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Probing Neurophysiological Processes Related to Self-Referential Processing to Predict Improvement in Adolescents With Depression Receiving Cognitive Behavioral Therapy

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ABSTRACT

BACKGROUND: Cognitive behavioral therapy (CBT) is a gold-standard approach for treating major depressive disorder in adolescents. However, nearly half of adolescents receiving CBT do not improve. To personalize treatment, it is essential to identify objective markers that predict treatment responsiveness. To address this aim, we investigated neurophysiological processes related to self-referential processing that predicted CBT response among female adolescents with depression.

METHODS: At baseline, female adolescents ages 13 to 18 years (N = 80) completed a comprehensive clinical assessment, and a self-referential encoding task was administered while electroencephalographic data were recorded. Baseline electroencephalographic data were utilized to identify oscillatory differences between healthy adolescents (n = 42) and adolescents with depression (n = 38). Following the baseline assessment, adolescents with depression received up to 12 weeks of CBT. Baseline differences in electroencephalographic oscillations between healthy adolescents and those with depression were used to guide CBT prediction analysis. Cluster-based event-related spectral perturbation analysis was used to probe theta and alpha event-related synchronization (ERS)/event-related desynchronization (ERD) response to negative and positive words.

RESULTS: Baseline analyses showed that, relative to the healthy adolescents, adolescents with depression exhibited higher levels of frontal theta ERS and greater posterior alpha ERD. Multilevel modeling identified primary neural pretreatment predictors of treatment response: greater theta ERS in the right prefrontal cortex after the onset of negative words and lower alpha ERD in both the right prefrontal cortex and posterior cingulate cortex. ERS and ERD associations with treatment response remained significant, with baseline depressive and anxiety symptoms included as covariates in all analyses.

CONCLUSIONS: Consistent with prior research, results highlighted that relative to healthy adolescents, adolescents with depression are characterized by prominent theta synchronization and alpha desynchronization over the prefrontal cortex and posterior cingulate cortex, respectively. Cluster-based event-related spectral perturbation analysis also identified key mechanisms underlying depression-related self-referential processing that predicted improved symptoms during the course of CBT. Ultimately, a better characterization of the neural underpinnings of adolescent depression and its treatment may lead to more personalized interventions.

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Adolescent depression is a significant public health concern, underscoring the urgency to improve clinical outcomes (1,2). Although cognitive behavioral therapy (CBT) is a gold-standard approach for addressing major depressive disorder (MDD) among adolescents, only half of adolescents respond to treatment (1,3,4). Accordingly, there is a pressing need to develop reliable, objective predictors of which adolescents with depression may respond to different treatment approaches.

CBT is designed to interrupt the cycle of negative thoughts, emotions, and behaviors associated with depressive symptoms (5), and accordingly, this approach targets negative self-referential processing biases (e.g., the tendency of individuals with depression to appraise depressogenic or negative content as being related to their own person and experience), a core feature of depression (6). Previous functional magnetic resonance imaging studies have investigated neural activity associated with negative biases in self-referential processing (6–8), with other studies demonstrating that pretreatment neural responses during self-referential processing predict clinical outcomes among patients with MDD receiving CBT or selective serotonin reuptake inhibitors

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(9–11). For example, pretreatment blunted activation within the anterior cingulate cortex following negative words predicted depressive symptom improvement following CBT (10). Although promising, there are many challenges associated with integrating functional magnetic resonance imaging into clinical settings, particularly given scalability and cost. In contrast, there are now several projects using electroencephalography (EEG), which is less invasive and provides exceptional temporal resolution, to predict treatment response among individuals with depression (12).

In our previous EEG studies probing self-referential processing in depression (13,14), adolescents with depression, in contrast to their healthy female counterparts, exhibited larger P1 and late positive potential (LPP) amplitudes in response to negative words, which correlated with a more maladaptive self-view and self-criticism. A significant number of existing studies have relied on time-domain event-related potentials (ERPs); however, event-related oscillation analysis offers a distinct advantage over ERPs by providing information about the power of different frequency bands. This potentially allows for a more comprehensive evaluation of neural processes compared with the single-point estimates provided by ERPs. This spectral information can be crucial for understanding mechanisms underlying self-referential processing and depression. Understanding the specific frequency bands involved in self-referential processing dysfunction in depression may pave the way for targeted brain stimulation techniques. Event-related desynchronization (ERD)/event-related synchronization (ERS) may offer temporal and frequency specificity, thereby facilitating a deep understanding of the neural mechanisms underlying self-referential processing and aiding in tailoring treatment strategies. ERD signifies a reduction in the power of brain oscillations within particular frequency bands, typically associated with cognitive engagement or motor function, while ERS indicates an augmentation in oscillatory power, reflecting neural synchronization (15). ERS is often observed during tasks that involve passive processing or when attention is focused on a particular stimulus (15). Specifically, emotional stimulus processing involves distinct brain oscillatory dynamics, particularly theta (4–8 Hz) synchronization and alpha (8–12 Hz) desynchronization (16). Frontal theta synchronization characterizes early stages of affective processing, potentially reflecting automatic and implicit processing (17,18), and increased prefrontal theta ERS has been observed in individuals with MDD (19). Moreover, posterior alpha-band activity has been linked to mental imagery and introspective cognitive processes (20–22). Taken together, previous studies suggest that frontal theta synchronization reflects early affective processing (17,18), and posterior alpha-band activity is associated with internal focus and cognitive processes, potentially indicating negative biases in self-referential processing (23,24).

Building on prior research, in the current study, we utilized cluster-based event-related spectral perturbation (ERSP) analysis to test cognitive-affective mechanisms associated with self-referential processing, focusing on theta and alpha ERS/ERD responses to negative and positive words. Given the novelty of this research and the limited understanding of the neural correlates of CBT prediction in treatment of adolescent depression, we adopted a data-driven approach wherein differences between participants with MDD and healthy control (HC) participants guided our hypotheses. Thus, we hypothesized that compared with their healthy counterparts, adolescents with depression would demonstrate aberrant theta and alpha activity during self-referential tasks involving negative stimuli. We also hypothesized that these neurophysiological markers would then predict individual responsiveness to CBT in adolescents with depression.

METHODS AND MATERIALS

Participants

The study included female adolescents (N = 80) ages 13 to 18 years. Healthy adolescents (n = 42) and adolescents with depression (n = 38) were recruited through community advertisements. Study advertisements targeted depressed adolescents seeking treatment or healthy adolescents. All participants were proficient in English and right-handed. For inclusion in the depression group, participants met criteria for a current major depressive episode. For HC participants, exclusion criteria comprised a history of depression, mania/hypomania, anxiety, eating disorders, substance use disorders, attention-deficit/hyperactivity disorder, psychosis, mental retardation, organic brain syndrome, and head injury resulting in loss of consciousness for 5 minutes or seizures. Individuals diagnosed with MDD were subject to the same exclusion criteria, with the exception that they could have a history of MDD. Adolescents with depression were permitted to be on antidepressant medication, with 4 participants reporting use of a selective serotonin reuptake inhibitor (Table 1).

Procedure

Study procedures were approved through the Partners Institutional Review Board. Informed assent and parental consent were obtained for 13- to 17-year-old adolescents, and 18-year-old adolescents consented. The initial assessment spanned 2 study visits. On the first visit, the adolescents completed a sociodemographic form, a semistructured clinical interview to assess lifetime psychiatric disorders, and self-report questionnaires measuring current depressive and anxiety symptoms. During the second study visit, participants completed the self-referential encoding task while 128-channel EEG data were recorded.

Following the baseline procedures, participants with depression completed up to 12 weekly CBT sessions, each lasting approximately 50 minutes. For details regarding the CBT sessions, see the Supplement.

Clinical Assessment

At baseline, participants were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL) (25). The K-SADS-PL is a structured clinical interview that assesses lifetime DSM-IV psychiatric disorders (26). Clinical interviews were administered by graduate students and research assistants with bachelor's degrees after they had received a comprehensive 40-hour training program, including didactics, simulated interviews, and direct supervision. To ensure consistency and reliability, the principal

Table 1. Descriptive Statistics for the Sample Stratified by Group

	Healthy Female Adolescents, n = 42	Female Adolescents With Major Depressive Disorder, n = 38	t/χ^2 Test	p Value
Age, Years	15.14 (1.60)	15.87 (1.69)	$t_{76.097} = -1.963$	.053
Race			$\chi^2_4 = 4.255$	.373
Asian	4 (9.52%)	2 (5.26%)		
Black/African American	0 (0%)	1 (2.63%)		
Multiracial	3 (7.14%)	6 (15.79%)		
Native American	0 (0%)	0 (0%)		
White	35 (83.33%)	28 (73.68%)		
Unknown or not reported	0 (0%)	1 (2.63%)		
Hispanic Ethnicity	3 (7.14%)	7 (18.42%)	$\chi^2_1 = 1.404$	.236
Family Income			$\chi^2_4 = 10.79$	.039
<$25,000	0 (0%)	4 (10.53%)		
$25,000–$49,999	0 (0%)	1 (2.63%)		
$50,000–$74,999	2 (4.76%)	7 (18.42%)		
≥$75,000	32 (76.19%)	22 (57.89%)		
Unknown or not reported	8 (19.05%)	4 (10.53%)		

Values are presented as mean (SD) or n (%).

investigator (RPA) reviewed a randomly selected 20% of the interviews from digital audio recordings. Interrater reliability was assessed using Cohen's kappa coefficients for depressive disorders, which yielded excellent results (κ = 1.00).

At baseline and prior to each CBT session, participants completed self-report measures of depression and anxiety symptoms. The Beck Depression Inventory II (BDI-II) was administered at baseline and during each of the 12 weekly sessions, totaling 13 assessments. To analyze symptom trajectories, we incorporated baseline BDI-II scores as a covariate. This approach allowed us to control for initial symptom severity and observe changes in depressive symptoms from session 1 through session 12. The BDI-II (5) includes 21 items and assesses the severity of depressive symptoms over the past 2 weeks. Each item is scored on a scale of 0 to 3, with higher scores indicating a higher degree of symptom severity. For the current study, Cronbach's alpha for BDI-II ranged from 0.882 to 0.966 across time points. Additionally, the Multidimensional Anxiety Scale for Children (MASC) (27) was used to assess anxiety symptom severity. To analyze the trajectories of anxiety symptoms, we included baseline MASC scores as a covariate. This approach enabled us to control for initial symptom severity and track changes in anxiety symptoms from session 1 through session 12, with assessments occurring every 2 sessions (at baseline and sessions 2, 4, 6, 8, 10, and 12, for a total of 7 sessions). The MASC includes 39 items, and each item is scored on a scale ranging from 0 to 3, with higher scores indicating more severe anxiety symptoms. In this study, Cronbach's alpha ranged from 0.809 to 0.928 across assessments.

Experimental Task

The self-referential encoding task included 80 trials, including 40 positive and 40 negative adjectives, selected from the Affective Norms for English Words (28). See the Supplement for further details about the experimental tasks.

EEG Recording and Data Analysis

EEG data were recorded using a 128-channel net from HydroCel GSN (Electrical Geodesics, Inc.). Continuous EEG data were sampled at 250 Hz and referenced to Cz. EEG data were processed using EEGLAB version 14.2. See the Supplement for details on EEG preprocessing.

Event-Related Spectral Perturbation

Following preprocessing and the activation of independent components for each trial, a spectrographic representation called ERSP was generated. This was achieved by applying 3-cycle Morlet wavelets in the frequency range of 3 to 50 Hz using the EEGLAB software (29,30). The ERSP allowed us to visualize the average event-related spectral power changes of selected clusters over time relative to an experimental event. To compute the ERSP, we averaged the power spectra across all trials of the independent components within each cluster. Each epoch was extracted within the time window of −200 to 1200 ms, with the baseline defined as the interval from −200 to 0 ms. In Figure 1, the ERSP results were then plotted on a 2-dimensional time-frequency plane as relative spectral log amplitudes from the baseline, with different colors representing distinct power values (29,30). A prestimulus baseline correction was applied to the resulting ERSP, which was averaged across all trials. This correction utilized the EEGLAB newtimef function (31). The function also generated a surrogate distribution at each frequency by permuting baseline values across both time and trials. It tested whether the original ERSP values lay in the 0.5% or 99.5% tail of the surrogate distribution at any given frequency. If a time-frequency point met this criterion, it was deemed significant at $\alpha < 0.01$ after correction for multiple comparisons using the false discovery rate procedure (31). Ultimately, only ERSP values that survived this bootstrap-based statistical analysis ($\alpha < 0.01$, number of permutations = 1000) concerning baseline were included in the group analysis.

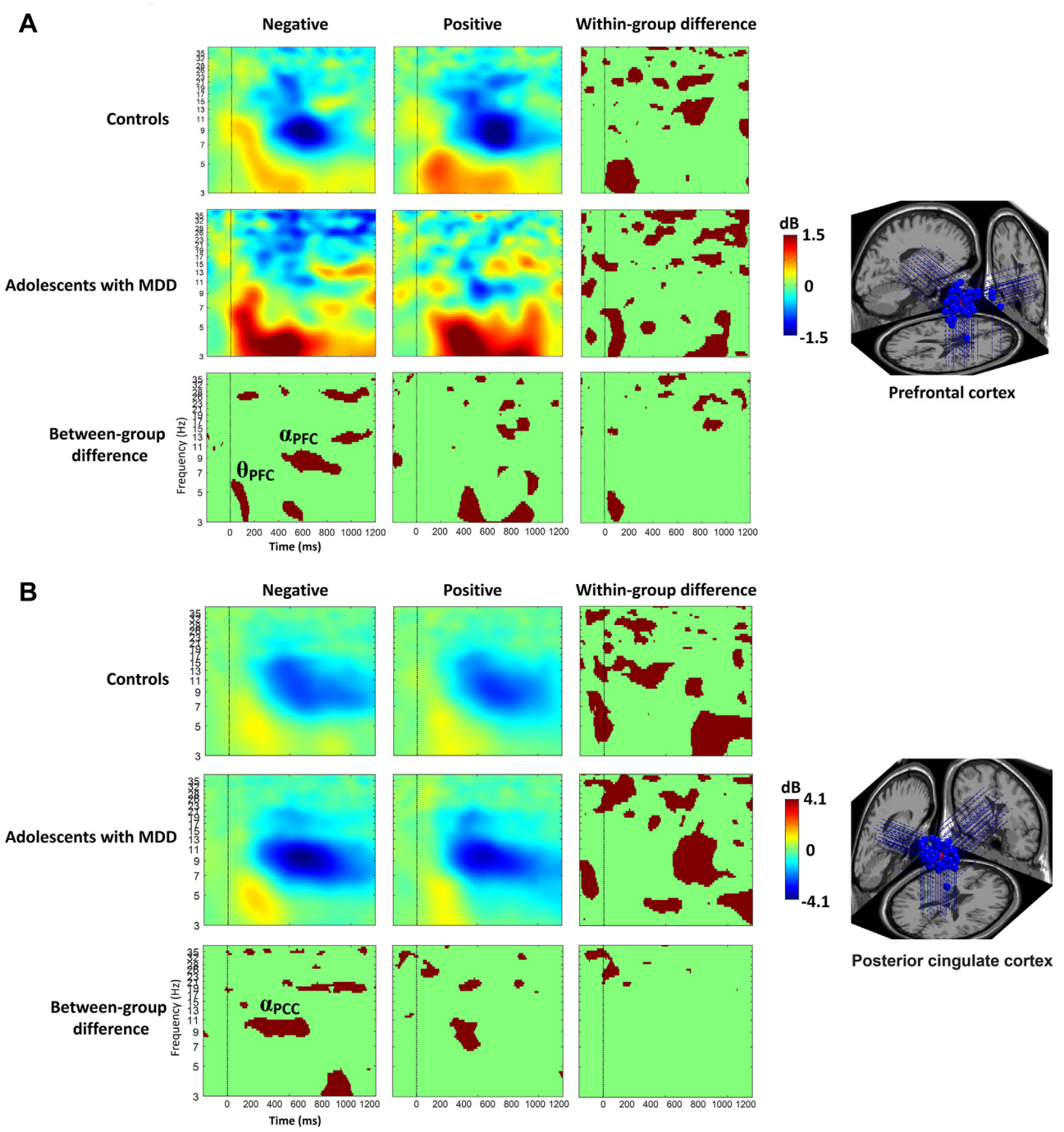

Figure 1. Heat maps of event-related power for each condition (negative vs. positive) and group (healthy control participants vs. adolescents with major depressive disorder [MDD]) with false discovery rate–corrected *p* values for each effect in **(A)** for the right prefrontal cortex (PFC) and in **(B)** for the dorsal posterior cingulate cortex (PCC). This figure illustrates the increases or decreases in event-related power between conditions from −200 to 1200 ms. Red corresponds to event-related synchronization, and blue corresponds to event-related desynchronization.

Statistical Analysis

Data from 4 participants were excluded due to poor EEG data quality (HC group, $n = 2$; MDD group, $n = 2$). The exclusion was based on a comprehensive quality control process, including the identification and removal of noisy channels, visual inspection for artifacts, and the application of the artifact subspace reconstruction method. These steps revealed significant issues that led to the identification of fewer than 3 independent

brain components during source localization, which prompted the exclusion of these participants from further analysis.

To predict treatment outcome, modified intent-to-treat analyses were utilized. However, patients with missing EEG data or those who dropped out before completing a minimum of 3 weeks of CBT were excluded (n = 3). Consistent with prior research, a minimum of 3 weeks of CBT was required to ensure meaningful exposure to the therapy and accurate assessment of treatment outcomes (1). Participants were offered 12 weekly sessions, and 58% of participants whose data were analyzed completed all sessions, with a range of 3 to 12 sessions completed. The average number of CBT sessions completed was 9.72 (SD = 3.22).

Baseline ERSP Analysis. Baseline ERSP group comparisons were analyzed using mixed-model analysis of variance models. The analysis of variance model assessed the condition (within group: negative vs. positive) and the group (between group: HC participants vs. participants with MDD). To address multiple comparisons, we applied permutation statistics using the EEGLAB toolbox.

Predicting CBT Treatment Outcome. To test whether baseline neurophysiological markers predicted improvements in symptoms among adolescents with depression, multilevel modeling using the lme4 (32) and lmerTest (33) R packages (version 4.3.1) were utilized. Based on the observed times and frequency ranges of the most pronounced effects, multilevel models included averaged theta ERSP values in the time windows 50 to 200 ms and averaged alpha ERSP values in the time windows 400 to 750 ms for the prefrontal cortex (PFC) and 200 to 600 ms for the posterior cingulate cortex (PCC). Multilevel models included ERSP features (theta and alpha) and time, with time grand mean centered to represent the estimated posttreatment BDI-II scores. Baseline BDI-II scores were included as a covariate to adjust for pretreatment levels of depression. Intercepts and slopes were treated as random effects within each model to account for variability across participants. Additionally, covariates such as age, medication use (yes/no), and their interactions with time were included in all models.

RESULTS

CBT Outcomes

To explore the relationship between the number of CBT sessions and changes in EEG measures, we examined Spearman's rank correlation coefficients. Overall, the results indicated no significant correlations between the number of CBT sessions and the ERSP measures: theta from the PFC (ρ = 0.013, p = .958), alpha from the PFC (ρ = −0.086, p = .728), and alpha from the PCC (ρ = −0.039, p = .885). The study also showed a significant difference in depressive symptoms from pre- to posttreatment among individuals with depression (t_{32} = 4.503, p < .001). Among treatment completers, the mean pretreatment BDI-II scores were in the severe range (mean = 31.73, SD = 10.76), whereas posttreatment scores were in the mild range (mean = 20.24, SD = 16.62).

Baseline Group Comparisons

Group differences emerged in the right PFC and PCC. Specifically, there were changes in ERSP within the right PFC cluster across 2 conditions, spanning from −200 to 1200 ms, with time 0 indicating the onset of positive or negative word presentation. As anticipated, we found prominent low-frequency synchronization and alpha desynchronization (Figure 1A). The first cluster contained independent components from 64 of 73 participants and had a dipole centroid approximately localized to the right PFC. Plots containing false discovery rate–corrected p values across all time-frequency points for the condition, group, and condition × group interaction effects are presented in Figure 1A. We found the group differences primarily within the negative word condition. Within the 0- to 300-ms window, the depression group exhibited significantly greater theta (4–7 Hz) ERS than the control group (p < .05), and for the 300- to 700-ms window, we observed that the alpha (8–13 Hz) ERD of the depression group showed a significant weakening compared with the control group. Additionally, the PCC cluster contained at least 1 independent component from 69 of 73 participants. It had a dipole centroid approximately localized to the PCC. Figure 1B shows ERSP plots within the PCC cluster across the 2 conditions and groups. We observed that participants with depression exhibited a higher alpha ERD than the HC participants (p < .05) within the 300- to 700-ms time window. Significant ERSP features for the negative condition were then used to predict changes in depression and anxiety symptoms.

Predicting CBT Outcome

Depression Symptoms. Modified intent-to-treat analyses revealed a significant effect of time (b = −1.16, p < .001). We then tested whether neurophysiological activity predicted treatment outcome (Figure 2; left column, Table 2). Specifically, within the right PFC, we found that there was a significant pretreatment $\text{theta}_{\text{PFC}}$ × time interaction (b = −0.325, $t_{160.28}$ = −2.219, p = .028), indicating that female adolescents with depression with a greater theta following negative words had a relatively greater reduction in depressive symptoms over the course of CBT. Similarly, there was a significant pretreatment $\text{alpha}_{\text{PFC}}$ × time interaction (b = −0.278, $t_{161.92}$ = −2.206, p = .029) wherein female adolescents with depression with greater alpha response following negative words were characterized by greater depressive symptom improvement. With regard to the PCC, the pretreatment $\text{alpha}_{\text{PCC}}$ × time interaction was also significant (b = −0.575, $t_{160.35}$ = −7.495, p < .001); adolescents with depression who exhibited greater pretreatment alpha following negative words were more likely to show greater depressive symptom improvement. To further examine the interaction effect between time and baseline ERD/ERS on depression symptoms, simple slope analyses (34) were estimated for low (i.e., 1 SD below the mean), average, and high (1 SD above the mean) values of baseline ERD/ERS. The association between time and depression severity (BDI-II) was greater for high values among those with increased PFC theta activity (β = −1.553, SE = 0.224, p < .001) and PFC alpha activity (β = −1.596, SE = 0.238, p < .001) compared with the average (theta: β = −1.179, SE = 0.146, p < .001; alpha: β = −1.168, SE = 0.147, p < .001) and low (theta: β = −0.804,

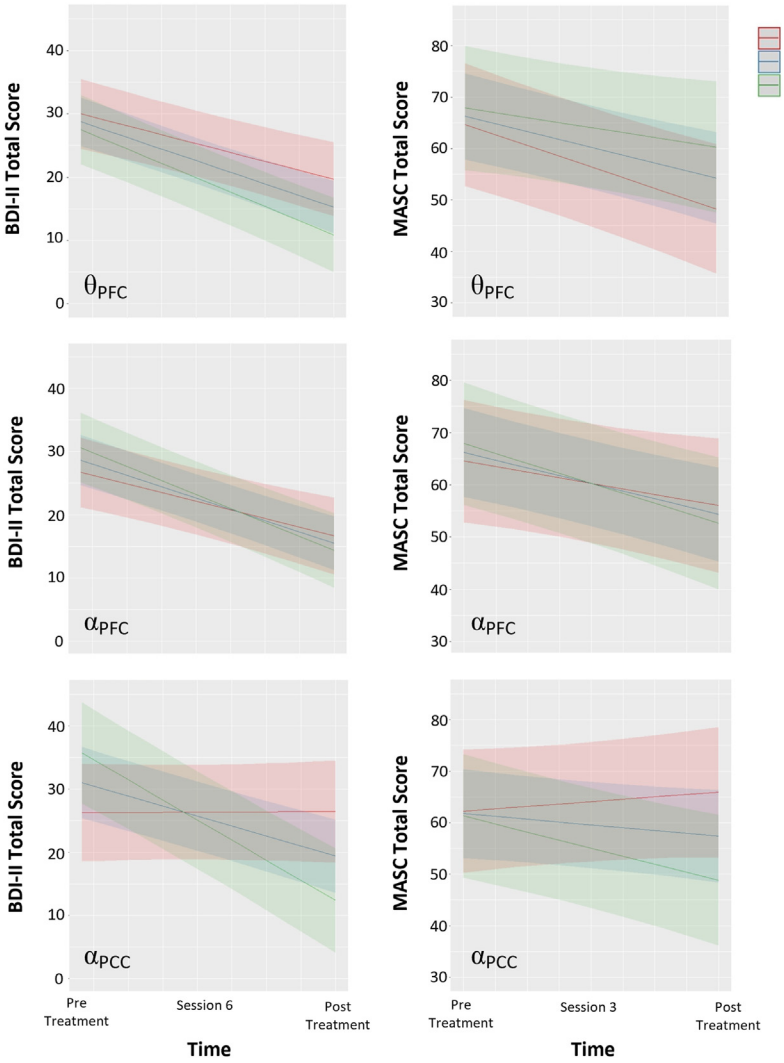

Figure 2. Plot of pretreatment event-related spectral perturbation responses × time interactions from the models. Each row corresponds to a different event-related spectral perturbation response to negative words. Top row: θ_{PFC} × time interaction; middle row: α_{PFC} × time interaction; bottom row: α_{PCC} × time interaction. The horizontal axis shows time (session), and the vertical axis shows Beck Depression Inventory II (BDI-II, left column) and Multidimensional Anxiety Scale for Children (MASC, right column) scores. PCC, posterior cingulate cortex; PFC, prefrontal cortex.

Table 2. Event-Related Spectral Perturbation Feature (Theta PFC, Alpha PFC, Alpha PCC) × Time Interactions Predicting Depressive Symptom Change During Cognitive Behavioral Therapy

Theta PFC			Alpha PFC			Alpha PCC		
Variable	b (SE)	*p* Value	Variable	b (SE)	*p* Value	Variable	b (SE)	*p* Value
(Intercept)	4.347 (25.07)	.864	(Intercept)	24.19 (26.32)	.367	(Intercept)	−96.00 (26.83)	.002[a]
Baseline BDI-II	0.572 (0.221)	.021[b]	Baseline BDI-II	0.588 (0.240)	.028[b]	Baseline BDI-II	0.857 (0.225)	.002[a]
Time	−1.736 (1.744)	.321	Time	−3.895 (1.808)	.033[b]	Time	−8.750 (1.443)	<.001[c]
Age	−0.271 (1.372)	.845	Age	1.291 (1.437)	.377	Age	4.209 (1.425)	.008[a]
Medication	7.850 (6.774)	.252	Medication	−1.568 (7.163)	.828	Medication	17.367 (6.957)	.021[b]
Theta PFC	−5.403 (1.791)	.005[a]	Alpha PFC	−1.198 (1.469)	.419	Alpha PCC	−5.507 (1.171)	<.001[c]
Time × Age	0.041 (0.107)	.706	Time × age	0.153 (0.110)	.166	Time × age	0.356 (0.089)	<.001[c]
Time × Medication	0.810 (0.605)	.182	Time × medication	−0.232 (0.623)	.710	Time × medication	1.914 (0.487)	<.001[c]
Time × Theta PFC	−0.325 (0.147)	.028[b]	Time × alpha PFC	−0.278 (0.126)	.029[b]	Time × alpha PCC	−0.575 (0.077)	<.001[c]

BDI-II, Beck Depression Inventory II; PCC, posterior cingulate cortex; PFC, prefrontal cortex.
[a]$p < .01$.
[b]$p < .05$.
[c]$p < .001$.

Table 3. Event-Related Spectral Perturbation Feature (Theta PFC, Alpha PCC, Alpha PCC) × Time Interactions Predicting Change in Anxiety Symptoms During Cognitive Behavioral Therapy

Theta PFC			Alpha PFC			Alpha PCC		
Variable	b (SE)	*p* Value	Variable	b (SE)	*p* Value	Variable	b (SE)	*p* Value
(Intercept)	−39.373 (36.573)	0.291	(Intercept)	−32.156 (37.053)	0.392	(Intercept)	−53.92 (44.86)	.247
Baseline MASC	0.788 (0.127)	<.001[a]	Baseline MASC	0.790 (0.124)	<.001[a]	Baseline MASC	0.806 (0.219)	.003[b]
Time	−6.489 (3.267)	.051	Time	−5.416 (3.395)	.115	Time	−5.340 (2.350)	.026[c]
Age	2.398 (2.058)	.252	Age	2.059 (2.074)	.327	Age	2.903 (2.324)	.228
Medication	21.94 (11.07)	.052	Medication	25.91 (11.20)	.024[c]	Medication	28.05 (9.900)	.009[b]
Theta PFC	−0.519 (2.763)	.852	Alpha PFC	2.342 (2.253)	.303	Alpha PCC	−3.371 (1.712)	.061
Time × Age	0.309 (0.200)	.128	Time × age	0.250 (0.206)	.228	Time × age	0.174 (0.145)	.235
Time × Medication	4.076 (1.158)	<.001[a]	Time × medication	4.454 (1.171)	<.001[a]	Time × medication	4.145 (0.828)	<.001[a]
Time × Theta PFC	0.035 (0.280)	.900	Time × alpha PFC	0.155 (0.239)	.519	Time × alpha PCC	−0.510 (0.127)	<.001[a]

MASC, Multidimensional Anxiety Scale for Children; PCC, posterior cingulate cortex; PFC, prefrontal cortex.
[a]$p < .001$.
[b]$p < .01$.
[c]$p < .05$.

SE = 0.223, $p < .001$; alpha: β = −0.740, SE = 0.248, $p = .003$) values. Similarly, the association between time and depression severity (BDI-II) was greater for increased PCC alpha activity (β = −1.798, SE = 0.268, $p < .001$) relative to the average value (β = −1.069, SE = 0.176, $p < .001$) but nonsignificant for the low value (β = −0.339, SE = 0.286, $p = .238$). Additionally, significant interactions ($p \leq .05$) were analyzed using the Johnson-Neyman technique (35) to plot the region of significance (Figure S2). The main effect of time on BDI-II scores was significant only when the values exceeded the following thresholds: (−1.243), PFC alpha (−3.224), and PCC alpha (−4.162). This finding suggests that over time, individuals with higher baseline levels of these neural markers tend to experience a significant reduction in depressive symptoms, indicating symptom improvement. We also estimated multilevel models to investigate whether ERPs (P1 and early LPP from posterior channels and the late LPP from frontal channels) predicted treatment response. Greater LPP activity in posterior channels over time was linked to better improvement in depressive symptoms for female adolescents with depression. However, neither the P1 nor late LPP predicted treatment response (see the Supplement for details).

Anxiety Symptoms. We tested whether neurophysiological activity predicted changes in anxiety symptoms during treatment (Figure 2; right column, Table 3). Within the right PFC, the pretreatment $theta_{PFC}$ × time interaction was nonsignificant (b = 0.035, $t_{71.64} = 0.126$, $p = .900$). We also found no significant $alpha_{PFC}$ × time interaction effect (b = 0.1548, $t_{74.09} = 0.648$, $p = .519$). However, within the PCC cluster, the pretreatment $alpha_{PCC}$ × time interaction emerged (b = −0.510, $t_{70.03} = -4.022$, $p < .001$); adolescents with depression who exhibited greater pretreatment alpha following negative words exhibited greater anxiety symptom improvement. Further analyses of the interaction effects on MASC scores, including a simple slope analysis and a Johnson-Neyman plot, are provided in the Supplement. The main effect of time on total MASC scores was significant only within the interval (−1.948, −0.160) for PCC alpha (Figure S3).

DISCUSSION

In the current study, we investigated neurophysiological processes related to self-referential processing among female adolescents with depression. Using cluster-based ERSP analysis, we first identified distinct theta ERS and alpha ERD patterns that differentiated adolescents with depression and healthy adolescents and then leveraged differences to predict CBT responsiveness. These findings are promising because nearly half of adolescents with depression do not respond to CBT; thus, developing tools that potentially predict responsiveness may help guide treatment decision making.

In general, theta ERS and alpha ERD likely reflect underlying neural processes related to cognitive and emotional processing (16). Theta activity is closely related to internal focus and is associated with emotions such as anxiety, and it has also been linked to learning and memory (36). Alterations in frontal theta related to emotional processing are primarily due to the hippocampus being the main generator of theta waves within the frontal lobe (37,38). Prior studies have shown increased theta activity in the PFC among individuals with MDD [for a review, see (39)]. This association is consistent with the greater theta ERS observed in our baseline analysis among adolescents with depression when categorizing negative words as self-referent, which suggests a potential link to an increased tendency toward sensitivity to negative self-referential processing bias among adolescents with depression.

Alpha power has been associated with higher-level cognitive functions such as imagination, internal attention, and self-reflection (23,40,41). Notably, increased right prefrontal activation when exposed to negative words has been shown to correspond to indicators of negative emotional states and potential depressive tendencies (42). Moreover, alpha oscillations in posterior brain regions are associated with top-down control and are active inhibitory mechanisms (43). Our findings showed greater alpha ERD in the PCC among adolescents with depression exposed to negative words. Although previous research on schizophrenia has linked reduced alpha ERD to increased negative self-referential processing (44), our results may indicate that greater alpha ERD reflects a distinct

mechanism in depression. This pattern could suggest increased allocation of attentional resources to negative stimuli rather than a shift away from internal introspection. This may imply that in depression, the neural dynamics associated with alpha ERD in the PCC are more complex and could reflect an enhanced focus on negative content, consistent with the attentional bias often observed in depression. However, without explicit behavioral data, this interpretation should be considered cautiously, and future studies are needed to clarify the underlying mechanisms.

ERSP features derived from the PFC indicated that greater theta power was associated with improvements in depressive symptoms, which is consistent with research investigating the association of frontal theta with a favorable treatment outcome (39,45). In the context of CBT, individuals are often encouraged to challenge and reframe negative self-referential biases to facilitate cognitive restructuring and behavioral change (46). Our findings suggest that higher theta power during self-referential processing may be a potential biomarker for CBT response. This is consistent with a deficit model of CBT (44) in which the therapy aims to improve cognitive and neural processes that are impaired in depression. Because the depression group exhibited higher theta than the HC group, it is possible that high theta reflects a process that goes awry in depression. Consequently, adolescents with higher baseline theta may have the most room for improvement through CBT interventions. Additionally, this heightened theta response could suggest greater neural plasticity or receptivity (47) to therapeutic interventions, enabling individuals with depression to better integrate cognitive and behavioral activities during CBT. By actively processing negative self-referential information, these individuals may be more inclined to confront and modify maladaptive thought patterns, thereby deriving enhanced benefits from the therapeutic strategies employed in CBT. Thus, one possible interpretation is that adolescents with depression with a heightened theta response to negative words during self-referential processing may be more likely to effectively engage in countering or alleviating negative self-referential biases and to derive benefits from cognitive and behavioral activities during the course of CBT.

Additionally, greater alpha power derived from the PCC is associated with better symptom changes in both depression and anxiety. Consistent with other studies, alpha activity is associated with the allocation of attentional resources (48) and cognitive flexibility (49), reflecting a shift away from persistent dwelling on negative thoughts, a key focus of CBT (50,51). Persistent fixation on a depressogenic thought reflects a difficulty in adaptively redirecting attention (52). The cognitive inflexibility hypothesis of rumination (53) posits that this challenge in shifting attention is due to compromised cognitive flexibility (9,54,55). In our prior work, we observed a direct relationship between alpha power and rumination among adolescents with depression (56), which may more broadly index challenges with cognitive flexibility (52). Because the cornerstone of CBT involves challenging and reframing negative thoughts, individuals with higher cognitive flexibility may exhibit greater receptivity to these therapeutic interventions.

Although the current study has several strengths, there are some notable limitations. First, the sample size is modest, and data were only collected from female adolescents. Thus, a larger and more diverse sample would be beneficial to ensure the generalizability of our findings. Second, we tested neurophysiological markers in the context of CBT with no comparison condition (e.g., adolescents randomly assigned to receive CBT vs. antidepressant medication). Thus, it is unknown whether our findings reflect a specific predictor of CBT or a broader indicator of treatment responsiveness. Third, given the high comorbidity between MDD and anxiety disorders, excluding individuals with anxiety disorders might have reduced the generalizability of our findings. Although this exclusion allows for a more targeted examination of the mechanisms that predict treatment response in the context of adolescent MDD, it may limit the generalizability of the results. Finally, EEG data were only acquired at baseline, precluding our ability to test changes in neurophysiological markers mid- and posttreatment. Understanding the dynamic neural changes together with the temporal progression of symptom change is critical.

Conclusions

This study identified cluster-based ERSP underlying self-referential processing that predicted improved depression and anxiety symptoms during the course of CBT among female adolescents with depression. These findings highlight the importance of considering individual differences in neural functioning when designing and implementing interventions. By clarifying predictors of treatment response over time, this may allow us to build clinical tools that optimize treatments for adolescents with depression. Ultimately, a better understanding of the neural underpinnings of adolescent depression and its treatment may lead to more effective and personalized interventions.

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