Reward-related Neural Predictors and Mechanisms of Symptom Change in Cognitive Behavioral Therapy for Depressed Adolescent Girls

Supplemental Information

Supplemental Methods

Participants

As expected, at the initial assessment session depression (Beck Depression Inventory-II; BDI-II (1)) scores were significantly higher in the MDD group (M = 33.00, SD = 11.14) relative to the HC group (M = 1.38, SD = 1.82)($t(63) = 16.76$, $p < .001$; Cohen's $d = 3.96$). At baseline, the MDD group also had significantly elevated anxiety (relative to HC) on the self-report Multidimensional Anxiety Scale for Children (MASC)(4) ($t(62.5)=6.19$, $p < .001$; Cohen's $d = 1.49$) and twelve MDD participants met criteria for a comorbid diagnosis of current GAD. MDD participants were, on average, approximately 1 year older than HC participants (15.83 ± 1.70 vs. 14.93 ± 1.56) ($t(63) = 2.21$, $p = .03$). As described in the analytic approach section, age was included as covariate in our analyses. Groups did not differ in terms of race ($\chi^2(4) = 2.66$, $p = .62$), with participants endorsing the following races: 75.4% White, 7.7 % Asian, 1.5% Black or African-American, 13.8% multiple races, and 1.5% not reported.

Therapists

Nine therapists (6 females) delivered 12 weeks of CBT (one 50-minute session per week) based on the following treatment manual of CBT for depressed adolescents (2). Four of the therapists were PhD-level clinical psychologists, and the other five were advanced Ph.D.

candidates in clinical psychology doctoral programs. Therapists received 1-hour of individual supervision per week by licensed psychologists (CAW & RPA).

Measures

The Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present (K-SADS-PL) (3)**.** The K-SADS-PL is a semi-structured clinical interview for assessing current and past *Diagnostic and Statistical Manual of Mental Disorders* (4^{th} ed.) disorders. The interviews were conducted by clinical psychology doctoral students and bachelor- level research assistants after receiving 40 hours of training (didactics, mock interviewing, direct supervision). The interviews were recorded, and twenty percent were selected at random to assess interrater reliability. The Cohen's kappa coefficients for depressive disorders were strong ($\kappa = 1.00$).

Beck Depression Inventory-II (BDI-II) (1)**.** The BDI-II is a 21-item self-report measure of depressive symptoms, and was administered every session in the MDD group and at each assessment in the HC group. Participants provide a score on each item from 0 to 3, with higher scores demonstrating higher levels of depressive symptoms. At each assessment, participants were asked to report on their depressive symptoms over the past week. Internal consistency in present sample was $\alpha = .98$ for the initial assessment.

Multidimensional Anxiety Scale for Children (MASC) (4)**.** The MASC is a 39-question self-report inventory to assess anxiety symptoms, and was administered every other session in the MDD group and at each assessment in the HC group. Internal consistency in present sample was $\alpha = .94$ for the initial assessment.

Experimental Task

The tones were constructed from a sine wave of linearly increasing/decreasing frequency: 400 to 1,320 Hz (Audacity software, http://audacity.sourceforge.net). Following each trial, a

fixation cross was presented for 1,000 ms. The magnitude of monetary rewards was double the magnitude of losses in order to approximately equate the subjective value of win and loss trials (see 5). The task included equal numbers of win and loss trials (90 each) presented over six blocks of 24-36 trials per block.

Each presentation of a green or red ball was superimposed onto one of three monochrome abstract pattern backgrounds. The gambling task described in the main text was embedded within an implicit preference conditioning procedure in which rewards and losses were paired with background patterns in a pre-determined pattern-reward/pattern-loss contingency. Namely, Pattern A was paired with reward feedback on 90% of trials and with loss feedback on 10% of trials. Pattern B was paired with rewards and losses each on 50% of trials, and Pattern C was accompanied with rewards on 10% of trials and losses on 90% of trials. Participants were counterbalanced across three versions of the task in order to avoid pattern-specific effects on preferences, and were administered different versions of the task at the follow-up assessments (i.e., "mid" and "final" EEG). Task version (A-C) was included as a covariate in relevant analyses. Participants were asked to estimate the number of green balls (i.e., reward feedback) they saw in each block in order to minimize participants' attention toward a preference conditioning procedure within the task. Following the guessing portion of the task, participants completed a subsequent behavioral task (judgment phase) that assessed preferences for the patterns presented. The second phase of this task (i.e., assessment of pattern preferences) were not the focus of this manuscript, and has been previously reported in a separate publication (6). Participants earned $12.45 - $14.70 from the gambling task, depending on the task version (and earned $40 for each of the two baseline assessments)

For the HC vs. the MDD group, the mean number of days between the initial and mid EEG/task assessment were 33.96 ± 11.6 vs. 37.89 ± 13.94, respectively ($t(50) = 1.11$, $p = .27$) and between the mid and final EEG (64.74 ± 21.7 vs. 77.48 ± 11.88, $t(42) = 2.44$, $p = .02$). As reported below, analyses remained significant when controlling for number of days between EEG assessments.

EEG Recording and Processing

Data were collected at a sampling rate of 250 Hz, referenced to Cz. Electrode impedances were kept below 75 kΩ. Data were re-referenced to the average of the two mastoid electrodes, and high-pass (0.1 Hz) and low-pass (30 Hz) filters were applied. Vertical and horizontal eye movement artifacts were identified and corrected using independent component analysis. Additionally, EEG channels with a high number of channel-specific artifacts were replaced with interpolated data based on the surrounding channels (spline interpolation (7)). Individual channel segments were rejected from analysis according to the following criteria for defining artifacts: (a) a voltage step > 50 μV between consecutive sample points, (b) a voltage difference > 300 μV within a trial, and (c) a maximum voltage difference of < 0.50 μV within any 100 ms interval. Additionally, all trials were subjected to channel-specific artifact rejection based on visual inspection. Groups did not differ in the percent of collected data that were unanalyzable due to artifact (HC median = 9.10% and MDD median = 9.35%; $t(63) = .705$, $p = .483$).

Time-Frequency Variables

For time-frequency analyses, a continuous wavelet transformation was implemented. Relative to time-domain analyses, a wider time window was utilized (-1,500 ms to 1,500 ms) to mitigate edge effects (6,8,9), and artifact rejection was conducted according to the steps described above. Time-frequency data were baseline corrected using the interval from -500 to -300 ms

prestimulus. To generate a measure of total power, wavelet-transformed data were averaged by subject and condition (win, loss). Wavelet layers corresponding to delta (central frequency: 2.3 Hz; spectral bandwidth: 1.32 Hz) and theta (central frequency: 5.6 Hz; spectral bandwidth: 3.2 Hz) activity were extracted (6). As in prior work, theta power was maximal at frontocentral electrodes and was computed as the mean activity at FCz from 250-350 ms poststimulus (6,8,10). By contrast, delta activity was centroparietally distributed and was scored as the mean activity at CPz from 200-400 ms poststimulus.

Supplemental Results

Sensitivity Analysis

The analysis revealing a significant *Group* x *Time* x *Condition* interaction for theta power was rerun (1) excluding the mid EEG assessment (i.e., only including data from initial and final EEG assessments), (2) including number of days between EEG assessments as a covariate, and (3) with imputed missing values. First, when excluding the mid EEG assessment, the *Group* x *Time* x *Condition* interaction remained significant for theta power, $F(1,41) = 7.56$, $p = 0.009$, $\eta^2 = 0.16$, such that the MDD group exhibited greater pre- to post-treatment reductions in theta response to losses relative to the HC participants. Similarly, the 3-way interaction remained significant when including the number of days between the initial and final EEG assessments as a covariate, $F(1,36) = 3.47$, $p = 0.042$, $\eta^2 = 0.16$. Finally, missing data were imputed via a Random Forest (RF) approach (missForest (11) package in R (12)). Four HC participants and 13 MDD participants dropped out prior to the final assessment. Three additional MDD participants were missing final EEG data due to EEG system malfunction (e.g., event markers not recorded, electrodes malfunctioning). MissForest generates a single imputed dataset based on averaging across multiple

regression trees. Inputs for imputation included baseline variables as well as longitudinal symptom data (BDI-II and MASC) and EEG/ERP variables (RewP, LPP, Delta and Theta to wins and losses). When analyses were rerun on the imputed dataset, the *Group* x *Time* x *Condition* interaction remained significant for Theta power, $F(1,60) = 3.50$, $p = 0.037$, $\eta^2 = 0.10$.

Comparing Pre-treatment LPP to Rewards Between HC and MDD Symptom Change Groups

In response to an anonymous reviewer, we dichotomized (via median split) the MDD group on the basis of the slope of symptom change derived from a multilevel model (i.e., modeling the effect of *Time*). This yielded MDD groups with (1) relatively greater (mean slope = -1.85) vs. (2) less (mean slope = -0.30) depressive (BDI-II) symptom change. An ANCOVA testing for group (HC and the latter two MDD groups) differences in the LPP to rewards (adjusting for LPP to losses, age, medication and task version) yielded a non-significant trend $F(2, 54) = 2.53$, $p = 089$). Although non-significant, the MDD group with greater symptom change had the numerically largest LPP to rewards, followed by the HC participants and finally the MDD group with less symptom change (Mean amplitude for LPP to rewards = 4.72, 3.39 & 3.20, respectively).

Examining the LPP at Different Electrode Sites

With regards to the LPP sites, we made an *a priori* decision to use the identical electrodes and timeframe for each ERP and time-frequency measure as Webb et al. (6), which reported the between-group differences in baseline/pre-treatment LPP and RewP (and both theta and delta) findings for the current treatment study. Specifically, consistent with the latter baseline/pre-treatment data publication (also see, e.g., 12,13), the LPP was examined across the average of frontocentral midline electrode sites Fz, FCz, and Cz from 600 to 1,000 ms poststimulus. The scalp topography of the LPP difference wave was distributed across frontal regions. If analyses are re-

run selecting the frontal electrodes at which the LPP to wins was maximal for the MDD group, the same pattern of finding emerges with a larger LPP to wins predicting greater depressive symptom improvement (for EEG17: $t(21.9) = 3.90$, $p < .001$; FPz-21: $t(24.2) = 3.62$, $p = .001$; and FPz-15: $t(27.0) = 2.18$, $p = .038$)). In addition, in response to an anonymous reviewer, we examined the LPP at more posterior electrode sites (Pz and CPz). For the MDD sample, the mean amplitude of the difference (wins minus losses) scores were near 0 (Pz = 0.00; CPz = -0.14), suggesting little to no differentiation of the LPP to wins vs losses at these more posterior electrodes (for HC, Pz = 0.21; CPz = 0.92). In addition, we re-ran our LPP multilevel models predicting treatment outcome substituting in the LPP to wins and losses at CPz and Pz. Neither the LPP (at CPz) to wins ($b = 0.14$, $p = .653$) or losses ($b = 0.10$, $p = .722$) predicted depressive symptom change. A larger LPP (at Pz) to losses ($b = 0.57$, $p = .042$), but not wins ($b = -0.27$, $p = .376$), predicted greater depressive symptom change. However, in contrast to the LPP analyses in the main text, when controlling for the significant Delta to losses effect, the LPP (at PZ) to losses was no longer significant ($b = 0.28$, $p = .196$).

Supplemental References

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Supplemental Table S1. *Correlations between time-domain and time-frequency variables*

Variable	1	2	3	4	5	6	7
1. RewP_Win							
2. RewP/FRN_Loss	.86**						
3. LPP_Win	.14	.05					
4. LPP_Loss	.19	.15	.82**				
5. Theta_Win	.00	-.03	-.02	.11			
6. Theta_Loss	.15	-.04	-.07	.00	.40**		
7. Delta_Win	.46**	.28*	.20	.21	.21	.50**	
8. Delta_Loss	.35**	.30*	.11	.09	.25*	.12	.27*

Note. Based on baseline data combining both groups. * indicates $p < .05$. ** indicates $p < .01$.

Supplemental Table S2. *Internal reliability (correlation between odd and even trials)*

Variable	HC	MDD
RewP_Win	.98**	.93**
RewP/FRN_Loss	.93**	.94**
LPP_Win	.98**	.98**
LPP_Loss	.98**	.99**
Theta_Win	.76**	.62**
Theta_Loss	.71**	.87**
Delta_Win	.78**	.94**
Delta_Loss	.95**	.79**

Note. Correlations adjust for the Spearman-Brown prophecy formula and are based on baseline data. * indicates $p < .05$. ** indicates $p < .01$.

Supplemental Table S3. *Test-retest reliability*

Time	Initial-Mid EEG			Initial-Final EEG		
Variable	HC	MDD	All	HC	MDD	All
RewP_Win	.60**	.82**	.73**	.62**	.88**	.75**
RewP/FRN_Loss	.64**	.85**	.73**	.64**	.88**	.76**
LPP_Win	.57**	.61**	.58**	.49*	.75**	.54**
LPP_Loss	.60**	.68**	.65**	.37	.53*	.46**
Theta_Win	.43*	.48*	.45**	.33	.58**	.48**
Theta_Loss	.35	.53**	.44**	.55*	.31	.46**
Delta_Win	.23	.46*	.36*	.32	.24	.29*
Delta_Loss	.61**	.57**	.55**	.54**	.36	.45**

Note. HC = Healthy Controls; MDD = Major Depressive Disorder; All = All subjects (both groups combined). * indicates $p < .05$. ** indicates $p < .01$.