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Neural Signaling of Cortisol, Childhood Emotional Abuse, and Depression-Related Memory Bias

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ABSTRACT

BACKGROUND: Cortisol has potent effects on learning and neuroplasticity, but little is known about its effects on negative memory biases in depression. Animal models show that aversive caregiving alters effects of glucocorticoids (primarily corticosterone in rodents and cortisol in primates) on learning and neuroplasticity into adulthood.

METHODS: We investigated whether history of childhood emotional abuse (EA) moderated effects of cortisol administration (CORT) versus placebo on emotional memory formation in depression. Participants included 75 unmedicated women with varying levels of depression severity and/or EA history. In a double-blind crossover investigation, we used functional magnetic resonance imaging to measure effects of CORT (vs. placebo) on neural function during emotional memory formation.

RESULTS: CORT eliminated the well-known relationship between depression severity and negative memory bias, a finding explained by EA severity. For women with a history of severe EA, CORT reduced depression-related negative memory bias and normalized recall for pleasant stimuli. EA severity also moderated CORT effects on neural function: in women with history of severe EA, CORT increased activation in the supplementary motor area during viewing of unpleasant relative to pleasant pictures. Additionally, supplementary motor area activation predicted reduced negative bias for pictures encoded during CORT.

CONCLUSIONS: These results suggest that increasing cortisol signaling may be neurocognitively beneficial in depressed women with a history of maltreatment. The findings corroborate prior research suggesting that presence or absence of adverse caregiving is etiologically important in depression. These findings suggest potential neurocognitive mechanisms of therapeutics targeting cortisol signaling, which show promise in treating affective disorders.

Key words: Cortisol, Depression, Emotional abuse, Emotional memory, fMRI, Supplementary motor area

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Childhood maltreatment is a predisposing factor for psychiatric disorders and triggers various biobehavioral alterations (1–3). In animal models, aversive caregiving causes lifelong changes in offspring, including alterations in neuroplasticity and stress-related neuromodulators, such as glucocorticoid (GC) hormones (i.e., cortisol and corticosterone) (1,4–6). GCs modulate neuroplastic mechanisms through binding at both type I (mineralocorticoid receptors [MRs]) and type II (glucocorticoid receptors [GRs]) corticosteroid receptors (7–9). It is not possible to directly measure neural signaling of GCs at corticosteroid receptors in humans, and little is known about how aversive caregiving alters effects of cortisol on neural function in humans.

Early life stress in rodents causes lifelong alterations in GC cellular signaling (4,6,10), which is partially due to influences of maternal care on epigenetic programming of GR expression (11). Furthermore, aversive caregiving in rodents causes alterations in GC effects on learning and neuroplasticity (4,6,10). Corticosterone eliminates reductions in hippocampal long-term potentiation associated with early experience of poor maternal care (4). Moriceau *et al.* (6) showed that infant rats exposed to paired maternal odor-shock conditioning exhibited deficits in fear learning at later developmental stages, which were rescued with corticosterone administration. These findings suggest that GC administration may eliminate deficient neuroplastic processes in adult rats that experienced aversive parenting.

Recent research highlights the role of altered neuroplastic mechanisms in animal models of psychiatric disorders (12). It has been hypothesized that altered effects of stress and GCs on neuroplastic mechanisms are key etiological factors in depression (8,13). Consistent with their effects on neuroplasticity, GCs have potent effects on emotional memory in humans (14–16). Despite decades of research implicating cortisol alterations in depression, relatively little is known about the role of GCs in biased emotional memory formation, which is a core feature of depression (17–20).

We used pharmacological manipulation of cortisol (CORT) versus placebo during functional magnetic resonance imaging (fMRI) scanning and memory formation for emotional pictures. Recall of pictures encoded during fMRI was tested 2 days after scanning. Because GC effects on emotional memory vary

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based on sex (21), only women were included. Women were recruited across a range of severity of childhood emotional abuse (EA) and depressive symptoms. We hypothesized that CORT would reduce depression-related memory bias and that EA would moderate this effect. We further hypothesized that brain regions associated with adrenal function and emotional memory would be related to effects of CORT on memory bias. Our laboratory previously found that effects of CORT on hippocampal function were related to memory bias in depression (18). Regions involved in emotional enhancement of memory (amygdala and medial prefrontal cortex) are influential in effects corticosteroids on learning (22,23). Recent research in nonhuman primates suggests a key role for premotor cortex (PMC) and supplementary motor area (SMA) in regulating adrenal function (24). These areas project to the adrenal gland and likely regulate the adrenal medulla sympathetic system, which moderates effects of corticosteroids on learning (24). Because sympathetic nervous system activation affects emotional memory (25,26), we tested whether variation in salivary α-amylase (sAA), as an index of sympathetic functioning (27), was related to neurocognitive effects of CORT.

METHODS AND MATERIALS

Participants

We recruited women between the ages of 18 and 45 with varying levels of EA and/or depression (see Supplement for inclusion and exclusion criteria). We did not specifically recruit women with anxiety disorder or posttraumatic stress disorder, but these were not exclusionary. Of 85 eligible participants, 80 completed the study. Full data were available for 75 participants (mean age, 27.6 years; 75% white, 17% Asian, 5% black, 8% Hispanic). Data were lost owing to experimenter error (1 participant), scanner malfunction (1 participant), fMRI signal drop out (2 participants), and a medical condition (1 participant). The University of Wisconsin Health Sciences Institutional Review Board approved study procedures. Participants provided written informed consent and were paid for participation.

Measurement of Childhood Emotional Abuse and Depressive Symptoms

We retrospectively assessed childhood EA, which predicts negative cognitive bias and incidence of depression over and above severity of physical and sexual abuse (28–31). To index severity of EA, we used the Emotional Abuse subscale of the Childhood Trauma Questionnaire (CTQ) (32). The Emotional Abuse subscale captures mild to severe aversive caregiving. The CTQ is a well-validated instrument that can be used continuously or to categorize participants into groups, which aids in interpreting results (32). Standard CTQ cut scores were used to categorize participants based on severity of EA. Of the final sample, 15 women experienced moderate to extreme (severe), 14 experienced low to moderate (moderate), and 46 experienced none to minimal (minimal) childhood EA. We examined timing of EA before 18 years of age using a life history calendar (33), which confirmed that all women endorsing EA experienced abuse before menarche, many of whom experienced ongoing EA from early childhood through adolescence.

Consistent with the National Institute of Mental Health Research Domain Criteria framework (34), we recruited women with a range of severity of depressive symptoms. Psychopathology was assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (35) with additional questions to assess DSM-5 criteria. Table 1 indicates DSM-5 diagnoses with respect to EA groups (full listing of DSM-5 diagnoses in Supplement). We indexed depression severity by taking the average of Beck Depression Inventory–II (BDI-II) (36) scores from the two scan sessions. As in previous research (37,38), we applied a square-root transformation of BDI-II data to reduce negative skew and undue influence of extreme BDI-II scores. BDI-II scores presented in scatter plots were back-transformed to preserve BDI-II score range. Because of the tight association between childhood EA and adult depression (28–31), it is not possible to disentangle variation in EA and depressive symptoms (correlation in this sample is $r_{73} = .45$, $p < .01$). Nonetheless, our goal was to recruit a sample in which EA and depressive symptoms were not entirely overlapping (Table 1).

Procedure

After screening, participation included a mock scan for acclimation to fMRI, two fMRI scans, and two recall test sessions (Figure 1). Cortisol was pharmacologically manipulated with oral administration of 20-mg encapsulated cortisol (i.e., hydrocortisone [CORT]) versus an identically appearing placebo capsule. Drug, i.e., CORT or placebo, was administered 50 minutes after participants arrived and 90 minutes before the memory encoding task in the scanner. CORT and placebo administration order was randomized and double-blinded. Capsules were prepared by the University of Wisconsin Pharmaceutical Research Center. The two scanning sessions began at approximately 4:15 PM (earliest start time was 4:03 PM and latest start time was 4:43 PM) and were typically separated by 1 week.

Memory Encoding Task and Free Recall for Emotional Pictures

For memory encoding tasks, we used emotionally normed pictures from the International Affective Picture System (39) to create two sets of 84 pictures, which were matched on valence and arousal. Each set contained 28 each of pleasant, unpleasant, and neutral pictures. During each fMRI scan, the encoding task entailed presenting one of the two picture sets. Participants engaged in a simple emotional response task during encoding, rating each picture as positive, neutral, or negative using a button box (Current Designs Inc., Philadelphia, PA). Pictures were presented for 5 seconds each, followed by a 3-second response period and a jittered interstimulus interval ranging from 4 to 9 seconds. Stimuli were back-projected onto a screen inside the scanner bore.

Recall test sessions were conducted in the afternoon to early evening, within 48 hours of scanning sessions (except for 1 participant in the minimal EA group whose post-CORT recall session was 9 days after scanning). Free recall for pictures encoded during scans was assessed using methods based on

Table 1. Demographic and Clinical Characteristics

Characteristics	CTQ Emotional Abuse Groups			Group Comparisons[a]
	Minimal (n = 46)	Moderate (n = 14)	Severe (n = 15)	
Age, Years	26.1 ± 6.4	31.4 ± 7.1	28.6 ± 7.9	$F_{2,74} = 3.37$, $p = .04$
Lifetime Depressive Disorder	23 (50.0)	9 (64.3)	14 (93.3)	$\chi^2_2 = 9.02$, $p = .01$
Current Depressive Disorder	12 (26.1)	7 (50.0)	13 (86.7)	$\chi^2_2 = 17.35$, $p < .001$
Current Anxiety Disorder	12 (26.1)	6 (42.9)	9 (60.0)	$\chi^2_2 = 7.02$, $p = .03$
Current PTSD	0	3 (21.4)	6 (40.0)	$\chi^2_2 = 17.53$, $p < .001$
Race[b,c]				$\chi^2_4 = 1.72$, $p = .79$
White	34 (73.9)	9 (64.3)	13 (86.7)	
Asian	8 (17.4)	3 (21.4)	2 (13.3)	
African American	3 (6.5)	1 (7.1)	0	
Unknown	1 (2.2)	1 (7.1)	0	
Ethnicity[b]				$\chi^2_2 = 2.27$, $p = .32$
Hispanic/Latina	4 (8.7)	2 (14.3)	0	
Not Hispanic/Latina	42 (91.3)	11 (78.6)	15 (100)	
Unknown	0	1 (7.1)	0	
Education Level[d]	4.4 ± 1.4	5.2 ± 1.1	4.8 ± 1.3	$F_{2,74} = 2.04$, $p = .14$
Childhood Caregivers' Education Level[d]	4.5 ± 1.7	4.9 ± 1.2	4.9 ± 1.8	$F_{2,74} = 0.56$, $p = .57$

Values are mean ± SD or n (%).
CTQ, Childhood Trauma Questionnaire; PTSD, posttraumatic stress disorder.
[a]N = 75 for all χ^2 statistics.
[b]χ^2 tests confirmed the CTQ Emotional Abuse groups did not significantly differ by racial or ethnic composition.
[c]Because of rounding, percentages may not total 100.
[d]Education categories: 1 = less than high school; 2 = high school diploma or equivalent (i.e., General Equivalency Diploma); 3 = some college, no degree; 4 = associate's degree; 5 = bachelor's degree; 6 = master's degree; 7 = doctoral degree.

our laboratory's prior studies (14,40). Participants were given 10 minutes to provide brief written descriptions of as many pictures as they could recall. If participants had not exhausted recall by 10 minutes, they were given additional time. Scoring was conducted blind to drug condition, depression severity, and EA. Recall descriptions were coded by two scorers. Any discrepancies between scorers were rectified by a third individual (RMH).

Salivary Analytes

Saliva samples were collected for measurement of cortisol and sAA (Table 2). We used Salivettes (Sarstedt, Nümbrecht, Germany) according to recommendations for cortisol and sAA collection (27). Cortisol concentrations were measured with high sensitivity chemiluminescence immunoassay (IBL International GmbH, Hamburg, Germany). sAA concentrations were measured with an enzyme kinetic method. Intra-assay and interassay coefficients of variation were less than 8% for cortisol and less than 11% for sAA. Log-transformed values for sAA and cortisol were used in analyses.

Image Collection and Preprocessing

Brain images were collected using a 3T Discovery MR750 MRI scanner (GE Medical Systems, Waukesha, WI) equipped with an eight-channel radiofrequency coil (GE Healthcare, Waukesha, WI). Structural anatomical brain data were acquired using a T1-weighted brain volume imaging (BRAVO) pulse sequence (inversion time = 450 ms, repetition time = 8.16 ms, echo time = 3.2 ms, flip angle = 12°, matrix = 256 × 256 × 160, field of view = 215.6 mm, slice thickness = 1 mm). Functional data were acquired using a series of sagittal T2*-weighted echo-planar images (repetition time = 2150 ms, echo time = 22 ms, flip angle = 79°, matrix = 64 × 64 × 40, field of view = 224 mm, slice thickness = 3 mm with 0.5-mm gap).

Data were processed in Analysis of Functional NeuroImages (AFNI) unless otherwise indicated (41). First, a rigid-body volume registration was implemented to compensate for participants' motion (3dvolreg, fourth volume as the base image volume for registration). Sagittal field maps were collected via a three-dimensional spoiled gradient recoil (SPGR) sequence (repetition time = 5 ms, echo time = 1.8 ms, flip angle = 7°, matrix = 192 × 128 × 44, field of view = 230 mm, slice thickness = 3.5 mm) to geometrically unwarp echo-planar images to reduce distortion caused by magnetic field inhomogeneities using FMRIB Software Library (42) and iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) sequence (43).

Functional echo-planar imaging data were corrected for slice-timing differences (3dTshift), aligned to their respective T1-weighted anatomical image (align_epi_anat.py), and transformed to Talairach atlas space (44) in a single interpolation to 2 × 2 × 2 mm^3 voxels. The three-dimensional time series were despiked (3dDespike) and spatially smoothed with a three-dimensional Gaussian kernel (full width at half maximum = 6 mm; 3dmerge). Nuisance regressors, including the six estimated motion realignment parameters and constant and linear trend, were removed (3dDeconvolve). Activation was estimated using multiple linear regression (3dDeconvolve) modeling the picture viewing for each valence as a 5-second block convolved with the hemodynamic response function (the BLOCK function in AFNI 3dDeconvolve).

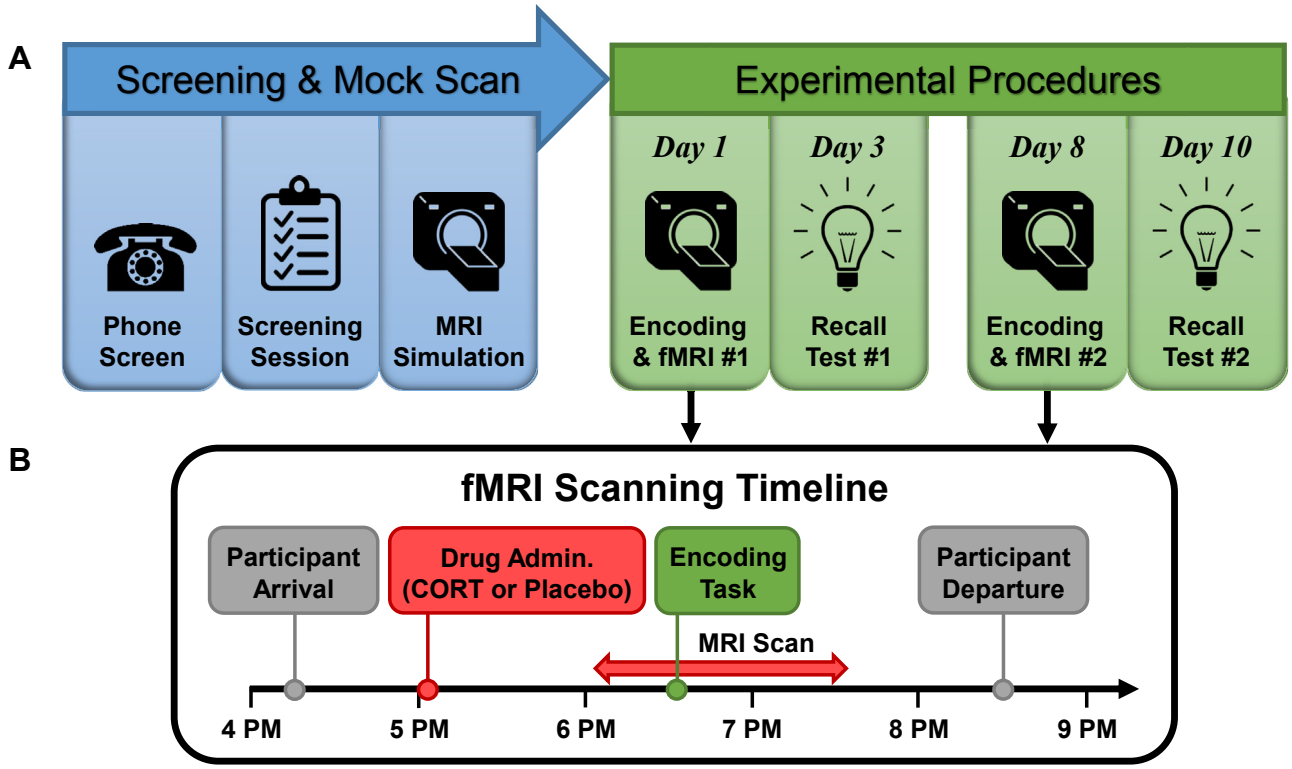

Figure 1. Study procedures and timeline. **(A)** Study timeline. Phone-based and in-person screening determined participant eligibility, after which participants completed a mock scan. In a double-blind crossover design, participants completed two memory encoding and functional magnetic resonance imaging (fMRI) sessions, which were typically separated by 1 week. During each memory encoding and fMRI session, participants were administered a pill containing either 20-mg cortisol (CORT) or placebo. Two days after each encoding and fMRI session, participants returned to the laboratory to be tested for memory recall of encoded pictures. **(B)** Encoding and fMRI sessions timeline. Encoding and fMRI sessions were conducted in the evening when endogenous cortisol levels are low. Participants arrived at approximately 4:15 PM; received study drug at 5:05 PM; and underwent MRI scanning from approximately 6:05 PM to approximately 7:35 PM, with the encoding task beginning at approximately 6:35 PM. Participants departed the laboratory at approximately 8:30 PM. Saliva samples were collected throughout the procedures, including a sample immediately after the encoding task, to index salivary cortisol and α-amylase levels.

Data Analysis

Memory bias is expressed as bias $= \frac{UR - PR}{UR + PR}$, where UR and PR represent unpleasant and pleasant pictures recalled, respectively, to index the difference in recall for unpleasant and pleasant pictures while adjusting for variation in overall recall. Each participant has two memory bias scores, one for pictures encoded during CORT and one for pictures encoded during placebo administration. Full models were analyzed first using continuous measures of EA severity. For purposes of interpretation, we also present results from analyses using categories for severity of EA based on standard CTQ cut scores (i.e., EA groups). We used analysis of covariance (PROC GLM, SAS 9.4; SAS Institute Inc., Cary, NC) to test whether EA, depression severity, or their interaction moderated effects of drug (CORT vs. placebo) on memory bias. To identify neural activation related to effects of CORT on memory bias, we analyzed whole-brain fMRI data (during unpleasant vs. pleasant trials) using linear mixed-effects analysis in AFNI (3dLME) in two separate analyses, first including EA as a continuous and second as a categorical independent variable, along with drug (CORT vs. placebo) as a categorical independent variable and depression severity and memory bias as continuous covariates. Activation refers to greater signal change during unpleasant with respect to pleasant stimuli. Data were corrected for multiple comparisons by first choosing an individual voxel p value threshold ($p = .005$ for main effects and $p = .01$ for EA $\times$ drug interaction in view of increased noise across multiple scan sessions) and then performing a Monte Carlo simulation (3dClustSim) to determine the minimum cluster size to achieve a false-positive rate of 0.05. This simulation uses an estimate of the autocorrelation function, determined from preprocessed data (3dClustSim), to address recent concerns over inflated false-positive rates (45,46). To examine whether neural findings could be explained by variation in sympathetic nervous system arousal, we conducted hierarchical regression with fMRI signal change as the dependent variable and the following predictors: sAA level at midscan, severity of childhood EA, and memory bias. We also confirmed that variation in endogenous cortisol (using baseline and midscan samples from placebo day) did not moderate findings.

RESULTS

Memory Bias

EA and depression severity jointly moderated effects of CORT on memory bias, as illustrated by an EA $\times$ depression

Table 2. Salivary Analytes and Recall Performance

Measure	CTQ Emotional Abuse Groups, Mean ± SD			Group Comparisons
	Minimal (n = 46)	Moderate (n = 14)	Severe (n = 15)	
Postencoding Salivary Cortisol Levels, nmol/L				
Placebo	1.3 ± 1.6	1.7 ± 2.1	1.2 ± 0.8	$F_{2,74}$ = 0.33, p = .72
CORT	55.4 ± 33.6	54.2 ± 32.7	49.7 ± 40.6	$F_{2,74}$ = 0.15, p = .86
Postencoding sAA Levels, U/mL				
Placebo	191.8 ± 155.9	172.9 ± 155.6	227.9 ± 189.8	$F_{2,74}$ = 0.61, p = .55
CORT	166.0 ± 115.1	221.7 ± 225.9	180.5 ± 131.9	$F_{2,74}$ = 0.10, p = .90
Recall for Pleasant Pictures				
Placebo	10.8 ± 4.1[a]	11.9 ± 6.1[a]	7.5 ± 3.4[a,b]	$F_{2,74}$ = 4.09, p = .02
CORT	11.1 ± 4.9	12.9 ± 4.8	10.4 ± 4.0[b]	$F_{2,74}$ = 0.11, p = .35
Recall for Unpleasant Pictures				
Placebo	12.9 ± 4.8	13.4 ± 4.9	11.7 ± 3.8	$F_{2,74}$ = 0.54, p = .59
CORT	12.8 ± 4.6	13.5 ± 3.7	12.3 ± 2.6	$F_{2,74}$ = 0.32, p = .72

Means for salivary cortisol and sAA samples taken immediately after memory encoding task show no differences related to severity of childhood EA.

CORT, cortisol administration; CTQ, Childhood Trauma Questionnaire; EA, emotional abuse; sAA, salivary α-amylase.

[a]Means for recall performance show that participants with severe EA recalled fewer pleasant pictures encoded during placebo administration than participants with minimal or moderate EA ($F_{2,74}$ = 4.09, p = .02).

[b]Means for recall performance show that participants with severe EA recalled more pleasant pictures encoded during CORT than placebo administration (t_{14} = 2.34, p = .03).

severity × drug (CORT vs. placebo) interaction ($F_{1,71}$ = 5.13, p < .03) (Figure 2). For pictures encoded during placebo administration, depression severity was associated with negatively biased memory ($F_{1,69}$ = 12.57, p < .001) (Figure 2A), which remains significant when accounting for variation in endogenous cortisol (p < .001). CORT abolished the relationship between depression severity and memory bias (r_{73} = .08, not significant) (Figure 2B). For pictures encoded during CORT administration, neither depression severity nor EA predicted negative memory bias (p > .43). However, the interaction between depression severity and EA predicted memory bias for pictures encoded during CORT administration ($F_{2,69}$ = 5.63, p < .01) (Figure 2B),[1] which remains significant when accounting for variation in endogenous cortisol (p < .01). CORT reversed the relationship between depression severity and emotional memory bias only in women with severe EA (Figure 2B). Group means for recall performance (Table 2) show that women with severe EA had a deficit in recall for pleasant pictures encoded during placebo administration, which was normalized for pictures encoded during CORT administration (t_{14} = 2.34, p = .03).

Effects of CORT on Neural Activation

Neural activation during placebo administration was not related to EA or depression severity. During CORT administration, EA, but not depression severity, moderated neural activation in left SMA, inferior parietal, and cerebellar clusters (p < .05 corrected for multiple comparisons) (Table 3). In addition, significant interactions (p < .05 corrected for multiple comparisons) showed that EA moderated effects of drug in a cortical region spanning left lateral (PMC) and medial (SMA) extent of Brodmann area 6, thalamus, and right PMC (spanning from Brodmann area 6 to Brodmann area 40) (Table 3). Interactive effects of drug × EA are displayed in Figure 3 for the model using the continuous measure of EA. Figure 4 displays effects categorically for EA groups, illustrating the drug × EA interaction in detail. Post hoc testing showed that CORT enhanced SMA activation in participants with severe childhood EA ($F_{2,74}$ = 4.33, p < .02) (Figure 4),[2] which remains significant when accounting for variation in endogenous cortisol (p < .02). The thalamus cluster significant for the EA × drug interaction was centered in the pulvinar nucleus; we observed activation in the pulvinar in women with minimal EA during both CORT and placebo administration, whereas women with moderate and severe EA showed pulvinar activation only during CORT administration (Figure 4).

Neural Function, Sympathetic Activation, and Memory

Because recent research in nonhuman primates suggests that SMA has top-down control over the sympathetic adrenal medullary system (24), we further interrogated the left SMA cluster (which showed a main effect of EA during CORT and an EA × drug interaction) by testing whether sympathetic activation (sAA levels during scanning) accounted for SMA activation. Hierarchical regression showed that during placebo administration, SMA activation was not related to predictors (i.e., sAA level during placebo scan, severity of EA, memory bias for pictures encoded during placebo, or interactions among these variables; all ps > .26). However, during CORT administration, sAA levels accounted for significant variance in SMA activation (Table 4). Even after accounting for sAA levels during the CORT scan, SMA activation was significantly related to severity of EA and memory

[1] EA significantly moderated effects of CORT when menstrual phase and age were included in the model ($F_{2,50}$ = 6.40, p < .005).

[2] Post hoc test remained significant when menstrual phase and age were included in the model ($F_{2,62}$ = 3.99, p < .03).

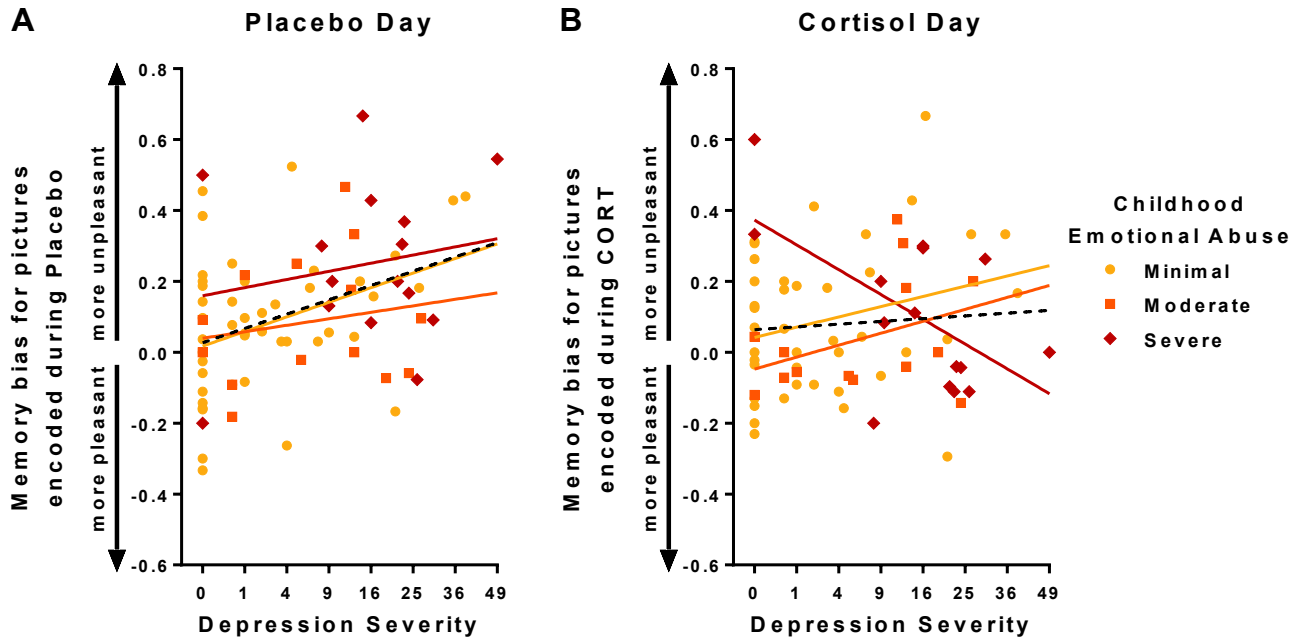

Figure 2. In participants with severe childhood emotional abuse (EA), cortisol administration (CORT) reversed the association between depression severity and negative memory bias. Dashed black lines represent regression fit for full sample. Colored lines represent regression fits for subjects with differing levels of childhood EA (see legend). Depression severity was indexed with Beck Depression Inventory–II (see text for details). **(A)** For pictures encoded following placebo administration, women with greater levels of depression recalled more unpleasant relative to pleasant pictures, i.e., showed greater negative memory bias (r_{74} = .38, $p < .001$). **(B)** Following CORT administration, there was no such correlation at the group level (r_{74} = .08, not significant), illustrating a drug (CORT vs. placebo) × depression severity interaction effect ($F_{1,73}$ = 5.31, $p < .03$) in which CORT abolishes the relationship between depression severity and negative memory bias for the entire sample. Childhood EA moderated the effect of CORT: in women with history of severe EA, CORT reversed the relationship between depression severity and negative memory bias ($F_{2,74}$ = 5.63, $p < .01$).

bias for pictures encoded during CORT but not interactions among these variables (Table 4). Zero-order correlations show that greater CORT-day activation of SMA was associated with higher sAA (r_{73} = .29, p = .01), more severe EA (r_{73} = .28, p = .01), and more positive memory bias for pictures encoded during CORT administration (r_{73} = −.26, p = .02). When tested separately for each of the three EA groups, the relationship between CORT-day SMA activation and memory bias was in the same direction for each group, although not significantly in participants with moderate or severe EA (minimal: r_{44} = −.33, p = .02, moderate: r_{12} = −.13, not significant, severe: r_{13} = −.21, not significant).

Table 3. Moderating Effects of Childhood EA Severity on BOLD Signal Contrasts for Unpleasant > Pleasant Pictures

Region	Volume (Voxels)	Coordinate (Peak)	Coordinate (CM)	Statistic (Peak)	*p* Value (Corrected)
Placebo					
None	—	—	—	—	—
CORT					
Left SMA	3409	(−4, −17, 62)	(−8, −25, 51)	Z = 4.8	.01
Cerebellum	1023	(24, −33, −47)	(18, −35, −45)	Z = 4.1	.01
Left inferior parietal lobule	781	(−55, −28, 31)	(−46, −39, 33)	Z = 4.4	.02
CORT vs. Placebo					
Left BA 6—whole cluster	1425	(−38, −13, 52)	(−18, 23, 51)	F = 12.4	.01
Left BA 6—medial aspect (SMA)[a]	—	(−4, −17, 60)	(−6, −17, 58)	F = 10.2	—
Bilateral thalamus	1188	(14, −33, 7)	(4, −25, 5)	F = 11.2	.02
Right BA 6/BA 40	1148	(28, −46, 59)	(28, −38, 52)	F = 9.1	.02

BA, Brodmann area; BOLD, blood oxygen level–dependent; CM, center of mass; CORT, cortisol administration; EA, emotional abuse; SMA, supplementary motor area.

[a]The full extent of left BA 6 activation for EA × drug (CORT vs. placebo) includes both SMA and premotor cortex, and peak significance falls in premotor cortex. Owing to significant main effect of EA on CORT day in SMA and for theoretical reasons (24), we also report coordinates for the local maxima in SMA alone.

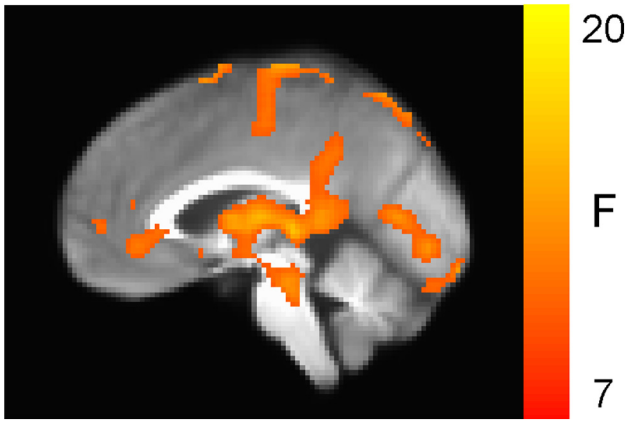

Figure 3. Brain regions showing significant drug (cortisol administration vs. placebo) × emotional abuse (EA) interaction for the model using the continuous measure of EA (i.e., Childhood Trauma Questionnaire Emotional Abuse subscale scores). Also see Table 3 and Figure 4, which display the drug × EA interaction in more detail for EA groups (based on Childhood Trauma Questionnaire Emotional Abuse cut scores).

DISCUSSION

We replicated the well-known relationship between greater depression severity and negative bias in emotional memory formation for pictures encoded during placebo administration (19). CORT administration eliminated the relationship between depression severity and memory bias, a finding that was explained by severity of childhood EA. In women with severe EA, CORT reversed the relationship between depression severity and memory bias and normalized deficient memory formation for pleasant pictures. Thus, in women with severe childhood EA, CORT normalized the emotional memory alterations associated with depression.

Our findings are consistent with rodent data showing that GCs can ameliorate alterations in neuroplasticity in rats with a history of aversive caregiving (4,6,10). Studies in rodents suggest that prior experiences can shift the dose-response relationship between GCs and plasticity (47,48). For instance, rats previously exposed to aversive caregiving show impairments in learning and neuroplasticity with low GCs but enhancements with high GCs (4,6,10). We can speculate that experience of aversive parenting may induce a cascade that results in persistent cellular resistance to GCs at nonstress levels, which may normalize or shift to cellular sensitization to GCs when elevated. Future research is needed to substantiate this speculation.

Our findings may suggest that individuals with versus without childhood EA show different neurocognitive responses to acute GC elevations. Heim *et al.* (49) have suggested that depressed adults with versus without a history of childhood adversity represent different subtypes, in part because depressed patients with a history of adversity are more likely to show peripheral hypothalamic-pituitary-adrenal axis dysregulation, negative feedback deficits, and GC resistance than depressed patients without a history of adversity. A number of studies suggest that different measures of GC resistance are interrelated and that peripheral measures of GC resistance may predict variation in GC effects on cognition (50–52). Future research should address to what extent peripheral measures of GC resistance reflect altered neural signaling of CORT.

CORT Effects on Neural Function

We did not replicate altered CORT effects on hippocampal function in depression (18), and we did not observe effects of CORT on frontolimbic circuitry directly involved in emotional memory (53–55). However, we found that severity of childhood EA moderated effects of CORT on activity in a cluster spanning left PMC and SMA. In women with severe EA, CORT increased SMA activation. We further showed that sympathetic activation was related to SMA activation during CORT, but not during placebo, administration. Despite this relationship, levels of sympathetic activation did not account for relationships between SMA activation and severity of EA or memory bias, each of which were uniquely related to SMA activation on the CORT, but not the placebo, day. Greater SMA activation was

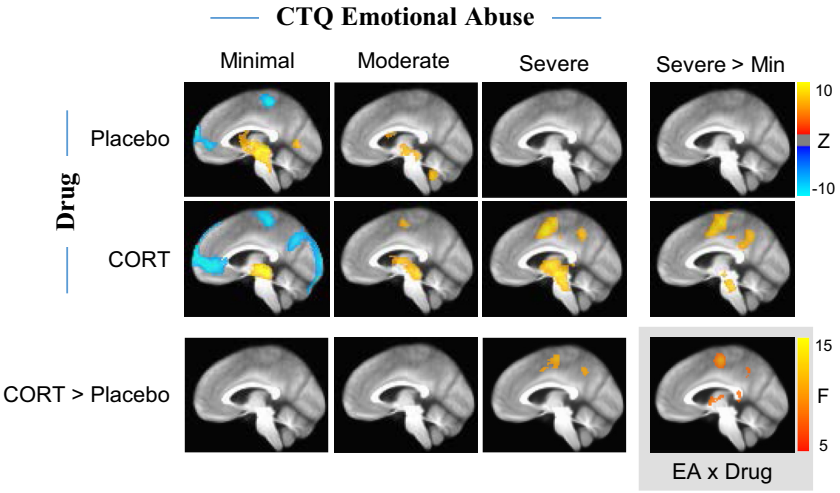

Figure 4. Cortisol administration (CORT)-related neural response to unpleasant > pleasant pictures varied by severity of childhood emotional abuse (EA). Shown are sagittal group difference maps for unpleasant > pleasant activations (centered on left supplementary motor area) for EA groups (minimal, moderate, and severe) during placebo and CORT conditions. Colors reflect *Z* scores for CORT > placebo and severe > minimal activation. At bottom right (gray box), colors reflect *F* values for significant clusters (supplementary motor area and thalamus) in the EA × drug interaction. For cluster statistics, see Table 3. Individual voxel *p* value threshold for placebo and CORT conditions was $p < .005$; a less stringent threshold of $p < .01$ was used for CORT > placebo. CTQ, Childhood Trauma Questionnaire.

Table 4. Hierarchical Regression Predicting Signal Change in Left SMA During CORT Administration

	R^2	Increment in R^2	F	p Value[a]
Midscan sAA	.08	.08	6.71	.01
EA	.15	.07	5.52	.02
Memory Bias	.21	.07	5.80	.02
sAA × EA	.25	.04	3.13	.08
sAA × Memory Bias	25	—	0.18	.67
sAA × EA × Memory Bias	.25	—	0.05	.83

This table shows results from a hierarchical regression predicting variation in left SMA activation during CORT administration. The findings listed show that during CORT administration, SMA activation is significantly related to midscan sAA (which indexes sympathetic activation). Even after accounting for variation in sAA, SMA activation during CORT administration is significantly related to severity of childhood EA (Childhood Trauma Questionnaire Emotional Abuse subscale) and emotional memory bias for pictures encoded during CORT administration. The full model is significant ($F_{6,74}$ = 3.78, $p <$ .003) and accounts for 25% of the variance in SMA signal change during CORT administration, which represents a medium to large effect size.

CORT, cortisol administration; EA, emotional abuse; sAA, salivary α-amylase; SMA, supplementary motor area.

[a]p values represent significance of increment in R^2 attributable to each variable.

associated with less negative memory bias for pictures encoded on the CORT day. The increase in SMA activation observed may have been protective in contributing to the CORT-driven normalization of emotional memory in women with severe EA.

Several lines of research support the interpretation that SMA may mediate relationships between stress neuromodulators and behavior. Recent retrograde tracing studies in nonhuman primates identified SMA and adjacent cingulate motor areas (56) as the cortical regions most densely projecting to adrenal medulla (24). Comparable regions in rodents (i.e., dorsomedial prefrontal areas) are necessary for GC (57) and noradrenergic (58) regulation of adrenal output, and stress alters the role of these circuits in behavior (59). SMA, pre-SMA, and cingulate motor areas are associated with integrating cognitive and affective inputs, especially negative affect, in motor planning (60) and ultimately guiding response selection (61). SMA recruitment may reflect a less passive, more action-oriented (62–64) cognitive response to negative stimuli. Human neuroimaging studies have found SMA involvement in directed emotion regulation (65) and in first-person emotional memory (66), supporting a role in embodied motor influence on emotional memory formation.

Severity of childhood EA also moderated the effects of CORT on thalamic activity centered in the pulvinar nucleus. Lesion and neuroimaging studies suggest a role for the pulvinar in emotional gating of attention and binding salient emotional features in working memory and alterations of these processes in mood disorders (67,68). Future research should investigate whether effects of CORT on emotional cognition are related to SMA, PMC, and thalamic activation.

Mechanisms of CORT Neural Signaling

Endogenous cortisol levels measured during placebo did not differ by EA severity, which suggests that neurocognitive effects of CORT administration may be altered even if circulating endogenous cortisol concentrations are relatively unaffected. Mechanisms that govern neuronal response to GCs are extremely complex, and recent research has elucidated many factors that alter GC effects on neuronal function (7,13,69). An extensive description of mechanisms underlying variation in GC cellular signaling is outside the scope of this article, and these mechanisms are reviewed elsewhere (8,70,71). Briefly, genetic and functional variations in MRs and GRs as well as many other mechanisms, such as *FKBP5* functioning, affect GC cellular signaling (8,70,71). Moreover, early life adversity is associated with alterations in both MR and GR function in relation to neuroplasticity and memory (72,73). The current study does not address whether GC actions at MRs or GRs (or any other intracellular or membrane-bound mechanisms) are responsible for observed effects. However, the memory encoding task was conducted in the evening when endogenous CORT levels are low and presumably GRs (with low affinity for cortisol) and MRs (with high affinity for cortisol) were not fully occupied by circulating CORT before drug administration (8). We can speculate that the normalization of emotional memory bias in women with a history of severe EA may be due to actions of CORT at MRs (8), although findings may be due to CORT effects at GRs or other mechanisms.

Central noradrenergic activation and peripheral sympathetic activation moderate GC effects on emotional memory (26,74). Interestingly, SMA has recently been identified as the cortical region most densely projecting to adrenal medulla in nonhuman primates, suggesting a key role in controlling adrenal medulla (sympathetic) output (24). We found that sAA levels (indexing sympathetic activation) were related to SMA activation during CORT administration but did not account for the relationship between SMA and EA or memory bias. These findings are suggestive of sympathetic nervous system involvement in CORT effects on activation in SMA, but this involvement does not fully account for the association between SMA activation and psychological variables under study.

Implications for Psychiatric Treatment

The MR agonist fludrocortisone may be beneficial in augmenting treatment for nonpsychotic depression (8,75), whereas GR antagonism (e.g., with mifepristone) may be beneficial in psychotic depression (76). While these treatment-related findings are promising, efforts to identify effective psychiatric medications directly targeting GC signaling have been largely unsuccessful (77). This may be partially attributable to the sheer number and complexity of factors affecting neuronal and cognitive responses to GCs (7,8,70,78). Greater success may stem from investigating how severity of early life adversity moderates efficacy of experimental therapeutics. Prior research shows that depression associated with prior experience of aversive caregiving requires a different treatment regimen than depression in the absence of early adversity (79,80). The current study paradigm can be adapted to investigate mechanisms and potential therapeutic efficacy of

corticosteroid receptor ligands and whether their neural actions vary based on childhood adversity.

Limitations

Although our overall study was well powered (N = 75), our primary findings reflected differences for the small subgroup of women (n = 15) with severe EA. The findings need to be replicated with a larger sample of individuals with severe EA with a wide range of severity of affective pathology. Results may have differed if women with a wider age range, women with more severe depression, or men were included (21) or if other methods regarding dose and timing were used (64). Our study is not adequately powered to test whether posttraumatic stress disorder, anxiety, or depression specifiers of melancholia or atypical depression moderate the effects of CORT. Finally, though the findings suggest that pharmacologically elevated cortisol may be beneficial in depressed women with EA, the findings do not necessarily suggest that acutely heightened endogenous cortisol owing to a stressor would be beneficial.

Conclusions

Consistent with the National Institute of Mental Health Research Domain Criteria framework, our study integrates across multiple levels of information (cognitive, hormonal, neural). In women with varying levels of depression, EA moderated the effects of CORT on neural activation during memory encoding for emotional stimuli and depression-related memory bias for these stimuli. The findings suggest that increasing cortisol signaling may be neurocognitively beneficial in women with depression who experienced aversive caregiving in childhood. These findings support past research suggesting that the presence or absence of childhood maltreatment is etiologically important in depression, which should be taken into account when developing experimental therapeutics targeting cortisol signaling (79,80). These findings also support previous research suggesting that aversive caregiving has the potential to fundamentally alter effects of GCs on neurocognitive function into adulthood (4,6,10).

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