Archival Report

Biological Psychiatry

Parsing Heterogeneity in the Brain Connectivity of Depressed and Healthy Adults During Positive Mood

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ABSTRACT

BACKGROUND: There is well-known heterogeneity in affective mechanisms in depression that may extend to positive affect. We used data-driven parsing of neural connectivity to reveal subgroups present across depressed and healthy individuals during positive processing, informing targets for mechanistic intervention.

METHODS: Ninety-two individuals (68 depressed patients, 24 never-depressed control subjects) completed a sustained positive mood induction during functional magnetic resonance imaging. Directed functional connectivity paths within a depression-relevant network were characterized using Group Iterative Multiple Model Estimation (GIMME), a method shown to accurately recover the direction and presence of connectivity paths in individual participants. During model selection, individuals were clustered using community detection on neural connectivity estimates. Subgroups were externally tested across multiple levels of analysis.

RESULTS: Two connectivity-based subgroups emerged: subgroup A, characterized by weaker connectivity overall, and subgroup B, exhibiting hyperconnectivity (relative to subgroup A), particularly among ventral affective regions. Subgroup predicted diagnostic status (subgroup B contained 81% of patients; 50% of control subjects; $\chi^2 = 8.6$, $p = .003$) and default mode network connectivity during a separate resting-state task. Among patients, subgroup B members had higher self-reported symptoms, lower sustained positive mood during the induction, and higher negative bias on a reaction-time task. Symptom-based depression subgroups did not predict these external variables.

CONCLUSIONS: Neural connectivity-based categorization travels with diagnostic category and is clinically predictive, but not clinically deterministic. Both patients and control subjects showed heterogeneous, and overlapping, profiles. The larger and more severely affected patient subgroup was characterized by ventrally driven hyperconnectivity during positive processing. Data-driven parsing suggests heterogeneous substrates of depression and possible resilience in control subjects in spite of biological overlap.

Keywords: Community detection, Depression, fMRI, Neural network connectivity, Positive mood, S-GIMME

http://dx.doi.org/10.1016/j.biopsych.2016.06.023

Research in psychiatry is moving toward a greater focus on biological heterogeneity. This new focus represents an effort to identify core biobehavioral features that differentiate individuals both within and across traditional diagnostic categories. The promise of this work is that a focus on understanding biological heterogeneity will reveal underlying disease mechanisms and, ultimately, aid in developing and prescribing targeted treatments for biologically based patient profiles or subgroups. To date, efforts to parse biobehavioral heterogeneity within broad disorder domains (attention deficit, psychosis) (1–3) have suggested that biologically based subtyping can indeed predict external measures of functioning, clinical outcomes, and neurobiology.

Like other psychiatric diagnoses, major depression exhibits marked heterogeneity in symptom presentation, with 16,400 possible combinations of symptoms contained within the 9 DSM-5 criteria that yield a single diagnosis (when considering all possible subtypes within each criterion) (4). Individuals with depression fully embody this hypothetical heterogeneity, with over 1000 unique symptom profiles endorsed within a representative treatment-seeking sample of 3703 patients (5). In spite of this heterogeneity, one well-documented feature of depressed participants is a pattern of decreased positive affect and, more broadly, decreased engagement with positive information. This pattern is evident across multiple levels of analysis, in 1) patient-reported symptoms (anhedonia), 2) cognitions (minimization of positive self-attributes, pessimism) (6), 3) observable behaviors (information processing biases away from positive stimuli and positive appraisals) (e.g., 7,8), and 4) brain function [decreased reward processing (9); decreased limbic responses to happy faces (10,11)]. However, just as multiple mechanisms are associated with abnormalities of negative affect in depression (12), similar heterogeneity may exist in positive affective information processing.

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ISSN: 0006-3223

Neural processing of positive information, like all other brain processes, may best be characterized as the coordinated activity of disparate brain regions over time (9,13). Functional connectivity analysis of neural networks is designed to capture this construct. Whereas brain activation patterns during reward processing in depression are well characterized (e.g., decreased ventral striatal responses) (14), network-level aberrations (e.g., connectivity) during positive information processing are relatively understudied, though initial reports demonstrate their relevance (9,15). Furthermore, the type of sustained, self-referential, and self-focused thought patterns that dominate depressive cognition in daily experience (6,16) have rarely been examined with neuroimaging. Accurate characterization of brain processes underlying positive information processing would have both theoretical and practical implications, suggesting novel biobehavioral targets for intervention, particularly given that depression treatments have historically focused on negative processing patterns (6).

By contrast, neural connectivity in depression has been well characterized at rest and during the generation and regulation of negative emotion (12,17). These studies reveal alterations in connectivity, although the direction of findings (e.g., hyper- vs. hypoconnectivity) is sometimes conflicting even when highly translatable (e.g., resting state) methods are used (17,18). Here, we consider whether the same types of network-wide mechanisms implicated at rest and in negative information processing may also be disrupted in (at least some) depressed individuals during positive information processing.

Neuroimaging analyses in depression have historically been dominated by group comparison of patients and control subjects. Although diagnosis is certainly not irrelevant or arbitrary, this approach likely fosters imprecision due to biological heterogeneity (19), hindering progress toward accurate identification of neural mechanisms. This is problematic in the analysis of brain processes, because group-level maps may not accurately represent even a single individual within the group (20–22). Thus, group comparisons have the potential to foster mixed or spurious findings, incomplete etiological models, and confusion within the literature. Such group comparison analyses overlook two important sources of information: 1) subgroups within a diagnostic group, possibly representing unique etiologies requiring unique treatments; and 2) individuals who share biological commonalities in spite of disparate clinical status (i.e., healthy and ill individuals). This latter issue—that is, heterogeneity within healthy control subjects that may overlap with patient profiles—has received less attention in psychiatry, but it is important because, if certain healthy individuals are able to overcome or "balance out" a biological dimension associated with risk, the question of how they do so becomes clinically informative.

In summary, conclusions predicated on depressed-versus-healthy comparisons may mask heterogeneity. A more novel approach is to focus explicitly on heterogeneity in biological mechanisms, search for detectable biologically derived subgroups, and then characterize these subgroups with respect to relevant observable characteristics and behaviors (including, but not limited to, diagnosis). During a sustained positive affect induction, we applied a connectivity method shown to reliably recover, for each individual, both the presence and the direction (i.e., does A predict B after controlling all other network-wide influences [including B's influence on itself]?) of connectivity among regions (23). This approach allowed for neural networks to be reliably constructed at the individual level and with greater precision than is possible in nondirected (e.g., correlational) approaches.

This data-driven, brain-based categorization approach was applied to functional connectivity maps across depression-relevant regions drawn from three networks implicated repeatedly in affective and at-rest processing: ventral affective network (VAN), spanning regions linked to processing of both positive/rewarding and negative stimuli; hubs of the default mode network (DMN), which have been linked to self-referential processing; and the cognitive control network (CCN). Given that both healthy and maladaptive functioning were expected to have heterogeneous substrates, a sample comprising healthy and depressed individuals was used (with data-driven subtyping, entirely blind to diagnostic status) to capture patterns characterizing both normative and maladaptive states of functioning and to assess overlap between the two. Participant-generated autobiographical memory scripts were used to probe self-relevant positive affective processing.

Connectivity maps were generated using Group Iterative Multiple Model Estimation (GIMME) (20) (see the Supplement for further discussion of connectivity method selection). Whereas concerns have been raised about the ability of many connectivity methods to reliably recover brain connections for individuals (24), validation tests suggest GIMME very reliably recovers both the presence and direction of paths within heterogeneous individuals (20,25). Such an ability at the individual level is a particularly useful feature for biological subtyping. Results from the GIMME modeling approach correspond to those found using dynamic causal modeling (26), but offer the added benefits of readily managing a greater number of regions of interest (ROIs) and not requiring an onset vector of stimuli presentations, allowing for application to resting-state and other block design data. Clustering on temporal features was performed during GIMME model selection, which further improved recovery of connectivity features in validation tests (27,28) and produces connectivity-based subgroups. External variables were then used to compare connectivity-based subgroups across multiple levels of analysis (diagnosis, symptoms, affect during mood induction, information processing, neural connectivity at rest), allowing for further subgroup characterization and assessment of external relevance. We aimed to reveal network-level mechanisms during positive affect induction that inform theoretical models of depression, while simultaneously allowing biological heterogeneity to express itself, both within and across diagnostic boundaries. Resulting biological subgroup distributions and characteristics could ultimately suggest novel mechanistic targets for treatment, including one or both of the following: 1) discrete depression etiologies (requiring discrete treatments) or 2) mechanisms that allow healthy individuals to "balance" biological features shared in common with depressed patients.

METHODS AND MATERIALS

Participants were 92 individuals (68 unmedicated patients with major depressive disorder, 24 never-depressed control subjects free of lifetime Axis I disorders) recruited for a larger