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Endogenous cortisol elevations are related to memory facilitation only in individuals who are emotionally aroused

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Abstract Animal research suggests that cortisol facilitates memory only during emotional arousal. Thus, we predicted that during mild emotion and stress elicitation, endogenous cortisol elevations would predict memory facilitation only in individuals who report high stress-related negative affect. Thirty-one men viewed neutral and emotional stimuli and then were subjected to a public speaking stress task. Area under the curve for overall cortisol output during the speech was computed. Negative affect (NA) using the PANAS state version [Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. J. Personality Social Psychol. 54, 1063–1070.] was measured at baseline and immediately after the speech stressor. Cortisol output during the speech and change in NA interactively predicted free recall performance assessed 2 days later. This interaction was due to the finding that higher cortisol output was related to memory facilitation only in subjects who reported high stress-related negative affect (i.e. only in those individuals whose NA increased compared to baseline). This relation was especially prominent for recall of unpleasant pictures. Subjects who reported low stress-related negative affect, no relation was found between cortisol output during the speeh and memory performance. Thus, the relation between cortisol and memory appears to depend on an increase in negative affect related to stress.

Emotionally-laden information is typically remembered better than neutral information (Bradley et al., 1992; Cahill and McGaugh, 1995). Amygdala activation during memory formation underlies the superiority of memory for emotional information (Cahill et al., 1996; Canli et al., 2000). Because glucocorticoids modulate noradrenergic processes in the amygdala associated with emotional memory

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(Roozendaal, 2000), many investigators have hypothesized that cortisol elevations are more likely to affect memory for emotional than neutral information.

Within recent years, there has been extensive interest in studying differential effects of cortisol elevations on explicit memory for emotional vs. neutral stimuli. While some studies have produced data consistent with the hypothesis that memory for emotional information is more sensitive to fluctuation in glucocorticoid levels than is memory for neutral information (Buchanan and Lovallo, 2001; Cahill et al., 2003), many studies have shown effects of manipulation of cortisol on memory for both neutral and emotional information (Abercrombie et al., 2003; Tops et al., 2003; Maheu et al., 2004).

The inconsistencies in this area of research may be due to the fact that the emotional stimuli used in these studies (e.g. photographs that vary with respect to emotional content) are not potent elicitors of emotional state. In other words, viewing these stimuli does not serve as a good emotion induction. However, exposure to a novel laboratory environment and psychological testing may serve to increase emotional arousal in the majority of research participants. Possibly, the relation among emotion, memory, and cortisol depends more on the emotional arousal of the participants than on the content of stimuli.

Extensive animal data suggest that the amygdala serves as a neural gateway for the effects of cortisol on memory (Roozendaal, 2000). Cortisol's effects on noradrenergic processes in the basolateral nucleus of the amygdala are necessary for its effects on memory (see Roozendaal, 2000 for review). In fact, glucocorticoid infusions directly into the hippocampus have no effect on memory if the basolateral nucleus of the amygdala is inactivated (Roozendaal and McGaugh, 1997; Roozendaal et al., 1999). This research suggests that amygdala activation is a necessary prerequisite for the effects of cortisol on memory.

Roozendaal and colleagues hypothesized that emotional arousal (putatively associated with amygdala activation[1]) during learning would interact with corticosterone's effects on memory. A difficulty with testing this hypothesis in a rodent model is that most animal learning tasks involve an aversive component, making it difficult to control for emotional arousal during encoding. Because of this, Roozendaal and colleagues used an object recognition memory task that does not entail aversive learning (Okuda et al., 2004). To manipulate emotional arousal, they altered the novelty of the context within which the learning task would take place, by previously habituating only half of the animals to the training environment. All animals received placebo or a dose of corticosterone immediately after training. Corticosterone enhanced 24-h retention performance only in animals that had not previously been habituated to the training environment, and had no effect on retention performance in previously habituated animals. These data are consistent with the hypothesis that corticosterone affects memory only in individuals who experience emotional arousal during encoding (Okuda et al., 2004). Moreover, recent human data suggest that cortisol's effects on working memory may require sympathetic activation (Elzinga and Roelofs, 2005).

To extend this work, we tested the hypothesis in humans that negative affective experience and cortisol would interactively predict memory performance, such that elevations in endogenous cortisol levels during an emotionally evocative laboratory session would predict memory facilitation *only* in individuals who reported high state negative emotional arousal in response to a laboratory-based stressor. We conducted our study late in the day when endogenous cortisol levels are relatively low, and therefore hypothesized that higher cortisol elevations would predict better subsequent memory performance in those individuals who responded with high negative emotional arousal.

1. Method

1.1. Participants

Thirty-four healthy college-aged males completed the experiment.[2] Men who met any of the following

[1] While the amygdala's role in affective processes is associated primarily with emotional learning and vigilance rather than subjective emotional arousal per se (e.g. Davis and Whalen, 2001), Roozendaal and colleagues hypothesize that corticosterone affects memory only under conditions of engagement of affective processes and amygdala activation.

[2] Women were excluded from participation due to limited funds available for the study. Because the relation between cortisol and memory has been shown to differ for men and women (Wolf et al., 2001), inclusion of both sexes requires large samples sizes to allow for examination of the effects of sex. In addition, oral contraceptive use and menstrual cycle have been shown to affect cortisol (Kirschbaum et al., 1995; Altemus et al., 1997; Harlow et al., 1997). Controlling these variables requires additional resources that were not available at the time this study was conducted. Future research must determine whether the results presented herein generalize to women.

criteria were excluded from participation: younger than 18 years old, previous exposure to the slides used in the study (i.e. International Affective Picture System; Lang et al., 2001), previous exposure to laboratory-based social stress testing, medical illness, history of head injury, self-reported mental or substance use disorder, daily tobacco use, night shift work, inability or unwillingness to complete the protocol, or treatment with psychotropic medications, narcotics, beta-blockers, steroids, or any other medication that affects central nervous system or endocrine systems. Written informed consent was obtained in accordance with the University of Wisconsin Health Sciences Human Subjects Committee guidelines.

In addition, three participants were excluded from the analyses. One of these participants revealed marijuana use that is suspected to have altered his data. The other two were excluded due to experimenter error during stimulus presentation.[3] Thus, the final *N* was 31 participants.

1.2. Procedure

Eligible participants were invited into the lab for two sessions: an initial session that always began at 16:30 h (Session 1), followed two evenings later by Session 2, which began at either 17:00 or 18:00 h. Session 1 consisted of encoding of stimuli and manipulation of endogenous cortisol levels using a speech stressor. Session 2 consisted of memory testing.

Participants were instructed to refrain from eating, exercising, and drinking anything but water for the hour prior to Session 1. Participants were also instructed to refrain from drinking alcohol for the 24 h prior to Session 1. Men who were occasional smokers (i.e. <1 pack/month) were instructed not to smoke for the 4 days prior to Session 1. Participants were tested individually, and tasks were administered on a computer, with the exception of self-report questionnaires, free recall task, and public speaking stressor.

1.2.1. Session 1: Encoding & manipulation of endogenous cortisol levels.

Session 1 lasted approximately 3 h and consisted of the following: application of sensors for electrophysiological data collection (electrophysiological data will be described elsewhere); encoding of emotionally-laden and neutral pictures; a public speaking stressor; and 50-min recovery from the stressor. Twelve salivary cortisol samples (Fig. 1) were obtained by having participants chew briefly on a cotton swab using the Salivette sampling device (Sarstedt, Inc., Newton, NC).

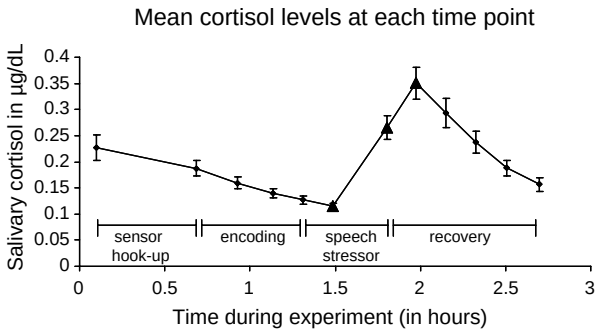

Figure 1 Mean salivary cortisol levels in µg/dL at each time point. Error bars represent standard error of the mean. Different phases of the experiment are indicated. 'Sensor hook-up' refers to application of sensors for electrophysiological data collection, which will be described elsewhere. The cortisol samples associated with the speech stressor, which were used to compute log cortisol AUC_G (i.e. post-anticipation, post-speech, 10-min post-speech), are indicated with triangles.

1.2.2. Encoding

Stimuli presented during the encoding task consisted of pleasant, neutral, and unpleasant photographs chosen from the International Affective Picture System (IAPS; Lang et al., 2001). Two sets of stimuli were developed to allow for counterbalancing of targets and distracters in tests of recognition memory using methods described previously (Abercrombie et al., 2003). Both picture sets included 63 pictures (including 21 pleasant, neutral, & unpleasant pictures). The sets were matched on normative ratings of pleasantness (i.e. valence) and arousal (Lang et al., 2001). To facilitate free-recall testing, content overlap among pictures was minimized within each set. Pictures were presented within the context of an emotion modulated startle paradigm (startle data to be presented elsewhere), in which pictures were presented for 6 s with a 17-s ITI between pictures. Participants were not told that memory for these stimuli would later be tested.

1.2.3. Speech stressor

For manipulation of endogenous cortisol levels, the stressor task was administered immediately after encoding. This order of tasks (i.e. encoding first

[3] Too many stimuli were presented during encoding for these two participants, rendering free recall data unusable.

and speech stressor second) was chosen because of the abundance of animal data showing that manipulation of cortisol levels *immediately after* encoding is most effective in altering memory consolidation (Lupien and McEwen, 1997; McGaugh, 2000; Roozendaal, 2000). The public speaking stressor was a modified version of the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). The task consisted of 5 min of anticipation and 15 min of videotaped public speaking in front of a two-person evaluative audience. Audience behavior was modeled on the TSST (Kirschbaum et al., 1993).

The topic of the speech was for participants to describe their emotional reactions to pictures presented during the encoding task. This speech topic was chosen for examination of the relation between emotional expressiveness and physiological response to public speaking (data to be presented elsewhere). Participants were not informed of the topic of the speech until immediately prior to the anticipation period. During the anticipation period, participants took notes in preparation for the speech (which they were not permitted to use during the speech). Saliva samples were taken at multiple time points prior to the speech stressor, as well as immediately after anticipation, immediately after completion of the speech, and at 10-min intervals for 50 min following the speech (Fig. 1).

1.2.4. Measurement of negative affect

Self-reported negative affective experience (NA) was measured at baseline (prior to application of physiological sensors) and immediately after the speech stressor using the Positive Affect and Negative Affect Schedule (PANAS State Version; Watson et al., 1988). We computed a difference score consisting of state NA following the speech minus baseline state NA. This metric shows the extent to which participants' NA following the stressor increases (or does not increase) compared to baseline NA. Hereafter, 'change in state NA' refers to this metric.

1.2.5. Session 2: Memory testing

During Session 2, explicit memory was tested for the pictures presented during Session 1 using free recall and recognition memory tasks, as described elsewhere (Abercrombie et al., 2003). Briefly, for the free recall task, participants were given 10 min to list short descriptions of all the pictures they could remember from Session 1. Because a degree of subjectivity was entailed in scoring the free-recall lists, inter-rater reliability between two independent raters was tested. Reliability was very high (IC = 0.99).

The recognition memory task involved use of a 2-button 'yes' or 'no' response pad to indicate whether test stimuli were presented during Session 1. Half of the test stimuli were targets (previously viewed) and half were distracters (new stimuli). Instructions emphasized both accuracy and speed. The participant's ability to discriminate between previously presented and new items (i.e., 'sensitivity') served as the dependent variable for recognition memory. The sensitivity index Pr was used (Snodgrass and Corwin, 1988). Pr is the proportion of old items (targets) endorsed minus the proportion of new items (distracters) endorsed, i.e. hits−false alarms, with positive scores reflecting more hits than false alarms. This metric does not require that the data are normally distributed, and provides a measure of sensitivity that is independent from bias (Snodgrass and Corwin, 1988). Cortisol was not hypothesized to be related to bias or reaction time, and these data are therefore excluded.

1.2.6. Cortisol processing

The assay method employed the Salimetrics (State College, PA) cortisol enzyme immunoassay kit. Prior to the assay, the samples were centrifuged for 10 min at 5000 rpm to remove cellular and bacterial debris that are inherent in saliva samples. Assay results were considered acceptable only if the coefficient of variation for the duplicate measurement of a sample is less than or equal to 20%. For this assay, the mean inter-assay CV% is 7.4%, and the mean intra-assay CV% is 3.8%. The detection limit for this assay is 0.007 μg/dl. Because the distribution of raw cortisol values is typically skewed, raw values were log transformed. Raw cortisol values are presented in Fig. 1, but all analyses were conducted on log transformed cortisol.

In order to determine the magnitude of endogenous cortisol elevations associated with the speech stressor, area under the curve (AUC; Pruessner et al., 2003) was computed using cortisol samples immediately after anticipation, immediately after speech, and 10 min after speech (when cortisol levels most typically peaked following the speech stressor; see Fig. 1). Pruessner and colleagues (2003) describe two formulas for computation of AUC: 'AUC with respect to ground (AUC_G),' and 'AUC with respect to increase (AUC_I).' The formula for AUC_G provides a measure of overall cortisol output that is independent of changes in cortisol over time, while AUC_I emphasizes changes over time. Because the abundance of past research has examined the association between memory and glucocorticoid *levels* (rather than rate of change of cortisol), we specifically hypothesized that cortisol

output (rather than change from pre-to-post-speech) would predict memory performance. Thus, AUC_G was used for the analyses presented here, rather than AUC_I.[4] Thus, the dependent variable for cortisol output associated with the speech stressor was log cortisol AUC_G. A benefit of using AUC is that it provides a summary metric of cortisol output and thus avoids tests of multiple comparisons involving each cortisol time point. Hereafter, 'AUC_G' refers to 'log cortisol AUC_G.'

1.3. Data analysis

To test the hypothesis that endogenous cortisol elevations and negative emotional arousal interactively predict explicit memory performance, hierarchical regression analyses were conducted. One set of regression analyses included recognition memory performance (Pr) as the dependent variable, and the other set included free recall performance (number of pictures recalled) as the dependent variable. In the regression analyses, independent variables were entered as follows: first, log cortisol AUC_G during the speech; second, negative affect (NA; either baseline NA or change in state NA); and third, the interaction between AUC_G and NA.

Significant regression analyses were followed by a series of illustrative analyses to disentangle the interaction effect. Specifically, a median split on change in state NA was used to create low and high stress-related NA groups. To illustrate how the relation between cortisol and memory differs depending on affective state, the correlations between log cortisol AUC_G and memory performance were compared for the low vs. high stress-related NA groups.

2. Results

Hierarchical regression analyses for recognition memory performance revealed no significant relations between Pr and AUC_G or either measure of NA, or the interaction between AUC_G and either measure of NA ($ps > 0.35$). Thus, recognition memory data will not be discussed further. Although low variability in recognition memory performance (e.g. ceiling effects) has the potential to obscure true memory effects, our null finding was not due to ceiling or low variability (Pr ranged from 0.44 to 0.95).

Table 1 Log cortisol AUC_G and change in state NA interactively predict free recall performance (DV: recall performance).

	R^2	Increment in R^2	F	p
Log cortisol AUC_G	0.05	-	1.52	n.s.
Change in state NA	0.07	0.02	0.75	n.s.
Log cortisol $AUC_G \times$ NA	0.24	0.17	5.81	<0.03

Table 1 displays results from a hierarchical regression analysis predicting free recall performance. The table shows that neither log cortisol AUC_G alone nor change in state NA predicted free recall performance. However, the interaction between log cortisol AUC_G and change in state NA significantly predicted free recall performance, accounting for 17% of the variance in free recall scores, over and above the variance accounted for by AUC_G and NA. In addition, neither baseline NA alone nor the interaction between log cortisol AUC_G and baseline NA predicted free recall ($ps > 0.25$). It is important to note that log cortisol AUC_G was not related to baseline NA ($r = -0.15$, n.s.) or to change in state NA ($r = -0.09$, n.s.).

In order to disentangle the significant interaction effect, and illustrate how AUC_G and change in state NA interactively predict free recall performance, a median split on change in state NA was used to create low and high stress-related NA groups. All individuals in the low stress-related NA group showed a slight to moderate decrease in negative affect after the speech compared to baseline (range in change in state NA was -1 to -14; mean change in state NA was -4.1). One individual in the high stress-related NA group showed no change in state NA, but the remaining individuals showed an increase in NA after the speech compared to baseline (range in change in state NA was 0 to 25; mean change in state NA was 7.4). Please see Table 2 for means and standard deviations for NA and other study variables for the low vs. high stress-related NA groups. It is important to note that the low and high stress-related NA groups did not differ on raw cortisol levels, AUC, or memory performance (see Table 2).

The correlation between free recall performance and AUC_G for the low stress-related NA group was

[4] While some research suggests that rate of rise of glucocorticoids is an important variable (Keller-Wood and Dallman, 1984) and change in cortisol levels in response to stress has at times predicted memory performance (e.g. Kirschbaum et al., 1996), AUC_G was not related to memory performance in the current study ($p > 0.37$). Similarly, our measures of NA did not interact with AUCI in the prediction of memory performance ($ps > 0.35$).

Table 2 Means (SD) for low and high stress-related NA groups.

	Stress-related NA group		
	Low	High	*p*
N	16	15	
Raw cortisol (in μg/dL)			
Baseline	0.22 (0.12)	0.24 (0.15)	n.s.
Post-sensor hook-up	0.19 (0.08)	0.19 (0.08)	n.s.
Encoding 1	0.16 (0.06)	0.16 (0.06)	n.s.
Encoding 2	0.14 (0.05)	0.14 (0.05)	n.s.
Encoding 3	0.13 (0.05)	0.12 (0.04)	n.s.
Post-anticipation	0.12 (0.04)	0.11 (0.03)	n.s.
Post-speech	0.25 (0.14)	0.28 (0.12)	n.s.
10-min post-speech	0.33 (0.19)	0.37 (0.15)	n.s.
20-min post-speech	0.28 (0.17)	0.31 (0.14)	n.s.
30-min post-speech	0.23 (0.13)	0.25 (0.10)	n.s.
40-min post-speech	0.17 (0.08)	0.20 (0.08)	n.s.
50-min post-speech	0.14 (0.06)	0.17 (0.07)	n.s.
Log cortisol AUC_G	−3033.8 (986.9)	−2785 (544.7)	n.s.
Log cortisol AUC_I	864.8 (707.2)	1130.7 (368.0)	n.s.
Free recall performance			
All stimuli combined	21.1 (4.5)	21.7 (5.7)	n.s.
Pleasant stimuli	5.6 (1.9)	6.1 (1.9)	n.s.
Neutral stimuli	4.4 (2.0)	4.5 (1.9)	n.s.
Unpleasant stimuli	11.1 (2.6)	11.1 (3.5)	n.s.
Recognition memory performance			
All stimuli combined	0.80 (0.12)	0.80 (0.09)	n.s.
Pleasant stimuli	0.78 (0.14)	0.78 (0.10)	n.s.
Neutral stimuli	0.70 (0.18)	0.71 (0.14)	n.s.
Unpleasant stimuli	0.85 (0.08)	0.85 (0.09)	n.s.
PANAS state negative affect (NA)			
Baseline state NA	19.6 (5.1)	14.8 (2.9)	<0.01
Post-speech state NA	15.5 (3.9)	22.2 (7.3)	<0.01
Change in state NA	−4.1 (3.6)	7.4 (6.8)	<0.01

Note. This table shows that there are no differences between the low and high stress-related NA groups on raw cortisol levels, AUC, or memory performance. The only differences between the groups are on measures of NA (which were used to construct the groups) and on the relation between cortisol and free recall performance (which is shown in Table 3).

$r=0.04$, n.s. However, for the high stress-related NA group, the correlation between free recall performance and AUC_G was $r=0.53$, $p<0.05$. Table 3 shows the correlations between cortisol AUC_G and free recall performance separately for pleasant, neutral, and unpleasant pictures (as well as for all pictures collapsed across valence). Results displayed in Table 3 show a strong relation within the high stress-related NA group between cortisol AUC_G and recall for unpleasant pictures, but not for recall of pleasant or neutral pictures. See Fig. 2 for scatter plots of the relation between AUC_G and recall of unpleasant pictures. In sum, cortisol was related to memory performance only in the group

Table 3 Pearson *r*-values for correlations between log cortisol AUC_G and free recall performance for low vs. high stress-related NA groups.

	All	Pleasant	Neutral	Unpleasant
Low NA group	0.04	0.21	0.08	−0.15
High NA group	0.53[a]	0.23	0.23	0.63[b]

Correlations are presented for recall performance for all pictures (collapsed across valence) and separately for pleasant, neutral, and unpleasant pictures.
[a] $p<0.05$.
[b] $p<0.02$.

who showed an increase in negative affect associated with the speech, and this relation was especially prominent for recall of unpleasant pictures.

3. Discussion

In the current study, change in negative affective state and cortisol output during the speech stressor interactively predicted free recall performance. This interaction was due to the finding that stress-related endogenous cortisol output was related to memory facilitation (primarily for unpleasant stimuli) only in the group of men who were negatively emotionally aroused in response to the speech stressor. Baseline negative affect by itself did not interact with cortisol in the prediction of memory performance. The important variable is the increase in negative affect specifically related to the speech. It is only in the group of men whose stress-related negative affect increased relative to baseline that cortisol predicts memory performance.

These data are consistent with animal literature that suggests that glucocorticoid effects on learning require emotional arousal (Okuda et al., 2004). The human literature to date examining the effects of manipulation of cortisol levels on memory for emotional vs. neutral stimuli has been inconsistent. While some studies have suggested that glucocorticoids are more likely to affect memory for emotionally arousing information (Buchanan and Lovallo, 2001), other studies have shown effects of manipulation of cortisol levels on neutral and emotional information (Abercrombie et al., 2003; Rimmele et al., 2003; Tops et al., 2003; Maheu et al., 2004).

The data from the current study suggest that emotional arousal is indeed important in the relation between cortisol and memory. Failure to observe greater glucocorticoid-related sensitivity in memory for emotional compared to neutral information in previous studies may be due to the fact that the stimuli typically presented do not consistently evoke emotional arousal. The current data suggest that in those men who experience negative emotional arousal related to the stressor, cortisol is more likely to affect memory performance.

A number of studies have shown that amygdala activation at encoding underlies the superiority of memory for emotional information and predicts subsequent memory of negatively emotionally arousing but not neutral information (Cahill et al., 1996; Canli et al., 2000). It should be noted that

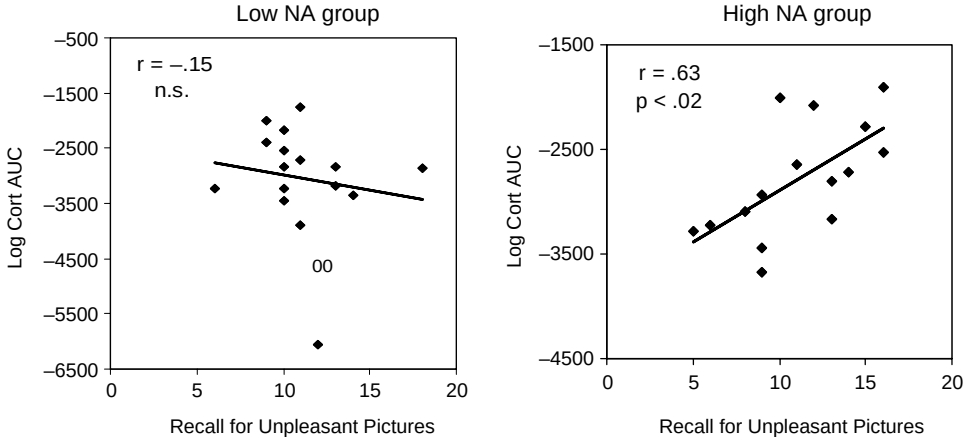

Figure 2 Scatter plots of the relation between log cortisol AUC_G and free recall performance for unpleasant pictures, separately for low and high stress-related NA groups. Removal of the outlier with very low cortisol from the low NA group does not alter the effects reported herein. The correlation presented here between log cortisol AUC_G and recall for unpleasant pictures after removal of the outlier is $r=0.23$, n.s. The interaction effect for the regression analysis presented in Table 1 after removal of the outlier is $R^2=0.29$, $F=4.48$, $p<0.05$.

cortisol elevations are not necessary for the superiority of memory for emotional information, i.e. emotional information tends to be better remembered even in the absence of cortisol elevation during encoding or consolidation (e.g. Abercrombie et al., 2003). However, amygdala activation at encoding may be necessary for glucocorticoids' effects on memory, as suggested by Roozendaal's research (Roozendaal, 2000).

Thus, cortisol may be most likely to affect memory during conditions that highly activate affective neural circuitry. In the current study, cortisol was related to memory only in the group of participants who responded to the stressor with an increase in negative affect, and this effect appears to be driven by memory for unpleasant rather than neutral or positive pictures. Compared to neutral stimuli, unpleasant pictures such as those used in the current study have been shown to activate the amygdala (e.g. Irwin et al., 1996). Amygdala activation associated with processing of unpleasant stimuli in combination with feelings of negative emotional arousal (entailing concomitant activation of affective neural circuitry) may create conditions in which glucocorticoids are most likely to affect memory.

Moreover, while the importance of glucocorticoids in the role of the hippocampus in learning have long been studied (e.g. McEwen and Sapolsky, 1995), recent research suggests that the effects of cortisol elevations on learning depend on concurrent activation of emotion-related brain circuitry. Specifically, the effects of glucocorticoids on memory appear to depend on glucocorticoid-modulation of noradrenergic mechanisms within the amygdala (Roozendaal, 2000). Furthermore, animal and human research shows that heightened memory for emotional information depends on increases in stress-related noradrenergic and amygdala activation (Cahill and McGaugh, 1998; Canli et al., 2000; Roozendaal, 2000). This line of research points specifically to amygdala activation, suggesting that the greater the amygdala activation during memory formation, the greater the effects of glucocorticoids on memory for emotion-related information. In addition, glucocorticoids modulate brain activation in other regions associated with affective processes and learning, such as the medial prefrontal cortex (PFC; Diorio et al., 1993; Akana et al., 2001). Schutter and van Honk (2005) have also recently demonstrated that cortisol levels are related to midfrontal delta–beta EEG coupling, which may have implications for cortical regulation of subcortical brain regions and emotional information processing. The PFC is an additional region likely to underlie interactive effects of emotional activation and glucocorticoids on learning.

3.1. State vs. trait negative affect

The current study showed that change in state negative affect interacted with cortisol output during stress in the prediction of free recall, such that cortisol output was related to free recall only in the group of participants who showed negative affect in response to the speech stressor. Baseline state negative affect was unrelated to free recall and did not interact with cortisol output in the prediction of free recall. These results suggest that the extent to which an individual experiences an increase in negative affective state related to a stressor may determine whether cortisol elevation associated with that stressor alters memory. However, the individual's level of baseline state negative affect (not associated with a specific stressor) may not be related to cortisol's effects on memory. While the results of the current study suggest these conclusions, it is important to note that the findings are agnostic with regard to a potential interaction between *trait* negative affect and cortisol's effects on memory. People who report experiencing high *trait* negative affect may be the very individuals who tend to consistently react to stressors with high *state* negative affect. Future research is required to determine whether trait negative affect interacts with cortisol's effects on memory.

3.2. Limitations and future directions

While the data presented here are consistent with the causal neurobiological model of enhanced noradrenergic activation in the amygdala underlying cortisol-related memory facilitation, these data do not adequately test the neural model. Human work using neuroimaging and pharmacological manipulation of stress-related hormones will be necessary for further corroboration of the neurobiological model stemming from animal research (Roozendaal, 2000).

Because negative affect measured with the PANAS represents both valence and arousal dimensions of negative affect (i.e. high scores represent a negatively valenced high arousal state), it is unclear specifically what aspects of negative affective experience interact with cortisol in the prediction of memory. In addition, because the study did not include a non-stress control group, it is unclear whether negative affect and cortisol levels would interactively predict memory in non-stress

conditions. Future research should include a control group not exposed to stress.

Furthermore, two types of memory (free recall and recognition memory) were tested, but corrections for multiple comparisons were not used. A benefit of testing both recognition memory and free recall as measures of explicit memory is that these two types of tests tap different aspects of memory and many variables affect recall and recognition differently (Brown, 1976, for review). Recognition memory is a relatively pure measure of memory storage, as it is not affected by processes that alter retrieval of items stored in memory, which are involved in free-recall. In addition, our test of free recall entailed verbal description of items, but the recognition memory test did not have a verbal component. Given that cortisol is known to affect the PFC (reviewed above), cortisol's effects on verbal vs. non-verbal memory tasks may differ. Future research must systematically determine which aspects of explicit memory are affected by cortisol and NA.

An additional limitation is that only males were studied. Effects of cortisol on memory appear to differ for men and women (Wolf et al., 2001). Thus, future studies must systematically determine whether sex interacts with the interactive effects of NA and cortisol on memory.

These data have potential implications for negative memory biases observed at times in depression, whereby depressed individuals tend to remember more negatively-laden than positive information (Matt et al., 1992; Gotlib and Neubauer, 2000). Depressed individuals have been found to show negative affect-related amygdala activation (Abercrombie et al., 1998) and greater sustained amygdala activation in response to negative stimuli than healthy individuals (Siegle et al., 2002). Because depressed individuals show heightened or sustained negative affect-related amygdala activation (Abercrombie et al., 1998; Siegle et al., 2002), cortisol may facilitate memory for negative information to a greater extent in depressed compared to healthy individuals. In other words, because the amygdalar 'neural gateway' for the effects of cortisol on memory may be more likely to be 'open' (or activated) in depressives, cortisol elevations may contribute to mood-congruent memory biases in depression. Emotion regulation techniques, which have been shown to modify amygdala activation (Ochsner et al., 2004), may reduce memory biases in depression if they can be successfully implemented by depressed individuals. Future research is needed to test these hypotheses.

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