# Archival Report

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

Heather C. Abercrombie, Carlton P. Frost, Erin C. Walsh, Roxanne M. Hoks, M. Daniela Cornejo, Maggie C. Sampe, Allison E. Gaffey, David T. Plante, Charlotte O. Ladd, and Rasmus M. Birn

## 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 un-medicated 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 neuro-cognitive 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

https://doi.org/10.1016/j.bpsc.2017.11.005

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 (gluco-corticoid 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 neuro-plasticity, 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

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 $\alpha$-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