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Differential effects of stress-induced cortisol responses on recollection and familiarity-based recognition memory

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ABSTRACT

Stress-induced changes in cortisol can impact memory in various ways. However, the precise relationship between cortisol and recognition memory is still poorly understood. For instance, there is reason to believe that stress could differentially affect recollection-based memory, which depends on the hippocampus, and familiarity-based recognition, which can be supported by neocortical areas alone. Accordingly, in the current study we examined the effects of stress-related changes in cortisol on the processes underlying recognition memory. Stress was induced with a cold-pressor test after incidental encoding of emotional and neutral pictures, and recollection and familiarity-based recognition memory were measured one day later. The relationship between stress-induced cortisol responses and recollection was non-monotonic, such that subjects with moderate stress-related increases in cortisol had the highest levels of recollection. In contrast, stress-related cortisol responses were linearly related to increases in familiarity. In addition, measures of cortisol taken at the onset of the experiment showed that individuals with higher levels of pre-learning cortisol had lower levels of both recollection and familiarity. The results are consistent with the proposition that hippocampal-dependent memory processes such as recollection function optimally under moderate levels of stress, whereas more cortically-based processes such as familiarity are enhanced even with higher levels of stress. These results indicate that whether post-encoding stress improves or disrupts recognition memory depends on the specific memory process examined as well as the magnitude of the stress-induced cortisol response.

1. Introduction

Stress can have detrimental effects on memory. For example, acute stress, such as that induced in the laboratory by briefly submerging one's arm in ice water (i.e., the cold-pressor test) can reduce the ability to retrieve information from memory (e.g., Smeets, Otgaar, Candel, & Wolf, 2008). This impairment can also be induced by administration of the stress-related hormone cortisol just prior to retrieval (e.g., Wolf, Kulhmann, Buss, Hellhammer, & Kirschbaum, 2004). Moreover, chronic stress can lead to long-term memory impairments, as seen in individuals suffering from post-traumatic stress disorder (PTSD, e.g., Lindauer, Olff, van Meijel, Carlier, & Gersons, 2006). But stress does not always have detrimental effects on memory, and a number of studies have now shown that acute stressful experiences that occur shortly after learning can facilitate memory (e.g., Andreano & Cahill, 2006; Cahill, Gorski, & Le, 2003; McCullough & Yonelinas, 2013). Because in each of those studies, the stress was administered after learning and well before retrieval, the enhancement of memory cannot be attributed to encoding or retrieval processes, but must reflect enhanced consolidation or slowed forgetting.

The effects of stress on memory are thought to be mediated by glucocorticoid and adrenergic hormones that act on the medial temporal lobe (MTL) regions supporting memory, such as the hippocampus and the amygdala (for reviews, see McEwen & Sapolsky, 1995; McGaugh & Roozendaal, 2002). For example, it is thought that acute stress leads to an increase in the glucocorticoid hormone cortisol, which can enhance the retention of recently encoded memories by facilitating long-term potentiation in the MTL (McEwen & Sapolsky, 1995). Prolonged stress, on the other hand, can lead to abnormal basal cortisol levels and diurnal rhythms (Schulz, Kirschbaum, Prüßner, & Hellhammer, 1998), which have been associated with hippocampal volume reductions and cell death (Lupien et al., 1998), and thus can have long-term detrimental effects on memory.

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The effects of post-encoding stress and cortisol release on memory, however, are not yet fully understood. For example, while a number of studies have found that post-encoding stress improved recall memory for emotional, but not neutral materials (e.g., Cahill et al., 2003; Smeets et al., 2008), other studies have found that post-encoding stress improved recall of neutral and emotional materials (e.g., Nielson & Lorber, 2009), and yet others have found recall enhancements for neutral, but not emotional materials (e.g., Preuß & Wolf, 2009). Studies of recognition memory have found that post-encoding stress induced by skydiving (Yonelinas, Parks, Koen, Jorgenson, & Mendoza, 2011) or by the cold pressor test (McCullough & Yonelinas, 2013) enhanced recognition for neutral pictures more than emotional pictures, while not influencing subsequent recall of either. In both of those studies, further analysis of the recognition data revealed that the stress-related enhancements were localized primarily to familiarity-based recognition, and recollection was unaffected by stress. Thus, stress after learning has generally been shown to enhance subsequent memory, but the reported effects of post-encoding stress have not been consistent with respect to the emotional content of the to-be-remembered information, and it is not yet clear when stress will influence different memory processes (e.g., recollection, familiarity, recall).

One potential explanation for these mixed results is that there could be a non-monotonic relationship between stress and memory. In fact, animal studies have shown that memory is related to glucocorticoid levels with an inverted-U shaped function (e.g., Roozendaal, 2000, 2002), suggesting that moderate levels of post-encoding stress may be associated with better subsequent memory performance than what is observed after lower or higher levels of stress. To our knowledge, there has only been one human study that has reported a non-monotonic relationship between an endogenous cortisol release and subsequent memory (Andreano & Cahill, 2006). In that experiment, participants first read a moderately arousing story and then completed either a cold-pressor test in which they submerged their arm in ice water for 3 min or a control task using warm water. On a subsequent free recall test they observed better overall performance in the stress group than the control group. Among male participants in the stress condition, however, recall performance was higher for those who showed a moderate stress-related cortisol increase, relative to participants who showed small or large cortisol increases.

However, it is unknown whether this type of non-monotonic response function relates stress-induced cortisol responses to other memory measures, such as recollection or familiarity processes supporting recognition memory. Recollection is thought to rely on the hippocampus whereas familiarity relies on the surrounding MTL cortex (for a review, see Eichenbaum, Yonelinas, & Ranganath, 2007). Given that the density of glucocorticoid and mineralocorticoid receptors is particularly high within the hippocampus (Seckl, Dickson, Yates, & Fink, 1991; Watzka et al., 2000), one may expect these two recognition processes to be differentially sensitive to stress-related changes in cortisol. In fact, given that different memory tests are supported by recollection and familiarity to different degrees, such a dissociation might help explain the mixed results in the literature.

In addition to stress-induced changes in cortisol, basal levels of cortisol vary widely across individuals, and little is known about how this variability relates to memory in healthy young adults. It is well established that basal cortisol levels can be abnormal in groups showing memory deficits such as in aging populations (Li et al., 2006; Lupien et al., 1994), patients with PTSD (Lindauer et al., 2006), and clinically depressed individuals (Belanoff, Kalehzan, Sund, Ficek, & Schatzberg, 2001; but see Barnhofer, Kuehn, & de Jong-Meyer, 2005), and in some cases basal cortisol levels have been associated with hippocampal volume in these populations (e.g., Lindauer et al., 2006; Lupien et al., 1998). A few studies have examined the relationship between pre-learning baseline cortisol levels and free recall in healthy young adults, and have either reported no significant relationship (e.g., Ackermann, Hartmann, Papassotiropoulos, de Quervain, & Rasch, 2013), or a significant association only under certain conditions, such as after intentional but not incidental encoding (Preuß, Schoofs, & Wolf, 2009), after a night of sleep but not after a no-sleep delay of equal length (Bennion, Steinmetz, Kensinger, & Payne, 2013), and when the materials are emotional rather than neutral (Preuß et al., 2009). Although in the two latter studies a positive association was observed between pre-learning cortisol levels and memory performance, negative relationships between baseline cortisol and memory performance have also been reported in healthy young adults (e.g., van Honk et al., 2003). However, no previous study that we are aware of has examined the relationship between pre-learning cortisol levels and recognition memory or the processes of recollection and familiarity.

In the current study, we examined the relationship between stress-induced cortisol responses and recognition memory processes, as well as between pre-learning baseline cortisol levels taken at the beginning of the study and recognition processes in a sample of healthy young adult men. We note that our measure of pre-learning baseline cortisol can be impacted by many factors such as the subject's expectation that they will be tested in a stressful experiment. Nonetheless, baseline levels of cortisol are important to examine as they may influence the learning phase itself and be related to memory in different ways than cortisol changes induced by the post-encoding experimental manipulation of stress. We restricted our sample to males because previous human and animal work has indicated that the effects of stress on memory are pronounced in males (e.g., Andreano & Cahill, 2006; Conrad et al., 2004). In addition, we used a common laboratory stressor (i.e., the cold-pressor test), which, in combination with brain imaging procedures, elicited a large change in cortisol levels.

Participants encoded both negative emotional images and neutral images. Immediately after encoding, participants in the stress group submerged one arm in ice water, whereas participants in the control group submerged one arm in warm water. After a 24-h delay, participants in both groups were given a recognition memory test, in which they were asked to indicate whether they recollected each image, and if not, to rate their recognition confidence (to assess familiarity). We used the confidence judgments to compute estimates of recollection and familiarity using a dual-process ROC approach and a Remember/Know approach (Yonelinas et al., 2011), as well as two measures of performance based on single process models of recognition: d' for medium-confidence responses and d' for high-confidence responses (MacMillan & Creelman, 2005).

Salivary cortisol was measured at the beginning of the experiment, then 20 min after the stressor, when stress-induced cortisol responses were expected to be maximal (Schwabe, Böhringer, Chatterjee, & Schachinger, 2008; Schwabe, Böhringer, & Wolf; 2009; Schwabe & Wolf, 2009), and again just prior to the recognition memory test. We examined the relationship between the magnitude of post-encoding stress-induced cortisol release, as measured by the difference in cortisol between the initial cortisol measure and the sample taken shortly after the stress manipulation, and recollection and familiarity-based recognition responses. In addition, we examined whether pre-learning levels of cortisol were differentially related to the processes supporting recognition memory, which we determined by examining the relation between the initial cortisol measure and estimates of recollection and familiarity.

2. Methods

2.1. Participants

A total of 50 males were recruited from on online participant pool, and received $15/hr for participating. All testing sessions began during the day (i.e., 09:00–17:00). Twenty-five participants were randomly assigned to the stress group (Mean age = 24.2 years, Mean years education = 16.6) and twenty-five participants to the control group (Mean age = 23.1 years, Mean years education = 15.6). Participants reported an average of 7.28 h of sleep during the night before the first session, and the average amount of sleep did not differ between the stress (Mean hours = 7.00, SD = 1.07) and control (Mean hours = 7.58, SD = 1.31) groups ($t(47) = 1.71$, $p = .09$). Memory data were not obtained from one control participant due to a problem with the experimental program, and only half of the memory data were obtained from two stress participants for similar reasons. None of the participants reported use of medications, and seven reported regular tobacco use (4 stress, 3 control). Of the seven smokers, three reported tobacco use within 24 h of the experiment. Removal of these participants did not alter the pattern of results, so those participants were included in the analyses reported below. The study was approved by the Institutional Review Board at the University of California, Davis.

2.2. Stimuli and materials

This study used a set of 312 pictures, half neutral and half negative, that was used in previous research (McCullough & Yonelinas, 2013). The pictures were selected primarily from the International Affective Photo Series (IAPS) based on their standard scores of emotional arousal and emotional valence (Lang, Bradley, & Cuthbert, 2008), as well as from an in-house set designed to balance the two sets for factors such as visual complexity, color, and the presence of people. Images were approximately 315 pixels square, with minor variation in size and shape. Eight of the images were used as example trials: four were presented before the encoding and recognition tasks, two were presented only before the encoding task, and two were presented before the recognition task only. In the encoding phase, 100 neutral and 100 negative images were presented to each participant in a random order. In the recognition test, each participant was presented with 200 studied images and 104 new images (52 neutral) in a random order.

Individual trait differences were measured using the Emotion Regulation Questionnaire (ERQ; Gross & John, 2003), the Arousal Predisposition Scale (APS; Coren, 1988), and a subset of questions from the Sensation Seeking Scale (SS; Zuckerman, Eysenck, & Eysenck, 1978). The trait measures were administered because prior studies suggest that individual differences in emotional regulation strategies and arousal predisposition can mediate responses to external stress (for a review, see van Ast et al., 2013) as well as effects of post-learning manipulations on memory (e.g., Nielson & Lorber, 2009). However, no significant relationship was observed between any of the trait measures and cortisol levels or responses, nor were any relationships observed between trait measures and memory performance, thus we do not discuss the measures further.

2.3. Procedure

The procedure is illustrated in Fig. 1. All participants were tested individually by a male experimenter. In the first session, after providing informed consent, participants completed a safety screening form and the ERQ, APS, and SS scales before providing a baseline saliva sample. The participant was offered a piece of gum and produced approximately 3 mL of saliva into a Salivette tube. The participant was then provided with instructions for the subsequent picture rating task on a laptop computer. The instructions included presentation of six example pictures. The participant was then put into a MR scanner,[1] where they completed the incidental encoding task, in which 200 IAPS pictures (100 neutral, 100 negative) were presented via computer (using e-Prime 2.0). Participants rated each picture for visual complexity on a scale of 1–6, using three buttons on each of two response boxes. These ratings were included to ensure that participants attended to each image, but were not analyzed. Each picture was presented for 1000 ms, after which the participant had up to 3000 ms to respond. After an inter-trial interval that varied from 2 to 8 s, the next trial was initiated. Following the encoding task, there was a 7-min resting-state scan, for which participants were instructed to remain awake and motionless.

Following the rest period, the participant was removed from the MR scanner, and completed questionnaires for approximately 10 min, providing demographic, medical, sleep, and strategy-related information, in addition to completing the SS scale again. Each participant then completed either the cold-pressor test or control task. The participant submerged their non-dominant arm in either an ice-water bath ($M = 0.06$ °C, SD = 0.12 °C) or tepid water ($M = 23.71$ °C, SD = 2.2 °C). The participant was instructed to keep their arm submerged for 3 min, or as long as possible, and to refrain from talking during the task. Participants then completed the SS scale and another strategy questionnaire, before returning to the MR scanner for approximately 12 min to complete another set of task-free scans (i.e., a 7-min resting-state scan, structural scans). The first session concluded with a second saliva sample.

The second session started 24 h after the first, and began with the participant providing a third saliva sample and a fourth measure of the SS scale. The participant was then put into the MR scanner, where 12 min of task-free scans (i.e., localizer scans, 7-min resting-state scan) preceded a surprise recognition test. For the test, a mix of 200 studied images and 104 new images (52 negative) were presented for 1000 ms each, after which the participant had up to 4000 ms to respond. Participants rated each picture as either being Recollected, or on a familiarity scale of 1–5, in which 1 = *Sure new* and 5 = *Sure old*. After the participant responded, an inter-trial interval that varied from 2 to 8 s preceded the subsequent trial. The recognition test was divided into four phases of equal length, and participants were allowed a brief break in between phases. Following the recognition test, participants completed a final set of task-free scans for approximately 10 min.

2.4. Analysis of saliva

Saliva was assayed for salivary cortisol in two batches. The minimum detectable value of the first batch was 1.3854 nmol/L, and one sample from a control participant fell below this threshold, so the minimum detectable value was substituted for that data point. Additionally, we did not obtain cortisol data from one control participant. Salivary cortisol measures were subjected to a repeated-measures ANOVA with stress group (control/stress) as a between-subjects factor and time of sample (sample 1/sample 2/sample 3) as a within-subject factor. For correlational analyses, we computed a measure of cortisol response (Cortisol Δ = sample 2 − sample 1). We predicted a stress-induced increase in salivary cortisol at sample 2, but no differences in cortisol between the control and stress groups at samples 1 or 3. Our primary analysis

[1] These data were collected as part of a functional neuroimaging study. We focus here on the cortisol and behavioral measures, and the neuroimaging methods and data will be reported separately.

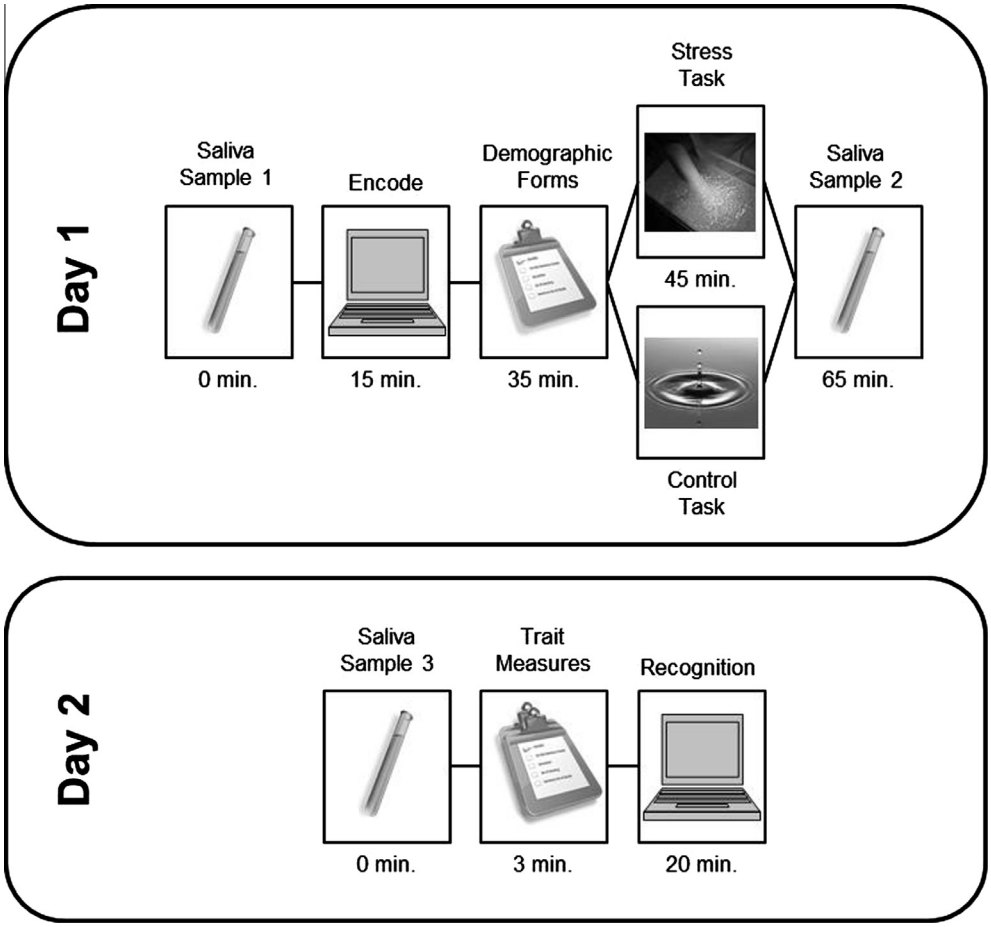

Fig. 1. Schematic depiction of the protocol. Time values represent the mean latency to begin each task (measured from the start of each session).

included all the subjects, but we also report secondary analyses in which we excluded any non-responders from the stress group (i.e., those subjects in the stress group that did not show a numerical increase in cortisol from sample 1 to sample 2). Although this biases the sample, it is useful for relating the results to prior studies (e.g., Andreano & Cahill, 2006).

2.5. Analysis of memory

Recognition confidence data were used to plot cumulative ROCs for each participant. A dual-process signal detection model was fit to each individual subject's data by minimizing the sum of squared errors, and a confidence-based ROC analysis was used to compute estimates of recollection and familiarity (Yonelinas, 1994). The relationships between each measure of memory and Cortisol Δ values were examined using hierarchical regression analyses, in order to determine whether each memory-cortisol relationship was best described by a linear or quadratic function. For each measure of memory, we first tested a linear model (Model 1) and compared it to a quadratic model (Model 2) using hierarchical regression:

$$\text{(Model 1) Memory} = \beta_0 + \beta_1\Delta + \beta_2 S + \beta_3 E + \varepsilon$$

where Δ = Cortisol response, S = Stress group, E = Emotion.

$$\text{(Model 2) Memory} = \beta_0 + \beta_1\Delta^2 + \beta_2\Delta + \beta_3 S + \beta_4 E + \varepsilon$$

We then examined whether the full model could be reduced by successively removing the terms with the least predictive value, and statistically comparing the reduced model to the previous model. We replicated this analysis using estimates of recollection and familiarity derived from a remember/know method (see Yonelinas, 2001). We also examined the relationship between each measure of memory and Cortisol Δ values when non-responders (i.e., subjects in the stress group who did not exhibit a positive Cortisol Δ value) were excluded. In addition, in order to examine relationships between cortisol and memory using a simple signal detection model, we also computed two measures of overall recognition performance (i.e., d') for each participant. We computed the standard d' statistic as a measure of medium-confidence recognition, by treating Remember, 5, and 4 responses as hits and false alarms. Finally, high-confidence d' was computed by treating only Remember responses as hits and false alarms.

3. Results

3.1. Salivary cortisol and cold-pressor duration

In order to verify that the cold-pressor test induced a stress response, we compared salivary cortisol levels between the stress and control groups (Fig. 2). We observed a significant Stress Group × Time interaction on salivary cortisol ($F(4, 92) = 6.75$, $MS_e = 126.33$, $p < .001$, $\eta^2_p = .23$). Post-hoc comparisons of group means at each time point revealed that the stress and control groups did not differ in salivary cortisol levels prior to encoding (time 1; $t(46) = 0.70$, $p = .49$), but the stress group had significantly higher salivary cortisol than the control group after the cold-pressor test (time 2; $t(46) = 5.54$, $p < .001$). Salivary cortisol levels did not differ between the two groups prior to retrieval (time 3; $t(46) = 0.05$, $p = .96$). Six participants in the stress group did not exhibit an increase in cortisol levels from time 1 to time 2.

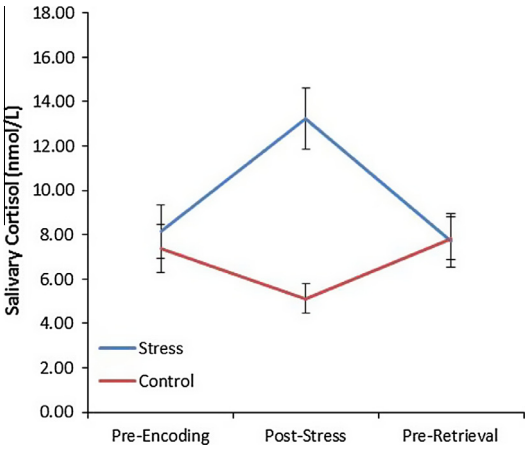

Fig. 2. Mean salivary cortisol for the stress (blue) and control (red) groups at each sample. Error bars represent SEs of the means. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Cortisol responses and memory

We examined the relationship between stress-related changes in cortisol and memory by plotting Cortisol Δ (i.e., the change in cortisol from the initial baseline sample to the sample shortly after the stress manipulation) against estimates of recollection (Fig. 3a and b). Fig. 3a and b show the relationship between recollection and Cortisol Δ for neutral and negative materials, for subjects in the stress and control conditions. The plots reveal an inverted-U shaped relationship between recollection and Cortisol Δ, such that recollection estimates are highest for participants with moderate cortisol responses, and lower for participants with larger or smaller cortisol responses. In addition, a comparison of Fig. 3a and b shows that emotional materials led to higher levels of recollection than did neutral materials, but the same inverted-U shaped function was observed for negative and neutral materials. Moreover, the figures suggest that overall recollection was lower in the stress group than the control group. The group means for recollection, familiarity, and overall recognition are presented in Table 1. These observations were corroborated by a hierarchical regression analysis, in which Stress group (S), Emotion (E) and Cortisol responses (Δ) were used as predictors of recollection.

Table 1
Mean estimates of memory parameters for the stress and control groups for negative and neutral images. Standard errors of the means are in parentheses.

	Recognition ROC estimates			
	Recollection		Familiarity	
	Neutral	Negative	Neutral	Negative
Stress (n = 25)	0.12 (0.03)	0.23 (0.04)	1.37 (0.13)	1.49 (0.10)
Control (n = 24)	0.23 (0.04)	0.31 (0.04)	1.49 (0.14)	1.59 (0.15)
	Recognition R/K estimates			
	Recollection		Familiarity	
	Neutral	Negative	Neutral	Negative
Stress (n = 25)	0.15 (0.03)	0.31 (0.04)	0.42 (0.03)	0.48 (0.03)
Control (n = 24)	0.28 (0.04)	0.39 (0.04)	0.44 (0.04)	0.47 (0.03)
	Recognition d' estimates			
	High confidence		Moderate confidence	
	Neutral	Negative	Neutral	Negative
Stress (n = 25)	2.58 (0.22)	2.57 (0.23)	1.96 (0.21)	1.90 (0.14)
Control (n = 24)	2.78 (0.22)	2.87 (0.24)	1.92 (0.13)	1.88 (0.13)

The analysis revealed a significant quadratic relationship with cortisol responses [$F(4, 93) = 6.51$, $p < .001$, $r^2 = .185$] that fit the data significantly better than a linear model [$F(1, 93) = 9.76$, $p < .005$]. In addition, further regression analyses revealed that both Stress [$F(1, 94) = 7.44$, $p < .01$] and Emotion [$F(1, 94) = 7.91$, $p < .01$] significantly predicted recollection.

We then examined the relationship between cortisol responses and familiarity-based recognition (see Fig. 3c and d). In contrast to recollection, visual examination of Fig. 3c and d suggest that familiarity and Cortisol Δ are linearly related, such that participants with larger cortisol responses had higher familiarity estimates. Moreover, familiarity was lower in the stress than control group, but was comparable for the emotional and neutral materials. These observations were confirmed by hierarchical regressions, which revealed a significant linear relationship between familiarity and cortisol responses [$F(3, 94) = 3.48$, $p < .025$, $r^2 = .071$]. The data were not better fit by a quadratic model [$F(1, 93) = 0.22$, $p = .64$]. Further regression analyses revealed that the Emotion term did not add significant predictive value to the model [$F(1, 94) = 0.78$, $p = .38$], and removing it resulted in the best linear model [$F(2, 95) = 4.85$, $p < .01$, $r^2 = .074$]. However, removing Stress group from the model did lead to a decrease in fit, [$F(1, 95) = 4.73$, $p < .05$] indicating that stress was associated with a slight decrease in familiarity when accounting for cortisol changes. Thus, stress and cortisol reactivity, but not emotion, predicted familiarity.

The mean hit rates and false alarm rates for each level of recognition confidence are presented in Supplemental Table 1. Note that, across stress and emotion conditions, the points are evenly spread along the ROC, suggesting no major difference in response bias between conditions. We replicated the prior analyses after excluding participants who did not exhibit an increase in salivary cortisol following the cold-pressor test. The same general pattern of results was observed when non-responders were excluded. That is, recollection was related to Cortisol Δ values with a quadratic function [$F(4, 81) = 4.52$, $p < .005$, $r^2 = .142$], which fit significantly better than a linear model [$F(1, 81) = 8.05$, $p < .01$]. In contrast to the prior analysis, the term for Stress group did not add significant predictive value [$F(1, 82) = 1.98$, $p = .16$], and so Recollection was best predicted by a quadratic model that included Cortisol Δ and Emotion, but not Stress group [$F(3, 82) = 5.30$, $p < .005$, $r^2 = .132$]. For familiarity, the full linear model was not significant ($p = .07$), nor was the quadratic model ($p = .13$). However, further analysis revealed that familiarity was significantly predicted by a linear model including only Cortisol Δ and Stress group [$F(2, 83) = 3.48$, $p < .05$, $r^2 = .055$]. To facilitate comparison to the extant literature, the Supplemental Text additionally includes the results of an analysis in which only the stress group was examined and non-responders excluded (c.f., Andreano & Cahill, 2006), as well as ANOVAs testing the effect of stress irrespective of cortisol responses.

The preceding analyses were based on estimates of recollection and familiarity derived using the dual-process ROC estimation method. To verify the validity of those results, we conducted two secondary regression analyses. First, we estimated recollection and familiarity using the subjective reports of remembering and knowing (Yonelinas, 2001), rather than basing the estimates on the shape of the confidence ROCs (see Table 1 for group means). Supplemental Fig. 1 shows the estimates obtained from the remember/know method plotted against Cortisol Δ values. The results of the remember/know regression analyses were similar to the results from the ROC method. That is, we found a significant quadratic relationship between recollection and Cortisol Δ [$F(4, 93) = 8.40$, $p < .0001$, $r^2 = .234$] that fit the data better than a linear model [$F(1, 93) = 9.80$, $p < .005$]. In addition, there was an effect of Emotion ($p < .001$), indicating that recollection was generally higher for emotional than neutral materials, and an effect of Stress ($p < .005$), indicating that recollection was lower in the stress

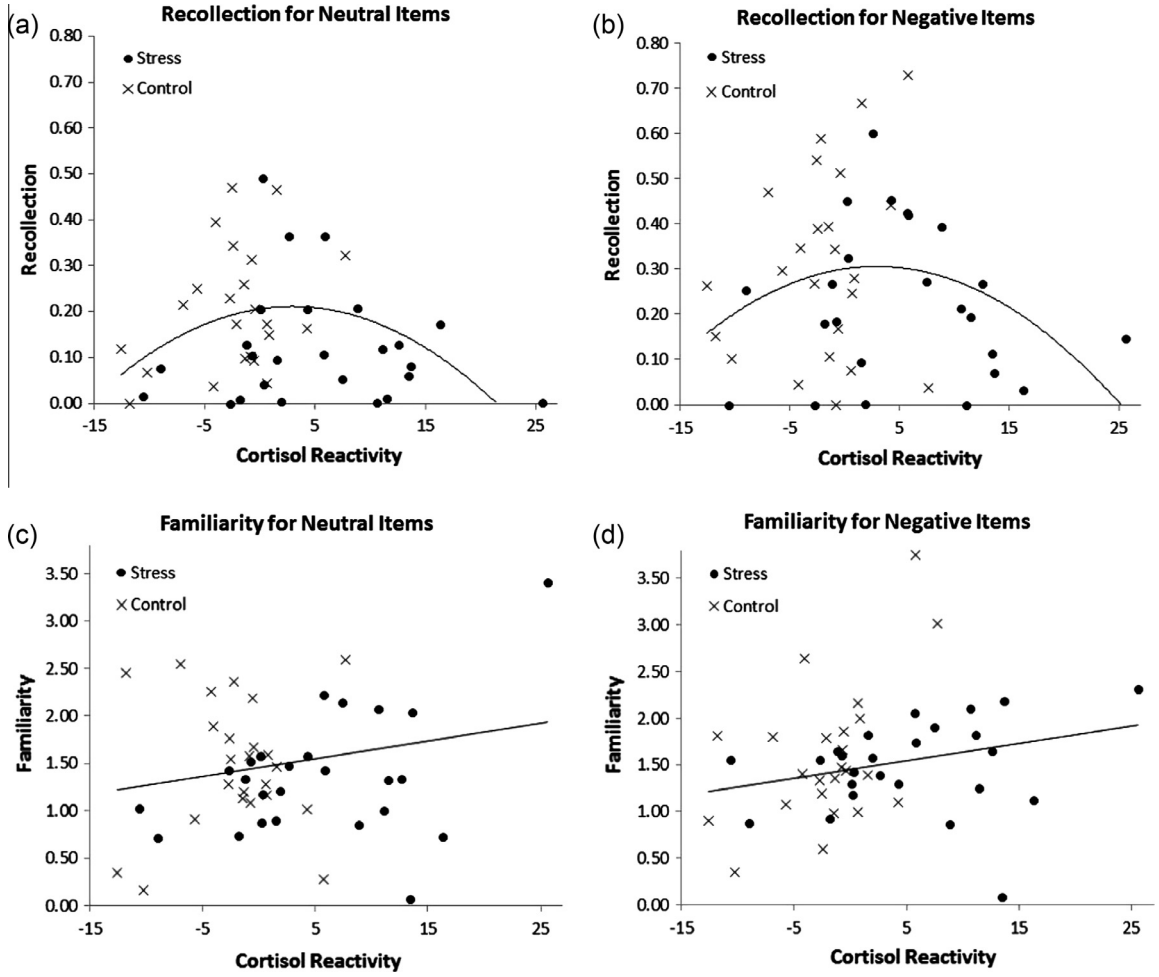

Fig. 3. Observed memory parameters plotted against observed cortisol responses, for subjects in the stress group (circles) and control group (×'s). Recollection (top row) and familiarity (bottom row) are plotted separately for neutral (left column) and negative images (right column) and are fit to quadratic and linear functions respectively.

group than the control group. In contrast, familiarity estimates increased slightly with increases in Cortisol Δ, but neither the linear [$F(3, 94) = 1.16$, $p = .32$, $r^2 = .005$] nor quadratic relationship reached significance, and there was no significant effects of Emotion or Stress on familiarity.

Second, we examined the data using a single process estimate of recognition (i.e., d') at a high level of response confidence (where only Remember responses were treated as hits and false alarms) and at a medium level of confidence (Remember, 5 and 4 responses were treated as hits and false alarms; see Table 1). The results were consistent with the results of the initial dual process model analysis. That is, for the high confidence responses (presumably driven strongly by recollection), there was a significant quadratic relationship [$F(4, 93) = 9.56$, $p < .0001$, $r^2 = .261$], which fit the data significantly better than the linear model [$F(1, 93) = 14.37$, $p < .001$]. This indicates that high-confidence recognition accuracy was best for participants with moderate elevations of cortisol, and decreased for participants with small or large elevations of cortisol. However, for medium levels of recognition confidence (presumably reflecting more familiarity), there was a significant linear relationship between d' and Cortisol Δ [$F(1, 96) = 4.83$, $p < .05$, $r^2 = .038$], and no significant quadratic component, indicating that overall recognition increased with cortisol responses.

Thus, whether recollection was estimated using the ROCs, the remember responses, or simply high-confidence recognition responses, it exhibited an inverted-U shaped relationship with stress-induced cortisol increases. However, this type of a relationship was not observed for all types of recognition responses, in the sense that familiarity as measured in the ROC analysis and by low-confidence recognition was found to exhibit a significant increasing linear relationship with stress-induced cortisol responses. While the results of the remember/know analysis suggested that the linear relationship between familiarity and cortisol responses was not significant, there was a numerical trend for familiarity estimates to increase with cortisol responses, in line with the other two sets of analysis.

3.3. Pre-learning cortisol and memory

Fig. 4a and b show the relationships between baseline cortisol (cortisol measured prior to the encoding and stress phases of the experiment) and recollection of neutral and negative images, respectively. The figure shows that recollection estimates decreased with higher pre-learning cortisol levels, and that recollection was greater for negative than neutral items. We performed a hierarchical regression analysis as described above, and observed a significant linear relationship, such that participants with higher baseline cortisol had lower estimates of recollection [$F(3, 94) = 6.22$, $p < .001$, $r^2 = .139$]. We also observed a significant quadratic model [$F(4, 93) = 4.62$, $p < .005$, $r^2 = .130$], but it was not significantly better than the linear model [$F(1, 93) = 0.007$, $p = .935$]. In addition, there were significant effects of Stress

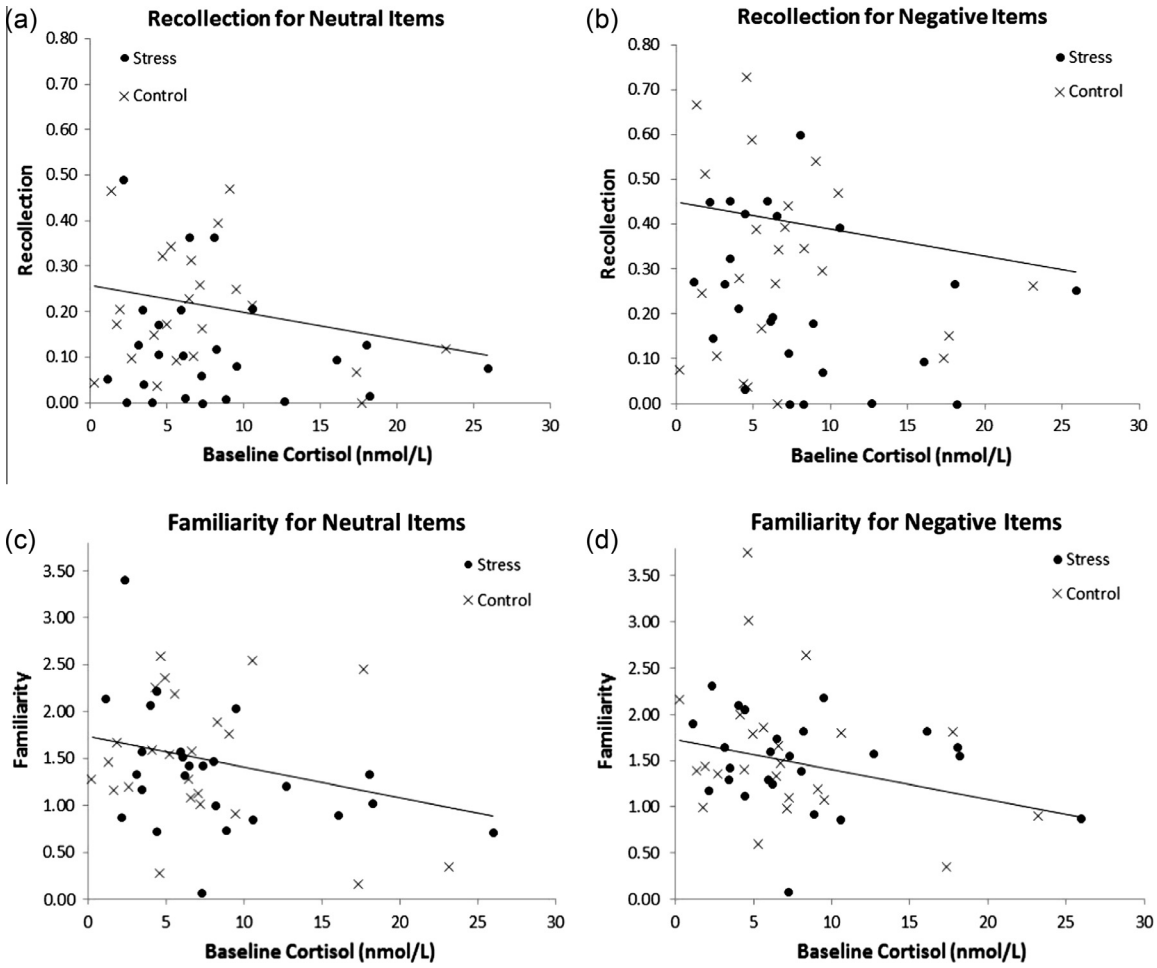

Fig. 4. Observed memory parameters plotted against observed baseline cortisol, for subjects in the stress group (circles) and control group (×'s). Recollection (top row) and familiarity (bottom row) are plotted separately for neutral (left column) and negative images (right column), and are fit to linear functions.

[$F(1, 95) = 6.37$, $p < .025$] and Emotion [$F(1, 95) = 7.48$, $p < .01$] on recollection.

Fig. 4c and d reveal the relationship between baseline cortisol and familiarity. We observed a significant linear relationship [$F(3, 94) = 3.14$, $p < .05$, $r^2 = .062$], but no significant quadratic relationship [$F(4, 93) = 2.35$, $p = .06$, $r^2 = .053$]. Further analysis revealed that the terms for Stress group and Emotion did not add significant predictive value (p's = .54 and .38, respectively). Thus, familiarity could be predicted by baseline cortisol alone [$F(1, 96) = 8.36$, $p < .005$, $r^2 = .071$], in that participants with higher baseline cortisol had lower estimates of familiarity. Subsequent analysis based on remember/know reports and high and low confidence recognition responses were consistent in indicating that both recollection and familiarity decreased linearly with higher levels of pre-learning cortisol levels.

Finally, in order to examine whether the effects of cortisol reactivity on memory differed for the subjects with lower or higher pre-learning cortisol levels, we conducted a median split on baseline cortisol and examined the best-fit regression equations for the high and low baseline cortisol groups separately. The results confirmed the whole-group results above, in that recollection was best described by a quadratic model for both groups ($r^2 = 0.52$ and 0.67 for the high and low baseline groups, respectively) and familiarity was best described by a linear model for both groups ($r^2 = 0.49$ and 0.41 for the high and low groups, respectively). These results indicate that the effects of stress-induced cortisol elevations are similar for individuals with high and low pre-learning levels of cortisol.

4. Discussion

The current study examined the relationships between processes of recognition memory (i.e., recollection and familiarity) and stress-induced changes in cortisol, as well as pre-learning cortisol levels. The study showed that stress-related changes in cortisol were related to increased familiarity; but that recollection exhibited an inverted-U shaped relationship with stress-related cortisol responses, such that subjects with moderate increases in cortisol showed the highest levels of recollection. In addition, individuals with higher cortisol at the onset of the experiment exhibited lower levels of both recollection and familiarity. Each of these effects were observed for both negative and neutral materials, and were evident based on the analysis of ROC shape, remember/know responses, and high/low confidence ratings.

The observed non-monotonic relationship between recollection and stress-induced cortisol increases is consistent with previous reports of such a relationship between memory and glucocorticoid responses after learning in rodents (see Roozendaal, 2000), and with a previous study of free recall in humans (Andreano & Cahill, 2006). Why would recollection be "tuned" more tightly to moderate increases in cortisol whereas familiarity increased linearly with post-learning cortisol increases? Recollection has been found to rely on the hippocampus, whereas familiarity relies on surrounding cortical regions such as the perirhinal cortex (Eichenbaum et al., 2007). The hippocampus may be particularly sensitive to stress in the sense that it has a high density of

glucocorticoid and mineralocorticoid receptors (Seckl et al., 1991; Watzka et al., 2000). In this way, hippocampal processes may benefit from moderate increases in cortisol, but over-saturation of the glucocorticoid receptors could impair hippocampal processing. In contrast, cortically-based processes may benefit to a lesser extent from stress in general but may not be adversely affected by over-saturation until much higher levels of cortisol are reached. Future work will test this hypothesis by examining the relationship between cortisol influences on memory processes and its modulation of neural activity in these brain structures.

This non-monotonic relationship between cortisol and recollection may explain why post-encoding stress manipulations have not always led to changes in human memory performance. For example, in a previous study using very similar procedures to those in the current experiment (McCullough & Yonelinas, 2013), we found that post-encoding stress did not impact recollection or free recall performance. In contrast, in the current experiment the stress manipulation led to a decrease in recollection. Importantly, however, and in line with prior research showing the MRI environment to be stressful (e.g., Peters, Cleare, & Papadopoulos, 2011; Tessner, Walker, Hochman, & Hamann, 2006), the stressor used here (i.e., cold-pressor during an MRI experiment) induced a larger average cortisol increase than the stressor in the previous experiment (i.e., cold-pressor alone). Thus, in the previous experiment, it is possible that the lack of an overall effect of stress on recollection arose because some subjects showed an increase in recollection while others showed a decrease. In contrast, in the current study, stress led to an overall decrease in recollection, as one might expect if more subjects fell into the higher range of stress-related cortisol responses.

So when will memory benefit from post-encoding stress and when will it not? The current results lead us propose that whether overall memory performance will benefit or suffer from post-encoding stress will depend critically on (a) the extent to which the memory task relies on recollection and familiarity, and (b) the level of the stress-related cortisol response. Tests such as recall and associative recognition, which are expected to rely heavily on recollection, should show evidence of the inverted-U shaped function, as long as performance is examined across a wide range of cortisol responses. In contrast, in tasks that rely more on familiarity, such as forced-choice recognition, performance should be less likely to follow an inverted-U shape and should instead show a moderate increase as cortisol responses increase – unless, perhaps, one manages to induce extremely high levels of stress-related cortisol (see Fig. 5).

Why might hippocampal-dependent and cortically-dependent memory be differentially influenced by stress-induced cortisol responses? There is good evidence, primarily from animals but also from human studies, that glucocorticoids influence memory via actions on mineralocorticoid (MR) and glucocorticoid receptors (GR) in medial temporal lobe structures, and that the MR/GR binding ratio can determine how stress impacts memory. Both GRs and MRs are found in the hippocampus (and amygdala), but MRs are found in much lower densities in cortical regions (for a review, see van Ast et al., 2013). Thus, the effects of stress on different memory processes may be a function of the ratio of GR and MR receptors in the brain regions supporting those processes.

In line with some prior studies (e.g., McCullough & Yonelinas, 2013; Nielson & Lorber, 2009; Yonelinas et al., 2011), our post-encoding stress manipulation did not influence memory differently for emotional and neutral information. However, this result conflicts with observations of post-encoding stress selectively enhancing memory for emotional (e.g., Cahill et al., 2003; Smeets et al., 2008) or neutral information (e.g., Preuß & Wolf, 2009). These conflicting results are not limited to studies of post-encoding stress. In one study, for example, stress prior to learning enhanced

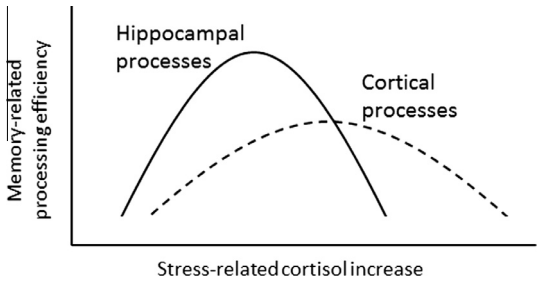

Fig. 5. Schematic depiction of the effects of post-encoding stress-related increases in cortisol on hippocampal and cortical dependent memory processes.

subsequent memory for emotional information but impaired memory for neutral information (Payne et al., 2007), but another study found that stress during encoding improved subsequent memory for emotional and neutral information (Henckens, Hermans, Pu, Joëls, & Fernández, 2009). Thus, it remains unclear exactly when and how stress interacts with the emotional content of the to-be-remembered information. There are a host of possible reasons why the reported effects of stress are not entirely consistent, including possible interactions with the emotional content of the to-be-remembered information (and the psychological arousal induced by the emotional information), and possible differences in stress effects on memory for "central" and "peripheral" details of the information (Payne et al., 2006). Other possible modulatory influences on stress effects include the timing of the stress with respect to memory phases, different actions of glucocorticoid and mineralocorticoid receptors in different brain regions, and individual differences in personality characteristics as well as genetic and epigenetic factors (reviewed by van Ast et al., 2013).

The finding that pre-learning cortisol levels are negatively related to recollection and familiarity is consistent with previous findings. In one study, pre-learning cortisol levels in healthy young adults were inversely associated with memory for the spatial location of emotional compared to neutral faces (van Honk et al., 2003). In another study, there was a negative relationship between cortisol and explicit cued recall performance in healthy aged adults (Lupien et al., 1994). Why are high baseline levels of cortisol related to lower recollection and familiarity? It is not yet clear, but the current results do suggest that the impact of pre-learning cortisol is at least somewhat distinct from the effects of stress-related cortisol increases. That is, the same inverted-U and linear relationships for recollection and familiarity respectively were observed for subjects with high as well as those with low pre-learning cortisol levels. Notably, this finding indicates that the effects of cortisol responses on memory were not dependent on baseline cortisol levels. An alternative outcome might have been that higher baseline cortisol levels simply shifted individuals up or down on the cortisol reactivity scale, such that participants with very high baseline cortisol would show either very large or very small cortisol responses to stress. However, if that were that case, then one would expect participants with high baseline cortisol levels to generally show lower recollection. In contrast, we observed the same quadratic relationship between recollection and cortisol responses in participants with higher and lower pre-learning cortisol levels, thus suggesting that the effects of baseline cortisol and cortisol reactivity on memory are distinct from one another.

What leads some subjects to have high or low levels of baseline cortisol? We can only speculate at this point, but individuals with higher baseline cortisol may be genetically predisposed to have higher levels or may experience higher levels of perceived daily stress (e.g., Melamed et al., 1999; van Eck & Nicolson, 1994). It is also possible that the baseline levels we measured were sensitive

to the subjects participating in the neuroimaging experiment, such that baseline levels were elevated in anticipation of entering the MRI scanner (see Peters et al., 2011). This anticipatory increase in cortisol may have been exacerbated by our lack of including any "acclimation time" prior to starting the experiment. However, this seems unlikely, as baseline levels appeared stable from day to day and were comparable to the levels we have observed in other studies that did not involve neuroimaging procedures. Nonetheless, future studies are needed to assess whether these effects are generalizable to other experimental contexts and to determine the stability of these measures over time.

There are a number of limitations to the current study and several questions that will need to be addressed in future work. First, the current study examined individual differences in cortisol at baseline and as a response to a single type of stressor. Whether the results generalize to other stressors is not known. Moreover, in order to determine whether cortisol plays a causal role in the observed memory effects, future studies are needed to assess whether similar response functions like the inverted-U observed here are seen when levels of stress or cortisol are experimentally manipulated. It is possible that an individual's stress response function might be quite different from the cortisol-memory function observed across individuals.

We suggest that pre-learning levels of cortisol have important effects on subsequent memory, but our single measure of pre-learning baseline cortisol may not provide an accurate index of more stable, basal cortisol levels in our participants. It should be noted that the majority of studies of young adults have not measured basal cortisol levels, *per se*, but used one or two samples as an index of basal cortisol (i.e., pre-learning cortisol or the average of pre- and post-learning cortisol levels). In the current study, there was considerable between-subject variability in pre-learning cortisol levels, as well as time-of-testing in our sample, but this is unlikely to have influenced the results because the majority of our sample (70%) was tested between 10:00 and 15:00, and there were no significant group differences in pre-learning cortisol or time-of-testing ($p = .77$).

The current study revealed that pre-learning cortisol levels and stress-induced cortisol responses have different relationships with the processes supporting recognition memory. The magnitude of stress-induced cortisol responses was related to recollection with an inverted-U, but had a positive linear relationship with familiarity, whereas pre-learning cortisol levels were negatively related to both recollection and familiarity. Thus, future investigations of the relationship between stress and memory should carefully consider the processes that support memory performance, as well as cortisol levels at different time points. Such an approach might help elucidate the causes of mixed effects reported in the literature, as well as illuminate how abnormal HPA activity, which is associated with many psychological disorders, impacts memory and cognition.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nlm.2015.04.007.

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