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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 week-long, identical placebos (described either as having active fast-acting, antidepressant effects or as inactive) followed by a 10-week open-label antidepressant medication treatment. Twenty-nine participants underwent an rsFC functional magnetic resonance imaging 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 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 1 week of active placebo and 10 weeks of antidepressant treatment. Machine learning further demonstrated that increased salience network rsFC, mainly within the rostral anterior cingulate, significantly predicts individual responses to placebo administration.

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 nonpharmacologic approaches or to develop biomarkers of placebo effects in clinical trials.

Keywords: Biomarkers of treatment response, Large-scale connectivity networks, Major depression, Placebo effects, Resting-state functional connectivity

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Major depressive disorder (MDD) has recently been conceptualized as a disorder with a network-based pathophysiology (1). Particularly, MDD manifests in corticolimbic 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 nonspecific elements of the treatment response, such as the placebo effect, is still limited, with very few studies specifically addressing biomarkers of nonspecific elements of antidepressant treatment response (14,15). This is not a small concern, as placebo response rates in antidepressant clinical trials average 31% to 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 to dissect the neural predictors of drug-specific and nonspecific 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 network (DMN), salience network (SN), and executive network (EN) (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 downregulation 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 cortex (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 (INS) and dorsal anterior cingulate cortex, is enlisted during the integration of salient stimuli and interoceptive information to guide motivated behavior (33). In particular, the anterior INS 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 hypoactivation 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 gray matter volume in the region is an indicator of nonresponse to standard MDD treatments (11).

Nodes within these three networks have also been implicated in the neurobiological mechanisms of nonspecific 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 1 week of placebo treatment; and 3) clinical response to 10 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 1week of placebo and 10 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, unmedicated subjects with a DSM-5 diagnosis of MDD were recruited via local advertisements (21 female subjects; age 18 to 59 years [mean ± SD: 32 ± 13]). See Supplemental Methods and Materials in Supplement 1 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 and Antidepressant Open-Label Trial

As previously described (61), subjects were randomized into either 1) 1 week active placebo treatment (two pills per day), with expectations that the pill represented a potentially fast-acting antidepressant agent, or 2) 1 week inactive placebo treatment described as a control condition, without pharmacologic effects (two pills per day). After a 3-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 (Figure 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: prerandomization, baseline (pre), post-active, and post-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.