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Acute Stress Throughout the Memory Cycle: Diverging Effects on Associative and Item Memory

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Acute stress can modulate memory for individual parts of an event (items), but whether it similarly influences memory for associations between items remains unclear. We used a within-subjects design to explore the influence of acute stress on item and associative memory in humans. Participants associated negative words with neutral objects, rated their subjective arousal for each pair, and completed delayed item and paired associative recognition tasks. We found strikingly different patterns of acute stress effects on item and associative memory: for high-arousal pairs, preencoding stress enhanced associative memory, whereas postencoding stress enhanced item memory. Preretrieval stress consistently impaired both forms of memory. We found that the influence of stress-induced cortisol also varied, with a linear relationship between cortisol and item memory but a quadratic relationship between cortisol and associative memory. These findings reveal key differences in how stress, throughout the memory cycle, shapes our memories for items and associations.

Keywords: acute stress, item memory, associative memory, emotion

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Memories of everyday events—like what happened when you woke up yesterday—encompass different forms of representations. You can remember individual parts of the event (the coffee cup and the cereal box) and also how they fit together (you drank the coffee standing in your kitchen with your partner). However, if you read a stressful work e-mail when you woke up, how would this change what you remember? As nationwide stress levels have significantly increased for the first time in a decade (American Psychological Association, 2017), understanding how stress influences such everyday processes is critical. Through decades of research, we have learned that memory for individual parts of an event, or *item* memories, can be strongly influenced by even mild stressors (Wolf, 2009). This relationship has been well-characterized: acute stress effects on item memory vary based on when the stressor occurred—before encoding, after encoding, or before retrieval (de Quervain, Schwabe, & Roozendaal, 2017; Roozendaal, 2002; Sandi & Pinelo-Nava, 2007; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012; Shields, Sazma, McCullough, & Yonelinas, 2017)—and can be specific to information perceived as emotionally intense or arousing (Cahill, Gorski, & Le, 2003; Okuda, Roozendaal, & McGaugh, 2004; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006; Segal et al., 2014; Smeets, Otgaar, Candel, & Wolf, 2008). Yet, we know surprisingly little about how stress impacts our memory for how different items fit together, or *associative* memory. Detrimental effects of traumatic stress on associative memory have been suggested to underlie the etiology of posttraumatic stress disorder (Acheson, Gresack, & Risbrough, 2012). As patients have difficulty associating items with the specific context of the trauma, they then experience fear responses to those items in inappropriate contexts (e.g., the soldier who is fearful of loud noises after returning home). How the pervasive mild stressors of daily life modulate this form of memory in humans remains unclear. Here we explore how acute stress influ-

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ences associative memory in humans, using a novel within-subjects design to discover whether (and when) these effects differ from stress effects on item memory.

One possibility is that stress would similarly impact both item and associative memory. Both are types of declarative memory (Squire, 1992) that depend on medial temporal lobe (MTL) structures (Davachi, Mitchell, & Wagner, 2003), a region that is highly sensitive to stress hormones (cortisol in humans; Joëls, Sarabdjitsingh, & Karst, 2012). In addition, some effects of stress on item memory in humans have been echoed in studies of stress and associative memory in nonhuman animals. For example, acute stress before a memory test (preretrieval) impaired item-level memory in humans (Domes, Heinrichs, Rimmele, Reichwald, & Hautzinger, 2004; Smeets, 2011) and also impaired spatial memory (that relies on associations) in rodents (de Quervain, Roozendaal, & McGaugh, 1998; Roozendaal et al., 2004). In humans, one study examining preretrieval cortisol administration found that it impaired associative memory (De Quervain et al., 2003) just as it had impaired item memory (de Quervain et al., 2000). Although exogenous cortisol administration differs from the body's endogenous stress response (Gagnon & Wagner, 2016), this preliminary evidence suggests that acute stress effects on item memory may correspond to effects on associative memory. Accordingly, we would predict that factors that modulate stress effects on item memory would also modulate stress effects on associative memory. One such factor is the timing of acute stress, namely, whether it occurs before encoding, after encoding (potentially changing consolidation), or before retrieval. For example, exposure to acute stress before encoding frequently impairs later item memory (Domes et al., 2004; Payne et al., 2006, 2007; Rimmele, Domes, Mathiak, & Hautzinger, 2003; Zoladz et al., 2011), whereas stress experienced soon after encoding often enhances item memory (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003; Beckner, Tucker, Delville, & Mohr, 2006; Buchanan & Lovallo, 2001; Cahill et al., 2003; McCullough & Yonelinas, 2013; Payne et al., 2007; although there are exceptions to both; see Payne et al., 2006; Preuß & Wolf, 2009; Rimmele et al., 2003; Segal et al., 2014; Smeets et al., 2008; Trammell & Clore, 2014). In addition, the affective salience of the memoranda influences stress effects on item memory (Roozendaal & McGaugh, 2011; Shields et al., 2017). For example, postencoding stress more consistently enhances memory for emotional or arousing items in both rodents (Okuda et al., 2004; Roozendaal et al., 2006) and humans (Cahill et al., 2003; Segal et al., 2014; Smeets et al., 2008; but see Trammell & Clore, 2014).

Although the simplest model assumes that item and associative memory are similarly modulated by stress, other evidence suggests that these effects are likely to diverge. Despite both being MTL-dependent processes, item and associative memory involve distinct subregions: item memory is more dependent on perirhinal cortex, whereas associative memory critically involves the hippocampus (Davachi, 2006; Davachi et al., 2003), the latter of which has the highest density of cortisol receptors in the rat brain (McEwen, Weiss, & Schwartz, 1969). The small number of studies in humans that have examined acute stress and delayed associative memory or recollection (that also recruits the hippocampus; Eichenbaum, Yonelinas, & Ranganath, 2007; Ranganath et al., 2004) found that acute stress after learning (postencoding) had effects that differed from those observed for item memory (Larra et al., 2014; McCullough, Ritchey, Ranganath, & Yonelinas, 2015; McCullough & Yonelinas, 2013). In fact, they found that stress had no significant effect (Larra et al., 2014; McCullough & Yonelinas, 2013) or only cortisol dose-dependent effects (McCullough et al., 2015) on associative memory, although in these studies there were also no group-level effects on item memory. Other studies have used tasks that may have tapped associative memory processes (although it is not clear that they measured associative memory per se) and have yielded mixed findings. For example, in contrast to the above-mentioned null effects on associative memory, one study found that postencoding stress enhanced memory for verbal film information (Beckner et al., 2006). With preencoding stress, studies examining memory "contextualization" (i.e., memory benefits for information tested in familiar compared with novel contexts) have reported both impairment (Schwabe, Böhringer, & Wolf, 2009) and cortisol dose-dependent enhancement (van Ast, Cornelisse, Meeter, & Kindt, 2014). Another study found that preencoding stress impaired spatial memory, but only in one of two tasks, and only in women (Guenzel, Wolf, & Schwabe, 2014). Finally, factors unrelated to stress (like whether memoranda were emotional or highly arousing) have divergent effects on item and associative memory. Memory for highly arousing items is often reported to be enhanced (Bisby & Burgess, 2014; Eysenck, 1976; Kensinger, Garoff-Eaton, & Schacter, 2007; Madan, Caplan, Lau, & Fujiwara, 2012), whereas memory for information associated with highly arousing items is frequently impaired (Bisby & Burgess, 2014; Madan et al., 2012; Rimmele, Davachi, Petrov, Dougal, & Phelps, 2011; but see Kleinsmith & Kaplan, 1963; Mackay et al., 2004). Thus, even if stressor timing and memoranda salience modulate stress effects on both item and associative memory, the pattern of effects may vary.

Our goal was to characterize the effects of acute stress on associative memory and test whether these were consistent with stress effects on item memory. We needed a design that would enable us to (a) maximize comparisons between these two forms of memory; (b) uncover both facilitating and impairing stress effects on item memory, to test whether each generalizes to associative memory; and (c) account for any baseline variability in memory performance, to interpret the magnitude of stress effects. We created a novel, four-session, fully within-subjects design to address these goals. Participants encoded associations between negative words and neutral object images, and were tested for word recognition (item memory) and recognition of the paired image (associative memory) 24 h later. Assessing both item and associative memory within the same participants allowed us to directly compare these forms of memory. To detect a full range of stress effects, we leveraged factors known to change the direction of stress effects on item memory (specifically, stressor timing and memoranda salience). We took the within-subjects design a step further by manipulating these factors for each participant. That is, we measured each participant's performance with no stress intervention, and with acute stress before learning (preencoding), immediately after learning (postencoding), as well as before a memory test (preretrieval). As the cortisol component of the stress response is particularly important for stress effects at different time-points (de Quervain et al., 2017), we timed the preencoding and preretrieval stress interventions such that cortisol levels would be significantly elevated during the tasks. We also determined, for each participant, which memoranda they considered to be highly

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arousing during encoding. This approach allowed us, for the first time, to directly compare how much stress at each time-point changed both item and associative memory, while accounting for baseline (no stress) memory performance. We discovered distinct patterns of stress effects on item and associative memory. These results reveal which manipulations widely influence memory and which have targeted effects on item or associative representations, with implications for understanding the varied effects of acute stress on human memory.

Method

Participants

Thirty participants (17 female; mean age, 23.4; range, 18–34) completed all four sessions of the experiment. This target *N* was determined before the start of data collection based on previous research in mixed-gender cohorts showing significant effects of the stress manipulation (described below) on later memory performance (Cahill et al., 2003; Goldfarb, Mendelevich, & Phelps, 2017) as well as other cognitive tasks (Brown, Raio, & Neta, 2017; FeldmanHall, Raio, Kubota, Seiler, & Phelps, 2015; Lighthall, Gorlick, Schoeke, Frank, & Mather, 2013). As these prior studies used between-subjects designs, the statistical power in the current experiment was relatively higher, because of the removal of error variance from individual differences (Greenwald, 1976). Participants were fluent in English, with normal or corrected-to-normal vision and normal color vision. To reduce factors that could influence the stress response, participants were excluded if they were pregnant or taking antidepressants, antianxiety medications, beta blockers, or corticosteroids. Five additional participants were excluded because of failure to complete the experiment ($N = 2$), experimenter error ($N = 1$), and poor memory performance (mean $d' < 0$ and more misses than hits: $N = 1$; mean false alarm rate >75%: $N = 1$). All procedures were approved by the New York University Committee on Activities Involving Human Subjects. All participants provided written consent and were compensated at a rate of $20 per hour for their participation. As the major findings did not differ significantly by gender, we collapse across male and female participants in all analyses.

Tasks

Encoding. Participants associated pairs of words and images, each of which were displayed for 3 s (Figure 1A, left). Participants were instructed to vividly imagine the word and image interacting. Next, participants used the keyboard to rate how they felt when imagining the word-image pair (happy/unhappy/neutral; 2 s), and then rated how intensely they felt that way (4-point scale; 1 = *not at all intense*, 4 = *extremely intense*; 2 s). This scale was later compressed to "high arousal" (3 and 4) and "low arousal" (1 and 2) to increase the number of trials in each bin. Responses were illuminated on the screen in green for the duration of the trial. The buttons that corresponded to each response were counterbalanced across participants. Trials were separated by a jittered intertrial interval (ITI), $M = 3$ s). Each encoding list contained 40 word-image pairs.

Word stimuli were selected from a normed list to be negatively valenced and highly arousing (Warriner, Kuperman, & Brysbaert, 2013). Valence and arousal ratings were equated across stress conditions, and across recognition targets and foils within each condition. To facilitate vivid encoding, we limited words to nouns. Neutral images were taken from an online database of common objects with perceptual lures (Yassa et al., 2011).

Memory. Twenty-four hours after encoding, participants returned to the laboratory to complete two memory tests. These were designed to assess item-level and paired associative recognition.

Item recognition. Participants were presented with all words studied during encoding intermixed with novel foils (2 s), and reported whether each word was "old" or "new" (3 s; Figure 1A, middle). They provided responses on a 4-point scale ("*confident old*," "*unsure old*," "*unsure new*," "*confident new*") and also had the option to indicate "don't know" to limit guessing. Trials were separated by a jittered ITI (M = 2 s). As with encoding, the buttons that corresponded to each response were counterbalanced. Recognition was divided into two blocks per condition, each with 20 old words and 20 foils. Item recognition was measured as the difference between hit and false alarm (FA) rates to account for participants' response biases.

Associative recognition. Following word recognition, participants were tested for their ability to recognize the image that was originally paired with each word for all word-image pairs studied at encoding (Figure 1A, right). First, each studied word was presented alone (3 s). Then, participants were shown the word with four images (2 s), and indicated which image was shown with the word previously. These four images showed two objects that had been seen during the experiment (controlling for familiarity), as well as two novel matched perceptual lures. In the example shown in Figure 1A, where the participant encoded the word "funeral" with an image of a safety pin, during associative recognition the participant would be shown two images of safety pins (one exactly the same as encoding) and two images of another object (watering can) that had been studied with a different word during encoding (again, one watering can was exactly the same as encoding). We defined "object" memory as the selection of an image portraying the correct object (either safety pin), and "specific" memory as the selection of the exact image from encoding. Participants were instructed that, if they remembered the correct object but not exactly which image was shown, they should guess between the two. If they had no memory for the associated image, they were asked to indicate "don't know" rather than guess. Participants had 2 s to make this response, followed by a brief (0.5 s) fixation, after which they rated their confidence in their decision. Each list consisted of 40 trials separated by a jittered ITI ($M = 2$ s). Unless otherwise noted, associative recognition was calculated as the proportion of trials with correct "specific" memory, out of all trials with intact item recognition.

Stress Manipulation

To induce an acute stress response, participants completed the cold pressor test (CPT), a validated laboratory stressor that has been shown to induce a hypothalamic-pituitary-adrenal (HPA) axis response; thus, increasing levels of salivary cortisol (Lovallo, 1975). During the task, participants submerged their nondominant arm in a bucket of ice water for three continuous minutes (Week A: mean temperature = 0.92 °C [$SD = 0.47$ °C], Week B: 0.82 °C [0.61 °C]; difference: $t(29) = .8$, $p > .25$). Immediately afterward,

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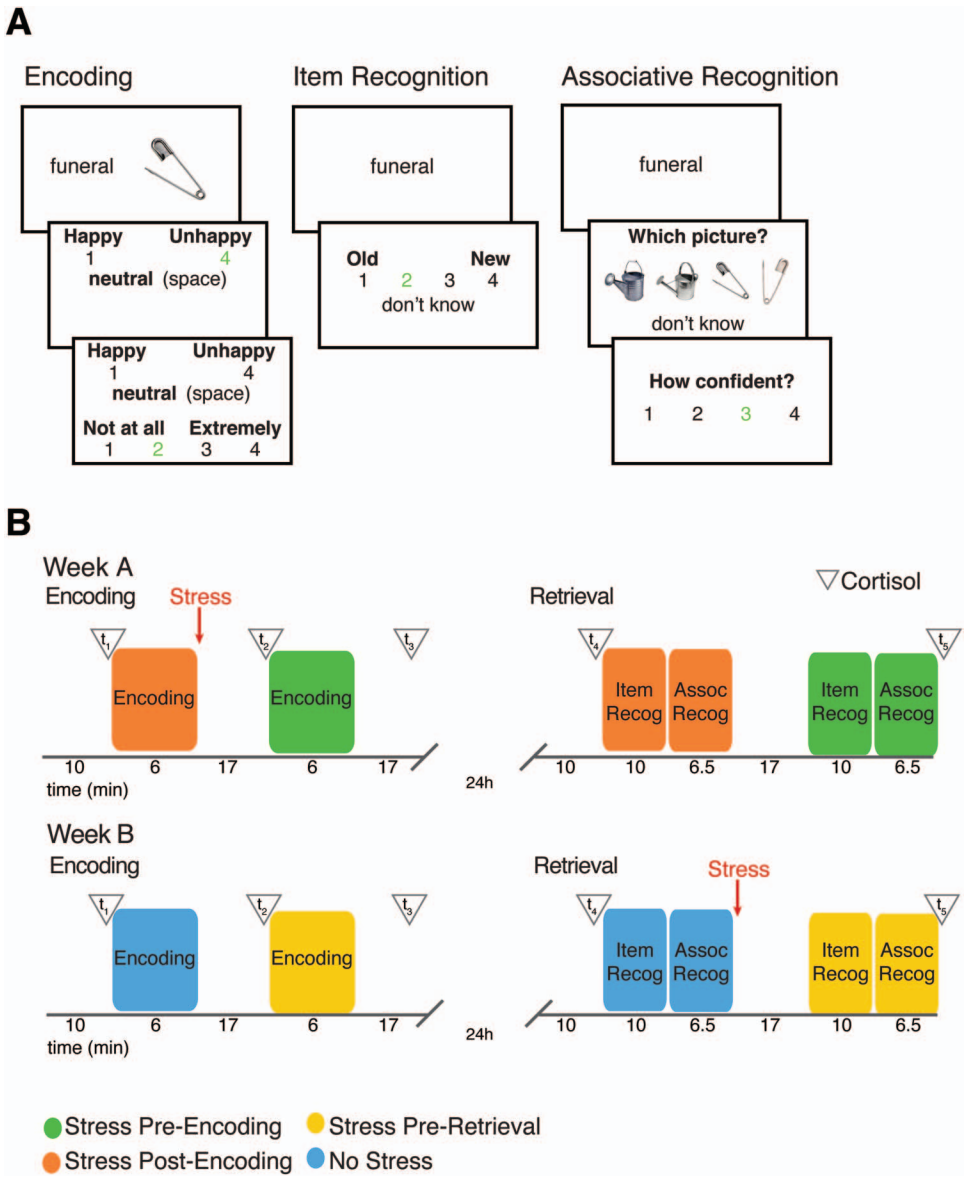

Figure 1. Experimental design. Panel A: Encoding and retrieval tasks. Participant responses were highlighted in green. During encoding (left), participants rated how they felt (valence) and how intensely they felt that way (arousal) for each word/image pair. Arousal ratings were collapsed into "Low" and "High" for analyses. During item recognition (middle), participants rated whether the word shown was old or new, with confidence (1 = confident old, 2 = unsure old, etc.). During associative recognition (right), participants indicated which image had been paired with each word during encoding and provided confidence ratings. Selecting a picture portraying the correct object was coded as "object" memory; selecting the exact picture was coded as "specific" memory. Panel B: Overview of the four experimental conditions, shown in different colors. Each participant completed all four sessions (week order counterbalanced). Triangles indicate points when salivary cortisol samples were collected.

participants were asked to rate the unpleasantness of the stressor (0 = *not at all unpleasant*; 10 = *extremely unpleasant*).

To assess the biological efficacy of the stress manipulation, saliva samples were taken throughout the experiment to measure cortisol concentration (Figure 1B, triangles). After collection, salivary samples were stored at −20 °C in sterile tubes, and were then shipped frozen to the laboratory of Dr. Andrea Gierens at the University of Trier for cortisol analysis. Three participants did not provide sufficient saliva to assess cortisol response to one or both stressors (retrieval stressor: $N = 1$) or had baseline cortisol levels >3 *SD* outside the mean in a stress session (encoding baseline, >5 *SD* outside mean: $N = 1$, retrieval baseline, >3 *SD* outside mean: $N = 1$), and are excluded from analyses with that measure. For analysis, we log-transformed cortisol levels to ac-

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count for skewed cortisol concentration distributions (Otto, Raio, Chiang, Phelps, & Daw, 2013).

Procedure

The full experimental procedure is shown in Figure 1B. Each participant came to the laboratory for all four sessions, which consisted of either encoding or memory tests. All sessions were conducted between 12:00 to 6:00 p.m. to control for circadian fluctuations in cortisol (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). Saliva samples (triangles, Figure 1B) were taken throughout the four sessions to assess levels of cortisol.

In Week A, participants were exposed to an acute stress manipulation (CPT) immediately after encoding the first list of word-image pairs. This created our "Post-Encoding Stress" condition. After a delay (~19 min), participants encoded a second list of pairs, creating our "Pre-Encoding Stress" condition. This delay was set based on previous work showing that, approximately 15–20 min poststress, levels of cortisol are significantly elevated in plasma (Ábrahám et al., 1998; Dorey, Piérard, Chauveau, David, & Béracochéa, 2012) and the dorsal hippocampus (Dorey et al., 2012). During the delay, participants rested with their eyes open (6 min), viewed a neutral movie clip (11-min), and provided a saliva sample (duration = 2 min). Twenty-four hours later, participants were given memory tests and not exposed to any further stressors. To match timing between weeks, there was a delay between memory tests for Post-Encoding and Pre-Encoding Stress (6-min rest plus 11-min movie clip).

In Week B, participants also encoded two separate lists of associates (separated by ~19 min, matching Week A timing). Twenty-four hours later, participants were given memory tests for the first list of encoded information, creating our "No Stress" condition. Immediately afterward, participants were exposed to the CPT. After a delay (~17 min), they were tested on memory for the second list of encoded information, creating our final "Pre-Retrieval Stress" condition. To account for order effects, the order was counterbalanced (14/30 participants completed Week A first; 16/30 completed Week B first). Week A and Week B always occurred during consecutive weeks. Further analyses and an additional control experiment demonstrated that the order of stimulus presentation did not significantly influence item recognition or associative recognition (online supplemental materials).

Results

Subjective Ratings of Stimuli

Participants rated the majority of word-image pairs (60.4%) as unhappy, consistent with our use of negatively valenced words (Warriner et al., 2013; Figure 2A). Using a repeated measures analysis of variance (rm-ANOVA) with valence rating and stress condition as within-subjects factors, we found that this proportion was significantly greater than those for other valence ratings (main effect of valence rating: $F(2, 58) = 39.06$, $p < .001$) and did not vary by stress condition (Valence Rating × Stress Condition: $F(6, 174) = 1.06$, $p > .25$). Of the word-image pairs rated as unhappy, 52.7% were also rated high-arousal. Unlike valence, participants rated approximately the same number of pairs as high-arousal (41.9%) and low-arousal (56.8%; Figure 2A), leading to a trend-level main effect of arousal rating, $F(1, 29) = 3.93$, $p = .06$. We also observed a trend-level Arousal Rating × Stress Condition interaction, $F(3, 87) = 2.54$, $p = .06$, driven by a change in ratings following preencoding stress: compared with no stress, participants rated a higher proportion of stimuli as low-arousal after preencoding stress, $t(29) = 2.52$, $p = .018$. For the distribution of stimuli rated as high-arousal for each participant and stress condition, see online supplemental material Figure 1. Subsequent

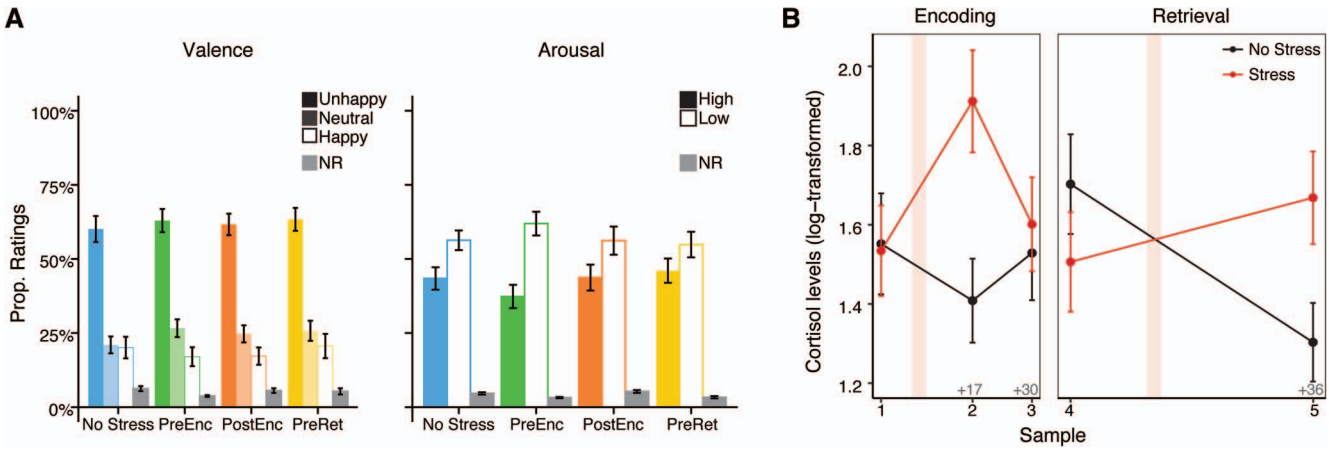

Figure 2. Manipulation checks. Panel A: Subjective ratings of stimuli at encoding. As expected, the majority of stimuli were rated as "unhappy" across stress conditions. Arousal ratings were mixed, enabling us to examine how stress differently influenced memory for high- and low-arousal stimuli. Panel B: Both exposures to stress (Cold Pressor Test [CPT], red lines) led to significant changes in cortisol levels relative to no stress (black lines). The pink bar indicates the timing of the CPT during the stress session, and the gray numbers indicate the time (in minutes) since the end of the CPT. Sample timing shown in Figure 1B (samples indicated by triangles). Error bars represent ±1 *SEM*.

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analyses separate stimuli based on these subjective arousal ratings during encoding.[1]

Stress Response

To test whether the stressor was effective, we ran rm-ANOVAs to compare cortisol levels by stress condition (stress vs. no stress) and saliva sample (Time 1 – Time 5; Figure 1B, triangles). We observed a significant Condition × Sample interaction across the three samples from encoding, $F(2, 56) = 5.46$, $p = .007$ and the two samples from retrieval, $F(1, 27) = 16.98$, $p < .001$, indicating that cortisol levels varied depending on exposure to CPT and time during the experimental session (Figure 2B; raw cortisol values in online supplemental material Table 2). These interactions remained significant when we included order (whether participants completed Week A or Week B first) as a covariate (encoding, Condition × Sample interaction: $F(2, 54) = 5.69$, $p = .006$; retrieval, Condition × Sample interaction: $F(1, 27) = 17$, $p < .001$; additional comparisons in online supplemental materials). Paired-sample t tests confirmed that there were no baseline differences in cortisol (encoding, stress vs. no stress, Time 1: $t(28) = -.22$, $p > .25$; retrieval, stress vs. no stress, Time 4: $t(27) = -1.44$, $p = .16$). However, after exposure to CPT, cortisol levels were significantly higher in the sessions with stress (encoding, stress vs. no stress, Time 2: $t(28) = 3.22$, $p = .003$; retrieval, stress vs. no stress, Time 5: $t(27) = 3.29$, $p = .003$).

Item and Associative Memory: No Stress

Participants were significantly above chance (50%) in their ability to recognize words shown the previous day (mean hits = 72.7%; $SD = 17.9\%$; $t(29) = 6.95$, $p < .001$). They also were able to discriminate between new and old words, with slightly below chance FA rates (44%, $SD = 15.8\%$; $t(29) = -2.05$, $p = .049$). Subsequent analyses will use hit—FA rates as the index of item recognition (no stress: 28.6%; see online supplemental material Table 1 for memory per condition).

Participants also successfully recognized the images associated with the words. Of the words that participants correctly recognized, they chose either of the two images portraying the correct object ("object memory") on 59.9% ($SD = 15.5\%$) of trials (chance = 50%; $t(29) = 3.5$, $p = .002$), and chose the exact image from encoding ("specific memory") on 36.1% ($SD = 14.9\%$) of trials (chance = 25%; $t(29) = 4.1$, $p < .001$). In the absence of stress, there were no significant differences in item recognition, $t(28) = .84$, $p > .25$ or specific associative recognition, $t(28) = .4$, $p > .25$ based on whether participants had rated the word-image pair as high or low arousal. When separating memory by arousal ratings, recognition rates were computed out of the total number of word-image pairs that received that arousal rating in each stress condition.

Item and Associative Memory: Effects of Acute Stress

We quantified the influence of stress at each time-point by subtracting memory performance on the no stress list from memory performance for each stress list, separately for word-image pairs rated as high and low arousal during encoding. To test whether stress-modulated memory performance varied as a function of memory test (item [hit-FA] vs. associative [specific recognition]), stressor timing (preencoding, postencoding, and preretrieval), and arousal rating (high vs. low), we ran an rm-ANOVA including each of these terms as within-subjects factors. We found a significant main effect of stressor timing, $F(2, 54) = 8.22$, $p < .001$, as well as an interaction between stressor timing, memory test, and arousal ratings, $F(2, 54) = 4.07$, $p = .023$. Having established that there were significant differences in how stressor timing and affective salience influenced item and associative memory, we next examined how these factors modulated stress effects on item and associative memory separately.

Acute stress and item recognition. To understand how stressor timing (preencoding, postencoding, and preretrieval) and arousal rating (high vs. low) influenced item recognition (hit - FA, relative to no stress), we ran an rm-ANOVA including these as within-subjects factors. As when collapsing across memory tests, we found a main effect of stressor timing, $F(2, 54) = 7.57$, $p = .001$, indicating that acute stress at different time-points had distinct effects on item memory. There was no main effect of arousal, $F(1, 27) = .19$, $p > .25$ or interaction between stressor timing and arousal, $F(2, 54) = 2.11$, $p = .13$; Figure 3A. Although the interaction was not significant, stressor timing significantly influenced recognition for pairs rated as high arousal, $F(2, 56) = 9.66$, $p < .001$ but not low arousal, $F(2, 56) = 2.13$, $p = .13$.

Acute stress and item recognition: Per time-point. As acute stress at different time-points had distinct effects on item recognition, we examined the effects of stress at each time-point separately. We ran separate rm-ANOVAs for each stressor time-point to predict raw recognition performance (hit-FA; raw = without subtracting the no stress list; see Figure 3A inset) with stress condition (no stress vs. stress) and arousal rating (high vs. low) as within-subjects factors.

Acute stress before encoding did not significantly influence item recognition (all $p > .25$). However, when that same stressor occurred after encoding, there was a significant main effect of arousal, $F(1, 27) = 9.7$, $p = .004$ but no main effect of stress condition, $F(1, 27) = .66$, $p > .25$. Participants had significantly better item recognition for items from high-arousal pairs relative to low-arousal pairs within the postencoding stress list, $t(28) = 3.64$, $p = .001$; Figure 3A inset, a difference that did not exist in the no stress list (see above); however, the Stress × Arousal interaction was not significant, $F(1, 27) = 2.85$, $p = .10$. Relative to no stress, postencoding stress also significantly improved item recognition for high-arousal, $t(28) = 2.08$, $p = .047$ but not low-arousal stimuli, $t(28) = -.33$, $p > .25$; Figure 3A. This enhanced recognition for items from high-arousal pairs was driven by a trend-level

[1] As the arousal categories were determined by the participants, there was variability in the number of trials assigned to each bin (for high arousal, see online supplemental material Figure 1). Specifically, two participants did not assign any trials to one or more bins (no "low arousal" trials with no stress: $N = 1$; no "high arousal" trials with postencoding or preretrieval stress: $N = 1$). These participants are included in comparisons for which they have assigned trials to the appropriate bins (e.g., t tests), but will be excluded from all relevant repeated measures analysis of variance (rm-ANOVAs) that include Arousal Rating.

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increase in hits, $t(28) = 1.89$, $p = .069$, and no significant change in FA, $t(28) = -.13$, $p > .25$ relative to no stress.

Finally, preretrieval stress significantly influenced item recognition (main effect of stress condition: $F(1, 27) = 14.98$, $p < .001$), and these effects did not vary by arousal (main effect arousal and interaction with arousal: both $p > .25$). Specifically, preretrieval stress impaired item memory relative to no stress (all pairs: $t(29) = -2.67$, $p = .012$; high-arousal: $t(28) = -2.72$, $p = .01$; low-arousal: $t(28) = -2.56$, $p = .016$; Figure 3A inset). We ran further analyses to discover which component of recognition was impaired, finding that preretrieval stress led to an overall increase in FA, $t(29) = 2.25$, $p = .032$, and not a change in hits, $t(29) = -.43$, $p > .25$ or response criterion, $t(29) = -1.06$, $p > .25$.

Acute stress and item recognition: Variability in arousal ratings. Recent findings have demonstrated that participants who rated more stimuli as highly arousing were also more susceptible to effects of salience (i.e., contrast) on later memory (Sutherland & Mather, 2017). To determine whether participants who rated more stimuli as highly arousing also showed stronger effects of stress on item recognition, we ran separate rm-ANOVAs for each stress condition. We predicted item recognition (hit-FA) as a function of stress condition (no stress vs. stress) as a within-subjects factor and subjective arousal (proportion of stimuli rated

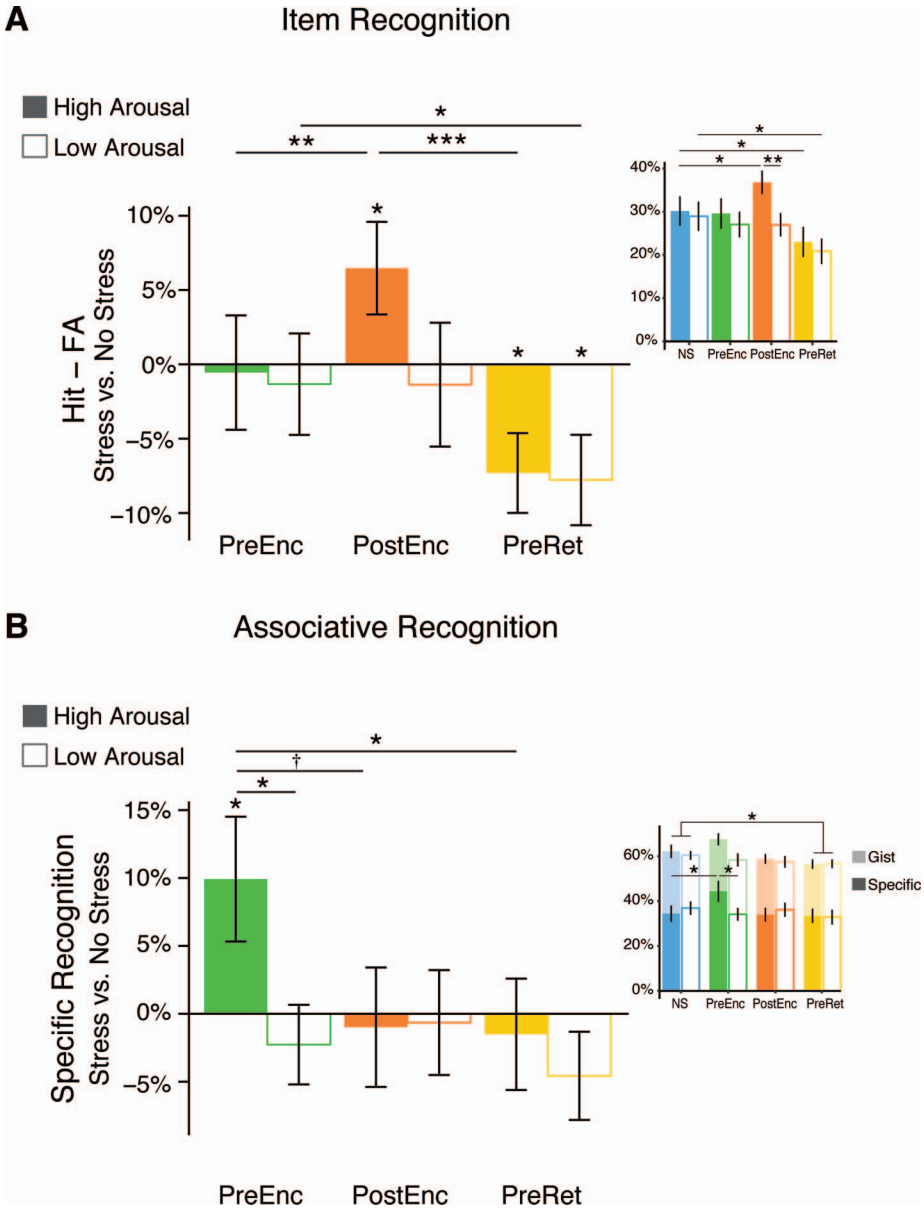

Figure 3 (opposite)

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high arousal in the stress condition) as a between-subjects factor. In the postencoding stress condition, there was a trend-level Stress × Subjective Arousal interaction, $F(1, 26) = 3.28$, $p = .08$, such that participants who rated more stimuli as highly arousing showed greater item recognition benefits with postencoding stress relative to no stress (Figure 4A). Variability in arousal ratings was not related to memory under preencoding stress (Stress × Subjective Arousal, $p = .2$) or preretrieval stress ($p > .25$).

Acute stress and item recognition: Variability over time. We compared the effects of stress at different time-points by running paired-sample t tests on stress-modulated memory performance (i.e., hit—FA relative to no stress; Figure 3A). For high-arousal pairs, postencoding stress significantly enhanced item recognition compared with preencoding stress, $t(28) = 2.98$, $p = .006$, and had the opposite effect of preretrieval stress on high-arousal pairs, $t(28) = 3.96$, $p < .001$. For low-arousal pairs, item recognition was significantly more impaired by preretrieval compared with preencoding stress, $t(28) = 2.11$, $p = .044$.

Acute stress and item recognition: Summary. The effects of acute stress on item recognition differed based on when the stressor occurred and the arousing content of the memoranda. Preencoding stress did not influence this form of memory, while postencoding stress enhanced high-arousal item recognition, and preretrieval stress impaired both high-arousal and low-arousal item recognition.

Acute stress and associative recognition. As with item recognition, we ran an rm-ANOVA with stressor timing (preencoding, postencoding, and preretrieval) and arousal rating (high vs. low) as within-subject factors to predict specific associative recognition. There was a trend-level main effect of stressor timing, $F(2, 54) = 2.49$, $p = .093$, but no main effect of arousal, $F(1, 27) = 0.61$, $p > .25$ or Stressor Timing × Arousal interaction, $F(2, 54) = 2.13$, $p = .13$. Similar to item recognition, there was a significant main effect of stressor timing on specific recognition for associates in high-arousal, $F(2, 56) = 3.21$, $p = .048$ but not low-arousal pairs, $F(2, 56) = .52$, $p > .25$.

Acute stress and associative recognition: Per time-point. To understand how stress at each time-point influenced associative recognition, we ran rm-ANOVAs to predict raw specific associative recognition with stress condition (no stress vs. stress) and arousal rating (high vs. low) as within-subject factors.

With preencoding stress, in contrast to item recognition, we found that specific associative recognition was modulated by a significant Stress × Arousal interaction, $F(1, 28) = 4.41$, $p = .045$ and no significant main effects (stress: $F(1, 28) = 2.05$, $p = .16$; arousal: $F(1, 28) = 2.22$, $p = .15$). Within the preencoding stress list, participants had significantly better specific recognition for associates in high-arousal compared with low-arousal pairs, $t(29) = 2.17$, $p = .038$, a difference that did not exist in the no stress list (see above; Figure 3B inset, online supplemental material Figure 2). Relative to no stress, preencoding stress enhanced specific associative recognition for high-arousal, $t(29) = 2.16$, $p = .039$ but not low-arousal stimuli, $t(28) = -.23$, $p > .25$.

In another difference from item recognition, postencoding stress did not significantly influence specific associative recognition (main effects or interactions with arousal: all $p > .25$). Within the postencoding stress list, there were no differences in specific associative recognition for high-arousal versus low-arousal stimuli, $t(28) = -.76$, $p > .25$; Figure 3B inset, online supplemental material Figure 2.

Finally, preretrieval stress did not significantly influence specific associative recognition (main effect stress: $F(1, 27) = 1.77$, $p = .2$), and there was no main effect or interaction with arousal (both $p > .25$). However, preretrieval stress led to a more general impairment in associative recognition, as evidenced by a significant main effect of stress on "object"-level (rather than "specific") associative recognition ($F(1, 27) = 4.33$, $p = .047$; Figure 3B inset, online supplemental material Figure 2). This effect was only significant after accounting for possible main effects or interactions with arousal (both $p > .25$). That is, when accounting for variability in memory because of arousal ratings, preretrieval stress significantly impaired recognition of associated objects.

Acute stress and associative recognition: Variability in arousal ratings. As with item recognition, we tested whether participants who rated more stimuli as highly arousing showed stronger effects of stress on associative recognition. We predicted associative recognition (specific) as a function of stress condition (no stress vs. stress) as a within-subjects factor and subjective arousal (proportion of stimuli rated high arousal in the stress condition) as a between-subjects factor. Variability in arousal ratings was not associated with modulation of associative recognition resulting from preencoding or postencoding stress (all $p > .25$). In contrast, there was a significant interaction between stress condition and subjective arousal for preretrieval stress, $F(1, 26) = 5.18$, $p = .031$, such that participants who rated more stimuli as high arousal were more impaired by preretrieval stress (Figure 4B).

Figure 3 (opposite). Divergent effects of acute stress effects on item and associate recognition. Stress-modulated memory performance (y-axis) was computed by subtracting performance with no stress from performance under each stress condition (positive values = better than no stress; negative values = worse than no stress). Inset graphs show raw memory performance for each condition (NS = no stress). Recognition for high arousal stimuli shown in filled bars; low arousal stimuli shown in open bars. Panel A: Item recognition. For word-image pairs rated as high arousal, participants showed significantly enhanced recognition for items (words) with postencoding stress, an effect that differed significantly from preencoding and preretrieval stress. Preretrieval stress significantly impaired item recognition for both high and low arousal stimuli. For stimuli rated as low arousal, preencoding stress led to significantly better item recognition than preretrieval stress. Panel B: Associative recognition. Preencoding stress enhanced specific associative recognition for images associated with words from high arousal pairs, an effect that differed significantly from preretrieval stress and at a trend-level from postencoding stress. The inset shows raw associative recognition for each condition, separated by arousal ratings. Darker bars indicate "specific" recognition (participant selected the exact image shown with the word, also shown in main part of panel); lighter bars indicate "gist"-level recognition (participant selected the correct object, but not the specific image). The total height of each bar indicates "object" recognition, or the total number of times participants selected the correct object (specific or gist). As shown in the inset, object associative recognition (correct recognition of the object associated with the word, but not necessarily the specific image) was impaired by preretrieval relative to no stress. Error bars represent ±1 *SEM*. † $p < .1$. * $p < .05$. ** $p < .01$. *** $p < .001$.

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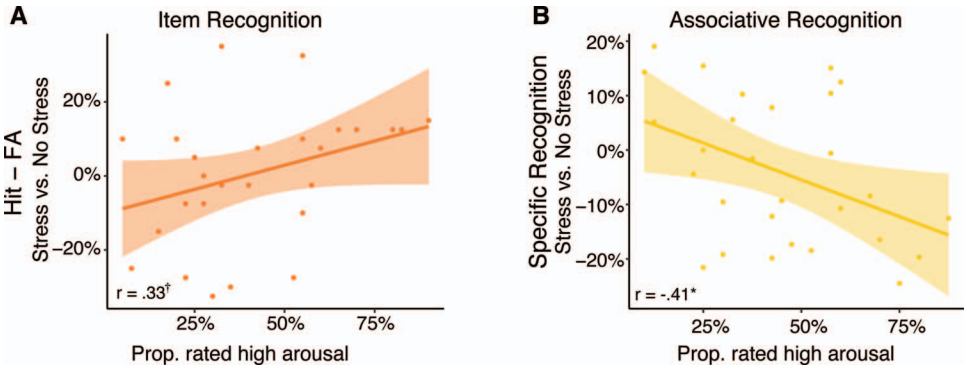

Figure 4. Subjective experience of arousal influences stress effects on memory. As in Figure 3, stress-modulated memory performance (*y*-axis) was computed by subtracting performance with no stress from performance with stress condition (positive values = better than no stress; negative values = worse than no stress). These graphs show stress-modulated memory performance collapsed over high and low arousal stimuli. Panel A: Item recognition. With postencoding stress, item recognition was especially enhanced for participants who rated a large proportion of stimuli in the postencoding stress list as high arousal. Panel B: Associative recognition. With preretrieval stress, specific associative recognition was especially impaired for participants who rated a large proportion of stimuli in the preretrieval stress list as high arousal. Error bars represent ±1 *SEM*. † $p < .1$. * $p < .05$.

Acute stress and associative recognition: Variability over time. As with item recognition, we compared the effects of stress at different time-points by running paired-sample *t* tests on stress-modulated memory performance (Figure 3B). For specific recognition of associates from high-arousal pairs, we found that preencoding stress significantly enhanced memory relative to preretrieval stress, $t(28) = 2.25$, $p = .033$, with a trend-level difference between preencoding and postencoding stress, $t(28) = 1.8$, $p = .082$.

Acute stress and associative recognition: Summary. As with item recognition, the effects of acute stress on associative recognition varied based on stressor timing and subjective arousal. However, the pattern of effects differed. Additional analyses provided further evidence that preretrieval stress impaired both item and associative memory, whereas preencoding and postencoding stress effects differed between memory tests (online supplemental materials). Preencoding stress enhanced recognition for associates from high-arousal pairs, postencoding stress did not influence this form of memory, and preretrieval stress (when accounting for variability in arousal ratings) impaired associative recognition.

Item and Associative Memory: Relationship to Cortisol

The above results demonstrated that acute stress, in tandem with the arousing content of the memoranda, modulated item and associative memory. Based on previous research indicating that acute stress effects on memory vary based on the magnitude of the stress-induced cortisol response (with reports of both linear, e.g., Beckner et al., 2006; Domes et al., 2004; Preuß & Wolf, 2009); and quadratic relationships, e.g., Andreano & Cahill, 2006; McCullough et al., 2015), we tested how the cortisol response related to stress-induced changes in item and associative memory.

Because the same stressor created preencoding and postencoding stress conditions, we could test whether there were interactions between when learning occurred (either pre- or poststressor) and the magnitude of endogenous cortisol release to predict later memory. This approach enabled us to identify relationships between cortisol and memory that were unique to preencoding or postencoding stress. As with stress-modulated memory performance, we quantified the stress-induced cortisol response by subtracting the change in cortisol with no stress (Week B, *log*(t2) – *log*(t1)) from the change in cortisol with stress (Week A, *log*(t2) – *log*(t1); timing in Figure 1B). This stress-modulated cortisol response reflects the change in cortisol response because of the CPT after accounting for any hormonal fluctuation because of the experience of performing the encoding task, providing a stronger baseline from which to interpret effects of acute stress on memory.

Cortisol and item recognition. We used a linear model to test whether the relationship between stress-induced cortisol response (compared with no stress) and stress-modulated memory (compared with no stress) varied by stress condition. We modeled stress-modulated item recognition (normalized hit-FA, relative to no stress) as a function of stressor timing (preencoding vs. postencoding), arousal rating (high vs. low), and stress-induced cortisol response, with all possible interactions. There were several significant main effects and interactions (Figure 5A, all effects in Table 1). Critically, there was a significant three-way interaction between stress-induced cortisol response, stressor timing, and arousal ratings ($\beta = -1.35$ [$SE = .40$], $p = .001$), showing that the relationship between cortisol and changes in item recognition varied as a function of stressor timing and the arousing content of the memoranda. The individual correlations with item recognition (hit-FA) were not significant (all $p > .25$). With preencoding stress, there was a numerically negative relationship between cortisol and item recognition for low-arousal stimuli, whereas with postencoding stress, there was a positive relationship between these factors.

Cortisol and associative recognition. As with item recognition, we assessed whether the magnitude of cortisol response differentially influenced specific associative recognition (normalized) based on whether the stressor occurred before or after learning (model parameters: stressor timing [preencoding vs. postencoding], arousal rating [high vs. low], stress-induced cortisol

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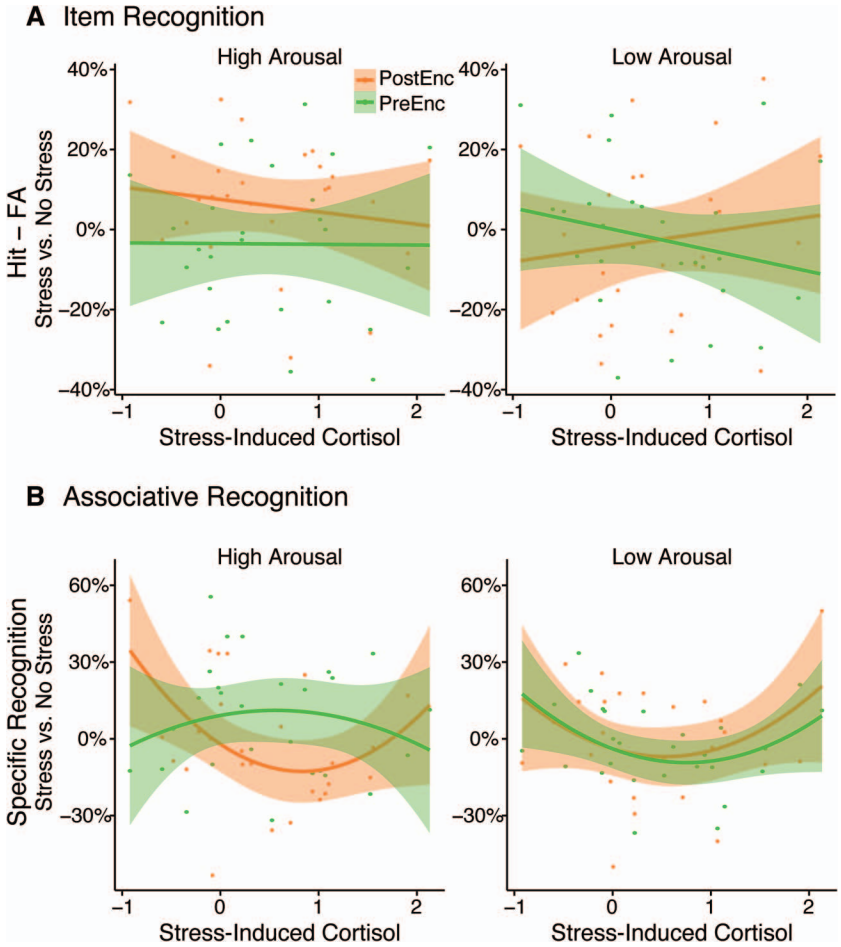

Figure 5. Relationship between endogenous cortisol response and stress-modulated memory performance. Stress-modulated memory performance (*y*-axis) was computed by subtracting performance with no stress from performance under each stress condition (as in Figure 3). Stress-induced cortisol (*x*-axis) was computed by subtracting the change in cortisol during the encoding session with no stress from the change in cortisol during encoding with stress. Panel A: Relationship between stress-induced cortisol and stress-modulated item recognition memory. There was a three-way interaction between stress condition (preencoding vs. postencoding), arousal rating, and stress-induced cortisol response predicting stress-modulated item recognition. The relationships between cortisol and memory were linear. Panel B: Relationship between stress-induced cortisol and stress-modulated associative memory. There was a three-way interaction between stress condition (preencoding vs. postencoding), arousal rating, and stress-induced cortisol response predicting stress-modulated associate recognition. The relationships between cortisol and memory were quadratic. Error bars represent 95% confidence interval (CI).

response, and all interactions; Figure 5B, all effects in Table 1). However, unlike item recognition, we found that the relationship between cortisol and specific associative recognition was better described by a quadratic model that allowed for interactions with stress-induced cortisol^2 (quadratic vs. linear model comparison: $F(4) = 2.58$, $p = .042$). When allowing for a quadratic relationship with the stress-induced change in cortisol, we found a three-way interaction between stress condition, arousal rating, and the squared stress-induced cortisol response ($\beta = 7.24$ [3.37], $p = .034$).

As shown in Figure 5B, postencoding stress led to a consistent U-shaped relationship between stress-induced cortisol and specific associative recognition across arousal ratings (high-arousal ~ stress-induced cortisol^2: $\beta = .52$ [.22], $p = .027$, low-arousal ~ stress-induced cortisol^2: $\beta = .37$ [.21], $p = .096$). With preencoding stress, this relationship differed marginally based on arousal ratings (stress-induced Cortisol^2 × Arousal rating: $\beta = .76$ [.39], $p = .059$), with a significant U-shaped relationship between cortisol and specific recognition of associates from low-arousal pairs ($\beta = .33$ [.16], $p = .047$).

Discussion

Using a within-subjects design, we directly compared the effects of acute stress on item and associative recognition. We tested whether factors that modulate the effects of stress on item memory, namely the timing of acute stress and the arousing content of memoranda, would similarly impact associative memory. We

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Table 1
Memory ~ Cortisol × Arousal Rating × Stress Condition

Predictor	Item recognition			Associative recognition		
	β	*SE*	*t*	β	*SE*	*t*
Stress condition	−.80	.26	−3.11**	.51	.23	2.21*
Arousal rating	−.91	.26	−3.49***	.25	.23	1.07
ΔCortisol	−.20	.20	−.97	−1.58	1.69	−.94
ΔCortisol^2	—	—	—	2.41	1.69	1.43
Stress Condition × Arousal Rating	1.16	.37	3.17**	−.69	.32	−2.14*
Stress Condition × ΔCortisol	.55	.29	1.92†	2.19	2.38	.92
Stress Condition × ΔCortisol^2	—	—	—	−7	2.38	−2.93**
Arousal Rating × ΔCortisol	.52	.29	1.81†	3.09	2.38	1.3
Arousal Rating × ΔCortisol^2	—	—	—	−1.44	2.38	−.61
Stress Condition × Arousal Rating × ΔCortisol	−1.35	.40	−3.34**	−4.25	3.37	−1.26
Stress Condition × Arousal Rating × ΔCortisol^2	—	—	—	−7.24	3.37	2.15*

Note. Dependent variables are normalized changes in item recognition (hit – false alarm, FA) and associative recognition (specific) relative to no stress. Stress conditions include Pre-Encoding and Post-Encoding (as these shared a stressor and, thus, the same cortisol response).
† $p < .1$. * $p < .05$. ** $p < .01$. *** $p < .001$.

found that stressor timing modulated stress effects on both item and associative memory, but the effects of acute stress pre- and postencoding varied. Stress before encoding enhanced recognition for associates from high-arousal pairs, whereas stress immediately after encoding enhanced item recognition for such pairs. In contrast, preretrieval stress impaired both forms of memory across arousal ratings. We also discovered that the relationship between endogenous cortisol release and memory varied based on whether the information was learned before or after the stressor, whether the stimuli were perceived as arousing, and whether item or associative recognition was assessed. Together, these results replicate prior effects of acute stress on item memory, and for the first time, delineate how and when the effects of acute stress on item and associative memory diverge. Below we highlight and discuss several key findings.

Preencoding Stress Influenced Associative Recognition, Whereas Postencoding Stress Influenced Item Recognition

Although both preencoding and postencoding stress enhanced memory for high-arousal relative to low-arousal stimuli, these effects were specific to different forms of memory. Preencoding stress enhanced participants' ability to recognize the specific image associated with the word cue, but did not influence recognition for the word itself. In contrast, postencoding stress enhanced participants' ability to recognize the word itself, but not its associated image.

These divergent stress effects on item and associative memory may be associated with the division of labor within the MTL mentioned earlier, with item recognition supported by perirhinal cortex (Davachi, 2006; Davachi et al., 2003) and associative memory supported by the hippocampus (Eichenbaum et al., 2007; Ranganath et al., 2004). Other manipulations have also been shown to differentially impact cortical and hippocampal-based memory, including the arousing content of the memoranda (negatively valenced stimuli frequently enhance item memory; Bisby & Burgess, 2014; Cahill & McGaugh, 1995; but impair memory for associated details; Kensinger et al., 2007; Mather, 2007; Rimmele et al., 2011) and the learning context (threat of punishment can enhance item memory, whereas reward-motivated contexts tend to enhance hippocampal memory; Murty, Labar, & Adcock, 2012; Murty, LaBar, Hamilton, & Adcock, 2011). This evidence suggested that acute stress would also differentially influence item and associative memory.

However, the finding that preencoding stress specifically enhanced associative memory was surprising. In rodents, preencoding stress has frequently been shown to impair hippocampal-dependent spatial memory (Kim, Koo, Lee, & Han, 2005; Kim, Lee, Han, & Packard, 2001; Park, Zoladz, Conrad, Fleshner, & Diamond, 2008). In humans, the "range of cue utilization" theory (Easterbrook, 1959) would predict that stress-induced arousal would lead to attentional narrowing; thus, enhancing memory for "central" details but impairing "peripheral" memory (in the current task, the peripheral feature could be the neutral image associated with the negative word). Critically, the current results revealed that preencoding stress specifically enhanced associative memory for word-image pairs that, as a unit, participants rated as highly arousing. This is consistent with findings in rodents, as preencoding stress has been shown to enhance hippocampal-dependent memory for high arousal associations (contextual fear conditioning; Sandi & Pinelo-Nava, 2007; Shors, 2006). It is also possible that, for these high-arousal associations, participants perceived the associated image as an integrated component of the high-arousal stimulus (rather than a peripheral detail), allowing preencoding stress to potentiate the positive effects of stimulus-linked arousal on "within-object" binding (Mather, 2007).

Conversely, we found that postencoding stress enhanced item memory, although preencoding stress did not, suggesting that this effect relied on mechanisms directly associated with consolidation. Postencoding stress has frequently been shown to enhance item memory, particularly for high-arousal information, in both rodents (McGaugh, 2004; Roozendaal et al., 2006) and humans (Cahill et al., 2003; Segal et al., 2014; Smeets et al., 2008). Two parts of the stress response—the glucocorticoid response, or the faster-acting adrenergic response (or the interaction between the two; see Roozendaal et al., 2006)—may critically contribute to these item

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memory effects. The CPT has been shown to elicit both adrenergic and glucocorticoid responses (e.g., van Stegeren, Wolf, & Kindt, 2008). However, as we did not measure a proxy for adrenergic response (salivary α-amylase would have returned to baseline before we measured poststress saliva; e.g., Plessow, Schade, Kirschbaum, & Fischer, 2012), we cannot determine which component of the stress response drove item memory enhancement. In contrast to item memory, previously reported effects of postencoding stress on memory for associations are mixed. In rodents, posttraining injections of an anxiogenic drug (inducing an adrenergic response) into the amygdala impaired hippocampal-dependent spatial memory (Wingard & Packard, 2008), but posttraining injections of noradrenaline into the amygdala enhanced hippocampal-dependent object-in-context memory (Barsegyan, McGaugh, & Roozendaal, 2014). In humans, studies have reported no overall effects of postencoding stress on associative memory (Larra et al., 2014; McCullough & Yonelinas, 2013) dose-dependent effects of cortisol (McCullough et al., 2015), or impaired memory for neutral contexts, if there was a high adrenergic response during encoding (Goldfarb et al., 2017). However, the studies in humans to date either did not measure item memory (Goldfarb et al., 2017) or did not find significant group-level effects of stress on item memory (Larra et al., 2014; McCullough et al., 2015; McCullough & Yonelinas, 2013). By revealing that associative memory was unchanged even when item memory was significantly enhanced, the current results demonstrate the limits of memory enhancement because of postencoding stress in humans.

As the postencoding and preencoding stress lists were encoded consecutively, it is possible that the effects of acute stress were driven by stress-induced modulation of proactive or retroactive interference (Elzinga, Bakker, & Bremner, 2005). Although we cannot rule out this possibility, several features of the experimental design and results suggest that such effects are unlikely to explain the current findings. First, by measuring recognition, each memory test contains only within-list cues. This differs from free recall, a standard assessment for interference (Melton & von Lackum, 1941), as participants do not have the option of responding using memory for information from another list. Second, as each word and image is only presented once, recognition could not be influenced by interference from an overlapping pair studied in a different list (Guez & Naveh-Benjamin, 2016). Third, performance on the preencoding and postencoding stress lists were significantly positively correlated (online supplemental material Table 1), indicating that successful memory for one list, at a minimum, did not block memory for the other list. Finally, the finding that memory for both lists was enhanced relative to no stress, but that these effects were specific to different memory tests and arousal ratings, suggests that the effects of stress extend beyond what would have been predicted by changes in interference.

Preencoding and Postencoding Stress Effects Varied by Arousing Content of Memoranda

Consistent with previous work, we found that preencoding (Buchanan & Lovallo, 2001; Payne et al., 2007, 2006) and postencoding stress (Cahill et al., 2003; Segal et al., 2014; Smeets et al., 2008) each enhanced memory for high-arousal stimuli, although the type of memory varied. We observed this enhancement in two major ways. First, memory for high-arousal stimuli with stress was significantly better than memory for high-arousal stimuli with no stress. Second, within preencoding and postencoding stress, high-arousal stimuli were remembered significantly better than low-arousal stimuli.

Converging effects of acute stress and stimulus-induced arousal on the amygdala may drive the stress-induced enhancement of memory for arousing stimuli (Roozendaal & Hermans, 2017). Like the hippocampus, the amygdala is highly sensitive to the acute stress response (Roozendaal, McEwen, & Chattarji, 2009). The amygdala has also been shown to modulate the function of the hippocampus in response to stress. Research in rodents has demonstrated that electrolytic lesions (Kim et al., 2001) and injections of muscimol (Kim et al., 2005) into the amygdala prevented stress-induced impairment of hippocampal long-term potentiation (LTP), and blocked the impairing effects of preencoding stress on spatial memory. Other work in rodents has revealed that the amygdala plays a critical role in the enhancement of memory for high-arousal stimuli because of postencoding stress. Specifically, infusing propranolol into the amygdala blocked the stress-induced enhancement of memory for arousing items (Quirarte, Roozendaal, & McGaugh, 1997; Roozendaal et al., 2006). These studies, together with the amygdala's broader role in supporting emotional episodic memory (Phelps, 2006); particularly consolidation; (McGaugh, 2004) support the idea that stress near the time of encoding would exert effects on hippocampal memory via the amygdala.

The positive effects of preencoding stress in particular may be supported by stress-induced changes in attention and perception. Acute stress has been shown to orient attention toward threatening stimuli (Mogg, Mathews, Bird, & Macgregor-Morris, 1990), perhaps through engaging the "salience network," and to facilitate enhanced BOLD responses to affectively salient stimuli (Hermans, Henckens, Joëls, & Fernández, 2014). Preencoding stress may also amplify the "priority" automatically assigned to affectively salient stimuli, which could enhance perception as well as later memory (Mather & Sutherland, 2011). For postencoding stress, enhanced memory for arousing stimuli may be due in part to the adrenergic response during encoding (produced when processing high-arousal stimuli) interacting with later cortisol release (Roozendaal & Hermans, 2017). This adrenergic response may serve as a "tag" to promote preferential strengthening of these memories with postencoding stress (McIntyre, McGaugh, & Williams, 2012; Payne & Kensinger, 2018 but see Ritchey, McCullough, Ranganath, & Yonelinas, 2017 for discussion). As we did not measure the adrenergic response during encoding (instead focusing on stimulus-level subjective experiences of arousal), the interaction between adrenergic and glucocorticoid responses could not be directly tested in this experiment (see Segal et al., 2014 for evidence supporting this idea in humans). Enhanced memory for previously encountered experiences is consistent with a neurobiological account of memory consolidation, whereby new, labile memories can be "tagged" for later strengthening through LTP (Frey & Morris, 1997). Recent findings in humans have also reported that postencoding arousal manipulations can retroactively strengthen item memory (Dunsmoor, Murty, Davachi, & Phelps, 2015; Patil et al., 2017), although more work in humans is needed to understand the mechanism by which postencoding stress enhances high-arousal item memory.

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It is noteworthy that, in the current experiment, stimuli were sorted based on the *participant's* perception of the memoranda as arousing, in contrast to categorizing based on normed lists that were rated by others (as in many experiments in humans). Research in rodents has demonstrated that the effects of acute stress critically depend on the rodent's perception of the stimuli. For example, whether postencoding stress enhanced a rodent's memory for an object depended on the rodent's unique history with that object: if the object was novel to the animal at encoding and, thus, evoked an arousal response, memory was enhanced (Okuda et al., 2004; Roozendaal et al., 2006). Beyond individual items, we also found that participants who rated a higher proportion of stimuli as high arousal showed stronger memory modulation after postencoding and preretrieval stress. Future studies examining stress and stimulus-linked arousal in humans should consider such idiosyncratic perceptions of the memoranda.

Relationship Between Endogenous Cortisol and Memory Varied Based on Stressor Timing, Arousing Content of Memoranda, and Form of Memory Tested

The relationship between endogenous cortisol release and stress-modulated memory performance differed between item and associative memory and for low- and high-arousal pairs. We also found that the relationship between cortisol and memory was distinct based on whether the stressor occurred preencoding or postencoding. For item memory, there was a linear interaction between cortisol, arousal ratings, and stressor timing that predicted memory performance. For low-arousal pairs, higher cortisol predicted worse memory if the stressor occurred preencoding, whereas it predicted better memory if the stressor occurred postencoding. In contrast, for associative memory, the interaction was curvilinear. For high-arousal pairs, there was an inverted U-shaped relationship between cortisol and memory if the stressor occurred preencoding, but a U-shaped relationship if the stressor occurred postencoding.

Previous studies have also found distinct relationships between cortisol and memory performance based on the type of memory tested. Dating back to the study by Yerkes and Dodson, the effects of arousal intensity (in that study, shock) on performance have been shown to vary based on the difficulty of the task, with a linear relationship for an easy task and a quadratic relationship for a more challenging task (Yerkes & Dodson, 1908; see Gagnon & Wagner, 2016 for discussion). In the current experiment, although participants were above chance in item recognition (no stress: 72.7% accuracy) and associative recognition (object: 59.9%; specific: 36.1%), the associative recognition task was substantially more difficult. A recent study examining postencoding stress (McCullough et al., 2015) also reported a linear relationship between cortisol response and familiarity (that, like item recognition, involves perirhinal cortex), and a quadratic relationship between cortisol response and recollection memory. The researchers suggest that these patterns may be driven by differences in cortisol receptor density, with few receptors in cortical regions (supporting familiarity and item memory) and a high receptor density in the hippocampus (supporting recollection and associative memory, Eichenbaum et al., 2007).

Although previous work suggests that the relationship between cortisol response and associative recognition would be quadratic, the direction of this effect for postencoding stress in the current study ("U"-shaped, rather than "inverted-U"-shaped) was surprising. One important difference between this experiment and previous studies is that we computed both memory performance and cortisol response relative to each participant's own behavior with no stress. That is, we looked at the change in cortisol from pre- to poststress after accounting for any changes in cortisol elicited by task performance, and quantified memory relative to what the same participants remembered with no stress. With between-subjects designs, these baseline measurements are not available; thus, the cortisol response resulting from stress is directly associated with memory (without subtracting the cortisol response to the memory task, or memory performance with no stress). The current approach allowed us to control for subject-level characteristics that could influence cortisol reactivity, identify relationships between cortisol release and memory that were unique to pre- or postencoding stress, and ensure that between-subjects variability in memory performance did not drive our results. This novel approach also requires careful interpretation when comparing these results to prior studies. For example, we found that a *higher* cortisol response to postencoding stress (relative to no stress) predicted *better* associative memory. This is consistent with the middle of the "inverted-U," in which a moderate increase in cortisol after encoding facilitated associative memory (Andreano & Cahill, 2006; McCullough et al., 2015). Thus, it is possible that with a more intense stressor, and a higher cortisol response, we would also have observed impaired associative memory. We also found that participants who had a *lower* cortisol response to postencoding stress (relative to no stress) showed *better* associative memory. These findings could not have been discovered without an analysis approach that controlled for memory and cortisol reactivity in the absence of stress, and will need to be replicated in further studies.

Preretrieval Stress Impaired Performance Across Memory Tests

Unlike preencoding and postencoding stress, preretrieval stress impaired both item and associative recognition. Negative effects of preretrieval stress on memory have been demonstrated previously (Andreano & Cahill, 2006; McCullough et al., 2015), and direct effects of stress on MTL regions may explain some of these deficits. For example, injecting a glucocorticoid receptor agonist into the hippocampus impaired retrieval of a water-maze task (e.g., De Quervain et al., 2003), and cortisone-induced impairments in associative retrieval have been linked to decreased blood flow to the MTL (Roozendaal et al., 2004). However, these studies both examined memory for associations and, as we have emphasized, the neural substrates underlying item and associative memory differ. Furthermore, we found that the same type of stressor that impaired both item and associative memory when administered preretrieval had uneven effects on these two forms of memory when the stressor occurred pre- or postencoding. In addition, impairments in item recognition because of preretrieval stress extended across subjective arousal ratings. These results suggest that the mechanism by which preretrieval stress instigated this widespread deficit involved the disruption of additional cognitive processes governed by regions outside the MTL.

One such process is the control of retrieval, which is thought to rely on frontal-parietal networks that are more broadly recruited for executive control processes and decision-making (De Quervain et al., 2003). In particular, the prefrontal cortex (PFC)—and its interplay with the hippocampus—is thought to support control processes that support memory retrieval, such as elaborating on memory cues, suppressing interfering memories, and maintaining attention (Sestieri, Shulman, & Corbetta, 2017). Acute stress exposure, through both adrenergic and glucocorticoid mechanisms, is known to impair PFC function (Arnsten, 2009; McEwen, Nasca, & Gray, 2016). In addition, the PFC is especially involved in more difficult memory retrieval tasks (Eichenbaum, 2017; Kuhl & Wagner, 2009), and such tasks have been shown to be more sensitive to preretrieval stress (Gagnon & Wagner, 2016). Thus, it is possible that impairments in both item and associative memory with preretrieval stress in the current experiment may have resulted from a stress-induced disruption in control processes dependent on the PFC.

We found that preretrieval stress impaired item recognition regardless of arousal ratings, whereas the negative effects on associative recognition varied based on subjective arousal ratings (specific recognition) or was only significant after accounting for differences between arousal bins ("object"-level recognition). Research examining interactions between affective salience of stimuli and preretrieval stress effects are mixed, as some studies report that impairment is specific to arousing content (Domes et al., 2004; Kuhlmann, Piel, & Wolf, 2005; Smeets et al., 2008), whereas others report more general deficits (de Quervain et al., 2000; Schwabe & Wolf, 2014; see Gagnon & Wagner, 2016 for discussion). The current results suggest that, although the effects of preretrieval stress were negative for both item and associative memory, the importance of affective salience for modulating these effects may vary based on the type of memory assessed.

A limitation for conclusions regarding the effects of preretrieval stress concerns the timing of the salivary cortisol samples. Although cortisol levels post-CPT differed significantly between the preretrieval and no stress conditions, the timing of the poststress sample (36 min post-CPT) did not enable us to capture the peak salivary cortisol response (typically occurring 10–20 min post-CPT), raising the possibility that this stress response may have been smaller than the encoding CPT. However, the difference in sample timing between the encoding and retrieval sessions precludes direct comparison between responses to encoding and retrieval CPT exposures. It is also important to note that the peak levels of cortisol observed peripherally in the saliva and bloodstream may not correspond to peak levels of central cortisol acting in the brain. Indeed, stress-induced changes in hippocampal BOLD responses have been reported before significant plasma cortisol elevation (Sinha, Lacadie, Constable, & Seo, 2016). More research is needed to characterize the time-course of acute stress effects on item and associative memory.

Conclusion

The results presented here reveal that exposure to acute stress can have distinct effects on item and associative memory. Even within the same participants, if the stressor occurred before encoding, it specifically enhanced associative memory; if it occurred after encoding, it specifically enhanced item memory; and if it occurred before retrieval, it impaired both forms of memory. These effects were modulated not only by the timing of exposure to stress, but also by participants' perceptions of the memoranda as arousing. By exploring the influence of stress on associative as well as item memory, this experiment provides insight into the diverse effects of acute stress on what we learn and remember.

Context of the Research

Acute stress can profoundly influence what we learn and remember, yet predicting whether memory for a given type of information will be enhanced or impaired remains a complicated question. As most of our knowledge of stress effects in humans concerns memory for items, we started this collaboration to compare stress-related changes in memory for items and associations between items. This question built on our earlier work examining how acute stress influences memory for neutral contexts (requiring spatial associations between items), which revealed the importance of stressor timing and subjective arousal during learning (first and last author), and work demonstrating how the neural mechanisms supporting memory for associations change over time (second and third author). To maximize comparisons between stress effects, and push the boundaries of memory modulation within a single individual, we created a design in which all our manipulations—item and associative memory assessments, subjective arousal ratings, and acute stressor timing—were within-subject. The current findings help delineate the scope of acute stress effects, demonstrating key differences between effects on item and associative representations.

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