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

Camarin E. Rolle, BS; Gregory A. Fonzo, PhD; Wei Wu, PhD; Russ Toll, PhD; Manish K. Jha, MD; Crystal Cooper, PhD; Cherise Chin-Fatt, PhD; Diego A. Pizzagalli, PhD; Joseph M. Trombello, PhD; Thilo Deckersbach, PhD; Maurizio Fava, MD; Myrna M. Weissman, PhD; Madhukar H. Trivedi, MD; Amit Etkin, MD, PhD

**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.

**TRIAL REGISTRATION** ClinicalTrials.gov identifier: NCT01407094
Despite substantive evidence supporting the efficacy of antidepressants vs placebo for major depressive disorder (MDD), 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 $d \sim 0.3$) 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, coupled with the low predictive value of clinical and sociodemographic variables, substantial attention has been directed at identifying pretreatment neural features that predict treatment response in MDD. 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.

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. 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. 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. 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.

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. 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.

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. 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, 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.

### 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. Outpatients aged 18 to 65 years with a diagnosis of MDD 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).
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 connectivity26 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 ≤ .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 1B and C). The regions associated with these connections were primarily frontal, parietal, temporal, and visual and somatosensory (Figure 1B and C).

jamapsychiatry.com
© 2020 American Medical Association. All rights reserved.
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.\textsuperscript{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.
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 $P \leq 0.0125$) 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-modulating 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 4A 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
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.
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 Sympt...
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

---

**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 in red on the cortical images. Diagonal lines indicate same ROI-to-ROI connections.
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.

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

ARTICLE INFORMATION
Accepted for Publication: October 5, 2019.
Published Online: January 2, 2020.

Author Affiliations: Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California (Rolle, Fonzo, Wu, Toll, Etkin); Wu Tsai Neuroscience Institute, Stanford University, Stanford, California (Rolle, Fonzo, Wu, Toll, Etkin); Veterans Affairs Palo Alto Healthcare System, Palo Alto, California (Rolle, Fonzo, Wu, Toll, Etkin); Sierra Pacific Mental Illness, Research, Education, and Clinical Center, Palo Alto, California (Rolle, Fonzo, Etkin); Department of Psychiatry, Dell Medical School, The University of Texas at Austin (Fonzo); School of Automation Science and Engineering, South China University of Technology, Guangzhou, Guangdong, China (Wu); Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas (Jha, Cooper, Chin-Fatt, Trombleo, Trivedi); Department of Psychiatry, Harvard Medical School, Boston, Massachusetts (Pizzagalli, Deickersbach, Fava); New York State Psychiatric Institute, Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York (Weissman); now at Altos Neuroscience Inc, Los Altos, California (Etkin).

Author Contributions: Ms Rolle had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Trivedi and Etkin contributed equally to this research.

Concept and design: Pizzagalli, Trivedi, Etkin.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Rolle, Deickersbach, Etkin.
Critical revision of the manuscript for important intellectual content: Rolle, Fonzo, Wu, Toll, Jha, Cooper, Chin-Fatt, Pizzagalli, Trombleo, Fava, Weissman, Trivedi, Etkin.
Statistical analysis: Rolle, Fonzo, Wu, Toll, Chin-Fatt, Trivedi, Etkin.
Obtained funding: Weissman, Trivedi.
Administrative, technical, or material support: Fonzo, Toll, Jha, Cooper, Pizzagalli, Trombleo, Fava, Weissman, Etkin.

Conflict of Interest Disclosures: Dr Pizzagalli reported receiving funding during the last 3 years from the National Institute of Mental Health, the Dana Foundation, and Brain and Behavior Research Foundation; and receiving consulting fees or honoraria from Akili Interactive Labs, Allergan, BlackThorn Therapeutics, Boehringer Ingelheim, Compass, and Post Science for activities unrelated to the current research. Dr Trombleo reported currently owning stock in Merck and Gilead Sciences, both of which are unrelated to the current project. Dr Deickersbach reported receiving research funding from the National Institutes of Health, the National Institute of Mental Health, National Alliance for Research on Schizophrenia and Depression, Tourette Syndrome Association, International OCD (Obsessive Compulsive Disorder) Foundation, Tufts University, Depressive and Bipolar Disorder Alternative Treatment Foundation, and Otsuka Pharmaceuticals; receiving honoraria, consultation fees, and/or royalties from the Massachusetts General Hospital Psychiatry Academy, BrainCells Inc, Clintara LLC Inc, Systems Research and Applications Corp, Boston University, the Catalan Agency for Health Technology Assessment and Research, the National Association of Social Workers Massachusetts, the Massachusetts Medical Society, Tufts University, the National Institute on Drug Abuse, the National Institute of Mental Health, Oxford University Press, Guilford Press, and Rutledge; participating in research funded by Defense Advanced Research Projects Agency, the National Institutes of Health, National Institute on Aging, the Agency for Healthcare Research and Quality, the Patient-Centered Outcomes Research Institute, Janssen Pharmaceuticals, The Forest Research Institute, Shire Development Inc, Medtronic, Cyberonics, NorthStar, and Takeda. Dr Fava reported receiving research support from Abbott Laboratories, Allergan Inc, American Cyanamid, Aspect Medical Systems, AstraZeneca, Avanir Pharmaceuticals, BioResearch, BrainCells Inc, Bristol-Myers Squibb, CereNeuro PharmaBio, Cephalon, Clintara LLC, Cerecor, Covance, Covidien, Eli Lilly and Company, EnVivo Pharmaceuticals Inc, Euthemics Bioscience Inc, Forest Pharmaceuticals Inc, Gained Biotech Inc, GlaxoSmithKline, Harvard Clinical Research Institute, Hoffmann-La Roche, Icon Clinical Research, i3 Innovus/Ingenix, Janssen R&D LLC, Jed Foundation, Johnson & Johnson Pharmaceutical Research & Development, Lichtwer Pharma GmbH, Loxeo Pharmaceuticals, Lundbeck Inc, MedAvante, Methylation Sciences Inc, National Alliance for Research on Schizophrenia & Depression, National Center for Complementary and Alternative Medicine, National Institute of Drug Abuse (NIDA), National Institute of Mental Health, Neuralstem Inc, Novartis AG, Organon Pharmaceuticals, Pamlab LLC, Pfizer Inc, Pharmacia-Upjohn, Pharmaceutical Research Associates Inc, Pharmavite LLC, PharmoRx Therapeutics, Photothera, Reckitt Benckiser, Roche Pharmaceuticals, RCT Logic LLC (formerly Clinical Trials Solutions LLC), Sanofi-Aventis US LLC, Shire, Solvay Pharmaceuticals Inc, Stanley Medical Research Institute, Synthelabo, Tal Medical, and Wyeth-Ayerst Laboratories; serving as advisor or consultant to Abbott Laboratories, Acadia, Afectis Pharmaceuticals AG, Alkermes Inc, Amarin Pharma Inc, Aspect Medical Systems, AstraZeneca, Auspex Pharmaceuticals, Avanir Pharmaceuticals, AXSOME Therapeutics, Bayer AG, Best Practice Project Management Inc, Biogen, BioMarin Pharmaceuticals Inc, Biovail Corporation, BrainCells Inc, Bristol-Myers Squibb, CereNeuro PharmaBio, Cephalon Inc, Cerecor, CNS Response Inc, Compells Pharmaceuticals, Cypress Pharmaceutical Inc, DiagnoSearch Life Sciences (P) Ltd, Dissonip Sumitomo Pharma Co Inc, Dov Pharmaceuticals Inc, Edgemont Pharmaceuticals Inc, Eisai Inc, Eli Lilly and Company, EnVivo Pharmaceuticals Inc, ePharmaSolutions, EPIX Pharmaceuticals Inc, Euthemics Bioscience Inc, Fabre-Kramer Pharmaceuticals Inc, Forest Pharmaceuticals Inc, Forum Pharmaceuticals Inc, Gained Biotech Inc, GlaxoSmithKline, Grunenthal GmbH, i3 Innovus/Ingenix, Intracelular, Janssen Pharmaceutica, Jazz Pharmaceuticals Inc, Johnson & Johnson Pharmaceutical Research & Development LLC, Knoll Pharmaceuticals Corp, Labopharm Inc, Loxeo Pharmaceuticals, Lundbeck Inc, MedAvante Inc, Merck & Co Inc, MSH Methylation Sciences Inc, Naurex Inc, Nestle Health Science, Neuralstem Inc, Neuronetics Inc, NextWave Pharmaceuticals,
Cortical Connectivity Moderators of Antidepressant vs Placebo Treatment Response in Depression

Novartis AG, Nutrition 21, Orexigen Therapeutics Inc, Organoon Pharmaceuticals, Osmotica, Otsuka Pharmaceuticals, Pamlab LLC, Pfizer Inc, Pharmastar, Pharmavite LLC, PharmRx Therapeutics, Precision Human Biobehavioral, Prexia Pharmaceuticals Inc, Puretech Ventures, Psychogenics, Psylin Neurosciences Inc, RCT Logic LLC (formerly Clinical Trials Solutions LLC), Rezalux Pharmaceuticals Inc, Ridge Diagnostics Inc, Roche, Sanofi-Aventis US LLC, Sepcor Inc, Servier Laboratories, Schering-Plough Corporation, Solvay Pharmaceuticals Inc, Somaxon Pharmaceuticals Inc, Somerset Pharmaceuticals Inc, Sunovion Pharmaceuticals, Supervenus Pharmaceuticals Inc, Synthelabo, Taisho Pharmaceutical, Takeda Pharmaceuticals North America, Takeda Pharmaceuticals Japan Ltd, Tal Medical Inc, Tetragenex Pharmaceuticals Inc, TransForm Pharmaceuticals Inc, Transcept Pharmaceuticals Inc, Vanda Pharmaceuticals Inc, and Vistagen; receiving speaking or publishing fees from Adamed Co, Advanced Meeting Partners, American Ibrahim, Akzo (Organon, American Society of Clinical Psychopharmacology, AstraZeneca, Belvoir Media Group, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Cephalon Inc, CME Institute/Physicians Postgraduate Press Inc, Eli Lilly and Company, Forest Pharmaceuticals Inc, GlaxoSmithKline, Intec Pharma, Intec Pharma Academy/Media, MGH Psychiatry Academy/Reed Elsevier, Novartis AG, Organon Pharmaceuticals, Pfizer Inc, Pharmastar, United BioSource Corp and Weyth-Ayter Laboratories; having equity holdings in Compellis and PsyBrain Inc; holding a patent for Sequential Parallel Comparison Design, which is licensed by MGH to Pharmaceutical Product Development LLC; having a patent application for a combination of ketamine plus scopolamine in major depressive disorder, licensed by MGH to Biohaven; receiving copyright royalties for the MGH Cognitive & Physical Functioning Questionnaire, Sexual Functioning Inventory, Antidepressant Treatment Response Questionnaire, Discontinuation-Emergent Signs & Symptoms, Symptoms of Depression Questionnaire, and SAFER; and receiving publishing royalties of books from Lippincott Williams & Wilkins, Wolters Kluwer, and World Scientific Publishing Co Ltd. Dr. Trivedi reported receiving funding in the past 2 years from the National Institute of Mental Health, the National Institute on Drug Abuse, the National Alliance for Research on Schizophrenia and Depression, the Sackler Foundation, and the Templeton Foundation; and receiving royalties from Oxford University Press, Perseus Press, the American Psychiatric Association Press, and MultiHealth Systems. Dr. Trivedi reported serving as an advisor or consultant and receiving fees from (lifetime disclosure) Abbott Laboratories Inc, Abdi Ibrahim, Akzo (Organon, American Society of Clinical Psychopharmacology, AstraZeneca, Avon Advisors, Bristol-Myers Squibb Company, Cephalon Inc, Cercor, CME Institute of Physicians, Concert Pharmaceuticals Inc, Eli Lilly & Company, Evotec, Fabre Kramer Pharmaceuticals Inc, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Global Services LLC, Janssen Pharmaceuticals Products LP, Johnson & Johnson PRD, Libby, Lundbeck, Meade Johnson, MedAvante, Medtronic, Merck, Mitsubishi Tanabe Pharma Development America Inc, Naurex, Neurotics, Otsuka Pharmaceuticals, Pamlab, Parke-Davis Pharmaceuticals Inc, Pfizer Inc, Pfizer Health, Phoenix Marketing Solutions, Rezax Pharmaceuticals, Ridge Diagnostics, Roche Products Ltd, Sepcor, SHIRE Development, Sierra, SK Life and Science, Sunovion, Takeda, Tal Medical/ Puretech Ventures, Tangenx Pharmaceuticals, VantagePoint, Vivion, and Weyth-Ayter Laboratories; and receiving grants and research support from the Agency for Healthcare Research and Quality, Cyberonics Inc, the National Alliance for Research in Schizophrenia and Depression, the National Institute of Mental Health, and the National Institute on Drug Abuse. Dr. Trivedi (lifetime disclosure) reported receiving salary and equity from Alto Neuroscience Inc; holding equity in Mindstrong Health, Akili Interactive, and Sizing for unrelated work; receiving research funding from the National Institute of Mental Health, Department of Veterans Affairs, Cohen Veterans Bioscience, Brain and Behavior Research Foundation, Dana Foundation, Brain Resource Inc, and the Stanford Neurosciences Institute; and serving as a consultant for Cerveal, Takeda, Posit Science, Acadia, Otsuka, Lundbeck, and Janssen. No other disclosures were reported.

Funding/Support: The EMBARC study was supported by the National Institute of Mental Health of the National Institutes of Health under awards U01MH092221 (Dr Trivedi) and U01MH092250 (Dr Weissman). This work was also funded in part by the Hersh Foundation (Dr Trivedi, principal investigator). Drs Wu and Etkin were funded by National Institutes of Health grant R01 MH116506. Dr Wu was funded by the National Key Research and Development Plan of China (grant 2017YFBI002050) and the National Natural Science Foundation of China (grants 61876063 and 61836003). Ms Rolle was funded by the National Science Foundation, Graduate Research Fellowship Program (grant 2016180976).

Role of the Funder/Sponsor: The National Institutes of Health had a role in the study design and conduct of the study, but had no role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; nor decision to submit the manuscript for publication.

REFERENCES


© 2020 American Medical Association. All rights reserved.


