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Exogenous Glucocorticoids Decrease Subgenual Cingulate Activity Evoked by Sadness

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The glucocorticoid hormone cortisol is known to have wide-ranging effects on a variety of physiological systems, including the morphology and physiology of the amygdala and hippocampus. Disruptions of cortisol regulation and signaling are also linked with psychiatric disorders involving emotional disturbances. Although there is much evidence to suggest a relationship between cortisol signaling and the brain physiology underlying emotion, few studies have attempted to test for direct effects of cortisol on the neurophysiology of emotion. We administered exogenous synthetic cortisol (hydrocortisone, HCT) using two different dosing regimens (25 mg/day over 4 days, 100 mg single dose), in a double-blind placebo-controlled functional magnetic resonance imaging (fMRI) study. During fMRI scanning, healthy subjects viewed images designed to induce happy, sad, and neutral emotional states. Subjective emotional reactions were collected for each experimental stimulus after fMRI scanning. Mood ratings were also collected throughout the 4 days of the study. Both dose regimens of HCT resulted in decreased subgenual cingulate activation during sadness conditions. The 25 mg/day regimen also resulted in higher arousal ratings of sad stimuli. No effects of HCT were observed on any mood ratings. Few reliable effects of HCT were observed on brain activity patterns or subjective emotional responses to stimuli that were not sad. The inhibitory effects of cortisol on sadness-induced subgenual cingulate activity may have critical relevance to the pathophysiology of major depression, as both subgenual hyperactivity and decreased sensitivity to cortisol signaling have been documented in patients with depression.
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INTRODUCTION

The glucocorticoid hormone cortisol has wide-ranging effects on many physiological systems, including the brain. When exogenous glucocorticoids are administered for behavioral studies (Buchanan and Lovallo, 2001; Reuter, 2002; Wirth *et al*, 2011) or given therapeutically for controlling inflammatory processes, they can induce substantial emotional changes, including depression and mania (Brown *et al*, 2004; Ling *et al*, 1981; Wada *et al*, 2001; Wada *et al*, 2000).

Although it is clear that glucocorticoids can influence emotion, the mechanism of these effects is unclear. There is evidence to suggest that glucocorticoids may be exerting these effects by directly influencing the activity of brain regions involved in emotion processing. Cortisol, crosses the blood–brain barrier with high efficiency (Pariante *et al*, 2004) and has receptors in brain regions implicated in emotion processes, including the amygdala, frontal lobe, and temporal lobe (Sarrieau *et al*, 1986; Watzka *et al*, 2000a, b). Glucocorticoids have also been shown to have effects on brain activation in the medial temporal lobe (De Quervain *et al*., 2003), amygdala (Henckens *et al*, 2010; Lovallo *et al*, 2010), and hippocampus (Abercrombie *et al*, 2011). In addition, previous studies have also demonstrated that glucocorticoids affect the morphology and physiology of neurons in brain regions associated with emotional behaviors, including the hippocampus, amygdala, ventral tegmentum, and prefrontal cortex (Brown *et al*, 2008; Cho and Little, 1999; De Kloet *et al*, 1998; Karst *et al*, 2002; Mitra and Sapolsky, 2008; Sapolsky, 2000; Wellman, 2001; Woolley *et al*, 1990).

The influence of glucocorticoids on emotion-related brain activity could be critically relevant for understanding the pathophysiology of emotion disturbances in psychiatric conditions. Major depressive disorder (MDD) in particular has been associated with changes in glucocorticoid signaling. Reduced glucocorticoid receptor mRNA expression (Webster *et al*, 2002) has been shown in MDD patients. Similarly, reduced glucocorticoid sensitivity in MDD predicts worse clinical outcomes in patients (Greden *et al*, 1980; Zobel *et al*, 2001; Zobel *et al*, 1999). This suggests that

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glucocorticoid signaling may be as critical as glucocorticoid secretion in MDD.

Objectives and Hypotheses

The broad objective of this study was to test how exogenous glucocorticoids affect brain activity patterns elicited by specific emotions. As little is known about the normal effects of glucocorticoids on human brain activity, we tested for these effects in young healthy subjects. However, as both glucocorticoid signaling abnormalities and abnormal brain activity patterns are well documented in major depression, we tested for glucocorticoid effects on specific brain regions and emotional processes impacted by MDD. These included the responses of the subgenual cingulate cortex, amygdala, and ventral medial prefrontal cortex to both happy and sad emotional stimuli.

We tested the effects of two different dose regimens of orally administered hydrocortisone (HCT) on brain activity elicited by sad, happy, and neutral emotions. We also tested the effects of HCT on the subjective emotional reactions to stimuli and on mood ratings. We hypothesized HCT would exert effects on sadness-evoked activity in the subgenual cingulate cortex, amygdala, and ventral medial prefrontal cortex. We also hypothesized that subjects would experience emotional changes that would mimic very small-scale depressive symptoms, namely that HCT would increase sadness and decrease happiness reactions to emotional stimuli, and that subjects would experience an increase in sad mood over the course of a 4-day exposure to HCT.

MATERIALS AND METHODS

Subjects

A total of 61 healthy (31 male, 30 female) subjects, ages 18–30 years, were recruited from the community via advertising and signed a local internal review board-approved informed consent document. Exclusion criteria consisted of a history of endocrine disorders, head injury, psychiatric or neurological disorders, current medication use, oral contraceptive use, recent major surgery, a history of traumatic life events, current illicit drug use, smoking, left handedness, and current exposure to self-reported excessive psychological stress, meeting MINI International Neuropsychiatric Interview (Sheehan *et al*, 1998) criteria for axis-1 psychiatric disorders, scoring more than 7 points on the Beck Depression inventory-II, or testing positive on urine-based drug or pregnancy tests. For female subjects, functional magnetic resonance imaging (fMRI) scanning was scheduled to coincide with the luteal phase of their menstrual cycle based on the last onset of menses.

Design

This study used a double-blind placebo-controlled between-groups design. We compared (1) measures of mood (2) subjective reactions to emotional stimuli, and (3) brain activation patterns elicited by happy, sad, and neutral stimuli between a control group receiving placebo and two groups each receiving one of two different dose regimens of HCT.

Matching and Randomization

Subjects were matched into triplets by age, weight, and gender. All three members of a triplet were required to be within 5 years of each other in age, 4.5 kg of each other in weight and of the same gender. Each member of a triplet was then randomly assigned into one of the three groups. Subjects received placebo (P), a single dose (SD) of 100 mg oral HCT, given 2 h before fMRI scanning, or an extended dose (ED) regimen of 25 mg daily over 4 days, given on a twice-daily schedule. Placebos were also administered to the SD and ED groups at various time points so that all the groups received an identical number of pills at identical times of day. The SD regimen was designed to test acute effects of cortisol by insuring high levels at the time of scanning. The ED regimen was designed to test the effects of persistent elevations, spread over 4 days. The last HCT dose given to the ED group was administered 8 h before scanning to allow adequate time for metabolism of the last dose. This procedure prevented both acute effects and extended exposure effects of HCT occurring at the same time in the ED group. The matching procedure successfully produced groups of similar age, weight, and gender distributions (P: age (years) = 21.8 (0.6), weight (kg) = 69.5 (2.8), gender = 10 M/10 F; SD: age = 21.5 (0.7), weight = 69.1 (2.7), gender 10 M/11 F; age = 21.7 (0.6), weight = 67.3 (4.0), gender 10 M/10 F). One extra subject was recruited to supplement one of the triplets after a single subject only completed half of the fMRI scanning session.

fMRI Task Design

During scanning subjects passively viewed happy, sad, and neutral stimuli taken from the International Affective Picture System (IAPS) and a collection of emotional face images (Gur *et al*, 2002). Individual stimuli were presented for 6 s at a time within a block of similar stimuli that lasted 18, 24, or 30 s. A block of stimuli consisted of only one of the following stimuli types: happy faces, sad faces, neutral faces, happy IAPS, sad IAPS, and neutral IAPS. Stimulus emotion (sad, happy, or neutral) or type (face or IAPS) were not mixed within a block. Each block was temporally flanked by 12 s of a fixation cross. Twelve blocks were then grouped into runs that lasted 6 min and 27 s each. Block order within a run, and image order within a block were pseudo-randomized to control for order effects of particular emotions, stimulus types (IAPS or face), gender of face, and the order/frequency, in which an individual model's face was presented. Each run contained identical and proportional representation of each emotion condition. Subjects were instructed to 'Look at each picture, and feel whatever you feel', and to perform a button press (right index finger) at the onset of each picture or fixation cross. The purpose of the button press was to verify task compliance.

Measurement of Mood States and Emotional Reactions to Stimuli

Ratings of mood states were collected outside of the laboratory using the expanded form of the positive and negative affect schedule (PANAS-X) (Watson *et al*, 1988), administered four times per day (0800 hours, 1200 hours,

1600 hours, and 2000 hours.) over 4 days. The PANAS-X consists of 60 adjectives that reflect current subjective emotional experience. It also contains 11 subscales comprised of groups of related adjectives: attentiveness, fatigue, fear, guilt, hostility, joviality, sadness, self-assuredness, serenity, shyness, and surprise (Watson and Clark, 1994).

The magnitude of happiness, sadness, neutrality, valence, and arousal experienced in reaction to each stimulus used in the fMRI session was also collected using a series of Likert scales in a separate ratings session, which immediately followed scanning. The valence and arousal rating scales used the self-assessment manikin system (Lang *et al*, 1999). Subjects were instructed to rate how the picture 'Actually makes you feel'.

Measurement of Cortisol

Nine saliva samples were collected via salivettes from each subject. Samples were collected every 20 min for 2 h before fMRI scanning (1400 hours–1600 hours) and then immediately after completion of scanning (1730 hours) and 20 min later (1750 hours). Cortisol was assayed using the standard direct, non-extraction, Coat-A-Count radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles, CA).

Statistical Analysis of Emotion and Cortisol Measures

Emotional reactions to experimental stimuli and PANAS-X mood ratings were both analyzed using multivariate ANOVA models, with gender and group as between-subjects factors. For the emotional reactions to experimental stimuli, we included ratings of the happiness, sadness, valence, and arousal in the multivariate model. For the PANAS-X mood ratings, each of the 11 subscales were used as dependent variables sampled repeatedly over the 4 days of the experiment. The sadness subscale was hypothesized (*a priori*) to be sensitive to cortisol and predicted to increase over the 4 days in the ED group. For the emotional reactions to experimental stimuli, sadness evoked by sad stimuli, happiness evoked by happy stimuli and arousal evoked by both sad and happy stimuli were each hypothesized to be sensitive to cortisol.

Cortisol assay results were log transformed (for normality) and analyzed using a repeated measures ANOVA model with gender and group as between-subjects factors and time as the repeated measure. Average cortisol during scanning (average of pre- and post-scan salivary cortisol) and average peak cortisol were also calculated and group differences were tested using separate univariate ANOVA models with gender and group as between-subjects factors.

fMRI Acquisition and Analysis

MRI imaging was performed on a 3.0 T GE system using a radio frequency head coil. A T1-weighted image was acquired for landmarking and positioning of subsequent scans. Whole-brain functional scans were acquired using a T2*-weighted, single shot, reverse-spiral pulse sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 22 cm, slice thickness = 3 mm, 40 slices) to minimize susceptibility artifact (Yang *et al*, 2002). At the beginning of each run, four volumes were discarded to allow for T1 equilibrium. High-resolution, T1-weighted, inversion-recovery SPGR anatomical images were also collected (TR = 10.5 ms, TE = 3.4 ms, flip angle = 25°, FOV = 24 cm, slice thickness = 1.5 mm, number of slices = 106) to facilitate normalization to standard MNI space.

Functional volumes were slice-time corrected, realigned, coregistered within the native anatomy, normalized to standard anatomical space and smoothed using a 5-mm^3 Gaussian kernel to improve the signal-to-noise ratio. Preprocessing and whole-brain statistical analysis were performed using the statistical parametric mapping (SPM) platform and Matlab.

Functional imaging data were analyzed using a standard SPM hierarchical general linear model approach. On the first level, model parameters were estimated for each conditions within each of the six runs. Contrast images were generated for each subject by applying linear contrasts between combinations of beta estimate images. Contrast images for each emotion were generated using the fixation cross reference (happy *vs* fixation, sad *vs* fixation, and neutral *vs* fixation) and also using neutral emotional stimuli as the reference (happy *vs* neutral, sad *vs* neutral). Using both reference, images was adopted as an approach to avoid common inference ambiguities inherent to fMRI imaging in between-groups designs. For example, positive group difference could derive from either differential activation or differential deactivation depending on the contrast. On the group analysis level (second level), contrasts images from the first level were used in emotion-specific SPM full factorial ANOVAs that modeled group (P, SD, ED) and gender (M, F) as factors. Statistical T-test maps were constructed to test for significant activations and deactivations in each group separately (T-test: P *vs* 0, SD *vs* 0, ED *vs* 0). T-test maps were also created to test group differences (P *vs* SD, P *vs* ED). Each of these statistical maps was subject to a threshold of $p < 0.05$ with family-wise error (FWE) corrections for multiple comparisons and a cluster threshold (k) of 10 voxels. Small volume corrections (SVCs) were also applied to *a priori* hypothesized regions. For clusters to be considered significant, they were required to meet minimum statistical thresholds of $p < 0.001$ uncorrected and a cluster size of 10 voxels and then also meet a FWE-corrected p-values of $p < 0.05$ within the small volume. Separate second-level multiple regression models were also constructed to test the contribution of salivary cortisol during scanning, valence and arousal ratings to the between-subject variance for first-level contrast images. In these models, average valence and arousal ratings that pertain to the first-level contrasts were used. If the first-level contrast used a neutral control, the differential valence or arousal ratings were used. For example, the difference between the average valence rating of sad stimuli and neutral stimuli were used in the second-level model that incorporated the sad *vs* neutral first level contrast.

Our *a priori* hypothesis was based on HCT affecting the subgenual cingulate (sgACC), ventral medial prefrontal cortex (VMPFC), and amygdala. As this hypothesis was specific to anatomical regions, we also compared groups using a region of interest (ROI) approach. In the ROI approach, functional activation from first-level contrasts is averaged across the anatomical space. ROI masks were

derived from the MNI Space Utility (http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html) and Anatomical Automatic Labeling software (Tzourio-Mazoyer *et al*, 2002). ROI spatial definitions were verified using three separate published brain atlases (Damasio, 2005; Mai *et al*, 2004; Sudheimer *et al*., 2002). The ROIs used were the bilateral rectal gyrus (VMPFC), Brodmann area 25 (sgACC), and amygdala. Contrast value averages were extracted using modified versions of SPM5/8 code and the Neurotools extension (Imfeld, 2009). Contrast extractions were performed for each ROI for each subject. These values were analyzed in contrast-specific multivariate ANOVAs using SPSS. Each of these models included ROI extractions from each brain region (sgACC, VMPFC, amygdala). They also included group (P, SD, ED) and gender as between group factors and used subject age and weight as covariates. *Post-hoc* comparisons were subject to Bonferroni corrections.

Subjective Awareness of HCT Administration

At the completion of each subject's involvement in the study, they were asked to guess if they had been assigned to the P, SD, or ED group. Each subject's guess was recorded, and response patterns from each group was analyzed using a Chi-square analysis.

RESULTS

HCT Administration and Brain Activation

Sadness-related brain activation was decreased in sgACC and VMPFC in one or both of the HCT groups compared with the P group. These group differences were not detected on whole-brain FWE-corrected maps but were apparent at FWE ($p<0.05$) after SVCs and also in ROI contrast extractions (Figure 1, Table 1, Table 2). HCT did not affect amygdala during sadness. Happiness related activation was increased in the sgACC and the amygdala for the SD group. This increase was apparent for happy faces, but not happy IAPS. HCT administration did not have any effects on brain activation evoked by neutral stimuli in any brain region. For both the happy and neutral conditions, no voxels survived FWE corrections for any group-level contrasts. The significant findings for happy faces were only apparent in the ROI contrast extractions.

Subgenual Cingulate

When comparing sgACC activations from the groups using the sad *vs* fixation contrast, the P group demonstrated activation of the sgACC in response to viewing sad stimuli. The HCT groups, however, showed deactivation of the sgACC to sad stimuli (Figure 1, Figure 2). There was a significant omnibus effect of group on sgACC activation, which was driven by decreased activation in both the SD group and the ED group relative to the P group (Table 1). These effects were significant after SVC at FWE rate of $p<0.05$ (Table 2) and in the ROI extractions (Figure 1, Table 1). Furthermore, the multiple regression model showed a negative relationship between average cortisol measured at scan time and sgACC activity across subjects (Table 2).

When comparing sgACC activations from the groups using the sad *vs* neutral contrast similar results were observed. The P group showed activation, the SD group showed no response, and the ED group showed a deactivation. There was a significant omnibus effect of group, which was driven by significantly decreased activation in the ED group but not the SD group. (Table 1). These effects were significant after SVC at FWE rate of $p<0.05$ (Table 2) and in the ROI extractions (Figure 1, Table 1), but not in the multiple regression model.

The ROI analysis also detected an increase in sgACC activation in the SD group relative to the P group when comparing activation induced by happy faces relative to neutral faces. This effect was significant in the ROI analysis as a Bonferroni-corrected *post-hoc* *t*-test, but not after a SVC, and not in the multiple regression model. This effect is the result of an interaction between a non-significant increase in the sgACC response to the happy faces and a decrease in the sgACC response to neutral faces (Table 1 and Figure 1 row 1, column 2).

Ventral Medial Prefrontal Cortex

When comparing VMPFC activations from the groups using the sad *vs* fixation contrast, the P group demonstrated activation of the VMPFC, the SD group showed no response, and the ED showed a deactivation (Figure 1). There was a significant omnibus effect of group on VMPFC activation, which was driven by decreased activation in the SD group and the ED group relative to the P group (Figure 1, Table 1)). These effects were significant after SVC at FWE rate of $p<0.05$ (Table 2), in the ROI extractions (Table 1), and in the multiple regression model.

When comparing VMPFC activations from the groups using the sad *vs* neutral contrast the results were similar although less robust than the sad *vs* fixation contrast. The P group demonstrated an activation of the VMPFC, the SD group showed no response, and the ED showed a deactivation. The omnibus effect of group was not significant. The SD group did not show significantly less activation than the P group, but the ED group did (Table 1). These results were significant after SVC at FWE rate of $p<0.05$ (Table 2), in the ROI extractions (Table 1), but not in the multiple regression model.

Amygdala

No significant group effects were observed in the amygdala using either the sad *vs* fixation or the sad *vs* neutral contrasts. A qualitative stepwise decrease across the groups was seen in the sad *vs* neutral contrast with the P group showing the strongest activation, the SD showing less activation, and the ED group showing the least activation (Figure 1). When comparing amygdala activations from the groups on the happy faces *vs* neutral faces contrast, there was a significant omnibus effect of group, driven by increased activation in the SD group. However, this difference did not survive Bonferroni correction (Table 1). This effect is the result of an interaction between a non-significant increase in the amygdala response to the happy faces and a decrease in the amygdala response to neutral faces (Figure 1 row 3, column 2).

Table 1 Group Differences are Shown for Emotion Evoked Brain Activations in Our Regions of Interest

Hydrocortisone effect on contrasts using both faces and IAPS pictures					Hydrocortisone effect on contrasts using faces only					Hydrocortisone effect on contrasts using IAPS pictures only				
Contrast	**Region**	**Test**	***F/T* value**	***p*-value**	**Contrast**	**Region**	**Test**	***F/T* value**	***p*-value**	**Contrast**	**Region**	**Test**	***F/T* value**	***p*-value**
Sad stimuli														
All sad stimuli *vs* fixation					Sad faces *vs* fixation					Sad IAPS *vs* fixation				
	Multivariate	Pillai's	$F(6,102) = 1.92$	0.0851		Multivariate	Pillai's	$F(6,102) = 0.42$	0.8623		Multivariate	Pillai's	$F(6,102) = 1.29$	0.2696
	sgACC	Omnibus	$F(2,52) = 4.32$	**0.0184***		sgACC	Omnibus	$F(2,52) = 0.83$	0.4425		sgACC	Omnibus	$F(2,52) = 3.56$	**0.0355***
		Single dose *vs* placebo	$T(40) = -2.55$	**0.0274***			Single dose *vs* placebo	$T(40) = -1.06$	0.5838			Single dose *vs* placebo	$T(40) = -2.36$	**0.0442***
		Extended dose *vs* placebo	$T(38) = -2.53$	**0.0286***			Extended dose *vs* placebo	$T(38) = -1.16$	0.5046			Extended dose *vs* placebo	$T(38) = -2.26$	0.0564
	VMPFC	Omnibus	$F(2,52) = 5.46$	**0.0071***		VMPFC	Omnibus	$F(2,52) = 0.84$	0.4355		VMPFC	Omnibus	$F(2,52) = 3.47$	**0.0386***
		Single dose *vs* placebo	$T(40) = -2.55$	**0.0274***			Single dose *vs* placebo	$T(40) = -0.80$	0.8596			Single dose *vs* placebo	$T(40) = -2.16$	0.0708
		Extended dose *vs* placebo	$T(38) = -3.09$	**0.0064***			Extended dose *vs* placebo	$T(38) = -1.29$	0.4072			Extended dose *vs* placebo	$T(38) = -2.38$	**0.0418***
	Amygdala	Omnibus	$F(2,52) = 1.25$	0.2958		Amygdala	Omnibus	$F(2,52) = 0.04$	0.9619		Amygdala	Omnibus	$F(2,52) = 1.15$	0.3234
		Single dose *vs* placebo	$T(40) = -1.53$	0.2652			Single dose *vs* placebo	$T(40) = -0.27$	1.0000			Single dose *vs* placebo	$T(40) = -1.46$	0.2984
		Extended dose *vs* placebo	$T(38) = -1.11$	0.5458			Extended dose *vs* placebo	$T(38) = -0.18$	1.0000			Extended dose *vs* placebo	$T(38) = -1.08$	0.5692
All sad stimuli *vs* all neutral stimuli					Sad faces *vs* neutral faces					Sad IAPS *vs* neutral IAPS				
	Multivariate	Pillai's	$F(6,102) = 1.13$			Multivariate	Pillai's	$F(6,102) = 0.63$			Multivariate	Pillai's	$F(6,102) = 0.58$	
	sgACC	Omnibus	$F(2,52) = 3.19$	**0.0492***		sgACC	Omnibus	$F(2,52) = 1.52$	0.2284		sgACC	Omnibus	$F(2,52) = 1.82$	0.1715
		Single dose *vs* placebo	$T(40) = -1.00$	0.6414			Single dose *vs* placebo	$T(40) = 0.50$	1.0000			Single dose *vs* placebo	$T(40) = -1.56$	0.2510
		Extended dose *vs* placebo	$T(38) = -2.51$	**0.0304***			Extended dose *vs* placebo	$T(38) = -1.20$	0.4748			Extended dose *vs* placebo	$T(38) = -1.74$	0.1770
	VMPFC	Omnibus	$F(2,52) = 2.76$	0.0726		VMPFC	Omnibus	$F(2,52) = 0.90$	0.4124		VMPFC	Omnibus	$F(2,52) = 1.53$	0.2259
		Single dose *vs* placebo	$T(40) = -1.07$	0.5784			Single dose *vs* placebo	$T(40) = 0.54$	1.0000			Single dose *vs* placebo	$T(40) = -1.47$	0.2960
		Extended dose *vs* placebo	$T(38) = -2.35$	**0.0456***			Extended dose *vs* placebo	$T(38) = -0.80$	0.8550			Extended dose *vs* placebo	$T(38) = -1.56$	0.2510
	Amygdala	Omnibus	$F(2,52) = 0.94$	0.3967		Amygdala	Omnibus	$F(2,52) = 0.98$	0.3810		Amygdala	Omnibus	$F(2,52) = 0.73$	0.4857
		Single dose *vs* placebo	$T(40) = -0.03$	1.0000			Single dose *vs* placebo	$T(40) = 1.02$	0.6270			Single dose *vs* placebo	$T(40) = -1.02$	0.6286

Table 1 (Continued)

Hydrocortisone effect on contrasts using both faces and IAPS pictures					Hydrocortisone effect on contrasts using faces only					Hydrocortisone effect on contrasts using IAPS pictures only				
Contrast	**Region**	**Test**	***F/T* value**	***p*-value**	**Contrast**	**Region**	**Test**	***F/T* value**	***p*-value**	**Contrast**	**Region**	**Test**	***F/T* value**	***p*-value**
		Extended dose *vs* placebo	$T(38) = -1.20$	0.4696			Extended dose *vs* placebo	$T(38) = -0.33$	1.0000			Extended dose *vs* placebo	$T(38) = -1.08$	0.5732
Happy stimuli														
All happy stimuli *vs* fixation					Happy faces *vs* fixation					Happy IAPS *vs* fixation				
	Multivariate	Pillai's	$F(6,102) = 0.59$			Multivariate	Pillai's	$F(6,102) = 1.06$			Multivariate	Pillai's	$F(6,102) = 0.59$	
	sgACC	Omnibus	$F(2,52) = 0.24$	0.7848		sgACC	Omnibus	$F(2,52) = 1.53$	0.2271		sgACC	Omnibus	$F(2,52) = 0.84$	0.4367
		Single dose *vs* placebo	$T(40) = 0.43$	1.0000			Single dose *vs* placebo	$T(40) = 1.72$	0.1816			Single dose *vs* placebo	$T(40) = -0.87$	0.7806
		Extended dose *vs* placebo	$T(38) = -0.27$	1.0000			Extended dose *vs* placebo	$T(38) = 1.11$	0.5474			Extended dose *vs* placebo	$T(38) = -1.27$	0.4200
	VMPFC	Omnibus	$F(2,52) = 0.63$	0.5392		VMPFC	Omnibus	$F(2,52) = 0.17$	0.8442		VMPFC	Omnibus	$F(2,52) = 1.43$	0.2481
		Single dose *vs* placebo	$T(40) = -0.81$	0.8384			Single dose *vs* placebo	$T(40) = 0.56$	1.0000			Single dose *vs* placebo	$T(40) = -1.37$	0.3534
		Extended dose *vs* placebo	$T(38) = -1.07$	0.5790			Extended dose *vs* placebo	$T(38) = 0.42$	1.0000			Extended dose *vs* placebo	$T(38) = -1.54$	0.2570
	Amygdala	Omnibus	$F(2,52) = 0.40$	0.6748		Amygdala	Omnibus	$F(2,52) = 0.86$	0.4285		Amygdala	Omnibus	$F(2,52) = 0.33$	0.7197
		Single dose *vs* placebo	$T(40) = 0.47$	1.0000			Single dose *vs* placebo	$T(40) = 1.16$	0.4988			Single dose *vs* placebo	$T(40) = -0.67$	1.0000
		Extended dose *vs* placebo	$T(38) = -0.42$	1.0000			Extended dose *vs* placebo	$T(38) = 0.06$	1.0000			Extended dose *vs* placebo	$T(38) = -0.73$	0.9342
Happy *vs* neutral					Happy faces *vs* neutral faces					Happy IAPS *vs* neutral IAPS				
	Multivariate	Pillai's	$F(6,102) = 1.16$			Multivariate	Pillai's	$F(6,102) = 1.33$			Multivariate	Pillai's	$F(6,102) = 0.53$	
	sgACC	Omnibus	$F(2,52) = 2.52$	0.0899		sgACC	Omnibus	$F(2,52) = 2.91$	0.0636		sgACC	Omnibus	$F(2,52) = 0.46$	0.6311
		Single dose *vs* placebo	$T(40) = 1.77$	0.1664			Single dose *vs* placebo	$T(40) = 2.31$	**0.0500**			Single dose *vs* placebo	$T(40) = -0.35$	1.0000
		Extended dose *vs* placebo	$T(38) = -0.32$	1.0000			Extended dose *vs* placebo	$T(38) = 0.55$	1.0000			Extended dose *vs* placebo	$T(38) = -0.95$	0.6906
	VMPFC	Omnibus	$F(2,52) = 0.54$	0.5841		VMPFC	Omnibus	$F(2,52) = 0.82$	0.4443		VMPFC	Omnibus	$F(2,52) = 0.66$	0.5233
		Single dose *vs* placebo	$T(40) = 0.29$	1.0000			Single dose *vs* placebo	$T(40) = 1.24$	0.4392			Single dose *vs* placebo	$T(40) = -0.96$	0.6876
		Extended dose *vs* placebo	$T(38) = -0.73$	0.9424			Extended dose *vs* placebo	$T(38) = 0.34$	1.0000			Extended dose *vs* placebo	$T(38) = -1.02$	0.6214

Table 1 (Continued)

Hydrocortisone effect on contrasts using both faces and IAPS pictures					Hydrocortisone effect on contrasts using faces only					Hydrocortisone effect on contrasts using IAPS pictures only				
Contrast	**Region**	**Test**	***F/T* value**	***p*-value**	**Contrast**	**Region**	**Test**	***F/T* value**	***p*-value**	**Contrast**	**Region**	**Test**	***F/T* value**	***p*-value**
	Amygdala	Omnibus	$F(2,52) = 2.20$	0.1210		Amygdala	Omnibus	$F(2,52) = 3.26$	**0.0464***		Amygdala	Omnibus	$F(2,52) = 0.58$	0.5651
		Single dose *vs* placebo	$T(40) = 1.31$	0.3888			Single dose *vs* placebo	$T(40) = 2.12$	0.0768			Single dose *vs* placebo	$T(40) = -0.57$	1.0000
		Extended dose *vs* placebo	$T(38) = -0.76$	0.8998			Extended dose *vs* placebo	$T(38) = -0.17$	1.0000			Extended dose *vs* placebo	$T(38) = -1.07$	0.5760
Neutral stimuli														
Neutral *vs* fixation					Neutral faces *vs* fixation					Neutral IAPS *vs* fixation				
	Multivariate	Pillai's	$F(6,102) = 1.04$			Multivariate	Pillai's	$F(6,102) = 0.74$			Multivariate	Pillai's	$F(6,102) = 0.21$	
	sgACC	Omnibus	$F(2,52) = 1.82$	0.1729		sgACC	Omnibus	$F(2,52) = 1.55$	0.2226		sgACC	Omnibus	$F(2,52) = 0.20$	0.8223
		Single dose *vs* placebo	$T(40) = -1.61$	0.2258			Single dose *vs* placebo	$T(40) = -1.38$	0.3464			Single dose *vs* placebo	$T(40) = -0.62$	1.0000
		Extended dose *vs* placebo	$T(38) = 0.08$	1.0000			Extended dose *vs* placebo	$T(38) = 0.26$	1.0000			Extended dose *vs* placebo	$T(38) = -0.22$	1.0000
	VMPFC	Omnibus	$F(2,52) = 0.87$	0.4263		VMPFC	Omnibus	$F(2,52) = 0.80$	0.4567		VMPFC	Omnibus	$F(2,52) = 0.10$	0.9031
		Single dose *vs* placebo	$T(40) = -1.29$	0.4068			Single dose *vs* placebo	$T(40) = -1.12$	0.5324			Single dose *vs* placebo	$T(40) = -0.31$	1.0000
		Extended dose *vs* placebo	$T(38) = -0.41$	1.0000			Extended dose *vs* placebo	$T(38) = -0.06$	1.0000			Extended dose *vs* placebo	$T(38) = -0.44$	1.0000
	Amygdala	Omnibus	$F(2,52) = 1.49$	0.2358		Amygdala	Omnibus	$F(2,52) = 1.89$	0.1614		Amygdala	Omnibus	$F(2,52) = 0.14$	0.8678
		Single dose *vs* placebo	$T(40) = -1.16$	0.4990			Single dose *vs* placebo	$T(40) = -1.53$	0.2636			Single dose *vs* placebo	$T(40) = -0.02$	1.0000
		Extended dose *vs* placebo	$T(38) = 0.52$	1.0000			Extended dose *vs* placebo	$T(38) = 0.27$	1.0000			Extended dose *vs* placebo	$T(38) = 0.45$	1.0000

Multivariate (Pillai's) tests detect group differences across all three brain regions included in the analysis (Subgenual cingulate sgACC, Ventral medial prefrontal cortex VMPFC, and the amygdala).
Omnibus effects of group (*F*-tests) and individual group differences (*T*-tests) are included.
T-test values indicate the direction of group differences.
Positive significant *T* values indicate the placebo group had higher evoked response than the single dose or extended dose group.
Negative *T* values indicate a higher evoked response in the placebo group.
Listed *p*-values are Bonferroni adjusted for multiple comparisons.
*Bold value indicate $p < 0.05$ for omnibus tests or after Bonferroni correction.

Table 2 Whole-Brain Results Demonstrating Group Differences in Brain Activation Evoked by Emotion Conditions

Contrast	Group comparison	Region	PeakVoxel (*x,y,z*)[a]	Cluster[b]	*Z*[c]	*p*-value (unc.)[d]	*p*-value (FWE-SVC)[e]
Hydrocortisone effect on contrasts using both IAPS and faces							
Sad *vs* fixation	Single dose *vs* placebo						
		BA25(sgACC), rectal gyrus (VMPFC)	9,15, – 21	13	– 3.86	0.000057	**0.039***
	Extended dose *vs* placebo						
		BA25(sgACC), rectal gyrus (VMPFC), subcallosal gyrus	– 15,12, – 21	15	– 3.62	0.000148	**0.015***
		BA40, inferior parietal lobule	45, – 51,57	12	– 3.53	0.000206	—
Sad *vs* neutral	Single dose *vs* placebo						
		No voxels survive	—	—	—	—	—
	Extended dose *vs* placebo						
		BA25(sgACC), rectal gyrus (VMPFC), subcallosal gyrus	6,12, – 21	34	– 3.72	0.000100	**0.010***
Happy *vs* fixation	Single dose *vs* placebo						
		Sup. temporal gyrus	– 57, – 18,6	19	3.97	0.000035	—
		BA7/19, Cuneus, Precuneus	12, – 90,36	38	3.62	0.000145	—
	Extended dose *vs* placebo						
		No voxels survive	—	—	—	—	—
Happy *vs* neutral	Single dose *vs* placebo						
		Precentral gyrus, inferior parietal lobule, postcentral gyrus	45, – 15,27	46	4.05	0.000026	—
		BA6/9/44	54,9,27	27	3.70	0.000109	—
		BA21, middle temporal gyrus	– 69, – 18, – 12	14	3.39	0.000347	—
	Extended dose *vs* placebo						
		No voxels survive	—	—	—	—	—
Hydrocortisone effect on contrasts using faces only							
Sad faces *vs* fixation	Single dose *vs* placebo						
		BA40, inferior parietal lobule	– 54, – 60,45	18	– 3.88	0.000053	—
		BA40, inferior parietal lobule	– 57, – 57,45	17	– 3.74	0.000092	—
		BA18/19, middle occipital gyrus	– 24, – 102,6	11	– 3.56	0.000186	—
	Extended dose *vs* placebo						
		BA40, inferior parietal lobule	48, – 51,57	10	– 3.54	0.000201	—
Sad faces *vs* neutral faces	Single dose *vs* placebo						
		BA40, inferior parietal lobule	54, – 36,30	10	3.80	0.000071	—
	Extended dose *vs* placebo						
		BA40, inferior parietal lobule	57, – 51,51	10	– 3.76	0.000086	—
		BA17, lingual gyrus	0, – 96, – 6	15	– 3.62	0.000149	—
Happy faces *vs* fixation	Single dose *vs* placebo						
		BA19, cuneus, precuneus	15, – 90,42	37	4.07	0.000024	—
		Sub—gyral,temporal lobe white matter	– 33, – 54, – 3	18	4.05	0.000025	—
		BA22, middle temporal gyrus, superior temporal gyrus	– 60, – 15,3	25	3.98	0.000034	—
		BA17/19, superior occipital gyrus, cuneus, precuneus	– 15, – 84,42	89	3.95	0.000039	—
		BA20, fusiform gyrus, inferior temporal gyrus	51, – 27, – 27	15	3.94	0.000041	—
		BA28/34	– 15,0, – 27	15	3.87	0.000055	—
		BA40/41, superior temporal gyrus	54, – 24,12	26	3.78	0.000080	—
		BA39, middle temporal gyrus, superior temporal gyrus	45, – 63,15	10	3.52	0.000218	—
	Extended dose *vs* placebo						
		No voxels survive	—	—	—	—	—

Table 2 (Continued)

Contrast	Group comparison	Region	PeakVoxel (*x*,*y*,*z*)[a]	Cluster[b]	*Z*[c]	*p*-value (unc.)[d]	*p*-value (FWE-SVC)[e]
Happy faces *vs* neutral faces	Single dose *vs* placebo						
		BA2/3/4/6/40/44, inferior parietal lobule, postcentral gyrus, precentral gyrus	48, −18,27	211	4.94	0.0000004	—
		BA13/20/22/36/37, inferior temporal gyrus, parahippocampal gyrus, middle temporal gyrus, superior temporal gyrus	−45, −30, −21	171	4.24	0.000011	—
		BA20, inferior temporal gyrus, middle temporal gyrus	51, −27, −24	43	4.20	0.000014	—
		BA22, middle temporal gyrus, superior temporal gyrus	−60, −15,0	22	3.88	0.000051	—
		BA19, middle occipital gyrus	51, −84,0	13	3.88	0.000052	—
		BA37, inferior temporal gyrus	45, −39, −24	13	3.88	0.000052	—
		Cerebellar culmen	21, −39, −30	11	3.82	0.000067	—
		BA21, middle temporal gyrus, superior temporal gyrus	66, −6, −3	11	3.63	0.000144	—
		BA44, inferior frontal gyrus	−51,12,12	13	3.62	0.000148	—
		BA20	−33, −9, −39	11	3.57	0.000176	—
		BA6/9, inferior frontal gyrus	−57, −3,39	28	3.51	0.000222	—
		BA13/41, insula, superior temporal gyrus	−42, −12,3	23	3.42	0.000316	—
	Extended dose *vs* placebo						
		Fusiform gyrus	−42, −12, −21	13	3.68	0.000119	—
Hydrocortisone effect on contrast using IAPS only							
Sad IAPS *vs* fixation	Single dose *vs* placebo						
		No voxels survive	—	—	—	—	—
	Extended dose *vs* placebo						
		BA25(sgACC), subcallosal gyrus, rectal gyrus (VMPFC)	−15,12, −21	13	−3.59	0.000162	**0.016***
		BA40, inferior parietal lobule	39, −51,51	16	−3.53	0.000204	
Sad IAPS *vs* neutral IAPS	Single dose *vs* placebo						
		No voxels survive	—	—	—	—	—
	Extended dose *vs* placebo						
		No voxels survive	—	—	—	—	—
Happy IAPS *vs* fixation	Single dose *vs* placebo						
		No voxels survive	—	—	—	—	—
	Extended dose *vs* placebo						
		BA18/19, fusiform gyrus	−27, −72, −18	23	−3.72	0.000100	—
		BA18, cuneus	−12, −93,6	21	−3.62	0.000147	
Happy IAPS *vs* neutral IAPS	Single dose *vs* placebo						
		BA18/19, middle occipital gyrus	42, −78, −15	10	−3.69	0.000114	—
	Extended dose *vs* placebo						
		BA18/18/37, middle occipital gyrus, lingual gyrus, fusiform gyrus	−33, −60, −18	58	−3.83	0.000065	—
		BA18/18/37, inferior occipital gyrus, lingual gyrus, fusiform gyrus	30, −84, −15	26	−3.72	0.000101	—
		BA18/19, middle occipital gyrus	45, −93,0	30	−3.69	0.000113	—
		BA19, cuneus	−24, −90,9	10	−3.55	0.000194	—
		BA18/19, inferior occipital gyrus, middle occipital gyrus	39, −72, −9	19	−3.48	0.000249	—
		BA22, middle temporal gyrus	36, −60,15	13	−3.39	0.000346	—
		BA18, middle occipital gyrus, cuneus	−12, −102,15	16	−3.34	0.000426	—
Multiple regression on contrasts using both IAPS and faces							
Sad *vs* fixation	Cortisol						
	Negative effect of cortisol	BA25(sgACC), rectal gyrus (VMPFC), subcallosal gyrus	6,12, −18	22	−4.27	0.000010	**0.001***
	Positive effect of cortisol	Cerebellum	21, −93, −30	18	3.83	0.000065	—

Table 2 (Continued)

Contrast	Group comparison	Region	PeakVoxel (*x,y,z*)[a]	Cluster[b]	*Z*[c]	*p*-value (unc.)[d]	*p*-value (FWE-SVC)[e]
	Positive effect of cortisol	Cerebellum	36, – 69, – 33	21	3.67	0.000122	—
	Valence						
	Negative effect of valence	BA6, precentral gyrus, middle frontal gyrus	33,0,45	33	– 4.56	0.000003	—
	Negative effect of valence	BA6/8, superior frontal gyrus	3,24,60	10	– 3.76	0.000086	—
	Negative effect of valence	Inferior frontal gyrus	33,12,27	17	– 3.75	0.000090	—
	Negative effect of valence	Fusiform gyrus, inferior occipital gyrus	– 24, – 96, – 21	11	– 3.68	0.000118	—
	Negative effect of valence	BA19, middle occipital gyrus	39, – 93,18	14	– 3.62	0.000148	—
	Negative effect of valence	BA9/10, medial frontal gyrus	0,60,12	15	– 3.55	0.000193	—
	Arousal						
	Negative effect of arousal	BA6, middle frontal gyrus	33,0,45	21	– 4.39	0.000006	—
	Positive effects of arousal	Pons	– 18, – 18, – 33	17	4.30	0.000069	—
	Negative effect of arousal	BA19, middle occipital gyrus, superior occipital gyrus	39, – 93,18	11	– 3.45	0.000275	—
Sad *vs* neutral	Cortisol						
	Positive effect of cortisol	BA38, superior temporal gyrus	– 30,21, – 39	15	4.41	0.000005	—
	Positive effect of cortisol	BA40, supramarginal gyrus	48, – 39,36	12	3.55	0.000195	—
	Valence						
	Negative effect of valence	BA7/19/39, Middle temporal gyrus, precuneus	39, – 72,33	165	– 4.44	0.000004	—
	Negative effect of valence	BA22/ Middle temporal gyrus, superior temporal gyrus	63, – 66,12	11	– 4.35	0.000007	—
	Negative effect of valence	Fusiform gyrus, cerebellum	30, – 60, – 9	59	– 4.15	0.000016	—
	Negative effect of valence	BA23, posterior cingulate	6, – 60,12	43	– 4.09	0.000021	—
	Negative effect of valence	BA39/40, inferior parietal lobule, supramarginal gyrus	54, – 60,33	62	– 3.89	0.000049	—
	Negative effect of valence	Insula	27,9, – 15	28	– 3.70	0.000106	—
	Negative effect of valence	Inferior frontal gyrus	– 42,45, – 21	17	– 3.68	0.000115	—
	Negative effect of valence	Lingual gyrus	24, – 69,3	22	– 3.65	0.000133	—
	Negative effect of valence	Lingual gyrus	30, – 75, – 12	12	– 3.64	0.000135	–
	Arousal						
	Negative effect of arousal	BA45, inferior frontal gyrus	57,24,21	17	– 3.85	0.000059	—
Happy *vs* fixation	Cortisol						
	Positive effect of cortisol	Cerebellum	36, – 66, – 33	60	3.81	0.000070	—
	Positive effect of cortisol	Cerebellum	24, – 93, – 33	32	3.98	0.000035	—
	Valence						
	Positive effect of valence	Inferior parietal lobule	33, – 42,45	15	4.01	0.000030	—
	Positive effect of valence	BA6, precentral gyrus	– 48, – 6,42	12	3.61	0.000155	—
	Negative effect of valence	Inferior parietal lobule	– 42, – 75,45	10	– 3.59	0.000168	—

Table 2 (Continued)

Contrast	Group comparison	Region	PeakVoxel (*x*,*y*,*z*)[a]	Cluster[b]	*Z*[c]	*p*-value (unc.)[d]	*p*-value (FWE-SVC)[e]
	Positive effect of valence	BA6/44, precentral gyrus, inferior frontal gyrus	60,3,15	10	3.47	0.000256	—
	Arousal						
	Positive effect of arousal	Inferior parietal lobule	−42,−72,45	15	3.94	0.000041	—
Happy *vs* neutral	Cortisol						
	Positive effect of cortisol	Middle temporal gyrus	51,−18,−18	13	3.86	0.000056	—
	Positive effect of cortisol	Medial frontal gyrus	−6,42,−15	10	3.38	0.000361	—
	Positive effect of cortisol	BA34, subcallosal gyrus	9,6,−15	12	3.60	0.000160	—
	Positive effect of cortisol	BA22/42, superior temporal gyrus	60,−9,6	21	3.88	0.000052	—
	Positive effect of cortisol	Extra—nuclear	3,24,9	11	3.69	0.000114	—
	Positive effect of cortisol	BA1/2/3, postcentral gyrus	60,−24,51	22	3.94	0.000041	—
	Valence						
	Positive effect of valence	Inferior frontal gyrus	−54,9,3	11	3.35	0.000407	—
	Arousal						
	—	No voxels survive	—	—	—	—	—
Multiple regression on contrasts using faces only							
Sad faces *vs* fixation	Cortisol						
	—	No voxels survive	—	—	—	—	—
	Valence						
	Negative effect of valence	BA38, superior temporal gyrus	30,24,−39	10	−4.14	0.000017	—
	Arousal						
	—	No voxels survive	—	—	—	—	—
Sad faces *vs* neutral faces	Cortisol						
	Positive effect of cortisol	BA11, superior frontal gyrus, medial frontal gyrus	−36,51,−15	89	4.59	0.000002	—
	Positive effect of cortisol	BA11, middle frontal gyrus	33,42,−9	31	4.42	0.000005	—
	Positive effect of cortisol	BA6/9/44/45, inferior frontal gyrus	−60,12,21	234	4.40	0.000005	—
	Positive effect of cortisol	BA10, superior frontal gyrus, medial frontal gyrus	−15,66,6	44	4.08	0.000023	—
	Positive effect of cortisol	BA11, superior frontal gyrus	15,51,−21	11	4.02	0.000029	—
	Positive effect of cortisol	Inferior parietal lobule, supramarginal gyrus	54,−36,30	17	3.73	0.000094	—
	Positive effect of cortisol	Superior frontal gyrus, medial frontal gyrus	−21,42,24	32	3.67	0.000120	—
	Positive effect of cortisol	Middle frontal gyrus	−27,12,33	11	3.55	0.000192	—
	Positive effect of cortisol	Inferior frontal gyrus	−36,3,36	12	3.44	0.000291	—
	Valence						
	—	No voxels survive	—	—	—	—	—
	Arousal						
	Positive effect of arousal	BA20/21, middle temporal gyrus, inferior temporal gyrus	−45,3,−36	17	3.63	0.000140	—
	Positive effect of arousal	BA8, superior frontal gyrus	18,39,54	17	3.53	0.000205	—

Table 2 (Continued)

Contrast	Group comparison	Region	PeakVoxel (*x,y,z*)[a]	Cluster[b]	*Z*[c]	*p*-value (unc.)[d]	*p*-value (FWE-SVC)[e]
Happy faces *vs* fixation	Cortisol						
	Negative effect of cortisol	Precentral gyrus	−30, −18,36	14	−3.76	0.000083	—
	Valence						
	Positive effect of valence	BA6/13/22, insula, superior temporal gyrus, precentral gyrus	57, −3,6	32	4.09	0.000022	—
	Negative effect of valence	Cerebellum	42, −72, −27	14	−3.57	0.000177	—
	Arousal						
	Negative effect of arousal	BA18/19, middle occipital gyrus	−36, −87,6	13	−3.53	0.000208	—
Happy faces *vs* neutral faces	Cortisol						
	Positive effect of cortisol	Postcentral gyrus, precentral gyrus	48, −18,27	32	4.04	0.000027	—
	Positive effect of cortisol	BA4/6, precentral gyrus	−57, −6,42	24	4.01	0.000031	—
	Positive effect of cortisol	BA1/3/4, postcentral gyrus, precentral gyrus	51, −21,57	35	3.82	0.000066	—
	Positive effect of cortisol	BA28, uncus	−21,3, −30	13	3.78	0.000079	—
	Positive effect of cortisol	BA44/45, inferior frontal gyrus	−51,12,21	11	3.73	0.000094	—
	Positive effect of cortisol	BA4/6, precentral gyrus	−63, −21,42	11	3.73	0.000097	—
	Positive effect of cortisol	BA5/7/31, precuneus, paracentral lobule	6, −36,48	14	3.68	0.000117	—
	Positive effect of cortisol	BA13/2, insula	45, −15,12	14	3.43	0.000302	——
	Positive effect of cortisol	BA6/13/44, insula	45, −6,9	10	3.41	0.000327	—
	Valence						
	—	No voxels survive	—	—	—	—	—
	Arousal						
	—	No voxels survive	—	—	—	—	—
Multiple regression on contrasts using IAPS only							
Sad IAPS *vs* fixation	Cortisol						
	Positive effect of cortisol	Cerebellum	27, −93, −30	15	4.00	0.000032	—
	Positive effect of cortisol	Cerebellum	36, −69, −33	21	3.92	0.000044	—
	Positive effect of cortisol	Cerebellum	24, −57, −27	12	3.69	0.000111	—
	Valence						
	Negative effect of valence	BA19/30, culmen	−9, −45, −6	27	4.30	0.000008	—
	Negative effect of valence	BA19, superior occipital gyrus	39, −93,21	49	4.16	0.000016	—
	Negative effect of valence	BA30, Posterior cingulate, cuneus	21, −72,6	25	−4.01	0.000030	—
	Negative effect of valence	BA6, Middle frontal gyrus	33,0,45	24	3.99	0.000032	—
	Negative effect of valence	BA18/30, Lingual gyrus, posterior cingulate	−21, −60,3	30	−3.79	0.000075	—
	Positive effect of valence	BA18/19, Cuneus	15, −96,21	12	3.64	0.000135	—
	Arousal						

Table 2 (Continued)

Contrast	Group comparison	Region	PeakVoxel (*x*,*y*,*z*)[a]	Cluster[b]	*Z*[c]	*p*-value (unc.)[d]	*p*-value (FWE-SVC)[e]
	Negative effect of arousal	BA6, middle frontal gyrus	33,0,45	22	−3.98	0.000034	—
	Negative effect of arousal	BA19, superior occipital gyrus	39, −90,24	24	−3.71	0.000105	—
Sad IAPS *vs* neutral IAPS	Cortisol						
	—	No voxels survive	—	—	—	—	—
	Valence						
	Negative effect of valence	BA19/22/39/40, superior temporal gyrus, supramarginal gyrus	57, −63,30	89	−4.73	0.000001	—
	Negative effect of valence	BA19/39, middle temporal gyrus, middle occipital gyrus, superior occipital gyrus, angular gyrus, precuneus	48, −84,15	135	−4.50	0.000003	—
	Negative effect of valence	BA7, precuneus	−3, −54,48	42	−4.12	0.000019	—
	Negative effect of valence	BA19, cuneus	−27, −90,27	23	−3.78	0.000077	—
	Negative effect of valence	BA31, cingulate gyrus, posterior cingulate gyrus	−9, −42,33	26	−3.77	0.000081	—
	Negative effect of valence	BA39, angular gyrus, middle temporal gyrus, superior temporal gyrus	−54, −66,27	19	−3.76	0.000085	—
	Negative effect of valence	BA40, supramarginal gyrus	−60, −54,30	17	−3.72	0.000098	—
	Negative effect of valence	BA5, postcentral gyrus	−3, −60,69	42	−3.71	0.000102	—
	Negative effect of valence	BA30, posterior cingulate	3, −48,18	11	−3.60	0.000157	—
	Negative effect of valence	BA23/30, posterior cingulate	−3, −63,9	20	−3.57	0.000176	—
	Arousal						
	—	No voxels survive	—	—	—	—	—
Happy IAPS *vs* fixation	Cortisol						
	Positive effect of cortisol	Cerebellum	18, −93, −30	12	3.47	0.000257	—
	Positive effect of cortisol	Cerebellum	27, −75, −30	28	3.44	0.000286	—
	Valence						
	—	No voxels survive	—	—	—	—	—
	Arousal						
	—	No voxels survive	—	—	—	—	—
Happy IAPS *vs* neutral IAPS	Cortisol						
	Positive effect of cortisol	Anterior cingulate	12,36,3	14	4.13	0.000018	—
	Valence						
	—	No voxels survive	—	—	—	—	—
	Arousal						
	Positive effect of arousal	Unidentified	−15,18, −33	16	4.14	0.000017	—
	Negative effect of arousal	Occipital lobe (R)	33, −54, −3	13	−3.72	0.000102	—

[a]Stereotactic coordinates from MNI152 reference.

[b]Cluster size in voxels.

[c]Negative *Z*-scores indicate a reduced activation of the hydrocortisone group relative to the placebo group.

[d]All foci meet min threshold of $p<0.001$, uncorrected with an extend threshold 10 voxels.

[e]Significant *p*-values after small volume correction.

*Foci are significant at a family-wise error corrected threshold of $p<0.05$ after small volume correction. *p*-values listed reflect the peak voxel within a cluster.

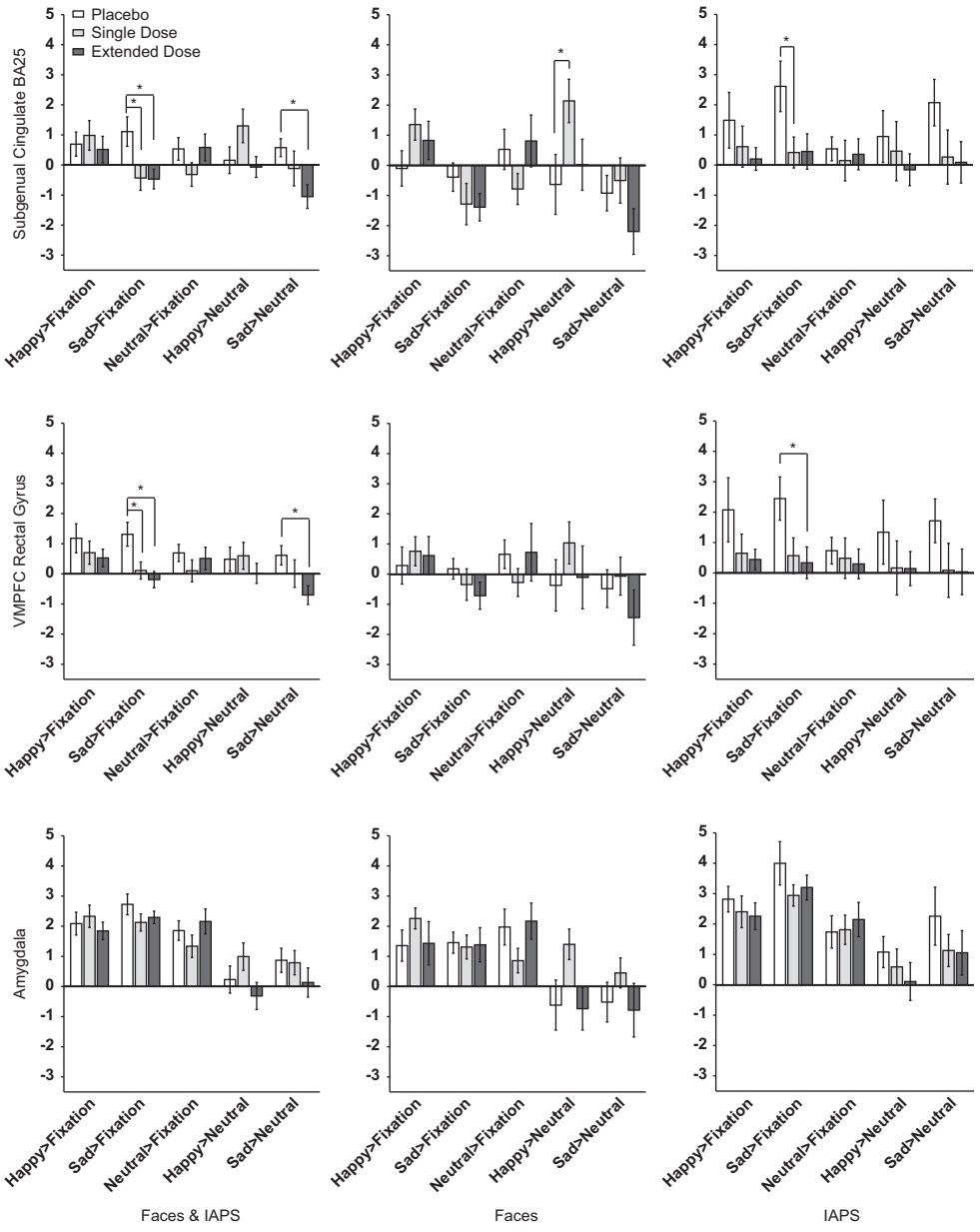

Figure 1 Regions of interest extractions from the subgenual cingulate (panel 1) ventral medial prefrontal cortex (panel 2), and the amygdala (panel 3). Significant group differences were detected for contrasts involving sad stimuli in the subgenual cingulate and the ventral medial prefrontal cortex (VMPFC). *$p < 0.05$ after Bonferroni correction.

Blinding

The majority of subjects (42/61, 69%) reported that they thought they received placebo, including those that received HCT (26/41, 63%). Overall, the groups did not significantly differ in their guesses χ^2 (4) = 5.136, $p = 0.274$ regarding their assigned dose regimen. There were also no significant differences in guessing patterns among just the HCT groups χ^2 (2) = 0.148, $p = 0.929$.

Subjective Emotional Reactions to Images and Mood

Across all groups the images selected as happy and sad stimuli successfully induced moderate feelings of the target emotions. Happy stimuli induced moderate feelings of happiness and sad stimuli induced moderate feelings of sadness (Figure 3). There was a significant omnibus effect of group on arousal ratings of sad stimuli but no effects for other stimuli types. The group effect on sad stimuli was driven by greater arousal in the ED relative to the placebo group. This effect was observed when all sad stimuli are pooled or when sad IAPS are considered alone (Figure 3). When sad faces are considered alone this effect of HCT on arousal is similar qualitatively but not statistically significant. We tested for emotion type (happy, sad, neutral) by group interactions on arousal ratings to formally determine if these effects were specific to sad stimuli. The interaction was not significant when IAPS stimuli and faces are pooled

Table 3 Subjective Emotional Reactions to Experimental Stimuli, PANAS Mood Measures Over 4 Days of HCT Exposure, and HCT-Induced Elevations in Salivary Cortisol Levels

PANAS mood ratings	**Measure**	**Test**	**Placebo**	**Single dose**	**Extended dose**	***F/T* value**	***p*-value**
Effects of hydrocortisone		Multivariate pillai's	—	—	—	$F(22,86) = 1.179$	0.288
	Attentivness	Omnibus effect of group	2.353 (0.146)	2.353 (0.143)	2.604 (0.146)	$F(2,52) = 0.994$	0.377
	Fatigue	Omnibus effect of group	1.861 (0.092)	1.908 (0.09)	1.886 (0.092)	$F(2,52) = 0.067$	0.935
	Fear	Omnibus effect of group	1.285 (0.059)	1.134 (0.058)	1.254 (0.059)	$F(2,52) = 1.863$	0.165
	Guilty	Omnibus effect of group	1.149 (0.044)	1.057 (0.043)	1.142 (0.044)	$F(2,52) = 1.386$	0.259
	Hostile	Omnibus effect of group	1.237 (0.058)	1.151 (0.056)	1.251 (0.058)	$F(2,52) = 0.908$	0.410
	Jovial	Omnibus effect of group	2.19 (0.135)	2.313 (0.132)	2.349 (0.135)	$F(2,52) = 0.383$	0.684
	Sad	Omnibus effect of group	1.158 (0.083)	1.126 (0.081)	1.372 (0.083)	$F(2,52) = 2.615$	0.083
	Self-assured	Omnibus effect of group	1.744 (0.143)	1.901 (0.139)	2.161 (0.143)	$F(2,52) = 2.185$	0.123
	Serenity	Omnibus effect of group	2.614 (0.13)	2.879 (0.128)	2.927 (0.13)	$F(2,52) = 1.684$	0.196
	Shy	Omnibus effect of group	1.237 (0.06)	1.105 (0.059)	1.177 (0.06)	$F(2,52) = 1.24$	0.298
	Surprise	Omnibus effect of group	1.361 (0.07)	1.257 (0.069)	1.228 (0.07)	$F(2,52) = 0.99$	0.378
Emotion evoked by stimuli	**Measure**	**Test**	**Placebo**	**Single dose**	**Extended dose**	***F/T* value**	***p*-value**
Effects of hydrocortisone		Multivariate Pillai's	—	—	—	$F(78,32) = 1.015$	0.497
Sad IAPS and faces	Happiness	Omnibus effect of group	1.9 (0.24)	1.87 (0.21)	1.59 (0.17)	$F(2,53) = 0.586$	0.560
	Sadness	Omnibus effect of group	4.32 (0.5)	5.41 (0.40)	4.38 (0.34)	$F(2,53) = 2.189$	0.122
	Valence	Omnibus effect of group	3.59 (0.21)	3.22 (0.16)	3.23 (0.13)	$F(2,53) = 1.681$	0.196
	Arousal	Omnibus effect of group	3.45 (0.43)	4.07 (0.32)	4.80 (0.31)	$F(2,53) = 3.292$	**0.045***
		—Single dose *vs* placebo				$T(39) = 1.215$	0.695
		—Extended dose *vs* placebo				$T(39) = 2.565$	**0.039***
Happy IAPS and face	Happiness	Omnibus effect of group	5.35 (0.42)	6.01 (0.40)	5.00 (0.35)	$F(2,53) = 2.068$	0.136
	Sadness	Omnibus effect of group	1.24 (0.08)	1.40 (0.17)	1.09 (0.04)	$F(2,53) = 1.787$	0.177
	Valence	Omnibus effect of group	6.49 (0.21)	6.59 (0.25)	6.34 (0.15)	$F(2,53) = 0.309$	0.736
	Arousal	Omnibus effect of group	3.64 (0.37)	4.00 (0.39)	4.32 (0.38)	$F(2,53) = 1.190$	0.312
Neutral IAPS and face	Happiness	Omnibus effect of group	2.91 (0.36)	3.19 (0.32)	2.62 (0.33)	$F(2,53) = 0.776$	0.465
	Sadness	Omnibus effect of group	2.02 (0.28)	2.54 (0.28)	1.75 (0.17)	$F(2,53) = 2.371$	0.103
	Valence	Omnibus effect of group	5.02 (0.04)	4.89 (0.09)	4.89 (0.06)	$F(2,53) = 1.180$	0.315
	Arousal	Omnibus effect of group	2.03 (0.27)	2.16 (0.17)	2.50 (0.29)	$F(2,53) = 1.016$	0.369
Sad faces	Happiness	Omnibus effect of group	1.89 (0.28)	1.98 (0.24)	1.62 (0.21)	$F(2,53) = 0.631$	0.536
	Sadness	Omnibus effect of group	3.91 (0.51)	4.64 (0.48)	3.57 (0.41)	$F(2,53) = 1.156$	0.322
	Valence	Omnibus effect of group	3.91 (0.20)	3.73 (0.18)	3.73 (0.18)	$F(2,53) = 0.524$	0.595
	Arousal	Omnibus effect of group	2.64 (0.39)	3.02 (0.37)	3.75 (0.48)	$F(2,53) = 1.748$	0.184
Happy faces	Happiness	Omnibus effect of group	4.75 (0.45)	5.34 (0.44)	4.29 (0.43)	$F(2,53) = 1.828$	0.171
	Sadness	Omnibus effect of group	1.33 (0.10)	1.49 (0.19)	1.14 (0.06)	$F(2,53) = 1.731$	0.187
	Valence	Omnibus effect of group	6.15 (0.21)	6.15 (0.23)	5.90 (0.25)	$F(2,53) = 0.315$	0.731
	Arousal	Omnibus effect of group	2.76 (0.38)	3.12 (0.39)	3.77 (0.47)	$F(2,53) = 1.378$	0.261
Neutral faces	Happiness	Omnibus effect of group	2.47 (0.36)	2.77 (0.33)	2.10 (0.34)	$F(2,53) = 0.949$	0.394
	Sadness	Omnibus effect of group	2.49 (0.37)	3.11 (0.36)	2.07 (0.26)	$F(2,53) = 2.246$	0.116
	Valence	Omnibus effect of group	4.88 (0.03)	4.70 (0.09)	4.76 (0.14)	$F(2,53) = 0.967$	0.387
	Arousal	Omnibus effect of group	1.85 (0.28)	2.00 (0.22)	2.67 (0.44)	$F(2,53) = 2.001$	0.145
Sad IAPS	Happiness	Omnibus effect of group	1.79 (0.22)	1.76 (0.21)	1.52 (0.16)	$F(2,53) = 0.433$	0.651
	Sadness	Omnibus effect of group	4.82 (0.51)	6.17 (0.38)	5.08 (0.43)	$F(2,53) = 3.026$	0.057
	Valence	Omnibus effect of group	3.32 (0.23)	2.70 (0.19)	2.89 (0.16)	$F(2,53) = 2.668$	0.079
	Arousal	Omnibus effect of group	4.23 (0.50)	5.13 (0.39)	5.87 (0.27)	$F(2,53) = 3.980$	**0.025***
		—Single dose *vs* placebo				$T(39) = 1.605$	0.349
		—Extended dose *vs* placebo				$T(39) = 2.813$	**0.019***

Table 3 (Continued)

PANAS mood ratings	Measure	Test	Placebo	Single dose	Extended dose	*F/T* value	*p*-value
Happy faces	Happiness	Omnibus effect of group	5.95 (0.41)	6.68 (0.43)	5.37 (0.41)	$F(2,53) = 2.191$	0.122
	Sadness	Omnibus effect of group	1.15 (0.08)	1.40 (0.17)	1.19 (0.11)	$F(2,53) = 1.578$	0.216
	Valence	Omnibus effect of group	6.83 (0.22)	7.02 (0.30)	6.59 (0.19)	$F(2,53) = 0.531$	0.591
	Arousal	Omnibus effect of group	4.52 (0.42)	4.88 (0.50)	5.13 (0.35)	$F(2,53) = 0.436$	0.649
Neutral IAPS	Happiness	Omnibus effect of group	3.26 (0.39)	3.61 (0.34)	3.03 (0.39)	$F(2,53) = 0.748$	0.478
	Sadness	Omnibus effect of group	1.61 (0.23)	1.97 (0.25)	1.51 (0.14)	$F(2,53) = 1.213$	0.306
	Valence	Omnibus effect of group	5.15 (0.07)	5.09 (0.12)	5.02 (0.03)	$F(2,53) = 0.448$	0.641
	Arousal	Omnibus effect of group	2.15 (0.27)	2.31 (0.19)	2.69 (0.25)	$F(2,53) = 1.423$	0.250
Saliva cortisol measures	**Measure**	**Test**	**Placebo**	**Single dose**	**Extended dose**	***F/T* value**	***p*-value**
Effects of hydrocortisone	Cortisol	Repeated Measures Time X Group (quadradic Fit)	—	—	—	$F(2,53) = 26.152$	**0.0000000125***
	Average cortisol during scanning	Omnibus effect of group	0.04 (0.02)	7.709 (1.0)	0.058 (0.01)	$F(2,52) = 204.24$	**0.005***
		—Single dose *vs* placebo				$T(39) = 8.34$	**0.00000000003***
		—Extended dose *vs* placebo				$T(38) = 0.006$	0.995
	Cortisol peak	Omnibus effect of group	0.14(0.03)	23.04(4.02)	0.16(0.03)	$F(2,53) = 95.056$	**0.010**
		—Single dose *vs* placebo				$T(39) = 6.47$	**0.00000003**

Extended Dose vs. Placebo $T(38) = 0.018$ 0.996. Subjective arousal was only significantly increased in reaction to viewing sad stimuli in the extended dose group. Similar non-significant effects of hydrocortisone on arousal were also seen on other types of stimuli (see also Figure 3 and Figure 4).
*Bold value indicate $p < 0.05$ for omnibus tests or after Bonferroni correction.

Pillai's trace $F(4,106) = 1.430$, $p = 0.229$) nor when faces $F(4,106) = 0.267$, $p = 0.899$) or IAPS $F(4,106) = 1.623$, $p = 0.174$) are considered separately. We observed no other effects of HCT on ratings of any other stimulus type.

HCT administered over 4 days did not alter mood states as measured by any of the 60 adjectives or the 11 PANAS-X subscales for the either of the HCT groups compared with the P group (Table 3).

Saliva Cortisol Levels

Cortisol levels measured in saliva were elevated in the SD group after taking HCT. The pattern of cortisol observed in the SD group fit a quadratic pattern of HCT absorption and then metabolism. There were highly significant group differences for this pattern (Table 3). The placebo and the ED maintained much lower and unchanging levels of salivary cortisol over the course of fMRI scanning with no significant differences between them. The peak levels of salivary cortisol and the average salivary cortisol levels during fMRI scanning were highly elevated in the SD group, but not in the ED or P groups (Table 3).

DISCUSSION

We examined the effects of a SD and a 4-day administration of HCT on activity in sgACC, VMPFC, and amygdala in response to viewing happy, sad, and neutral emotional stimuli. HCT administration reduced sgACC and VMPFC activations evoked by sad stimuli. HCT administration had few other consistent effects on activity evoked by other emotions or in other brain regions. We also found that 4-day exposure to HCT increased the subjective arousal participants report after viewing sad stimuli but did not affect general mood ratings.

Previous neuroimaging studies have found that exogenous glucocorticoid administration can increase medial temporal lobe (De Quervain *et al*, 2003) and hippocampus (Abercrombie *et al*, 2011) activity, and decrease amygdala activity and connectivity with the VMPFC (Henckens *et al*, 2010; Lovallo *et al*, 2010), though none of these previous studies specifically addressed sadness-related emotion activity. In contrast, our study focused explicitly on emotional processes and brain regions implicated in MDD, including sadness. Both sgACC hyperactivity (Mayberg *et al*, 1997, 1999) and decreased brain sensitivity to cortisol signaling (glucocorticoid resistance) have been associated with the symptoms in MDD (Holsboer, 2000; Pariante, 2006). Our results suggest a mechanism that could link these two findings. If cortisol functions to reduce sgACC activity in response to sad stimuli in a healthy state, as we show here, then the development of glucocorticoid resistance in MDD may disinhibit sadness-induced sgACC activity. This disinhibition would then create the sgACC hyperactivity that has been observed in MDD patients relative to healthy subjects. These findings fit well within the predictions of an overarching corticosteroid receptor hypothesis of depression (Holsboer, 2000). Our study extends this theory and predicts that hyperactivity of the

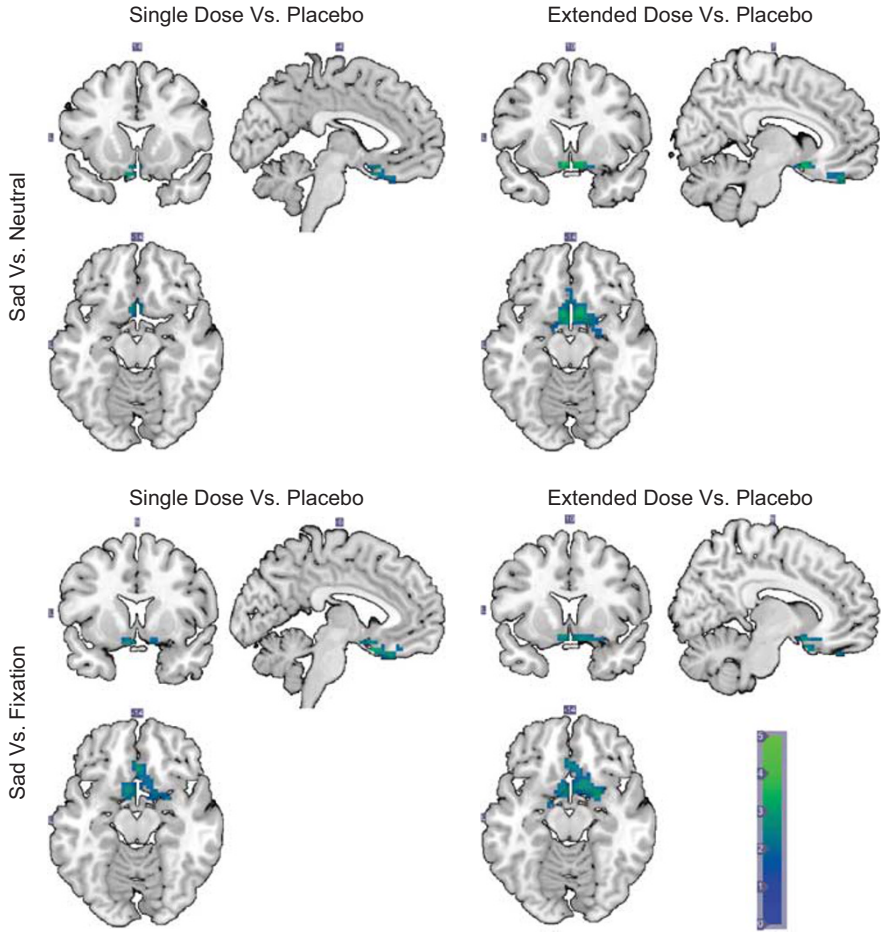

Figure 2 Decreased activation of the subgenual cingulate cortex in groups receiving hydrocortisone (HCT) on contrasts involving sad stimuli. Qualitatively similar effects were seen in both HCT groups. Voxel-wise statistical tests at $p<0.05$ after family-wise error and small volume correction are only significant for peak voxels in the extended dose group on the sad *vs* neutral contrast (upper-right panel). The maps above are subject to a $p<0.05$ threshold and a cluster threshold of five voxels for qualitative display purposes. See Table 2 for statistics.

sgACC should occur subsequent to glucocorticoid receptor downregulations in the development of MDD. We also predict that pharmacological treatments that increase glucocorticoid receptors in the sgACC should also decrease sgACC hyperactivity.

It is noteworthy that we observe similarly decreased sgACC after both acute and 4-day HCT administration. This finding supports the idea that sgACC activity is sensitive to glucocorticoids, but raises questions about the mechanisms involved, as saliva cortisol levels were very different at the time of scanning in the two groups. One explanation for these similarities could be that the effects on the brain are driven by a recent acute rise in glucocorticoid levels. At the time of scanning, both HCT regimens had a recent rise in cortisol levels. The ED subject took the final dose of their HCT regimen 8 h before scanning. Although it was metabolized by the time of the scanning, it may be producing effects similar to the dose administered to the SD subjects, taken 2 h before scanning. The effects of glucocorticoids can have a rapid onset and produce effects that outlast the elevated circulating glucocorticoids that caused them. Such fast and long-lasting effects of glucocorticoids have previously been demonstrated in animal studies (Rose, 2000) and may be mediated through fast-acting membrane-bound corticosteroid receptors (Orchinik *et al*, 1991).

HCT administered over 4 days increased arousal experienced when viewing sad stimuli, but did not affect general PANAS mood ratings. Previous work has demonstrated that in healthy subjects glucocorticoid administration can improve memory for arousing stimuli (Buchanan and Lovallo, 2001). However, one recent study has shown no effect of glucocorticoids on arousal (Abercrombie *et al*, 2011). This recent finding was based on general mood measures of arousal (PANAS), where we also find no effects of HCT. The arousal enhancing effect of HCT in our study was only observed when participants were reporting arousal that was evoked by a sad stimulus, as opposed to rating their generally aroused mood. Our results suggest that HCT may also be increasing arousal to other stimuli as well, although to a lesser extent (Figure 3). By increasing arousal evoked from sad stimuli to a greater degree than other types of stimuli glucocorticoids could be generating a temporary bias toward attending to negative emotional stimuli in healthy subjects. As high levels of glucocorticoid often occur during times of high physiological or psychological stress, such a bias may be appropriate in many cases. However, additional studies are needed to determine how

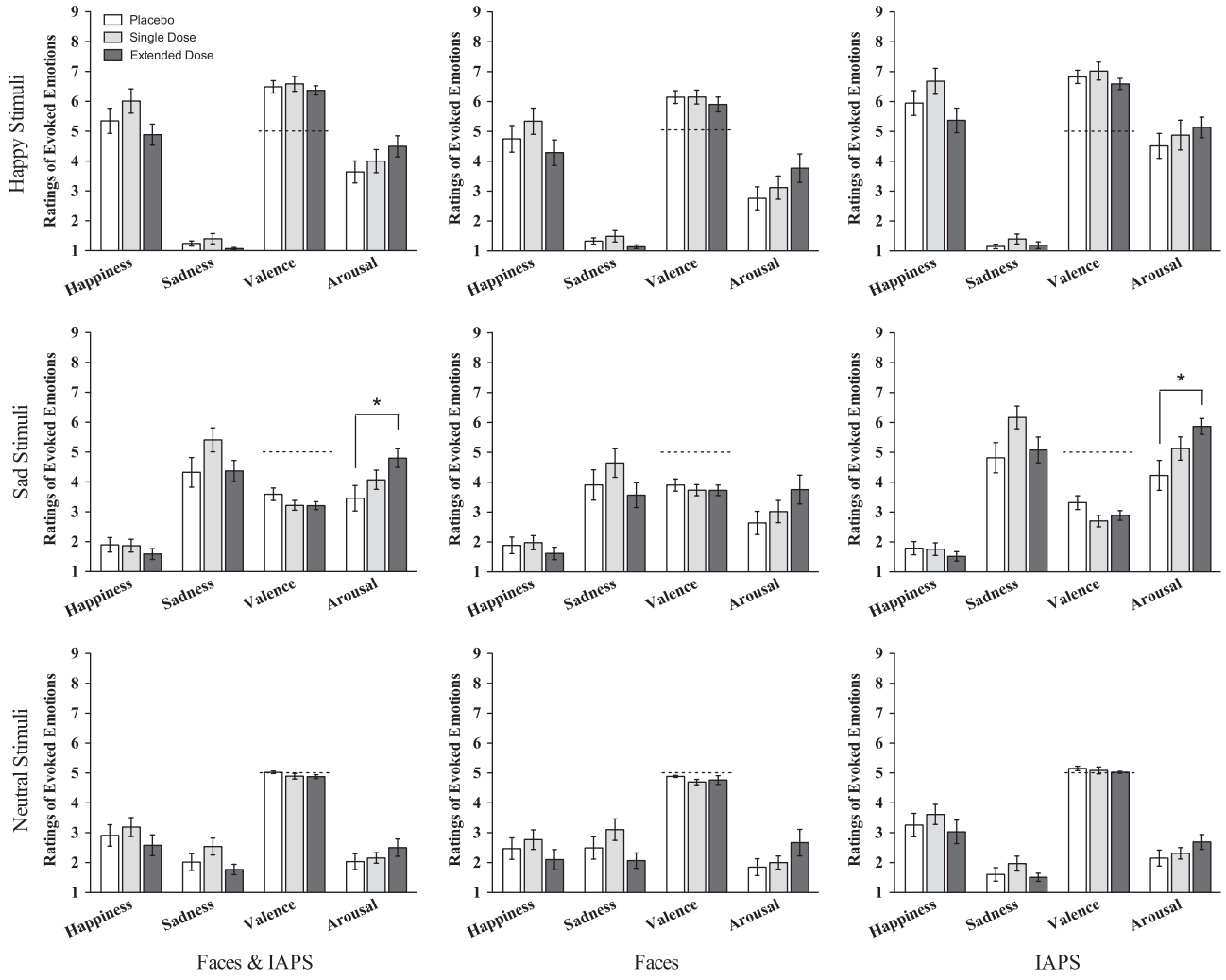

Figure 3 Subjective ratings are displayed for each type of experimental stimuli. The first column displays data for the each kind of emotional stimuli (happy, sad, neutral). The second and third column displays the same data when only faces or only International Affective Picture System (IAPS) stimuli are considered. The dashed line above the valence measure denotes the neutral valence rating. Stimuli ratings above 5 indicate a positive valence and below 5 indicate a negative valence. In the hydrocortisone groups, the ratings of arousal across all stimuli are elevated. However, this elevation in arousal only achieves statistical significance for sad stimuli rated by the extended dose group. $*p<0.05$ after Bonferroni correction.

cortisol effects arousal across its physiological range. These findings may also fit predictions made by the corticosteroid receptor hypothesis of depression (Holsboer, 2000). If one of cortisol's normal physiological functions is to increase arousal, then a reduced sensitivity to cortisol in depression could result in more vegetative symptoms and psychomotor slowing, particularly in response to evocative stimuli. Low-arousal symptoms are commonly found in melancholic depression subtypes, which also have amongt the most reliable HPA dysregulation (Stetler and Miller, 2011).

Our results confirm previous findings (Britton *et al*, 2005) that IAPS stimuli are generally more emotionally evocative than faces (Figure 3). Correspondingly, the sgACC and VMPF showed more robust activations when sad IAPS were being viewed as compared with sad faces. However, our multiple regression models failed to show a direct linear relationship between the strength of these activations and the valence/arousal ratings of either faces or IAPS pictures. Nevertheless, future studies investigating sgACC or VMPFC sensitivity to HCT may consider choosing more evocative stimulus sets to maximize the contrast with HCT-induced suppression in these regions.

One limitation of our study is that the dose of HCT that we used in the SD group achieved salivary cortisol concentrations that were in excess of most normal physiological stress responses. Although this is an important consideration, it is worth noting that receptor binding is the limiting factor of the physiological effects of HCT. Therefore, the high concentrations generated in our study may not result in exaggerated physiological effects as receptor binding has a limited capacity. The similar results we observed among the SD and ED groups seem to support the notion that our higher dose is not generating non-physiological effects.

As a manipulation check, we analyzed which brain regions responded to sad stimuli in healthy controls. We observed typical visual-emotion-related patterns (activation in the visual cortex, thalamus, superior colliculus, amygdala, hippocampus, caudate, putamen, dorsal medial prefrontal cortex, dorsal lateral prefrontal cortex, sgACC, VMPFC, and deactivation in the superior temporal gyrus, insula, anterior cingulate, dorsal lateral prefrontal cortex, and

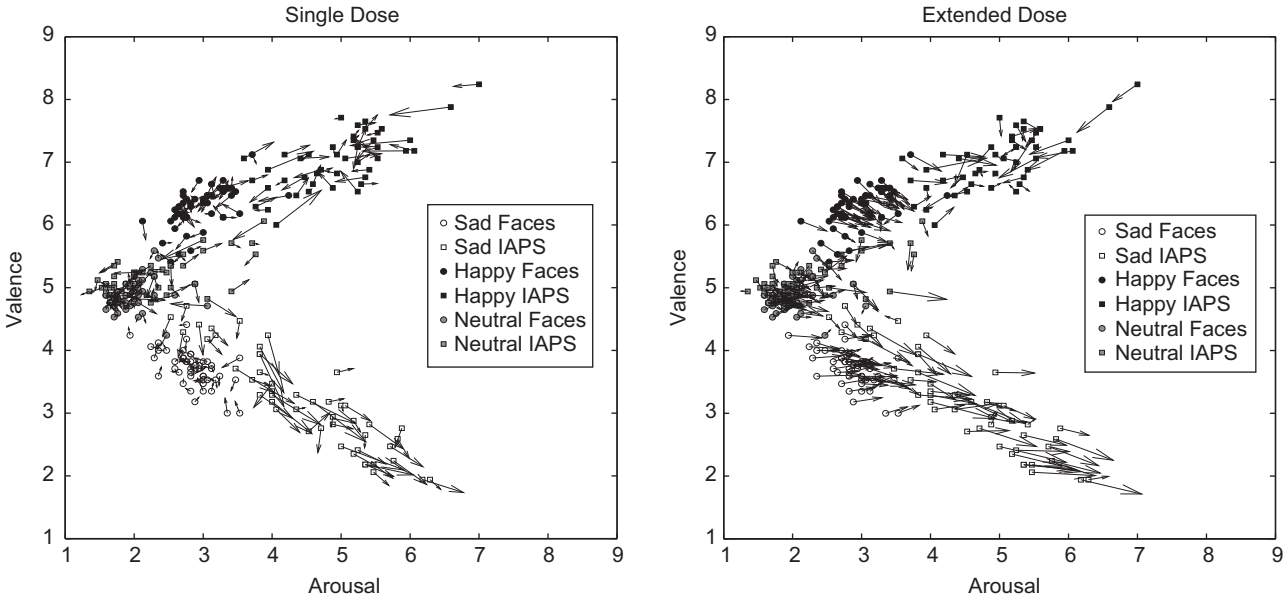

Figure 4 Subjective ratings of each of the experimental stimuli are plotted in valence/arousal space for the placebo group. Arrows indicate the vector of shifts toward increasing arousal in the hydrocortisone groups. The left panel quiver plot demonstrates placebo group to single-dose group change vectors. The right panel demonstrates placebo group to extended dose group change vectors. In the extended dose group, the most prominent shifts are in the stimuli occupying the low valence portions of the valence/arousal space, which correspond to sad stimuli. IAPS, International Affective Picture System.

posterior cingulate/precuneus (data not shown), when applying the false-discovery rate correction for multiple comparisons ($p < 0.05$, $k = 10$).

In conclusion, we present evidence suggesting that HCT decreases the sgACC and VMPFC activity evoked by sad stimuli. We also demonstrate that HCT increases the subjective arousal experienced while viewing sad stimuli. These findings may have important implications for research on the pathophysiology of MDD, as this is the first study to demonstrate that elevated cortisol can cause functional decreases in activation in the sgACC during sad conditions. This finding suggests a plausible theory of glucocorticoid resistance causing sgACC hyperactivity in MDD.

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DISCLOSURE

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