

Neural Indicators of Anhedonia: Predictors and Mechanisms of Treatment Change in a Randomized Clinical Trial in Early Childhood Depression

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ABSTRACT

BACKGROUND: Early childhood depression is associated with anhedonia and reduced event-related potential (ERP) responses to rewarding or pleasant stimuli. Whether these neural measures are indicators of target engagement or treatment outcome is not yet known.

METHODS: We measured ERP responses to win and loss feedback in a guessing task and to pleasant versus neutral pictures in young (4.0–6.9 years of age) depressed children before and after randomization to either 18 weeks of Parent-Child Interaction Therapy–Emotion Development (PCIT-ED) or waitlist.

RESULTS: Analyses included reward positivity (RewP) data from 118 children randomly assigned to PCIT-ED ($n = 60$) or waitlist ($n = 58$) at baseline and late positive potential (LPP) data from 99 children (44 assigned to PCIT-ED vs. 55 assigned to waitlist) at baseline. Children undergoing PCIT-ED showed a greater reduction in anhedonia ($F_{1,103} = 10.32, p = .002, \text{partial } \eta^2 = .09$). RewP reward responses increased more ($F_{1,86} = 5.98, p = .02, \text{partial } \eta^2 = .07$) for PCIT-ED, but a greater change in RewP was not significantly associated with a greater reduction in major depressive disorder symptoms ($r = -.12, p > .4$). Baseline RewP did not predict treatment change. LPPs to positive pictures did not change across treatment, but greater baseline LPPs to positive pictures predicted a higher likelihood of remission from major depressive disorder in children undergoing PCIT-ED ($B = 0.14; SE = 0.07; \text{odds ratio} = 1.15; p = .03$).

CONCLUSIONS: The ERP reward response improved in young children with depression during a treatment designed to enhance emotion development, providing evidence of target engagement of the neural systems associated with reward. Further, greater baseline LPP responses to positive pictures was associated with a greater likelihood of depression remission, suggesting that this ERP measure can predict which children are most likely to respond to treatment.

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Major depressive disorder (MDD) is often characterized by impairments in the ability to experience reward and pleasure (1,2). These disruptions contribute to functional impairment, are associated with deficits in specific neural systems (2,3), and are a central target of treatments (4). MDD has been validated to manifest as early as 3 years of age (5–9), with prevalence rates similar to those found at school age (1%–2%) (9–12). Young children with MDD show many of the same clinical features as adults (8,13) as well as disruptions in associated neural systems (14,15). The absence of positive affect, especially to rewarding events, is a salient feature of early childhood MDD (7,8,13,16,17) and is referred to as anhedonia (18,19). Reduced positive affect at age 3 predicts depressive cognitive styles at age 7 (20). Further, the specificity of anhedonia for preschool MDD is evidenced by the fact that preschoolers with MDD are 17 times more likely than healthy peers, 7 times more likely than peers with disruptive

disorder, and 5 times more likely than peers with anxiety disorder to exhibit behavioral manifestations of anhedonia (8). Reductions in positive affect associated with MDD may be particularly important in younger children, given that joyful play is a central activity known to facilitate multiple dimensions of development (21,22).

We recently completed a randomized controlled trial of parent-child psychotherapy for early childhood depression using a modified Parent-Child Interaction Therapy (PCIT) with an added novel Emotion Development module (PCIT-ED) (23). This treatment targeted emotion development, including enhancing the ability to sustain joy and regulate loss and sadness, and was highly effective for remediating depression and general impairment (23). In our randomized controlled trial of PCIT-ED, significant reductions in depression were found in depressed children after treatment (23), providing motivation for the investigation of both reductions in anhedonia

symptoms and modulation of the neural correlates of anhedonia. In this article, we examined whether two event-related potential (ERP) components that are neural indicators of either 1) response to reward—i.e., the reward positivity (RewP)—or 2) affective stimuli (including but not limited to positive stimuli)—i.e., the late positive potential (LPP)—predict clinical response to PCIT-ED or index modulation of the neural systems targeted by the treatment.

Consistent evidence in adults, adolescents, and children with or at risk for depression demonstrates impaired responses to reward using behavioral assessments and both ERP and functional magnetic resonance imaging measures of brain function (24–28). A number of studies have examined the RewP, an ERP component elicited by feedback indicating rewards versus losses, which is thought to reflect activity of the reward circuit (i.e., ventral striatum, caudate, and dorsal anterior cingulate cortex) (29–31). Depressed adults show decreased RewPs (32,33), and increased depression in children and adolescents is related to a reduced RewP (26,34,35). A reduced RewP predicts later depression in adolescents (25,34) and is related to the severity of anhedonia in adults (36). We have shown that preschool-aged children with MDD also show decreased RewPs (15), with the effects being driven by reduced response to win feedback. Further, a reduced RewP among adults with anxiety and depression predicted a greater response to cognitive behavioral therapy (4), with a similar finding in children (37). Together, these findings suggest that the reduced RewP is an important biomarker of anhedonia in MDD. If reductions in the RewP are more of a trait-related marker of anhedonia or risk for depression, RewP may serve to predict who might respond to treatment targeting anhedonia, with either individuals most impaired showing a greater response to treatment or individuals least impaired best able to respond to PCIT-ED. Alternatively, if reduced RewP is more of a state-related marker of current anhedonia and/or depression, it may improve as a function of treatment and serve as a measure of target engagement or modulation of the neural systems associated with hedonic processing by treatment.

Another neural indicator of processing of positive stimuli is the LPP, which is larger to arousing stimuli capable of eliciting emotional responses (pleasant and unpleasant) compared with neutral stimuli (38–41). Adolescents and adults with depression demonstrate a reduced LPP to pleasant stimuli (42–44). Further, children and adolescents at risk for depression show a reduced LPP to pleasant stimuli (45,46), and a reduced LPP to pleasant pictures is associated with the experience of depression following stressful events (47). We have also shown that young children with depression show a reduced LPP to pleasant pictures (48). Thus, LPP responses to pleasant stimuli may be another neural correlate of anhedonia. As with the RewP, if reductions in the LPP are more of a trait-related marker of depression risk, LPP may predict who responds to treatment. Alternatively, if it is a more state-related marker, LPP may be modulated by treatment and serve as a measure of target engagement of relevant neural systems.

The goal of the current study was to use ERPs to examine neural responses to reward and pleasant pictures among children with MDD before and after undergoing PCIT-ED. We predicted that compared with the waitlist (WL) control,

children undergoing PCIT-ED would show an increase in the RewP to wins and an increase in the LPP to pleasant pictures and that the magnitude of the increase would correlate with the degree of depression and anhedonia reduction. We also predicted that children who showed lower RewP and LPP responses at baseline would show a greater response to treatment.

METHODS AND MATERIALS

Participants

Children (3.0–6.9 years of age) were participants in a randomized controlled trial of PCIT-ED compared with WL control. Analyses of the depression outcome measures are reported elsewhere (23). Details about recruitment, study design, and inclusion/exclusion criteria are provided in the [Supplemental Methods and Materials](#), which also includes a CONSORT (CONsolidated Standards Of Reporting Trials) diagram. Study materials and procedures were approved by the Washington University School of Medicine in St. Louis Institutional Review Board, and written informed consent was obtained from caregivers with verbal assent obtained from children. The trial was registered with [ClinicalTrials.gov](#) ([ClinicalTrials.gov](#) Identifier NCT02076425).

The ERP component was added 18 months after trial initiation (see [Figure S1](#) for CONSORT Diagram), and 194 of 216 children approached agreed to participate (4.0–6.9 years of age). Of these children, 156 were randomly assigned to treatment, and 124 completed at least one ERP task. There were no significant demographic or clinical differences between the randomly assigned children who did or did not complete at least one ERP task ([Table S1](#)). Of the children completing at least one task, 118 had data that survived quality control ([Supplemental Methods and Materials](#)) for the RewP analyses (60 randomly assigned to PCIT-ED and 58 randomly assigned to WL), of whom 47 in the PCIT-ED group and 45 in the WL group completed the posttreatment assessment. Of children, 99 had data that survived quality control for the LPP (44 in PCIT-ED group and 55 in WL group), of whom 44 in the PCIT-ED group and 41 in the WL group completed the posttreatment assessment. Children who did not have usable ERP data ([Table S2](#)) were younger (RewP and LPP), more likely to have a comorbid externalizing disorder (RewP, not LPP), and more likely to be on a medication (LPP, not RewP), though children on any antidepressant were excluded at baseline. The comparison of baseline data between depressed children and a healthy control sample has already been reported for the RewP (15) and the LPP (48).

Parent-Child Interaction Therapy–Emotion Development

This treatment is a dyadic parent-child psychotherapy expanded and adapted from the well-validated PCIT (49). A novel ED module (8 sessions) was added after the standard PCIT modules (12 sessions). The ED modules build on empirical findings in emotional development using the basic techniques of PCIT (teaching of parent followed by coaching the parent in interactions with the child in vivo using a bug-in-the-ear device) to focus on enhancing the child's emotional

experience, emotional competence (50), and emotion regulation (51). This approach addresses early childhood depression impairments in the ability to recognize, understand, and regulate emotions in self and others as well as helping the child and parent increase reactivity to positive stimuli and decrease reactivity to negative stimuli.

Measures

Psychopathology. The Schedule for Affective Disorders and Schizophrenia for School-Age Children–Early Child Version (K-SADS-EC), a semistructured clinical interview for DSM-5 disorders adapted for use in children 3.0 to 6.11 years of age, was used to assess severity of MDD and other Axis I comorbidities at baseline and posttreatment or WL. This measure has good test-retest reliability and construct validity and generates both categorical and dimensional measures of DSM-5 Axis I disorders (14,52). The MDD score was the number of core MDD symptoms endorsed on the K-SADS-EC. All K-SADS-EC interviews were conducted by master's level clinicians, videotaped, reviewed for reliability, and calibrated for accuracy. Satisfactory interrater reliability was maintained on a monthly basis with overall κ values of $\kappa = 0.74$ for MDD and all diagnoses $\kappa = 0.88$ achieved during the study period. The anhedonia score was the sum of boredom, anhedonia, and amotivation items from the KSADS-EC (Cronbach's $\alpha = .48$).

Preschool Feelings Checklist. The Preschool Feelings Checklist (PFC) scale (53), a 23-item Likert scale, adapted from the PFC, was administered at baseline and after assessments to measure depression severity via caregiver report (23,54).

Tasks

Children were given practice trials on both tasks to ensure that they understood how to do the tasks. Tasks were administered on a computer using Presentation (Neurobehavioral Systems, Inc., Berkeley, CA) software, and children used an F310 Gamepad (Logitech, Newark, CA) game controller to respond.

Doors Guessing Task to Assess RewP. Children completed the Doors Guessing Task (Figure S2), which has been used in numerous previous studies of older children, adolescents, and adults with depression (25,27,32,46,55). Participants were shown a graphic displaying two adjacent doors and told to select a door to win or lose points to pick a prize. Following each choice, a feedback stimulus (green up arrow or red down arrow) appeared on the screen informing the children whether they lost or gained points. See [Supplemental Methods and Materials](#) for details.

Picture Task to Assess LPP. Children were told that they would see lots of different pictures and that we wanted them to simply look at all of the pictures that showed up on the screen. Children were told that an arrow pointing to the left or the right would appear on the screen after each picture (Figure S3). Children were instructed to press the left or right button on the game controller that matched the direction of the arrow on the screen. Forty developmentally appropriate pictures were selected from the International Affective Picture System (56):

20 depicted pleasant/affectively positive scenes (e.g., smiling faces and candy), and 20 depicted neutral scenes (e.g., neutral faces and household object such as a towel). Each picture was displayed twice in a random order in color and occupied the entirety of a 20-inch monitor. See [Supplemental Methods and Materials](#) for details.

Psychophysiological Recording and Data Reduction

See [Supplemental Methods and Materials](#) for details.

Data Analysis

Reward Positivity in the Doors Task. The 200-ms window before feedback onset served as the baseline. We measured the mean amplitude between 300 ms and 500 ms at electrode site Pz separately for win and loss trials, focusing on Pz because of our prior work showing reduced reward-related amplitudes at Pz in depressed preschool children (15). To be included in analyses, children had to have at least 20 usable ERP segments per condition (win vs. loss outcomes). Six children were excluded for this reason. Based on recommendations in the literature (57–59), we used linear regression to create residualized scores for both baseline and posttreatment that allowed us to examine treatment effects for wins, partialing out the effect of loss (analogous scores of losses were created by partialing out the effect of win). Such scores have good internal consistency and reliability (60). These residual scores reflected variation in the response to wins not accounted for by loss responses (Win_{resid}). We used these residual scores in 3 analyses: 1) whether response to reward changed as a function of treatment, using an analysis of covariance with treatment groups as a between-subject factor (PCIT-ED vs. WL) and Win_{resid} posttreatment as the dependent measure, with baseline ERP response, $Loss_{resid}$ posttreatment age, and baseline PFC scale score as covariates (intent-to-treat analyses are in [Supplemental Methods and Materials](#)); 2) whether changes in Win_{resid} from pretreatment to posttreatment in PCIT-ED were correlated with depressive or anhedonia symptom change, using partial correlations of difference scores (post – baseline), controlling for age; and 3) whether baseline ERP responses to Win_{resid} predicted treatment response, either reduction in MDD or anhedonia scores (linear regression) or remission from MDD (binary logistic regression). The same analyses with raw scores are in [Supplemental Methods and Materials](#).

LPP in the Picture Task. The 200-ms window before picture onset served as the baseline. We focused on 250 to 600 ms as the average of the electrode sites O1, Oz, and O2 for pleasant and neutral pictures, as our prior work demonstrated that children with early childhood depression showed reduced LPP to pleasant pictures in this time window (48). The LPP has good internal reliability (61). To be included in LPP analyses, first, the subjects had to have at least 20 usable ERP segments per condition (positive and neutral pictures). Second, to keep the subjects engaged and attentive to the task and stimuli presentation, they had to press an arrow that matched the direction of an arrow presented on the screen. Thus, to be included in the analyses, children had to have responded to at least half of the trials. Of the 124 children who

Table 1. Demographic Characteristics of Participants at Baseline with Usable ERP Data

| | Reward Positivity Analyses | | | Late Positive Potential Analyses | | |
|---------------------------------------|------------------------------|-------------------------------|----------------------------|----------------------------------|-------------------------------|----------------------------|
| | Waitlist (<i>n</i> = 58) | Treatment (<i>n</i> = 60) | Group Comparison | Waitlist (<i>n</i> = 55) | Treatment (<i>n</i> = 44) | Group Comparison |
| Sex, Male, % | 64 | 65 | $\chi^2_1 = 0.02, p = .89$ | 67 | 64 | $\chi^2_1 = 0.14, p = .71$ |
| Race, White/African American/Other, % | 80/9/12 | 78/12/10 | $\chi^2_2 = 0.39, p = .82$ | 79/9/13 | 80/11/9 | $\chi^2_2 = 0.42, p = .81$ |
| Age, Years, Mean (SD) | 5.83 (0.80) | 5.46 (0.84) | $t_{116} = 2.44, p = .02$ | 5.79 (0.84) | 5.64 (0.81) | $t_{97} = 0.83, p = .41$ |
| PFC Scale Score, Mean (SD) | 41.76 (11.82) | 37.73 (9.17) | $t_{116} = 2.07, p = .04$ | 42.04 (11.45) | 37.32 (10.22) | $t_{97} = 2.14, p = .04$ |
| Anhedonia Sum Score, Mean (SD) | 1.40 (1.11) | 1.38 (1.01) | $t_{116} = 0.07, p = .95$ | 1.45 (1.12) | 1.32 (1.05) | $t_{97} = 0.62, p = .54$ |
| Comorbid Externalizing Disorders, % | 55 | 47 | $\chi^2_1 = 0.85, p = .36$ | 60 | 46 | $\chi^2_1 = 2.08, p = .15$ |
| On Nonantidepressant Medications, % | 2 | 7 | $\chi^2_1 = 1.77, p = .18$ | 2 | 2 | $\chi^2_1 = 0.03, p = .87$ |
| Income-to-Needs, Mean (SD) | 2.85 (1.38) | 2.99 (1.26) | $t_{116} = -0.57, p = .57$ | 2.86 (1.34) | 3.04 (1.25) | $t_{97} = -0.68, p = .50$ |

ERP, event-related potential; PFC, Preschool Feelings Checklist.

completed the LPP assessment, 25 children (PCIT-ED, *n* = 19; WL, *n* = 6) were excluded because either they had fewer than 20 usable ERP segments in one condition (*n* = 7) or they did not press enough buttons during the stimulus presentation (*n* = 18). We again used regression to create residual scores (i.e., $\text{Pleasant}_{\text{resid}}$, reflecting variation in the neural response to pleasant stimuli not accounted for by the response to neutral stimuli) separately for baseline and posttreatment. We conducted parallel analyses to those described above looking at change as a function of treatment and prediction of treatment outcome.

RESULTS

Demographic and Clinical Characteristics

The PCIT-ED and WL groups did not differ in sex for the RewP or LPP (Table 1), but the PCIT-ED group was slightly younger and had lower baseline PFC scale scores. Therefore, age and PFC scale scores were used as covariates.

Change in Anhedonia

The analyses of the primary outcome measures have been reported (23), with the same primary analysis for the ERP subsample in Table S3, but did not include anhedonia symptoms specifically. General linear model analysis of anhedonia after treatment, controlling for baseline anhedonia, indicated that the PCIT-ED group (mean [SD] = 0.13 [0.44]) exhibited significantly fewer anhedonia symptoms compared with WL (mean [SD] = 0.51 [0.67]) ($F_{1,103} = 10.32, p = .002$, partial $\eta^2 = .09$).

Reward Positivity

Response to Treatment. The grand average ERP waveforms for win and loss feedback across groups and assessment points are shown in Figure S4, a headmap for win responses from 300 to 500 ms is shown in Figure S5, ERPs for win response before and after treatment for PCIT-ED and WL are shown in Figure 1, and means and standard deviations for all ERP measures are presented in Table 2. The reward analysis of covariance showed a significant effect of treatment group on the $\text{Win}_{\text{resid}}$ score post assessment, after controlling for age, PFC scale score, $\text{Win}_{\text{resid}}$ at baseline, and $\text{Loss}_{\text{resid}}$ at post assessment ($F_{1,86} = 5.98, p = .02$, partial $\eta^2 = .07$). Follow-up repeated measures analyses of variance (pretreatment to

posttreatment change) within each treatment group separately were not significant ($ps > .3$), though the effect size of the positive change in the PCIT-ED group ($\eta^2 = .01$) was larger than the negative change in the WL group ($\eta^2 = .003$). Further, the mean residualized score for the treatment group (mean [SE] = 0.99 [1.03]) was significantly more positive than the WL group (mean [SE] = -1.03 [0.97]). These results held if we also included the LPP to positive pictures after treatment as an additional covariate ($\eta^2 = .072$). The same results in intent-to-treat analyses are provided in Supplemental Methods and Materials.

Does Change in ERP Response to Reward or Loss Relate to Change in Depressive Symptoms?

Partial correlations controlling for age demonstrated that in the treatment group a greater increase in $\text{Win}_{\text{resid}}$ from baseline to posttreatment (Figure 2) was not significantly associated with a greater decrease in MDD symptoms ($r = -.12, p = .45$, 95% CI -.43 to .19), PFC scale score ($r = .04, p = .80$, 95% CI -.27 to .35), or anhedonia ($r = -.01, p = .95$, 95% CI -.32 to .30).

Do Baseline Reward or Loss Responses Predict Treatment Outcome?

Baseline $\text{Win}_{\text{resid}}$ did not predict change in MDD symptoms or PFC scale scores, change in anhedonia, or remission from MDD (all $ps > .18$).

Late Positive Potential

Response to Treatment. The grand average ERP waveforms for the LPP are shown in Figure S6, a headmap for positive picture responses from 250 to 600 ms is shown in Figure S7, and means and SD are presented in Table 2. One-way analyses of covariance on $\text{Pleasant}_{\text{resid}}$ at posttreatment with age, PFC scale scores, and baseline $\text{Pleasant}_{\text{resid}}$ as covariates indicated no significant treatment group differences in the residualized responses to pleasant pictures ($F_{1,79} = 0.16, p = .69$, partial $\eta^2 = .002$). The same results in intent-to-treat analyses are in Supplemental Methods and Materials.

Does Change in LPP Response to Pleasant Pictures Relate to Change in Depressive Symptoms?

Partial correlations controlling for age demonstrated that in the treatment group, $\text{Pleasant}_{\text{resid}}$ from baseline to posttreatment was not associated with change in MDD symptoms ($r = -.01$,

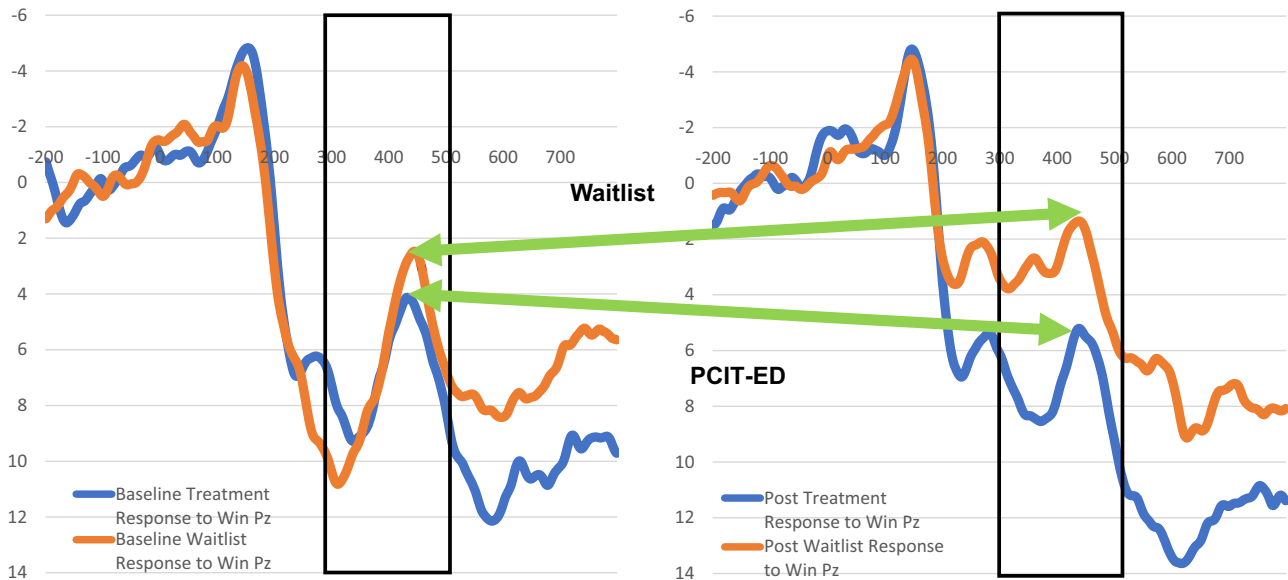


Figure 1. Reward positivity at baseline and posttreatment. Event-related potential waveforms at Pz to win outcomes at baseline (graph on the left) and after treatment (graph on the right). The blue lines are responses in the Parent-Child Interaction Therapy–Emotion Development (PCIT-ED) condition, and the orange lines are responses in the waitlist control condition. Voltages are plotted with the more negative values at the top of the graph, as is the frequent convention in event-related potential reports.

$p = .48$, 95% CI $-.09$ to $.09$), PFC scale scores ($r = -.09$, $p = .30$, 95% CI $-.53$ to $.27$), or anhedonia ($r = -.17$, $p = .14$, 95% CI $-.07$ to $.03$).

Do Baseline LPP Responses to Pleasant Pictures Predict Treatment Outcome? $Pleasant_{resid}$ did not predict change in MDD symptoms, PFC scale scores, or anhedonia symptoms (all $ps > .41$). However, baseline $Pleasant_{resid}$ did predict remission from depression ($B = 0.30$; $SE = 0.15$; odds ratio = 1.35 ; $p = .04$), as shown in Figure 3.

DISCUSSION

Children in the PCIT-ED group compared with WL group showed a greater reduction in anhedonia. Further, as predicted, children in the PCIT-ED group showed a greater increase in the RewP to rewards from baseline to posttreatment, though the magnitude of this increase did not correlate with the magnitude of reduction in MDD symptoms. In contrast, the LPP to pleasant pictures did not change as a function of treatment, though greater baseline LPP responses to pleasant pictures predicted likelihood of remission from depression in

Table 2. Means and Standard Deviations for Event-Related Potential Measures

| | Reward Positivity Analyses | | | | Late Positive Potential Analyses | | | |
|--------------------------------|----------------------------|------|-------|------|----------------------------------|-------|-----------------|-------|
| | Win | | Loss | | Pleasant Picture | | Neutral Picture | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Raw Components | | | | | | | | |
| Baseline | | | | | | | | |
| PCIT-ED | 5.74 | 9.68 | 4.84 | 9.27 | 48.43 | 13.69 | 48.48 | 14.42 |
| Waitlist control | 5.62 | 7.65 | 4.68 | 7.44 | 47.61 | 14.11 | 45.13 | 13.34 |
| Posttreatment | | | | | | | | |
| PCIT-ED | 6.63 | 8.78 | 4.52 | 8.82 | 47.58 | 14.49 | 43.44 | 13.30 |
| Waitlist control | 3.30 | 7.38 | 1.71 | 8.32 | 47.22 | 11.84 | 42.75 | 12.18 |
| Residualized Components | | | | | | | | |
| Baseline | | | | | | | | |
| PCIT-ED | -0.03 | 5.79 | 0.12 | 5.52 | -1.59 | 6.04 | 1.84 | 6.43 |
| Waitlist control | -0.03 | 5.34 | 0.05 | 5.21 | 0.43 | 5.92 | -0.79 | 5.38 |
| Posttreatment | | | | | | | | |
| PCIT-ED | 0.65 | 5.83 | 0.09 | 5.86 | -0.14 | 6.15 | 0.18 | 5.61 |
| Waitlist control | -0.67 | 5.01 | -0.10 | 5.64 | 0.14 | 5.63 | -0.19 | 5.75 |

PCIT-ED, Parent-Child Interaction Therapy–Emotion Development.

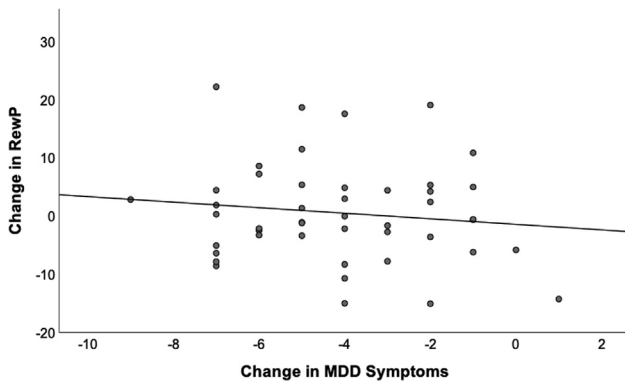


Figure 2. Association between change in depression symptoms and change in reward positivity (RewP). Graph illustrating the relationship between change in RewP at Pz and change in major depressive disorder (MDD) symptoms. The RewP score is the difference between posttreatment Win_{resid} and baseline Win_{resid} , and the MDD score is the difference between posttreatment and baseline MDD symptom scores.

PCIT-ED. These data provide novel evidence that a treatment designed to enhance the ability to experience joy and pleasure can enhance a neural indicator of hedonic response. The intriguing finding that baseline LPP responses to pleasant pictures predicted treatment response but did not change as a function of treatment suggests important dissociations among indicators of response to reward and emotional pictures and their role in treatment evaluation.

Numerous studies have shown that the RewP is reduced in depression (26,32–35) and predicts the likelihood of developing depression (25,34). The current findings add to this literature by showing that the RewP can be enhanced through a treatment designed to augment response to reward and pleasure. These findings contribute to the literature on biomarkers of treatment response in depression (62,63), providing

the first evidence of a biomarker that can be used effectively even in very young children. However, we should note that while the effect size of improvement in the treatment group was significantly larger than in the WL group, change when analyzed within the treatment group alone was not significant. In future work it will be important to determine whether the degree of RewP change during treatment predicts subsequent outcomes, such as maintenance of treatment gains or likelihood of depression reemergence, including whether such prediction has power over and above clinical assessments of depression change. If so, the RewP could have utility in helping to predict who needs further intervention or booster sessions to help maintain treatment response. Of note, while we found that the RewP showed a greater increase over treatment in the PCIT-ED group compared with the WL group, we did not find that the degree of change in the RewP correlated significantly with the degree of change in depression. This pattern contrasts with work in adults with MDD or anxiety disorder that found that the amount of decrease in depression symptoms over the course of treatment with either cognitive behavioral therapy or selective serotonin reuptake inhibitors correlated with the increase in the RewP over 12 weeks (64). It is possible that this difference across studies reflects the age of the samples (children vs. adults), the diagnostic category (all depression vs. mixed anxiety/depression), or the type of treatment (PCIT-ED vs. cognitive behavioral therapy or selective serotonin reuptake inhibitors).

The LPP to pleasant pictures did not change with treatment, though higher pleasant picture LPP at baseline predicted a greater likelihood of response to PCIT-ED. The RewP and the LPP have different neural generators, with the RewP more reflective of reward circuit functioning (29–31) commonly found to be altered in depression in relation to hedonic processing (28), while the LPP is more reflective of activity in occipital, inferotemporal, and parietal regions involved in emotion processing (65–67). In addition, the RewP is a response to

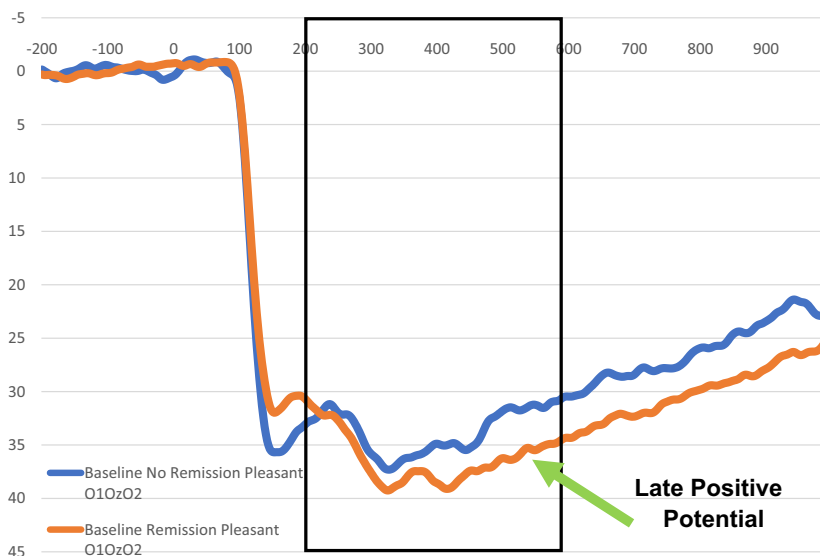


Figure 3. Baseline late positive potential and remission. Event-related potential waveforms at the average of O1, Oz, and O2 to pleasant pictures at baseline in children who did not remit from depression (blue lines) and children who did remit from depression (orange lines). Voltages are plotted with the more negative values at the top of the graph, as is the frequent convention in event-related potential reports.

feedback about an active choice made by an individual, while the LPP is thought to index more general attention to salient stimuli, both pleasant and unpleasant (68). It is possible that the more attentional nature of processes driving the LPP may make it less sensitive to change as a function of treatment, as PCIT-ED focused more on changing the active responding of the child in both positive and negative emotion processing during interactions with the caregiver than on the child's general attention to salient stimuli. At the same time, this characteristic of the LPP might make it a more sensitive indicator of emotion responsivity in an individual, such that individuals with greater attention to salient stimuli are more likely to benefit from treatment. Another possibility is that not all children understood or evaluated the differences between the positive and the neutral stimuli. We did not have the children make explicit ratings of the emotional content of the stimuli, and some of the children may not have perceived a difference between the two, though this would be unusual in children 4 years of age and older. If so, another intriguing possibility is that the children at baseline who were more sensitive to the difference between positive and neutral stimuli had more intact emotional processing that allowed them to benefit more from PCIT-ED. This hypothesis can be tested in future studies by having children make explicit ratings of the stimuli.

These findings need to be interpreted in the context of several limitations. The control condition was WL, which is not the most stringent comparator. There are no other empirically proven treatments for young children with depression, and thus using a WL control is an important first step. Future studies will need to dismantle PCIT-ED and determine the active ingredients compared with active control conditions. These data are also from a relatively short follow-up. While promising, it will be important to determine whether findings of increased RewP is maintained over time. Further, the measure of anhedonia was based on the sum of 3 clinically rated symptoms and may have had some limitation in range that might have reduced the magnitude of individual difference relationships. In addition, it may be that parent report of anhedonia in a child may miss variance that might be captured by self-report in samples from older subjects. We also do not have information about the temporal relationships between improvements in depression and increases in the RewP. Future studies using dense sampling designs will allow for analyzing leading and lagging relationships. In addition, the LPP task included only responses to pleasant and neutral pictures and did not include responses to negative pictures because of time constraints. As such, we cannot tell whether the relationship between treatment response and LPP that was specific to positive stimuli or reflected responses to emotionally evocative stimuli in general. Further, this study has a smaller population than the parent treatment study (23), as the ERPs were added after the parent study started. Lastly, we did not include multiple comparison correction given our a priori hypotheses.

In summary, the current study makes a novel and clinically relevant contribution to the literature on treatment of early childhood depression by demonstrating that both clinical ratings of anhedonia and RewP responses improved in depressed children undergoing PCIT-ED, a treatment

designed to enhance emotion development. These findings are particularly novel given that they are in very young children, where the speculative hope is that plasticity is greater and thus the impact may be more enduring. Further, greater baseline LPP responses to pleasant pictures was associated with a greater reduction in depression during PCIT-ED, consistent with LPP's being a useful tool to predict which children are most likely to respond to treatment. In addition, the fact that we saw these results with ERP measures of responses to reward and pleasant stimuli has clinical relevance, as ERP measures may end up being more feasible to implement in a clinical setting than other measures of neural responding, such as functional magnetic resonance imaging.

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DBM, DW, KG, and JLL had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JLL, DMB, and GH were responsible for concept and design. DMB, DW, KG, ESK, DK, GH, and JLL were responsible for acquisition, analysis, or interpretation of data. DMB, DW, KG, and DK were responsible for drafting of the manuscript. JLL, ESK, and GH were responsible for critical revision of the manuscript for important intellectual content. DMB, DW, and KG performed statistical analysis. DMB, JLL, and GH obtained funding. DMB, DW, KG, ESK, DK, GH, and JLL provided administrative, technical, or material support. DMB and JLL provided supervision.

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ClinicalTrials.gov: A Randomized Controlled Trial of PCIT-ED for Pre-school Depression; <https://clinicaltrials.gov/ct2/show/NCT02076425>; NCT02076425.

ARTICLE INFORMATION

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