under low to moderate acute stress (Yuen et al., 2009). Under high stress, norepinephrine levels and dopamine levels rise and shut down the PFC (Arnsten, 2000; Barsegyan, Mackenzie, Kurose, McGaugh, & Roozendaal, 2010; Birnbaum, Podell, & Arnsten, 2000; Roozendaal, McReynolds, McGaugh, 2004). There appears to be a narrow range for optimal norepinephrine (Aston-Jones & Cohen, 2005) and dopamine activity in the PFC (Arnsten & Goldman-Rakic, 1998; Murphy, Arnsten,

Goldman-Rakic, & Roth, 1996; Zahrt, Taylor, Mathew, & Arnsten, 1997). In addition, stress effects are rapid in the PFC (Diamond, Campbell, Park, Halonen, & Zoladz, 2007; Lupien, Gillin, & Hauger, 1999; Roozendaal, McReynolds, McGaugh, 2004) it is inhibited under high stress immediately, unlike the gradual hippocampal inhibition, and remains inhibited as long as stress hormones are secreted (Diamond, Campbell, Park, Halonen, & Zoladz, 2007).

Overall, stress hormones permit a limited period of optimal PFC function while hippocampal function may remain optimized for longer. Some have suggested an evolutionary perspective on the tolerance of stress hormones in the hippocampus. Memory consolidation via the hippocampus is left relatively intact, to encode stressful events as a survival mechanism (Barsegyan, Mackenzie, Kurose, McGaugh, & Roozendaal, 2010; Liang, 2001; Roozendaal, McReynolds, McGaugh, 2004). As a consequence of this ability to better remember aversive events, our ability to retrieve and modulate information under stress may suffer. PFC is important for updating memories (Nyberg et al., 2009) but this ability may be impaired under high stress. Under impaired performance conditions, the retrieval abilities of the hippocampus and PFC may result in inferior reactivation of memories or failure to maintain reactivated information. Research has shown impairing effects of stress on working memory (Luethi, Meier, & Sandi, 2009; Murphy, Arnsten, Goldman-Rakic, & Roth, 1996; Robinson, Qin, Hermans, van Marle, Luo, & Fernández, 2009; Shansky, Rubinow, Brennan, & Arnsten, 2006; Scoofs, Preuß, & Wolf, 2008). If reactivated memories cannot be maintained in an active state long enough to be updated, this may result in poor integration of new learning with existing

memory representations. The few studies that have looked at these interactions are discussed in the next section.

2. EXPERIMENT 1: EFFECTS OF STRESS ON EPISODIC MEMORY REACTIVATION

2.1. Objective

Most studies of the effects of stress on memory retrieval have focused on the time during or just after stress induction. Very few studies have explored the effect on memory of stress during reactivation or during a retrieval test in humans. Tollenaar and colleagues (2008a) trained participants to learn 20 neutral and 20 negative paired associates over 2 learning trials. Participants returned either 1 day or 5 weeks later. Following a stress or control manipulation they performed a cued recall task. Six months after their second visit, all participants were tested for recall during a telephone session. The control and stress participants that returned a day later for their second session did not show any significant difference in memory recall at 6 months. Participants who were stressed 5 weeks later in their second session had impaired recall memory for neutral and negative paired associates compared to the corresponding control group. These results suggest that stress during reactivation can impair memory but that impairment is only seen if there is an interval between learning and reactivation. Stress effects on reactivation persisted up to 6 months after reactivation.

A similar study was conducted by Tollenaar and colleagues (2009a). They had participants learn 15 emotional and 15 neutral words over two training trials. On return a week later for a second session, they were administered 30mg of hydrocortisone, or placebo. After a wait period of 75 min for the synthetic cortisol to peak, participants were

given a free recall and cued recall test. They returned again a week later (2 weeks after the first learning session) for a third session and were given a recall and recognition test. Participants from the hydrocortisone group had impaired recall memory for emotional and neutral words in the second session and the impairment persisted during the third session. On the other hand, the placebo group showed no impairing effects. These results suggest that reactivation of memories when cortisol levels are high leads to attenuation of those memories, regardless of emotionality.

Taken together, these studies show that stress prior to reactivation impairs memory and that this impairment persists over several days to months. It is reasonable to assume that the original memory has been modified in both cases. However, to our knowledge, there has been no study so far that attempted to investigate effects of stress on memory updating, especially updating with related or congruent information. Hence, we decided to explore effects of stress at reactivation on memory updating. As discussed before, the brain regions engaged in memory reactivation include the PFC and hippocampus. Both regions are affected by stress hormones and both show impaired function under moderate to high stress levels. Therefore, it is reasonable to hypothesize that memory updating might be impaired under stress, a possibility we decided to explore. We used a well-established episodic memory updating paradigm recently described for humans (Hupbach, Gomez, Hardt, & Nadel, 2007; Hupbach, Hardt, Gomez, & Nadel, 2008; Hupbach, Gomez, & Nadel, 2009). This updating paradigm involves learning a list of objects on Day 1. Forty-eight hours later, participants return to the lab and are reminded of their learning episode on Day 1 in order to reactivate that memory

representation, followed by the learning of another list of objects. Two days later, participants are tested for their memory of objects from the list on Day1. The authors found that in addition to objects from the first list, participants unknowingly recalled objects from the second list as being from the first list. It was concluded that memory for the first list had been updated by objects from the second list as a function of being reminded of the initial training before the second round of learning. The authors did not find an updating effect in control participants who were not reminded before learning the second list.

To explore the possible effects of stress on memory updating, we decided to stress participants on Day 2, before they were reminded of List 1. Stress could influence the reactivation of the memory for List 1 in several ways illustrated in Figure 1: (1) it could prevent reactivation altogether; (2) it could alter reactivation such that it is qualitatively different than in control participants; or (3) it could weaken reactivation such that it does not last long enough. As discussed earlier, frontal projections to temporo-parietal regions are important for maintaining active memory traces. Stress may reduce this ability of frontal areas (which are highly susceptible to stress) to maintain List 1 in an active state while the participant is learning List 2. An active but impoverished memory reactivation process may lead to a failure of updating with new related information (such as the objects on List 2) and instead may result in an entirely new representation of the novel information on List 2, i.e. no updating at all, or poorer integration of information from List 2 into List 1, which would reflect weaker updating.

Figure 1: Some possible effects of stress on memory reactivation, as explored in Experiment 1.

2.2. Methods

2.2.1. Participants

Forty-seven undergraduate students (28 females & 19 males; mean age = 18.72 years, S.D. = 0.92 years) from the University of Arizona consented to participate for course credits. They were randomly assigned to the study groups.

2.2.2. Materials

List 1 and List 2 objects were identical to the objects from Hupbach and colleagues (2007).

List 1 had 20 objects (balloon, bow, calculator, toy car, crayon, cup, dice, feather, flashlight, flower, glue, key, sock, sponge, spoon, sunglasses, teabag, toothbrush, tennis ball, and whistle).

List 2 had 20 different objects (apple, band-aid, battery, book, cassette-tape, cell phone, comb, dollar bill, toy frog, envelope, paper clip, toy pot, puzzle piece, rock, straw, thread, tissue, watch, shovel, and zipper).

2.2.3. Procedure

Figure 2 outlines the serial order of the tasks in Experiment 1.

2.2.3.1. List Learning

The procedure was exactly the same as in Hupbach and colleagues (2007).

Participants attended 3 sessions with 48 hours interval between sessions (M-W-F or T-R-S) in a week. On their first visit (Day 1), objects (List 1) were removed from a basket, placed on the table one by one and then put back in a different container, a bucket.

Participants were instructed to name the objects aloud when they were placed on the table

and observe them carefully. The objects were then taken away and placed out of view following which the experimenter engaged the participant in a neutral conversation for 30 seconds that prevented rehearsing. Next, the participants had to recall as many of those 20 objects as possible. This cycle continued until participants reached a learning criterion of 17/20 objects or at the most 4 trials, whichever occurred first.

On their second visit (Day 2), participants learned another list of objects (List 2), different from those in the first session. In the second session, the learning procedure was modified to distinguish it from the procedure used in the first session. All objects were placed on the table in front of the participant and they had to name each object loudly without touching it. They were given an additional 30 sec to look at them carefully. The objects were then taken away and placed out of view followed by 30 seconds of neutral conversation. The participant then had to recall as many of those 20 objects as possible. Again, the cycle continued until participants recalled 17/20 objects or had at most 4 learning trials.

On their third visit (Day 3), participants were instructed to recall as many objects as possible from their first session on Day 1. We conducted 4 recall trials and between trials the experimenter conversed with the participants for 30 seconds to temporarily disengage them from the task.

2.2.3.2. Stress Manipulation

On arrival on Day 2, participants were randomly assigned to the stress induction or control group. To induce stress, participants performed the Trier Social Stress Test (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993). They were given 5 min to prepare a speech, which they then had to deliver for 5 min in front of two judges. The room had a video camera and microphone to give the impression that their speech was being recorded. They were informed that their verbal and non-verbal performance would be evaluated using a movement and voice inflection analyzer. At the end of 5 min, participants were instructed to perform a math subtraction task involving the subtraction of a 2 digit number from a 4 digit number (17 from 1873).

The control group wrote a job essay for the first 5 minutes, then read and edited the essay for the next 5 min and finally solved simple two digit subtraction problems for 5 min.

2.2.3.3. Reminder Manipulation

On Day 2, following the stress or control manipulation, the reminder manipulation was incorporated. Before list 2 learning began, participants were randomly assigned to a reminder or no-reminder group. The reminder group had the same experimenter and went to the same room as on Day 1. In addition, they were shown the basket from Day 1 and asked a reminder question, “Do you remember this basket and

what we did with it?” On the other hand, the no-reminder group had a different experimenter, went to a different room, and participants were not asked the reminder question. Following these manipulations, List 2 learning ensued.

On Day 3, all participants had the same experimenter and went to the same room as on Day 1.

2.2.3.4. Salivary Cortisol and Subjective Anxiety Measures

Saliva samples and subjective anxiety measures were collected at regular intervals on all 3 days. Every saliva sample was paired with a subjective anxiety measure. Spielberger’s State Anxiety Inventory was administered to assess subjective anxiety at (#1) baseline upon arrival on Day 1, (#2) baseline on Day 2, (#3) immediately after TSST or control task on Day 2 (20 minutes after #2) , (#4) end of List 2 learning on Day 2 (35-40 minutes after #2) , and (#5) baseline on Day 3. Additional subjective anxiety measures were administered after each list learning, TSST/control manipulation, and recall to indicate how the participants felt while performing those tasks and towards the end of those tasks, totaling to 11 subjective anxiety measures across 3 days.

Figure 2: Serial order of experimental tasks in Experiment 1. Numbers at the top of the figure illustrate the time points at which saliva samples were collected with corresponding subjective anxiety ratings. Additional subjective anxiety ratings were collected at time points not illustrated in the graph.

2.3. Results

2.3.1. Subjective Anxiety Scores

Subjective anxiety scores were scored using Spielberger's State Anxiety Inventory. The scores can range from a minimum of 20 to a maximum of 80. A 2 factor repeated measures ANOVA with stress and reminder conditions as between group factors and subjective anxiety time points as within subject factors revealed that subjective anxiety changed across some of the 11 different time points ($F_{(5.72, 240.17)} = 44.3, p < 0.0001$). There was a significant effect of the stress manipulation on subjective anxiety ($F_{(5.72, 240.17)} = 10.94, p < 0.0001$). Values reported are Greenhouse-Geisser corrected values since the sphericity assumption was violated. Independent samples t-tests revealed

that on Day 2 the stress no-reminder group reported being more stressed than the control no-reminder group during TSST ($t_{(21)} = 4.405$, $p < 0.001$) and immediately after TSST ($t_{(21)} = 3.807$, $p = 0.001$), Figure 4. Similarly, the stress reminder group reported being more stressed than the control reminder group during TSST ($t_{(22)} = 2.576$, $p = 0.017$) and immediately after TSST ($t_{(22)} = 3.038$, $p = 0.006$). There were no significant differences in subjective anxiety between control and stress groups at any of the other time points. Figures 3, 4, and 5 summarize the subjective anxiety scores across different time points across the 3 days.

Figure 3: Subjective anxiety scores on Day 1 in Experiment 1.

Figure 4: Subjective anxiety scores on Day 2 in Experiment 1; during TSST/control (stress reminder > control reminder, $p = 0.017$) & (stress no-reminder > control no-reminder, $p = 0.001$); post TSST/control (stress reminder > control reminder, $p = 0.005$ & stress no-reminder > control no-reminder, $p = 0.05$).

Figure 5: Subjective anxiety scores on Day 3 in Experiment 1.

2.3.2. Salivary Cortisol Levels

A repeated measures ANOVA with stress manipulation as the between group factor and the 5 salivary cortisol measures as within group factors was conducted. Since the sphericity assumption was violated, Hyunh-Feldt values are reported. Salivary cortisol changed across measured time points ($F_{(2.72, 116.79)} = 12.47, p < 0.001$). This analysis revealed a main effect of stress ($F_{(1,43)} = 9.19, p < 0.004$) and a significant interaction between stress manipulation and salivary cortisol concentration ($F_{(2.72, 116.79)} = 13.36, p < 0.001$). Independent samples t-tests showed that on Day 2 salivary cortisol levels were higher immediately post TSST in the stress no-reminder group in comparison to the control no-reminder group just after the control task ($t_{(21)} = 1.97, p = 0.06$) and remained high until the end of List 2 learning ($t_{(21)} = 3.376, p = 0.003$) in the stress no reminder group. Similarly, the stress reminder group showed higher salivary cortisol levels immediately after TSST in comparison to the control reminder group just after the control task ($t_{(22)} = 3.12, p = 0.005$) and remained high until the end of List 2 learning ($t_{(22)} = 2.96, p = 0.007$) in the stress reminder group. There were no significant differences in salivary cortisol measures at other time points. The salivary cortisol measures collected over 3 days and across 5 time points are summarized in Figure 6.

Figure 6: Salivary cortisol (nmol/L) across 5 different timepoints over 3 days in Experiment 1; at post TSST/control timepoint (stress reminder > control reminder, $p = 0.005$ & stress no-reminder > control no-reminder, $p = 0.05$); post List 2 learning time point (stress reminder > control reminder, $p = 0.007$ & stress no-reminder > control no-reminder, $p = 0.003$).

2.3.3. Learning Performance on Day 1

Participants who did not reach criterion by their 4th trial received a score of 5.

Participants from all groups on an average reached criterion (17 or more objects) in 3.17 trials (SD = 1.07) on Day 1. Groups on Day 1 had no procedural differences. There was no significant difference in the number of trials to reach criterion between groups ($F_{(3,43)} = 0.609$, $p = 0.61$) using a 2 x 2 ANOVA.

2.3.4. Learning Performance on Day 2

On Day 2 participants took an average of 2.91 trials (SD = 1.1) to reach criterion. There was no difference in the trials required to reach criterion between groups ($F_{(3,43)} = 2.27$, $p = 0.094$) using a 2 x 2 ANOVA. There were no main effects of reminder ($F_{(1,43)} = 1.69$, $p = 0.2$) on learning of List 2. There was a borderline significant effect of stress manipulation ($F_{(1,43)} = 3.76$, $p = 0.059$) on List 2 learning. Independent samples t-test showed a borderline significant difference in the learning of List 2 only in the no-reminder groups. The stress no-reminder group took longer to learn List 2 (mean trials = 3.58, SD = 1.38) than did the control no-reminder group (mean trials = 2.64, SD = 0.92) ($t_{(21)} = 1.91$, $p = 0.069$).

2.3.5. Recall Performance on Day 3

2.3.5.1. Recall of List 1

Recall performance on Day 3 was scored for correctly recalled objects from List 1 and falsely recalled objects from List 2 (intrusions). A 2 (stress, control) x 2 (reminder, no reminder) x 4 (recall trials) repeated measures ANOVA was conducted on the recall data for List 1. As the test of sphericity was significant Huynh-Feldt corrected values are reported for the repeated measures effects. There was a main effect of recall trial ($F_{(2,19,94.05)} = 9.46$, $p < 0.001$). Within subjects polynomial contrasts confirmed a linear trend in recall across trials ($F_{(1,43)} = 14.15$, $p = 0.001$), i.e. the number of objects recalled

from List 1 increased as the trials progressed; trial 1 ($M = 31.49\%$), trial 2 ($M = 33.94\%$), trial 3 ($M = 36.70\%$), and trial 4 ($M = 37.77\%$). There were no effects of stress manipulation ($F_{(1,43)} = 0.009$, $p = 0.92$) or reminder condition ($F_{(1,43)} = 1.57$, $p = 0.22$) on recall of List 1 objects. Figure 7 summarizes Day 3 recall performance.

2.3.5.2. Intrusions

List 2 objects falsely recalled as List 1 objects were termed “intrusions”. A 2 (stress, control) x 2 (reminder, no reminder) x 4 (recall trials) repeated measures ANOVA revealed a main effect of reminder manipulation ($F_{(1,43)} = 8.91$, $p = 0.005$, $r = 0.41$). Stress had no main effect on the number of intrusions ($F_{(1,43)} = 2.12$, $p = 0.15$, $r = 0.22$). The interaction of stress and reminder revealed no effects ($F_{(1,43)} = 1.61$, $p = 0.21$, $r = 0.19$). T-test comparisons with Bonferroni correction ($0.05/4 = 0.013$) revealed that:

- i) The control reminder group ($M = 22.08\%$, $SE = 4.35$, $n = 12$) had higher average intrusions than the control no-reminder group ($M = 7.61\%$, $SE = 2.89$, $n = 11$) ($t_{(21)} = 2.71$, $p = 0.013$, $r = 0.5$) on Day 3.
- ii) There was no difference in average intrusions between the stress reminder group ($M = 12.81\%$, $SE = 3.48$, $n = 12$) and stress no-reminder group ($M = 6.98\%$, $SE = 2.47$, $n = 12$) ($t_{(22)} = 1.36$, $p = 0.19$, $r = 0.28$) on Day 3.
- iii) There was no difference between the stress reminder and control reminder groups in terms of intrusions ($t_{(22)} = 1.66$, $p = 0.11$, $r = 0.33$) on Day 3.

iv) There was no difference between the stress no-reminder and control no-reminder groups in terms of intrusions ($t_{(21)} = 0.17$, $p = 0.87$, $r = 0.04$) on Day 3. Figure 7 summarizes intrusion averages on Day 3.

We also conducted correlational analyses to look at effects of stress on subtle reactivation of List 1 or learning of List 2 on Day 2 in the stress reminder group. Recall of List 1 on Day 3 was not related to subjective anxiety during TSST ($r = 0.26$, $p = 0.42$) or salivary cortisol post TSST ($r = -0.36$, $p = 0.24$) on Day 2 in the stress reminder group. Similarly, intrusions in List 1 (from List 2) on Day 3 were not related to subjective anxiety during TSST ($r = 0.16$, $p = 0.62$) or salivary cortisol post TSST ($r = -0.15$, $p = 0.64$) on Day 2 in the stress reminder group.

Figure 7: Mean percentage recall of List 1 objects and intrusions (falsely recalled List 2 objects) on Day 3 in Experiment 1. Error bars indicate standard errors of means.

Figure 8: Error bars representing 95% confidence intervals in the groups from Experiment 1.

2.4. Discussion

Experiment 1 explored the effects of stress on memory reactivation followed by updating. Participants were stressed before receiving a reminder for List 1. The objective was to observe whether stress impaired the reactivation of List 1 such that it would impair the updating of List 1 with List 2 items that is typically observed after reactivation of List 1 memory. The TSST successfully elevated cortisol levels in the stress groups.

There were no differences in the average recall of List 1 between any of the 4 groups. The updating effect as reported in Hupbach, Gomez, Hardt, and Nadel (2007) was replicated. The control reminder group had significantly higher intrusions than the control no reminder group. There was no significant difference in the average intrusions between the stress reminder and control reminder groups. Contrary to our hypothesis, average intrusion rates in the stress reminder group failed to reflect any statistically significant impairment due to stress, although there was a 10% reduction in the average intrusions in the stress reminder group. The updating effect in the stress reminder group is not different than the updating effect in the control reminder group (since there is no statistical difference between these groups). However, there is also an absence of updating in the stress reminder group when compared to stress no reminder group (from which it also does not differ). Figure 8 explains this overlap. The upper bound 95% confidence interval of the stress reminder group overlaps with the control reminder group while the lower bound overlaps with the stress no-reminder group. Due to the high variance in the stress reminder group, we fail to see any statistically significant effects even with noticeably reduced intrusions.

One factor that may be responsible for these highly variable results is the differential effect of TSST on participants. The response to the stressor varies between individuals. Although all stress participants showed an increase in cortisol, the extent of that increase likely differed across individuals. In some participants it may have induced a mild stress response, while for others it may have been extremely stressful. Such variability in stress response could account for the variation observed in the updating

effect. We see a reduced updating under stress, but not sufficient for the difference to be significant. There was an effect size of 0.33 for the difference in intrusions between the stress reminder and the control reminder groups. Such a medium effect size suggests that there might be a genuine difference between the groups but that the sample size may not be sufficient, given the differences in stress response to the TSST.

To rule out any effects of stress on List 2 learning on Day 2, we ran an additional 12 participants in the stress reminder condition and 12 in the control reminder condition who recalled only List 2 on Day 3. All other procedures were similar to those used for the participants in the reminder conditions in Experiment 1 described above. While we did not collect saliva samples for cortisol in these participants, their subjective anxiety scores indicated that the stress group experienced higher anxiety during TSST ($p < 0.0001$) and post TSST ($p < 0.0001$) than control participants during and after the control tasks respectively; anxiety during TSST ($M = 66$, $SE = 2.24$), post TSST ($M = 59$, $SE = 3.36$), during control task ($M = 36$, $SE = 1.92$), post control task ($M = 31$, $SE = 1.53$). Figure 9 displays the mean recall percentage of List 2 and intrusions (from List 1) on Day 3. We found no difference between the stress reminder and control reminder for recall of List 2 ($t_{(22)} = 0.09$, $p = 0.93$) or intrusions from List 1 ($t_{(22)} = 0.18$, $p = 0.86$). These results suggest that there was no effect of stress on learning of List 2 on Day 2.

Figure 9: List 2 recall on Day 3 in stress (n=12) and control (n=12) reminder participants. These participants are different than those discussed in the methods section of Experiment 1. Saliva samples for cortisol were not collected for these participants.

Tollenaar and colleagues (2008a, 2009a) had participants learn paired associates over two learning trials. However, they do not report the learning over those two trials or whether any criterion was set for learning. In our study, learning to criterion could take anywhere from 1 to 4 trials. Recurring trials may strengthen memory for List 1 to an extent that a stress induced impairment at reactivation does not occur. As a consequence the normal updating effect would persist in the stress reminder group. Given the difficulty of observing stress effects on reactivation itself, we decided to explore the effects of stress on the next stage of the process initiated by reactivation, that is, the reconsolidation of an updated memory.

3. EXPERIMENT 2: EFFECTS OF STRESS ON RECONSOLIDATION OF AN UPDATED EPISODIC MEMORY

3.1. Objective

A few studies investigating the effect of stress on memory reconsolidation have been reported recently. Schwabe and Wolf (2010) investigated the effects of post retrieval stress, i.e. stress effects on reconsolidation. Participants were asked to recall recent neutral, positive and negative autobiographical memories. After recall, participants performed a control task or were stressed. They returned a week later and were asked to recall the same autobiographical memories that they had recalled a week earlier. The stressed group showed impaired recall for only neutral memories while positive and negative memories were preserved. The control group did not show any impairment. These results suggest a specific impairment of reconsolidation of neutral autobiographical memories. However, it is difficult to draw conclusions from this study since autobiographical memories cannot be controlled for several factors such as vividness and the intensity of emotional state during those events. Marin, Pilgrim, & Lupien (2010) studied post-reactivation stress effects on immediate versus delayed memories for emotional and neutral information. Participants saw a video with emotional and neutral information on Day 1. Two days later (Day 2) participants returned and were assigned to one of three conditions. The first group recalled the story from Day 1 and then was exposed to a stress condition (reactivation – stress). The second group recalled the story from Day 1 and performed a control task (reactivation – control). A third group did not

recall the story but was exposed to the stress condition (no reactivation – stress). After the stress/control task, all groups performed an immediate recall test. Participants returned 5 days later and performed another recall test (delayed recall). The reactivation stress group showed an increase in immediate memory recall for emotional information but not neutral information when compared to the reactivation control group. This enhancement persisted during delayed recall 5 days later. The no-reactivation stress group did not show any change in immediate or delayed memory. These results suggest that stress after reactivation enhances memory for emotional information in a lasting way while neutral information remains unaffected.

Zhao and colleagues (2009) tested effects of post-retrieval stress in abstinent heroin addicts. On Day 1, participants learned a list of 10 heroin-positive, 10 heroin-negative, and 10 heroin-neutral words over two learning trials. A day later, they recalled as many words as possible and then underwent stress induction or completed a control task. They returned 24 hours later for another recall test. Four weeks later all participants performed the experiment again but this time stress participants were allotted to the control group and vice versa. Results show that post-reactivation stress increased recall for heroin-positive words, decreased recall for heroin-negative words, while recall of heroin-neutral words remained unchanged.

We need to be cautious in interpreting these results since a single conclusion cannot be drawn from the studies that look at effects of stress after reactivation. Stress affects emotional and neutral memories differently. The only general conclusion that can

be drawn from the existing literature is that stress may strengthen or weaken reactivated memories, as a function of the type of information.

All the studies discussed above tested memory for items learned prior to reactivation without additional items being learned after reactivation – that is, without the possibility of memory updating. No study so far has explored the effects of stress on the reconsolidation of memories updated with related or congruent information during reactivation.

Stressing people after reactivating List 1 and learning List 2 on Day 2 might reveal an effect of stress exclusively on reconsolidation of an updated memory. Hupbach, Gomez, Hardt, and Nadel (2007) showed that updating effects are not observable immediately, though they are apparent after two days of learning List 2 in the reminder condition. Therefore, stress during the onset of reconsolidation may result in impaired updating. In this case, we would expect to see a reduction in intrusions in the stress reminder group in comparison to the control-reminder group. We did not collect data from no-reminder groups for this experiment.

3.2. Methods

3.2.1. Participants

Thirty-five undergraduate students of the University of Arizona consented to participate and were given course credit for participation (13 females & 22 males; mean age = 19.37 years, SD = 1.75). Participants were randomly assigned to the groups in the experiment.

3.2.2. Materials

The objects from Experiment 1 were also used in Experiment 2.

3.2.3. Procedure

The procedure was similar to the procedure used in Experiment 1. The only difference was in the order of the manipulation tasks. The stress manipulation in this experiment was administered after learning List 2, which followed the List 1 reminder manipulation. As noted before, we omitted the no-reminder groups. Figure 10 outlines the serial order of the tasks.

Figure 10: Serial order of experimental tasks in Experiment 2. Numbers at the top of the figure illustrate the time points at which saliva samples were collected with corresponding subjective anxiety ratings. Additional subjective anxiety ratings were collected at time points not illustrated in the graph.

3.2.3.1. List Learning

The procedures used for List learning on Days 1 and 2 and List recall on Day 3 were identical to those used in Experiment 1.

3.2.3.2. Reminder Manipulation

On arrival on Day 2, before list 2 learning began, all participants were reminded of List 1 learning, by exposure to the same experimenter and by going to the same room as on Day 1. In addition, they were shown the basket from Day 1 and asked a reminder

question, “Do you remember this basket and what we did with it?” The reminder manipulation was followed by List 2 learning.

On Day 3, all participants had the same experimenter and went to the same room as on Day 1.

3.2.3.3. Stress Manipulation

On Day 2 after learning List 2, participants were randomly assigned to a stress induction task or control task. Stress was induced in the same manner as in Experiment 1.

As, in Experiment 1, the control group wrote a job essay for the first 5 min, then read and edited the essay for the next 5min, and finally solved simple two digit subtraction problems for 5 min.

3.2.3.4. Salivary Cortisol and Subjective Anxiety Measures

Saliva samples and subjective anxiety measures were collected at regular intervals on all 3 days. Every saliva sample was paired with a subjective anxiety measure.

Spielberger’s State Anxiety Inventory was administered to assess subjective anxiety at (#1) baseline upon arrival on Day 1, (#2) baseline on Day 2, (#3) end of List 2 learning on Day 2(15-20 minutes after #2) , (#4) immediately after TSST or control task on Day 2 (35-40 minutes after #2) , and (#5) baseline on Day 3. Additional subjective anxiety

measures were administered after each list learning, TSST/control manipulation, and recall to indicate how the participants felt while performing those tasks and towards the end of those tasks, totaling 11 subjective anxiety measures across 3 days.

3.3. Results

3.3.1. Subjective Anxiety Scores

Spielberger's state anxiety inventory was used to record the subjective anxiety of participants at 11 time points over 3 days. The inventory score ranges from a minimum of 20 to a maximum of 80. A repeated measures ANOVA with stress manipulation (stress, control) as the between group factor and the 11 time points as within group factors revealed that subjective anxiety was the same across all 11 time points in both groups ($F_{(3.5, 53.2)} = 19.62, p < 0.001$) (Greenhouse – Geisser value). On Day 2, TSST was significant in inducing stress in the stress group participants ($F_{(3.5, 53.2)} = 4.12, p = 0.007$) (Greenhouse – Geisser value). Independent samples t-tests show that stressed participants reported higher anxiety during TSST ($t_{(33)} = 6.77, p < 0.001$) and post-TSST ($t_{(33)} = 6.16, p < 0.001$) than control participants during the control task on Day 2, Figure 12. At all other subjective anxiety time points on Day 2 and the other days, there were no significant differences in subjective anxiety between control and stress groups. Figures 11, 12, and 13 summarize the subjective anxiety scores across different time points across the 3 days.

Figure 11: Subjective anxiety scores on Day 1 in Experiment 2.

Figure 12: Subjective anxiety scores on Day 2 in Experiment 2; during TSST/control time point (stress > control, $p < 0.001$); post TSST/control time point (stress > control, $p < 0.001$).

Figure 13: Subjective anxiety scores on Day 3 in Experiment 2.

3.3.2. Salivary Cortisol Levels

A repeated measure ANOVA revealed a main effect of stress on salivary cortisol levels ($F_{(1, 29)} = 8.36$, $p = 0.007$) on Day 2. A significant interaction between stress and cortisol was seen ($F_{(2.4, 72.42)} = 3.22$, $p = 0.035$) (Greenhouse-Geisser corrected value). Independent samples t-tests confirmed that stressed participants had higher cortisol levels after the TSST than control participants had after a control task ($t_{(31)} = 3.45$, $p = 0.002$, $r = 0.53$) on Day 2. Unexpectedly, stressed participants had higher baseline cortisol levels on Day 3 than control participants ($t_{(31)} = 2.5$, $p = 0.02$, $r = 0.4$), although we found no significant difference between groups in their corresponding baseline subjective anxiety on the same day ($t_{(31)} = 1.85$, $p = 0.074$, $r = 0.3$). There were no significant differences in salivary cortisol measures at the remaining time points on Day 1 and Day 2. The salivary cortisol measures collected over 3 days and across 5 time points are summarized in Figure 14.

Figure 14: Mean salivary cortisol in stress and control groups in Experiment 2; post TSST/control timepoint (stress > control, $p = 0.002$)

3.3.3. Learning Performance on Day 1

The average number of trials taken by participants to learn List 1 (i.e. reach a criterion of 17 out of 20 objects) was 3.09 trials (SD = 1.09). The stress and control groups were exposed to the same procedures on Day 1. Repeated measures ANOVA showed that there was no difference in the number of trials taken to reach criterion between the stress and control groups ($F_{(1,33)} = 0.57$, $p = 0.47$).

3.3.4. Learning Performance on Day 2

On Day 2, participants from both groups took an average of 2.43 trials (SD = 1.09) to reach criterion of learning List 2. There were no procedural differences before or

during the learning of List 2 between the stress and control groups. One way ANOVA revealed no difference in learning between these groups ($F_{(1,33)} = 0.28$, $p = 0.6$).

3.3.5. Recall Performance on Day 3

Recall on Day 3 was scored for correctly recalled objects from List 1 and falsely recalled objects from List 2 attributed to List 1 (intrusions). The participants also subsequently recalled List 2 items. Recall of List 2 items was scored for correctly recalled objects from List 2 and misattributed objects from List 1 (intrusions). Recall performance on Day 3 is summarized in Figure 15 and Figure 16.

3.3.5.1. Recall of List 1

A 2 (stress, control) x 4 (recall trials) repeated measures ANOVA revealed a within subjects main effect of recall trial ($F_{(3, 99)} = 12.32$, $p < 0.001$). Within subjects polynomial contrasts confirmed a linear trend of recall across trials ($F_{(1,33)} = 25.1$, $p < 0.001$), i.e. the number of objects recalled from List 1 increased as the trials progressed; trial 1 ($M = 27.86\%$), trial 2 ($M = 31.14\%$), trial 3 ($M = 33.57\%$), and trial 4 ($M = 36.43\%$). There was no effect of stress manipulation ($F_{(1,33)} = 0$, $p = 0.96$) on recall of List 1 objects; stress group ($M = 32.15\%$, $SE = 2.8$) & control group ($M = 32.35\%$, $SE = 3.32$).

3.3.5.2. Intrusions in List 1 (from List 2)

List 2 objects falsely recalled as List 1 objects were termed intrusions. A 2 (stress, control) x 4 (recall trials) repeated measures ANOVA revealed a main effect of stress on the number of intrusions ($F_{(1,33)} = 5.75$, $p = 0.02$, $r = 0.39$) such that the stress group ($M = 9.37\%$, $SE = 1.94$) had fewer intrusions than the control group ($M = 18.97\%$, $SE = 3.59$).

3.3.5.3. Recall of List 2

A repeated measures ANOVA revealed a within subject main effect of trial ($F_{(2.3, 75.86)} = 4.51$, $p = 0.01$) with a linear trend of recall with progressive trials ($F_{(1,33)} = 9.51$, $p = 0.004$); trial 1 ($M = 35.43\%$), trial 2 ($M = 38.0\%$), trial 3 ($M = 38.0\%$), and trial 4 ($M = 39.14\%$). There was no effect of stress on recall of List 2 ($F_{(1,33)} = 1.31$, $p = 0.261$); stress group ($M = 40.21\%$, $SE = 2.31$) & control group ($M = 34.93\%$, $SE = 4.08$).

3.3.5.4. Intrusions in List 2 (from List 1)

List 1 objects falsely recalled as List 2 objects were termed intrusions. A 2 (stress, control) x 4 (recall trials) repeated measures ANOVA revealed no effect of stress on the number of intrusions ($F_{(1,33)} = 1.19$, $p = 0.28$); stress group ($M = 2.01\%$, $SE = 0.64$) & control group ($M = 3.16\%$, $SE = 0.84$).

3.3.5.5. Recall of List 1 vs List 2

Paired sample t-tests were performed on recall of List 1 vs List 2 in the stress and control groups. In the stress group, we found a close to significant difference ($t_{(17)} = 2.0$, $p = 0.06$, $r = 0.44$). There was no difference in the recall of the two lists in the control group ($t_{(16)} = 0.58$, $p = 0.58$).

Since we observed a marginal difference between List 1 recall and List 2 recall in the stress group, we wondered if there was a relation between this enhancement in List 2 recall and the reduction of intrusions in the stress group. There was a negative relationship between List 2 recall and intrusions in List 1 recall in the control group ($r = -0.55$, $p = 0.021$), Figure 17. There was no relationship between the two in the stress group ($r = -0.42$, $p = 0.08$), Figure 18. This suggests that we not try to make much of the marginal difference between List 1 and List 2 recall in the stress group. Subjective anxiety during TSST ($r = -0.16$, $p = 0.52$) or salivary cortisol post TSST ($r = 0.17$, $p = 0.53$) on Day 2 were not correlated to the intrusions into List 1 (from List 2) on Day 3 in the stress group. Similarly, subjective anxiety during TSST ($r = -0.33$, $p = 0.18$) or salivary cortisol post TSST ($r = -0.23$, $p = 0.4$) on Day 2 were not correlated to recall of List 2 on Day 3.

Figure 15: Mean percentage recall and intrusions on Day 3 in Experiment 2. Error bars indicate standard errors or means; mean of List 1 intrusions (control > stress, $p = 0.02$); in stress group (List 2 recall > List 1 recall, $p = 0.06$)

Figure 16: Error bars representing 95% confidence intervals in the groups from Experiment 2.

Figure 17: Correlation scatter-plot of List 2 recall vs List 1 intrusions (from List 2) in the control group ($p = 0.021$).

Figure 18: Correlation scatter-plot of List 2 recall vs List 1 intrusions (from List 2) in the stress group ($p > 0.05$).

3.4. Discussion

In Experiment 2 we explored the effects of stress on reconsolidation of an updated memory. Participants were stressed on Day 2 after learning List 2, at the onset of reconsolidation. We found an impairing effect of stress on memory updating. Stress reminder participants showed significantly fewer intrusions than control reminder participants. There were no significant differences between the groups for recall of List 1, recall of List 2, or intrusions from List 1 into recall of List 2.

We did not find any impairing effects of stress on the memory for List 1, which was reactivated on Day 2 prior to experiencing a stressor. The few studies in humans that investigated the effects of stress on reconsolidation have reported impairment in the original memory (Marin, Pilgrim, & Lupien, 2010; Schwabe & Wolf, 2010; Zhao, Zhang, & Shi, 2009). These studies had participants explicitly recall the original memory before experiencing stress. Since our participants did not explicitly recall the original List 1 objects, its original content remained unaffected by stress after subtle reactivation. This is evident from a similar performance on List 1 recall between stress and control groups. However, the subtle reactivation was sufficient to update the original memory with new objects from List 2, which is reflected in the intrusion means in the stress and control groups. Stress prior to reconsolidation did not entirely abolish updating with 9.38% intrusions from List 2 into List 1 recall, but it did impair updating: the stress group showed intrusions, but fewer than seen in the control group.

In the control group, List2 recall and intrusions in List 1 from List 2 were negatively correlated. The better the participants remembered List 2, the fewer intrusions they had. We expected the stress group to show a similar relationship considering the reduced updating observed, however, the stress group did not show any such relationship. The stress group had overall fewer intrusions but the reduction was not related to subjective anxiety levels, cortisol levels, or List 2 recall. In the control group, the intrusion rate has a graded relationship to List 2 recall (Figure 16) although List 2 recall was not correlated to the rate of learning (no. of trials) on Day 2.

Therefore, we can conclude that stress impaired the reconsolidation of the updating of original memory (List 1) with new items from List 2. It did not impair the ability to recall List 1.

4. GENERAL DISCUSSION

The experiments in this dissertation were aimed at exploring the effects of stress on memory updating when stress was induced either before reactivation or after reactivation but before reconsolidation. We found that stress prior to reactivation does not statistically impair memory updating. On the other hand, stress after reactivation but before reconsolidation of List 1 or consolidation of List 2, reduced the updating effect resulting in fewer intrusions in List 1 recall, as seen in Experiment 2.

Many studies have shown impairing effects of stress on memory retrieval (Buchanan & Tranel, 2008; Buchanan, Tranel, & Adolphs, 2006; de Quervain, Aerni, & Roozendaal, 2007; Domes, Heinrichs, Rimmele, Reichwald, & Hautzinger, 2004; Kuhlmann, Piel, & Wolf, 2005; Merz, Wolf, & Hennig, 2010; Tollenaar, Elzinga, Everaerd, & Spinhoven, 2008a, 2008b, 2009a, 2009b). As mentioned before, stress may impair memory retrieval by diverting resources to encode the stressful episode that otherwise would have been used in retrieving a memory. From an adaptive perspective, it is more important to encode an adverse event for future reference than to remember a past event that is not relevant to the current stressful situation (de Kloet, Oitzl, & Joels, 1999; Roozendaal, 2002). The stress at retrieval studies cited above used retrieval tasks that had participants explicitly remember items from their first learning episode. A subtle reminder, as in our experiments, did not require the recall of details of List 1 learning. Rather, participants were merely required to describe the procedure used on Day 1. Although direct evidence is lacking, it may be the case that stress impairs explicit item

recall while having little or no effect on a subtle reminder. One could speculate that item recall requires more effort than the gist recall likely initiated by our subtle reminder. Memory systems may be able to retrieve gist information even under stress, but may not be able to extract specific details such as items from List 1, in a stressful situation. In both forms of reactivation – item recall or gist recall, a memory representation is activated, but the qualitative nature of these representations may differ. Stress may have failed to impair reactivation in our first experiment because of the absence of any explicit item recall during reactivation.

On the other hand, one could argue that stress impairs all forms of reactivation. We did see a reduction in intrusions in Experiment 1, although it failed to reach statistical significance. This lack of a significant difference between the mean intrusions in stress and control reminder groups may have been due to the high variance in intrusions in participants within the stress reminder group, which itself may have reflected the variability in stress responses to the TSST. The relatively small number of participants in our study may have further limited our ability to detect a difference. Since the stress response to the TSST can vary from participant to participant, increasing the number of participants may overcome the variance. Therefore, clarity on the effects of stress on reactivation requires further research.

In Experiment 2, we considered the possibility that the marginally enhanced consolidation of List 2 in the stressed participants was reducing the intrusions into List 1. Correlational analyses failed to support this idea. We found no gradient of learning of

List 2 that affected the extent of intrusions in the stress group. Stress seems to act solely by preventing updating.

It is possible that the reduction in intrusions into List 1 is related to the saliency of stress on Day 2. That is, participants might be utilizing the stressful state to help distinguish objects learned on Day 2 from those learned on Day 1. Were this to be the case, we should see the effect in both experiments, since stress was induced only on Day 2 in both cases. What we actually see is a trend in reduced intrusions across both experiments, but the reduction is significant only in Experiment 2, where stress was induced post reactivation. Stress prior to reactivation in Experiment 1 did not result in impairment. This suggests that the saliency of stress is not the cause of the reduction in intrusions.

Two animal studies have reported impairing effects of stress on reconsolidation. Maroun and Akirav (2008) examined the effects of stress on consolidation and reconsolidation of object recognition memory in rats. They showed that in habituated and non-habituated rats (i.e. regardless of arousal differences due to a novel context in non-habituated rats) stress enhanced consolidation but impaired reconsolidation of object recognition memory. Similarly, Wang, Zhao, Ghitza, Li, and Lu (2008) found that conditioned place preference for morphine was disrupted when the memory was reactivated by re-exposing rats to the conditioning chamber followed by cold water stress, i.e. stress disrupted the reconsolidation of morphine place preference. These two

studies corroborate our finding from Experiment 2, which extends this effect to human memory reconsolidation.

In conclusion, stress effects on reactivation need further examination. As for the reconsolidation of ‘updating’, stress can modify neural processes and impair reconsolidation of an updating memory representation. This finding has important implications for stress effects on problem solving processes that likely benefit from memory updating.

To use memory adaptively, we need to understand the varied ways in which stored information can be transformed. Information can of course be utilized in the way it was originally learned, but it could be made more useful, multifaceted, and flexible by allowing memory representations to connect and associate with other existing or newly acquired representations to generate new knowledge. Memory updating is just such a process. List 2 items that were falsely recalled as List 1 items in the reminder condition, had in some way been connected to List 1 items. Recall of List 1 and List 2 on Day 3 suggested that both representations exist, though some of the content from List 2 overlapped with the contents of List 1, resulting in intrusions. From one perspective, our memory appears to be flawed, as it is no longer reliable -- but from another perspective, from a problem solving perspective, this might be a boon. The memory updating paradigm demonstrates that memories can be combined to produce new and interesting outcomes. Such outcomes may provide the basis for novel solutions to problems.

It is also imperative to understand behavioral factors that can impair memory updating. As discussed in the introduction, brain regions involved in memory processes are affected by stress neuro-modulators. The experiments in this dissertation attempted to understand how these stress effects could impact memory updating processes. Memory updating occurs by virtue of two crucial processes – reactivation and reconsolidation. Although we were not able to confirm an impairing effect of stress on reactivation, as hypothesized, we were able to demonstrate impairing effects of stress on reconsolidation. Stress at reactivation will require further investigation. Overall, our experiments provide insight into the possible drawbacks of stressful conditions during memory updating and hence problem solving. Stressful conditions impair memory updating which in turn may lower our ability to form novel associations and consequently our ability to create new knowledge.

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