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Salience Network Functional Connectivity Predicts Placebo Effects in Major Depression

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Abstract

Background—Recent neuroimaging studies have demonstrated resting-state functional connectivity (rsFC) abnormalities among intrinsic brain networks in Major Depressive Disorder (MDD); however, their role as predictors of treatment response has not yet been explored. Here, we investigate whether network-based rsFC predicts antidepressant and placebo effects in MDD.

Methods—We performed a randomized controlled trial of two weeklong, identical placebos (described as having either “active” fast-acting, antidepressant effects or as “inactive”) followed by a ten-week open-label antidepressant medication treatment. Twenty-nine participants underwent a rsFC fMRI scan at the completion of each placebo condition. Networks were isolated from resting-state blood-oxygen-level-dependent signal fluctuations using independent component analysis. Baseline and placebo-induced changes in rsFC within the default-mode, salience, and executive networks were examined for associations with placebo and antidepressant treatment response.

Results—Increased baseline rsFC in the rostral anterior cingulate (rACC) within the salience network, a region classically implicated in the formation of placebo analgesia and the prediction of treatment response in MDD, was associated with greater response to one week of active placebo and ten weeks of antidepressant treatment. Machine learning further demonstrated that increased salience network rsFC, mainly within the rACC, significantly predicts individual responses to placebo administration.

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Conclusions—These data demonstrate that baseline rsFC within the salience network is linked to clinical placebo responses. This information could be employed to identify patients who would benefit from lower doses of antidepressant medication or non-pharmacological approaches, or to develop biomarkers of placebo effects in clinical trials.

Keywords

resting-state functional connectivity; large-scale connectivity networks; biomarkers of treatment response; placebo effects; Major Depression

INTRODUCTION

Major depressive disorder (MDD) has recently been conceptualized as a disorder with a network-based pathophysiology (1). Particularly, MDD manifests in cortico-limbic network dysregulation reflected by deficits in cognitive control and increased sensitivity of limbic networks (2-5), which is thought to result in excessive and negatively-skewed focus on introspective processes, difficulty regulating emotions, and persistent difficulties in sustaining attention (6, 7). Regions involved in these networks have emerged as biological markers of response to antidepressant treatments (8-13). Yet, the ability of these biomarkers to selectively distinguish drug-specific effects from other non-specific elements of the treatment response, such as the placebo effect, is still limited, with very few studies specifically addressing biomarkers of non-specific elements of antidepressant treatment response (14, 15). This is not a small concern, as placebo response rates in antidepressant clinical trials average 31-45% compared with response rates to antidepressants of ~50% and have increased at a rate of 7% per decade over the last 30 years (16, 17). Hence, further investigation is warranted in order to dissect the neural predictors of drug-specific and non-specific effects in MDD treatment.

Of the major functionally connected networks identified within the brain's inherent organization (18-20), three have received special attention in MDD and the prediction of treatment response: the default-mode (DMN), salience (SN) and executive (EN) network (21, 22). The DMN, with key regions in the posterior cingulate, medial prefrontal, and bilateral parietal and temporal cortices (23), is associated with introspective cognition (24) and demonstrates heightened connectivity and abnormal down-regulation in MDD, which may contribute to the disorder's hallmark attributes of excessive self-focus, inattention and rumination (25-28). Elevated pretreatment activity of the rostral anterior cingulate (rACC), a region encompassed within the main anterior DMN node (24) has consistently been identified as a predictive marker of treatment response across imaging and treatment modalities (9, 10, 29, 30). It has been hypothesized that heightened baseline rACC activity fosters better treatment outcome in patients with MDD by implementing adaptive self-reflection through its connectivity within the DMN (31). Moreover, antidepressant medication has been shown to decrease functional connectivity of the DMN (32). The SN, anchored by the anterior insula (aINS) and dorsal anterior cingulate cortex (dACC), is enlisted during the integration of salient stimuli and interoceptive information to guide motivated behavior (33). In particular, the aINS is a hub of meta-awareness and affective processing (34, 35) and has long been associated with MDD pathophysiology (25, 36-39). A

recent meta-analysis illustrates its activity as a neural predictive marker of MDD treatment response, where increased baseline insular activity is associated with poor clinical response (40). Finally, MDD is characterized by reduced functional connectivity of the EN (4) and hypo-activation of the network's key node: the dorsolateral prefrontal cortex (dlPFC) (41). The EN, which includes cohesive functional communication between the dlPFC and parietal cortex, is responsible for orienting to and engaging in attentive, goal-directed behavior (33); its dysfunction may contribute to a lack of control over heightened affective responses in MDD (21, 42). The dlPFC is involved in current MDD treatments and successful recovery from the disorder (43-45); while reduced grey matter volume in the region is an indicator of non-response to standard MDD treatments (11).

Nodes within these three networks have also been implicated in the neurobiological mechanisms of non-specific treatment effects in the field of placebo analgesia, where substantial headway has been made to identify the cognitive, neural, and molecular bases of the neurobiology of placebo effects (46-51). These studies have demonstrated a key role of the rACC in the formation of placebo analgesia (48, 52, 53), potentially through its interactions with additional subcortical brain areas involved in endogenous opioid-mediated analgesic effects, such as the amygdala (54) and the periaqueductal gray (48), but also the anterior and posterior INS (50, 51, 55). A number of neuroimaging studies have also reported placebo-associated changes in dlPFC function, thought to be related to expectancies and anticipatory mechanisms (56-58), consistent with the role of this region in cognitive executive function (59). In this regard, activity in EN-associated regions during pain anticipation was found to be predictive of the magnitude of placebo analgesia (60). Conversely, minimal information has been acquired as to the mechanisms implicated in antidepressant placebo effects, with notable exception of one investigation demonstrating an overlap in regions involved in placebo and medication effects (15) and our recent work describing the role of the opioid system in the formation of placebo responses in MDD (61).

Here, we take a network-based univariate and multivariate approach to the prediction of the response to placebo and antidepressant treatment using resting-state functional connectivity (rsFC) with independent component analysis (ICA) (62), a data-driven approach that produces results within a framework of the brain's intrinsic connectivity networks and allows for identification of reliable, exploratory-based treatment response predictors. We investigated the relationship between baseline rsFC of three networks (DMN, SN, left and right EN) and: 1) depression severity; 2) clinical response to one-week of placebo treatment; and 3) clinical response to ten-weeks of open-label antidepressant treatment. First, among the three networks, only the DMN has been previously related to MDD duration (63) and maladaptive rumination (25); therefore, we hypothesized that increased baseline DMN rsFC would be associated with greater depression severity. Second, with respect to the prediction of treatment response, none of the connectivity networks have been specifically related to placebo or antidepressant medication responses in patients with MDD. However, central regions of the DMN, SN, and EN — specifically the rACC, INS, and dlPFC, respectively — have a key role in mechanisms implicated in antidepressant and placebo responses, as described above, as well as the role of these networks in processes necessary for treatment responses: internal monitoring, saliency and higher-level cognition, respectively. Therefore, we hypothesized that increased baseline functional connectivity within central regions of the

DMN, SN and EN would predict response to both one-week of placebo and ten-weeks of open-label antidepressant treatment. Finally, we applied multivariate relevance vector regression (RVR) to evaluate the hypothesis that baseline rsFC maps of the three networks would allow for prediction of placebo and antidepressant responses at an individual level.

METHODS and MATERIALS

Subjects

Twenty-nine right-handed, un-medicated subjects with a DSM-V diagnosis of MDD were recruited via local advertisements [21 females; age: 18-59 (mean $\pm$ S.D.: 32 ± 13)]. See Supplemental Methods and Material for additional subject information and description of informed consent and authorized deception. All of the procedures used were approved by the University of Michigan Investigational Review Board for Human Subject Use Research Committee.

Placebo Randomized Controlled Trial (RCT) and Antidepressant Open-Label Trial

As previously described (61), subjects were randomized into either 1) one-week “active” placebo treatment (two pills/day), with expectations that the pill represented a potentially fast-acting antidepressant agent or 2) one-week “inactive” placebo treatment described as an control condition, without pharmacological effects (two pills/day). After a three-day “washout” period of no pills, subjects crossed over into the alternative condition to which they had not been assigned. After each week of placebo, subjects underwent a resting-state scanning session (Fig. 1).

Depression symptoms were assessed using the 16-item self-rated version of the Quick Inventory of Depressive Symptomatology (QIDS) (64) at the following time points: pre-randomization, baseline (pre-), and post- *active* and *inactive* conditions. This measure was selected as a primary outcome measure for its sensitivity to fluctuations in depression symptoms and its availability as a self-reported measure. Additionally, patients completed the Montgomery Asberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HDRS) at pre-randomization and during each visit within the antidepressant trial.

The change in QIDS ($QIDS = QIDS_{\text{BASELINE}} - QIDS_{\text{POST}}$) was calculated for active and inactive treatment conditions, and the difference between conditions was taken as an index of placebo response ($QIDS_{\text{ACTIVE}} - QIDS_{\text{INACTIVE}}$). Positive values reflected greater reductions in depressive symptoms as a result of “active” placebo administration.

Following the placebo RCT and the two resting-state fMRI scan sessions, subjects received a ten-week open-label antidepressant trial with citalopram as an initial agent (starting at 20 mg/day and up to 40 mg/day in 45% of cases). When citalopram was not clinically indicated (e.g. prior non-response or side-effects), another antidepressant was given [sertraline (n=1), mirtazapine (n=1), fluoxetine (n=2), duloxetine (n=1), and bupropion (n=1)]. Participants’ symptom changes were evaluated at weeks 0, 2, 4, 8, and 10. Antidepressant response was measured by the difference in QIDS between week 0 and 10 ($QIDS = \text{Week 0} - \text{Week 10}$). In four cases, participants began the antidepressant treatment less than three days after the

placebo experiment; because of this, a baseline QIDS Week 0 measure was created to measure antidepressant treatment response.

Resting State Functional Connectivity Networks

Image data acquisition, preprocessing, movement analysis, and ICA are detailed in Supplemental Methods. Among available rsFC analytical methods, in our opinion, ICA, a data-driven approach, is an optimal choice for isolating connectivity networks, to provide an inherent framework for any resultant predictors, versus manual selection of a seed region. Briefly, 20 components were output through ICA utilizing the Infomax algorithm within the Group ICA methodology in GIFT software (Medical Image Analysis Lab, University of New Mexico, Albuquerque, New Mexico; <http://icatb.sourceforge.net/>). Of the resultant components, the networks of interest were selected using templates from the BrainMap (<http://www.brainmap.org/icns>) database: a comprehensive resting-state fMRI data source (65). To determine the component with the “best-fit” for each particular network, a linear-template matching procedure was performed on all 20 components, as described elsewhere (63). Briefly, for each network template: all 20 components were scored based on their best-fit with the template by computing the average z-score of voxels falling outside the template in the component subtracted from the average z-score of voxels falling within the template. The component with the greatest value of this measure was identified as the network-of-interest: DMN, SN, right or left EN. For all networks, the component-of-interest had a best-fit score of at least two SD greater than the mean [network: best-fit score (mean $\pm$ SD); DMN: 15.7 (1.63 $\pm$ 3.58); SN: 5.2 (0.7 $\pm$ 1.45); LEN: 12.0 (1.1 $\pm$ 2.7); REN: 4.6 (0.7 $\pm$ 1.4)].

Data Analysis

All data analysis was performed using SPM8 (Wellcome Department of Cognitive Neurology, University College, London, England) and Matlab (MathWorks, Natick, Massachusetts) software. One-sample t-tests and paired t-tests were used to analyze within-network functional connectivity within- and between-conditions, respectively (see Supplemental Methods for paired t-tests). For each network, one-sample t-tests were performed: network-of-interest components from all 29 subjects during the “post-inactive” scan (baseline) were entered into the analysis and ICA-assigned z-scores at each voxel were averaged across all subjects and compared to zero (Fig. 2). Significance threshold was set at $p < 0.05$ family-wise corrected (FWE).

For each network, a whole brain voxel-by-voxel regression analysis was performed between network functional connectivity (z-score of the weight on the ICA component of interest) at baseline (post-inactive) with the following variables: 1) depression severity (as measured by QIDS score at pre-randomization); 2) reductions in depression symptoms in response to placebo administration with expectations of antidepressant effects [(QIDS_{ACTIVE} –

QIDS_{INACTIVE}), see above]; and 3) reductions in depression symptoms in response to ten weeks of antidepressant treatment (as measured by QIDS scores = Week 0 - Week 10). All analyses were restricted to voxels within those defined by the network-of-interest’s one-sample t-test composed of corresponding network component maps from all 29 subjects’ inactive scan (masked at $p < 0.05$ -FWE). Depression severity score and scan order were input as covariates in all analyses.

All results were constrained within network component maps [one-sample t-test (above) masked at $p < 0.05$ -FWE]. For all *a priori* regions (rACC, INS, dlPFC), significance was set at a threshold height of $p < 0.005$ uncorrected and 3dClustSim [AFNI (<http://afni.nimh.nih.gov>)] was used with 1000 Monte Carlo simulations to determine cluster-based, whole-brain correction at $p < 0.005$ to account for testing of three bilateral regions-of-interest and four networks (total of ten). See Supplemental Material for extent cluster information, which is network-size dependent. Significance for all other peaks was set at $p < 0.05$ -FWE. These significant data clusters were extracted using MarsBar (66), for quantification of regional functional connectivity at baseline and placebo-induced changes, graphing, determination of correlation coefficients (Pearson/Spearman correlations at $p < 0.05$). Data are expressed as the mean $\pm$ one S.D., unless otherwise indicated.

Multivariate Relevance Vector Regression (RVR) Analysis

We also investigated single-subject predictability of baseline ('inactive' scan) rsFC onto measured placebo responses using multivariate RVR as implemented in PRoNTo (<http://www.mlnl.cs.ucl.ac.uk/pronto/>) running under Matlab (Mathworks, 2012a release). RVR is detailed elsewhere (67). Briefly, it is a sparse kernel learning multivariate regression method formulated in Bayesian framework. The model weights are assigned a zero-mean Gaussian prior in which each weight is governed by its own hyperparameter. Iterative estimation from the fMRI data identifies the most probable values for these hyperparameters with sparseness achieved due to the posterior distributions of many of the weights peaking around zero. The voxels associated with non-zero weights are marked as relevance vectors, which can then be used to predict the target value (placebo-induced QIDS) for a novel input vector (e.g. baseline SN rsFC). RVR's major strength relative to other multivariate machine learning techniques [i.e. support vector machine (SVM), reviewed (68)] is that it computes quantitative prediction of a variable of interest without a need for discrete categorical estimation (e.g. patients vs. controls) (69). Here, the subjects' SN components were mean centered and input into the RVR analysis. An estimate for the model's predictability was calculated via leave-one-out cross validation, indexed using the Pearson correlation coefficient and mean squared error (MSE) between actual and the predicted placebo response measure. The significance of these metrics was determined through non-parametric permutation tests. In a single iteration, we randomly paired subjects' SN functional connectivity with subjects' placebo response values. Subsequently, we calculated the MSE and correlation for the random pairing. This was completed for 5000 iterations and built a distribution of MSE and correlation values from which p-values were calculated for accuracy of placebo response prediction.

RESULTS

Patient Characteristics

Twenty-nine participants with MDD [QIDS-16SR (mean $\pm$ SD): 16.1 ± 4.1 ; Hamilton Rating Scale for Depression (HRSD-17): 21.6 ± 5.1] were enrolled in the study and completed the two-week randomized placebo trial and entered the ten-week treatment with an open-label antidepressant (Fig. 1). 79% of them (23/29) completed the entire open-label antidepressant treatment portion; those who dropped out before full completion were not

significantly different in their depression severity and placebo responsiveness from those who completed the study (see Supplemental Results, also for additional participant data).

Placebo- and Medication-induced Changes in Depression Symptoms

Reductions in depression symptoms after one week of the “active” placebo were significantly greater than after the “inactive” placebo treatment [QIDS: 2.0 ± 3.4 for active; 0.17 ± 2.4 for inactive; $F = 7.2$, $df = 1$, $p = 0.012$]. The total placebo response measure ($QIDS_{ACTIVE} - QIDS_{INACTIVE}$) was highly variable, ranging from -8 to 11 (mean $\pm$ S.D.: 1.8 ± 4.2). Ten weeks of open-label antidepressant treatment was also associated with a significant reduction in depression symptoms [QIDS at Week 0: 11.6 ± 4.3 ; at Week 10: 6.9 ± 3.9 ; $t = 4.9$, $df = 22$, $p < 0.001$].

Association of Baseline Resting Functional Connectivity, Pre-Randomization Depression Severity, Response to Placebo, and Response to Antidepressant Medication

Statistical component maps for each network were examined against symptoms of depression severity (QIDS-16SR) at time-point of pre-randomization. We did not find a significant relationship with any of the networks (*a priori*: $p > 0.005$, $mm^3 > \text{network-specific } mm^3$; other: $p > 0.05\text{-FWE}$).

Statistical component maps for each network were then examined against reductions in depression symptoms in response to one-week of placebo administration with expectations of antidepressant effects (Fig. 3) and in response to ten weeks of open-label antidepressant treatment. Significance was established at $p < 0.005$ and extent $> 928 \text{ mm}^3$ for the SN (Supplemental Material). Increased baseline rsFC of the rACC within the SN was significantly associated with greater placebo response: rACC: 0, 38, 4, 1784 mm^3 ; $Z = 4.35$. No other significant effects were observed.

A linear regression analysis that included baseline rsFC of the rACC within the SN predicted 65% of the variance in placebo responsiveness (adjusted $R^2 = 0.65$).

Based on this initial finding and the rACC's essential involvement in placebo effects (50-52) and the prediction of antidepressant treatment response (70, 71), we allowed subsequent activation of rACC rsFC to be significant after small volume correction ($p < 0.05\text{-FWE}$) using a rACC region-of-interest sphere centered around the MNI coordinates 4, 42, 6 (72) with a 6mm radius [created using MarsBar (66)].

Increase baseline rsFC of the rACC within the SN was significantly associated with reductions in depression symptoms in response to ten weeks of open-label antidepressant treatment (rACC: 0, 40, 8; 64 mm^3 ; $Z = 3.09$; $p < 0.05\text{-SVC:FWE-corr}$). No other effects were observed.

Placebo-induced Changes in Network Functional Connectivity Predicts Response to Placebo and Antidepressant Medication

As expected, one-week of placebo administration with expectations of antidepressant effects did not result in significant changes within rsFC of the networks—as measured by the changes in rsFC from “active” to “inactive”—given high inter-individual variation in

response to placebo (*a priori*: $p > 0.005$; other: $p > 0.05$ -FWE-corr, see Supplemental for network-specific cluster size).

In order to account for the variability inherent in the placebo response measure, statistical component maps of rsFC changes in response to one-week of placebo administration were then examined against associated reductions in depression symptoms in response to one-week of placebo administration and ten weeks of open-label antidepressant treatment. Placebo-induced rsFC reduction in the rACC within the SN was significantly associated with greater placebo response (rACC: 0, 38, 4; 192 mm³; $Z = 3.97$; $p < 0.05$ -SVC:FWE-corr). No other significant effects were observed.

Multivariate Relevance Vector Regression (RVR): Single-Subject prediction of placebo and treatment response

Based on the results described above, we first applied RVR to rsFC of the entire SN, where significant results were observed, in order to enable quantitative prediction of depression symptom reductions in response to placebo administration and in response to ten weeks of antidepressant treatment at the individual level. RsFC of the SN was significantly predictive of placebo responses [correlation = 0.41; p -value = 0.018; mean sum of squares = 14.36; p -value = 0.019; (Fig. 4)], with the greatest weights contributing to placebo response prediction within the rACC. SN rsFC was not a significant predictor of response to antidepressant treatment (correlation = 0.03; p -value = 0.34; mean sum of squares = 21.31; p -value = 0.36). No effects were found in the other networks.

DISCUSSION

In this study, we illustrated the viability of network-based rsFC to identify potential imaging-based predictive markers of treatment response in MDD. We found that more cohesive rsFC of the SN, through connectivity of the rACC, predicted greater reductions in depressive symptoms following one-week of placebo administration with expectations of antidepressant effects and ten weeks of open-label antidepressant treatment. In addition, the clinical response to one-week of placebo treatment was also associated with placebo-induced decreases in rsFC of the rACC within the SN. Finally, multivariate RVR demonstrated that SN rsFC predicted placebo responses with significant accuracy at an individual level.

Elevated baseline rsFC of the rACC within the SN predicted greater reductions in depression symptoms in response to placebo administration with expectations of antidepressant effects. Specifically, the rACC alone predicted 65% of the response variance. This finding potentially advances a more general understanding of the neurobiology of placebo effects across diseases: Both opioidergic and BOLD activity within the rACC have been consistently implicated in placebo analgesia (48, 52, 53) which evinces a hypothesis that corresponding mechanisms of action are involved in the formation of placebo effects across disorders (47), with recent evidence in further support of this notion (61). Our data, to our knowledge, are also the first demonstration of SN involvement in MDD placebo effects and thus, supplement the small existing body of work in the neurobiology of placebo in patients with MDD (15, 61). This is consistent with the role of the SN in saliency attribution:

particularly, selecting and integrating biologically relevant stimuli with interoceptive states to guide input of attentional resources and behavior (73). In this case, the network was involved in attending to and incorporating a set of expectations within a therapeutic environment with internal states resulting in a reduction of depression symptoms. If the former hypothesis remains valid, SN rsFC may be the functional context of prior placebo analgesia-associated rACC findings.

Mounting evidence from studies employing a variety of neuroimaging modalities and treatments indicate that increased pretreatment activity in the rACC is associated with better response to antidepressant treatment, as recently reviewed (31). More specifically, metabolism in the region has been observed to differentiate responders from non-responders to antidepressant medication (70). However, the open-label nature of these and prior studies (10, 70, 74, 75) makes it difficult to dissect drug-specific from non-specific treatment effects. Our study is an initial attempt in isolating predictors for different aspects of treatment effects, such as placebo. Here, we demonstrated that greater baseline rsFC of the rACC within the SN to be a significant predictor of placebo response *and* separately, open-label antidepressant treatment response. Consistent with these data, a recent RCT found that elevated pretreatment theta current density in the rACC predicted treatment outcome in both the medicated and placebo group (14).

In all, these findings point to the predictive role of rACC within the SN in the response to placebo and the overall response to antidepressant treatment (antidepressant + placebo + other non-specific effects). Furthermore, we observed the normalization of heightened baseline rACC rsFC after placebo administration to be associated with greater placebo responses; this illustrates that rACC modulation may be an important element of placebo neurobiology. A relevant hypothesis may state that enhanced rACC rsFC within the SN may represent a greater capacity for integrating salient stimuli with adaptive cognitive-affective functioning, which is conducive for the manifestation of a placebo effect. Normalization of heightened rACC activity has also been demonstrated in MDD responders to sleep deprivation, but absent in non-responders (a placebo-arm was not incorporated) (76). Thus, malleability within the rACC may extend to necessitate a successful antidepressant treatment response or to placebo mechanisms inherent in the antidepressant response.

Finally, we demonstrated that multivariate RVR application to baseline SN rsFC, with the greatest weight within the rACC, was significantly predictive of placebo responses at an individual-subject level, although this was not the case for antidepressant responses. The utilization of a similar method, SVM, has gained substantial attention in the last years as a predictive classifier in MDD with diagnostic and prognostic qualities (77-79). For example, in a sample of 37 depressed patients and 37 healthy controls, whole-brain structural MRI significantly classified nearly 90% of patients exhibiting clinical remission and nearly 70% of those with an MDD diagnosis (80). Instead, we employed RVR to enable quantitative prediction without need for group classification, as it has been recently described (69). The potential applicability of SN rsFC as an individual-subject predictor of placebo response will need to be further confirmed in larger samples; yet, this information could ultimately augment clinical treatment through identification of patients who possess a greater likelihood in benefiting from lower dosages of antidepressant medication or cognitive

interventions. This may also be relevant in the context of clinical trials to better distinguish patients with greater susceptibility to placebo effects, allowing for patient stratification and possibly, more detailed clarification of the effects of treatment components (specific versus non-specific).

A limitation of the current study was the small sample size ($N = 29$ for the placebo phase; $N = 23$ for the antidepressant phase). This is especially relevant to the RVR analysis, where independent confirmation is needed to establish whether SN rsFC is a predictor of placebo response at an individual level. Finally, the subsequent nature of the open-label treatment after the placebo phase was not optimal for dissecting drug and placebo-specific effects. Future RCTs with parallel placebo and drug arms will need to be conducted to better identify and separate predictors of treatment response. However, our data have the potential to inform future designs of antidepressant clinical trials and personalized medicine for MDD patients by identifying individuals with greater likelihood in responding to non-pharmacologically specific interventions and who may ultimately be selected for less intensive treatments, lower dosages of medication, or for enhanced patient-clinician interaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Experimental Design

A) After pre-randomization (screening), subjects are randomized into one of two conditions each lasting seven days: 1) *Active*: placebo administration with disclosure that it may provide antidepressant-like treatment effects; 2) *Inactive*: placebo administration with disclosure that it is an inactive agent. B) A three day washout occurs during which the patient receives no medication. C) Subjects cross-over to the alternative condition. D) Resting-state fMRI scans are obtained immediately after each condition. E) After full completion of the placebo trial, subjects undergo ten weeks of open-label antidepressant treatment. Depression measures are administered (* marks QIDS-16SR administration) at pre-randomization, pre- and post-active, pre- and post-inactive, and week 0, 2, 4, 8, 10 of the antidepressant trial.

Figure 2. Functional Connectivity of Networks

One-sample t-tests including baseline (inactive condition) resting-state fMRI scans for all 29 subjects for each ICA-component corresponding to the network: A) Default-mode, B) Salience, C) Left (left-side) and right (right-side) executive networks. The t-score bars are shown at the right; all images are displayed at a threshold of $p < 0.05$ family-wise corrected. Images are shown in standard space of the Montreal Neurological Institute (MNI) template. $N=29$.

Figure 3. Baseline Functional Connectivity of the Salience Network Predicts Response to Placebo Administration

N=29. (Top left and right): Voxel-by-voxel correlational analysis between baseline functional connectivity of the SN and decreases in depression symptoms in response to placebo administration. Clusters passing significance threshold are labeled. Image display is at $p < 0.01$; t-score bar is shown in the bottom right. (Bottom Left): Association between reductions in depression symptoms in response to placebo administration and functional connectivity of rACC within the SN. Functional connectivity of this region predicted 65% of the variance in placebo responses ($p < 0.001$).

Figure 4. Multivariate Relevance Vector Regression

Left: Mean predictor map with an arbitrary threshold of >50% of minimum and maximum voxel weight values. The map shows the relative contribution of each voxel to the regression function in relation to all other voxels. Color bar signifies weight value for all voxels. Right: Scatter plot showing the predicted placebo response value derived from each subject's baseline SN functional connectivity using RVR leave-one-out cross validation versus their actual placebo response *value* ($r = 0.41$; $p\text{-value} = 0.018$).