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Reward-related neural predictors and mechanisms of symptom change in cognitive behavioral therapy for depressed adolescent girls

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Abstract

Background: Approximately half of depressed adolescents fail to respond to cognitive behavioral therapy (CBT). Given the variability in response, it is important to identify pre-treatment characteristics that predict prognosis. Knowledge of which depressed adolescents are likely to exhibit a positive vs. poor outcome to CBT may have important clinical implications (e.g., informing treatment recommendations). Emerging evidence suggests that neural reward responsiveness represents one promising predictor.

Method: Adolescents with major depressive disorder (n = 36) received CBT and completed a reward task at three timepoints (pre-treatment, mid-treatment and post-treatment) while 128-channel electroencephalogram (EEG) data were acquired. Healthy control participants (n = 29) completed the same task at three corresponding timepoints. Analyses focused on event-related potentials (ERPs) linked to two stages of neural processing: initial response to rewards (reward-related positivity [RewP]) and later, elaborative processing (late positive potential [LPP]). Moreover, time-frequency analyses decomposed the RewP into two constituent components: reward-related delta and loss-related theta activity.

Results: Multilevel modeling revealed that greater pre-treatment reward responsiveness, as measured by the LPP to rewards, predicted greater depressive symptom change. In addition, a *Group* x *Condition* x *Time* interaction emerged for theta activity to losses, reflecting normalization of theta power in the MDD group from baseline to post-treatment.

Conclusions: An ERP measure of sustained (LPP)—but not initial (RewP)—reward responsiveness predicted symptom improvement, which may help inform which depressed

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adolescents are most likely to benefit from CBT. In addition to alleviating depression, successful CBT may attenuate underlying neural (theta) hypersensitivity to negative outcomes in depressed youth.

Keywords

Cognitive Behavioral Therapy; Depression; Reward Positivity; Time Frequency Decomposition; Late Positive Potential; Adolescence

Introduction

Depression rates increase substantially during adolescence, and by age 18, an estimated 15% of teens will have experienced at least one episode of major depressive disorder (MDD), with females twice as likely as males to have developed MDD (1). Despite these alarming statistics, approximately 40-66% of adolescents do not receive treatment for their depression (1,2). A range of psychotherapeutic and pharmacological treatment options are available for depressed adolescents, and cognitive behavioral therapy (CBT) is among the most empirically supported intervention (3). However, approximately 40-50% of depressed youth fail to respond to CBT (3,4). Given the variability in response, it is important to identify pre-treatment patient characteristics that predict treatment prognosis, as this may have important clinical implications regarding treatment recommendations (e.g., suggesting a more intensive, alternative or combination treatment for those individuals predicted to have a poor response to CBT)(5,6).

Reward-Related Predictors of Treatment Outcome

Several studies have identified pre-treatment neural response to rewards as a predictor of treatment outcome among adults (7,8) and youth (9,10) receiving CBT or SSRI. To assess neural reward responsiveness, researchers have utilized the *reward positivity* (RewP), an event-related potential (ERP) most commonly examined within monetary reward tasks (11). The RewP, also known as the *feedback-related negativity* (FRN), is a frontocentral ERP component occurring approximately 250-350ms following rewarding feedback (relative to losses or the omission of rewards). Studies combining ERPs and functional magnetic resonance imaging (fMRI) reveal that the RewP is associated with activation of the mesocorticolimbic reward circuit, including the ventral striatum and medial prefrontal cortex (12,13). Two initial studies in adults with anxiety and/or depression indicated that a reduced pre-treatment RewP (i.e., reflecting blunted reward responsiveness) predicted greater depressive symptom improvement to CBT (8) and SSRI (7, but see 14). Similarly, a more recent study (9) in a sample of children and adolescents with generalized anxiety disorder (GAD) or social anxiety disorder (SAD) receiving CBT or SSRI reported that a reduced RewP to monetary rewards predicted greater depressive—but not anxiety—symptom improvement. Although sample size was small (n = 16 for CBT; n = 11 for SSRI), exploratory analyses suggested that the pattern of reduced RewP predicting depressive symptom change was specific to CBT, and not SSRI. Taken together, these findings are consistent with a “compensatory” model, such that CBT may be well-suited to those with blunted—rather than intact or enhanced—reward responsiveness. However, the first two studies (7,8) focused on adults, whereas the latter study (9) included children and

adolescents with GAD or SAD, none of whom had current MDD. The extent to which a blunted RewP to rewards predicts better outcome in CBT for depressed adolescents is unknown. In addition, it may be that depression-related abnormalities in the RewP (11) improve or normalize following successful CBT. CBT may exert its beneficial effects at least in part through ameliorating depression-related deficits in the neural processing of rewards (e.g., via behavioral activation skills aimed at systematically increasing exposure to and engagement with rewarding activities and experiences)(15) and/or attenuating neural hyperreactivity to negative outcomes (e.g., via cognitive reappraisal skills). Of relevance, recent research using time-frequency decomposition approaches reveals that the RewP consists of both delta (< 3 Hz) and theta (4-7 Hz) activity (16–18). Critically, these studies indicate that, whereas delta activity is more sensitive to rewards than losses, theta activity displays the opposite pattern. As a result, time-frequency decomposition may isolate “purer” and more distinguishable measures of neural responsiveness to rewards (delta) vs. losses (theta) than traditional time-domain ERPs. The extent to which CBT modulates these two time-frequency measures of sensitivity to rewards vs. losses is unknown.

Late Positive Potential

In contrast to the RewP, the LPP is a later ERP component (beginning approximately 300 ms post-stimulus and lasting several hundred ms or seconds) linked to the elaborative processing of emotional or motivationally salient stimuli (including–but not specific to–rewards). The LPP is initially observed over parietal regions and then propagates to frontal electrodes later in its time course (19). Previous research has shown that the LPP is enhanced to emotional words, images and rewards, which is consistent with the notion that this ERP reflects sustained cognitive processing of motivationally salient stimuli. The LPP has been shown to be enhanced to monetary rewards in adolescent (16,20) and young adult samples (21). For example, Webb et al.(16) found potentiated LPPs to monetary rewards relative to losses in healthy adolescent girls, and the opposite pattern in depressed teens. Notably, a recent study indicated that a blunted RewP (to monetary rewards) and LPP (to pleasant pictures) are independent predictors of MDD status (i.e., account for unique variance in depression)(22). The extent to which the RewP and LPP account for significant and unique variance in predicting treatment outcome among depressed youth has yet to be examined. Interestingly, and of relevance to CBT, previous research has shown that the LPP can be modulated via cognitive reappraisal (23–26). Accordingly, given its emphasis on the development of cognitive reappraisal skills, successful CBT may modulate the LPP. In addition, pre-treatment LPP may predict depression treatment outcome. For example, Barch et al.(14) recently found that a larger pre-treatment LPP to pleasant pictures predicted better outcomes for young depressed children (4-7 years of age) who received Parent Child Interaction Therapy (PCIT). The latter finding suggests that relatively enhanced elaborative processing of rewarding or positive stimuli among depressed youth may signal an increased likelihood of benefiting from psychotherapy.

The Present Study

The present study tested (1) whether the RewP and/or LPP, assessed at pre-treatment, predict symptom change among depressed adolescents receiving CBT; and (2) the extent to which a course of CBT modulates the RewP and LPP, while addressing several limitations in the

literature. First, none of the abovementioned studies (7–9,14) testing the RewP as a predictor of treatment outcome examined whether these effects were attributable to reward-related delta and/or loss-related theta activity. As described above, the latter two components of the RewP can be disaggregated via time-frequency decomposition. Second, with the exception of one study (14), prior research testing neural predictors of treatment response in depression focused on *either* initial (RewP)(7–9) or later (LPP)(27) neural stages of processing. To test whether early or later neural responsiveness to rewards predicts outcome, we simultaneously examined an ERP probing initial neural responsiveness to rewards (RewP) and later, elaborative processing of rewards (LPP). Given their excellent temporal resolution, ERPs can distinguish between initial vs. later stages of reward responsiveness (28). Finally, with the exception of one recent study of PCIT in young children which included three EEG timepoints (29), prior studies have relied on a single pre-treatment neural assessment (8,9) or pre- and post-treatment measures (7,14). These designs do not allow for the examination of the time course of change in neural abnormalities. For example, similar to the commonly observed curvilinear pattern of depressive symptom change (i.e., greater change early in treatment) in psychotherapy and pharmacotherapy (30–33), neural changes may not be linear. To address a gap in the treatment literature, in the present study we included pre-, mid- and post-treatment EEG assessments.

In summary, based on prior literature (e.g., 7, 8, 9, 14), we hypothesized that blunted delta power to rewards during the timeframe of the RewP and potentiated LPP to rewards will predict greater depressive symptom improvement in CBT for depressed adolescents. In addition, we expected pre- to post-treatment increases in neural sensitivity to rewards (i.e., reflected by increased delta power) and decreased reactivity to losses (i.e., decreased theta power).

Methods and Materials

Participants

Female adolescents (MDD = 36; Healthy Controls [HC] = 33) ages 13-18 years were recruited from the local greater Boston area via community and internet advertisements. All participants were fluent in English and right-handed. Participants in the MDD group were required to meet DSM-IV criteria for a current major depressive episode according to the K-SADS-PL (34). Exclusion criteria for HC participants included a history of MDD, bipolar disorder, psychosis (including mood disorder with psychotic features), anxiety disorders, eating disorders, substance use disorders, attention-deficit/hyperactivity disorder, mental retardation, organic brain syndrome, and head injury with loss of consciousness for ≥5 min or seizures. Similarly, MDD participants could not meet current criteria for any of the above diagnoses (other than MDD [without psychotic features]), with the exception of a secondary diagnosis of generalized anxiety disorder (GAD; n=12). With regards to medications, four participants were prescribed a selective serotonin reuptake inhibitor (SSRI). See Supplement for additional details.

Procedure

Study approval was provided by the Partners Health Care Institutional Review Board. The baseline assessment was conducted over 2 days. On Day 1, adolescents were administered the K-SADS-PL to assess lifetime mental disorders and completed self-report measures of depressive and anxiety symptoms. On Day 2, adolescents completed a monetary reward gambling task while 128-channel EEG data were recorded. Following Day 2, the MDD group were offered 12 weekly sessions of CBT (one 50-minute session per week) based on the following manual (35)(for additional details, see (16)). The EEG assessment and monetary reward task were re-administered 5 weeks after the initial assessment and at post-treatment. The HC participants, who did not receive treatment, completed EEG assessments and the reward task at three corresponding timepoints (n=4 were excluded due to poor EEG quality). For simplicity and consistency of terms across groups, we henceforth refer to these EEG assessments as “initial”, “mid” and “final”. Baseline (i.e., pre-treatment) clinical and EEG data have previously been published on a subset (51/65) of these participants (16,36).

Measures

Depressive symptoms were assessed via the Beck Depression Inventory-II (BDI-II)(37). Both the MDD and HC participants completed the BDI-II at each assessment. The MDD group completed additional BDI-II assessments at the start of each therapy session. Anxiety symptoms were assessed via the Multidimensional Anxiety Scale for Children (MASC)(38), and administered every other session in the MDD group and at each assessment in the HC group.

Experimental Task.—Participants completed a 180-trial monetary reward gambling task while EEG data were recorded (39–41,16). On each trial, participants were presented with three black boxes and instructed to guess which box contained a green ball (the other boxes contained red balls) using a button box. If participants identified the correct box, the green ball was presented for 2,500 ms along with a rising tone (500 ms), which indicated a monetary gain of 30 cents. If a participant selected a box with a red ball, the red ball would appear for 2,500 ms alongside a falling tone (500 ms) and a monetary loss of 15 cents. There were 90 win and 90 loss trials. For additional details, see Supplement and (16).

EEG Recording and Data Reduction

EEG data were recorded using a 128-channel HydroCel Geodesic Sensor Net (Electrical Geodesics, Inc., Eugene, OR) in an electrically and acoustically shielded room. BrainVision Analyzer 2.1.1 (Brain Products, Munich, Germany) was used for EEG data processing. For time-domain analyses, EEG data were segmented from 200 ms before stimulus onset (win or loss feedback) up to 1,000 ms after stimulus onset. A baseline correction was applied using the average amplitude over 200 ms prior to stimulus onset. Consistent with prior work (16), RewP values were computed as the mean amplitude from 250-350 ms post-stimulus at electrode FCz (see Figure 1, Panel A), and the LPP was assessed using the average of frontocentral midline electrode sites (Fz, FCz, and Cz) between 600-1,000 ms post-stimulus (16,36,42,43)(Figure 2). For time-frequency analyses, and consistent with prior work isolating RewP-linked theta and delta power (16), a complex Morlet wavelet transformation

was applied (Morlet parameter $c = 3.5$) from 0.5 to 20 Hz using 30 frequency steps distributed on a logarithmic scale (44)(Figure 1, Panel B). See Supplement for additional details.

Analytic approach

Given the longitudinal, multilevel data structure (i.e., repeated depressive symptom assessments nested within patients), we used a multilevel modeling (MLM; via lme4 (45) and lmerTest (46) packages in R) approach to test whether pre-treatment time-domain (RewP & LPP) and time-frequency (theta and delta power) variables predict depressive symptom improvement. Specifically, to test whether the RewP to wins and/or losses predict symptom change, an MLM simultaneously including $RewP_{Wins}$ x *Time* and $RewP_{Losses}$ x *Time* interactions was modeled (*Time* centered to represent estimated post-treatment BDI-II scores, while adjusting for pre-treatment BDI-II scores).[1] Corresponding models were run for the LPP, theta power, and delta power (i.e., similar to the above RewP model, including the win and loss interactions in the same model). As stated above, our primary hypotheses focused on whether (1) the delta power to rewards (during the timeframe of the RewP) and (2) the LPP to rewards predicted depression outcome (BDI-II total score). In each model, intercepts and slopes were treated as randomly varying across patients. To adjust for the effect of age, antidepressant medication (on SSRI vs not), and task version (versions A, B or C), *Age* x *Time, Medication* x *Time*, and *Task Version* x *Time* interactions were included in all models. All available data were used, including from dropouts, rendering these intent-to-treat analyses. However, patients missing baseline EEG/ERP data or who dropped out prior to completing at least 3 weeks of CBT were excluded (n=4). To examine change in time-domain or time-frequency variables over the course of treatment, we tested *Group (MDD/HC)* x *Time (Initial/Mid/Final)* x *Condition (Wins/Losses)* interactions, separately for the RewP, LPP, theta, and delta (adjusting for age and medication). (In contrast, Group was not included as a factor in the analyses presented in the below *CBT Outcomes* and *Prediction of CBT Outcomes* sections given that these analyses pertained only to the MDD group). As described in our hypotheses, we expected significant pre- to post-treatment increased delta power to rewards and decreased theta power to losses in the MDD group (relative to the HC group). All analyses were conducted in R with the exception of the latter *Group* x *Time* x *Condition* interactions which were conducted in SPSS Version 24.

Results

Internal (split-half) reliability and test-retest reliability for time-domain and time-frequency measures, as well as their intercorrelations, are reported in the Supplement.

[1] A subtraction-based difference score approach (i.e., RewP to wins minus losses) was not used given recent evidence of its relatively poor psychometric properties (47–49). Instead, and similar to recent treatment outcome prediction efforts using the RewP (9), we included the RewP to wins and losses as separate variables, entered simultaneously in the same model. In other words, the resulting parameter estimate for the *RewP to wins* x *Time* interaction adjusts for the *RewP to losses* x *Time* interaction (and vice-versa) (see 47–49).

CBT Outcomes

Intent-to-treat MLM analyses revealed that depressive (BDI-II) symptoms improved significantly over the course of treatment for the MDD group, *Time*: $b = 1.08$, $t(28.2) = 4.52$, $p < .001$. Among treatment completers, mean pre-treatment BDI-II scores were in the severe range (M = 30.35; SD = 11.57), whereas post-treatment scores were in the mild range (M = 16.93; SD = 14.24). This pre- to post-treatment change represents a large effect (Cohen's $d = 1.00$)(Figure 3).

Prediction of CBT Outcomes

The pre-treatment RewP did not predict depressive symptom change (i.e., $RewP_{Wins}$ x *Time* and $RewP_{Loss}$ x *Time* interactions were not significant; *p*s >.61). When using the conventional subtraction-based difference score approach (see Footnote 1), the *RewP* x *Time* interaction was not significant, $p = 0.62$). However, a pre-treatment LPP_{Wins} x *Time* interaction emerged, $b = 0.81$, $t(27.6) = 2.38$, $p = .024$, indicating that adolescents with a larger LPP response to wins had greater depressive symptoms improvement (Table 1 & Figure 4). A pre-treatment $delta_{Losses}$ x *Time* interaction emerged, $b = 0.53$, $t(27.1) = 2.49$, $p = .019$, indicating that adolescents with a larger delta response to losses had greater depressive symptoms improvement (see Table 2, Figure 5). Corresponding pre-treatment *theta x Time* interactions were not significant (*p*s >.86). When both the significant LPP_{Wins} x *Time* and $delta_{Losses}$ x *Time* interactions are included in the same model (residualized to adjust for LPP_{Loss} and $delta_{wins}$, respectively) both remained significant: ($b = 0.40$, $t(27.0) = 2.15$, $p = .041$; $b = 0.41$, $t(25.6) = 2.06$, $p = .049$, respectively).

Changes in Neural Response Following CBT

No significant *Group* x *Time* x *Condition* interactions emerged for the RewP, LPP or delta power (all *p*s > .08). A *Group* x *Time* x *Condition* interaction emerged for theta power, $F(2,37) = 4.00$, $p = .027$, $\eta^2 = 0.18$, such that the MDD group exhibited greater pre- to post-treatment reductions in theta response to losses relative to the HC participants (Figure 6). Greater pre- to post-treatment reductions in theta to losses were non-significantly associated with greater anxiety symptom improvement over the course of treatment, $r = .44$, $p = 0.052$ (depressive symptoms: $r = .01$; $p = 0.971$). Similarly, early reductions in theta to losses (i.e., from pre- to mid-treatment) were non-significantly associated with greater pre- to post-treatment anxiety symptom improvement, $r = .43$, $p = 0.060$, (depressive symptoms, $r = .05$; $p = 0.828$). Sensitivity analyses excluding the mid EEG assessment (i.e., only including data from initial and final EEG assessments), including number of days between EEG assessments as a covariate, and with imputed missing values yielded the same pattern of findings (see Supplemental Results).

Discussion

The present study evaluated whether the RewP and/or LPP, assessed prior to the start of treatment, predicted symptom change among depressed adolescent girls receiving CBT. In addition, we tested whether CBT modulated the RewP and LPP. Strengths of the study include (1) the use of time-frequency decomposition to isolate reward-related (delta power) and loss-related (theta power) neural signals, (2) simultaneous examination of ERPs linked

to initial response to rewards (RewP) vs. later, elaborative processing (LPP), and (3) incorporation of pre-, mid- and post-treatment ERP assessments. Multilevel modeling revealed that the pre-treatment LPP, but not RewP, to rewards predicted symptom improvement during CBT. Similarly, Barch et al.(14) showed that larger pre-treatment LPP to pleasant pictures, but not the RewP to rewards, predicted better outcomes for young depressed children receiving PCIT. Although our findings are generally consistent with the latter study, they diverge from two initial studies in adults with depression and/or anxiety indicating that a reduced pre-treatment RewP to monetary rewards predicted greater depressive symptom improvement to CBT (8) and SSRI (7). In other words, in contrast to the latter two studies, our results do not support a "compensatory" model whereby individuals with more blunted—as opposed to intact or enhanced—neural reward responsiveness exhibit greater depressive symptom improvement. Additional research is needed to determine whether these inconsistencies may be due, at least in part, to differences in sample (adolescent girls vs. adults of both genders), diagnosis (MDD vs. depressive or anxiety disorders) and the variant of monetary reward task. It is also important to note that the average adolescent in our sample had severe levels of depression (mean pre-treatment BDI-II = 33), which may have influenced findings.

A consideration of the distinct neural generators of the RewP and LPP may help account for their differential pattern of prediction. Specifically, the RewP has been linked to activity within the mesocorticolimbic reward circuit (e.g., ventral striatum and medial prefrontal cortex) (12,13) and dACC (17); conversely, the LPP has been associated with a more distributed set of cortical and subcortical regions linked with visual, attentional and emotion processing, including occipital, parietal, inferotemporal and lateral prefrontal regions, as well as the amygdala and insula (50–54). In addition, in contrast to the RewP which reflects initial reactivity to the receipt of rewards (but see studies linking the RewP/FRN to unexpected outcomes or feedback indicating safety)(e.g.,56), the LPP reflects more sustained attention towards and engagement with emotional or motivationally salient content (and not specific to only rewards). Although speculative, depressed adolescents exhibiting more sustained neural engagement to rewarding or motivationally salient feedback may be relatively more likely to successfully engage in and benefit from cognitive and behavioral activities prescribed in CBT. Subsequent research including active comparison conditions (e.g., an SSRI or a different psychotherapy modality) are needed to test whether an enhanced LPP to rewards is a *prescriptive* (i.e., treatment-specific) or *prognostic* (i.e., treatment non-specific) predictor of outcome among depressed adolescents.

With regards to neural changes in treatment, only theta activity exhibited a significant *Group* x *Time* x *Condition* interaction. As displayed in Figure 6, the elevated pre-treatment theta activity to losses in the MDD group (relative to HC) is attenuated over the course of CBT. Importantly, the inclusion of a mid-treatment EEG assessment revealed that the majority (88.9%) of this pre- to post-treatment reduction occurred early in CBT (i.e., by the time of the mid-treatment EEG assessment). These findings suggest that CBT may attenuate neural hypersensitivity to negative feedback among depressed adolescents (16). In addition, both overall (pre- to post-treatment) and early (pre- to mid-treatment) reductions in theta activity to losses correlated moderately (*r*s =.43-.44) with pre- to post-treatment improvement in anxiety symptoms, but exhibited weak associations (*r*s =.01-.05) with depressive symptom

improvement. Previous studies indicate that frontal midline theta power is more strongly associated with anxiety than depressive symptoms (56,57,57–59). Frontal midline theta activity is elicited not only by tasks involving negative or loss feedback, as in the present study, but by a range of paradigms requiring the deployment of cognitive control (e.g., tasks involving the commission of errors, stimulus-response conflict and novelty)(56,60). As others have argued, frontal midline theta elicited during these tasks is most likely generated from frontocingulate regions, in particular the ACC, which may be signaling the need to increase cognitive control in the service of adjusting behavior adaptively (56,60). In addition to being correlated with anxiety symptoms, enhanced theta response to aversive/incorrect feedback has been linked to heightened avoidance learning (59,61), suggesting one mechanism through which neural (theta) hypersensitivity to negative feedback may contribute to maladaptive behavior (e.g., anxiety-related avoidance)(56). Research is needed to test whether CBT-related reductions in theta power to negative outcomes are associated with normalization of avoidance learning.

In contrast, we did not observe increases in neural markers of reward sensitivity (RewP and delta power) over the course of CBT. These findings may reflect the fact that anhedonia and associated reward-related deficits in depression are among the most common residual symptoms following psychotherapy or pharmacotherapy and are particularly challenging to successfully target (62–64). Treatments that more directly target anhedonia, such as Behavioral Activation (BA) (15) and positive affect-focused treatments (64), may be more likely to modulate reward related-circuitry (e.g., for a relevant BA example, see (65)). Although CBT includes BA interventions, a substantial proportion of treatment is devoted to teaching patients cognitive skills to identify and modify maladaptive thinking patterns. In contrast, BA may be more likely to target reward circuitry function given its greater focus on teaching depressed individuals an array of behavioral strategies aimed at gradually and systematically increasing their exposure to and engagement with rewarding experiences and activities. Ultimately, a comparative trial is needed in which depressed adolescents are randomly assigned to BA vs. CBT to test for treatment group differences in “target engagement” of reward circuitry function. Finally, the fact that neural markers predicting treatment outcome (LPP to rewards) did not exhibit significant pre- to post-treatment change (relative to HCs), and vice versa (i.e., theta to losses did not predict outcome but did demonstrate significant change from pre- to post-treatment) suggests a dissociation between neural markers predicting symptom improvement vs. neural mechanisms of change.

Several limitations should be noted. First, sample size was small, in particular for detecting interactions, and thus replication in a larger cohort is required. Second, the inclusion of a HC group who completed ERP tasks at three timepoints corresponding to the MDD group controlled for the effect of repeated EEG assessments and task practice effects. However, an active control condition is needed to test the specificity of findings to CBT vs. relevant alternative interventions (e.g., BA or SSRIs) for the treatment of MDD in adolescents. Third, although EEG is a relatively low-cost imaging approach (i.e., compared to fMRI) and has excellent temporal resolution (e.g., allowing us to isolate ERPs linked to initial vs. later, elaborative stages of neural processing), it suffers from poor spatial resolution (e.g., cannot isolate neural activity within relevant subcortical reward-related and emotion-related regions). Fourth, a relatively large number of statistical tests were conducted. Fifth, CBT

fidelity was not measured. These limitations notwithstanding, the present study provides initial evidence that an ERP measure of sustained responsiveness to rewards predicts depressive symptom change in CBT. In addition, findings indicate that neural (theta) hypersensitivity to negative outcomes among depressed youth may be attenuated within the first few weeks of CBT. Ultimately, such research may help inform which depressed adolescents are better suited to CBT and may clarify the neural mechanisms underlying depressive symptom improvement.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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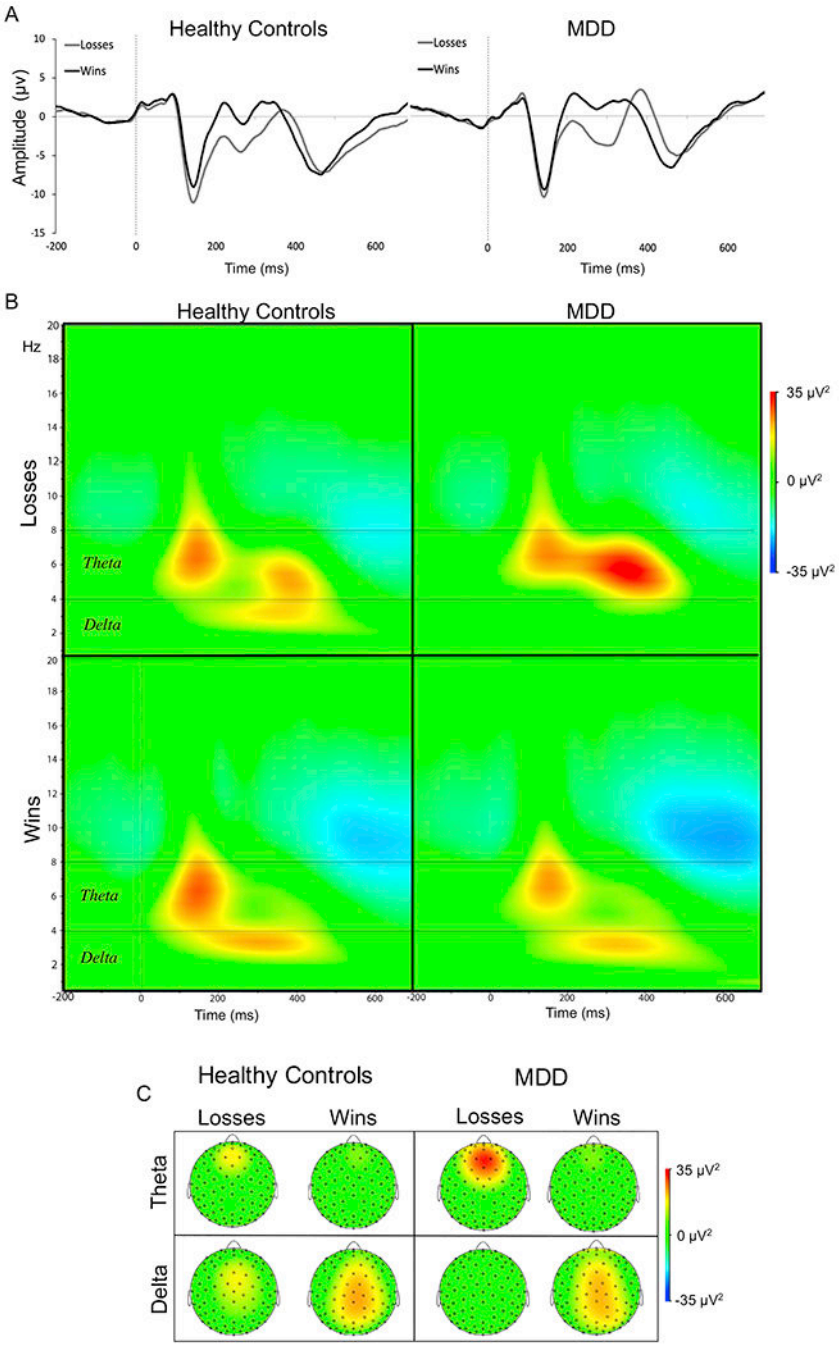

Figure 1.

(A) Event-related potentials (Reward Positivity; RewP) elicited by monetary rewards (black) and losses (gray) for healthy controls (left panel) and adolescents with major depressive disorder (MDD) (right panel) shown in the time-domain at electrode FCz at baseline. (**B)** Time-frequency plots for monetary losses (top panel) vs. rewards (bottom panel) for both groups highlighting theta and delta power. (**C).** Scalp distribution for theta power (top panel) and delta power (bottom panel) at 300ms for both groups and conditions (wins and losses).

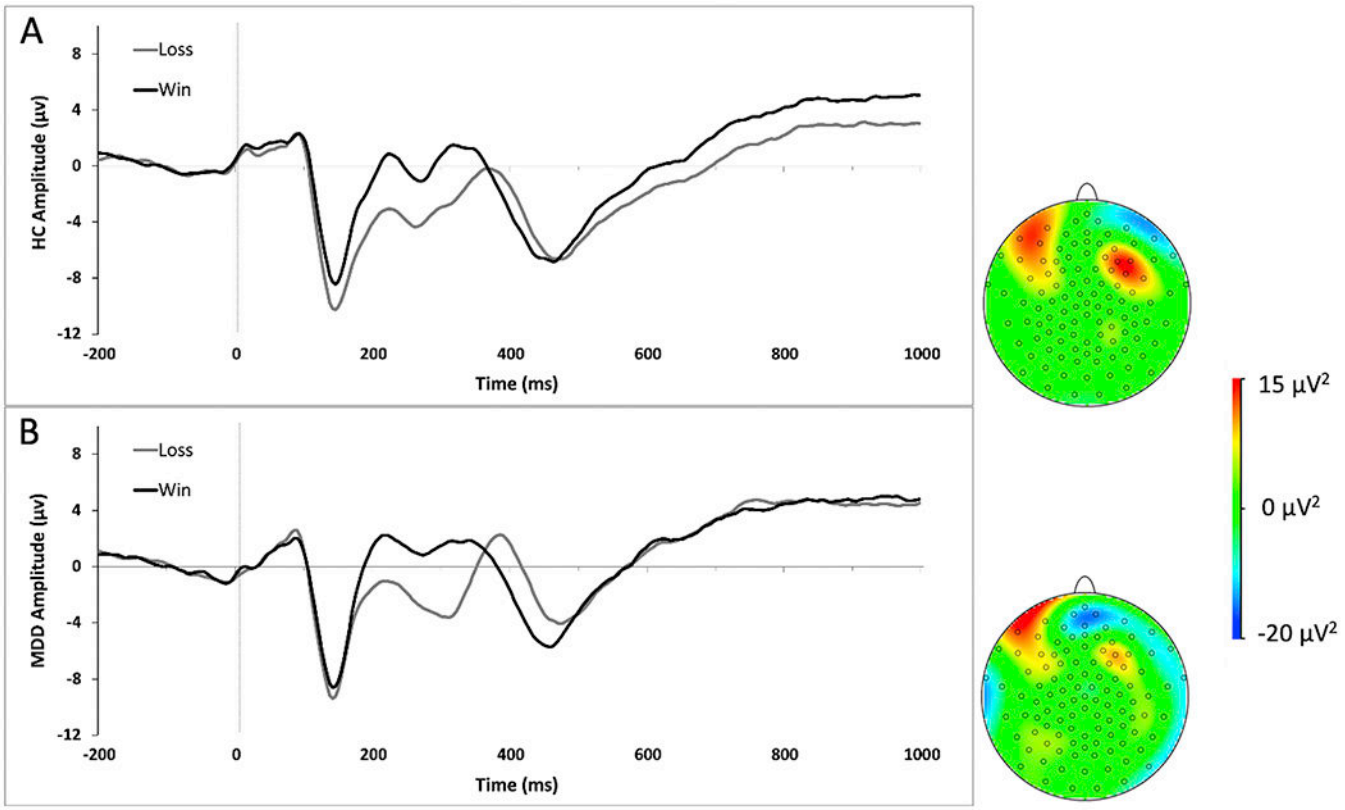

Figure 2.

Plots of Late Positive Potential (LPP) for healthy controls **(A)** and adolescents with major depressive disorder (MDD) at baseline (**B)** in response to monetary wins (black) and losses (gray). The LPP was averaged across electrodes Fz, FCz and Cz from 600-1,000ms. Scalp distribution of the difference wave from 600-1,000ms are displayed.

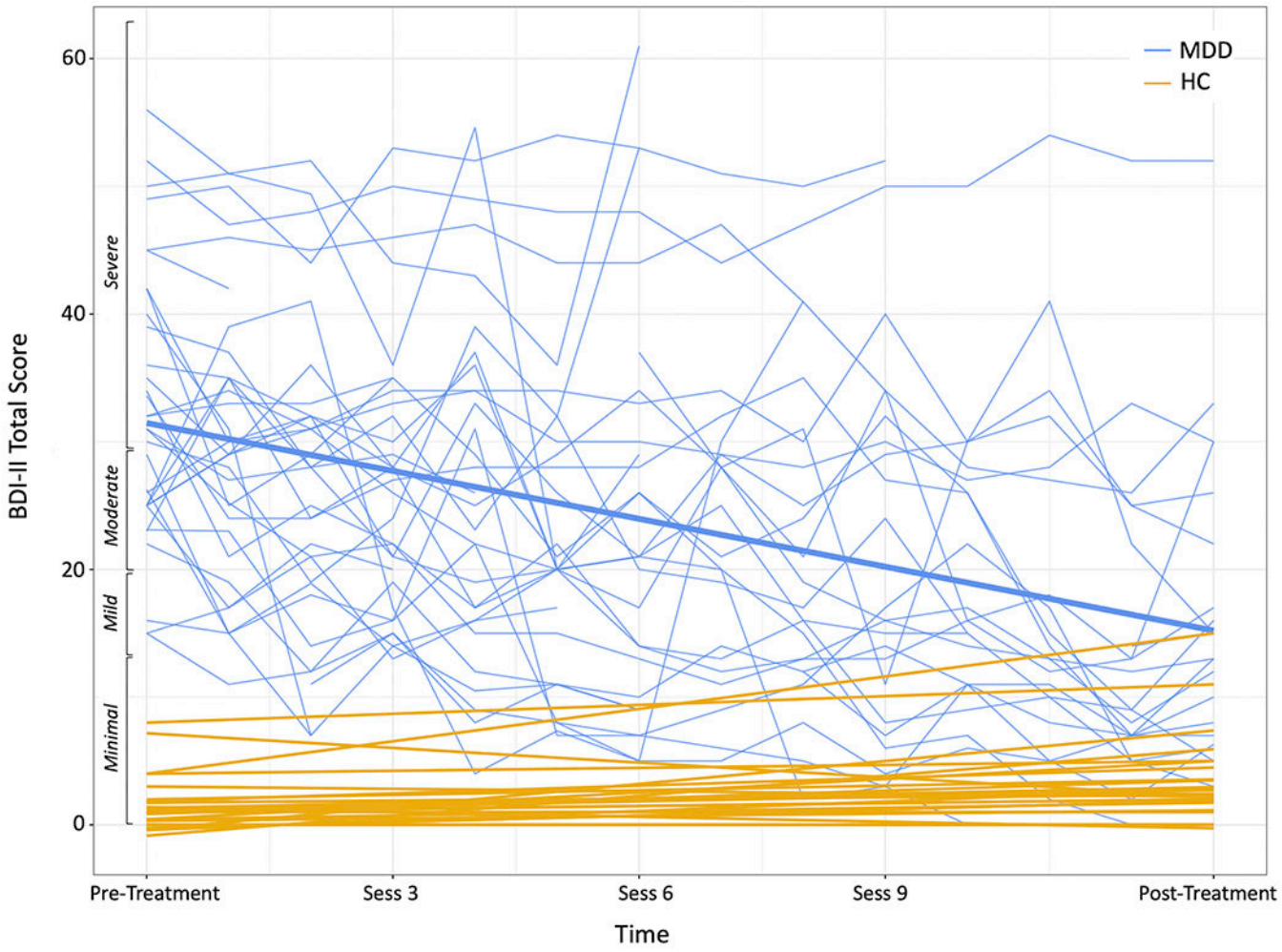

Figure 3.

Session-by-session Beck Depression Inventory-II (BDI-II) scores for MDD participants (blue). Thicker blue line represents the regression line. HC participants' BDI-II scores (gold) are also plotted for comparison (at 2 timepoints corresponding to pre- and post-treatment)

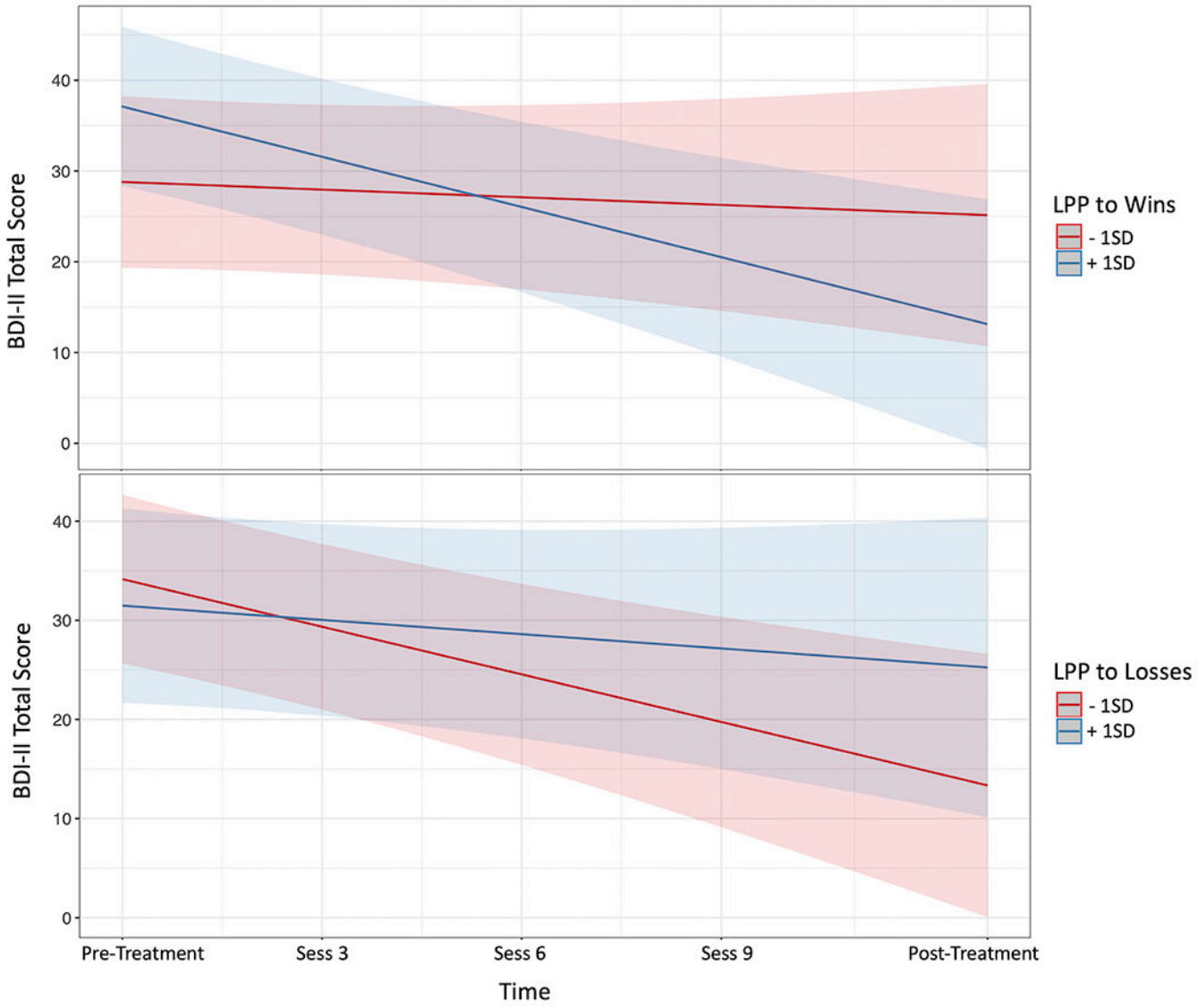

Figure 4.

Plot of pre-treatment LPP by time interactions from the model. LPP to wins by time interaction is shown in the top panel, and LPP to losses by time interaction in the bottom panel.

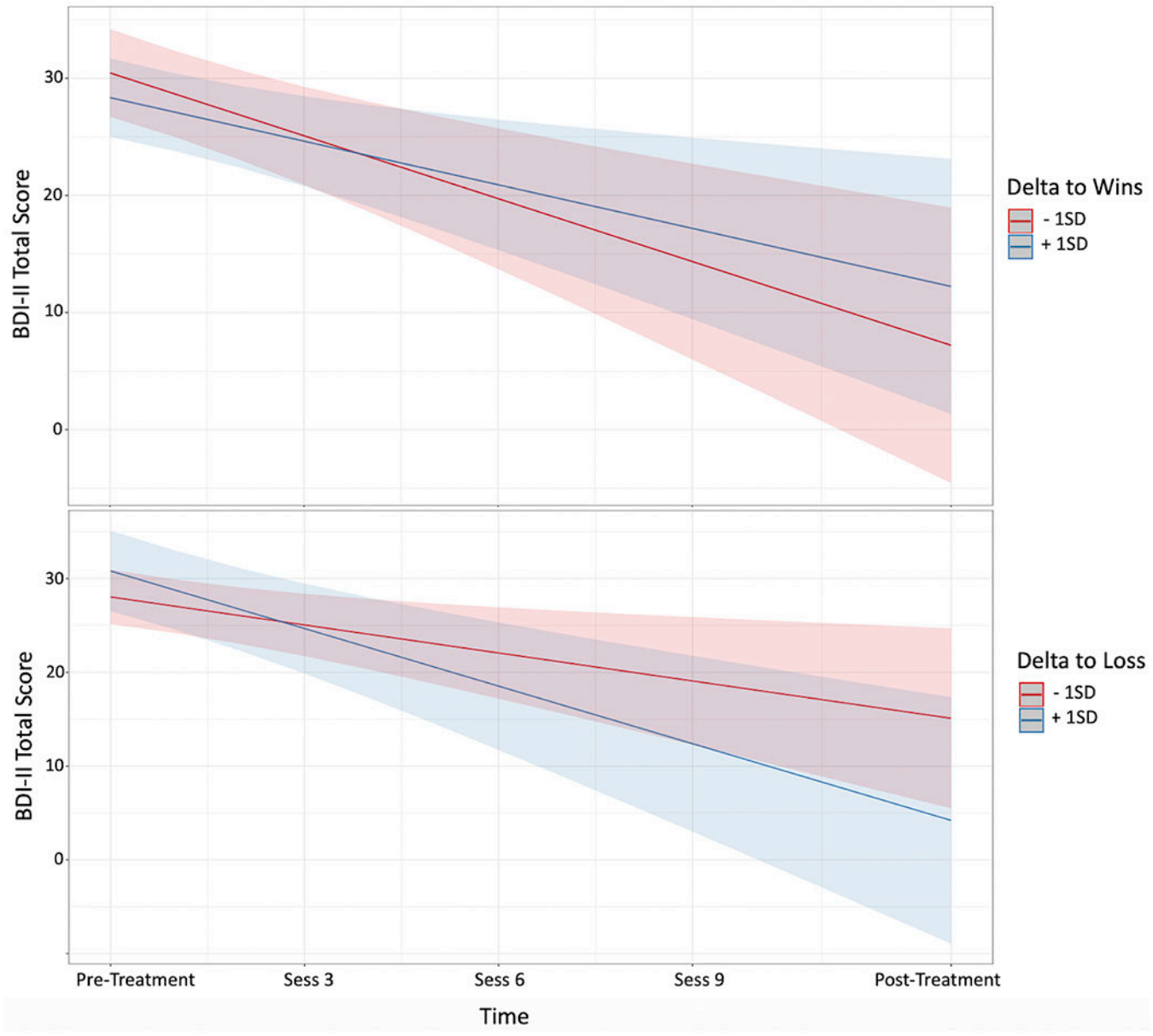

Figure 5.

Plot of pre-treatment delta power by time interactions from the model. Delta to wins by time interaction is shown in the top panel, and delta to losses by time interaction in the bottom panel.

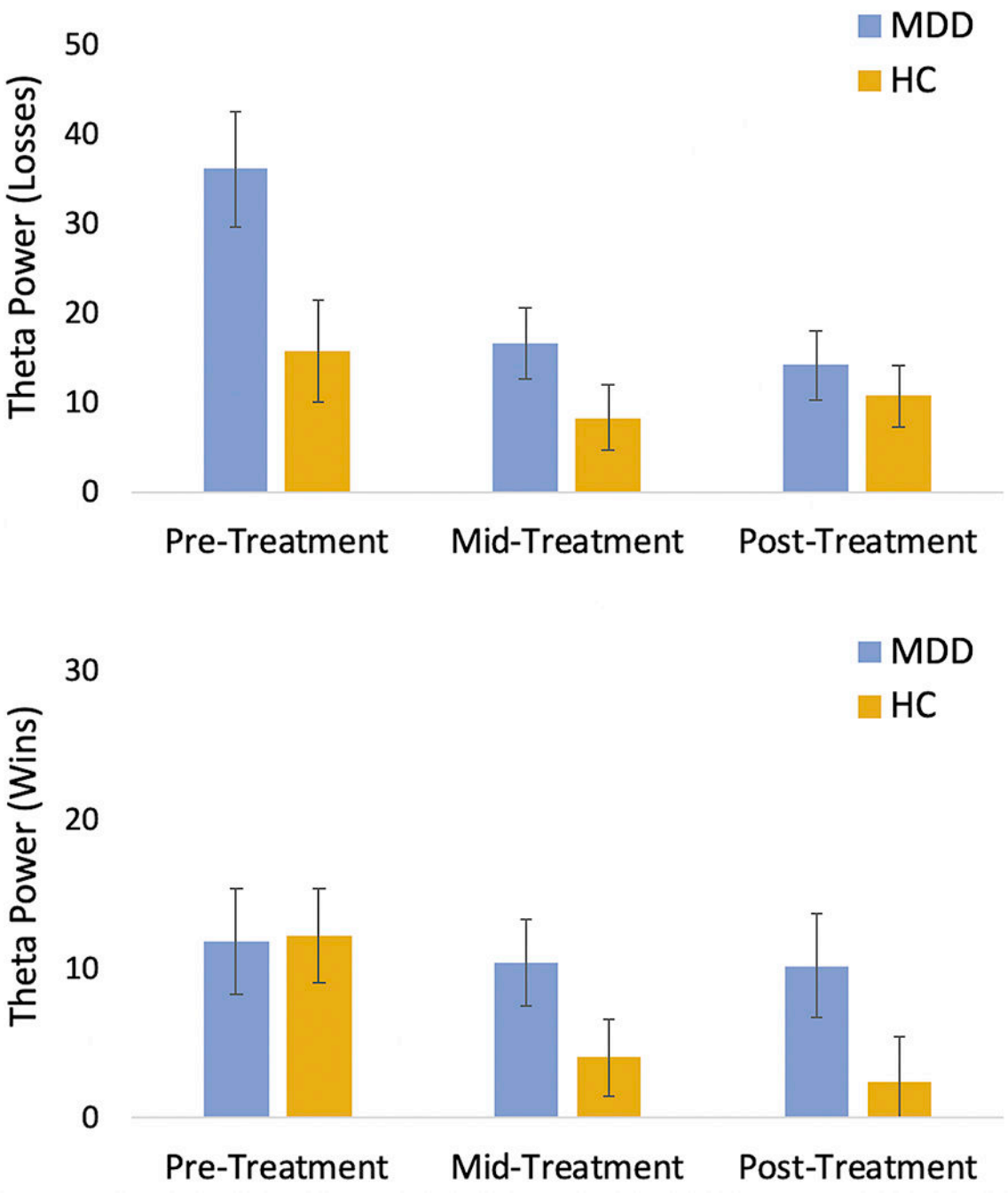

Figure 6.

Change in theta power to losses (top panel) and wins (bottom panel) in the MDD participants (blue) vs. HC participants (gold) over time (model-derived estimated marginal means). Error bars represent standard error

Table 1.

LPP by time interactions predicting BDI-II symptom change

Variable	*B*	*SE*	*p* value
(Intercept)	14.48	4.86	0.01**
Baseline BDI	10.24	0.85	0.00**
Time	1.12	0.38	0.01**
Medication	−10.81	5.41	0.06+
Age	6.49	2.48	0.01*
Task Version	9.01	6.13	0.15
LPP_{Wins}	−9.14	4.32	0.04*
LPP_{Losses}	6.05	4.44	0.18
Time x Medication	0.92	0.42	0.04*
Time x Age	−0.46	0.19	0.02*
Time x Task Version	−0.53	0.48	0.45
Time x LPP_{Wins}	0.81	0.34	0.02*
Time x LPP_{Losses}	−0.53	0.35	0.14

+ $p < 0.10$.

* $p < 0.05$.

** $p < 0.01$.

Table 2.

Delta by time interactions predicting BDI-II symptom change

Variable	*B*	*SE*	*p* value
(Intercept)	10.69	5.17	0.04 *
Baseline BDI	9.90	0.89	0.00 **
Time	1.48	0.40	0.00 **
Medication	−6.19	5.35	0.26
Age	8.35	2.66	0.00 **
Task Version	12.04	6.35	0.09 +
$Delta_{Wins}$	2.52	2.58	0.34
$Delta_{Losses}$	−5.45	2.76	0.06 +
Time x Medication	0.48	0.41	0.25
Time x Age	−0.66	0.21	0.00 **
Time x Task Version	−0.83	0.49	0.13
Time x $Delta_{Wins}$	−0.27	0.20	0.18
Time x $Delta_{Losses}$	0.53	0.21	0.02 *

+ $p < 0.10$.

* $p < 0.05$.

** $p < 0.01$.