Journal of Affective Disorders 287 (2021) 247–254

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Cortisol effects on brain functional connectivity during emotion processing in women with depression

Charlene N. Rivera-Bonet [a,*], Rasmus M. Birn [a,b,c], Charlotte O. Ladd [b], Mary E. Meyerand [a,c,d], Heather C. Abercrombie [e]

[a] Neuroscience Training Program, University of Wisconsin-Madison, Madison, WI, United States
[b] Department of Psychiatry, University of Wisconsin-Madison, Madison, WI, United States
[c] Department of Medical Physics, University of Wisconsin-Madison, Madison, WI, United States
[d] Department of Biomedical Engineering, University of Wisconsin-Madison, Madison, WI, United States
[e] Center for Healthy Minds, University of Wisconsin-Madison, Madison, WI, United States

ARTICLE INFO

Keywords:
Cortisol
Depression
Task-based functional connectivity
Psychophysiological interaction
Emotion Processing
Hippocampus

ABSTRACT

Background: Depression is associated with altered functional connectivity and altered cortisol sensitivity, but the effects of cortisol on functional connectivity in depression are unknown. Previous research shows that brief cortisol augmentation (CORT) has beneficial neurocognitive effects in depression.

Methods: We investigated the effects of CORT (20mg oral cortisol) on functional connectivity during emotion processing in women with depression. Participants included 75 women with no depression or a depressive disorder. In a double-blind, crossover study, we used functional magnetic resonance imaging to measure effects of CORT vs. placebo on task-based functional connectivity during presentation of emotionally-laden images. We performed psychophysiological interaction (PPI) to test interactions among depression severity, cortisol administration, and task-dependent functional connectivity using the hippocampus and amygdala as seeds.

Results: During the presentation of negative images, CORT (vs. placebo) increased functional connectivity between the hippocampus and putamen in association with depression severity. During the presentation of positive pictures CORT increased functional connectivity between the hippocampus and middle frontal gyrus as well as superior temporal gyrus in association with depression.

Limitations: Because cortisol was pharmacologically manipulated, results cannot be extrapolated to endogenous increases in cortisol levels. The sample did not permit investigation of differences due to race, ethnicity, or sex. Co-morbidities such as anxiety or PTSD were not accounted for.

Conclusions: The results suggest that CORT has normalizing effects on task-dependent functional connectivity in women with depression during emotion processing. Increasing cortisol availability or signaling may have therapeutic benefits within affective disorders.

1. Introduction

Depression is a leading cause of disability (World Health Organization, 2017), affecting around 300 million people worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; World Health Organization, 2017), with women being twice as likely to have depression than men (Brody et al., 2018). Depressive disorders are often associated with glucocorticoid (GC) resistance, which reflects insufficient GC cellular signaling and systemic insensitivity to GCs (de Kloet et al., 2016; Gaffey et al., 2019; Holsboer, 2001). Cortisol is the primary endogenous GC in primates. Cortisol is a stress-related adrenal hormone that crosses the blood-barrier and modulates brain activity particularly in the prefrontal cortex, amygdala, and hippocampus (Patel et al., 2000; Sánchez et al., 2000). Although peripheral cortisol dysregulation and alterations in GC signaling are well established in depression, very little experimental research has examined the effects of GCs on functional brain connectivity.

Beyond the well-known systemic cortisol alterations, such as hypothalamic pituitary adrenal negative feedback deficits related to GC resistance, research implicates altered cognitive and neural sensitivity to

* Corresponding author.
E-mail address: riverabonet@wisc.edu (C.N. Rivera-Bonet).

https://doi.org/10.1016/j.jad.2021.03.034
Received 10 February 2021; Received in revised form 10 March 2021; Accepted 15 March 2021
Available online 19 March 2021

GCs in depression (Gaffey et al., 2019; Pariante, 2018; Rohleder et al., 2010). Findings in humans from our own (Abercrombie et al., 2018, 2011; Gaffey et al., 2019) and others' labs (Bremner et al., 2004; Otte et al., 2015) show that a variety of neurocognitive alterations can be normalized by acutely elevated cortisol or brief administration of exogenous GCs. These findings are consistent with rodent research showing that GC augmentation normalizes learning and hippocampal neuroplasticity in animal models of depression and stress related pathology (Bagot et al., 2009; Champagne et al., 2008; Moriceau et al., 2009). In healthy humans, elevated GCs have varied and context-dependent effects on emotional cognition and response selection strategies in relation to changes in frontal and/or hippocampal activation mediated by cortisol and noradrenergic activation (Schwabe and Wolf, 2013; Smeets et al., 2019). In depression, acute GC administration has been observed to benefit (Bremner et al., 2004; Gaffey et al., 2019; Otte et al., 2015) or not impair (Terfehr et al., 2011a, 2011b) cognition and other psychological processes, even when having deleterious effects in healthy individuals (Terfehr et al., 2011a, 2011b).

Abundant research has shown that functioning of the hippocampus is closely tied to variation in cortisol with relevance for depression (Abercrombie et al., 2011; Hinkelmann et al., 2009; Lyons et al., 2001; McEwen, 2002; Pittenger and Duman, 2008). For example, the concentration of glucocorticoid receptors (GR) in the hippocampus is reduced in depression (Klok et al., 2011; Medina et al., 2013) and alterations of GR co-chaperone FKBP5, which aids in the process of GR translocation to the nucleus, have been associated with impaired GC insensitivity in depression and other stress disorders (Lee et al., 2011). FKBP5 dysfunction has also been related to altered hippocampal connectivity and risk to depression (Córdova-Palomera et al., 2017). Research in animal models shows that administration of glucocorticoids (Menke et al., 2012) normalizes FKBP5 expression in the hippocampus (Scharf et al., 2011).

Circulating cortisol levels might be insufficient to modulate neural activity due to GC insensitivity in the hippocampus, thus GC augmentation may be beneficial (Raison and Miller, 2003). Consistent with this suggestion are findings showing that administration of GCs improves declarative memory in MDD patients compared to healthy subjects (Bremner et al., 2004). Studies in our laboratory have also shown positive effects of brief cortisol augmentation (CORT) in women with depression, particularly for the formation of emotional memories (Abercrombie et al., 2018, 2011). In one of these studies, CORT's effects on hippocampal activation and emotional memory formation were related in depressed participants. Possibly, circulating levels of cortisol (despite being elevated at times) and/or cortisol signaling in the brain are insufficient to optimally modulate brain function and networks in depression, and thus briefly augmenting cortisol levels may normalize functional connectivity. However, to our knowledge, no studies have addressed the effect of CORT on task dependent functional connectivity in women with depression.

The aim of this study was to investigate the effects of brief cortisol augmentation (CORT) on hippocampal functional connectivity during an emotional picture-viewing task in women with depression. We hypothesized that CORT (vs. placebo) in women with depression will normalize hippocampal task-based functional connectivity to mimic that of women without depression. As a comparison region, we also tested effects of CORT (vs. placebo) on amygdala task-based connectivity. The study included women with a range of depressive symptoms who underwent two functional Magnetic Resonance Imaging (fMRI) visits, each with of viewing emotionally-laden images from the International Affective Picture System (IAPS) (Lang et al., 2008) and double-blind, crossover administration of either cortisol or placebo prior to scanning. Psychophysiological interaction (PPI) (Friston et al., 1997), i.e., context-dependent connectivity analysis, was performed to determine the interactions among depression severity, cortisol administration, and task-dependent functional connectivity.

2. Methods and materials

2.1. Participants

This study consists of a community-based sample of unmedicated pre-menopausal women between the ages of 18-45 with varying levels of depression severity. Women with anxiety disorders or post-traumatic stress disorder (PTSD) were not excluded, although not specifically recruited. Eighty out of 85 eligible participants completed the study (mean age = 27.7 years; 75% White, 17% Asian, 5% Black, 8% Hispanic) (Table 1). Data was lost to experimenter error (1 participant), scanner malfunction (1 participant), poor image quality (2 participants), and a medical condition (1 participant). Inclusion and exclusion criteria can be found in the Supplemental File. The study protocol was approved by the University of Wisconsin Health Sciences Institutional Review Board (IRB). All participants provided written informed consent and were paid for their participation in the study.

2.2. Depression severity

Women recruited for this study had a range of depressive symptoms from never depressed to Major Depressive Disorder (MDD). Psychopathology was assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (First et al., 2002) with additional questions to assess DSM-V criteria. Depression severity was determined using the average of Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) scores from the two scan sessions.

2.3. Study design

Each participant came to the lab for two fMRI scanning visits during which they received placebo or CORT, the order of which was randomized and double-blinded. During the fMRI tasks on each of the placebo and CORT days (Fig. 1), participants were presented with one of two matched sets of emotionally-normed images from the International Affective Picture System (IAPS) (Lang et al., 2008), containing 84 pictures matched on valence and arousal presented during the placebo and cortisol scanning sessions. Both sets contained equal numbers of pleasant, unpleasant and neutral pictures (28 each). During the task, participants engaged in a simple emotional response task, rating each picture as positive, negative or neutral using a button box (Current Designs Inc., Philadelphia, PA). Pictures were presented for 5 seconds

Table 1
Subject Demographics.

Characteristics	No Depression (n=43)	Current Depression (n=32)	Total (n=75)
Age[a,b]	27.1 ± 7.1	28.1 ± 7.1	27.7 ± 7
BDI Score[c]	0.99 ± 1.6	18.9 ± 9.9	8.6 ± 11.1
Race	-	-	-
White	33	23	56
Asian	7	6	13
African American	3	1	4
Unknown	0	2	2
Ethnicity	-	-	-
Hispanic/Latina	1	5	6
Non- Hispanic/ Latina	42	26	68
Unknown	0	1	1
Education Level[a,d]	4.5 ± 1.4	4.8 ± 1.3	4.6 ± 1.4

[a] t-test showed no significant difference for age (t= 0.56; $p = 0.56$) or education level (t= 1.13; $p= 0.26$).
[b] years±standard deviation.
[c] Beck Depression Inventory (t=10.1, $p<0.001$).
[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.

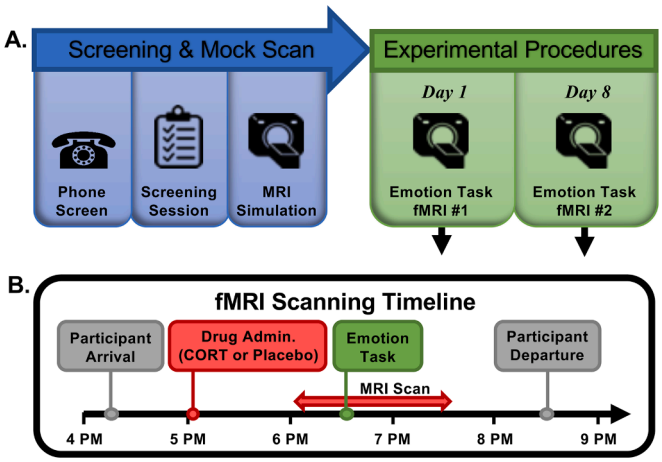

Fig. 1. Study timeline. Participants were screened to determine eligibility, after which they underwent a mock MRI scan for acclimation. On days 1 and 8 of the study, participants completed an emotion task during fMRI scanning. Participants received either placebo or 20mg cortisol (order randomized and double-blinded) 90 minutes before the emotion task administered during fMRI scanning.

each, followed by a 3-second response period and a jittered interstimulus interval ranging from 4-9 seconds. Stimuli were back-projected onto a screen inside the scanner bore. The emotion task was conducted in the evening when endogenous CORT levels are low.

2.4. Timing of cortisol administration

Prior to the two MRI scans, participants received either cortisol or placebo in a randomized, crossover, double-blinded manner (Fig. 1C). Tablets were encapsulated so that cortisol and placebo appear identical. Our previous work using this method of oral cortisol administration show that cortisol levels peak 90 minutes after drug administration (Supplementary Fig. 1). For this reason, ninety minutes before the fMRI task, cortisol levels were pharmacologically manipulated with oral administration of 20-mg encapsulated cortisol (i.e., hydrocortisone), which causes extreme but physiologic elevations in cortisol. 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.

2.5. Image collection and processing

Participants had a mock scan for acclimation to the MRI before the scans (Fig. 1). 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 pre-processing can be found in detail in Abercrombie and Frost et al., 2018 (Abercrombie et al., 2018). Briefly, data were processed using Analysis of Functional NeuroImages (AFNI) (Cox, 1996) unless indicated otherwise. First, a rigid-body volume registration was performed for motion correction (3dvolreg). 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) and iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) sequence (Reeder et al., 2005) to geometrically unwarp echo-planar images to reduce distortion caused by magnetic field inhomogeneities using FMRIB Software Library (Jenkinson et al., 2012). 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 (Talairach, 1988). 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).

2.6. Data analysis

Context-dependent correlation analysis or generalized psychophysiological interactions (PPI) was performed to determine functional connectivity during the IAPS viewing fMRI-task. First, a seed time series was created (3dmaskave) by averaging the preprocessed fMRI signal over a region of interest, in this case right, left and bilateral hippocampus and amygdala. The hippocampus was chosen based on abundant research showing inter-related alterations in cortisol and hippocampal functioning in depression. The amygdala was chosen as a comparison seed because of its known roles in affective disorders and in HPA axis drive (Drevets et al., 2002; Erickson et al., 2003). Linear [or 2 order polynomial] trends were removed from this time series (3dDetrend). This time series was then resampled (3dUpsample) and deconvolved of the hemodynamic response function (3dTfitter) to obtain an estimate of the neuronal activity during the task. This processed fMRI signal was then multiplied by the task timing in order to obtain the psychophysiological interaction regressor. This regressor was then used in a multiple linear regression analysis together with the seed time series, to provide an estimate of the seed-based connectivity as well as the interaction of this connectivity with the emotion task. A paired t-test was performed (3dttest++) between cortisol and placebo day using BDI scores as a covariate. Multiple comparison correction was performed by estimating the spatial autocorrelation function (3dFWHM) and performing a Monte Carlo simulation to estimate the minimum cluster size to achieve a corrected p-value of 0.05 (3dClustSim).

2.7. Post-hoc analysis

To visualize and determine the direction of the effects, we performed post-hoc statistical analysis in R (R Core Team, 2017) for each significant finding. For visualization, functional correlation values were extracted (3dROIstats) for both placebo and cortisol day and compared between No Depression and Current Depression.

3. Results

3.1. Effects of cortisol on functional connectivity

3.1.1. Negative IAPS pictures

PPI provides information on task-specific functional connectivity between brain regions.

During the presentation of negative IAPS pictures, brief cortisol augmentation (CORT) vs placebo altered task-dependent functional connectivity between the right hippocampus seed (Fig. 1A) and the left putamen ($p < 0.03$) (Fig. 1B1) (Table 2), in association with depression severity. Without depression severity in the model, there were no significant effects of CORT vs placebo. Posthoc analyses showed that on the placebo day, greater depression severity was associated with lower task-dependent functional connectivity between the hippocampus and the putamen (Supplementary Fig. 1). On the CORT day, depression severity

Table 2
Effects of cortisol vs placebo administration on PPI (task-dependent functional connectivity) of the hippocampus during the presentation of IAPS pictures correlated with depression severity.

Seed	Stimulus	Cluster	Volume (voxels 2×2×2mm^3)	Coordinates (x, y, z)	P-value (individual voxel)	Corrected p-value (∝)
Right hippocampus		-	-	30, -24, -9	-	-
	Negative	Putamen	658	22, -4, -4	0.005	0.03
Right hippocampus		-	-	30, -24, -9	-	-
	Positive	Superior Temporal Gyrus	1312	52, 22, 12	0.01	0.02
Bilateral hippocampus		-	-	30, -24, -9; -30, -24, -9	-	-
	Positive	Superior Temporal Gyrus	1542	66, 28, 14	0.005	0.01
	Positive	Medial Frontal Gyrus	1766	12, 18, 60	0.005	0.01

is not associated with hippocampus-putamen connectivity. Fig. 2B2 depicts functional connectivity correlation coefficients and clarifies the significant interaction by showing that CORT increased task dependent functional connectivity between the right hippocampus and left putamen in association with depression severity. This suggests CORT (vs placebo) normalized connectivity to levels apparent in women without depression. No significant correlations were observed for the amygdala during presentation of negative IAPS pictures.

3.1.2. *Positive IAPS pictures*

During the presentation of positive IAPS pictures, CORT (vs. placebo) altered task-dependent functional connectivity between the bilateral hippocampus seed and the left superior temporal gyrus ($p>0.01$) (Fig. 3B1), as well as the left medial frontal gyrus ($p>0.01$) (Fig. 3C1) (Table 2) in relationship with depression severity. There were no significant effects of CORT vs placebo when depression severity was removed from the model. An effect of cortisol administration was also found for the right hippocampus and the superior temporal gyrus (Table 2). Posthoc analysis showed that on the placebo day, greater depression severity was associated with lower task-dependent functional connectivity between the hippocampus and the middle frontal gyrus (Supplementary Fig. 2). On CORT day, depression severity was not associated with hippocampal-middle frontal gyrus connectivity. Fig. 3B2 clarifies the significant interaction by showing that CORT increased task-dependent functional connectivity between the right hippocampus and left middle frontal gyrus, as well as left temporal lobe, thus normalizing connectivity to levels apparent in women without depression. No significant correlations were observed for the amygdala during presentation of positive IAPS pictures.

3.1.3. *Neutral pictures*

No significant effects of CORT on functional connectivity were observed during the presentation of neutral pictures. This suggests CORT's effect is only significant during the presentation of images with emotional valence.

4. Discussion

Our results show normalizing effects of brief cortisol augmentation (CORT) on hippocampal functional connectivity in women with depression. Using the hippocampus as a seed region, we observed that CORT increased functional connectivity between the hippocampus and the putamen, middle frontal gyrus and superior temporal gyrus of women with depression during the presentation of emotion-eliciting pictures. This led to functional connectivity in women with depression that mimics that of women with no depression. The novel finding that cortisol administration normalizes hippocampal functional connectivity in depression is consistent with prior research showing beneficial effects of brief corticosteroid augmentation in both depressed humans (Abercrombie et al., 2018; Bremner et al., 2004; Gaffey et al., 2019; Otte et al., 2015) and animal models (Bagot et al., 2009; Champagne et al., 2008; Moriceau et al., 2009).

4.1. *CORT effects on hippocampal task-based functional connectivity*

We investigated the effect of CORT on task-dependent functional connectivity during the presentation of emotionally-laden IAPS pictures in relation to depression severity. During the presentation of negative images, task-dependent functional connectivity between the hippocampus and the putamen was reduced in women with depression during placebo administration. CORT normalized the hippocampal-putamen

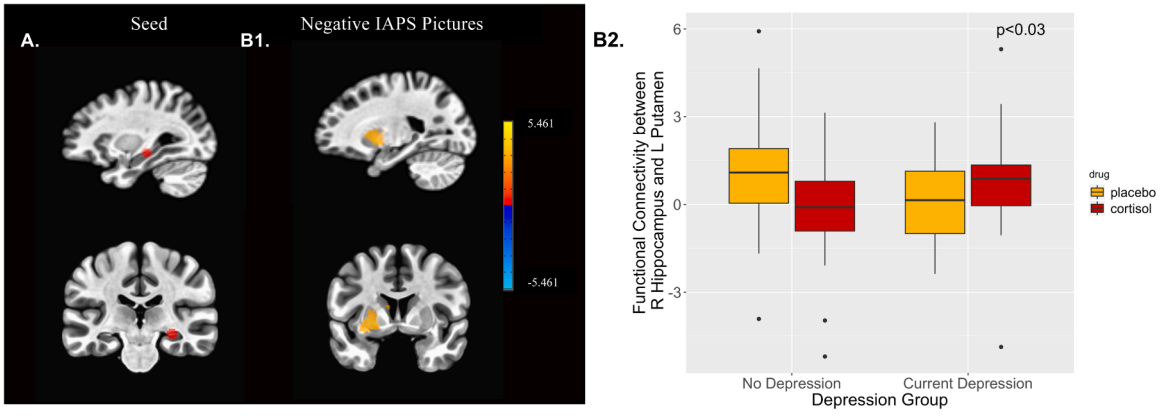

Fig. 2. Effects of cortisol on hippocampal functional connectivity during presentation of negative pictures. Psychophysiological interactions were tested to investigate task-dependent functional connectivity during negative pictures in relation to depression severity. (A) The right hippocampus (30, -24, -9) was selected as region of interest. (B1) During the presentation of negative IAPS pictures, administration of cortisol increased functional connectivity between the right hippocampus and the left putamen (22, -4, -4; p>0.005; ∝ = 0.03). There were no significant differences in functional connectivity with the left hippocampus as a seed region. (B2) Boxplots for illustration purposes depict correlation coefficients extracted for the putamen (in relation to hippocampus) and compared between no depression and current depression groups. Cortisol administration increased functional connectivity in relation to depression severity. R= right; L=left.

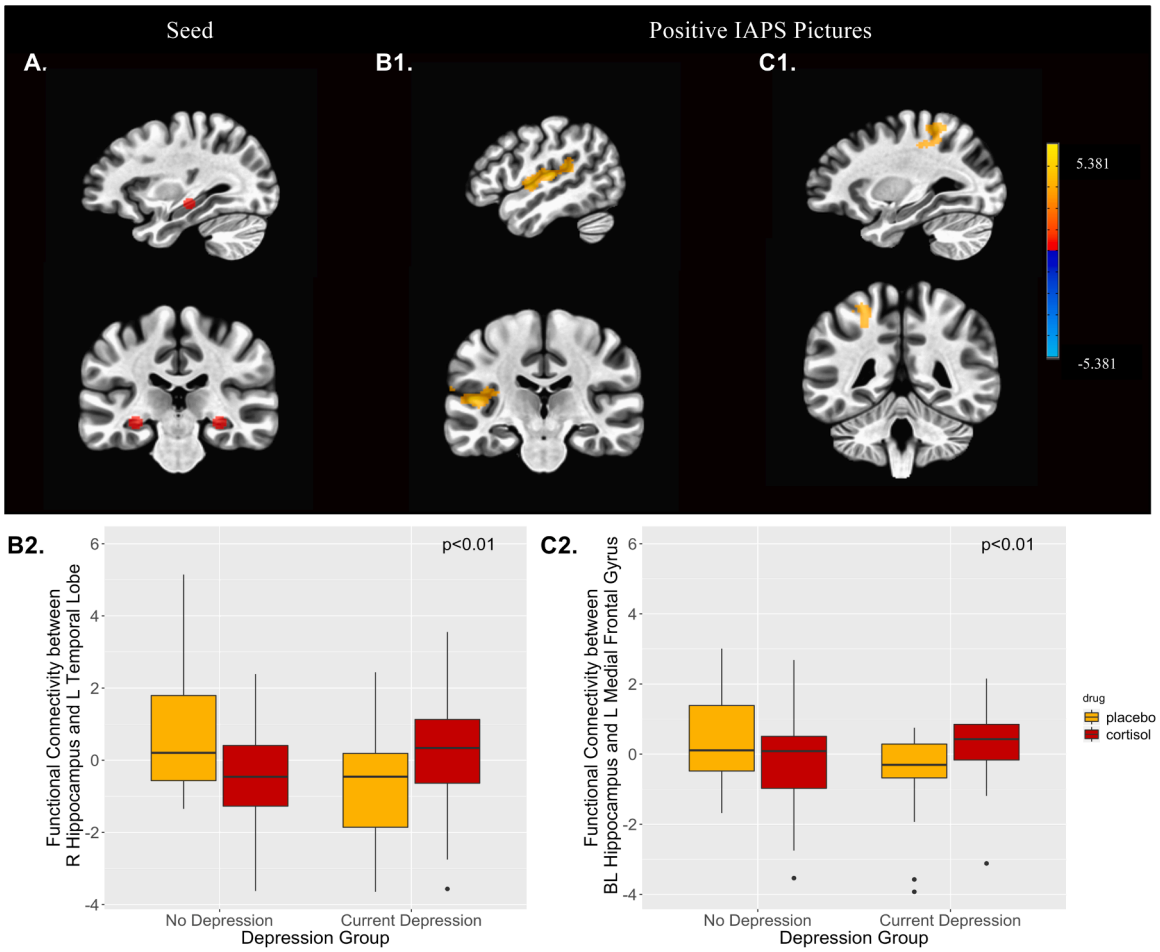

Fig. 3. Effects of cortisol on hippocampal functional connectivity during presentation of positive pictures. Psychophysiological interactions were tested to investigate task-dependent functional connectivity during positive pictures in relation to depression severity. (A) Bilateral hippocampus (right= 30, -24, -9; left= -30, -24, -9) was chosen as a seed region. (B1) During the presentation of positive IAPS images, cortisol administration increased functional connectivity between bilateral hippocampus and the superior temporal gyrus (66, 28, 14; $p>0.005$, $\propto = 0.01$) and the (C1) middle frontal gyrus (12, 18, 60). Boxplots for illustration purposes depict correlation coefficients extracted for the (B2) medial frontal gyrus and the (C2) temporal lobe and compared between no depression and current depression groups. Cortisol administration increased functional connectivity in association with depression severity. BL=bilateral; L=left.

connectivity in depressed participants. The putamen, along with the caudate nucleus, form the dorsal striatum, which is a subcortical region within the basal ganglia. The putamen is involved in learning and cognitive functioning, reward processing, and sensorimotor function (Haber, 2016). Reduction in putamen volume and regional shape deformation has been associated with major depressive disorder, particularly in unmedicated individuals (Lu et al., 2016). Other studies demonstrated alterations in task-dependent functional connectivity between the hippocampus and the striatum (Admon et al., 2016). Admon and colleagues (Admon et al., 2016) observed altered functional connectivity between the hippocampus to the striatum (caudate and putamen) in relation to cortisol levels in individuals with remitted depression, which is consistent with our findings suggesting that this circuitry is sensitive to cortisol. Research has also shown altered connectivity between the hippocampus and the ventral striatum in relation to emotion processes (Heller et al., 2020). Although our cluster did not encompass the ventral striatum, future research should address hippocampal striatal connectivity with a focus on dorsal and ventral striatum.

In a pattern similar to that of the negative pictures, during the presentation of positive IAPS pictures, we observed in women with depression that CORT increased functional connectivity between the bilateral hippocampus and other brain regions, specifically the medial frontal gyrus and the superior temporal gyrus. The middle frontal gyrus has been associated with neural activity in response to positive versus negative stimuli in depression (Diler et al., 2013) and elaboration of episodic memory retrieval for positive and negative images (Ford et al., 2014). This region has also been linked to motor learning (Fink et al., 1997) and sensorimotor control (Beudel et al., 2011).

No significant findings emerged from analyses of our comparison seed region, the amygdala. This suggests that CORT's effects on hippocampal functional connectivity in relation to depression are focal rather than diffuse within the medial temporal lobe. Furthermore, CORT administration had no effect on functional connectivity of the hippocampus or amygdala during the presentation of neutral IAPS images. This is consistent with previous studies that show relationships between corticosteroids and emotional cognition but not for processing of neutral information (Buchanan and Lovallo, 2001; van Stegeren et al., 2010).

All or most of our findings point to motor and premotor functions and effects of CORT on the motor system in relation to depression severity. In addition to the role of the middle frontal gyrus in motor planning, the hippocampus and striatum are thought to have distinct but cooperative function in the process of motor sequence memory consolidation (Albouy et al., 2015, 2008). Previous studies in our lab have identified effects of CORT in relation to motor system circuitry such as the supplementary motor area (SMA) (Abercrombie et al., 2018) and the corticospinal white matter tracts (Frost et al., 2018). Motor-related systems play a dual role in depression, modulating the psychomotor symptoms of depression and directly or indirectly affecting stress regulation

(Canbeyli, 2013; Dum et al., 2016). Dum and colleagues suggest that control of the adrenal cortex –involved in stress neuromodulation and the sympathetic arm of the autonomic nervous system – is embedded in cortical areas involved in motor planning (Dum et al., 2016). In addition, recent research points to the importance of motor planning regions in emotion regulation (Domes et al., 2010; Shackman et al., 2011). Recruitment of motor regions such as the medial frontal cortex appear to reflect a more action-oriented cognitive response to negative stimuli (Isoda and Hikosaka, 2007; Rushworth et al., 2002). Findings from our study provide further support for the relevance of motor and motor planning neurocircuitry in stress neuromodulation, emotion, and depression.

4.2. Potential mechanisms of GC sensitivity

Decades of research in depression have pointed to alterations in peripheral GC sensitivity. Our findings suggest that neural sensitivity to cortisol is also relevant in depression. We observed that functional connectivity was low during placebo administration and was normalized by CORT, which readily crosses the blood-brain barrier and modulates neural function. The findings may suggest that circulating cortisol levels are insufficient to regulate neural connectivity and that brief cortisol augmentation may boost the cortisol neural signal and thus normalize neural connectivity. Insufficient GC signaling might occur as a result of decreased hormone bioavailability or attenuated cellular responsiveness to glucocorticoids (Raison and Miller, 2003). GC insufficiency in depression could be associated with molecular intraneuronal alterations, including alterations in receptor number or function. Cortisol receptors, both glucocorticoid and mineralocorticoid receptors, show reduced number and/or density in regions such as the hippocampus and prefrontal cortex in depression (de Kloet et al., 2016; Klok et al., 2011; Medina et al., 2013; Pariante and Miller, 2001; Sapolsy et al., 1984). Functional capacity and binding affinity of GR are also compromised in people with depression (Pariante and Miller, 2001; Raison and Miller, 2003). Moreover, genetic variation in relation to the GR co-chaperone, FKBP5, is associated with increased GC resistance (Binder, 2009; Klengel et al., 2013), risk of mood and anxiety disorders (Zannas and Binder, 2014) and hippocampal connectivity deficits in risk of depression (Córdova-Palomera et al., 2017). For instance, polymorphism of the FKPB5 gene have been shown in relation to alterations in communication patterns between the hippocampus and the rest of the brain in depression (Córdova-Palomera et al., 2017). While the current study does not identify which of these mechanisms is responsible for the observed effects, the findings do suggest that neural cortisol signaling is relevant to depression and suggest that future research should investigate mechanisms of altered neural sensitivity to GCs.

4.3. Implications for treatment

Previous research as well the present study suggest that brief corticosteroid augmentation normalizes neurocognitive function in depression (Abercrombie et al., 2018; Bremner et al., 2004; Otte et al., 2015). However, cortisol administration is not a feasible treatment due to the noxious effects it can have long-term. Alternative ways to increase GC sensitivity have been a subject of research for many years. Neural signaling of cortisol is a relevant but under-studied mechanism of standard antidepressant medication (Anacker et al., 2011; Pariante et al., 2012). Antidepressants increase both the number and functional capacity of cortisol receptors in brain regions such as the hippocampus (Pittenger and Duman, 2008; Raison and Miller, 2003) by activating GR translocation and regulating neurogenesis through GR activation (Anacker et al., 2011). Pre-treatment of healthy individuals with antidepressants interacts with effects of cortisol on EEG alpha power and on working memory, suggesting that antidepressants may tonically activate GR and affect the potency of acute cortisol administration on neural function (Pariante et al., 2012). In addition to traditional antidepressants, because of its role in nuclear translocation of bound glucocorticoid receptors, FKBP5 offers a potential target as treatment for affective and stress-related disorders, and *in vitro* studies in rodent models have shown promising results of pharmacological agents that target FKBP5 (Gaali et al., 2015; Zannas et al., 2016). Increasing bioavailable cortisol instead of cortisol administration offers an opportunity to naturally increase GCs and can be achieved through mild stressors such as physical exercise. Although the mechanism remains unknown, exercise modulates GC sensitivity (Beserra et al., 2018), and research performed in a rodent model suggests that beneficial effects of exercise are related to greater hippocampal GC signaling (Zheng et al., 2006). Thus, a variety of mechanisms may relate to GC neural signaling as treatment target in psychiatric disorders and this remains an under-investigated area of study.

4.4. Limitations

Because we pharmacologically manipulated cortisol, we cannot extrapolate our results to brief endogenous, natural increase in cortisol levels. We did not account for co-morbidities such as anxiety or PTSD. Because we don't have a large enough sample to study differences in ethnicity, we cannot determine whether these results are generalizable to all populations. Future research should address these issues.

4.5. Conclusions

We found that brief cortisol augmentation (CORT) increased hippocampal functional connectivity in association to depression during an emotion task-fMRI. Paired with emotional pictures, CORT increased functional connectivity between the hippocampus and other regions to the level of connectivity observed in healthy control subjects, suggesting that brief cortisol augmentation normalized hippocampal functional connectivity in women with depression. These findings contribute to the literature on GC sensitivity alterations in depression by showing that neural connectivity is sensitive to cortisol. The findings emphasize the importance of continuing to investigate the relevance and potential therapeutic implications of altered neural and peripheral GC sensitivity in depression.

CRediT authorship contribution statement

Charlene N. Rivera-Bonet: Conceptualization, Methodology, Formal analysis, Writing - review & editing, Visualization. **Rasmus M. Birn:** Conceptualization, Methodology, Software, Data curation, Writing - review & editing. **Charlotte O. Ladd:** Conceptualization, Resources, Methodology, Writing - review & editing. **Mary E. Meyerand:** Conceptualization, Supervision, Writing - review & editing. **Heather C. Abercrombie:** Data curation, Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors report no biomedical financial interests or potential conflicts of interest.

Acknowledgements

Research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under Award Number T32MH018931. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Prior to issuing a press release concerning the outcome of this research, please notify the National Institutes of Health awarding IC in advance to allow for coordination. This research was supported by the NIMH (R01MH094478), UW-Madison OVCRGE

with funding from the Wisconsin Alumni Research Foundation (WARF), and UW-Madison WISELI/The Office of the Provost. The authors would like to thank the study participants for their valuable contribution.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.03.034.

References

Abercrombie, H.C., Frost, C.P., Walsh, E.C., Hoks, R.M., Cornejo, M.D., Sampe, M.C., Gaffey, A.E., Plante, D.T., Ladd, C.O., Birn, R.M., 2018. Neural signaling of cortisol, childhood emotional abuse, and depression-related memory bias. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3, 274–284. https://doi.org/10.1016/j.bpsc.2017.11.005.

Abercrombie, H.C., Jahn, A.L., Davidson, R.J., Kern, S., Kirschbaum, C., Halverson, J., 2011. Cortisol's effects on hippocampal activation in depressed patients are related to alterations in memory formation. J. Psychiatr. Res. 45, 15–23. https://doi.org/10.1016/j.jpsychires.2010.10.005.

Admon, R., Holsen, L.M., Aizley, H., Remington, A., Whitfield-, S., Goldstein, J.M., Pizzagalli, D.A., Hospital, M., Biology, G., Hospital, W., Hospital, W., Hospital, M.G., Sciences, C., Hospital, M., 2016. Striatal hyper-sensitivity during stress in remitted individuals with recurrent depression Roee. Biol. Psychiatry 78, 67–76. https://doi.org/10.1016/j.biopsych.2014.09.019.Striatal.

Albouy, G., Fogel, S., King, B.R., Laventure, S., Benali, H., Karni, A., Carrier, J., Robertson, E.M., Doyon, J., 2015. Maintaining vs. enhancing motor sequence memories: Respective roles of striatal and hippocampal systems. Neuroimage 108, 423–434. https://doi.org/10.1016/j.neuroimage.2014.12.049.

Albouy, G., Sterpenich, V., Balteau, E., Vandewalle, G., Desseilles, M., Dang-Vu, T., Darsaud, A., Ruby, P., Luppi, P.-H., Degueldre, C., Peigneux, P., Luxen, A., Maquet, P., 2008. Both the hippocampus and striatum are involved in consolidation of motor sequence memory. Neuron 58, 261–272. https://doi.org/10.1016/j.neuron.2008.02.008.

Anacker, C., Zunszain, P.A., Cattaneo, A., Carvalho, L.A., Garabedian, M.J., Thuret, S., Price, J., Pariante, C.M., 2011. Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor. Mol. Psychiatry 16, 738–750. https://doi.org/10.1038/mp.2011.26.

Bagot, R.C., van Hasselt, F.N., Champagne, D.L., Meaney, M.J., Krugers, H.J., Joëls, M., 2009. Maternal care determines rapid effects of stress mediators on synaptic plasticity in adult rat hippocampal dentate gyrus. Neurobiol. Learn. Mem. 92, 292–300. https://doi.org/10.1016/j.nlm.2009.03.004.

Beck, A.T., Steer, R.A., Ball, R., Ranieri, W.F., 1996. Comparison of beck depression inventories-ia and-ii in psychiatric outpatients. J. Pers. Assess. 67, 588–597. https://doi.org/10.1207/s15327752jpa6703_13.

Beserra, A.H.N., Kameda, P., Deslandes, A.C., Schuch, F.B., Laks, J., de Moraes, H.S., 2018. Can physical exercise modulate cortisol level in subjects with depression? a systematic review and meta-analysis. Trends Psychiatry Psychother. 40, 360–368. https://doi.org/10.1590/2237-6089-2017-0155.

Beudel, M., Zijlstra, S., Mulder, T., Zijdewind, I., de Jong, B.M., 2011. Secondary sensory area SII is crucially involved in the preparation of familiar movements compared to movements never made before. Hum. Brain Mapp. 32, 564–579. https://doi.org/10.1002/hbm.21044.

Binder, E.B., 2009. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. Psychoneuroendocrinology 34, 186–195. https://doi.org/10.1016/j.psyneuen.2009.05.021.

Bremner, J.D., Vythilingam, M., Vermetten, E., Anderson, G., Newcomer, J.W., Charney, D.S., 2004. Effects of glucocorticoids on declarative memory function in major depression. Biol. Psychiatry 55, 811–815. https://doi.org/10.1016/j.biopsych.2003.10.020.

Brody, D.J., Pratt, L.A., Hughes, J.P., 2018. Prevalence of Depression Among Adults Aged 20 and Over: United States, 2013-2016. NCHS Data Brief 1–8.

Buchanan, T.W., Lovallo, W.R., 2001. Enhanced memory for emotional material following stress-level cortisol treatment in humans. Psychoneuroendocrinology 26, 307–317. https://doi.org/10.1016/S0306-4530(00)00058-5.

Canbeyli, R., 2013. Sensorimotor modulation of mood and depression: In search of an optimal mode of stimulation. Front. Hum. Neurosci. 7, 1–13. https://doi.org/10.3389/fnhum.2013.00428.

Champagne, D.L., Bagot, R.C., Van Hasselt, F., Ramakers, G., Meaney, M.J., De Kloet, E. R., Joëls, M., Krugers, H., 2008. Maternal care and hippocampal plasticity: Evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. J. Neurosci. 28, 6037–6045. https://doi.org/10.1523/JNEUROSCI.0526-08.2008.

Córdova-Palomera, A., de Reus, M.A., Fatjó-Vilas, M., Falcón, C., Bargalló, N., van den Heuvel, M.P., Fañanás, L., 2017. FKBP5 modulates the hippocampal connectivity deficits in depression: a study in twins. Brain Imaging Behav 11, 62–75. https://doi.org/10.1007/s11682-015-9503-4.

Cox, R., 1996. AFNI : software for analysis and visualization of functional magnetic resonance. Neuroimages 173, 162–173.

de Kloet, E.R., Otte, C., Kumsta, R., Kok, L., Hillegers, M.H.J., Hasselmann, H., Kliegel, D., Joëls, M., 2016. Stress and depression: a crucial role of the mineralocorticoid receptor. J. Neuroendocrinol. 28 https://doi.org/10.1111/jne.12379.

Diler, R.S., de Almeida, J.R.C., Ladouceur, C., Birmaher, B., Axelson, D., Phillips, M., 2013. Neural activity to intense positive versus negative stimuli can help differentiate bipolar disorder from unipolar major depressive disorder in depressed adolescents: a pilot fMRI study. Psychiatry Res. - Neuroimaging 214, 277–284. https://doi.org/10.1016/j.pscychresns.2013.06.013.

Domes, G., Schulze, L., Böttger, M., Grossmann, A., Hauenstein, K., Wirtz, P.H., Heinrichs, M., Herpertz, S.C., 2010. The neural correlates of sex differences in emotional reactivity and emotion regulation. Hum. Brain Mapp. 31, 758–769. https://doi.org/10.1002/hbm.20903.

Drevets, W.C., Price, J.L., Bardgett, M.E., Reich, T., Todd, R.D., Raichle, M.E., 2002. Glucose metabolism in the amygdala in depression: Relationship to diagnostic subtype and plasma cortisol levels. Pharmacol. Biochem. Behav. 71, 431–447. https://doi.org/10.1016/S0091-3057(01)00687-6.

Dum, R.P., Levinthal, D.J., Strick, P.L., 2016. Motor, cognitive, and affective areas of the cerebral cortex influence the adrenal medulla. Proc. Natl. Acad. Sci. U. S. A. 113, 9922–9927. https://doi.org/10.1073/pnas.1605044113.

Erickson, K., Drevets, W., Schulkin, J., 2003. Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. Neurosci. Biobehav. Rev. 27, 233–246. https://doi.org/10.1016/S0149-7634(03)00033-2.

Fink, G.R., Frackowiak, R.S.J., Pietrzyk, U., Passingham, R.E., 1997. Multiple Nonprimary Motor Areas in the Human Cortex. J. Neurophysiol. 77, 2164–2174. https://doi.org/10.1152/jn.1997.77.4.2164.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 2002. Structured clinical interview for DSM-IV-TR axis I disorders. New York Biometrics Res. New York State Psychiatr. Inst.

Ford, J.H., Morris, J.S., Kensinger, E.A., 2014. Effects of emotion and emotional valence on the neural correlates of episodic memory search and elaboration. J. Cogn. Neurosci. 26, 825–839. https://doi.org/10.1162/jocn.

Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J., 1997. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 6, 218–229. https://doi.org/10.1006/nimg.1997.0291.

Frost, C.P., Meyerand, M.E., Birn, R.M., Hoks, R.M., 2018. Childhood emotional abuse moderates associations among corticomotor white matter structure and stress neuromodulators in women with and without depression 12, 1–13. https://doi.org/10.3389/fnins.2018.00256.

Gaali, S., Kirschner, A., Cuboni, S., Hartmann, J., Kozany, C., Balsevich, G., Namendorf, C., Fernandez-Vizarra, P., Sippel, C., Zannas, A.S., Draenert, R., Binder, E.B., Almeida, O.F.X., Rühter, G., Uhr, M., Schmidt, M.V., Touma, C., Bracher, A., Hausch, F., 2015. Selective inhibitors of the FK506-binding protein 51 by induced fit. Nat. Chem. Biol. 11, 33–37. https://doi.org/10.1038/nchembio.1699.

Gaffey, A.E., Walsh, E.C., Ladd, C.O., Hoks, R.M., Abercrombie, H.C., 2019. Alterations in systemic and cognitive glucocorticoid sensitivity in depression. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 4, 310–320. https://doi.org/10.1016/j.bpsc.2018.11.007.

GBD, 2017. Disease and Injury Incidence and Prevalence Collaborators, 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 392, 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7.

Haber, S.N., 2016. Corticostriatal circuitry. Dialogues Clin. Neurosci. 18, 7–21. https://doi.org/10.1007/978-1-4614-6434-1_135-1.

Heller, A.S., Shi, T.C., Ezie, C.E.C., Reneau, T.R., Baez, L.M., Gibbons, C.J., Hartley, C.A., 2020. Association between real-world experiential diversity and positive affect relates to hippocampal–striatal functional connectivity. Nat. Neurosci. 23, 800–804. https://doi.org/10.1038/s41593-020-0636-4.

Hinkelmann, K., Moritz, S., Botzenhardt, J., Riedesel, K., Wiedemann, K., Kellner, M., Otte, C., 2009. Cognitive impairment in major depression: association with salivary cortisol. Biol. Psychiatry 66, 879–885. https://doi.org/10.1016/j.biopsych.2009.06.023.

Holsboer, F., 2001. Stress, hypercortisolism and corticosteroid receptors in depression: Implicatons for therapy. J. Affect. Disord. 62, 77–91. https://doi.org/10.1016/S0165-0327(00)00352-9.

Isoda, M., Hikosaka, O., 2007. Switching from automatic to controlled action by monkey medial frontal cortex. Nat. Neurosci. 10, 240–248. https://doi.org/10.1038/nn1830.

Jenkinson, M., Beckmann, C.F., Behrens, T.E.J., Woolrich, M.W., Smith, S.M., 2012. FSL. Neuroimage 62, 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015.

Klengel, T., Mehta, D., Anacker, C., Rex-haffner, M., Jens, C., Pariante, C.M., Pace, T.W. W., Mercer, K.B., Helen, S., Ressler, K.J., Rein, T., Binder, E.B., 2013. Gene-stress-epigenetic regulation of FKBP5: clinical and translational implications. Nat. Neurosci. 16, 33–41. https://doi.org/10.1038/nn.3275.Allele-specific.

Klok, M.D., Alt, S.R., Irurzun Lafitte, A.J.M., Turner, J.D., Lakke, E.A.J.F., Huitinga, I., Muller, C.P., Zitman, F.G., Ronald de Kloet, E., DeRijk, R.H., 2011. Decreased expression of mineralocorticoid receptor mRNA and its splice variants in postmortem brain regions of patients with major depressive disorder. J. Psychiatr. Res. 45, 871–878. https://doi.org/10.1016/j.jpsychires.2010.12.002.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2008. International affective picture system (IAPS): Affective ratings of pictures and instruction manual. University of Florida, Gainesville, FL. Technical Report A-8.

Lee, R.S., Tamashiro, K.L.K., Yang, X., Purcell, R.H., Huo, Y., Rongione, M., Potash, J.B., Wand, G.S., 2011. A measure of glucocorticoid load provided by DNA methylation of Fkbp5 in mice. Psychopharmacology (Berl) 218, 303–312. https://doi.org/10.1007/s00213-011-2307-3.

Lu, Y., Liang, H., Han, D., Mo, Y., Li, Z., Cheng, Y., Xu, X., Shen, Z., Tan, C., Zhao, W., Zhu, Y., Sun, X., 2016. The volumetric and shape changes of the putamen and thalamus in first episode, untreated major depressive disorder. NeuroImage Clin. 11, 658–666. https://doi.org/10.1016/j.nicl.2016.04.008.

Lyons, D.M., Yang, C., Sawyer-Glover, A.M., Moseley, M.E., Schatzberg, A.F., 2001. Early life stress and inherited variation in monkey hippocampal volumes. Arch. Gen. Psychiatry 58, 1145–1151. https://doi.org/10.1001/archpsyc.58.12.1145.

McEwen, B.S., 2002. Sex, stress and the hippocampus: Allostasis, allostatic load and the aging process. Neurobiol. Aging 23, 921–939. https://doi.org/10.1016/S0197-4580(02)00027-1.

Medina, A., Seasholts, A.F., Sharma, V., Burke, S., Bunney Jr,, W., Myers, R.M., Schatzberg, A., Akil, H., Watson, S.J., 2013. Glucocorticoid and mineralocorticoid receptor expression in the human hippocampus in major depressive disorder. J. Psychiatr. Res. 47, 307–314. https://doi.org/10.1038/jid.2014.371.

Menke, A., Arloth, J., Pütz, B., Weber, P., Klengel, T., Mehta, D., Gonik, M., Rex-Haffner, M., Rubel, J., Uhr, M., Lucae, S., Deussing, J.M., Müller-Myhsok, B., Holsboer, F., Binder, E.B., 2012. Dexamethasone stimulated gene expression in peripheral blood is a sensitive marker for glucocorticoid receptor resistance in depressed patients. Neuropsychopharmacology 37, 1455–1464. https://doi.org/10.1038/npp.2011.331.

Moriceau, S., Raineki, C., Holman, Jennifer, Holman, Jason, Sullivan, R., 2009. Enduring neurobehavioral effects of early life trauma mediated through learning and corticosterone suppression. Front. Behav. Neurosci.

Otte, C., Wingenfeld, K., Kuehl, L.K., Kaczmarczyk, M., Richter, S., Quante, A., Regen, F., Bajbouj, M., Zimmermann-Viehoff, F., Wiedemann, K., Hinkelmann, K., 2015. Mineralocorticoid receptor stimulation improves cognitive function and decreases cortisol secretion in depressed patients and healthy individuals. Neuropsychopharmacology 40, 386–393. https://doi.org/10.1038/npp.2014.181.

Pariante, C.M., 2018. Too Much Is Still Not Enough, When Talking About Cortisol. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3, 207–208. https://doi.org/10.1016/j.bpsc.2018.01.012.

Pariante, C.M., Alhaj, H.A., Arulnathan, V.E., Gallagher, P., Hanson, A., Massey, E., McAllister-Williams, R.H., 2012. Central glucocorticoid receptor-mediated effects of the antidepressant, citalopram, in humans: a study using EEG and cognitive testing. Psychoneuroendocrinology 37, 618–628. https://doi.org/10.1016/j.psyneuen.2011.08.011.

Pariante, C.M., Miller, A.H., 2001. Glucocorticoid receptors in major depression: Relevance to pathophysiology and treatment. Biol. Psychiatry 49, 391–404. https://doi.org/10.1016/S0006-3223(00)01088-X.

Patel, P.D., Lopez, J.F., Lyons, D.M., Burke, S., Wallace, M., Schatzberg, A.F., 2000. Glucocorticoid and mineralocorticoid receptor mRNA expression in squirrel monkey brain. J. Psychiatr. Res. 34, 383–392. https://doi.org/10.1016/S0022-3956(00)00035-2.

Pittenger, C., Duman, R.S., 2008. Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology 33, 88–109. https://doi.org/10.1038/sj.npp.1301574.

R Core Team, 2017. R: A language and environment for statistical computing [WWW Document]. URL https://www.r-project.org.

Raison, C.L., Miller, A.H., 2003. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. Am. J. Psychiatry 160, 1554–1565. https://doi.org/10.3109/10253890.2013.793303.

Reeder, S.B., Pineda, A.R., Wen, Z., Shimakawa, A., Yu, H., Brittain, J.H., Gold, G.E., Beaulieu, C.H., Pelc, N.J., 2005. Iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL): Application with fast spin-echo imaging. Magn. Reson. Med. 54, 636–644. https://doi.org/10.1002/mrm.20624.

Rohleder, N., Wolf, J.M., Wolf, O.T., 2010. Glucocorticoid sensitivity of cognitive and inflammatory processes in depression and posttraumatic stress disorder. Neurosci. Biobehav. Rev. 35, 104–114. https://doi.org/10.1016/j.neubiorev.2009.12.003.

Rushworth, M.F.S., Hadland, K.A., Paus, T., Sipila, P.K., 2002. Role of the human medial frontal cortex in task switching: a combined fMRI and TMS study. J. Neurophysiol. 87, 2577–2592. https://doi.org/10.1152/jn.2002.87.5.2577.

Sánchez, M.M., Young, L.J., Plotsky, P.M., Insel, T.R., 2000. Distribution of corticosteroid receptors in the rhesus brain: relative absence of glucocorticoid receptors in the hippocampal formation. J. Neurosci. 20, 4657–4668. https://doi.org/10.1523/jneurosci.20-12-04657.2000.

Sapolsy, R.M., Krey, L.C., McEwen, B.S., 1984. Stress down-regulates corticosterone receptors in a site-specific manner in the brain*. Endocrinology 114, 287–292. https://doi.org/10.1210/endo-114-1-287.

Scharf, S.H., Liebl, C., Binder, E.B., Schmidt, M.V., Müller, M.B., 2011. Expression and regulation of the Fkbp5 gene in the adult mouse brain. PLoS One 6, 1–10. https://doi.org/10.1371/journal.pone.0016883.

Schwabe, L., Wolf, O.T., 2013. Stress and multiple memory systems: From "thinking" to "doing. Trends Cogn. Sci. 17, 60. https://doi.org/10.1016/j.tics.2012.12.001.

Shackman, A.J., Salomons, T.V., Slagter, H.A., Fox, A.S., Winter, J.J., Davidson, R.J., 2011. The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat. Rev. Neurosci. 12, 154–167. https://doi.org/10.1038/nrn2994.

Smeets, T., van Ruitenbeek, P., Hartogsveld, B., Quaedflieg, C.W.E.M., 2019. Stress-induced reliance on habitual behavior is moderated by cortisol reactivity. Brain Cogn 133, 60–71. https://doi.org/10.1016/j.bandc.2018.05.005.

Talairach, J., 1988. Co-planar stereotaxic atlas of the human brain-3-dimensional proportional system. an approach to Cereb. Imaging.

Terfehr, K., Wolf, O.T., Schlosser, N., Fernando, S.C., Otte, C., Muhtz, C., Beblo, T., Driessen, M., Spitzer, C., Löwe, B., Wingenfeld, K., 2011a. Effects of acute hydrocortisone administration on declarative memory in patients with major depressive disorder: a placebo-controlled, double-blind crossover study. J. Clin. Psychiatry 72, 1644–1650. https://doi.org/10.4088/JCP.10m06240.

Terfehr, K., Wolf, O.T., Schlosser, N., Fernando, S.C., Otte, C., Muhtz, C., Beblo, T., Driessen, M., Spitzer, C., Löwe, B., Wingenfeld, K., 2011b. Hydrocortisone impairs working memory in healthy humans, but not in patients with major depressive disorder. Psychopharmacology (Berl) 215, 71–79. https://doi.org/10.1007/s00213-010-2117-z.

van Stegeren, A.H., Roozendaal, B., Kindt, M., Wolf, O.T., Joëls, M., 2010. Interacting noradrenergic and corticosteroid systems shift human brain activation patterns during encoding. Neurobiol. Learn. Mem. 93, 56–65. https://doi.org/10.1016/j.nlm.2009.08.004.

World Health Organization, 2017. Depression and Other Common Mental Health Disorders. Global Health Estimates, Geneva.

Zannas, A.S., Binder, E.B., 2014. Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism. Genes. Brain Behav. 13, 25–37. https://doi.org/10.1111/gbb.12104.

Zannas, A.S., Wiechmann, T., Gassen, N.C., Binder, E.B., 2016. Gene-stress-epigenetic regulation of FKBP5: clinical and translational implications. Neuropsychopharmacology 41, 261–274. https://doi.org/10.1038/npp.2015.235.

Zheng, H., Liu, Y., Li, W., Yang, B., Chen, D., Wang, X., Jiang, Z., Wang, H., Wang, Z., Cornelisson, G., Halberg, F., 2006. Beneficial effects of exercise and its molecular mechanisms on depression in rats. Behav. Brain Res. 168, 47–55. https://doi.org/10.1016/j.bbr.2005.10.007.