Journal of Affective Disorders 239 (2018) 180–191

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

A pilot investigation of differential neuroendocrine associations with fronto-limbic activation during semantically-cued list learning in mood disorders

A.T. Peters[a], R.A. Smith[a], M.T. Kassel[b], M. Hagan[c,d], P. Maki[a], A. Van Meter[e], E.M. Briceño[f], K.A. Ryan[f], A.L. Weldon[g], S.L. Weisenbach[h,i], M.N. Starkman[f], S.A. Langenecker[a,*]

[a] Department of Psychiatry, University of Illinois at Chicago, USA
[b] Department of Psychology, University of Wisconsin-Milwaukee, USA
[c] Department of Psychology, San Francisco State University, USA
[d] Department of Psychiatry, University of California, San Francisco, USA
[e] Department of Psychiatry Research, The Feinstein Institute for Medical Research, Zucker Hillside Hospital, USA
[f] Department of Psychiatry, University of Michigan Medical Center, USA
[g] Department of Psychology, University of Illinois Urbana-Champaign, USA
[h] Department of Psychiatry, University of Utah, USA
[i] VA Salt Lake City Healthcare System, USA

ARTICLE INFO

Keywords:
Mood disorders
Cortisol
Memory
Functional imaging

ABSTRACT

Background: : Decreased volume and disrupted function in neural structures essential for memory formation (e.g. medial temporal lobe and prefrontal cortex) are common among individuals with depression. Hypothalamic-pituitary-axis function, as reflected by measurement of cortisol levels, is linked to neural activity during memory encoding in healthy people. However, it is not as well understood whether cortisol is associated with alterations in fronto-temporal recruitment during memory encoding in depression.

Methods: : In this pilot study, we evaluated associations between cortisol and neural activation during memory encoding in 62 adults (18–65 years) with mood disorders (MD; n = 39, 66.7% female), including major depression (n = 28) and bipolar I disorder (n = 11), and healthy controls (HC; n = 23, 43.5% female). Participants provided salivary cortisol samples before and after completing a semantically-cued list-learning task during 3-Tesla fMRI. Links between pre-scan cortisol (and cortisol change) and activation during encoding were evaluated using block and event-related models.

Results: : Overall, pre-scan cortisol level was positively associated with greater engagement of fronto-limbic activation during the encoding block. However, in MD, pre-scan cortisol was associated with attenuated activation during encoding in medial frontal, superior and middle temporal gyri, insula, lingual gyrus, and claustrum relative to HCs. Cortisol-related attenuation of activation in MD was also observed during encoding of words subsequently recalled in the ventral anterior cingulate, hypothalamus, and middle temporal gyrus. By and large, cortisol change (pre/post scan) predicted the same pattern of findings in both block and event-related contrasts.

Limitations: : Although analyses accounted for variations in scanner time of day, circadian alterations in cortisol may have introduced variability into the results.

Conclusions: : Pre-scan cortisol may selectively interfere with recruitment of important fronto-temporal memory circuitry in mood disorders. The inverted associations between cortisol and neural function in MD relative to HC also elucidate potentially unique pathophysiological markers of mood disorders.

1. Introduction

Mood disorders (MD), such as major depressive disorder (MDD) and bipolar disorder (BD) are characterized by objective impairments in episodic memory of moderate effect sizes; these include tests of verbal list learning, recall, and working memory (Ahern and Semkovska, 2017; Langenecker et al., 2010). The neural basis for learning and memory decrements may relate to significant overlap between brain regions recruited for encoding and retrieval and the neural alterations characteristic of depression (Okon-Singer et al., 2015). Fundamentally,

* Corresponding author.
E-mail addresses: slangenecker@psych.uic.edu, slangen@uic.edu (S.A. Langenecker).

https://doi.org/10.1016/j.jad.2018.07.006
Received 13 March 2018; Received in revised form 18 June 2018; Accepted 1 July 2018
Available online 07 July 2018

encoding and recall are thought to rely upon the integrity of the Papez Circuit (Papez, 1937), including the hippocampus, fornix, parahippocampal gyrus, mammillary bodies, insula, and cingulate gyrus. Because successful encoding and retrieval additionally rely on intact attention, working memory, and executive functioning, memory processes are also understood to draw upon fronto-parietal networks (Kizilirmak et al., 2015; Luckmann et al., 2014). Indeed, hippocampal and frontal lobe volumes are inversely linked to memory performance in MDD (Ajilore et al., 2015; Cao et al., 2016; Engvig et al., 2014; Jayaweera et al., 2016; Marano et al., 2015; Turner et al., 2012). Increasingly, functional MRI (fMRI) has also revealed alterations in limbic, fronto-parietal, and fronto-subcortical circuitry during verbal memory tasks (Kassel et al., 2016; Kelley et al., 2013; Miskowiak et al., 2016; Oertel-Knochel et al., 2013; Rao et al., 2016; Weisenbach et al., 2014).

Hypothalamic-pituitary-adrenal (HPA)-axis function represents a possible pathway in the development of alterations in neural structures and circuitry supporting encoding and subsequent recall in mood disorders (Tsigos and Chrousos, 2002). The HPA-axis has a central role in regulating many homeostatic systems in the body, in large part through secretion of corticosteroid hormones from the adrenal glands (Bifulco et al., 2000; Lupien et al., 2009a). In humans, cortisol exerts its effects on cognitive, emotional, and metabolic processes by binding to glucocorticoid receptors (GR) diffusely located throughout cerebral structures (Parker et al., 2003) and mineralocorticoid (MR) receptors predominantly located in limbic structures (Funder, 2005). Cortisol has a preferential impact in the hippocampus, amygdala, and prefrontal cortex where GR and MR receptors are co-localized (Bao et al., 2008; Lupien et al., 2009b). Continuous hyper-activation of the HPA-axis has been associated with dendritic retraction, neuronal death, and suppressed neurogenesis in these areas, thereby increasing susceptibility to a variety of mental and physical health conditions (Magarinos et al., 1996; Sapolsky, 1994, 2000). Indeed, hyperactivity of the HPA-axis has been found in several case control studies of MDD and BD reflected by high basal cortisol levels, an altered diurnal rhythm, decreased escape from dexamethasone suppression, and exaggerated responses in the combined dexamethasone-CRH challenge test (Barden, 2004; Kamali et al., 2012; Stokes, 1995; Watson et al., 2006). However, there is a degree of variability in these findings, as low basal cortisol has also been associated with depression (Maripuu et al., 2014, 2017; Wardenaar et al., 2011).

There is also significant variability with respect to whether cortisol relates to improved versus impaired learning and recall (Shields et al., 2017) and increased or decreased activation of the Papez circuit during encoding and recall (van Stegeren, 2009). Variability in the effects of cortisol on memory encoding and consolidation, specifically, are especially pronounced in depression (de Quervain et al., 2009; Finsterwald and Alberini, 2014; Wolf, 2009), with both enhancing (Kukolja et al., 2008; Pruessner et al., 2007) and impairing (Elzinga et al., 2005; van Stegeren, 2009) effects reported. Moreover, emotional state at the time of glucocorticoid elevations also alters cortisol effects on neural function and subsequent recall (de Kloet et al., 1999; Joels and Krugers, 2007; Okuda et al., 2004; Roozendaal et al., 2006). Additionally, variability might relate to the methodological challenges of isolating memory functions from executive organizational strategies or the possible influence of immediate rehearsal, which facilitates memory consolidation (Schallmo et al., 2015a). Thus, the integration of fMRI with measurement of cortisol and encoding with limited reliance on executive function in mood disorders, may provide increased clarity regarding role of the HPA-axis in the integrity of encoding circuitry and pathophysiology of mood disorders (Peters et al., 2016b; Weldon et al., 2015a).

The aim of the present pilot study was to evaluate associations between blood-oxygen-level dependent (BOLD) activation during encoding and pre-scan cortisol among healthy individuals and those with active mood disorders. Critically, the present study extends previous work by measuring how levels of endogenous cortisol prior to fMRI might relate to functional activation patterns and memory task performance. Specifically, we use the Semantic Learning Task (Schallmo et al., 2015), which employs a Brown-Peterson paradigm to minimize rehearsal of recent words. This method diminishes the contributions of individual variability in working memory to overall memory recall, thereby isolating encoding processes. The task also includes semantic organizational cues (e.g. semantic clustering) for both encoding and recall to minimize the influence of executive functioning resources on performance. Finally, we compare patterns of activation between healthy individuals and those with a mood disorder to dissociate global and disease-specific associations between cortisol and memory circuitry. As endocrine alterations are associated with both unipolar depression and bipolar disorder (Barden, 2004; Kamali et al., 2012; Stokes, 1995; Watson et al., 2006), the inclusion of both diagnoses was intentional - leveraging individual differences to better understand how neuroendocrine function may contribute to cognitive sequalae across the full range of mood dysfunction. This approach is directly in line with the Research Domain Criteria (RDoC) initative to better delineate the shared and overlapping, rather than distinct, neurobiological features of psychiatric constructs.

Given the evidence for HPA hyperactivity in mood disorders, and the preferential impact of cortisol on brain regions dense in GR and MR receptors, we hypothesized that higher pre-scan cortisol levels would predict decreased activity in frontal and medial temporal regions that often characterizes encoding among MD individuals (Kassel et al., 2016; Weisenbach et al., 2014). We were specifically interested in the effects of pre-scan cortisol because fMRI scans have been shown to evoke an anticipatory stress response (that is present before but normalizes after the scan) in both depressed (Peters et al., 2011) and healthy (Weldon et al., 2015) individuals. In contrast, consistent with prior healthy control (HC) findings (van Stegeren, 2009), we expected that neural activation in HCs would remain robust to variations in pre-scan cortisol. Exploratory analyses evaluated whether these neural alterations were associated with change in cortisol before/after scanning and subsequent memory recall performance.

2. Methods and materials

2.1. Participants

Adults aged 18–65 (M = 38.84, SD = 16.21) years with a mood disorder (MD: MDD [n = 28] or BD I disorder [BD; n = 11]) and healthy comparisons without a mood disorder (HC; n = 23) were recruited for one of three studies; a study of emotion processing in HC (Langenecker et al., 2012), an investigation of emotion processing in MDD and HC (Briceno et al., 2013) and a study of emotion processing in BD I and HC (Ryan et al., 2015). At the time of enrollment and scanning, MD participants were in a depressed state or in partial-remission from a major depressive episode and currently reporting at least two residual depressive symptoms. All MD participants had a mimimum score of 10 on the Hamilton Depression Rating Scale [HDRS; (Hamilton, 1960a)] and partial remission was defined as an HDRS between 10–13. Based on these criteria, n = 15 of 39 MD participants were in partial remission. Suicidality was assessed via the HDRS and the Structured Clinical Interview for DSM-IV [SCID-I; (First, 1995)]; participants with passive suicidality were not excluded, but participants were excluded for acute plan with intent.

The research was conducted at the University of Michigan and participants were recruited de novo from the surrounding community, and consented in accordance with Institutional Review Board approval. Participants were excluded for any medical disorder (including hypertension or diabetes) or recent infection, medication use to treat physical conditions (including hormonal contraceptives or menopausal hormone therapy and antibiotics), use of tobacco products, current alcohol or substance use disorder, history of head injury or neurological

Table 1
Demographic and clinical characteristics of MD and HC participants.

Variable	MD (n = 39) *M (SD)*	HC (n = 23) *M (SD)*	*t or* X^2	p-value
Age	40.26 (15.57)	36.43 (17.33)	−0.89	.37
Female % (n)	66.7% (n = 26)	43.5% (n = 10)	3.20	.08
Education in years	15.89 (2.13)	15.65 (1.95)	−0.45	.65
Shipley Verbal IQ Estimate	111.29 (9.01)	112.80 (6.36)	.57	.56
Co-morbid Anxiety % (n)	28.2% (n = 11)	–	–	–
Age of MDE[a] Onset	21.28 (11.07)	–	–	–
AD[b] % (n)	11.8% (n = 4)	–	–	–
Current AD Plus[c] % (n)	38.2% (n = 13)	–	–	–
Anticonvulsant	23.1% (n = 9)	–	–	–
Antipsychotic	17.1% (n = 7)	–	–	–
Anxiolytic	20.5% (n = 8)	–	–	–
HDRS[d,*]	15.44 (5.75)	.65 (1.04)	−11.35	<0.001
HARS[e,*]	14.92 (7.03)	1.05 (1.88)	−8.64	<0.001
Recall Hits	68.59 (29.02)	76.17 (22.44)	1.08	.29
Recall False Positives	10.31 (13.07)	11.35 (14.50)	.29	.77
Recognition Hits	123.05 (34.18)	124.70 (23.79)	.20	.84
Pre-scan Cortisol (ug/dL)	.78 (0.41)	.64 (0.42)	−1.37	.17
Post-scan Cortisol (ug/dL)	.57 (0.26)	.54 (0.55)	−0.33	.74
Average Daily Cortisol[f]	.61 (0.26)	.58 (0.23)	−0.72	.48

[*] Group differences at $p < 0.05$.
[a] MDE = Major Depressive Episode.
[b] AD = Antidepressant; All participants taking an antidepressant were on a selective serotonin reuptake inhibitor.
[c] Refers to currently taking an antidepressant and additional psychiatric medications.
[d] Hamilton Depression Rating Scale.
[e] Hamilton Anxiety Rating Scale.
[f] Subsample of n = 14 MD and n = 11 HC participants provided to conceptually illustrate pre-scan cortisol elevations relative to diurnal basal cortisol.

disorder, or weight greater than 250 pounds (BMI > 35) for scanning purposes. All participants were also instructed not to deviate from their typical caffeine consumption in order to ensure they were alert during the scan. HC participants had no personal current or lifetime history of psychiatric diagnoses as assessed by the SCID-I, nor any first degree family history of a current or past psychiatric disorder based on participant report. Use of current psychiatric medications was permitted amongst MD participants (Table 1). To our knowledge, all participants were scanner novices, but this was not systematically queried or noted.

2.2. Procedure

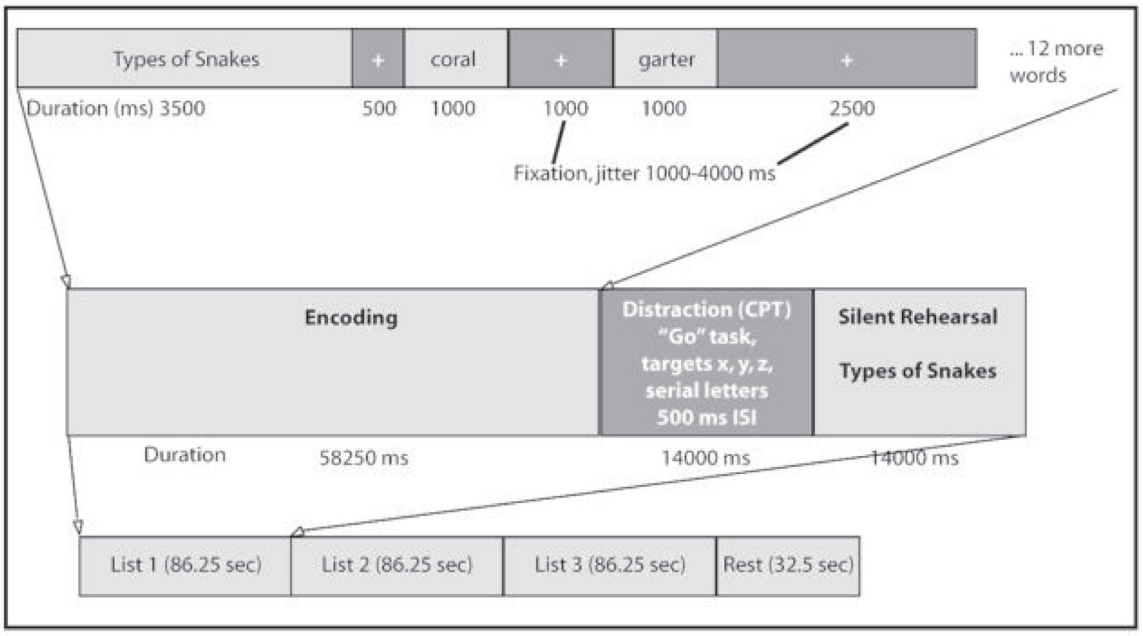
All participants underwent the same series of informed consent, screening, diagnostic, pre-scan salivary collection, and 3-Tesla neuroimaging procedures. The consent, screening, and diagnostic procedures were conducted in the first study visit. The diagnostic assessment included the SCID-I and current symptom ratings via the HDRS and Hamilton Anxiety (HARS) Rating Scales (Hamilton, 1960b; Shear et al., 2001), as well as a verbal IQ estimate via the Shipley-2 Vocabulary Scale (Shipley, 2009) administered by a psychologist or clinical psychology graduate student. fMRI data were collected during a separate visit following the initial clinical assessment. After arriving at the scan center, salivary samples were collected prior to and immediately following the fMRI. To limit learning or novelty bias, participants were provided a practice description of the study task, the Semantic List Learning Task [SLLT (Schallmo et al., 2015)], outside of the scanner. The SLLT was then administered in the scanner, in addition to an emotion-processing task (Peters et al., 2016a), for a total scan time of 70 minutes, including placement. Participants were compensated between $10 and $30 per hour for completion of diagnostic interviewing, fMRI, and cortisol collection.

2.3. Saliva sample collection and cortisol assay

Saliva samples for cortisol assay were collected using Salivettes (Sarstedt AG & Co.). For each participant, a single, pre-scan saliva sample was collected 15–30 minutes before MRI data acquisition and a second, post-scan saliva sample was collected immediately after the completion of the MRI scans. Saliva samples were stored at −80 °C until they were processed at the Clinical Ligand Assay Service Satellite Laboratory at the University of Michigan School of Public Health Department. The immunoassay was conducted using a Siemens Centaur automated analyzer via chemiluminescent technology. The assay range is 0.07–7.84 ug/dL; Inter-assay coefficient of variation (CV): 12.4% at 0.7 ug/dL, 5.2% at 5.2 ug/dL. Intra-assay CV: 3.6% at 0.7 ug/dL, 4.2% at 5.2 ug/dL (Kamali et al., 2012). Average pre-scan cortisol was 0.73 μg/dl ($SD = 0.42$). Average post-scan cortisol was 0.57 μg/dl ($SD = 0.39$). Cortisol values were highly right skewed and thus subjected to a natural log transformation prior to analyses. The log-transformed and raw cortisol values were highly correlated (pre-scan value: $r = 0.86$, $p < .01$; post-scan value: $r = 0.85$, $p < .01$) and achieved normal distribution after log transformation. fMRI scans were administered between the hours of 8:00 am and 4:00 pm, with the majority (n = 40, 65%) beginning and ending in the morning. Strategies were employed to reduce the impact of the cortisol awakening response on anticipatory cortisol levels (Peters et al., 2016a). First, all participants were awake for at least one hour before the saliva collection (typical arrival time is 45 min before the scan). Second, we ensured that there was minimal variation in the time between arrival at the scan center and time of salivary sampling across participants (five minutes or less due to variations in time in the restroom). Third, as scanner start time (transformed into continuous 24 h variable, i.e., military time) was significantly correlated with the pre-scan ($r = -0.39$, $p < .01$) and post-scan ($r = -0.43$, $p < .01$) cortisol measurements, the scanner start time was included in imaging regression analyses to statistically adjust for variations in circadian profile across the day. Last, we verified that the average scanner start time did not differ ($t = -0.19$, $p = .85$) between HC ($M = 1120.65$, $SD = 217.51$) and MD ($M = 1132.95$, $SD = 257.33$) groups.

2.4. Semantic list learning task (SLLT)

The SLLT is a word list learning and recall task, conducted during fMRI and designed for translation to clinical applications (Kassel et al., 2016; Schallmo et al., 2015; Weisenbach et al., 2014). It utilizes semantic cues in the encoding, rehearsal and recall of word lists to provide structure and reduce the confounding effects of individual variability in executive functioning (EF) skills on memory performance. The low dependence upon EF skills for variations in performance was confirmed in this sample – there were non-significant correlations between SLLT performance and other study tasks measuring EF. The SLLT consists of three blocks: Encoding, Distraction, and Silent Rehearsal (Fig. 1). The task consists of 15 lists of 14 semantically related words presented in five runs, for a total of 210 words. During the encoding block, a semantic category cue is presented visually for 3.5 seconds at the start of each list, followed by a 500 ms fixation cross. Subsequently, subjects are instructed to attend to 14 words shown on the screen, one at a time, for an average display time of 1 s. The inter-stimulus interval is a 1- to 4-second jittered range, where a fixation cross is displayed. The total time for one Encoding block is approximately 58.25 seconds, depending upon jitter variation. Following an Encoding block, a Distraction task requires attending to letters on the screen and making a button press response each time an “x”, “y”, or “z” is presented (Langenecker et al., 2007). Each Distraction block is 14 seconds in length. Last, the Silent Rehearsal block instructs participants to remember the list of words associated with the semantic cue for 14 seconds, with a category cue prompt appearing on the screen instructing the participant to silently rehearse the words from the word list. The



Participants are presented with 15 lists of 14 semantically related words (210 words total). Each list is preceded by its semantic category cue. A period of instructed silent rehearsal follows a distractor task after each list in the fMRI scanner, whereas free recall is conduced upon completion of the scanning session, outside of the scanner.

Fig. 1. Task diagram of semantic list learning test.

SLLT repeats this series of Encoding, Distractor, and Silent Rehearsal blocks for a new semantic cue and list of words. There are three lists presented in each of the five runs, and each run ends with a rest condition, during which participants are instructed to focus on a fixation cross. Lists are randomized within runs, and words are randomized within lists to avoid any order by position by frequency confounds (Schallmo et al., 2015). The SLLT includes a post-scan written cued recall task with semantic category cues provided for each of the 15 lists, where participants are asked to write down as many words as they recall from each category. After completing the recall task, participants undergo a recognition trial, where they are asked to circle words they recognize from any of the lists, amidst distractor words. Both recall and recognition tasks are completed after exiting the scanner, typically a 45-min delay after encoding.

2.5. fMRI acquisition and processing

Whole-brain imaging was conducted on a GE Signa 3-Tesla scanner. fMRI series consisted of 30 contiguous oblique-axial sections and were acquired using a forward-reverse spiral sequence. The image matrix was 64 × 64 over a 24-cm field of view (FOV) for 3.75 × 3.75 × 4 mm voxels. The 36-slice volume was acquired serially at 1,750 ms temporal resolution for a total of 770 time points for the SLLT [TE 30 ms, 90° flip angle]. One-hundred-six to 124 high-resolution Fast SPGR IR axial anatomic images [TE = 3.4 ms, TR = 10.5 ms, 27° flip angle, number of excitations = 1, slice thickness = 1–1.2 mm, FOV = 24 cm, matrix size = 256 × 256] were obtained for each participant for co-registration and normalization purposes.

Processing of images was conducted using SPM8, including despiking, slice timing, realignment, motion correction, co-registration, DARTEL warping (using VBM8 toolbox), normalization to the MNI space, and smoothing with a 5 mm FWHM filter.

2.6. Data analytic approach

Clinical, demographic, neuroendocrine, and behavioral measures were inspected for normal distribution and were compared between HC and MD groups using independent samples t tests and chi-square tests. Associations between log-transformed cortisol measurements and demographic, clinical, behavioral, and fMRI data were analyzed using Pearson's bivariate correlations and t tests, as appropriate. A repeated measures ANOVA was used to assess change in cortisol from pre- to post-scan; residual change scores were calculated using linear regression. These a-priori comparisons were evaluated using a false-discovery rate adjusted alpha threshold of $p < .007$ (Benjamini and Hochberg, 1995).

BOLD response was modeled using the SPM8 hemodynamic response function model. Both block and event-related analyses were completed. The Encoding, Silent Rehearsal, Distraction, and Rest blocks were initially entered into first level models. Subsequently, contrast images were derived by subtracting the BOLD signal during the Silent Rehearsal blocks from the BOLD signal during Encoding blocks (Encoding minus Silent Rehearsal). This contrast was chosen because both encoding and silent rehearsal include a semantic cue and consolidation of information via rehearsal. The primary way in which the two conditions differ is that words are visually presented in the Encoding block, but not during Silent Rehearsal. Images from the event-related models were derived using behavioral data for recall hits (words correctly recalled) to estimate the hemodynamic response for encoding of words subsequently recalled (Words Recalled minus Words Not

Recalled).

Whole-brain, multivariate linear regression analyses were conducted from the individual group contrasts in SPM8. All coordinates for activation are reported in MNI space. Statistical significance for second-level regression contrasts in SPM8 were set at $p < .005$, with a minimum cluster size of 57 2 mm cubic voxels. This whole-brain corrected alpha of 0.01 is achieved with this combined height by extent threshold strategy based upon 10,000 Monte Carlo simulations with the modified 3dClustSim inside the whole-brain search region [updated and 'bug-free' as of December 2015; https://afni-nimh-nih-gov.proxy.cc.uic.edu/pub/dist/doc/program_help/3dClustSim.html (Ward, 2000)].

All SPM8 regression models included a main effect of pre-scan cortisol and an interaction term (pre-scan cortisol x group [MD vs. HC]) to assess if pre-scan cortisol was differentially related to activation in MD versus HC. Covariates of no interest included sex, age, recall false positives, and time of scan (transformed to a 24-hour time variable). The dependent variables of interest were brain activation for Encoding minus Silent Rehearsal (block model) and Words Recalled minus Words Not Recalled (event-related model). The MarsBaR toolbox was used to extract spatially averaged data for each contrast and for each participant and merged into SPSS. Subsequently, for each contrast, we conducted secondary posthoc analyses to evaluate whether cortisol change between the pre-scan and post-scan measurement was correlated with the same brain regions. Cortisol change was computed by taking the residual value from regressing the pre-scan measurement onto the post-scan measurement. Last, we conducted post hoc exploratory analyses for behavioral performance associations, clinical (MDD vs. BD, medication), and sex effects on cortisol-related BOLD activation.

3. Results

3.1. Participants

Demographic and clinical characteristics of the sample are reported in Table 1. MD and HC participants were not significantly different on demographic variables. MD participants reported higher scores on measures of depression and anxiety. Mean scores on the HDRS and HARS in MD participants were consistent with mild depression and anxiety. MD and HC participants did not differ in terms of behavioral performance on recall hits, recall false positives, or recognition hits.

MDD and BD were clinically and demographically similar, but differed in medication status; 90.0% of BD participants were on psychiatric medications versus 33.3% of MDD participants ($X^2 = 9.07$, $p = .003$). Eighty percent of BD participants were treated with a combination of psychiatric medications (80.0%) as compared to 20.8% of MDD participants ($X^2 = 11.15$, $p = .01$).

3.2. Demographic, clinical, and behavioral performance correlates of pre-scan cortisol (Log-transformed values)

There was no association between pre-scan cortisol and age ($r = -0.16$, $p = .23$). Pre-scan cortisol did not differ ($t = 0.74$ $p = .46$) between male ($M = -0.39$, $SD = 0.47$) and female ($M = -0.51$, $SD = 0.70$) participants. Pre-scan cortisol levels were not statistically different ($t = -1.37$, $p = .17$) between HC ($M = -0.59$, $SD = 0.77$) and MD ($M = -0.37$, $SD = 0.49$) participants. Additionally, pre-scan cortisol levels did not differ ($t = 0.59$, $p = .55$) between medicated ($M = -0.36$, $SD = 0.60$) and unmedicated (M = −0.46, $SD = 0.58$) participants. Pre-scan cortisol values were not correlated with the HDRS ($r = 0.05$, $p = .70$) or HARS ($r = 0.03$, $p = .81$). Pre-scan cortisol was not related to semantically-cued recall hits among HC, ($r = -0.18$, $p = .42$), or among MD participants ($r = -0.19$, $p = .25$) for the fMRI paradigm. Pre-scan cortisol was not related to recall false positives among HC ($r = 0.17$, $p = .44$) or among MD participants ($r = 0.01$, $p = .95$). These correlations and comparisons remained unchanged after adjusting for scan start time (time of day).

3.3. Pre/Post-Scan change in cortisol

There was a significant overall decrease in cortisol between the pre-scan and post-scan measurement (Fig. 2) across all participants (main effect; [$F(1,60) = 7.57$, $p < .01$]). The rate of decrease between the pre-scan and post-scan measurement did not differ between HC and MD (interaction; [$F(1,60) = 2.53$, $p = .12$]). Pre-scan cortisol levels were modestly correlated with the pre/post-scan residual change score ($r = 0.26$, $p = .04$).

3.4. Cortisol and BOLD activation to semantic list learning

Results for pre-scan cortisol levels regressed onto activation for the Encoding minus Silent Rehearsal contrast (block model) and Words Recalled minus Words Not Recalled contrast (event-related model) are reported in Table 2.

3.4.1. Encoding-silent rehearsal

For the encoding minus silent rehearsal contrast, cortisol was positively associated, across all participants (main effect) with activation of a broad fronto-temporal network. Specifically, pre-scan cortisol was positively associated with increased activation in the left superior temporal, bilateral middle temporal, and right inferior temporal gyri, right insula, right middle and medial frontal gyri, right posterior cingulate, left lingual gyrus, left claustrum, and various right cerebellar regions (Fig. 3a). Secondary post hoc analyses indicated that of these regions, pre/post cortisol change were also significantly correlated with activation in the right posterior cingulate, right insula, right inferior temporal gyrus, right middle temporal gyrus, right anterior cerebellum, left lingual gyrus, left claustrum, and left middle temporal gyrus (all $ps < 0.03$).

3.4.2. Encoding of words recalled-not recalled words

For the event-related analysis of Words Recalled minus Not Recalled Words, a main effect of cortisol was related to activation in fronto-parietal executive regions and limbic memory areas. Specifically, pre-scan cortisol was related to convergence in activation (smaller difference between words recalled and not recalled) of the right dorsal anterior cingulate, left ventral anterior cingulate, left inferior frontal gyrus, right inferior parietal lobule, left middle and inferior temporal gyri, right insula, left hypothalamus, and various cerebellar regions (Fig. 3b). Secondary posthoc analyses indicated that pre/post cortisol change was also significantly correlated with activation in all of these same regions (all $ps < 0.02$), except for the left middle temporal gyrus, which was not significant ($r = -0.25$, $p = .060$).

3.5. Cortisol and BOLD activation to semantic list learning in MD versus HC

Results for the pre-scan cortisol x group interaction term, regressed onto activation for the Encoding-Silent Rehearsal contrast (block model) and Words Recalled-Not Recalled Words contrast (event-related model) are reported in Table 3.

3.5.1. Encoding-silent rehearsal

For the Encoding-Silent Rehearsal contrast, the interaction term indicated that pre-scan cortisol was positively associated with activation in fronto-temporal regions among HCs but inversely associated with activation among MD participants. Specifically, within the MD

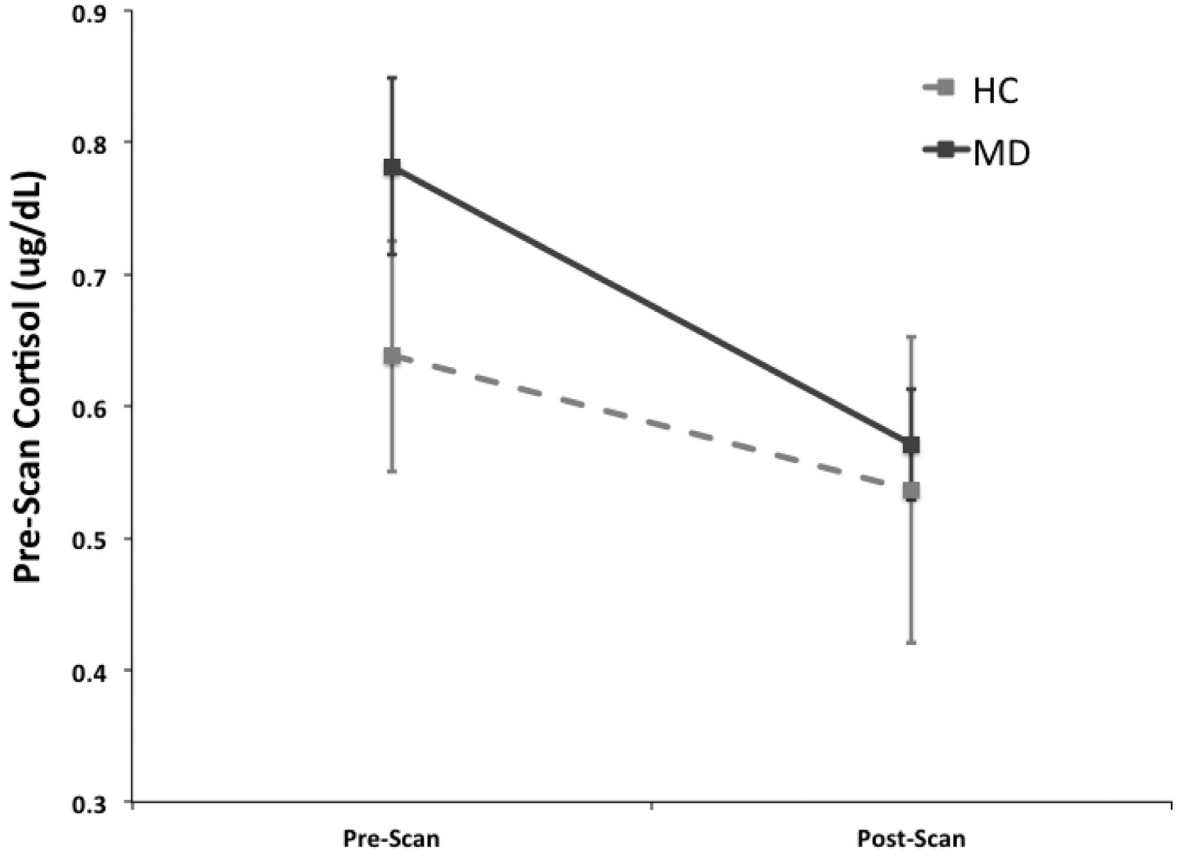


Fig. 2. Change in cortisol between pre-scan and post-scan measurement in HC and MD.

group, increases in pre-scan cortisol were associated with hypo-activation (extracted beta weights below zero) of the right medial frontal, bilateral superior and right middle temporal gyri, right insula, left lingual gyrus, left claustrum, and various cerebellar regions (Fig. 3a). Illustratively, a scatterplot of this cortisol x group interaction of activation are provided for the right medial frontal and middle temporal gyrus (Fig. 4a). Secondary post hoc analyses indicated that of these regions, the same diagnostic group interaction effect was observed for pre/post cortisol change in the right insula, right middle temporal gyrus, right anterior cerebellum, left lingual gyrus, left claustrum, and left superior temporal gyrus (all *ps* < 0.03). The left insula (r = 0.25, p = .06) and right medial frontal gyrus (r = 0.24, p = .06) were not significant.

3.5.2. Encoding of words recalled minus words not recalled

For the event-related analysis of Words Recalled minus Words Not Recalled, the interaction term indicated that pre-scan cortisol was associated with *relative hypoactivation* in several fronto-temporal regions among MD participants; that is, extracted beta values in the MD group for the BOLD response were smaller for encoding of words recalled compared to words not recalled (Fig. 3b). Specifically, within the MD group, increases in pre-scan cortisol were associated with relative hypoactivation of the left ventral anterior cingulate, left hypothalamus, and left middle temporal gyrus. In contrast, HCs demonstrated greater or comparable activation for encoding of words recalled compared to words not recalled in these regions. Illustratively, the beta weights are plotted for the right anterior cingulate cluster of each event (Words Recalled, Words Not Recalled) by diagnostic group in Fig. 4b (and in relation to cortisol in Supplemental Figure 1). Secondary post hoc analyses indicated that the same diagnostic group interaction effect was observed for pre/post cortisol change for all regions (all *ps* < 0.02).

3.6. BOLD activation patterns and subsequent recall

An exploratory post hoc analysis tested whether extracted clusters of significant activation in the block model were associated with subsequent recall. Increasing activity in the right middle frontal gyrus during encoding (as a function of cortisol) was predictive of greater recall (r = 0.38, p = .02) in MD participants, but not HC participants, (r = 0.04, p = .86).

3.7. Effects of diagnosis, medication, and sex on BOLD activation during encoding and SLLT performance

Overall group differences in task activation between MD and HC participants (independent from the effects of cortisol) are displayed in Fig. 5. Within the MD group, MDD and BD participants demonstrated largely similar patterns of activation as a function of cortisol; however, for Encoding minus Silent Rehearsal, BD participants demonstrated greater activation in the posterior cerebellum than MDD (p = .03). For Words Recalled minus Words Not Recalled, BD participants demonstrated less activation in the left inferior temporal gyrus (p = .04) and more activation in the right inferior parietal lobule (p = .02) compared to MDD. Co-varying for MDD/BD diagnosis, there were no effects of

Table 2
Whole-brain corrected ($p < 0.01$) foci of activation for pre-scan cortisol regression (MD and HC).

Contrast/lobe	BA	MNI coordinates				
		x	y	z	Z	k
Encoding minus silent rehearsal						
Positive Regressor						
Frontal						
Middle Frontal[a]	9	32	24	28	3.7	69
Medial Frontal[a]	6	8	−2	70	3.31	64
Parietal						
Cingulate[a]	23	12	−22	−30	4.31	81
Posterior Cingulate	23	2	−56	28	3.21	59
Dorsal Posterior Cingulate	31	2	−20	40	3.03	57
Temporal						
Superior Temporal[a]	41	−44	−28	4	3.29	146
Middle Temporal[a]	22	−58	−34	12	3.28	109
	39	48	−72	20	3.36	59
Inferior Temporal[a]	20	46	−10	−20	4.17	114
Insula[a]	13	44	−20	12	3.46	98
Occipital						
Lingual Gyrus[a]	17	−10	−88	10	3.81	304
Subcortical						
Claustrum[a]		−26	30	12	4.03	227
Cerebellum, Culmen		10	−48	−12	3.71	79
Cerebellum, Anterior Cerebellar[a]		36	−44	−28	4.17	257
Cerebellum, Posterior Declive[a]		28	−72	−14	3.44	151
Recalled versus Not Recalled Words						
Negative Regressor						
Frontal						
Ventral Anterior Cingulate[a]	24	−8	−2	38	4.18	357
Dorsal Anterior Cingulate	32	8	26	40	2.97	59
Inferior Frontal[a]	47	−26	16	−12	3.43	60
Parietal						
Inferior Parietal[a]	40	54	−34	48	3.15	70
Temporal						
Middle Temporal[a]	21	−68	−28	−8	4.20	125
Inferior Temporal[a]	20	−60	−12	−30	3.96	69
Insula[a]	13	48	−16	22	3.78	136
Subcortical						
Hypothalamus[a]		0	−2	−6	3.88	174
Cerebellum, Tuber[a]		46	−66	−30	3.97	89
Cerebellum, Culmen[a]		−40	−40	−20	4.07	233
Cerebellum, Anterior Cerebellar[a]		32	−36	−22	3.57	76
Cerebellum, Inferior Semi Lunar[a]		−32	−62	−36	3.39	74

[a] Denotes clusters that remain significant when excluding bipolar I disorder participants from the analysis. Mm^3 is computed by multiple 8 x k.

psychiatric medication status on any foci of BOLD activation (MD with meds [n = 17)] vs. MD without meds [n = 22], all *ps* > 0.12). Within the MD group, females had greater activation during encoding than males in the right posterior cingulate ($p = .01$) and left claustrum ($p = .03$). For Words Recalled minus Words Not Recalled, females also showed greater activation in the left ventral anterior cingulate ($p = .01$), but less activation in the inferior semi lunar lobule ($p = .01$). No other sex differences were significant (all *ps* > 0.18). Last, within the MD group, MDD and BD participants did not differ in behavioral performance on the SLLT, as measured by recall hits ($p = .25$) or recognition hits ($p = .81$).

4. Discussion

This pilot study examined whether salivary cortisol level, prior to and change after an fMRI scan, was associated with differentially distributed brain activation during a semantically-cued list learning task in participants with mood disorders compared to HCs. Pre-scan cortisol was broadly associated with increased activation in fronto-parietal regions involved in attention, conflict monitoring, and cognitive control, as well as in temporo-limbic associative memory regions. Importantly, these effects were characterized by a diagnostic specific dissociation such that cortisol in MD participants related to attenuated activation in medial frontal and temporal areas supporting encoding, whereas this association was inverted in HC. This suggests that HPA-axis function may interfere with recruitment of neural systems subserving encoding and retrieval of new information in participants with MD who are depressed.

Consistent with our hypothesis, pre-scan cortisol was positively associated with activation in fronto-temporal regions, and subcortical and occipital regions, across all participants. Intriguingly, current endogenous cortisol may contribute to the integrity and efficiency of neural circuitry underlying encoding. For convergence, the majority of the effects were retained when using pre/post scan change in cortisol as the predictor. Coupled with other studies that indicate that an enhanced acute cortisol response is broadly related to engagement of a system for complex attentional control (Chica et al., 2013; Shomstein, 2012) and verbal learning (Kassel et al., 2016; Rao et al., 2016), this finding raises the possibility that cortisol levels prior to fMRI have a strong association with subsequent fronto-temporal engagement during encoding. In MD participants the right middle frontal gyrus, proposed to be a site of convergence and reorientation between dorsal and ventral attention networks (Japee et al., 2015), emerged as one particularly important node of this circuitry; activation was positively correlated with later recall of words in MD participants.

Although the beneficial effects of cortisol on encoding have obvious adaptive and evolutionary value for remembering both dangerous and favorable situations, in some circumstances these influences might underlie memory distortions in psychological disorders (Kukolja et al., 2008). Indeed, among MD participants, pre-scan cortisol was associated with hypo-activation in medial frontal and lateral temporal regions, as well as the bilateral anterior insula during encoding. These are regions with projections to the Papez Circuit that work to relay information involved in regulation, decision-making, and attention (Cauda et al., 2011; Suzuki, 2012). Thus, cortisol might serve to suppress activation of regions that traditionally down-regulate the Papez Circuit through MR and GR receptor function. Alternatively, the way in which cortisol serves as an affective tag for enhancement of memory may be altered in mood disorders (Abercrombie et al., 2011; Brown et al., 2004; Brown et al., 2007; Starkman et al., 1999; Starkman et al., 2003). It is also possible that there is a curvilinear relationship between anticipatory cortisol and the neural circuitry involved in recall facilitation, and that the optimal boost in cortisol which may aid in HC, overshoots in MD.

For encoding of words recalled, we also observed relative hypoactivation of the anterior cingulate, middle temporal gyrus, and hypothalamus in MD participants; that is, these units of the Papez Circuit were *less* active for encoding of words recalled than words not recalled among those with MD. Importantly, MD and HC participants did not differ in the number of words recalled after the delay. Therefore, group differences in functional brain recruitment might serve a compensatory or adaptive purpose. For instance, the anterior cingulate cortex has been implicated in error detection and conflict monitoring in mood disorders, generally showing increased activity after making impulsive errors (Pizzagalli, 2011). Through this lens, cortisol may promote successful encoding among those with MD through disengagement of regions vulnerable to emotional interference. However, in light of the comparably smaller portion of BD participants in the MD group and findings showing convergent degrees of impairment in BD and schizophrenia (Kuswanto et al., 2016), it will be important to replicate these findings in larger samples powered to draw between diagnostic

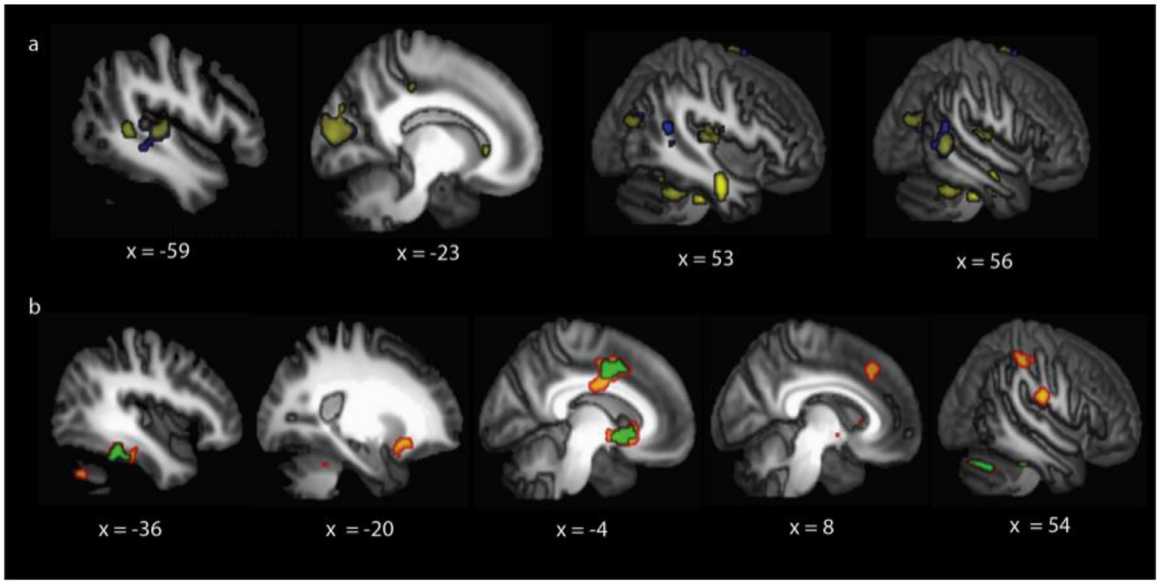


Fig. 3. Differential and overlapping patterns of activation related to cortisol in MD versus HC participants.
*Panel A, Block Enc minus SR Contrast: Yellow = Areas of significant activation positively related to pre-scan cortisol (main effect of cortisol only); Blue = Areas of significant activation as a function of the interaction between cortisol and group (MD decreasing vs. HC increasing).
*Panel B, Event Related Rcl minus NRcl Contrast: Orange = Areas of significant activation positively related to pre-scan cortisol; Green = Areas of significant activation as a function of the interaction between cortisol and group (MD increasing vs. HC decreasing).

Table 3
Whole brain corrected ($p < 0.01$) *foci* of activation for cortisol x group (MD vs. HC) interaction.

Contrast/lobe	BA	MNI coordinates				
		x	y	z	Z	k
Encoding minus Rehearsal						
Cortisol x Group Interaction						
Frontal						
Medial Frontal[a]	6	10	−2	70	3.37	82
Temporal						
Superior Temporal[a]	41	−44	−28	4	3.27	96
	39	46	−48	16	3.81	227
	22	−54	−34	10	3.33	115
Middle Temporal	21	50	−70	20	3.44	60
Insula[a]	13	−62	−34	24	3.52	72
	13	44	−20	12	3.38	68
Occipital						
Lingual Gyrus[a]	18	−10	−88	10	3.47	224
Subcortical						
Claustrum[a]		−28	30	14	3.54	72
Cerebellum, Culmen		10	−48	−12	3.44	99
Cerebellum, Anterior Cerebellar[a]		36	−44	−28	3.71	124
Cerebellum, Posterior Declive[a]		30	−74	−14	3.06	78
Recalled versus Not Recalled Words						
Cortisol x Group Interaction						
Frontal						
Ventral Anterior Cingulate[a]	24	−10	−2	40	3.38	115
Temporal						
Middle Temporal[a]	21	−68	−28	−8	3.64	67
Subcortical						
Hypothalamus[a]		0	−2	−6	3.59	69
Cerebellum, Tuber[a]		46	−66	−30	3.97	83
Cerebellum, Culmen[a]		−38	−40	−22	3.76	123
		36	−32	−26	3.49	66

[a] Denotes clusters that remain significant when excluding bipolar I disorder participants from the analysis.Mm^3 is computed by multiple 8 x k.

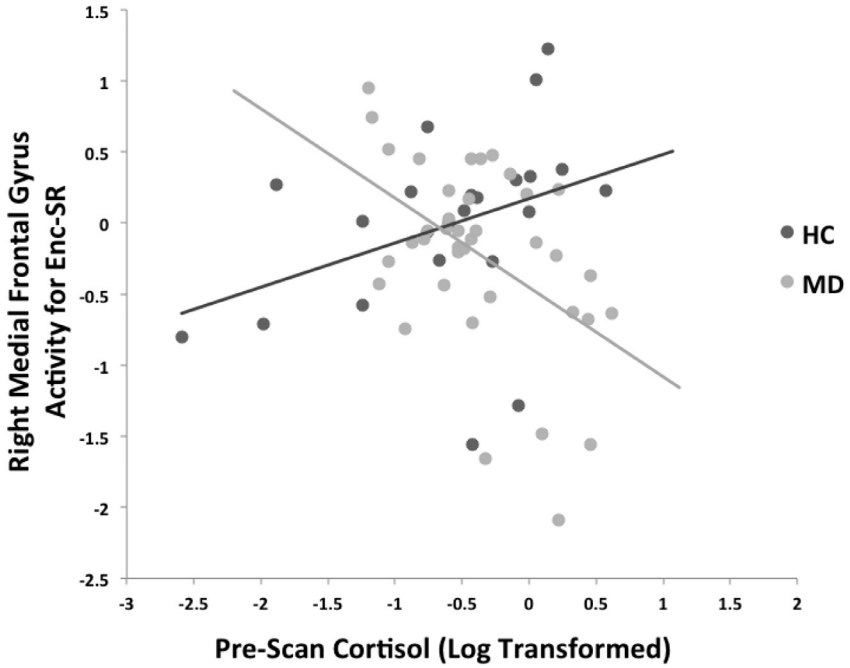
comparisons; it may be the case that behavioral differences would be more pronounced in a larger sample of BD participants with greater overall illness severity. Such a design could further attest to whether underlying neural recruitment serves an adaptive or maladaptive role. Further, while there is some indication that MD and BD may also differ in cortisol patterns (Becking et al., 2015), many existing studies fail to evaluate the potential confound of symptom severity between groups. The present sample was characterized by overall mild levels of depression and anxiety; hence, replication of these findings in more severe affective disturbance is warranted.

Regardless, there is nevertheless indication in the current sample that there is a divergent relationship between endocrine and brain function associated with disease. We can only speculate as to the molecular and genetic processes underlying this dissociation, but one compelling hypothesis relates to allostatic overload of the HPA-axis in depression. The terms allostatic load and overload were introduced to describe how chronic over or under activity of mediators whose effects are designed to retain physiological fitness, may lead to wear and tear within metabolic systems and eventually to impaired functioning (Beauchaine et al., 2011). That is, maintaining physiological stability by changing parameters of the internal milieu by matching them appropriately to environmental demands is not always functionally successful. In the context of depression and HPA-axis function, short-term activation may be acutely adaptive, but continued exposure to disease and stress, which is reported disproportionately in depression (Liu and Alloy, 2010), could contribute to long-term dysregulation and dysfunction of the HPA-axis. In fact, there is indication that this may occur due to permanent epigenetic modification of the glucocorticoid receptor and related sensitivity parameters (Pariante, 2017). Corticoid-mediated abnormalities may affect neurogenesis in the early course of depression, which tend to coalesce during critical periods of brain development such as late adolescence and early adulthood (Hagan et al.,

2015), and may further contribute to neurotoxicity on systems that subserve cognition (and emotion) over time (Wilkinson and Goodyer, 2011). As the initiation of allostatic programming and coordination depends on the brain's evaluation of bottom-up physiological signals and top down execution of behavioral and physiological regulatory response, modification of HPA systems may cause neurotoxicity and disrupted function of limbic-fronto-subcortical circuits, preferentially in depression.

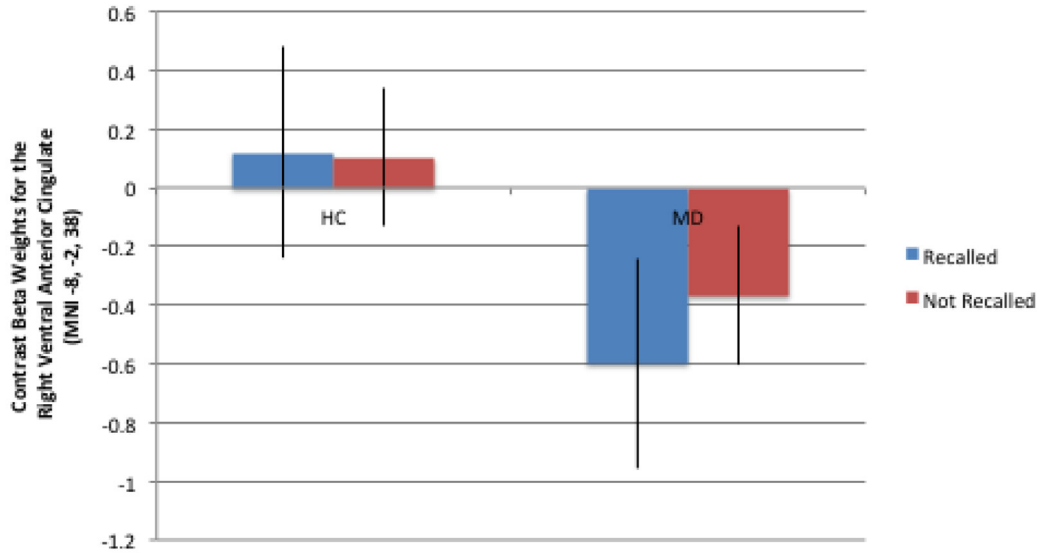
There are several limitations to acknowledge of this pilot study. First, although we undertook a series of post hoc analyses in effort to isolate the effects of a sample heterogeneous in terms of sex, diagnosis, and partial-remission status, future studies would profit from stratifying the sample according to these factors *a priori*. Second, the cortisol awakening response and circadian rhythm represents an intrinsic confound in neuroendocrine assessment (Stalder et al., 2016). In the future, scanning all participants in the afternoon, a period when circulating cortisol levels are typically much lower, could offer better control over variability that may have been introduced from cortisol elevations related to the awakening response. Nevertheless, it is worth noting that circadian alterations in cortisol in mood disorders may be most pronounced in the evening (Keller et al., 2006). A third limitation is that we did not include a subjective measurement of stress prior to fMRI, which could help elucidate the extent to which the observed cortisol-BOLD correlations may or may not be involved in stress regulation. Fourth, we did not exclude individuals taking psychiatric medication, which may confound observed group differences, as psychiatric medication use was disproportionately present in bipolar subjects. Moreover, as we did not randomly assign participants based upon medication status, any medication comparisons could be related to several clinical and SES variables. By contrast, we did exclude participants taking hormonal contraceptives due to their possible impact on cortisol (Gaffey et al., 2014; Roche et al., 2013) and memory (Nielsen et al., 2014); this criterion may reduce the generalizability of the sample as hormonal contraceptives are common adjuvant treatments in females. The sample size is not large enough to specifically investigate the contribution of medications on results. Finally, endogenous cortisol levels are subject to multiple influences, including stress, physical activity, common viruses, caffeine ingestion, sleep and circadian rhythm. As it is challenging in a sample of any size to adequately adjust for these factors, subsequent studies manipulating endogenous cortisol via acute stress paradigms or using glucocorticoid administration would offer a tightly controlled methodology to correct for these potential confounds. Additionally, future studies would benefit from this integration of distinct but convergent stress response systems (cortisol and salivary alpha amylase) as the ratio of HPA activity and sympathetic nervous system response has shown particular sensitivity to depression and stress in comparison to either salivary biomarker alone (Ali and Pruessner, 2012).

In summary, the present pilot study revealed disease-specific links between cortisol and brain activity involved in verbal memory encoding. These novel findings are some of the first to highlight that neuroendocrine response in MD is related to a reduced functional integrity of distributed fronto-temporal regions during encoding. The dissociation between healthy and depressed individuals elucidates potentially unique pathophysiological markers of MD. These findings hold potential clinical utility, as salivary cortisol is a non-invasively attained biomarker that could help us better delineate clinical subtypes or help clinician's provide personalized treatment for depressed patient's with mood disorder. For instance, a clinical phenotype of depression with cortico-mediated frontal-limbic dysregulation may warrant different treatment than another patient of the same phenotype sub-served by different neurobiological substrates. Therefore, whether coregulation of endocrine and neural function portend differential response to existing treatment options for depression represents a critical subsequent line of



**Correlation in MD participants: r = -.48, medium-large effect; Correlation in HC participants: .37, medium effect; Fischer's exact test indicates significant difference between correlations (z = -3.22, p <.01).*

Fig. 4. a Association between cortisol and medial frontal gyrus activity during memory encoding in MD versus HC participants. b Fig. 5. Foci of activation predicted by pre-scan cortisol is marked by attenuated signal for encoding of words recalled versus words not recalled in mood disorder subjects but not healthy controls.



HC and MD subject's beta-weights for words recalled events differ significantly (t = 2.37, p = .02).

Fig. 4. (*continued*)

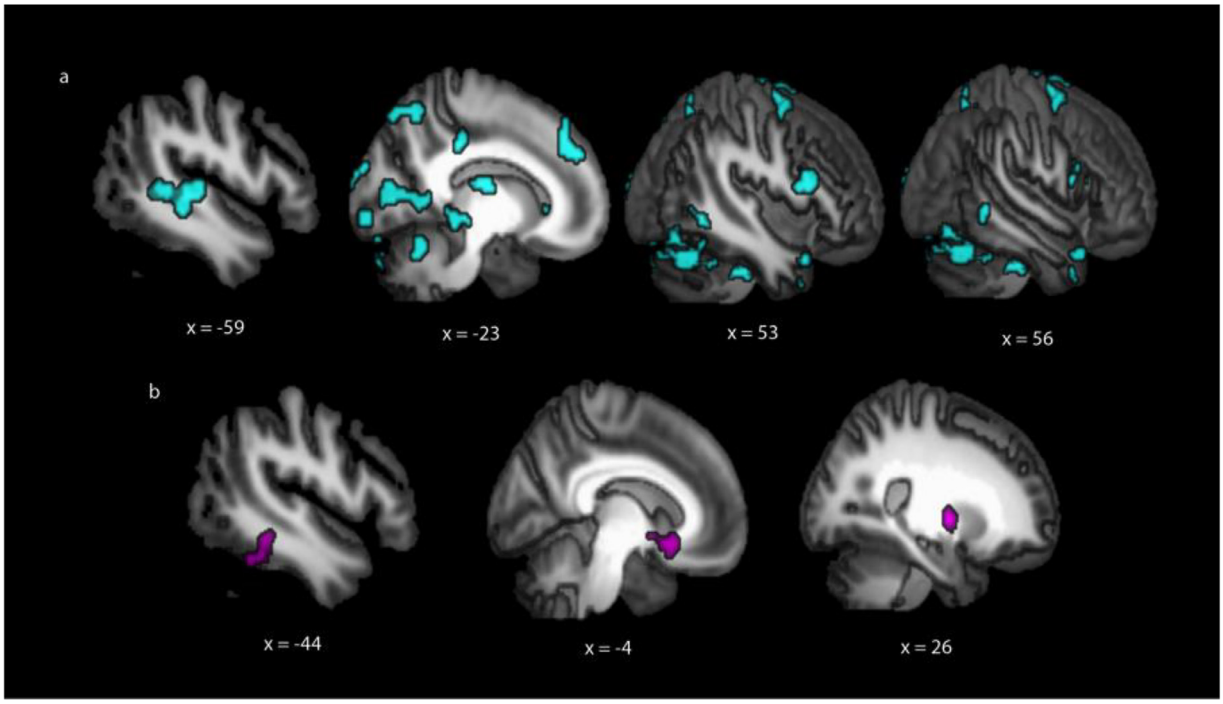


Fig. 5. Areas of hypoactivation in MD compared to HC during a) Enc-SR and b) Rcl-NRcl.

research. Findings also underscore the importance of attending to the HPA-axis function in the design of fMRI studies, particularly in mood disorders where individual differences in cortisol are likely to be substantial.

Disclosures

The authors have no conflicts of interest to disclose.

Conflict of interest

None.

Funding

Support for this work was provided to Dr. Langenecker by the NIMH (MH 091811, MH 101487) and a National Alliance for Research in Schizophrenia and Depression Award.

Authors' Contributions

ATP conducted all analyses, wrote the manuscript and incorporated revisions. RAS, AVM, MH, and ALW assisted with analytic plan, analyses, figures, and reviewed and edited the manuscript. MTK assisted with data collection and provided feedback on the manuscript. EMB, KAR, PM, MNS, and SLW assisted with overall study design and provided input on the analyses and final draft of the manuscript. SAL

oversaw all aspects of manuscript preparation, including study design, analytic plan, and analyses.

Acknowledgments

We thank the University of Michigan fMRI Laboratory for assistance in collecting data, and some pilot (control) fMRI scans from the University of Michigan Functional MRI lab (SAL, SLW). Support for this work was provided by the MH 091811 (SAL), MH 101487 (SAL) and a National Alliance for Research in Schizophrenia and Depression Award (SAL).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.07.006.

References

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.
Ahern, E., Semkovska, M., 2017. Cognitive functioning in the first-episode of major depressive disorder: a systematic review and meta-analysis. Neuropsychology 31, 52–72.
Ajilore, O., Lamar, M., Medina, J., Watari, K., Elderkin-Thompson, V., Kumar, A., 2015. Disassociation of verbal learning and hippocampal volume in type 2 diabetes and major depression. Int. J. Geriatr. Psychiatry 30, 393–399.
Ali, N., Pruessner, J.C., 2012. The salivary alpha amylase over cortisol ratio as a marker to assess dysregulations of the stress systems. Physiol. Behav. 106, 65–72.
Bao, A.M., Meynen, G., Swaab, D.F., 2008. The stress system in depression and neurodegeneration: focus on the human hypothalamus. Brain Res. Rev. 57, 531–553.
Barden, N., 2004. Implication of the hypothalamic-pituitary-adrenal axis in the physiopathology of depression. J. Psychiatry Neurosci. 29, 185–193.
Beauchaine, T.P., Neuhaus, E., Zalewski, M., Crowell, S.E., Potapova, N., 2011. The effects of allostatic load on neural systems subserving motivation, mood regulation, and social affiliation. Dev. Psychopathol. 23, 975–999.
Becking, K., Spijker, A.T., Hoencamp, E., Penninx, B.W., Schoevers, R.A., Boschloo, L., 2015. Disturbances in hypothalamic-pituitary-adrenal axis and immunological activity differentiating between unipolar and bipolar depressive episodes. PLoS One 10, e0133898.
Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. Series B (Methodological) 289–300.
Bifulco, A., Bernazzani, O., Moran, P., Ball, C., 2000. Lifetime stressors and recurrent depression: preliminary findings of the adult life phase interview (ALPHI). Soc. Psychiatry Psychiatr. Epidemiol. 35, 264–275.
Briceno, E.M., Weisenbach, S.L., Rapport, L.J., Hazlett, K.E., Bieliauskas, L.A., Haase, B.D., Ransom, M.T., Brinkman, M.L., Pecina, M., Schteingart, D.E., Starkman, M.N., Giordani, B., Welsh, R.C., Noll, D.C., Zubieta, J.K., Langenecker, S.A., 2013. Shifted inferior frontal laterality in women with major depressive disorder is related to emotion-processing deficits. Psychol. Med. 43, 1433–1445.
Brown, E.S., Varghese, F.P., McEwen, B.S., 2004. Association of depression with medical illness: does cortisol play a role? Biol. Psychiatry 55, 1–9.
Brown, E.S., Vera, E., Frol, A.B., Woolston, D.J., Johnson, B., 2007. Effects of chronic prednisone therapy on mood and memory. J. Affect. Disord. 99, 279–283.
Cao, B., Bauer, I.E., Sharma, A.N., Mwangi, B., Frazier, T., Lavagnino, L., Zunta-Soares, G.B., Walss-Bass, C., Glahn, D.C., Kapczinski, F., Nielsen, D.A., Soares, J.C., 2016. Reduced hippocampus volume and memory performance in bipolar disorder patients carrying the BDNF val66met met allele. J. Affect Disord. 198, 198–205.
Cauda, F., D'Agata, F., Sacco, K., Duca, S., Geminiani, G., Vercelli, A., 2011. Functional connectivity of the insula in the resting brain. Neuroimage 55, 8–23.
Chica, A.B., Bartolomeo, P., Lupianez, J., 2013. Two cognitive and neural systems for endogenous and exogenous spatial attention. Behav. Brain Res. 237, 107–123.
de Kloet, E.R., Oitzl, M.S., Joels, M., 1999. Stress and cognition: are corticosteroids good or bad guys? Trends Neurosci. 22, 422–426.
de Quervain, D.J., Aerni, A., Schelling, G., Roozendaal, B., 2009. Glucocorticoids and the regulation of memory in health and disease. Front. Neuroendocrinol. 30, 358–370.
Elzinga, B.M., Bakker, A., Bremner, J.D., 2005. Stress-induced cortisol elevations are associated with impaired delayed, but not immediate recall. Psychiatry Res. 134, 211–223.
Engvig, A., Fjell, A.M., Westlye, L.T., Skaane, N.V., Dale, A.M., Holland, D., Due-Tonnessen, P., Sundseth, O., Walhovd, K.B., 2014. Effects of cognitive training on gray matter volumes in memory clinic patients with subjective memory impairment. J. Alzheimers Dis. 41, 779–791.
Finsterwald, C., Alberini, C.M., 2014. Stress and glucocorticoid receptor-dependent mechanisms in long-term memory: from adaptive responses to psychopathologies. Neurobiol. Learn. Mem. 112, 17–29.
First, M.B., Spitzer, R.L., Gibbon, M., 1995. Structured Clinical Interview For DSM-IV Axis I disorder. Biometrics Research Department, New York State Psychiatric Institute, New York.
Funder, J.W., 2005. Mineralocorticoid receptors: distribution and activation. Heart Fail. Rev. 10, 15–22.
Gaffey, A.E., Wirth, M.M., Hoks, R.M., Jahn, A.L., Abercrombie, H.C., 2014. Circulating cortisol levels after exogenous cortisol administration are higher in women using hormonal contraceptives: data from two preliminary studies. Stress 17, 314–320.
Hagan, C.C., Graham, J.M., Wilkinson, P.O., Midgley, N., Suckling, J., Sahakian, B.J., Goodyer, I.M., 2015. Neurodevelopment and ages of onset in depressive disorders. Lancet Psychiatry 2, 1112–1116.
Hamilton, M., 1960a. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56.
Hamilton, M., 1960b. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Japee, S., Holiday, K., Satyshur, M.D., Mukai, I., Ungerleider, L.G., 2015. A role of right middle frontal gyrus in reorienting of attention: a case study. Front. Syst. Neurosci. 9, 23.
Jayaweera, H.K., Hickie, I.B., Duffy, S.L., Mowszowski, L., Norrie, L., Lagopoulos, J., Naismith, S.L., 2016. Episodic memory in depression: the unique contribution of the anterior caudate and hippocampus. Psychol. Med. 46, 2189–2199.
Joels, M., Krugers, H.J., 2007. LTP after stress: up or down? Neural Plast. 2007, 93202.
Kamali, M., Saunders, E.H., Prossin, A.R., Brucksch, C., Harrington, G., Langenecker, S.A., McInnis, M.G., 2012. Suicide attempts and elevated bedtime salivary cortisol levels in bipolar disorder. J. Affect. Disord. 136, 350–358.
Kassel, M.T., Rao, J.A., Walker, S.J., Briceno, E.M., Gabriel, L.B., Weldon, A.L., Avery, E.T., Haase, B.D., Pecina, M., Considine, C.M., Noll, D.C., Bieliauskas, L.A., Starkman, M.N., Zubieta, J.K., Welsh, R.C., Giordani, B., Weisenbach, S.L., Langenecker, S.A., 2016. Decreased fronto-limbic activation and disrupted semantic-cued list learning in major depressive disorder. J. Int. Neuropsychol. Soc. 22, 412–425.
Keller, J., Flores, B., Gomez, R.G., Solvason, H.B., Kenna, H., Williams, G.H., Schatzberg, A.F., 2006. Cortisol circadian rhythm alterations in psychotic major depression. Biol. Psychiatry 60, 275–281.
Kelley, R., Garrett, A., Cohen, J., Gomez, R., Lembke, A., Keller, J., Reiss, A.L., Schatzberg, A., 2013. Altered brain function underlying verbal memory encoding and retrieval in psychotic major depression. Psychiatry Res. 211, 119–126.
Kizilirmak, J.M., Rosler, F., Bien, S., Khader, P.H., 2015. Inferior parietal and right frontal contributions to trial-by-trial adaptations of attention to memory. Brain Res. 1614, 14–27.
Kukolja, J., Thiel, C.M., Wolf, O.T., Fink, G.R., 2008. Increased cortisol levels in cognitively challenging situations are beneficial in young but not older subjects. Psychopharmacology (Berl) 201, 293–304.
Kuswanto, C., Chin, R., Sum, M.Y., Sengupta, S., Fagiolini, A., McIntyre, R.S., Vieta, E., Sim, K., 2016. Shared and divergent neurocognitive impairments in adult patients with schizophrenia and bipolar disorder: whither the evidence? Neurosci. Biobehav. Rev. 61, 66–89.
Langenecker, S.A., Saunders, E.F., Kade, A.M., Ransom, M.T., McInnis, M.G., 2010. Intermediate: cognitive phenotypes in bipolar disorder. J. Affect Disord. 122, 285–293.
Langenecker, S.A., Weisenbach, S.L., Giordani, B., Briceno, E.M., Guidotti Breting, L.M., Schallmo, M.P., Leon, H.M., Noll, D.C., Zubieta, J.K., Schteingart, D.E., Starkman, M.N., 2012. Impact of chronic hypercortisolemia on affective processing. Neuropharmacology 62, 217–225.
Langenecker, S.A., Zubieta, J.K., Young, E.A., Akil, H., Nielson, K.A., 2007. A task to manipulate attentional load, set-shifting, and inhibitory control: convergent validity and test-retest reliability of the parametric Go/No-Go Test. J. Clin. Exp. Neuropsychol. 29, 842–853.
Liu, R.T., Alloy, L.B., 2010. Stress generation in depression: A systematic review of the empirical literature and recommendations for future study. Clin. Psychol. Rev. 30, 582–593.
Luckmann, H.C., Jacobs, H.I., Sack, A.T., 2014. The cross-functional role of frontoparietal regions in cognition: internal attention as the overarching mechanism. Prog. Neurobiol. 116, 66–86.
Lupien, S.J., McEwen, B.S., Gunnar, M.R., Heim, C., 2009a. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. 10, 434–445.
Lupien, S.J., McEwen, B.S., Gunnar, M.R., Heim, C., 2009b. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. 10, 434–445.
Magarinos, A.M., McEwen, B.S., Flugge, G., Fuchs, E., 1996. Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. J. Neurosci. 16, 3534–3540.
Marano, C.M., Workman, C.I., Lyman, C.H., Munro, C.A., Kraut, M.A., Smith, G.S., 2015. Structural imaging in late-life depression: association with mood and cognitive responses to antidepressant treatment. Am. J. Geriatr. Psychiatry 23, 4–12.
Maripuu, M., Wikgren, M., Karling, P., Adolfsson, R., Norrback, K.F., 2014. Relative hypo- and hypercortisolism are both associated with depression and lower quality of life in bipolar disorder: a cross-sectional study. PLoS One 9, e98682.
Maripuu, M., Wikgren, M., Karling, P., Adolfsson, R., Norrback, K.F., 2017. Hyper- and hypocortisolism in bipolar disorder - a beneficial influence of lithium on the HPA-axis? J. Affect Disord. 213, 161–167.
Miskowiak, K.W., Macoveanu, J., Vinberg, M., Assentoft, E., Randers, L., Harmer, C.J., Ehrenreich, H., Paulson, O.B., Knudsen, G.M., Siebner, H.R., Kessing, L.V., 2016. Effects of erythropoietin on memory-relevant neurocircuitry activity and recall in mood disorders. Acta Psychiatr. Scand. 134, 249–259.
Nielsen, S.E., Ahmed, I., Cahill, L., 2014. Postlearning stress differentially affects memory for emotional gist and detail in naturally cycling women and women on hormonal contraceptives. Behav. Neurosci. 128, 482–493.
Oertel-Knochel, V., Reinke, B., Feddern, R., Knake, A., Knochel, C., Prvulovic, D., Fusser, F., Karakaya, T., Loellgen, D., Freitag, C., Pantel, J., Linden, D.E., 2013. Verbal

episodic memory deficits in remitted bipolar patients: a combined behavioural and fMRI study. J. Affect Disord. 150, 430–440.
Okon-Singer, H., Hendler, T., Pessoa, L., Shackman, A.J., 2015. The neurobiology of emotion-cognition interactions: fundamental questions and strategies for future research. Front. Hum. Neurosci. 9, 58.
Okuda, S., Roozendaal, B., McGaugh, J.L., 2004. Glucocorticoid effects on object recognition memory require training-associated emotional arousal. Proc. Natl. Acad. Sci. U S A 101, 853–858.
Papez, J.W., 1937. A proposed mechanism of emotion. Archives Neurol. Psychiatry 38, 725–743.
Pariante, C.M., 2017. Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. Eur. Neuropsychopharmacol. 27, 554–559.
Parker, K.J., Schatzberg, A.F., Lyons, D.M., 2003. Neuroendocrine aspects of hypercortisolism in major depression. Horm. Behav. 43, 60–66.
Peters, A.T., Van Meter, A., Pruitt, P.J., Briceno, E.M., Ryan, K.A., Hagan, M., Weldon, A.L., Kassel, M.T., Vederman, A., Zubieta, J.K., McInnis, M., Weisenbach, S.L., Langenecker, S.A., 2016a. Acute cortisol reactivity attenuates engagement of frontoparietal and striatal regions during emotion processing in negative mood disorders. Psychoneuroendocrinology 73, 67–78.
Peters, A.T., Van Meter, A., Pruitt, P.J., Briceno, E.M., Ryan, K.A., Hagan, M., Weldon, A.L., Kassel, M.T., Vederman, A.C., Zubieta, J.-K., McInnis, M.G., Weisenbach, S.L., Langenecker, S.A., 2016b. Acute cortisol reactivity attenuates engagement of frontoparietal andstriatal regions during emotion processing in negative mood disorders. Psychoneuroendocrinology 73, 67–78.
Peters, S., Cleare, A.J., Papadopoulos, A., Fu, C.H., 2011. Cortisol responses to serial MRI scans in healthy adults and in depression. Psychoneuroendocrinology 36, 737–741.
Pizzagalli, D.A., 2011. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology 36, 183–206.
Pruessner, M., Pruessner, J.C., Hellhammer, D.H., Bruce Pike, G., Lupien, S.J., 2007. The associations among hippocampal volume, cortisol reactivity, and memory performance in healthy young men. Psychiatry Res. 155, 1–10.
Rao, J.A., Jenkins, L.M., Hymen, E., Feigon, M., Weisenbach, S.L., Zubieta, J.K., Langenecker, S.A., 2016. Differential resting state connectivity patterns and impaired semantically cued list learning test performance in early course remitted major depressive disorder. J. Int. Neuropsychol. Soc. 22, 225–239.
Roche, D.J., King, A.C., Cohoon, A.J., Lovallo, W.R., 2013. Hormonal contraceptive use diminishes salivary cortisol response to psychosocial stress and naltrexone in healthy women. Pharmacol. Biochem. Behav. 109, 84–90.
Roozendaal, B., Okuda, S., de Quervain, D.J., McGaugh, J.L., 2006. Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. Neuroscience 138, 901–910.
Ryan, K.A., Dawson, E.L., Kassel, M.T., Weldon, A.L., Marshall, D.F., Meyers, K.K., Gabriel, L.B., Vederman, A.C., Weisenbach, S.L., McInnis, M.G., Zubieta, J.K., Langenecker, S.A., 2015. Shared dimensions of performance and activation dysfunction in cognitive control in females with mood disorders. Brain 138, 1424–1434.
Sapolsky, R., 1994. Glucocorticoids, stress and exacerbation of excitotoxic neuron death. Semin. Neurosci. 6, 323–331.
Sapolsky, R., 2000. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch. Gen. Psychiatry 57, 925–935.
Schallmo, M.-P., Kassel, M.T., Weisenbach, S.L., S.L., Walker, S.J., Guidotti-Breting, L.M., Rao, J.A., Hazlett, K.E., Considine, C.M., Sethi, G., Vats, N., Pecina, M., Welsh, R.C., Starkman, M.N., Giordani, B., Langenecker, S.A., 2015a. A new semantic list learning task to parse the functioning of the Papez circuit. J. Clin. Exp. Neuropsychol. 37, 816–833.
Schallmo, M.P., Kassel, M.T., Weisenbach, S.L., Walker, S.J., Guidotti-Breting, L.M., Rao, J.A., Hazlett, K.E., Considine, C.M., Sethi, G., Vats, N., Pecina, M., Welsh, R.C., Starkman, M.N., Giordani, B., Langenecker, S.A., 2015b. A new semantic list learning task to probe functioning of the Papez circuit. J. Clin. Exp. Neuropsychol. 37, 816–833.
Shear, M.K., Vander Bilt, J., Rucci, P., Endicott, J., Lydiard, B., Otto, M.W., Pollack, M.H., Chandler, L., Williams, J., Ali, A., Frank, D.M., 2001. Reliability and validity of a structured interview guide for the hamilton anxiety rating scale (SIGH-A). Depress. Anxiety 13, 166–178.
Shields, G.S., Sazma, M.A., McCullough, A.M., Yonelinas, A.P., 2017. The effects of acute stress on episodic memory: a meta-analysis and integrative review. Psychol. Bull. 143, 636–675.
Shipley, W.C., 2009. Shipley-2: Manual. WPS.
Shomstein, S., 2012. Cognitive functions of the posterior parietal cortex: top-down and bottom-up attentional control. Front. Integr. Neurosci. 6, 38.
Stalder, T., Kirschbaum, C., Kudielka, B.M., Adam, E.K., Pruessner, J.C., Wust, S., Dockray, S., Smyth, N., Evans, P., Hellhammer, D.H., Miller, R., Wetherell, M.A., Lupien, S.J., Clow, A., 2016. Assessment of the cortisol awakening response: expert consensus guidelines. Psychoneuroendocrinology 63, 414–432.
Starkman, M.N., Giordani, B., Gebarski, S.S., Berent, S., Schork, M.A., Schteingart, D.E., 1999. Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. Biol. Psychiatry 46, 1595–1602.
Starkman, M.N., Giordani, B., Gebarski, S.S., Schteingart, D.E., 2003. Improvement in learning associated with increase in hippocampal formation volume. Biol. Psychiatry 53, 233–238.
Stokes, P.E., 1995. The potential role of excessive cortisol induced by HPA hyperfunction in the pathogenesis of depression. Eur. Neuropsychopharmacol. 5 Suppl, 77–82.
Suzuki, A., 2012. Emotional functions of the insula. Brain Nerve 64, 1103–1112.
Tsigos, C., Chrousos, G.P., 2002. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J. Psychosom. Res. 53, 865–871.
Turner, A.D., Furey, M.L., Drevets, W.C., Zarate Jr., C., Nugent, A.C., 2012. Association between subcortical volumes and verbal memory in unmedicated depressed patients and healthy controls. Neuropsychologia 50, 2348–2355.
van Stegeren, A.H., 2009. Imaging stress effects on memory: a review of neuroimaging studies. Can. J. Psychiatry 54, 16–27.
Ward, B.D., 2000. Simultaneous Inference for FMRI Data. Biophysics Research Institute, Medical College of Wisconsin.
Wardenaar, K.J., Vreeburg, S.A., van Veen, T., Giltay, E.J., Veen, G., Penninx, B.W., Zitman, F.G., 2011. Dimensions of depression and anxiety and the hypothalamo-pituitary-adrenal axis. Biol. Psychiatry 69, 366–373.
Watson, S., Thompson, J.M., Ritchie, J.C., Ferrier, I.N., Young, A.H., 2006. Neuropsychological impairment in bipolar disorder: the relationship with glucocorticoid receptor function. Bipolar Disord. 8, 85–90.
Weisenbach, S.L., Kassel, M.T., Rao, J., Weldon, A.L., Avery, E.T., Briceno, E.M., Ajilore, O., Mann, M., Kales, H.C., Welsh, R.C., Zubieta, J.K., Langenecker, S.A., 2014. Differential prefrontal and subcortical circuitry engagement during encoding of semantically related words in patients with late-life depression. Int. J. Geriatr. Psychiatry 29, 1104–1115.
Weldon, A.L., Hagan, M., Van Meter, A., Jacobs, R.H., Kassel, M.T., Hazlett, K.E., Haase, B.D., Vederman, A.C., Avery, E., Briceno, E.M., Welsh, R.C., Zubieta, J.K., Weisenbach, S.L., Langenecker, S.A., 2015a. Stress response to the functional magnetic resonance imaging environment in healthy adults relates to the degree of limbic reactivity during emotion processing. Neuropsychobiology 71, 85–96.
Weldon, A.L., Hagan, M., Van Meter, A., Jacobs, R.H., Kassel, M.T., Hazlett, K.E., Haase, B.D., Vederman, A.C., Avery, E., Briceno, E.M., Welsh, R.C., Zubieta, J., Weisenbach, S.L., Langenecker, S.A., 2015b. fMRI is a mild stress challenge and is related to degree of engagement of limbic structures during emotion processing in healthy individuals. Neuropsychobiology 71, 85–96.
Wilkinson, P.O., Goodyer, I.M., 2011. Childhood adversity and allostatic overload of the hypothalamic-pituitary-adrenal axis: a vulnerability model for depressive disorders. Dev. Psychopathol. 23, 1017–1037.
Wolf, O.T., 2009. Stress and memory in humans: twelve years of progress? Brain Res. 1293, 142–154.