

# Alterations in Systemic and Cognitive Glucocorticoid Sensitivity in Depression

## *Supplemental Information*

### **Supplemental Methods**

#### **Participant Inclusion and Exclusion Criteria**

##### *Inclusion Criteria*

- Female
- 18 to 45 years of age
- English fluency
- Able to lie still on their back for up to 90 minutes
- Willing and able to return for all visits
- Able to provide written informed consent prior to participation
- In good physical health as determined by medical history
- If a nicotine user, able to refrain from nicotine use for 2 hours prior to fMRI scanning and throughout the scan visits
- Additional criteria for never-depressed subjects: Free of current or past DSM-5 diagnoses of MDD or other depressive disorders
- Additional criteria for subjects with current or past depression: Meets DSM-5 criteria for a current or past depressive disorder diagnosis
- Adherence to home saliva collection methods and timing of sample collection

##### *Exclusion Criteria*

- Lifetime history of psychosis or mania
- Substance use disorder within the last 6 months
- Significant risk for suicide
- Claustrophobia

- Acute or chronic physical (non-psychiatric) illness
- Daily nicotine use
- Use of antidepressants, other psychotropic medication, or medications that alter glucocorticoids
- Hormonal contraceptives
- Peri- or postmenopausal signs
- Highly irregular periods
- Pregnancy or breastfeeding within the last 6 months
- Illicit drug use within the last 4 weeks (verified by negative urinary drug test)

### **Additional Methods for Home Saliva Collection**

In addition to detailed instructions, participants received a phone or text reminder to begin saliva collection on Day 1 and to take the dexamethasone pill on Day 3. Adherence to the saliva collection protocol was monitored with Medication Event Monitoring System (MEMS) 6 TrackCaps (AARDEX Group Ltd., Sion, Switzerland), which recorded a timestamp when each Salivette was removed from a container for collection. Additionally, participants completed a Home Saliva Collection Log each time they provided a sample, which asked them to record the time of collection, sleep diary information, and information about naps, exercise, illnesses, allergies, menstrual cycle, emotional/stressful events, medications, caffeine use, food/beverage intake, and drug/alcohol use.

### **Null Effects of Menstrual Cycle Phase**

Menstrual cycle phase did not moderate findings reported in the body of the article: Menstrual phase was not related to dexamethasone suppression test (DST) feedback sensitivity or memory bias, either for cortisol administration (CORT) or placebo,  $p$ 's > 0.32. Depression

severity remains a significant predictor of DST feedback sensitivity when menstrual cycle phase is included in the model,  $F(1,48) = 6.23$ ,  $p = 0.016$ . In addition, the relation between DST feedback sensitivity and memory bias for pictures encoded during placebo remains when menstrual phase is included in the model,  $F(1,61) = 4.07$ ,  $p = 0.048$ . Most importantly, the relation remains between DST feedback sensitivity and reduction in memory bias for pictures encoded during CORT (vs. placebo),  $F(1,61) = 7.25$ ,  $p = 0.009$ . It should be noted, however, that the current study is not the ideal test of the potential role of menstrual cycle phase in cortisol sensitivity, because menstrual phase varied for the different segments of the study, and timing with respect to menstrual phase was not controlled.

**Table S1. DSM-5 Diagnoses for Each Participant by Depression Group**Table S1a. Depression Group: **Never Depressed**

<b>Participant</b>	<b>Depressive Disorder Diagnoses</b>	<b>Other Current Diagnoses</b>
1	None	None
2	None	None
3	None	None
4	None	None
5	None	None
6	None	None
7	None	None
8	None	None
9	None	None
10	None	None
11	None	None
12	None	None
13	None	None
14	None	None
15	None	None
16	None	None
17	None	None
18	None	None
19	None	Social Anxiety Disorder, Performance Only
20	None	None
21	None	None
22	None	None
23	None	None
24	None	None
25	None	None
26	None	None

Table S1b. Depression Group: **Other Depression**

<b>Participant</b>	<b>Depressive Disorder Diagnoses</b>	<b>Other Current Diagnoses</b>
1	Major Depressive Disorder, Single Episode, In Full Remission	Specific Phobia, Animal
2	Major Depressive Disorder, Single Episode, In Full Remission	None
3	Major Depressive Disorder, Recurrent Episode, In Full Remission	None
4	Persistent Depressive Disorder, Early Onset, With Intermittent Major Depressive Episodes, Without Current Episode, Moderate	Social Anxiety Disorder
5	Other Specified Depressive Disorder (Depressive episode with insufficient symptoms)	Generalized Anxiety Disorder Posttraumatic Stress Disorder, With Dissociative Symptoms (Depersonalization)
6	Major Depressive Disorder, Recurrent Episode, In Full Remission	None
7	Persistent Depressive Disorder, Early Onset, With Intermittent Major Depressive Episodes, Without Current Episode, Mild	Social Anxiety Disorder
8	Persistent Depressive Disorder, In Full Remission, Early Onset, With Intermittent Major Depressive Episodes, Without Current Episode	None
9	Major Depressive Disorder, Single Episode, In Full Remission	None
10	Persistent Depressive Disorder, In Full Remission, With Intermittent Major Depressive Episodes, Without Current Episode	None
11	Major Depressive Disorder, Recurrent Episode, In Partial Remission	Social Anxiety Disorder
12	Persistent Depressive Disorder, In Full Remission, With Intermittent Major Depressive Episodes, Without Current Episode	Social Anxiety Disorder Binge-Eating Disorder, In Partial Remission
13	Major Depressive Disorder, Recurrent Episode, In Partial Remission, With Seasonal Pattern	None

<b>Participant</b>	<b>Depressive Disorder Diagnoses</b>	<b>Other Current Diagnoses</b>
14	Persistent Depressive Disorder, With Anxious Distress, In Partial Remission, Early Onset, With Intermittent Depressive Episodes, Without Current Episode	Social Anxiety Disorder
15	Major Depressive Disorder, Recurrent Episode, In Full Remission, With Anxious Distress	None
16	Persistent Depressive Disorder, With Anxious Distress, In Full Remission, Early Onset, With Intermittent Major Depressive Episodes, Without Current Episode	None
17	Major Depressive Disorder, Recurrent Episode, In Full Remission, With Anxious Distress	None
18	Major Depressive Disorder, Recurrent Episode, In Full Remission	None
19	Other Specified Depressive Disorder (Depressive episode with insufficient symptoms)	None
20	Major Depressive Disorder, Recurrent Episode, In Partial Remission	None
21	Major Depressive Disorder, Recurrent Episode, In Partial Remission	Generalized Anxiety Disorder Posttraumatic Stress Disorder
22	Persistent Depressive Disorder, With Intermittent Major Depressive Episodes, Without Current Episode, Moderate	None
23	Other Specified Depressive Disorder (Short-duration depressive episode)	None
24	Major Depressive Disorder, Recurrent Episode, In Partial Remission	Social Anxiety Disorder

Table S1c. Depression Group: **Current MDD**

<b>Participant</b>	<b>Depressive Disorder Diagnoses</b>	<b>Other Current Diagnoses</b>
1	Persistent Depressive Disorder, Early Onset, With Intermittent Major Depressive Episodes, With Current Episode, Mild	Posttraumatic Stress Disorder, With Dissociative Symptoms
2	Major Depressive Disorder, Recurrent Episode, Moderate	Social Anxiety Disorder Generalized Anxiety Disorder
3	Persistent Depressive Disorder, Early Onset, With Intermittent Major Depressive Episodes, With Current Episode, Moderate	Social Anxiety Disorder Binge-Eating Disorder, Mild
4	Persistent Depressive Disorder, Early Onset, With Intermittent Major Depressive Episodes, With Current Episode, Moderate	None
5	Major Depressive Disorder, Recurrent Episode, Moderate	Social Anxiety Disorder, Performance Only Binge-Eating Disorder, In Partial Remission
6	Major Depressive Disorder, Single Episode, Mild, With Anxious Distress	Specific Phobia, Animal Social Anxiety Disorder
7	Major Depressive Disorder, Recurrent Episode, Moderate	Social Anxiety Disorder Agoraphobia with Panic Attacks
8	Major Depressive Disorder, Recurrent Episode, Severe, With Anxious Distress, With Seasonal Pattern	Social Anxiety Disorder
9	Persistent Depressive Disorder, Early Onset, With Persistent Major Depressive Episode, Moderate	Social Anxiety Disorder Specific Phobia, Blood-Injection-Injury Posttraumatic Stress Disorder with Panic Attacks, With Dissociative Symptoms
10	Persistent Depressive Disorder, With Intermittent Major Depressive Episodes, With Current Episode, Moderate	None
11	Major Depressive Disorder, Recurrent Episode, Moderate	Generalized Anxiety Disorder with Panic Attacks Social Anxiety Disorder
12	Persistent Depressive Disorder, With Anxious Distress, Early Onset, With Persistent Major Depressive Episode, Moderate	Social Anxiety Disorder Posttraumatic Stress Disorder with Panic Attacks
13	Major Depressive Disorder, Recurrent Episode, Moderate	Specific Phobia, Natural Environment

<b>Participant</b>	<b>Depressive Disorder Diagnoses</b>	<b>Other Current Diagnoses</b>
14	Persistent Depressive Disorder, With Anxious Distress, With Persistent Major Depressive Episode, Moderate	Generalized Anxiety Disorder Obsessive Compulsive Disorder, With Good Insight Specific Phobia, Natural Environment Posttraumatic Stress Disorder
15	Major Depressive Disorder, Recurrent Episode, Moderate, With Anxious Distress	Bulimia Nervosa, In Partial Remission



**Table S2. Pictures Presented During Memory Encoding from the International Affective Picture System (IAPS) (1).** These picture sets are psychometrically matched on affective valence (i.e., pleasantness) and arousal with minimal content overlap to support testing of memory formation in a repeated measures design.

Set A			
1202	3150	7040	8312
1340	3170	7057	8380
1670	3195	7090	8492
1710	4597	7130	8496
1720	4612	7175	8502
1999	5215	7217	9008
2102	5450	7224	9210
2205	5534	7230	9250
2300	5629	7234	9300
2310	5731	7300	9342
2347	5829	7400	9415
2357	5910	7405	9421
2393	6020	7491	9429
2397	6241	7501	9440
2411	6563	7508	9471
2456	6838	7700	9561
2518	7001	8090	9599
2688	7002	8185	9620
2692	7026	8200	9810
2840	7034	8280	9902
3063	7037	8300	9927

Set B			
1111	2890	7050	8186
1463	2900.1	7060	8370
1650	3019	7100	8460
1811	3062	7140	8497
2045	3160	7205	8531
2154	3261	7233	9040
2156	4624	7255	9186
2191	5301	7330	9187
2216	5460	7350	9220
2221	5471	7359	9404
2272	5833	7451	9409
2377	5971	7470	9413
2384	6150	7502	9426
2396	6250	7650	9435
2480	6415	7710	9470
2550	7000	7950	9520
2593	7010	8001	9560
2595	7019	8030	9611
2694	7020	8116	9800
2710	7038	8163	9832
2880	7045	8180	9922

**Table S3. Raw Cortisol Levels (in  $\mu\text{g/dL}$ ) for Samples Collected at Home Before and After Dexamethasone Administration by Group**Table S3a. Depression Group: **Never Depressed**

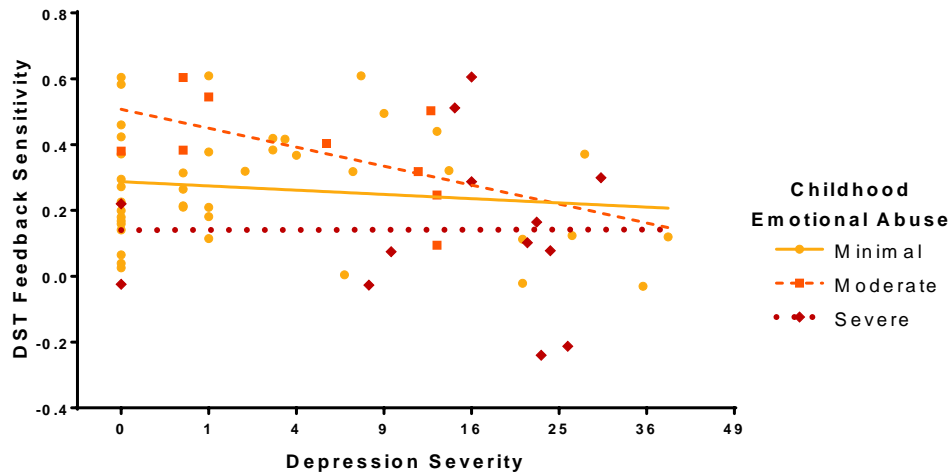
Participant	Pre-Dexamethasone Cortisol Levels for the Morning Peak Sample (averaged across Days 1-3)	Post-Dexamethasone Cortisol Levels for the Morning Peak Sample on Day 4
1	0.440	1.023
2	0.514	0.832
3	0.376	0.793
4	0.314	0.918
5	1.072	1.097
6	0.930	0.969
7	0.341	0.613
8	0.174	0.634
9	0.209	0.632
10	0.213	0.590
11	0.207	0.579
12	0.291	0.315
13	0.252	0.317
14	0.079	0.304
15	0.031	0.414
16	0.227	0.607
17	0.061	0.325
18	0.242	0.383
19	0.155	0.269
20	0.322	0.726
21	0.062	0.276
22	0.090	0.699
23	0.086	0.469
24	0.443	0.624
25	0.562	0.537
26	0.192	0.737

Table S3b. Depression Group: **Other Depression**

<b>Participant</b>	<b>Pre-Dexamethasone Cortisol Levels for the Morning Peak Sample (averaged across Days 1-3)</b>	<b>Post-Dexamethasone Cortisol Levels for the Morning Peak Sample on Day 4</b>
1	0.542	0.836
2	0.323	0.482
3	0.054	0.264
4	0.494	0.812
5	0.045	0.548
6	0.101	0.310
7	0.379	0.473
8	0.022	0.389
9	0.027	0.206
10	0.687	0.906
11	0.723	0.696
12	0.076	0.275
13	0.028	0.275
14	0.684	0.759
15	0.605	1.209
16	0.083	0.502
17	0.307	0.475
18	0.509	0.823
19	0.219	0.590
20	0.338	0.342
21	0.015	0.302
22	0.052	0.547
23	0.336	1.088
24	0.352	0.792

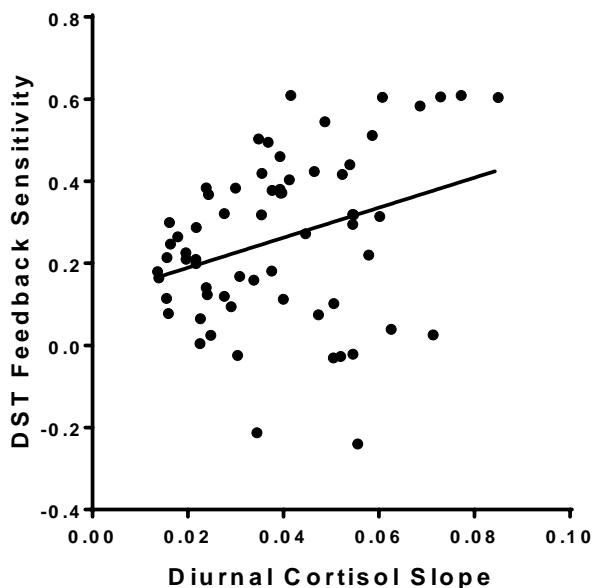
Table S3c. Depression Group: **Current MDD**

<b>Participant</b>	<b>Pre-Dexamethasone Cortisol Levels for the Morning Peak Sample (averaged across Days 1-3)</b>	<b>Post-Dexamethasone Cortisol Levels for the Morning Peak Sample on Day 4</b>
1	0.269	0.780
2	0.895	0.865
3	0.048	0.213
4	0.161	0.239
5	0.228	0.351
6	0.001	0.322
7	0.293	0.412
8	0.674	0.653
9	0.387	0.992
10	1.065	0.824
11	0.426	0.743
12	0.685	0.472
13	0.451	0.563
14	0.007	0.306
15	0.716	0.817



**Figure S1. Scatter Plot Illustrating Relations Among Childhood Emotional Abuse (EA), Depression Severity, and Dexamethasone Suppression Test (DST) Feedback Sensitivity**

Regression slopes shown in color (see legend) are based on Childhood Trauma Questionnaire (CTQ) Emotional Abuse (EA) groups. When both EA and depression severity were included in the model predicting DST feedback sensitivity, there was a marginal association between EA and feedback sensitivity,  $F(2,59) = 2.84$ ,  $p = 0.07$ , with a relative pattern of severe EA associated with reduced feedback sensitivity and moderate EA associated with enhanced feedback sensitivity relative to minimal EA (illustrated in figure). Despite the appearance of an interaction with depression severity in the plot, the interaction between EA and depression severity was not significant,  $F(2,59) = 0.63$ , *n.s.* These findings may suggest that history of severe early adverse caregiving is related to feedback sensitivity across the continuum of depression severity, which as described in the main text of the article, is also associated with reduced feedback sensitivity. Both severe depression and severe EA appear to be associated with reduced feedback sensitivity. In addition, our findings may suggest that moderate EA is associated with enhanced feedback sensitivity, but our sample size of women with moderate EA ( $n = 9$ ) is too small to draw a firm conclusion. For display purposes, Beck Depression Inventory II (BDI-II) scores are square-root transformed to reduce skew and back-transformed to maintain the original BDI-II score range as done in previous research (2,3). We also ran the analyses with CTQ total scores. When we use CTQ-total score (either the continuous score or categorical groups based on validated cut-offs) no new findings emerge and the marginal association with DST feedback sensitivity disappears,  $p$ 's  $> 0.19$ .



**Figure S2. Scatter Plot Illustrating Relations Among Dexamethasone Suppression Test (DST) Feedback Sensitivity and Diurnal Cortisol Slope Across All Participants**

Diurnal cortisol slope was computed as reported by Jarcho et al. (4), in which slope was the absolute value of the change in cortisol levels from the morning peak sample to the 10 PM sample divided by the time between the two samples, averaged across Days 1-3. Higher numbers indicate a steeper diurnal cortisol slope. When collapsing across depression and emotional abuse (EA) groups, diurnal cortisol slope and DST feedback sensitivity were positively correlated,  $r(64) = 0.32$ ,  $p = 0.01$ , such that steeper decline of cortisol throughout the day was related to greater feedback sensitivity (i.e., more DST suppression). When including EA and depression severity in the model, diurnal cortisol slope remained a significant predictor of DST feedback sensitivity,  $F(1,53) = 7.87$ ,  $p = 0.007$  and did not interact with either EA or depression severity,  $p$ 's  $> 0.12$ .

**Supplemental References**

1. Lang PJ, Bradley MM, Cuthbert BN (2008): *International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8*. Gainesville, FL: University of Florida.
2. Roelofs J, van Breukelen G, de Graaf LE, Beck AT, Arntz A, Huibers MJH (2013): Norms for the Beck Depression Inventory (BDI-II) in a large Dutch community sample. *J Psychopathol Behav* 35: 93-98.
3. van Minnen A, Wessel I, Verhaak C, Smeenk J (2005): The relationship between autobiographical memory specificity and depressed mood following a stressful life event: a prospective study. *The British journal of clinical psychology / the British Psychological Society* 44: 405-415.
4. Jarcho MR, Slavich GM, Tylova-Stein H, Wolkowitz OM, Burke HM (2013): Dysregulated diurnal cortisol pattern is associated with glucocorticoid resistance in women with major depressive disorder. *Biol Psychol* 93: 150-158.