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Cortisol Administration Normalizes Aberrant Functional Connectivity in Women with Depression

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Abstract

Previous resting-state functional connectivity (rsFC) research has identified aberrant connectivity in several large brain networks in depression, including the default mode (DMN), frontoparietal (FPN), and salience networks (SN). Connectivity of these networks is also related to depressive symptom severity and is affected by cortisol levels. To our knowledge, this is the first study to investigate the effects of acute cortisol administration on rsFC of DMN, FPN, and SN in individuals varying in depression history and severity. We collected resting-state fMRI scans for 74 women with and without a history of depressive disorder after administration of cortisol and placebo using a double-blind, crossover design. We conducted seed-based rsFC with seed regions from the DMN, FPN, and SN to examine the relationship between rsFC changes in these networks after cortisol, with depression history group predicting changes in rsFC after cortisol vs. placebo. To investigate rsFC changes in DMN, FPN, and SN due to the administration of cortisol as a function of depression severity we assessed the relationship between Beck Depression Inventory-II scores and rsFC changes in the networks of interest after cortisol vs. placebo administration for the entire sample. Results revealed that those with a history of depression exhibited increased connectivity between the left amygdala of the SN and left medial temporal gyrus of the DMN regardless of treatment. Further, we found that those who received cortisol had increased connectivity between the anterior insula of the SN and regions within the SN and DMN. Lastly, we found an interaction between depression symptom severity and rsFC between the PCC of the DMN and the right cerebellum of the SN, with greater depression symptoms associated with increased rsFC of the PCC and cerebellum. These findings are the first to show that...
women with greater depression severity may be more likely to normalize aberrant connectivity of DMN and SN regions after acute cortisol administration. Our results could help inform clinical treatments for depression that naturally increase endogenous cortisol levels and efficiency of glucocorticoid receptors, such as long-term daily exercise. Overall, these findings contribute to the literature on the neurobiological effects of exogenous cortisol in depression.

*Key words: depression, cortisol, resting-state functional connectivity, default mode network, frontoparietal network, salience network*
1. Introduction

1.1. Depression Prevalence

Over 8% of adults living in the United States self-report experiencing depression symptoms in any given year (Brody et al., 2018; Ettman et al., 2020). Further, the prevalence rate of depression in recent years (e.g., 2021) is approximately three to seven times greater than that of previous years (e.g., 2019), which is thought to be due to the COVID-19 pandemic and social restrictions that followed (Bueno-Notivol et al., 2021; Ettman et al., 2020; Shah et al., 2021). Past research provides evidence that depression is two to three times more common in women than men (Brody et al., 2018; Rivera-Bonet et al., 2021) and recent research suggests that women were more adversely affected by the pandemic showing greater levels of psychiatric symptoms compared to men (Liu et al., 2020). Therefore, it is important to understand the neurobiological correlates of depression and to investigate potential treatment targets for depression as individuals are suffering from depression symptoms now more than ever.

1.2. Resting-State Functional Connectivity in Depression

Functional magnetic resonance imaging (fMRI) has been used to characterize abnormalities in cortical and subcortical brain networks in depression. For example, one fMRI method applied to resting-state fMRI data is resting-state functional connectivity (rsFC), which allows for the study of neural networks by examining the communication between brain regions to determine if anatomically distant regions reflect similar blood-oxygenated-level-dependent (BOLD) responses during a resting-state scan (Power et al., 2014). Regions that show similar BOLD time courses over the scan are considered functionally connected with one another, indicating the regions may be part of the same
neural network. On the other hand, regions exhibiting no correlation or negative correlations with one another are typically part of different networks. Past reviews of rsFC research provide support for the existence of large-scale brain networks in healthy individuals and further suggest that normal connectivity of these networks may be altered in various psychiatric disorders, including depression (Greicius, 2008; Menon, 2011).

The characteristic symptoms of depression (e.g., guilt and self-blame, deficits in cognition, sad or depressed mood) are relevant to the functions associated with several neural networks, including the default mode network (DMN), frontoparietal network (FPN), and salience network (SN). For example, the DMN is typically most active and functionally connected when turning attention inward, such as when thinking about oneself or during negative self-focused thought (Andreasen et al., 1995; Buckner et al., 2008; Buckner & Carroll, 2007; Gusnard et al., 2001; Philippi & Koenigs, 2014; Van Oort et al., 2017; Yeo et al., 2011). The FPN is composed of brain regions that are most active and functionally connected when completing cognitive tasks, such as attention or working memory tasks, which may be more difficult for individuals with depression who suffer from impairments in attention (Cabeza & Nyberg, 2000; Corbetta & Shulman, 2002; Fox et al., 2005; Kaiser, Andrews-Hanna, Wager, et al., 2015; Owen et al., 2005; Vincent et al., 2008; Yaple et al., 2019). The SN has been implicated in emotional processing, such as when processing sad stimuli or recalling sad events (Hermans et al., 2014; Van Oort et al., 2017).

In a metanalysis of seed-based rsFC, researchers reported aberrant connectivity within and between several neural networks in those with major depressive disorder compared to healthy controls, including the DMN, FPN, and SN (Kaiser, Andrews-
Hanna, Wager, et al., 2015). Specifically, Kaiser and colleagues (Kaiser, Andrews-Hanna, Wager, et al., 2015) found that individuals with depression had hyperconnectivity of regions within the DMN and hypoconnectivity of regions within the FPN compared to controls. Other research has shown that connectivity within the SN in individuals with depression is mixed, with both hypo- and hyper-connectivity reported (Mulders et al., 2015; Philippi et al., 2020). Alterations of within-SN connectivity in those with a history of depression are thought to explain certain symptoms of depression, such as sad and ruminative thought patterns (Peters, Burkhouse, et al., 2016). Further, overactivity of SN has been shown to impair the anticipation of emotional outcomes in those with depressive symptomology (Rzepa & McCabe, 2016). In addition, past research posits that the SN is responsible for controlling attentional resources depending on task demands by facilitating the switch between DMN and FPN, or switching attention to internal or external information (Bernhardt et al., 2014; Peters, Van Meter, et al., 2016; Provenzano et al., 2019; Sridharan et al., 2008). In summary, hyperconnectivity of within-DMN regions, hypoconnectivity of within-FPN regions, and dysregulated within-SN connectivity relate to sad and ruminative thought patterns and cognitive impairments in individuals with a history of depression.

In terms of between network connectivity, past research in healthy adults has shown reliable negative correlations between DMN and task-active networks, such as the FPN and SN (Douw et al., 2016; Fox et al., 2005; Hellyer et al., 2014). In other words, under normal conditions, when attention is directed outward, such as during a working memory paradigm, task-active networks are most active, whereas the DMN is less active. Previous research indicates that this negative correlation between the DMN and task-
active networks is disrupted in individuals with depression or those prone to ruminative thought (Kaiser, Andrews-Hanna, Spielberg, et al., 2015; Lydon-Staley et al., 2019). Recent studies suggest that the inverse relation between DMN and FPN is diminished in those with depression, resulting in heightened connectivity between these networks (Kaiser, Andrews-Hanna, Wager, et al., 2015; Philippi et al., 2018). More specifically, past research has shown that there is hyperconnectivity between the pregenual anterior cingulate cortex (pgACC), a key node in the DMN, and the dorsolateral prefrontal cortex, a key node in the FPN, in those with depression (Philippi et al., 2018). Previous studies suggest that dysregulation of DMN-FPN connectivity in those with a history of depression may also explain the symptoms associated with depression, including rumination (Philippi et al., 2018), repetitive negative thought (Lydon-Staley et al., 2019), and impairments in working memory, attention, and emotion regulation (Hellyer et al., 2014; Kaiser, Andrews-Hanna, Spielberg, et al., 2015; Murphy et al., 2020). In terms of between-SN connectivity, Kaiser and colleagues (Kaiser, Andrews-Hanna, Spielberg, et al., 2015; Kaiser, Andrews-Hanna, Wager, et al., 2015) reported overall reduced connectivity between DMN and SN regions in those with depression. However, they also noted that results are mixed, suggesting that hypo- or hyperconnectivity between these networks may depend on whether patients with depression are directing their attention internally or externally. Said another way, the SN plays a key role in determining whether the DMN or FPN is more active and functionally connected depending on environmental situations.

In summary, within-DMN hyperconnectivity, within-FPN hypoconnectivity, and within-SN abnormal connectivity along with elevated between FPN-DMN connectivity
and dysregulated between SN-DMN connectivity relates to the previously mentioned depression symptoms, including sad and ruminative thought patterns, and deficits in working memory, attention, and emotion regulation.

1.3. Cortisol & rsFC

Activation of the hypothalamic-pituitary-adrenal (HPA) axis is responsible for the stress response, and dysfunction within the HPA-axis is consistently reported in depression (Bao et al., 2008; Holsen et al., 2013; Pariante, 2009; Parker et al., 2003; Peters et al., 2019; Peters, Van Meter, et al., 2016; Tofoli et al., 2011; Weinstein et al., 2010; Welberg & Seckl, 2001). Further, individuals with depression are known to have lower glucocorticoid receptor (GR) concentrations and may also exhibit impairments in GR-mediated negative feedback on the HPA-axis, which normally functions to inhibit further endogenous cortisol secretion (Anacker et al., 2011; Nemeroff et al., 1992; Pariante, 2009). Interestingly, the release of cortisol is known to modify connectivity of the DMN, SN, and FPN in healthy adolescents and adults, as well as those with depression symptoms (Kalafatakis et al., 2021; Peters, Burkhouse, et al., 2016; Soares et al., 2017; Taren et al., 2017; Thomason et al., 2011). For example, one study investigating endogenous levels of cortisol in individuals with a history of depression found that higher levels of endogenous cortisol were associated with greater rsFC between the DMN and FPN as well as between the SN and FPN (Peters et al., 2019). Given that endogenous cortisol has been associated with altered rsFC connectivity, it is possible that acute administration of cortisol (i.e., exogenous cortisol) may disrupt normal connectivity within and between the DMN, FPN, and SN in healthy populations. To our knowledge, only one study has examined the effects of acute cortisol administration on
rsFC in healthy male participants (Henckens et al., 2012). Henckens and colleagues (2012) reported that the administration of cortisol reduced negative correlations between the SN and DMN at rest in healthy male participants with no history of depression. A few studies using task-based fMRI suggest that exogenous cortisol can normalize connectivity of DMN regions during an emotional task in participants with a history of depression (Abercrombie et al., 2011; Rivera-Bonet et al., 2021). However, it remains unclear how acute administration of cortisol would affect rsFC in those with depression as there is limited research to date.

1.4. Conclusion of Past Literature

Several rsFC studies indicate that there is abnormal connectivity within and between the DMN, FPN, and SN in those with a history of depression compared to those with no history of depression (Hellyer et al., 2014; Kaiser, Andrews-Hanna, Spielberg, et al., 2015; Kaiser, Andrews-Hanna, Wager, et al., 2015; Lydon-Staley et al., 2019; Murphy et al., 2020; Peters et al., 2019; Philippi et al., 2018). It is plausible that an overactive HPA-axis leads to heightened levels of endogenous cortisol, which may cause the DMN to become overactive and less functionally specialized while also interfering with the between-network communication of DMN and FPN as well as DMN and SN (Peters et al., 2019). To our knowledge, no study has investigated the effect of acute cortisol administration on rsFC of these same networks in women with varying levels of depression. Acute cortisol administration in depression could have implications for the development of new treatments or interventions and understanding the mechanisms of acute cortisol administration in depression could lead to better depression treatments.
Lastly, to address a transdiagnostic perspective, we seek to understand how cortisol administration may change the connectivity of women with varying depression severities.

1.5. Aims & Hypotheses

Aim 1: The current study aims to investigate changes in rsFC of the DMN, FPN, and SN following administration of exogenous cortisol in women with different depression histories.

Hypothesis 1: Individuals with a history of depression, versus no history of depression, will have significantly decreased connectivity within DMN regions after cortisol administration compared to placebo.

Hypothesis 2: Individuals with a history of depression, versus no history of depression, will have significantly greater connectivity within FPN regions after administration of cortisol compared to placebo.

Hypothesis 3: Individuals with a history of depression, versus no history of depression, will have significantly altered connectivity within SN regions after administration of cortisol compared to placebo.

Hypothesis 4: Individuals with a history of depression, versus no history of depression, will have significantly decreased connectivity between DMN and FPN after the administration of cortisol compared to placebo.

Hypothesis 5: Individuals with a history of depression, versus no history of depression, will have significantly greater connectivity between DMN and SN after administration of cortisol compared to placebo.
Aim 2: Investigate the changes in rsFC of the DMN, FPN, and SN due to the administration of cortisol as a function of depression severity across the entire sample of women.

Hypothesis 6: Women with greater depression severity will have within FPN connectivity increases, within DMN connectivity decreases, within SN connectivity differences, and decreased connectivity between DMN-FPN and between DMN-SN after cortisol administration compared to placebo.
2. Method

2.1. Participants

Participants recruited for the current study were enrolled as part of a larger National Institutes of Health funded project examining the effects of cortisol on cognitive and neural function in depression (Abercrombie et al., 2018; Gaffey et al., 2019; Rivera-Bonet et al., 2021). Complete neuroimaging data were available for 74 participants who self-identified as ‘female’ for their biological sex. Participants ranged in age from 18 to 45 years old ($M_{\text{age}} = 27.42$, $SD_{\text{age}} = 7.13$). Sixty-nine percent of participant completed at least a Bachelor’s degree, and 76% of participants were White (16% Asian and 5% Black). To investigate the role of depression history, participants were classified into one of two groups: (i) no history of depression ($n = 28$; NoDep); and (ii) any history of a Depressive Disorder ($n = 46$; DepHist) according to the Diagnostic and Statistical Manual of Mental Disorders-5 (American Psychiatric Association, 2013). Lastly, all participant data was collected before the start of the COVID-19 pandemic.

Participants were excluded for the following reasons: daily nicotine use; illicit drug use within four weeks of participation; current Substance Use Disorder, or within the last six months; recent pregnancy or breastfeeding (i.e., within the last six months); self-reported use of antidepressants or other psychotropic medications; hormonal contraceptive use; peri- or postmenopausal signs; highly irregular periods; claustrophobia; significant risk for suicide; lifetime history of psychosis or mania. All participants that met these criteria self-reported that they had not used antidepressants or other psychotropic medications within the half-life time frame of the particular drug. Participants were not excluded based on psychotherapeutic history. Many participants
reported taking antidepressant medications in the past and reported side effects, among other reasons, for not continuing to take medication. Psychotherapy was not provided to participants as a part of the study. Participants completed urine drug tests on three of the seven visits to the study site (diagnostic interview day and both fMRI scan days) in order to confirm no illicit drug use for the following drugs: marijuana, opiate, cocaine, amphetamine, and methamphetamine. Researchers also asked participants about illicit drug use during every session. Lastly, due to the repeated-measure nature of the research, five participants were excluded because they did not complete one of the two required scans (e.g., placebo or cortisol).

2.2. Procedures

Participants completed two fMRI scans separated by about one week. One hour before each scan, participants received either the placebo or the 20mg hydrocortisone pill for oral administration. The pills were identical in appearance and prepared by the University of Wisconsin Pharmaceutical Research Center. Past work using oral hydrocortisone administration showed peak cortisol levels 90 minutes after administration (Abercrombie et al., 2018). Administration of cortisol was double-blinded and randomized for each participant across both scan days. Importantly, previous researchers who used double-blinding in cortisol administration reported that participants were not able to perform above chance-level at guessing which condition cortisol was administered (Frost et al., 2018; Henckens et al., 2012). Finally, all participants went through a mock scan, which was completed before either scan day, to acclimate to the MRI scanning environment.
All participants were recruited from Madison, Wisconsin (WI), or the surrounding area, via paper and digital flyers posted online and in community areas, and through advertisements sent to counseling centers and clinics in the local area. All participants provided written informed consent and were paid for their participation in accordance with the local IRB.

2.3. Measures

2.3.1. Beck Depression Inventory (BDI-II)

Participant depression severity was assessed using the Beck Depression Inventory-II (BDI-II) at each visit (Beck et al., 1996). The BDI-II is composed of 21 self-report items used to measure depression-related symptom severity within the past two weeks. An example item from the BDI-II would be, “How often have you found that you could not cope with all the things you had to do?” Items on the BDI-II are ranked on a Likert scale from 0, indicating a “never” response, to 4, indicating a “very often” response. Some BDI-II items are reverse scored before a final BDI-II score is computed. A recent review examining the reliability of the BDI-II reported an average Cronbach Alpha of 0.90 (Eser & Asku, 2021), and test-retest reliability of the BDI-II, after one-week, is also high at 0.93 (Beck et al., 1996; Eser & Asku, 2021). The test-retest reliability of BDI-II scores for the current study was high at 0.98. Therefore, the average of BDI-II scores from the two fMRI scan visits (i.e., placebo and cortisol) was used for all analyses.
2.3.2. Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (SCID)

The Structured Clinical Interview for the DSM-IV (SCID-I/P for DSM-IV TR; First, 1997) modified to assess DSM-5 criteria, was used for the psychopathology screening for all participants. The SCID is a structured interview used to assess Axis I disorders, which include depression, anxiety, posttraumatic stress disorder, and phobias, among other disorders. Only one participant in the NoDep group was found to have a diagnosis of a psychiatric condition in remission, Social Phobia.

2.4. MRI Data Acquisition

As part of the dissertation, I used previously collected MRI data (Abercrombie et al., 2018; Gaffey et al., 2019; Rivera-Bonet et al., 2021). The two MRI scans (i.e., placebo and cortisol) were collected using a 3T GE MRI scanner (Discovery MRI 750; GE Medical Systems, Waukesha, WI) equipped with an 8-channel radiofrequency coil array (GE Healthcare, Waukesha, WI). As mentioned above, the participants were scanned in a randomized and double-blinded manner, meaning roughly half of the participants received placebo during the first scan day. The resting-state fMRI data were collected using T2*-weighted Echo Planar Imaging (EPI) sequence (TR/TE/FA: 2150 ms/22ms/79°, matrix: 64 x 64, FOV: 22.4 cm, slice thickness: 3.5 mm, voxel size: 3.5 mm x 3.5 mm x 3.5 mm, slices: 40 sagittal, 280 total volumes) using thin slices and short echo time in order to minimize signal dropout in the ventromedial prefrontal cortex. Each participant was instructed during each resting-state scan (~10 min) to remain “calm, still, and awake” with their eyes open fixating on a cross back-projected onto a screen via an LCD projector (Avotec, Stuart, FL). To enable image registration and group comparison
of the functional data, high-resolution T1-weighted structural imaging data were acquired using a weighted BRAVO pulse sequence (TI: 450ms, TR/TE/flip angle (FA): 8.16 ms/3.2 ms/12°, matrix: 256 x 256 x 160, field of view (FOV): 215.6 mm, slice thickness: 1 mm, voxel size: 1 mm x 1 mm x 1 mm, slices: 156).

2.5. Preprocessing and Motion Analysis

As part of the dissertation, I completed the following steps using previously collected MRI data. The two resting-state fMRI scans were preprocessed using AFNI (Cox, 1996) and FSL (FMRIB Software Library; ). A rigid-body volume registration was done first to compensate for participant motion during scanning (3dvolreg, fourth volume as the base image volume). Second, field map correction was done using sagittal field maps for all participants (collected via a 3D SPGR sequence; TR/TE/FA: 5ms/1.8ms/7°, matrix: 192 x 128 x 44, FOV: 230mm, slice thickness: 3.5mm) to geometrically unwarp EPIs to reduce distortion caused by magnetic field inhomogeneities (IDEAL sequence; Reeder et al., 2005) and FMRIB Software Library (Woolrich et al., 2009). Next, the following preprocessing steps were performed for all participant data for each of the scans: (1) slice-time correct EPI slices (3dTshift, using first slice as a reference), (2) omitted first three volumes (3dcalc), (3) aligned EPI data to respective T1-weighted anatomical images (align_epi_anat.py) and transformed images to MNI-152 atlas space (LPI) in a single interpolation to 3 x 3 x 3mm³ voxels, (4) the 3D + time series were despiked (3dDespike), and (5) data were temporally filtered (band-pass: .01 Hz < f < .08 Hz) and spatially smoothed with a 6-mm full-width half-maximum (FWHM) Gaussian kernel (3dBandPass). Normalized T1 anatomical images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF) using FAST in FSL (Zhang et al.,
White matter and CSF segments were used as masks to extract a representative time series from each tissue type for nuisance regression. Then, a voxelwise multiple linear regression was performed (3dDeconvolve) to remove signal associated with motion and other typical nuisance variables (Ciric et al., 2017) including: six motion parameters (three translations, three rotations) which were obtained from the rigid body alignment of EPI volumes and their six derivatives, white matter time series, ventricular CSF time series, and finally a second-order polynomial to model baseline signal and slow drift. In order to further control for participant motion, volumes used in the GLM were censored for excessive motion, as described in the paragraph below. This final preprocessed file for each participant was used in the rsFC analyses.

We also examined motion for each participant, as individual differences in participant motion can contribute to resting-state correlations, and clinical populations have been found to move more during scan time compared to controls (Power et al., 2015). Participants were excluded based on the following criteria: mean framewise motion displacement >3mm (i.e., volume to volume movement across the time series), and/or total scan time <4 min after censoring all time points with framewise motion displacement >.2mm and extreme timeseries displacement (i.e., time points were >10% of voxels were outliers; Power et al., 2015). These thresholds were selected to provide the most conservative criteria for motion correction (Power et al., 2012; Yan et al., 2013). Average root-mean-squared (RMS) displacement was used as a summary of participant motion, as has been done in previous work (Ciric et al., 2017; Philippi et al., 2020, 2021). We investigated associations between average RMS and depression group, depression severity, and treatment order (placebo versus cortisol).
2.6. Functional Connectivity Analysis

We performed seed-based voxelwise rsFC analyses (Biswal et al., 1995) using six seed regions of interest (ROIs) from the DMN, FPN, and SN. Specifically, we used two seed ROIs from the DMN, the mPFC and the posterior cingulate cortex (PCC; Buckner et al., 2008; Sheline et al., 2009). Coordinates for the mPFC and PCC seeds were selected from a network-perspective, coming from a seminal paper investigating self-referential thought in depression (Sheline et al., 2009). In addition, the dorsolateral prefrontal cortex, a key node in the FPN was used as a seed ROI (Peters, Burkhouse, et al., 2016; Van Oort et al., 2017) and the coordinates for this seed were based on previous research (Peters, Burkhouse, et al., 2016). Finally, we used three ROIs from the SN, the bilateral amygdala and anterior insula, which are considered key nodes in the network (Kaiser, Andrews-Hanna, Wager, et al., 2015; Peters et al., 2019; Seeley et al., 2007; Vaisvaser et al., 2013; Wang et al., 2007). The bilateral amygdala coordinates for this study were created using the Harvard-Oxford subcortical atlas and the coordinates for the anterior insula were based on previous research using a network-perspective (Seeley et al., 2007).

To create the seed ROIs for the rsFC analysis, we first used the coordinates for these ROIs to create 6-mm radius seed masks in MNI space. Next, the transformation matrix from the registration procedure was used to align the seed ROIs masks to MNI template space.

To compute rsFC for each participant for each treatment, the mean resting-state BOLD time series from each seed ROI was included in a GLM (3dDeconvolve) to calculate the correlation between each seed ROIs time series and all other voxels in the brain. To create correlation maps for each ROI, the following steps were performed: (1)
used GLM output to convert $R^2$ values to correlation coefficient values ($r$) and (2) used Fisher’s $r$-to-$z$ transformation to convert $r$ to $z$-scores. The resulting $z$-scores were entered into the second-level statistical analyses to determine support for or evidence against the current hypotheses.

2.7. rsFC Statistical Analyses

2.7.1 Aim 1

To examine the relationship between rsFC changes of DMN, FPN, and SN due to acute cortisol administration in women with different depression histories ($N = 74$) we performed a mixed-model analysis of variance (ANOVA) with depression history group predicting connectivity changes after cortisol administration for each network seed region. Furthermore, for Aim 1, a sensitivity analysis in G*Power (Faul et al., 2007, 2009) using ‘ANOVA: Repeated measures, within-between interaction’ indicated that with sample sizes of 28 (NoDep) and 46 (DepHist) and an alpha of 5% (two-sided), we would have 80% power to detect a moderate effect size of $f = 0.17$ (small = .10; medium = .25). The same sensitivity analysis with a Bonferroni corrected alpha value of .008 revealed a medium effect of $f = 0.24$.

To correct for multiple comparisons, we used a family-wise error (FWE) correction approach at the cluster level using a whole-brain mask in AFNI (3dClustSim; Carp, 2012; Forman et al., 1995) and applied cluster-extent thresholding. To address the non-Gaussian nature of fMRI data (Eklund et al., 2016), the auto-correlation function in AFNI (-acf) was used to calculate FWHM for each subject (3dFWHMx). The cluster-extent threshold corresponds to the statistical probability of $\alpha = .05$ of identifying a random noise cluster at a predefined voxelwise threshold of $p < .001$ (uncorrected). Using
this whole-brain FWE cluster correction, a cluster-corrected size was identified and clusters larger than 52 voxels were identified as statistically significant in the analyses ($p_{FWE} < .008$ Bonferroni corrected for number of seed ROIs; 32 voxels whole-brain cluster-corrected without Bonferroni correction, $p < .05$).

### 2.7.2 Aim 2

Aim 2 investigated the rsFC changes in DMN, FPN, and SN due to the administration of cortisol as a function of depression severity. We performed repeated-measures ANOVAs using the entire sample ($N = 74$) to assess the relationship between the average BDI-II scores from the two fMRI visits, a continuous predictor, and the average rsFC changes in the networks of interest as a result of cortisol administration. For Aim 2, a sensitivity analysis in G*Power (Faul et al., 2007, 2009) using ‘ANOVA: Repeated measures, within-between interaction’ indicated that with a total sample of 74 participants and an alpha of 5% (two-sided), we would have 80% power to detect a moderate effect of $f = 0.15$. The same sensitivity analysis with a Bonferroni corrected alpha value of .008 revealed a medium effect of $f = 0.21$. Lastly, the same multiple comparisons correction method described in Aim 1 was applied in Aim 2.

### 2.8. Statistical Assumptions Checks

For each of the significant results we examined whether statistical assumptions were met for the mixed-design ANOVAs for aim one and the repeated measures ANOVAs for aim 2.

#### 2.8.1 Aim 1 Assumptions

For aim 1, the assumption of normality was met as Box’s M = 4.37, $F = 1.41$, $p = 0.24$. We also met the assumption of sphericity for aim 1, as Mauchley’s W = 1.00. The
assumption of independence was also met as rsFC of one participant did not influence the rsFC data of a second participant. Outlier checks for aim one identified one potential outlier. The 5% trim mean and mean values for aim one were not significantly different, therefore no data were removed as outliers for aim one.

2.8.2 Aim 2 Assumptions

For aim 2, the assumption of sphericity was met, as Mauchley’s W = 1.00. The assumption of independence was also met as the rsFC data of one participant did not influence the rsFC data of other participants. Potential outliers were identified during an outlier check for the significant findings for aim 2. However, the 5% trimmed values did not significantly differ from the mean values of the results for aim 2, thus no values were removed as outliers for the analyses included under aim 2.
Results

3.1. Demographic Variable Results

We first examined whether there were any differences between the two depression groups (NoDep and DepHist) in age, education, or race. Specifically, we performed an independent-samples t-test for age and two Pearson’s chi-square tests for education and race. We found no significant differences in age, $t(72) = -0.53, p = .44$, education, $\chi^2(5) = 2.41, p = .79$, or race, $\chi^2(2) = 2.32, p = .31$, between the participants in the NoDep and DepHist groups (Table 1). Given that there were no differences between the depression history groups, we did not include these demographic variables as covariates in the analyses for Aim 1 and Aim 2 described below.

3.2. Aim 1 Results

3.2.1 rsFC After Cortisol Administration in Women with Different Depression Histories

To address aim 1, we performed 2 (treatment) x 2 (group) mixed-design ANOVAs using 3dMVM in Afni to determine whether there were any differences in rsFC for the DMN, FPN, and SN seed ROIs between the two treatments (placebo and cortisol) and the two depression history groups (NoDep and DepHist). We found a significant main effect of depression group for connectivity between the left amygdala seed of the SN and a significant cluster in the left middle temporal gyrus (MTG) of the DMN, $F(1,72) = 19.47, p < 0.001, \eta_{p}^2 = .213$ (Figure 1). This effect was driven by the rsFC between the SN and DMN regions being lower in the depression history compared to the no depression history group (Table 2). There was no significant main effect of treatment, $F(1,72) = .83, p = .366$, and no interaction between treatment and depression...
group, $F(1,72) = .78$, $p = .38$, for the left amygdala seed of the SN. For Aim 1, all other mixed-model ANOVAs conducted in Afni for the remaining DMN, FPN, and SN seed ROIs were not significant ($p_{FWE} > .05$). Although the significant main effect of group for the left amygdala was significant after correction for multiple comparisons ($p_{FWE} < .05$), it did not remain significant after a Bonferroni correction for the six network seed ROIs used in the present study ($p_{FWE} > .008$). This finding does not provide support for the hypotheses in aim 1.

3.3. Aim 2 Results

3.3.1. rsFC After Cortisol Administration as a Function of Depression Severity

To address aim 2, we performed repeated measures ANOVAs using 3dMVM in Afni to investigate the interaction between depression severity (BDI) and treatment (placebo vs. cortisol) across women with different depression symptom severities. There was a significant main effect of treatment for rsFC between the right anterior insula of the SN and the left inferior frontal gyrus of the ventral attention network, $p_{FWE} < .05$, $F(1,72) = 14.38$, $p < .001$, $\eta_p^2 = 0.166$. Specifically, there was greater rsFC between the right anterior insula of the SN and left inferior frontal gyrus of the ventral attention network after acute cortisol administration as compared with placebo scans (Figure 3a). We also found a significant main effect of treatment for rsFC between the right anterior insula seed of the SN and the left superior temporal gyrus (STG) of the DMN, $p_{FWE} < .05$, $F(1,72) = 16.25$, $p < .001$, $\eta_p^2 = 0.184$. Specifically, there was greater rsFC between the right anterior insula of the SN and the left STG of the DMN after acute cortisol administration compared with placebo scans (Figure 3b; Table 2). There was no
interaction between depression severity and treatment for the right anterior insula seed 

\( p_{FWE} > .05 \)

We found a significant interaction between depression severity and treatment for 
rsFC between the posterior cingulate cortex (PCC) seed of the DMN and lobule VIIIa of 
the right cerebellum, part of the ventral attention network, \( p_{FWE} < .05, F(1,72) = 22.58, p \) 
< .001, \( \eta_p^2 = 0.239 \) (Figure 2b). Figure 3c shows that greater depression severity was 
associated with increased rsFC connectivity between the PCC of the DMN and right 
cerebellum (VIIIa) of the ventral attention network after cortisol administration compared 
to placebo (Table 2). Although this interaction was significant after correction for 
multiple comparisons \( p_{FWE} < .05 \), this result did not remain significant after Bonferroni 
correction for the six seed ROIs \( p_{FWE} > .008 \). There were no significant main effects of 
depression severity or treatment for the PCC seed \( p_{FWE} > .05 \). All other repeated 
measure ANOVAs for the other DMN, FPN, and SN seed ROIs did not meet the 
threshold for statistical significance \( p_{FWE} > .05 \).
4. Discussion

To our knowledge, this is the first study to investigate the effects of acute cortisol administration on rsFC of large-scale neural networks in women with different depression histories and severities. The present study examined the relationship between rsFC changes of DMN, FPN, and SN due to acute cortisol administration in women with different depression histories. Additionally, we investigated the interaction between depression severity and treatment type across women with different depression symptom severities.

4.1. Aim 1 Discussion

4.1.1. Main Effect of Depression Group

Overall, there was little support for aim 1 of the current study. Hypothesis 5 predicted that cortisol would increase SN-DMN connectivity in depression and decrease in no depression. Although the results do not support the interaction predicted in hypothesis 5, there was a main effect of depression history group. Specifically, the history of depressive disorders group had reduced rsFC between the left amygdala of the SN and the left MTG of the DMN compared to the no depression group, regardless of cortisol. These findings are consistent with previous research showing reduced rsFC between SN-DMN in depression (Kaiser, Andrews-Hanna, Spielberg, et al., 2015). The SN is thought to control, at least in part, the activity and connectivity of the DMN depending on situations and task demands (Peters et al., 2019; Peters, Van Meter, et al., 2016; Provenzano et al., 2019). Additionally, decreased SN-DMN connectivity in individuals with depression may also explain the role of the SN in hyperactivity in the DMN (Sridharan et al., 2008). All other models assessing main effects of treatment
(cortisol or placebo) and group (no history of depression and history of depression) did not reach statistical significance, nor did interactions between the two factors for the remainder of DMN, FPN, and SN seed ROIs. The lack of results supporting Aim 1 hint at depression severity, not depression group, being a key factor in understanding how cortisol may be able to normalize rsFC of individuals with a history of depression. In other words, grouping individuals into one of two groups (e.g., no history of depression group and history of depressive disorders group) may not be the best way to investigate cortisol’s effect on brain connectivity in individuals with depression.

4.2. Aim 2 Discussion

Aim 2 investigated the interaction between depression severity (BDI-II scores) and treatment type (placebo vs. cortisol) related to connectivity of the DMN, FPN, and SN across women with different depression symptom severities. First, we found a main effect of treatment for rsFC of the anterior insula, part of the SN, and two separate clusters, the left inferior frontal gyrus (IFG) of the ventral attention network and the left superior temporal gyrus (STG) of the DMN. There was also an interaction between treatment and depression severity for the rsFC of the PCC of the DMN and the right Lobule VIIIa of the cerebellum, part of the ventral attention network. The functions and networks of each significant cluster for aim 2 are discussed below.

4.2.1. Main Effects of Treatment

The IFG is thought to be part of the ventral attention network (Vossel et al., 2014; Yeo et al., 2011) which overlaps with regions in the salience network (SN; Seeley et al., 2007). Thus, the SN and ventral attention network are functionally similar such that both networks show increased activity and rsFC during emotional processing or when
orienting attention toward the internal or external environment for further processing (Hermans et al., 2014; Seeley et al., 2007; Van Oort et al., 2017; Vossel et al., 2014; Yeo et al., 2011). Due to the function of these networks, the connectivity patterns of the IFG likely change given the specifics of mental states and task demands (Baer et al., 2019; Sezer et al., 2022). The finding of increased rsFC between the right anterior insula of the SN and the left IFG of the ventral attention network/SN during the cortisol scan compared to the placebo scan provides partial support for Aim 2. Said another way, the administration of cortisol increased within-SN connectivity regardless of depression severity.

The STG is thought to be a main component of the DMN (Bilevicius et al., 2018; Yeo et al., 2011). The finding of increased rsFC of the right anterior insula of the SN and the left STG of the DMN during the cortisol treatment compared to placebo provides partial support to aim 2. We predicted increased rsFC between DMN-SN after cortisol administration in those with the highest depression severity. We found a main effect of treatment showing that, regardless of depression severity, connectivity between DMN-SN (e.g., STG-anterior insula) increased. In other words, the administration of cortisol reduced the normal negative correlation between the DMN and SN. Although no interaction was present, the increased DMN-SN connectivity regardless of depression severity is interpreted that there are natural negative DMN-SN correlations in those with depression (Kaiser, Andrews-Hanna, Spielberg, et al., 2015; Kaiser, Andrews-Hanna, Wager, et al., 2015) and that cortisol eliminates these correlations. This finding is also consistent with previous research which reported that cortisol administration reduced negative correlations between DMN-SN in male participants with no history of
depression (Henckens et al., 2012). Currently, we believe that the administration of cortisol may allow for individuals, regardless of depression severity, to more easily switch between task-active and task-inactive networks (Bernhardt et al., 2014; Holtzheimer & Mayberg, 2011; Peters et al., 2019; Provenzano et al., 2019; Sridharan et al., 2008). In other words, increasing exogenous, and potentially endogenous, cortisol may prevent individuals from getting stuck in one network (Holtzheimer & Mayberg, 2011).

4.2.2. Interaction of Treatment and Depression Symptom Severity

The only significant interaction between treatment and depression severity for aim 2 occurred for the rsFC between the PCC seed of the DMN and Lobule VIIIa of the right cerebellum, thought to be part of the ventral attention network (Buckner et al., 2011; Stoodley & Schmahmann, 2009). Figure 3C shows that those with heightened depression severity had increased rsFC between the PCC of the DMN and Lobule VIIIa of the cerebellum of the ventral attention network after cortisol administration compared to placebo. Given that the ventral attention network and SN are part of the same functional network (Seeley et al., 2007), our findings indicate that greater depression severity was associated with increased DMN-SN connectivity after cortisol treatment versus placebo. Previous research findings of reduced DMN-SN connectivity in those with a history of depression (Kaiser, Andrews-Hanna, Spielberg, et al., 2015; Kaiser, Andrews-Hanna, Wager, et al., 2015), coupled with the current results, suggest that cortisol may be normalizing rsFC between DMN-SN in individuals with greater depression severity. Similar to the current study, previous task-dependent rsFC findings revealed that abnormal task-dependent rsFC of a DMN seed was normalized after cortisol
administration in women with depression (Rivera-Bonet et al., 2021). In summary, the present findings provide support to a neurocognitive model in which alterations in neural networks are closely linked with psychiatric conditions such as depression (Kaiser, Andrews-Hanna, Wager, et al., 2015).

4.3. Clinical Implications and Future Directions

Given that greater depression severity was associated with normalization of between network connectivity in response to acute cortisol administration, the findings from the current study have several clinical implications. First, practicing mindfulness may be one way to strengthen aberrant connectivity between DMN and SN (Sezer et al., 2022) which may result in more effective modulation of endogenous cortisol during acute social stressors that negatively impact those with depression (Peters, Burkhouse, et al., 2016; Peters, Van Meter, et al., 2016; Sezer et al., 2022). In other words, strengthening abnormal connectivity between these networks during task-active states, such as during mindfulness or during specific therapies, may be one way to normalize the connectivity between these networks during rest and result in remediation of depression symptoms. Further, another viable option for treating depression is improving the efficiency or function of glucocorticoid receptors (GR) in humans (Anacker et al., 2011). For example, research investigating the efficacy of exercise to ameliorate depressive symptoms found that it does not differ from antidepressant medications (Cooney et al., 2013), which have their molecular effects on GR function (Anacker et al., 2011). Said another way, exercise is thought to be a viable alternative treatment for depression, specifically for those who may have tried multiple antidepressant regimens or for those who view side effects of antidepressant to outweigh the benefits of the medication (Cooney et al., 2013; Gomes de
Assis & Cieszczyk, 2020). It is also possible that daily physical exercise, whether being resistance, strength, or anaerobic exercise, can ameliorate depressive symptoms by improving GR function. Lastly, researchers believe that exercise could be used as a treatment option for those with depression, though exercise in conjunction with pharmacological (e.g., antidepressants) and/or psychological treatments (e.g., psychotherapy) may be the best form of treatment for those with greater than mild or moderate depression (Beesley & Mutrie, 1997; Cooney et al., 2013; Gomes de Assis & Cieszczyk, 2020).

4.4 Limitations

The current study had several limitations that are important to mention. First, there are obvious sex differences that appear in the cortisol literature (Abercrombie et al., 2011; Kirschbaum et al., 1992; Stroud et al., 2002) and these should be considered when conceptualizing future aims and hypotheses involving samples with men and women, and generalizing results across all biological sexes is cautioned.

Second, the number of participants in each group was uneven, including twenty-eight women ($n = 28$) with no history of depression (NoDep), and forty-six women ($n = 46$) who had differing depression histories (DepHist). Thus, future work using larger sample sizes are needed to replicate the current results and to potentially find a greater effect of cortisol on rsFC of large-scale neural networks.

Additionally, factors other than the impaired functionality of the HPA axis and GR functionality should be discussed when trying to understand the effects of cortisol on rsFC in those with depression. For example, past research found factors such as childhood trauma and childhood emotional abuse often have a moderating effect on
cognitive and neurobiological outcome variables when studying samples with varying levels of depression (Abercrombie et al., 2011, 2018; Heim et al., 2008). This is consistent with animal models of early life trauma which reveal that rats who experience early life trauma show enhanced learning under high-stress whereas animals with no history of early life trauma show enhanced learning under reduced stress (Champagne et al., 2008). Future research investigating the role of cortisol on rsFC in depression should include childhood trauma and emotional abuse measures in their models to determine if they, in addition to depression severity, impact rsFC in depression after cortisol administration.

Further, the depression history group (DepHist, \( n = 46 \)) included individuals who have current depressive disorders as well as individuals who have remitted depression. This large depression history group may be considered a heterogeneous group to some, which may also be viewed as a limitation of the current analyses. Also, due to the clinical nature of the research participants were recruited through convenience sampling via flyers and ads and were included in the study if they met all inclusion criteria (see participants section).

Lastly, the administration of cortisol as a potential treatment mechanism for depression needs to be discussed. The acute and chronic effects of excess cortisol are well-known, and we do not believe that the administration of cortisol should serve as a primary treatment for persons with any level of depression (Pariante & Lightman, 2008).

**4.5 Conclusion**

In summary, this study is the first to demonstrate that the administration of cortisol normalizes rsFC between DMN and SN regions in women with greater
depression severity. Although this study increased exogenous cortisol through pharmacological manipulation, researchers suggest that those with severe depression symptomology will benefit more from psychotherapeutic treatment in conjunction with other interventions such as daily physical exercise.
Figures

**Figure 1. Bar Graph Showing the Main Effect of Group for rsFC Between the Left Amygdala, a SN Seed, and the Left Middle Temporal Gyrus, a FPN Cluster, by Depression History Group for Aim 1.**

![Bar Graph](image)

**Note.** A. For Aim 1, there was a main effect of depression history group for rsFC between the left amygdala of the SN (B.) and the left middle temporal gyrus extending to the superior temporal gyrus (C.), of the DMN, F(1,71) = 21.45, p < 0.001, \( \eta^2_p = 0.232 \). The effect appears to be driven by the no depression history group (NoDep) such that there is significantly increased connectivity between the left amygdala of the SN and the left middle temporal gyrus of FPN in the no depression group compared to the depression history group. The error bars on each bar graph depict +/- 1 standard error, and all results survived whole-brain cluster correction \( p_{FWE} < .05, p < .001 \) uncorrected. Acronyms: SN = Salience Network; FPN = Frontoparietal Network; L_Amyg = Left amygdala; L_MTG = Left middle temporal gyrus; CORT = cortisol; NoDep = no depression group; DepHist = depression history group. (B) Picture of the left amygdala seed in red. (C) Picture of left middle temporal gyrus cluster.
Figure 2. Pictures of the Anterior Insula and PCC Seeds with significant clusters for Aim 2.

**A**

- Depicts the right anterior insula seed (red) and the two significant clusters (orange) at the left inferior frontal gyrus (middle), $p_{FWE} < .05$, $F(1,72) = 14.38$, $p < .001$, $\eta^2_p = 0.166$ (Figure 3A), and the left superior frontal lobe (right), $p_{FWE} < .05$, $F(1,72) = 16.25$, $p < .001$, $\eta^2_p = 0.184$ (Figure 3B). The right anterior insula is a SN seed, the left inferior frontal gyrus cluster ($x = -43$) is a ventral attention network region, and the left superior temporal gyrus cluster ($x = -55$) is a DMN region. F-values for the clusters range from 0 (red) to 36 (yellow).

**B**

- Depicts the significant interaction of treatment and depression symptoms for rsFC between the left posterior cingulate cortex (PCC) seed of the DMN in red and a cluster at the right lobule VIIIa of the cerebellum, part of the...
ventral attention network, in yellow/orange, $F(1, 72) = 9.43, p = .003, \eta^2 = 0.116$ (Figure 3c). The $F$-values for this cluster range from 0 (red) to 26 (yellow).
Figure 3. Bar Graphs of Main Effects of Treatment for rsFC Between Ant_Ins Seed and L_IFG and L_STG Clusters and Scatterplot of Interaction between Treatment and Depression Severity for rsFC of PCC Seed with R_Cb Cluster for Aim2.

**Note.**

A. Depicts the bar graph showing the significant main effect of treatment for the rsFC between the right anterior insula (Ant_Ins) seed and the left inferior frontal gyrus (L_IFG) cluster, $p_{FWE} < .05$, $F(1,72) = 14.38$, $p < .001$, $\eta_p^2 = 0.166$.

B. Depicts the bar graph showing the significant main effect of treatment for mean rsFC between the right Ant_Ins seed and the left superior temporal gyrus (L_STG) cluster, $p_{FWE} < .05$, $F(1,72) = 16.25$, $p < .001$, $\eta_p^2 = 0.184$.

C. Depicts the scatterplot showing the significant interaction between treatment and depression severity for rsFC of the posterior cingulate cortex seed and lobule VIIIa of the right cerebellum, $F(1,72) = 9.43$, $p = .003$, $\eta_p^2 = 0.116$. Regression lines are plotted separately for cortisol (light blue lines and dots) and placebo (dark green lines and dots) scans showing the relationship between rsFC and average BDI.
Acronyms: PCC = posterior cingulate cortex; DMN = Default Mode Network; R_Cb = lobule VIII of the right cerebellum; CORT = cortisol; Avg_BDI = average BDI-II scores from both scan days.
Tables

Table 1

Demographic variables by depression group

<table>
<thead>
<tr>
<th></th>
<th>NoDep (n = 28)</th>
<th>DepHist (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26.9 (7.7)</td>
<td>27.8 (6.8)</td>
</tr>
<tr>
<td><strong>Education Level</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>diploma/equivalent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some college, no</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>degree</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associate’s degree</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Master’s degree</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Doctoral degree</td>
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<td>2</td>
</tr>
<tr>
<td><strong>Race</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Black</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Avg. BDI-II</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.9 (1.4)</td>
<td>14.3 (12.2)</td>
</tr>
</tbody>
</table>

*Notes. BDI-II = Beck Depression Inventory-II; NoDep = no history of depression group; DepHist = depression history group*

<sup>a</sup> There were no significant differences between depression groups in age, t(72) = -0.53, p = .44, education, χ² (74, 5) = 2.41, p = .79, or race, χ² (74, 2) = 2.32, p = .31, between the participants in the NoDep and DepHist groups.

<sup>b</sup> BDI-II scores ranged from 0 to 47; as expected, we found significant differences between the two groups in depression severity, t(72) = -5.79, p < .001.
Table 2

**Group Resting-State Functional Connectivity Results for Networks of Interest**

<table>
<thead>
<tr>
<th>Seed ROI</th>
<th>Cluster location</th>
<th>MNI coordinates (x, y, z)</th>
<th>Cluster size (voxels)</th>
<th>F-value</th>
<th>^aAverage connectivity NoDep</th>
<th>^aAverage connectivity DepHist</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCC</td>
<td>Right Cerebellum Lobule VIIIa</td>
<td>9, -72, -51</td>
<td>44</td>
<td>22.58</td>
<td>Cortisol: -0.06 (0.13) Placebo: -0.00 (0.15)</td>
<td>Cortisol: 0.02 (0.13) Placebo: 0.00 (0.13)</td>
</tr>
<tr>
<td>Anterior Insula</td>
<td>Left inferior frontal gyrus</td>
<td>-43, 19, 25</td>
<td>40</td>
<td>5.86</td>
<td>Cortisol: 0.04 (0.16) Placebo: -0.00 (0.21)</td>
<td>Cortisol: 0.06 (0.18) Placebo: -0.05 (0.19)</td>
</tr>
<tr>
<td>Anterior Insula</td>
<td>Left superior temporal gyrus</td>
<td>-55, 4, -12</td>
<td>33</td>
<td>16.25</td>
<td>Cortisol: -0.03 (0.19) Placebo: -0.10 (0.16)</td>
<td>Cortisol: 0.01 (0.14) Placebo: -0.09 (0.14)</td>
</tr>
<tr>
<td>Left Amyg</td>
<td>Left middle temporal gyrus extend to superior temporal gyrus</td>
<td>-52, -24, -9</td>
<td>32</td>
<td>18.87</td>
<td>Cortisol: 0.22 (0.15) Placebo: 0.17 (0.17)</td>
<td>Cortisol: 0.07 (0.11) Placebo: 0.08 (0.14)</td>
</tr>
</tbody>
</table>

*Note.* Regression results from resting-state analysis were not significant at \( p_{\text{FWE}} = 0.05, p = 0.001 \) voxelwise uncorrected threshold. ROI = region of interest; PCC = posterior cingulate cortex; Amyg = amygdala.

^aAverage raw connectivity scores correspond to z-scores; means and standard deviations are reported for each group.
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CORTISOL NORMALIZES CONNECTIVITY IN DEPRESSION


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cortisol is differentially associated with enhanced connectivity to the cognitive control network in young adults with a history of depression.

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