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Determining the biological associates of acute cold pressor post-encoding stress effects on human memory: The role of salivary interleukin-1β

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Abstract

Although stress generally hurts many aspects of memory, an interesting finding to emerge from the stress and memory literature is that stress that occurs shortly after learning (i.e., *post-encoding stress*) usually benefits memory. Although this effect is well established, the biological mechanisms underpinning this effect are not well characterized—especially in humans. We addressed this gap in the present study by collecting saliva samples from 80 participants who were randomized to a post-encoding stress (i.e., cold pressor for 3min) or control task (i.e., warm water for 3min) and 48hrs later completed a recognition memory task. Saliva was collected both prior to and 15min after the offset of (18min after the onset of) the stress/control manipulation. Drawing on animal and human work, we examined how five stress-responsive biomarkers—cortisol, salivary α-amylase, progesterone, estradiol, and the proinflammatory cytokine interleukin (IL)-1β, all assessed in saliva—related to the effects of stress on memory. We found that stress enhanced recollection of negative images and these effects were selectively related to salivary IL-1β. Moreover, we found that the beneficial effects of stress on memory were statistically mediated by salivary IL-1β. We found no associations with any other biomarker, either linearly or quadratically, nor did we find significant interactions between biomarkers in predicting memory. These results suggest that immune system activity indexed by salivary IL-1β may play an important role in contributing to post-encoding stress effects on human memory.

Keywords

stress; memory; cytokines; cortisol; sex hormones

1. Introduction

Stress affects memory (de Quervain et al., 1998; Schwabe et al., 2012). This simple fact, often experienced in everyday life, has spawned a plethora of studies aimed at understanding the underlying mechanisms. One particularly surprising finding that has come out of this

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work is that exposure to acute stress *after* encoding has ended (post-encoding stress) typically enhances memory (e.g., Cahill et al., 2003; Shields et al., 2017; for review, see Sazma et al., 2019). The reasons for this post-encoding stress effect are not entirely clear, though cortisol has been hypothesized to play a central role (e.g., de Kloet et al., 1999; Finsterwald and Alberini, 2014; McGaugh, 2000; Roozendaal, 2002; Schwabe et al., 2012). However, as we describe below, the idea that cortisol plays a central role in producing the memory benefit does not explain all results observed in prior work. Therefore, in this study, we attempted to elucidate the biological correlates of post-encoding stress effects on memory in humans in order to help determine the role cortisol and a number of other hormones and immune system processes play in effects of post-encoding stress on memory.

The glucocorticoid (“stress hormone”) cortisol is often at the forefront of any discussion of stress effects on memory (de Quervain et al., 1998; Schwabe et al., 2012). Work with rodents has shown that post-encoding administration of the glucocorticoid stress hormone corticosterone—analogous to cortisol in humans—can enhance memory (McGaugh, 2015; Sazma et al., 2019b). These effects thus parallel the timecourse and effects of post-encoding stress on memory in humans: stress after learning upregulates cortisol, and post-encoding stress enhances memory much as corticosterone administration does in rodents (McGaugh, 2000; Roozendaal and McGaugh, 1997). Despite this, some empirical findings are inconsistent with the idea that cortisol is responsible for the effects of post-encoding stress on human memory. For example, a recent meta-analysis found that post-encoding stress effects on cortisol were not related to post-encoding stress effects on memory across studies (Shields et al., 2017). Additionally, the effects of post-encoding stress on memory appear to differ from the effects of post-encoding glucocorticoid administration on memory (Sazma et al., 2019b). Therefore, cortisol may not be solely responsible for the effects of post-encoding stress on memory.

One often underappreciated component of the stress response is modulation of the immune system. For example, circulating and salivary concentrations of proteins used by immune system cells to communicate and that coordinate the inflammatory response—proinflammatory cytokines—increase following stress (Marsland et al., 2017; Segerstrom and Miller, 2004; Slavish et al., 2015). Recently, the role of these proteins in learning and memory has become clear, as they contribute to memory processes such as long-term potentiation and synaptic plasticity under normal conditions in rodents (Donzis and Tronson, 2014; Yirmiya and Goshen, 2011). The proinflammatory cytokine IL-1β, in particular, has been studied in this context because of its effects on memory in rodents when administered post-encoding (i.e., after learning) (Goshen et al., 2007; Huang and Sheng, 2010; Pugh et al., 2001). For example, intracerebroventricular administration of a small dose of IL-1β post-encoding enhances memory, whereas administration of a large dose of IL-1β or an IL-1β receptor antagonist impairs memory in mice (Goshen et al., 2007). Moreover, much like stress, IL-1β appears to selectively modulate hippocampus-dependent memory without influencing hippocampus-independent memory in rats (Pugh et al., 2001). Because stress modulates IL-1β, therefore, it is possible that post-encoding stress acts through IL-1β to affect memory.

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In addition to impacting cortisol and the immune system, acute stress also modulates the sympathetic-adrenal-medullary (SAM) axis, the hypothalamic-pituitary-gonadal (HPG) axis (Lennartsson et al., 2012), and other catecholaminergic systems (Arnsten, 2009). Moreover, hormones and proteins involved in each of those systems are known to have effects on memory. For example, the sex hormones estradiol and progesterone, both previously found to be upregulated by acute social stress (Childs and De Wit, 2009; Lennartsson et al., 2012), also retroactively enhance memory when administered post-encoding (Barros et al., 2015; Inagaki et al., 2010). Importantly, acute stress modulates these systems differently across people (e.g., Engert et al., 2013). This symphony of hormone and protein interactions that varies across individuals may complicate effects of post-encoding stress on memory, which may explain why some evidence suggests that cortisol alone is insufficient to account for effects of post-encoding stress on memory.

1.1. Current Research

Much research has established that acute stress after learning retroactively enhances memory for that learned information, but the biological mechanisms behind this effect are relatively unclear. To address this gap, we randomly assigned 40 people to an acute stress induction and 40 people to a control task after they completed an encoding task that consisted of viewing both negative and neutral images. We collected saliva samples both immediately pre- stressor and 15min post-stressor offset in order to determine baseline and reactivity levels of analytes of interest, respectively. After a 48hr delay, participants returned to the lab to complete a surprise memory test. Although our analytes of interest follow different time-dependent response curves to stress, we collected the reactivity saliva sample at 15min post-stressor because prior work indicated that each of these analytes should be elevated at this time in at least some stressor paradigms (Childs and De Wit, 2009; Dickerson and Kemeny, 2004; Dugué et al., 1996; Gassen et al., 2019; Herrera et al., 2019; Lennartsson et al., 2012; Mastrolonardo et al., 2007; Moons and Shields, 2015; Skoluda et al., 2015), with the possible exception of salivary α-amylase (see Skoluda et al., 2015, who found that this marker was elevated 15min post-stressor for some stressors but not others). It should be noted, however, that to date no study has eamined the effects of the cold pressor on estradiol or salivary IL-1β, so it is currently unclear whether the cold pressor will exert a significant influence on these markers 15min post-offset. Drawing on animal work, we considered cortisol, salivary α-amylase (sAA; a marker for norepinephrine; Ditzen et al., 2014; Thoma et al., 2012), estradiol, progesterone, and the proinflammatory cytokine interleukin (IL)-1β as potentially important predictors of the effects of post-encoding stress on memory. The primary aim of the study was to determine how these biomarkers related to stress-induced enhancements in memory. To assess this, we examined recollection and familiarity for both negative and neutral materials because previous studies have suggested that magnitude of stress effects may vary across these factors (Cahill et al., 2003; McCullough and Yonelinas, 2013; Sazma et al., 2019a).

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2. Method

2.1. Participants

80 (42 female) young adults (M_{age} = 19.96, SD_{age} = 1.90, range: 18 – 26) attending a large university on the west coast of the United States participated in this study in exchange for extra course credit. A sample size of 80 was chosen because it provided approximately 80% power to detect correlations moderate in magnitude (i.e., correlations of $r = .30$ or above) in a two-tailed test. Notably, a prior power analysis showed that only 70 participants (35 per group) were required to achieve 80% power to detect effects of post-encoding stress on memory under the conditions of this study (Shields et al., 2017).

We only invited participants without a current illness, diabetes, history of stroke, neurological disorders, current or former diagnosis of posttraumatic stress disorder, hospitalization for a psychiatric disorder within the past year, current injury or illness within the past week, major sleep disturbances within the past six weeks, or consumption of more than eight caffeinated beverages a day. Similarly, individuals who were pregnant, nursing, on any form of medication (including hormonal birth control or asthma medication) or illegal drugs, had taken any mood-altering medications within the past two months, or had taken oral or injected corticosteroids within the past three months were not invited to participate. Participants were instructed not to eat, drink anything besides water, use tobacco, brush their teeth or floss, or engage in any exercise for two hours prior to the start of the study. Compliance with these instructions and inclusion criteria (e.g., no brushing/flossing teeth within the past two hours, no illnesses, drug use, or hormonal contraceptive use) was assessed using a self-report questionnaire at the beginning of the study.

Male and female participants were separately randomly assigned to the stress and control conditions, resulting in a condition composition of 20 males and 20 females in the control condition, and 18 males and 22 females in the stress condition. Of the 80 participants, 50% identified as Asian American/Asian, 25.7% as Hispanic, 18.9 as non-Hispanic White, 4.1% as Black/African American, and 1.4% as American Indian/Alaskan Native.

2.2. Materials

2.2.1. Memory task.—Participants completed an incidental encoding task and returned 48 hours later for a surprise memory retrieval task.

2.2.1.1. Encoding.: In the encoding task, participants viewed a series of 120 sequentially presented images (60 negative, 60 neutral) selected from the International Affective Picture System (Lang et al., 2008). Participants were told that their task was to rate each image's "visual complexity" using a 1(*not at all complex*) to 6(*very complex*) scale. The visual complexity ratings were obtained to ensure participants attended to each image in an incidental encoding paradigm; these responses were not analyzed. Images were presented in a randomized order for each participant. Each trial began with a fixation cross, which was presented for 600ms and then was removed for another 400ms. Each image was then presented for 800ms, after which time the image was removed from the screen and the response scale was presented for up to 2000ms. Participants were able to provide their

judgments of visual complexity for the preceding image during this response window, and the trial finished after either the participant responded with the judgment of visual complexity or the scale had been presented for the full 2000ms.

2.2.1.2. Retrieval.: Participants completed the retrieval task 48hrs after the encoding task. Participants were presented with a randomized list of studied (60 negative, 60 neutral) and new (60 negative, 60 neutral) images and were asked to rate their memory for each image. Participants rated each picture on a 1–5 or Recollect scale. Participants were told to classify a picture as "Recollect" only if they could provide episodic or contextual details regarding their memory of first seeing the picture. Participants classified any picture that was not recollected on a 1–5 scale, where "5" expressed high confidence that the picture was studied (but without recollecting details about the experience), and "1" expressed high confidence that the picture was new. The first 16 test trials were practice trials in which participants made memory judgements and verbally justified each response to the experimenter in order to ensure that each participant understood the test instructions. Each trial began with a blank screen, presented for 1000ms, followed by a fixation cross, presented for 600ms, and then a blank screen, presented for 400ms and then was removed for another 400ms. Each picture was then presented for 2000ms, after which time the response scale appeared and participants were given unlimited time per picture to provide a response.

2.2.2. Stress manipulation.—Participants completed either the cold-pressor task or a lukewarm water control task depending upon their assigned condition. In the stress condition, each participant submerged his/her nondominant arm up to the wrist joint in ice water ($M = 2.93$°C) while being observed by the experimenter who held a clipboard, pen, and paper. Participants were told that they were not to touch the bottom of the ice water container and that they were not allowed to make a fist during the task. In the control condition, each participant submerged his/her nondominant arm up to the wrist joint in lukewarm water ($M = 27.91$°C) with the experimenter out of the participant's view. In both conditions, each participant was instructed to keep his/her arm in the water for a full 3min. After 3min had elapsed, each participant was instructed to remove his/her arm from the water, provided with paper towels, and given 30sec to dry his/her arm.

2.2.3. Negative affect (PANAS).—To verify the effectiveness of the stress manipulation, negative affect was assessed using the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). Participants were asked to report the extent to which they currently felt 10 negative and 10 positive emotions (20 items total). Responses to each item were provided on a 1 (*Very slightly or not at all*) to 5 (*Extremely*) scale, and responses to the 10 questions assessing negative affect were then averaged to create an overall index of negative affect, with higher scores indicating more negative affect. Internal consistency for the scale was good both pre- and post- manipulation, αs .87.

2.3. Saliva Assays

Unstimulated saliva was collected via passive drool and stored at –20°C until batch assayed. All saliva samples were assayed for cortisol, salivary α-amylase (sAA), progesterone, estradiol, and salivary interleukin-1β (sIL-1β) using commercially available ELISA kits

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from Salimetrics (high sensitivity kits were used when available, i.e., for cortisol and estradiol). Batch assays of cortisol, progesterone, estradiol, and sIL-1β were conducted in the Behavioral Neuroendocrinology Lab at UC Davis by G.S.S. and T. D. after the study was completed. Salivary α-amylase was batch assayed in the Clinical Endocrinology Lab at UC Davis after the study was completed. Four participants did not provide enough saliva to assay all analytes at both timepoints; for each of these participants, we selected which analytes we would assay based upon the sample volume needed for assay; these are described below. Samples below detectable limits for each assay were imputed with zero; excluding these samples did not influence any of the results.

2.3.1. Cortisol.—The intra- and inter-assay coefficients of variation (CVs) for cortisol were 5.58% and 7.63%, respectively. All controls were in the expected ranges. No sample fell outside the lower or upper limit of detection. Assay sensitivity was < 0.007μg/dL; values are presented in nmol/L. All participants were assayed for cortisol.

2.3.2. sAA.—The intra- and inter-assay CVs for sAA were 4.85% and 2.44%, respectively. All controls were in the expected ranges. No sample fell outside the lower or upper limit of detection. Assay sensitivity was 0.4U/mL; values are presented in U/mL. All participants were assayed for sAA.

2.3.3. Progesterone.—The intra- and inter-assay CVs for progesterone were 9.05% and 10.64%, respectively. All controls were in the expected ranges. Two samples fell below the lower limit of detection. Assay sensitivity was 5pg/mL; values are presented in pg/mL. Due to insufficient saliva, three participants were not assayed for progesterone.

2.3.4. Estradiol.—The intra- and inter-assay CVs for estradiol were 7.36% and 7.77%, respectively. All controls were in the expected ranges. Assay sensitivity was 0.1pg/mL; values are presented in pg/mL. Three samples fell below the lower limit of detection. Due to insufficient saliva, two participants were not assayed for estradiol.

2.3.5. Salivary interleukin-1β.—The intra- and inter-assay CVs for sIL-1β were 4.20% and 2.68%, respectively. All controls were in the expected ranges. No sample fell outside the lower or upper limit of detection. Assay sensitivity was < 0.37pg/mL; values are presented in pg/mL. Due to insufficient saliva, two participants were not assayed for IL-1β.

2.4. Procedure

Figure 1 depicts the study procedure. After arriving at the lab, participants provided informed consent and then acclimated to the testing environment for 10min. Participants then completed the memory encoding task described above. After completing the encoding task, participants completed the baseline affect questionnaire described above and subsequently provided the baseline saliva sample. Then, participants completed the stress or control task depending upon their randomly assigned condition. Participants then completed the post-manipulation affect questionnaire before waiting 15min post-manipulation offset (18min post-stress/control onset) to provide the post-manipulation saliva sample. During the 15min waiting period participants were offered short pre-selected articles to read if they

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chose to do so. After the post-manipulation saliva sample was collected, participants were dismissed for the day and told to return in 48 hours to complete the study. Upon returning to the lab 48 hours later, participants were again provided 10min to acclimate before completing the memory retrieval task described above. After completing the memory retrieval task, participants were thanked, debriefed, and dismissed. All materials and procedures were approved by the university's Institutional Review Board.

2.5. Data Reduction and Analysis

2.5.1. Memory.—A dual-process model of recognition memory was fit to the recognition memory data using standard confidence-based receiver operator characteristic (ROC) procedures (Yonelinas, 2002). In this model, participants are assumed to respond "old" to an old item if it is either recollected (R), or if the familiarity of the item exceeds the participant's response criterion (F_o) when the item is not recollected. Mathematically, then, Hits = $R + (1 - R)F_o$. Participants are assumed to respond "new" to a new item whenever the item's familiarity exceeds the participant's response criterion (F_n); mathematically, false alarms = F_n. Familiarity is assumed to be described by signal detection theory, which means that the proportion of old and new items that will be labeled "old" is equal to the proportion of those items that exceed the participant's response criterion at a given level of confidence. Mathematically, $F_o = \Phi(d'/2 - c_i)$ and $F_n = \Phi(-d'/2 - c_i)$, where d' is the distance between the old and new Gaussian familiarity distributions. These equations can be combined into a single equation for each level of confidence, $p(\text{"old"}|\text{old})_i = R + (1 - R)\Phi(d'/2 - c_i) + p(\text{"old"}|\text{new})_i - \Phi(-d'/2 - c_i)$, and this equation was fit to each participant's observed ROC using maximum likelihood estimation, providing estimates of recollection (R) and familiarity (d'). Notably, analyzing the memory data as d' at various confidence points produced equivalent results for both the effects of stress on memory and associations between memory and analytes.

2.5.2. Salivary analytes.—Because of skew, salivary analytes values were log transformed prior to analyses. Residualized change scores were calculated for use in analyses examining associations between the analytes and memory; residualized changes were used instead of simple change scores because residual change scores are more reliable than simple change scores (Cronbach and Furby, 1970). Residualized changes in each analyte were calculated by regressing each log-transformed post-manipulation analyte on the corresponding log-transformed pre-manipulation analyte. Analyses using simple change scores were similar.

2.5.3. Analytic strategy.—All analyses were conducted in R, version 3.5.1. Condition by Time interactions were examined in repeated measures ANOVAs in the car package, version 3.0–2. Reported means and standard errors are estimated marginal means and standard errors, estimated using the emmeans package, version 1.3.2. Bayesian analyses—producing Bayes factors—were conducted in the BayesFactor package, version 0.9.12–2. A Bayes factor of BF_{10} quantifies the evidence in favor of the alternative hypothesis relative to the null hypothesis; for example, $BF_{10} = 2.0$ entails that the data were twice as likely to have been observed under the alternative hypothesis as the null hypothesis. By convention, a Bayes factor BF_{10} less than .33 indicates substantial evidence in favor of the null hypothesis,

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whereas a BF_{10} greater than 3.0 indicates substantial evidence in favor of the alternative hypothesis, and a BF_{10} less than .10 or greater than 10.0 indicates strong evidence in favor of the null and alternative hypotheses, respectively. Associations between memory and analyte values are presented both as bivariate correlations and as linear models controlling for age, sex, BMI, and race/ethnicity.

3. Results

3.1. Preliminary Analyses

3.1.1. Effects of stress on analytes.—We first examined whether our stress manipulation altered levels of each analyte in repeated measures ANOVAs examining Stress (i.e., experimental condition) by Time interactions. As expected, we found significant Stress × Time interaction effects for cortisol, $F(1, 77) = 25.73$, $p < .0001$, progesterone, $F(1, 74) = 4.19$, $p = .044$, and IL-1β, $F(1, 75) = 4.92$, $p = .030$ (see Figure 2). Surprisingly, however, we did not find significant Stress × Time interaction effects on estradiol, $F(1, 75) = 0.07$, $p = .799$, or sAA, $F(1, 77) = 3.41$, $p = .140$ (Figure 2). In addition, we did not find any significant Sex × Stress × Time interactions, ps > .164. Table 1 provides the raw (untransformed) mean and standard errors for each analyte pre- and post-manipulation by condition.

Decomposing the observed interactions (see also Figure 2), for cortisol, we found that participants in the stress and control conditions did not differ at baseline, $t(77) = -1.12$, $p = .267$, but participants in the stress condition significantly increased in cortisol following the manipulation, $t(77) = 5.66$, $p < .0001$, $d_z = 0.65$, whereas participants in the control condition nonsignificantly decreased, $t(77) = 1.59$, $p = .116$, $d_z = -0.18$. Similarly, for progesterone, participants in the stress and control conditions did not differ in progesterone at baseline, $t(74) = -0.43$, $p = .667$, but participants in the stress condition significantly increased in progesterone following the manipulation, $t(74) = -2.86$, $p = .006$, $d_z = 0.33$, whereas participants in the control condition nonsignificantly decreased, $t(74) = 0.11$, $p = .913$, $d_z = -0.01$. Somewhat surprisingly, for sIL-1β, although participants in the stress and control conditions did not differ at baseline, $t(75) = 0.48$, $p = .636$, participants in the stress condition nonsignificantly decreased in sIL-1β following the manipulation, $t(75) = 0.51$, $p = .610$, $d_z = -0.06$, whereas participants in the control condition significantly increased in sIL-1β, $t(75) = 2.56$, $p = .013$, $d_z = 0.30$.

3.1.2. Effects of stress on negative affect.—We also examined whether the stressor increased negative affect from pre- to post-manipulation in a Stress × Time repeated measures ANOVA. As expected, we found a significant Stress × Time interaction, $F(1, 72) = 12.32$, $p < .001$. Decomposing this interaction, we found that although the stress condition ($M = 1.74$, $SE = 0.12$) did not differ from the control condition ($M = 1.79$, $SE = 0.13$) in negative affect at baseline, $t(72) = 0.27$, $p = .789$, $d = -0.04$, the stress condition ($M = 1.89$, $SE = 0.11$) reported significantly more negative affect than the control group ($M = 1.41$, $SE = 0.11$) post-manipulation, $t(72) = 3.07$, $p = .003$, $d = 0.51$. Thus, our stress manipulation successfully induced stress relative to our control group.

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3.2. Effects of Post-Encoding Stress on Memory

We first examined whether post-encoding stress produced the typical enhancement in memory relative to a control group in a Stress × Valence mixed ANOVA for estimates of recollection and familiarity. For recollection, as expected, we found a significant main effect of Valence, $F(1, 78) = 6.05$, $p = .016$, a significant main effect of Stress, $F(1, 78) = 8.10$, $p = .006$, and a Stress × Valence interaction, $F(1, 78) = 4.37$, $p = .040$. Simple effect analyses indicated that negative items were recollected more than neutral items, $t(78) = 2.46$, $p = .016$, and that participants in the stress condition recollected more items than those in the control condition, $t(78) = 2.85$, $p = .006$. Decomposing the Stress × Valence interaction, participants in the stress condition had significantly better recollection of negative items ($M = .271$, $SE = .029$) than participants in the control group ($M = .137$, $SE = .029$), $t(78) = 3.22$, $p = .002$, $d = 0.72$, $BF_{10} = 17.89$ (Figure 3a), but—although the difference was in the same direction as in negative items—participants in the stress group did not significantly differ in recollection of neutral items ($M = .178$, $SE = .024$) from participants in the control group ($M = .129$, $SE = .024$), $t(78) = 1.42$, $p = .161$, $d = 0.32$, $BF_{10} = 0.55$ (Figure 3b). Familiarity, in contrast, showed no effects of stress on memory performance, ps > .169, indicating that the effects of post-encoding stress on memory were restricted to hippocampus-dependent memory (i.e., recollection) in this study. There was no evidence that the effects of stress on recollection were moderated by sex, ps > .729.

3.3. Associations between Analytes and Memory Performance

Given the selective effects of stress on recollection of negative items, we next examined how the assayed analytes were related to recollection of those items. We found significant associations between recollection and changes in sIL-1β, $r(74) = -.404$, $p < .0001$, $BF_{10} = 119.47$ (Figure 4a), and changes in sAA, $r(76) = -.230$, $p = .042$, $BF_{10} = 1.76$ (Figure 4b). Notably, a BF_{10} of 119.47 indicates that the association of negative image recollection with sIL-1β was considered "extreme" evidence in favor of the alternative hypothesis (with the alternative hypothesis being over 119 times more likely than the null hypothesis), but a BF_{10} of 1.76 indicates that the association of negative image recollection with sAA was only "anecdotal" evidence in favor of the alternative hypothesis. We found no significant associations between recollection of negative images and changes in cortisol, $r(73) = .140$, $p = .221$, $BF_{10} = 0.52$, progesterone, $r(73) = .113$, $p = .335$, $BF_{10} = 0.41$, or changes in estradiol, $r(74) = -0.01$, $p = .916$, $BF_{10} = 0.26$, with substantial evidence in favor of the null in the association with estradiol. Similarly, in a regression model including all analytes predicting recollection of negative materials, only changes in sIL-1β emerged as a significant predictor of negative image recollection, $\beta = -.395$, $t(68) = -3.66$, $p < .001$; no other analyte was significantly related to negative image recollection, ps > .111.

We next examined whether any of the analytes were related to recollection of negative images in a nonlinear manner. We found that changes in sIL-1β showed a significant quadratic association with recollection of negative images, $\beta_{linear} = -.516$, $p_{linear} < .0001$, $\beta_{quadratic} = .244$, $p_{quadratic} = .040$, $R^2 = .211$ (Figure 4a). This quadratic function essentially describes a leveling off: participants with decreases to small increases in sIL-1β show an inverse association between recollection of negative images and sIL-1β, whereas participants have almost no recollection of negative images at larger increases in sIL-1β. (Figure 4a). To

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determine if far-right case of sIL-1β influenced this observed quadratic association, we excluded this case and re-ran the analysis. Excluding this case did not alter the quadratic association between sIL-1β and negative image recollection: sIL-1β remained significantly associated, $\beta_{linear} = -.434$, $p_{linear} = .0001$, $\beta_{quadratic} = .239$, $p_{quadratic} = .026$, $R^2 = .216$. No other analyte was associated with negative image recollection in a quadratic function, $ps_{quadratic} > .283$.

We also examined whether cortisol was related to recollection through interactions with sAA or sIL-1β. We found no evidence for any of these associations, ps > .401.

Next, we attempted to determine if the above patterns held while controlling for relevant covariates (i.e., age, sex, race/ethnicity, and BMI). In these adjusted analyses, sIL-1β remained a significant predictor of recollection of negative materials, $\beta = -.478$, $p < .001$, whereas no other analyte (including sAA) was associated with recollection of negative materials, ps > .212. In addition, the quadratic association between sIL-1β and recollection of negative materials remained significant, $\beta_{linear} = -.609$, $p_{linear} < .001$, $\beta_{quadratic} = .298$, $p_{quadratic} = .029$.

Finally, we conducted mediation analyses to determine whether sIL-1β statistically mediated the effects of post-encoding stress on memory. We restricted these analyses to sIL-1β because this was the only analyte to both be significantly affected by stress and relate to recollection of negative images. We found that sIL-1β significantly statistically mediated the effect of stress on recollection of negative images, $b = -0.032$, $p = .034$, accounting for 21.1% of the total effect of stress on recollection of negative images (proportion mediated = 0.211, 95% CI [0.014, 0.575]). There was no evidence that any of the other analytes had any indirect effect from stress to recollection, ps > .221.

We present additional analyses, examining associations between memory and each analyte by condition (e.g., in the stress condition alone), within the Supplemental Material for the interested reader.

4. Discussion

Stress shortly after learning generally enhances human memory (Joëls et al., 2011; Schwabe et al., 2014, 2012, 2010; Shields et al., 2017), but the biological associates of this effect are inconsistent (Shields et al., 2017). Drawing on prior animal and stress work, we examined associations between five analytes previously found to be stress responsive and memory performance in a post-encoding stress study. As expected, our post-encoding stress manipulation enhanced memory—specifically, recollection of negative images—and this enhancement was statistically mediated by effects of stress on salivary IL-1β. Although these results are correlational, they suggest that salivary IL-1β 15min post-stressor offset may be more closely linked to recollection than other stress-responsive analytes at this same time post-stressor, therefore providing justification for studies experimentally manipulating levels of this analyte in humans.

Although we found expected stress effects on cortisol and progesterone, salivary IL-1β decreased in response to the cold pressor—rather than increased, as we had expected. It

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should be noted, however, that although our prediction of a stress-induced sIL-1β increase was based on prior work showing that social and emotional stressors increase sIL-1β (Dias and Neto, 2017; Maydych et al., 2018; Shields et al., 2016), to date no study has examined how the cold pressor or other pain-based stressors influence sIL-1β—or, to our knowledge, IL-1β. Moreover, and importantly, different stressors influence different components of the stress response in different ways (Skoluda et al., 2015). At least two studies have examined salivary inflammatory markers in response to pain-based stressors and—similar to our study—have found these salivary inflammatory markers decreased following those stressors (Goodin et al., 2012a, 2012b). The answer to why this occurs, and why our stress condition evidenced a decrease from baseline and relative to our control condition, may be related to salivary cytokine responses to stress reflecting redistribution of immune system resources rather than de novo synthesis (Shields et al., 2016). In particular, it is possible that in response to pain-based stressors, immune system resources are diverted to the site of pain, resulting in a reduction in salivary cytokine levels relative to the control condition. Alternatively, because ice is commonly used to reduce inflammation, it is possible that the cold pressor task decreases IL-1β for this reason; to our knowledge, no study has examined blood IL-1β in response to the cold pressor. Future studies should investigate the mechanisms through which the cold pressor reduces salivary IL-1β.

In contrast, our control condition increased in sIL-1β from baseline to the post-manipulation assessment. This increase is not unexpected given the characteristics of our memory paradigm. In particular, the negative pictures used in the encoding task are highly aversive, and simple presentation of these pictures is a potent induction of anxiety and disgust (Caseras et al., 2007; Lang et al., 1993; Mikels et al., 2005; Schienle et al., 2005). Importantly, inductions of both disgust and anxiety upregulate salivary levels of proinflammatory cytokines, including sIL-1β (Dickerson et al., 2004; Moons and Shields, 2015; Shields et al., 2016). Therefore, it is expected that participants in our control condition would evidence an increase in sIL-1β from immediately prior to the encoding task to 23min post-encoding, because our memory encoding task is an anxiety/disgust induction. This small increase in sIL-1β brought about by disgust/anxiety may itself impair memory (e.g., Barrientos et al., 2002), and the blunting of this increase by the cold pressor may facilitate the better memory seen in the stress induction condition.

Our most interesting result was the statistical mediation of the effects of stress on memory by sIL-1β. In particular, stress decreased sIL-1β and improved recollection of negative images, and greater increases in sIL-1β from pre- to post-manipulation were strongly inversely associated with recollection of negative images. To our knowledge, this is the first study that has shown that the immune system may play a role in the effects of post-encoding stress on human memory. These results are in agreement with animal literature, which has frequently found that IL-1β administration impairs memory retention (Donzis and Tronson, 2014; Goshen et al., 2007; McAfoose and Baune, 2009), specifically for hippocampus-dependent memory (Barrientos et al., 2002; Czerniawski et al., 2015; Pugh et al., 2001).[1] This comparison must be made with caution, because these rodent studies examined effects

[1]It should be noted that this literature is not completely straightforward; in particular, one study (Goshen et al., 2007) found that a small post-encoding dose of IL-1β enhanced hippocampus-dependent memory, whereas seven others (Barrientos et al., 2002, 2004;

of hippocampal IL-1β whereas we examined associations of salivary IL-1β and memory, and salivary and circulating levels of IL-1β are not strongly correlated because IL-1β is too large to pass through the salivary ducts easily (Riis et al., 2014); nonetheless, the similarity of effects is notable. Regardless, our results suggest that salivary IL-1β may have an important but largely unconsidered role in human memory performance, even if only as a distal indicator for more central immune system processes (see also Harrison et al., 2014). At the very least, future studies attempting to understand the biological mechanisms underpinning the effects of post-encoding stress on memory should consider IL-1β or sIL-1β.

Salivary IL-1β is an index of immune system function (e.g., interleukins are proteins through which immune system cells present in the mouth communicate), though some have argued that salivary IL-1β indexes local immune system function rather than systemic, central, or circulating immune system function (e.g., Riis et al., 2014). However, sleep deprivation (El-Sheikh et al., 2007), early adversity (Tyrka et al., 2015), acute stress (Slavish et al., 2015), and obesity (Goodson et al., 2014) all modulate levels of salivary cytokines—such as IL-1β—in the same way as they modulate levels of cytokines. Moreover, salivary cytokines such as IL-1β are higher in individuals suffering from various diseases—such as rheumatoid arthritis (Mirrielees et al., 2010), lung cancer (Koizumi et al., 2018), and asthma (Little et al., 2014)—and these levels decrease with systemic anti-cytokine treatment (Mirrielees et al., 2010). Therefore, although salivary IL-1β indexes local immune system activity, it provides at least a window into systemic immune system activity. In our data, this window indicates that immune system activity may play a role in the effects of post-encoding stress on memory.

Somewhat surprisingly, we found that two out of five of our assessed analytes (i.e., estradiol and salivary α-amylase) were unaffected by stress in our paradigm. The reasons behind this lack of effect are unclear, but we can speculate. In the case of estradiol, prior work demonstrating that this analyte increased in response to stress examined these effects in blood, and in the context of social stress (Lennartsson et al., 2012). Our stressor was a pain-based stressor (i.e., the cold-pressor task), and we assessed estradiol in saliva rather than blood. One intriguing possibility is that estradiol responds to social stress in particular, rather than psychological stress in general (see also Skoluda et al., 2015); alternatively, it is possible that estradiol levels in saliva take longer than 18min to respond to stress. Conversely, the lack of a significant effect of stress on salivary α-amylase, may have arisen because this analyte decreased back to normal by the 15min post-stressor saliva sample (e.g., Hidalgo et al., 2014). Future research should address these possibilities.

Limitations and Future Directions

This study has numerous strengths, including an appropriate sample size determined *a priori* by a power analysis, sensitive quantification of recognition memory performance and its component processes via computational modeling, and assessment of numerous stress-relevant biomarkers spanning multiple stress-responsive systems. Nonetheless, some limitations of this study should be noted. First, the sample was a healthy young adult

Pugh et al., 1999; Thomson and Sutherland, 2005, 2006; Song et al., 2004; Yirmiya et al., 2002; reviewed by Huang and Sheng, 2010) found that small post-encoding doses of IL-1β either exerted no effect on or impaired hippocampus-dependent memory.

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sample, and it is possible that some of the effects and associations we observed here may differ in other populations. Second, basal measures of immune system activity do not correlate well between saliva and blood (Riis et al., 2014; Williamson et al., 2012), so correlations observed with salivary IL-1β should be considered with caution. Third, although we required participants not to eat, brush their teeth, or floss for two hours prior to the study, we did not assess oral health. This is a limitation of the current study, because oral health can influence basal salivary cytokine concentrations (Slavish et al., 2015; cf. Shields et al., 2019). Importantly, however, although oral health influences basal sIL-1β levels, prior work has found that oral health does not alter sIL-1β *responses* to acute stress (Newton et al., 2017) or the sIL-1β/sIL-10 ratio in response to acute stress (Szabo et al., 2016). Moreover, we know of no reason to expect that oral health could account for the statistical mediation of the effect of stress on memory through changes in sIL-1β. Therefore, we know of no reason to expect that controlling for oral health would have in any way altered our observed results. Fourth, and similar to the above, illnesses were self-reported, entailing that participants may have completed the study while sick if they lied. However, we have no reason to expect that this possibility altered the effects of stress on memory, the assayed analytes, or the statistical mediation.

In addition, although we assessed numerous analytes, we could not assess all potentially relevant hormones and biomarkers (e.g., dehydroepiandrosterone; Sripada et al., 2013), and so there may be important associations and/or interactions that we failed to quantify. For example, the overall activity of IL-1β is critically dependent on the balance between IL-1β and IL-1 receptor antagonist (IL-1ra), and it is possible that stress altered IL-1ra in a different way than it did IL-1β. For this reason and others, our results should be interpreted as showing that the effects of stress on immune processes—reflected in changes in salivary IL-1β—play a role in the effects of post-encoding stress on human memory. Importantly, though, our results are the first to show this.

Finally, we only assessed each analyte at one timepoint, which may have failed to capture each analyte's peak response as well as important information about analyte recovery. It is possible, for example, that greater a cortisol response at 30min post-stressor would be associated with better memory, without cortisol responses at 15min post-stressor being associated with memory. Our study was an appropriate step to determine the biological associates of the post-encoding stress effect on memory, and we determined that IL-1β changes from baseline to 15min post-stressor played an important role in the effects of post-encoding stress on memory. It should be stressed, though, that other analytes may play a larger role in the effects of post-encoding stress on memory, though these effects may only be detectable if the analytes are assessed at different times post-stressor. Therefore, future research should sample multiple analytes at various timepoints to determine if any analyte might be differentially associated with memory when assessed at a different point in its response and recovery.

Conclusion

In this study we examined the effects of post-encoding stress on memory performance as well as correlations between memory performance and changes in five biomarkers from pre-

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to post-manipulation. As expected, we found that post-encoding stress enhanced hippocampus-dependent memory (i.e., recollection), and that the effects of stress on recollection were statistically mediated by manipulation-induced changes in salivary IL-1β. Although our assessment of these analytes at only one timepoint post-stressor may have prohibited us from detecting associations between some analytes and the effects of post-encoding stress on memory, these findings suggest—at the very least—that biological processes besides those indexed by cortisol increases may contribute to the effects of post-encoding stress on memory, and they indicate that stress-induced changes in immune function may play an important role in the effects of post-encoding stress on memory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Post-encoding stress (i.e., cold pressor) enhanced memory.
- Post-encoding stress effects on memory were unrelated to assayed hormones (i.e., cortisol, progesterone, and estradiol) and salivary α-amylase.
- Post-encoding stress effects on memory were mediated by salivary IL-1β.

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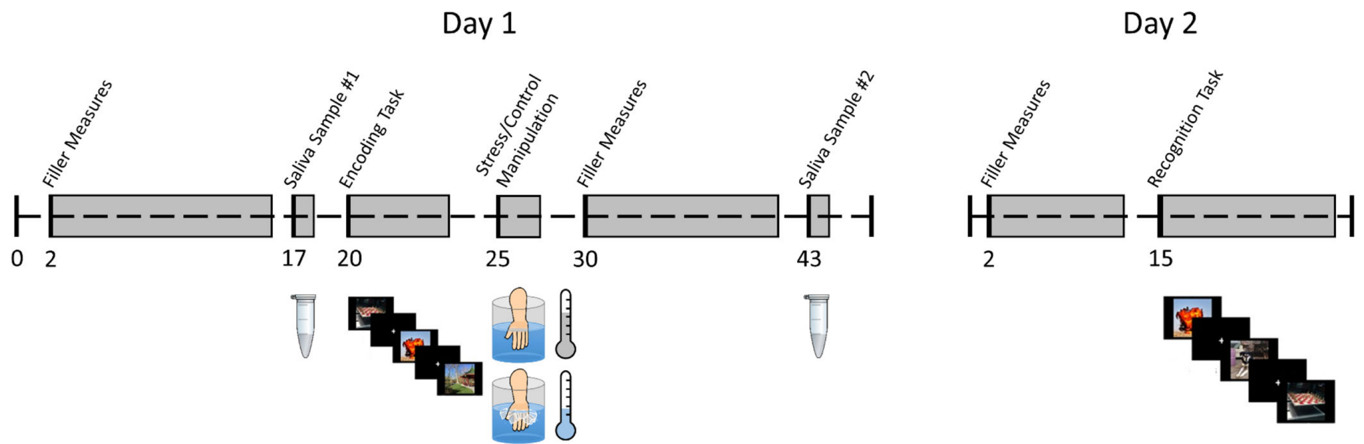

Figure 1.
Depiction of study procedure.

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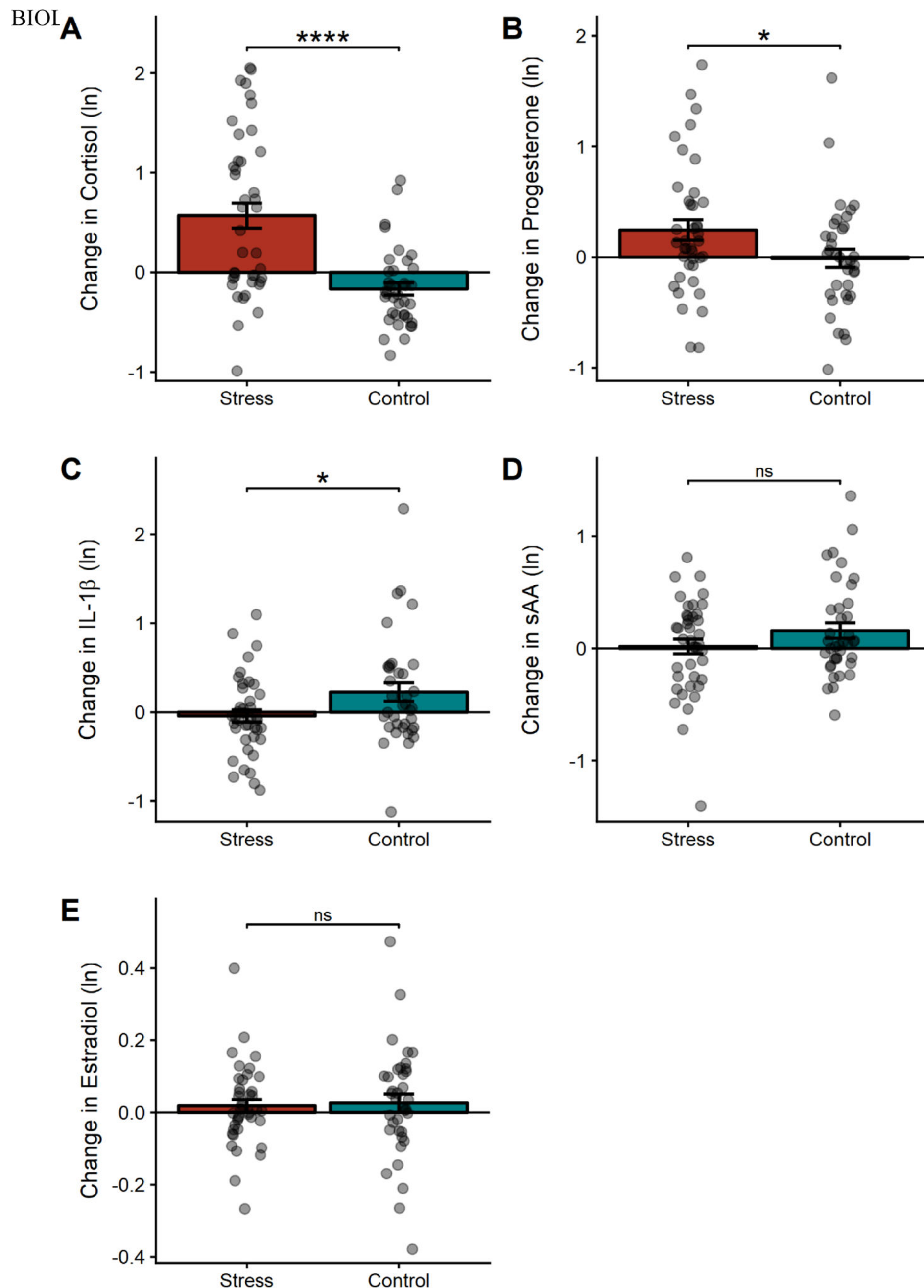

Figure 2.

Changes in analytes of interest by condition. We found significant differences between the stress and control conditions in changes cortisol, progesterone, and salivary IL-1β. Simple change scores (e.g., -cortisol) are presented here to depict the magnitude of the log-transformed change. Figures depicting residualized change scores (used in analyses, see Method) were very similar.

****$p < .0001$, *$p < .05$.

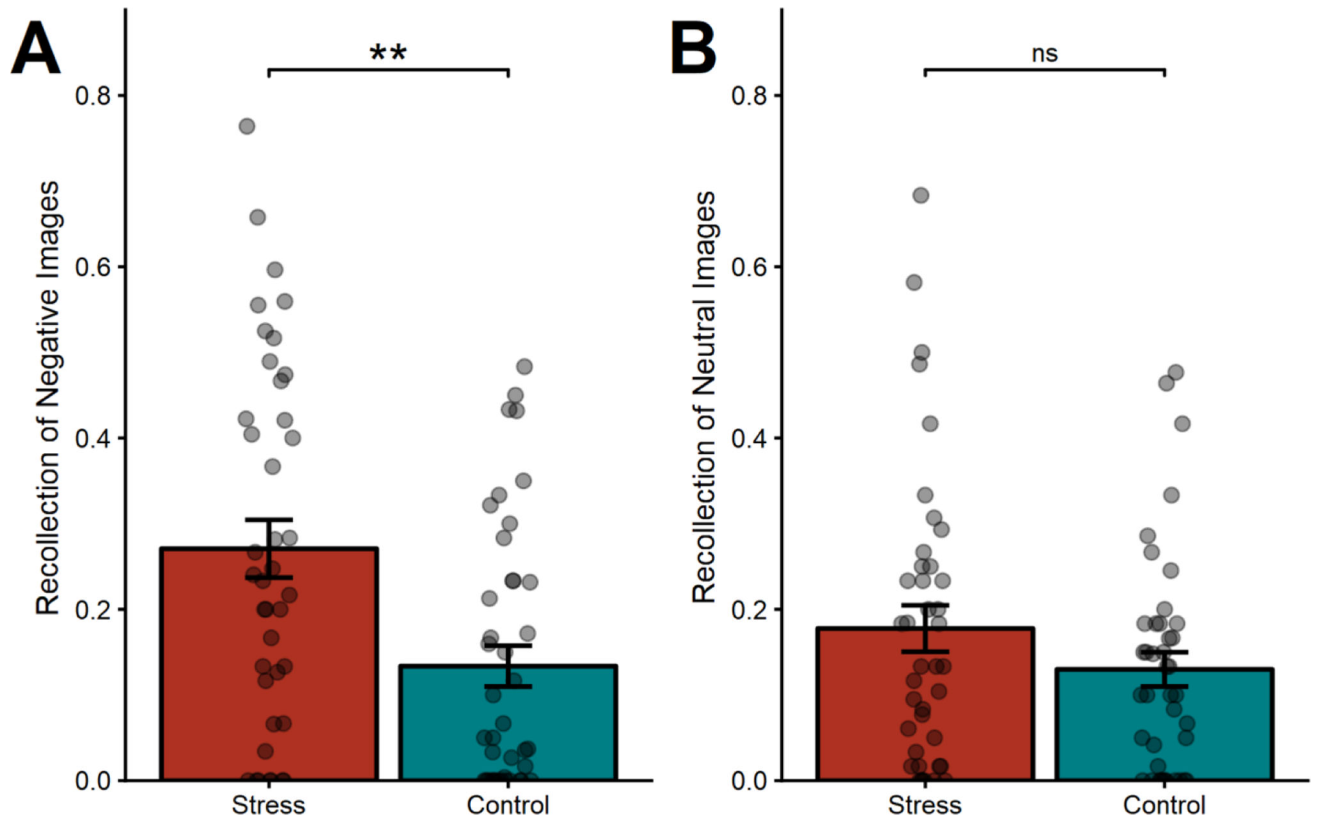

Figure 3.

Recollection by valence and condition. Decomposing the Stress by Valence interaction ($p = .040$), we found that participants in the stress condition evidenced significantly greater recollection of negative images than participants in the control condition, $p = .002$, whereas participants in the stress condition did not significantly differ in recollection of neutral images from participants in the control condition, $p = .161$.

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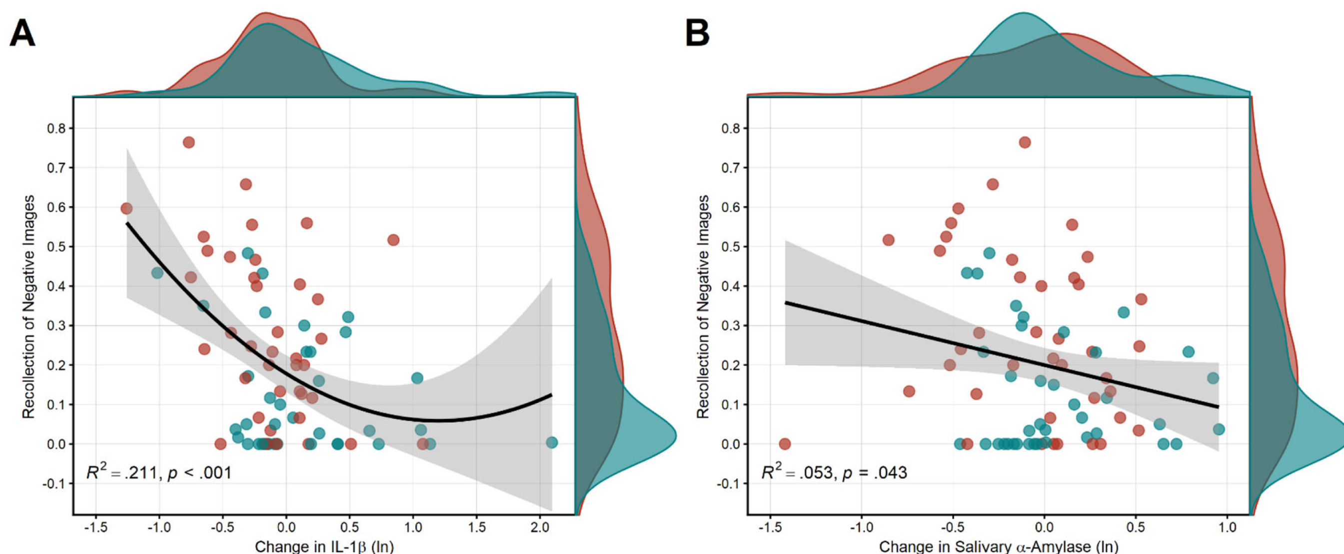

Figure 4.

Associations between recollection of negative images and changes in salivary IL-1β (A) and salivary α-amylase (B). We observed significant linear ($r = -.404$, $p < .001$) and quadratic ($\beta_{quadratic} = .244$, $p_{quadratic} = .040$) associations between recollection of negative images and changes in salivary IL-1β, with greater changes predicting worse recollection of negative images. We also observed a significant inverse association between recollection of negative images and changes in salivary α-amylase ($r = -.230$, $p = .043$); however, only the association between salivary IL-1β and recollection of negative images remained significant after controlling for covariates. Participants in the stress condition are shown in red, and participants in the control condition are shown in blue. Distributions of each variable by condition are presented in density plots on the corresponding axis, such that the density plots on the top of each panel show distributions of changes in analytes by condition, and the density plots on the right of each panel show distributions of recollection of negative images by condition.

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Table 1

Analyte Levels Pre- and Post-Manipulation By Condition

	Baseline		Reactivity	
Variable	**Mean**	**(SE)**	**Mean**	**(SE)**
Cortisol (nmol/L)				
Stress	3.29	(0.44)	6.33	(0.71)
Control	4.14	(0.50)	3.31	(0.35)
Progesterone (pg/mL)				
Stress	76.34	(10.88)	93.11	(13.09)
Control	76.54	(9.25)	76.37	(11.17)
Salivary IL-1β (pg/mL)				
Stress	286.63	(36.41)	274.36	(35.63)
Control	301.81	(49.26)	382.10	(60.15)
Salivary α-amylase (U/mL)				
Stress	66.26	(6.83)	69.50	(8.02)
Control	74.78	(9.15)	82.26	(8.53)
Estradiol (pg/mL)				
Stress	0.88	(0.08)	0.93	(0.09)
Control	0.84	(0.08)	0.88	(0.08)

Note: Although log transformed values were used for analyses, raw data are presented here for informational purposes. Baseline refers to the pre-manipulation sample, whereas Reactivity refers to the sample taken 15min post-manipulation offset.