

Parsing Heterogeneity in Mood Disorders: The Challenges of Modeling Stable Mood Disorder–Related Functional Connectomes

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Despite the reported links between mood disorders and neural network abnormalities, discrepancies in findings abound. Given the heterogeneous nature of depression, attempts to use resting-state connectivity to identify different depression subgroups have sometimes failed to be replicated (1,2). Examining functional neural networks during active clinical states of depression involving thousands of combinations of different symptoms across individuals may result in the identification of unstable biomarkers of mood disorders. Focusing on remitted or euthymic clinical phases that reduce symptom variability may elucidate more stable and trait-like mood disorder biomarkers.

In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Langenecker *et al.* (3) use a graph theory–based approach focusing on resting-state functional network edges in a transdiagnostic mood disorder sample in the remitted or euthymic phase. Notably, Langenecker *et al.* (3) combine both diagnostic category and the National Institute of Mental Health’s Research Domain Criteria (RDoC) frameworks to examine associations between functional network edges with mood disorder diagnostic status and mood disorder–relevant RDoC constructs of response inhibition and reward responsiveness. The authors report interactions between mood disorder diagnostic status and these RDoC-defined constructs, with better response inhibition or greater reward responsiveness among the mood disorder group being linked to different functional network patterns compared with the healthy control group. These results highlight the value of combining both frameworks to enhance the understanding of mood disorder pathophysiology.

There has been growing enthusiasm for the use of resting-state functional magnetic resonance imaging (fMRI) as a potentially powerful tool for identifying biomarkers of psychiatric disorders. Resting-state fMRI is a particularly desirable neuroimaging modality for clinical applications as it is easy to collect, is less burdensome for participants than cognitively demanding tasks, and has been shown to reliably derive large-scale intrinsic functional neural networks across both healthy control subjects and clinical populations (4). Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), have been linked to abnormalities involving the default mode network (DMN), the cognitive control network (CCN), and the salience and emotion network (SEN) (5,6). The DMN is a functional network that is involved in internal/self-referential thought processes and has core brain hubs in the medial prefrontal cortex and the posterior cingulate cortex. The

CCN has core hubs in the lateral prefrontal and posterior parietal cortex regions and is involved in the top-down regulation of attention and emotion. The SEN includes the insula and the dorsal anterior cingulate cortex, which are involved in drawing attention toward salient events as well as limbic regions involved in emotion processing.

Given the difficulties in reliably mapping heterogeneous clinical diagnostic categories such as MDD or BD to neural circuits, the National Institute of Mental Health proposed a new strategy for classifying mental health disorders called RDoC. RDoC emphasizes the study of psychological constructs (e.g., subdomains of reward responsiveness, working memory) that are relevant to many psychological disorders and cut across a spectrum of normal to abnormal behavior, rather than diagnoses (7). These constructs are then mapped onto specific neural mechanisms. While RDoC has played a valuable role in identifying cognitive and affective processes and their associated neural underpinnings relevant to psychiatric symptoms, researchers have demonstrated that combining information from the RDoC and clinical diagnostic frameworks may lead to a more nuanced understanding of clinical phenomenology [e.g., (8)].

Langenecker *et al.* (3) expand on these efforts in a sample of 132 individuals with mood disorders with either partially or fully remitted MDD ($n = 116$) or in a euthymic phase of BD ($n = 16$), along with a sample of healthy control subjects ($n = 65$). Participants with MDD or BD were categorized into a single mood disorder group. All participants completed a resting-state fMRI scan. Outside of the scanner, participants completed a parametric Go/NoGo test (9) and a titrated monetary incentive delay task (10) to measure the RDoC constructs of response inhibition, defined as accuracy in inhibiting responses to the NoGo stimuli, and reward responsiveness, defined as the amount of money earned on the last 2 runs of the reward task, respectively. With respect to the resting-state data, Langenecker *et al.* (3) explore the possible main effects of diagnostic status, RDoC constructs, and interactions between diagnostic status and RDoC constructs on edges (i.e., a measure of functional connectivity that reflects the degree to which the blood oxygen level–dependent signal between 2 brain regions are temporally correlated). Brain regions or nodes were parsed into a DMN, CCN, SEN, and a network consisting of brain parcellations that were implicated in more than 1 network (referred to as MultiN). The authors hypothesized differences in 47 edges based on previous resting-state studies of mood disorders.

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With respect to diagnostic status, there were no group differences in any of the hypothesized edges. However, exploratory analyses revealed that the mood disorder group was characterized by greater connectivity between regions involved in the hypothesized networks with regions outside of the hypothesized networks. In addition, contrary to hypotheses that better response inhibition performance would be linked to greater connectivity within the CCN but to decreased SEN–CCN and CCN–DMN connectivity, better performance was predominately associated with decreased DMN connectivity. Regarding reward responsiveness, associations with edges were partially in line with a priori hypotheses, with greater reward responsiveness being largely associated with decreased within SEN connectivity.

Interestingly, however, the RDoC construct main effects were further qualified by interactions with diagnostic status. Specifically, connections between the SEN, CCN, and MultiN, as well as within the SEN, were implicated in interactions between diagnostic status and response inhibition. Among edges with negative beta weights, lower connectivity was associated with better response inhibition accuracy within the mood disorder group. However, the opposite pattern was found among healthy control subjects, with greater connectivity being associated with better response inhibition. Regarding edges with positive beta weights, lower connectivity was associated with better response inhibition performance only among the healthy control subjects. Interactions between reward responsiveness consisted of cross-network edges with positive beta weights, with lower connectivity being associated with greater reward responsiveness within the healthy control group. However, the opposite relationship was true within the mood disorder group, with greater connectivity being associated with better performance on the reward task. Sensitivity analyses revealed that these results were not driven by MDD versus BD diagnostic status, medication status, or differences in the number of previous mood episodes.

Together, these results indicate complex relationships between mood disorder diagnosis and RDoC constructs on functional network edges. These data suggest that relative to healthy control subjects, individuals with a history of a mood disorder may engage functional neural networks in different ways to support cognitive and emotional functioning, which might contribute to mood disorder–related dysfunction. In addition, the study highlights the importance of reducing the confounds associated with sample heterogeneity, which might obscure the identification of reliable functional network biomarkers of mood disorders. The authors attempted to parse mood disorder heterogeneity on several fronts, including incorporating only those in remitted or euthymic mood disorder phases, integrating well-characterized RDoC constructs, and imposing study sample age restrictions to minimize potential developmental confounds.

On the other hand, the study findings also underscore some important challenges that have broader implications for researchers engaging in neuroimaging research. Regarding interactions between mood disorder diagnostic status and RDoC constructs on resting-state edges, these results are situated within the context of a lack of behavioral differences between the mood disorder and healthy control groups on response inhibition and reward task performance. This is not

an uncommon occurrence in neuroimaging work and complicates the interpretation of fMRI findings. However, the authors note that the increased cross-network connectivity seen in the mood disorder group relative to the healthy control group may point to decreased functional neural network efficiency among those with a history of a mood disorder. The lack of convergence between resting-state edges and response inhibition performance associations in the present study and the findings of relevant CCN regions in previous task-based fMRI research highlight the potentially important differences between resting-state network versus task-based fMRI associations with mood disorder–relevant cognitive mechanisms. Resting-state fMRI may reveal additional cross-network functional connectivity that may be central for supporting cognition. In addition, these data illuminate the challenge of appropriately defining nodes to delineate stable and accurate functional connectomes. How should a node be defined? Is it appropriate to apply atlases derived from healthy control populations to psychiatric populations? What level of granularity should we apply when defining nodes? These are open, unresolved questions and likely pose a tremendous challenge for deriving sensitive and easily replicable functional network models.

Despite these challenges, the authors' inclusion of RDoC constructs along with diagnostic information in the absence of confounds associated with active clinical states presents a valuable contribution toward the goal of finding stable and trait-related functional network biomarkers of mood disorders. These findings were derived from a well-characterized, carefully selected, and relatively large sample of individuals with a history of mood disorders. Future work should focus on longitudinal investigations charting mood disorder illness progression from pre-morbid vulnerability to onset, and from remission to relapse to determine which functional network patterns represent stable features of mood disorders and which functional network patterns change over time and characterize certain phases or symptom profiles of mood disorders.

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Article Information

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