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# Cortical Connectivity Moderators of Antidepressant vs Placebo Treatment Response in Major Depressive Disorder
## Secondary Analysis of a Randomized Clinical Trial

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**IMPORTANCE** Despite the widespread awareness of functional magnetic resonance imaging findings suggesting a role for cortical connectivity networks in treatment selection for major depressive disorder, its clinical utility remains limited. Recent methodological advances have revealed functional magnetic resonance imaging–like connectivity networks using electroencephalography (EEG), a tool more easily implemented in clinical practice.

**OBJECTIVE** To determine whether EEG connectivity could reveal neural moderators of antidepressant treatment.

**DESIGN, SETTING, AND PARTICIPANTS** In this nonprespecified secondary analysis, data were analyzed from the Establishing Moderators and Biosignatures of Antidepressant Response in Clinic Care study, a placebo-controlled, double-blinded randomized clinical trial. Recruitment began July 29, 2011, and was completed December 15, 2015. A random sample of 221 outpatients with depression aged 18 to 65 years who were not taking medication for depression was recruited and assessed at 4 clinical sites. Analysis was performed on an intent-to-treat basis. Statistical analysis was performed from November 16, 2018, to May 23, 2019.

**INTERVENTIONS** Patients received either the selective serotonin reuptake inhibitor sertraline hydrochloride or placebo for 8 weeks.

**MAIN OUTCOMES AND MEASURES** Electroencephalographic orthogonalized power envelope connectivity analyses were applied to resting-state EEG data. Intent-to-treat prediction linear mixed models were used to determine which pretreatment connectivity patterns were associated with response to sertraline vs placebo. The primary clinical outcome was the total score on the 17-item Hamilton Rating Scale for Depression, administered at each study visit.

**RESULTS** Of the participants recruited, 9 withdrew after first dose owing to reported adverse effects, and 221 participants (150 women; mean [SD] age, 37.8 [12.7] years) underwent EEG recordings and had high-quality pretreatment EEG data. After correction for multiple comparisons, connectome-wide analyses revealed moderation by connections within and between widespread cortical regions—most prominently parietal—for both the antidepressant and placebo groups. Greater alpha-band and lower gamma-band connectivity predicted better placebo outcomes and worse antidepressant outcomes. Lower connectivity levels in these moderating connections were associated with higher levels of anhedonia. Connectivity features that moderate treatment response differentially by treatment group were distinct from connectivity features that change from baseline to 1 week into treatment. The group mean (SD) score on the 17-item Hamilton Rating Scale for Depression was 18.35 (4.58) at baseline and 26.14 (30.37) across all time points.

**CONCLUSIONS AND RELEVANCE** These findings establish the utility of EEG-based network functional connectivity analyses for differentiating between responses to an antidepressant vs placebo. A role emerged for parietal cortical regions in predicting placebo outcome. From a treatment perspective, capitalizing on the therapeutic components leading to placebo response differentially from antidepressant response should provide an alternative direction toward establishing a placebo signature in clinical trials, thereby enhancing the signal detection in randomized clinical trials.

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Supplemental content

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Despite substantive evidence supporting the efficacy of antidepressants vs placebo for major depressive disorder (MDD),[1,2] the lack of an accepted signature of placebo response has stymied the development of antidepressant drugs. As a result, trials in an otherwise heterogeneous sample of patients with MDD include many placebo responders, resulting in modest effect sizes (Cohen $d$ ~ 0.3)[1,3,4] and many failed trials. One avenue for improving the yield of drug development lies in grounding an understanding of the neural functioning associated with placebo response.

With 40% to 50% of patients with MDD not responding to antidepressant treatment,[5-7] coupled with the low predictive value of clinical and sociodemographic variables,[8,9] substantial attention has been directed at identifying pretreatment neural features that predict treatment response in MDD.[6,7] Resting-state functional magnetic resonance imaging (fMRI) studies, for example, found that increased connectivity with the cognitive control network and decreased connectivity with the default mode network have been associated with antidepressant treatment response.[6,7,10,11] However, prior work has not included a placebo control group, thus confounding treatment effects with nonspecific symptom change across time. Functional MRI is also ultimately limited by its cost and requirement for significant technical expertise.[12]

Electroencephalography (EEG), by contrast, provides a financially and logistically favorable neural assessment tool, with the additional benefits of its high temporal resolution and more direct measurement of neural function. With the use of EEG, increased frontal and parieto-occipital alpha power, increased anterior cingulate theta power, and greater global signal entropy have been found to be associated with better antidepressant treatment response.[7,10,11,13-23] However, as with fMRI, the identification of EEG neural markers predictive of antidepressant response is limited by the lack of placebo-controlled clinical trials with sufficient statistical power.[10,13] Moreover, one of the most promising treatment predictive findings from antidepressant treatment studies (namely, rostral cingulate theta power) appears to predict outcome for antidepressants and placebo.[18,24] A recent meta-analysis suggests that, while there is great promise in EEG-guided MDD biomarker prediction, the field is currently limited by several factors, including sample size and lack of out-of-sample validation.[19]

Although EEG has great promise with respect to clinical translation, its low spatial precision and sensitivity to volume conduction (which leads to signal blurring) limit its utility for network-level connectivity analyses. This challenge has been addressed by recent advances in analytical methods, first in magnetoencephalography and then in EEG.[25,26] By orthogonalizing source-estimated signals for instantaneous correlations, which arise primarily owing to volume conduction, and then correlating the power envelope (ie, instantaneous power) time series across different parts of the brain, studies have found large-scale connectivity patterns consistent with an fMRI-derived understanding of canonical human cortical networks.[25,27]

We therefore sought to investigate how individual differences in EEG power envelope connectivity (PEC)-estimated cortical networks in MDD differentially predicted outcome with an antidepressant vs placebo (ie, whether it could serve as a baseline moderator of treatment response). We did so using the largest neuroimaging-coupled, placebo-controlled randomized clinical trial in depression to date, to our knowledge—the Establishing Moderators and Biosignatures of Antidepressant Response in Clinic Care (EMBARC) study.[27] We calculated resting-state interregional PEC and graphed theoretical centrality measures to characterize EEG functional connectivity networks at baseline, and we examined within an intent-to-treat analytic framework how connectivity associated with treatment outcomes. Consistent with prior work,[6,7,10,11] we hypothesized that greater PEC and node strength localized to the frontal and parietal cortices would predict better antidepressant treatment response specific to the antidepressant sertraline hydrochloride vs placebo.

### Key Points

**Question** What electroencephalographic connectivity features are neural moderators of antidepressant treatment response?

**Findings** In this secondary analysis of a randomized clinical trial, greater alpha-band and lower gamma-band connectivity—most prominently parietal—predicted better placebo treatment response and worse antidepressant treatment response. Lower connectivity levels in these moderating connections were associated with higher levels of anhedonia.

**Meaning** Key cortical features differentiating placebo response from antidepressant response were identified, providing an alternative direction toward establishing a placebo signature in clinical trials.

## Methods

### Participants

This study is a nonprespecified secondary analysis of a randomized clinical trial. Additional details on study methods and participant characteristics are in eAppendix 1 and eTable 1 in the Supplement and in prior publications.[18,27] Outpatients aged 18 to 65 years with a diagnosis of MDD[28] were recruited from July 29, 2011, to December 15, 2015, and assessed at 4 clinical sites (Columbia University, Massachusetts General Hospital, University of Michigan, and University of Texas Southwestern Medical Center). The study was approved by the institutional review boards of all sites, and participants provided written consent and received financial compensation. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

### Assessments and Treatment Protocol

The EMBARC trial used a double-blind design, with randomization to 8 weeks of sertraline or placebo (N = 296; eFigure 1 in the Supplement). Randomization was stratified by site, depression severity, and chronicity using a block randomization procedure. The primary clinical outcome was total score on the 17-item Hamilton Rating Scale for Depression, administered at each study visit (baseline and weeks 1, 2, 3, 4, 6, and 8).



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## Electroencephalography

Each study site recorded data with a different EEG system and channel-space montage (eTable 2 in the Supplement). All data were sampled at 250 Hz, over 60 to 128 channels, depending on the site. Variables corresponding to site differences, including their multiplicative interaction with all other terms in the linear mixed models, were controlled for to reduce the possibility of site effects on results (see Statistical Analysis subsection; eTable 3 in the Supplement). Electroencephalography was performed during 8 total minutes of resting-state activity by alternating between 2-minute blocks of eyes-open (REO) and eyes-closed (REC) conditions.[18]

## Analyses

A total of 268 treatment-randomized patients underwent EEG. Of these, 221 (82.5%) were included in the analyses (217 of whom had both REO and REC conditions), excluding 47 data sets because of poor EEG data quality. Of these patients, 106 were randomized to receive sertraline and 115 were randomized to receive placebo (eFigure 1 in the Supplement). Final data included 217 REC data sets (105 sertraline and 112 placebo) and 221 REO data sets (106 sertraline and 115 placebo) (see eTable 5 in the Supplement for participant identifiers included in the analyses). See eAppendix 1 in the Supplement for EEG preprocessing and analysis details. A repeated k-fold cross validation analysis was conducted and reported in eTable 12 in the Supplement. Receiver operator characteristics (area under the curve), odds ratios, and effect sizes are reported for all analyses in eTable 13 in the Supplement. Analyses controlling for effects of sex and age are reported in eTable 15 in the Supplement.

### Power Envelope Connectivity

All connectivity analyses were performed in source-space owing to the variability in montages across sites; therefore, each site's montage was retained. Source localization was performed in MATLAB 2014b (MathWorks Inc) using custom code for nonparametric minimum norm estimates.[29] All connectivity analyses were computed at the vertex level using 3003 vertices in MNI (Montreal Neurological Institute) template space, then averaged into 31 regions of interest (ROIs) in MNI space (eTable 4 in the Supplement). Power envelope connectivity[26] was derived from the following 4 canonical frequencies: theta (4.5-7.5 Hz), alpha (8-12 Hz), beta (12.5-30 Hz), and gamma (31-50 Hz). Further details can be found in eAppendix 1 and eFigure 2 in the Supplement.

### Node Strength Computation

The graph theoretical metric of node strength was computed for each ROI using MATLAB's implementation of the Brain Connectivity Toolbox.[30] Undirected node strength, quantified as the sum of weights of links connected to the node, was calculated on the orthogonalized PEC estimates.[31]

## Statistical Analysis

Statistical analysis was performed from November 16, 2018, to May 23, 2019. Because our primary investigation was of the moderation of the linear trajectory of treatment outcome, we chose to perform prediction linear mixed-effects models, which furthermore maintained an intent-to-treat framework. Linear mixed-effects models were applied to each ROI-to-ROI connectivity estimate and node strength measure.[32]

Models predicted a linear trajectory of repeated 17-item Hamilton Rating Scale for Depression scores across time at baseline and week 1, 2, 3, 4, 6, and 8 (ie, end point) assessment points. Analyses were conducted using the NLME package in R, version 3.4.4 (R Foundation for Statistical Computing).[33] The brain metric × treatment group × time interaction, the primary term of interest, assessed differential symptom trajectories by treatment group as a function of EEG connectivity moderators (eTable 3 and eAppendix 1 in the Supplement). All *P* values were false discovery rate (FDR) corrected for multiple comparisons across all ROIs and frequency bands to control for type I errors (eAppendix 1 in the Supplement). All *P* values were from 2-sided tests and results were deemed statistically significant at an FDR-corrected $P \leq .0125$.

To further understand the clinical significance of treatment-moderating connectivity measures, we performed Pearson correlations of the FDR-significant connectivity and nodal strength effects with several clinical indices (correcting for multiple corrections across all correlations performed) across the entire sample. The clinical measures were the Childhood Trauma Questionnaire,[34] the Quick Inventory of Depressive Symptomatology,[35] the Mood and Anxiety Symptom Questionnaire,[36] the State-Trait Anxiety Questionnaire,[37] and the Snaith-Hamilton Pleasure Scale,[38] as well as the duration of the current depressive episode. *P* values extracted from the correlational analyses between clinical scales and connectivity features were FDR-corrected for multiple comparisons simultaneously across all pairwise comparisons of all scales and FDR-significant connectivity features. A supplementary analysis was conducted to assess connectivity features that change from baseline to 1 week into treatment (eTable 14, eFigure 3, and eAppendix 2 in the Supplement).

# Results

A total of 221 participants underwent EEG recordings and had high-quality pretreatment EEG data. Participants included in the analyses were aged 18 to 65 years (150 women; mean [SD] age, 37.8 [12.7] years). The group mean (SD) score on the 17-item Hamilton Rating Scale for Depression was 18.35 (4.58) at baseline and 26.14 (30.37) across all time points.

## PEC Moderators of Treatment Outcome

### Initial Identification of Moderators

After correcting for multiple comparisons across all pairwise connectivity features and frequency bands, significant moderation effects for the REC condition were identified at 40 ROI-to-ROI pairwise power envelope connections using the alpha carrier frequency and at 31 connections using the gamma carrier frequency (eTable 6 in the Supplement; **Figure 1**B and C). The regions associated with these connections were primarily frontal, parietal, temporal, and visual and somatosensory (Figure 1B and C).



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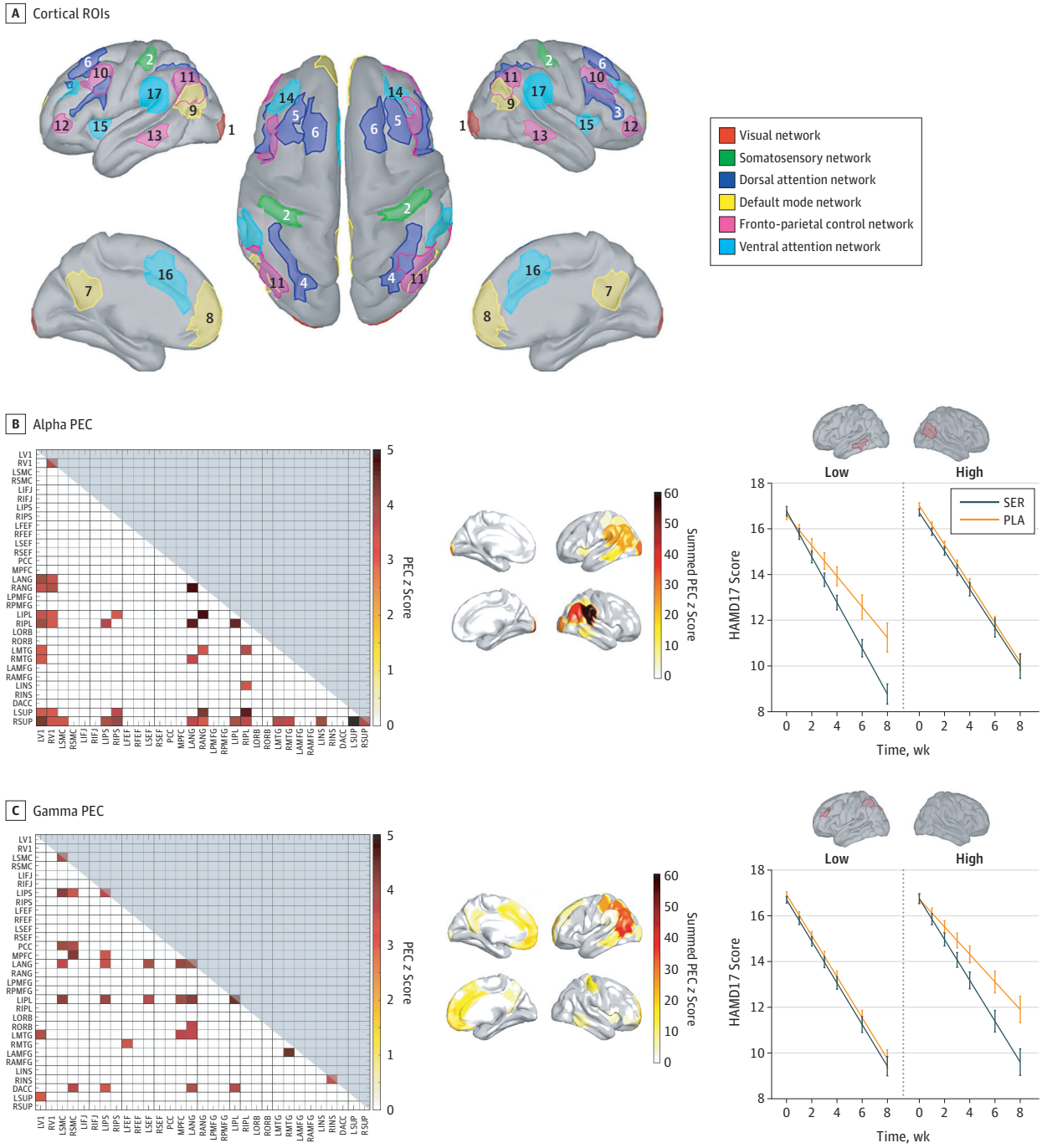
Figure 1. Cortical Regions of Interest (ROIs), Alpha Power Envelope Connectivity (PEC), and Gamma PEC




A, A total of 31 ROIs (right and left ROIs are numbered the same; 14 bilateral ROIs [28 total] and 3 midline ROIs) were defined in Montreal Neurological Institute space, derived from independent components analysis parcellation of resting-state functional magnetic resonance imaging connectivity from 38 participants.[26] B, Resting eyes-closed PEC between left mid-temporal gyrus and right angular gyrus moderation of outcome with sertraline (SER) vs placebo (PLA) treatment within the alpha band. C, Resting eyes-closed PEC between left anterior mid-frontal gyrus and right mid-temporal gyrus moderation of outcome with SER vs PLA treatment within the gamma band. Left panel: *z* scores for significantly moderating ROIs are represented in the ROI × ROI matrix plots. Middle panel: summed cortical connectivity (*z* scores) at each significantly moderating ROI. Right panel: visualization of moderation results reveals that significant prediction of treatment only in the PLA group was probably the cause of the moderation results. Shown are model-predicted 17-item Hamilton Rating Scale for Depression (HAMD17) values for the PLA and SER groups using an arbitrary median split on PEC for visualization purposes only. Low = below-median connectivity and high = above-median connectivity. The 2 ROIs comprising the pairwise connectivity feature visualized are outlined in red on the cortical images. AMFG indicates anterior mid-frontal gyrus; ANG, angular gyrus; DACC, dorsal anterior cingulate cortex; FEF, frontal eye fields; IFJ, inferior frontal junction; INS, insular cortex; IPL, inferior parietal lobe; IPS, inferior parietal sulcus; L, left; MPFC, medial prefrontal cortex; MTG, mid-temporal gyrus; ORB, orbitofrontal cortex; PCC, posterior cingulate cortex; PMFG, posterior mid-frontal gyrus; R, right; SEF, superior eye fields; SMC, sensorimotor cortex; SUP, supramarginal gyrus; and VI, bilateral primary visual cortex.



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A total of 24 connections within the alpha, gamma, and beta frequencies significantly moderated treatment effect within the REO condition. Alpha-band moderators were primarily within the visual and parietal regions, whereas beta-band moderators were specific to parietal and frontal regions, and gamma-band moderators within the temporal, parietal, anterior cingulate, and visual and somatosensory cortices (eTable 7 in the Supplement; **Figure 2**).

### Examining Moderation as a Function of Within-Group Treatment

To next understand whether these significant moderators were due to prediction of outcome in the sertraline group, placebo group, or both groups, we performed mixed models for each group separately. Because this analysis was performed to investigate what was causing the connectivity × time × treatment group interactions, we constrained our analyses only to FDR-significant connections (FDR-corrected $P \leq .0125$) identified as moderating in the full analysis. As such, we did not correct again for multiple comparisons because it was performed for visualization purposes only. We found that the moderating connections within the REC condition from the alpha and gamma carrier frequency analyses significantly predicted outcome primarily in the placebo group, with only a few predicting outcome in the sertraline group (eTable 6 in the Supplement). Within the REO condition, while the significantly predictive features across alpha, beta, and gamma carrier frequencies were predominately within the placebo group, most of these features were also predictive within the sertraline group (eTable 7 in the Supplement). Thus, REC connectivity moderators predominantly reflected placebo-driven effects, whereas those in the REO condition reflected effects from both groups.

### Visualization of Within-Group Moderation Effects

To visualize treatment-moderating connections within the REC condition (with no further statistical analyses to avoid "double dipping"), we divided the sample with depression using a median split for each of the ROI-to-ROI PEC values found to significantly moderate treatment outcome (Figure 1B and C and Figure 2). This visualization revealed that greater alpha-band PEC within parietal, temporal, and visual regions predicted better treatment outcome with placebo (ie, steeper symptom change slopes) and worse treatment outcome with sertraline. In addition, reduced gamma-band PEC within the frontal, visual, somatomotor, parietal, and temporal regions also predicted better treatment outcomes with placebo and worse treatment outcomes with sertraline (Figure 1).[26]

Within the REO condition, better outcomes in the placebo group and worse treatment outcomes in the sertraline group were predicted by greater alpha-band PEC within the visual and parietal regions; reduced gamma-band PEC within the frontal, temporal, parietal, anterior cingulate, and visual and somatosensory regions; and reduced beta-PEC within the frontal and parietal regions (Figure 2).

### Power Envelope Node Strength Moderators of Treatment Outcome

As a complement to the connection-wise analyses, we next conducted the same linear mixed model analyses on node-level connectivity strength measures, which provide a summary metric of the overall connectivity of each ROI. Of the 31 ROIs and 4 frequency bands entered in the linear mixed-effect model analyses, 3 regions within the alpha-band REC condition survived FDR correction in the moderation analysis (brain × treatment group × site interaction; eTable 8 in the Supplement; **Figure 3**). These regions were the right inferior parietal lobe, the right angular gyrus, and the right supramarginal gyrus. As in the analyses, visualizing the results using a median split, we found that a higher alpha-band nodal strength predicted better treatment outcome with placebo (Figure 3). Alpha-band nodal strength did not significantly predict treatment outcome with sertraline.

### Association Between Clinical Severity Measures and PEC

We ran correlations between questionnaire data and FDR-significant connectivity pairs from the analyses. Correlations with the Snaith-Hamilton Pleasure Scale, which measures anhedonia,[39] survived correction. Baseline anhedonia ratings across the entire sample were negatively associated with alpha- and gamma-band connectivity metrics within the REC condition (eTable 9 in the Supplement; **Figure 4**A and B). The Snaith-Hamilton Pleasure Scale was also negatively associated with alpha node strength in the right inferior parietal lobe, the angular gyrus, and the supramarginal gyrus (Figure 4C; eTable 10 in the Supplement). In addition, greater symptom severity on the Quick Inventory of Depressive Symptomatology was positively associated with greater baseline gamma PEC within the frontal, parietal, temporal, insular, and cingulate cortical regions within the REC condition (eTable 11 in the Supplement). No REO connectivity measures survived correction.

## Discussion

Here we establish pretreatment resting-state EEG connectivity features that moderated the treatment effect of the antidepressant sertraline vs placebo in a large randomized clinical trial in outpatients with MDD. Moderation effects were largely associated with outcomes in the placebo group and, to a lesser extent, in the sertraline group, a subset of which were associated with anhedonia and depressive symptom severity.

### Neural Moderators of Treatment Response

The PEC measures found to significantly moderate treatment outcome were predominantly within the alpha-band, gamma-band, and, to a lesser extent, beta-band carrier frequencies. The synchronization of slow fluctuations in the power envelope of the band-limited oscillatory signal has been suggested to underlie large-scale functional network dynamics in both fMRI and magnetoencephalography.[40-42] Further supporting these findings, entraining the power envelopes of regions within a given resting-state network has been found to strengthen fMRI connectivity within the targeted networks.[43] Prior work has supported a negative association between alpha or beta oscillations and neural



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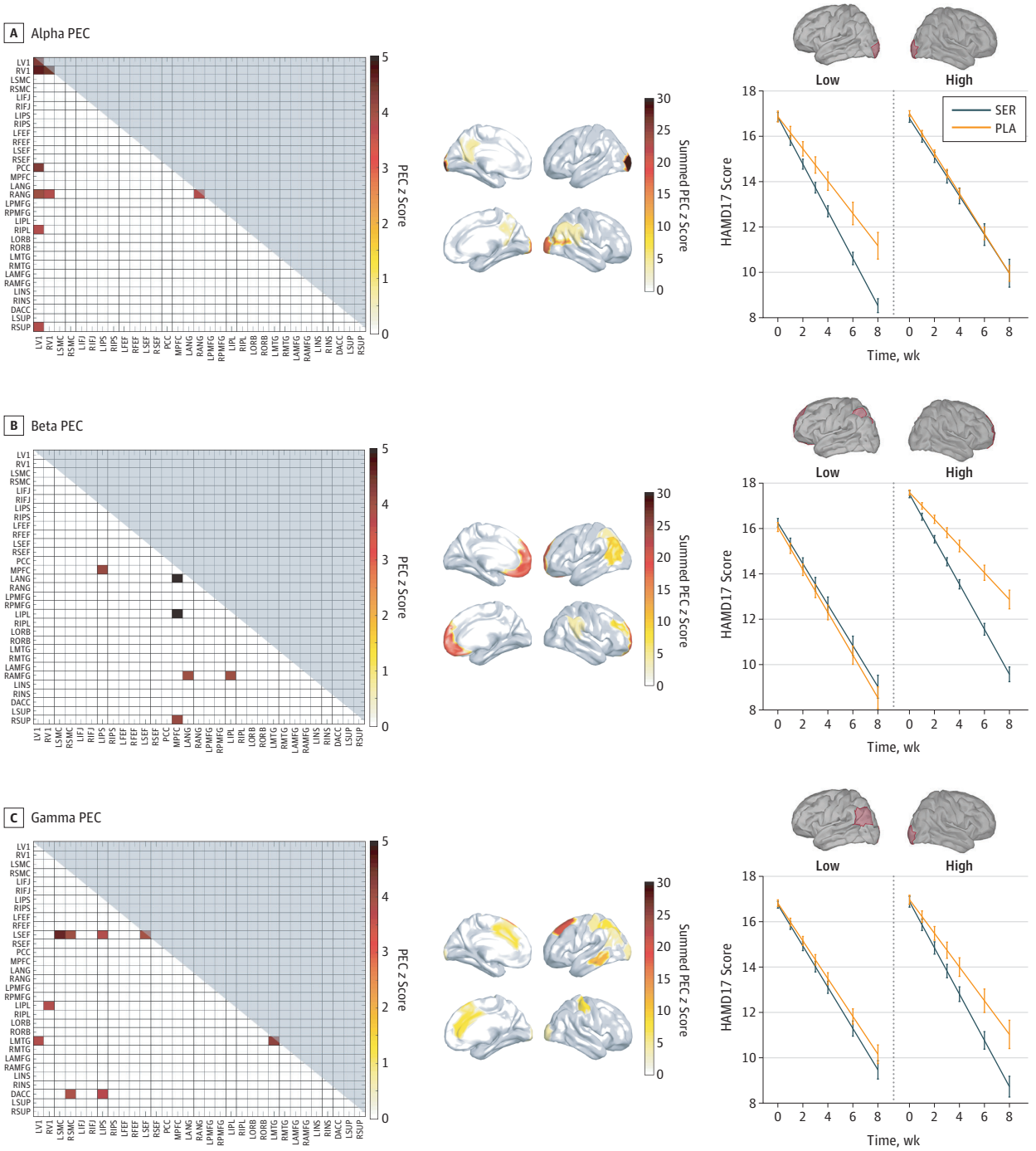
Figure 2. Resting Eyes-Open Power Envelope Connectivity (PEC) Moderation of Outcome With Sertraline (SER) vs Placebo (PLA) Treatment Within the Alpha, Beta, and Gamma Bands




A, Alpha PEC between left and right primary visual cortex. B, Beta PEC between medial prefrontal cortex and left inferior parietal sulcus. C, Gamma PEC between left inferior parietal lobe and right primary visual cortex. Left panel: *z* scores for significantly moderating regions of interest (ROIs) are represented in the ROI × ROI matrix plots. Middle panel: summed cortical connectivity (*z* scores) at each significantly moderating ROI; ROIs with greater summed *z* scores are those with greater total moderating connectivity. Right panel: visualization of moderation results reveals that significant prediction of treatment only in the PLA group was probably the cause of the moderation results. Shown are model-predicted 17-item Hamilton Rating Scale for Depression (HAMD17) values for the PLA and SER groups using an arbitrary median split on PEC for visualization purposes only. Low = below-median connectivity, high = above-median connectivity. Two ROIs comprising the pairwise connectivity feature visualized are outlined in red on the cortical images. AMFG indicates anterior mid-frontal gyrus; ANG, angular gyrus; DACC, dorsal anterior cingulate cortex; FEF, frontal eye fields; IFJ, inferior frontal junction; INS, insular cortex; IPL, inferior parietal lobe; IPS, inferior parietal sulcus; L, left; MPFC, medial prefrontal cortex; MTG, mid-temporal gyrus; ORB, orbitofrontal cortex; PCC, posterior cingulate cortex; PMFG, posterior mid-frontal gyrus; R, right; SEF, superior eye fields; SMC, sensorimotor cortex; SUP, supramarginal gyrus; and VI, bilateral primary visual cortex.



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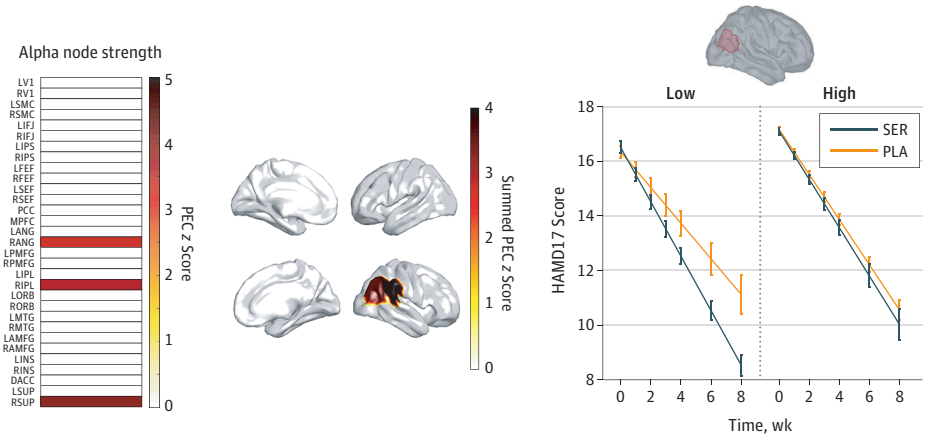
Figure 3. Alpha Power Envelope Connectivity (PEC) Node Strength Moderation of Outcome With Sertraline (SER) vs Placebo (PLA) Treatment




Left panel: *z* scores for significantly moderating features are represented in the above matrix plots. Right angular gyrus (RANG), right inferior parietal lobe (RIPL), and right supramarginal gyrus (RSUP) node strength significantly moderated treatment outcome within the alpha carrier frequency. Middle panel: summed cortical connectivity (*z* scores) at each significantly moderating region of interest. Right panel: visualization of RANG (outlined in red on cortical image) moderation results reveals that significant prediction of treatment only in the PLA group was probably the cause of the moderation results. Shown are model-predicted 17-item Hamilton Rating Scale for Depression (HAMD17) values for the PLA and SER groups using an arbitrary median split on PEC for visualization purposes only. Low = below-median connectivity, high = above-median connectivity. AMFG indicates anterior mid-frontal gyrus; DACC, dorsal anterior cingulate cortex; FEF, frontal eye fields; IFJ, inferior frontal junction; INS, insular cortex; IPS, inferior parietal sulcus; L, left; MPFC, medial prefrontal cortex; MTG, mid-temporal gyrus; ORB, orbitofrontal cortex; PCC, posterior cingulate cortex; PMFG, posterior mid-frontal gyrus; R, right; SEF, superior eye fields; SMC, sensorimotor cortex; and VI, bilateral primary visual cortex.

activation, as well as a positive association between gamma oscillations and neural activation, as measured by the fMRI blood oxygen level–dependent signal[44-46] and intracranial recordings.[47-49] See further discussion regarding band specificity in PEC in eAppendix 2 in the Supplement.

The alpha-band connectivity features significantly moderating treatment response were predominantly between the parietal, visual, and temporal regions. Parietal alpha-band power has been heavily associated with reward anticipation[50-52] and has been shown to be reduced in patients with depression at rest and during reward anticipation.[53-55] In addition, reduction in frontoparietal alpha power has been associated with reduced reward anticipation in depression.[55] Gamma-band connectivity was also found to significantly moderate treatment outcome, specific to the frontal, parietal, and sensorimotor regions. Some prior work has implicated gamma oscillations as a state-related marker of depression.[56,57] Reductions in gamma-band power, complexity, and connectivity in the frontal-parietal cortices have been found in depression,[58] with gamma oscillation power increases with treatment correlating with improved treatment outcome.[59,60] However, the relevance of band power to band-limited PEC is unknown and was not examined in these studies. Moreover, to our knowledge, no prior work examined the relevance of alpha-band or gamma-band power to placebo clinical outcome. As such, our findings provide important new insights in an area that has received relatively little research. The effect of these findings is further underscored by the size of the EMBARC trial relative to prior studies, which either lacked placebo groups or had samples 5 to 10 times smaller than those in the EMBARC trial.

### Neural Predictors of Antidepressant Treatment Response

Placebo treatment can reduce depressive symptoms, so much so that it has become an increasing barrier to medication effectiveness research during the past few decades.[1,4,61-69] This difficulty separating antidepressant from placebo treatment responses has motivated treatment prediction and moderation research, with the EMBARC trial being the largest such study using neuroimaging to date. Although some studies have found baseline neural features predictive of treatment response, most did not find these features to differentiate between antidepressant and placebo response.[18,70-72] Moreover, because most used an open-label design without a placebo group, we still lack knowledge regarding the neural basis of response to placebo vs antidepressant medication.

Although all the significant features predicting treatment response were associated with placebo, a number of connectivity measures predicted antidepressant outcome in the opposite direction as placebo outcome. These measures were predominantly alpha-band connectivity within the parietal cortex (REC) and visual cortex (REO), beta-band connectivity within the frontal and parietal regions (REO), and gamma-band connectivity within and between the parietal, temporal, and visual and somatosensory cortices (REC and REO). This subset of features in particular may help identify individuals who will experience greater antidepressant and worse placebo responses, whereas the other measures would inform only placebo prediction. One known factor delineating placebo vs treatment responders is depressive symptom severity.[73] However, the connectivity features predictive of sertraline treatment response were not associated with the baseline metrics of Quick Inventory of Depressive Symp-



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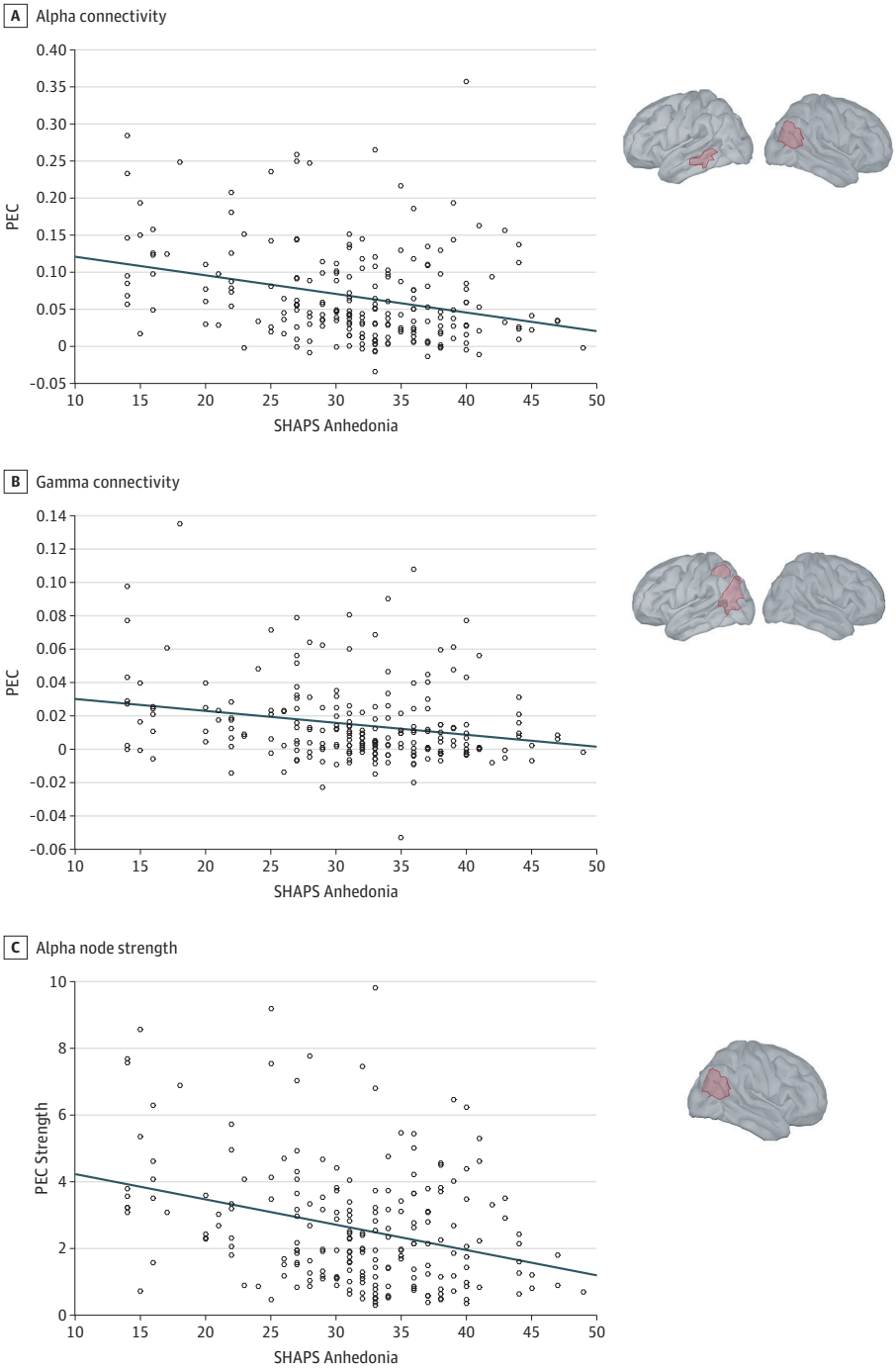
Figure 4. Association Between Electroencephalography Connectivity Moderators and Anhedonia




A, Alpha power envelope connectivity (PEC) between the left middle temporal gyrus and right angular gyrus. B, Gamma PEC between left angular gyrus and left inferior parietal sulcus (see eTable 7 in the Supplement for statistics). C, Greater anhedonia (as measured by the Snaith-Hamilton Pleasure Scale [SHAPS]) is associated with lower alpha PEC node strength in the right angular gyrus (see eTable 8 in the Supplement for statistics). Two regions of interest (ROIs) comprising the pairwise connectivity feature, or single ROI comprising the node strength feature, are visualized are outlined in red on the cortical images. Diagonal lines indicate same ROI-to-ROI connections.

tomatology depressive symptom severity, reducing the possibility that these features simply reflect symptoms.

### Neural Predictors of Placebo Treatment Response

Although a number of studies have examined the neurobiology of placebo response, only a handful have examined the neurobiological substrates of placebo response in depression.[67,71,72] This work has also focused mostly on neural changes associated with placebo antidepressant responses, rather than pretreatment outcome prediction. The primary study within the literature investigating the baseline functional connectivity predictive of placebo treatment response differentially from antidepressant treatment response identified increased rostral anterior cingulate cortex connectivity within the salience network as predictive of placebo treatment response.[72]

The clinical significance of the treatment-moderating connectivity is further suggested by their association with



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anhedonia, whereby greater neural connectivity and nodal strength was associated with reduced anhedonia. Anhedonia, or the loss of pleasure in activities, is a prominent symptom in depression.[74] Previous research has shown an association between anhedonia and disrupted neural reward processing.[75,76] We speculate therefore that parietal PEC, in particular to the temporal and visual regions within the alpha band, may reflect in part the action of reward processing systems, which in turn predicts placebo response.

### Limitations

This study has some limitations. The mechanism by which alpha-band and gamma-band features differentially influence treatment response requires further investigation. Future work will be needed to understand how pretreatment EEG connectivity predicts longer-term outcomes beyond 8 weeks as well as clinically important events such as relapse. The effect sizes were small for most of the significant features found to moderate treatment outcome and, therefore, call for replication. Although both anhedonia and depressive severity were significantly associated with resting-state EEG treatment moderators, they explained only approximately 5% to 10% of variance in connectivity.

## Conclusions

Our findings provide insight into the neural connectivity features that are specifically predict placebo response in depression, differentially from sertraline treatment response, potentially involving a role for anhedonia. From a treatment perspective, capitalizing on the therapeutic components leading to placebo response differentially from antidepressant response could provide an alternative direction toward clinical treatment of patients with depression.[68]

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