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

Rebecca B. Price[1], **Stephanie Lane**[2], **Kathleen Gates**[2], **Thomas E. Kraynak**[1], **Michelle S. Horner**[1], **Michael E. Thase**[3], and **Greg J. Siegle**[1]

[1]Johns Hopkins University School of Medicine

[2]University of North Carolina, Chapel Hill

[3] Perelman School of Medicine of the University of Pennsylvania and the Philadelphia Veterans Affairs Medical Center

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—92 individuals (68 depressed patients, 24 never-depressed controls) completed a sustained positive mood induction during fMRI. Directed functional connectivity paths within a depression-relevant network were characterized using Group Iterative Multiple Model Estimation, 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 controls;χ^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

Corresponding author: Rebecca B. Price, Ph.D., Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213, ph: 412-383-5443, fax: 412-383-5426, rebecca.price@stanfordalumni.org.

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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 controls 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 controls in spite of biological overlap.

Keywords

depression; positive mood; neural network connectivity; fMRI; community detection; S-GIMME

Introduction

Research in psychiatry is moving towards a greater focus on biological heterogeneity, in 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 sub-types 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 patient-reported symptoms (anhedonia), cognitions [minimization of positive self-attributes, pessimism; (6)], observable behaviors [information processing biases away from positive stimuli and appraisals; (e.g., 7,8)], and 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.

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. While 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/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 controls. Although diagnosis is certainly not irrelevant or arbitrary, this approach likely fosters imprecision due to biological heterogeneity (19), hindering progress towards accurate identification of neural mechanisms. This is problematic in 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 analyses overlook two important sources of information: 1) subgroups within a diagnostic group, possibly representing unique etiologies requiring unique treatments; 2) individuals who *share* biological commonalities in spite of disparate clinical status (i.e., healthy and ill individuals). This latter issue, i.e., heterogeneity within healthy controls that may overlap with patient profiles, has received less attention in psychiatry, but 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-vs-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 non-directed (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 (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 comprised of 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 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 **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 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) 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 a) discrete depression etiologies (requiring discrete treatments) and/or b) mechanisms that allow healthy individuals to ‘balance’ biological features shared in common with depressed patients.

Methods

Participants were 92 individuals (68 unmedicated MDD patients, 24 never-depressed controls free of lifetime Axis I disorders) recruited for a larger treatment study [see Table 1; (28); **Supplement**].

Positive mood induction

As described previously (29), prior to scanning, participants selected happy music from a list of non-linguistic pieces, and composed an idiographic paragraph about a vivid, extremely happy personal experience, one of the best times in their lives when they felt happy or exuberant [rated >=7 on a scale of 1 (neutral) to 9 (the happiest they had ever been]. Just prior to scanning, participants were instructed to “try to re-experience” the event and to “try to feel that happiness as strongly as you did when it occurred.” The script (stationary text)

and music were presented for 7min while participants made continuous ratings of their affect using a mouse and visual analog scale ranging from “very sad”(-100%) to “very happy” (100%). Protocol deviations and other sources of missing data are discussed and analyzed in the **Supplement**.

fMRI acquisition and preprocessing

T2*-weighted images depicting BOLD contrast (TR=1500;TE=27;FOV= 24cm;flip angle=80°;29 3.2mm slices;280 TRs) were acquired on a 3T Siemens Allegra (n=11) or a 3T Siemens Trio (n=81). Scanner was included as a covariate in all analyses. Standard preprocessing steps were applied as in (28)(**Supplement**). AFNI’s ANATICOR algorithm was applied to remove artifacts (hardware, motion) influencing connectivity data.

The GIMME connectivity algorithm (described below) performs particularly well for analysis of 5-15 ROIs. 15 ROIs were selected *a priori* based on prior literature in depression (emphasizing replicated and meta-analytic findings) with the goal of spanning networks relevant to ventral affective processing (VAN), self-referential processing (DMN), and top-down regulation (CCN). See **Supplement** and **Figure 1** for details of ROI definitions. Mean timeseries data were extracted per-participant for each ROI. We removed timepoints with excessive motion from analysis and verified that motion parameters were unrelated to any finding (**Supplement**).

Directed connectivity and community detection

The full sample of 92 individuals was processed and clustered without regard to diagnosis. Directed paths [i.e., establishing which of two ROIs statistically predicts the other after controlling for other candidate regions (including lagged auto-regressions)] between all pairs of ROIs (both contemporaneous and at lag=1TR) were derived for each individual using S-GIMME (27,30). GIMME and clustering with GIMME have been previously described and validated (20,27,31). In simulated data across multiple conditions, S-GIMME recovers the true subgroup assignments nearly perfectly, even in sample sizes comparable to our control subsample alone (27).

Briefly, using a unified structural equation framework (32) and a Bayes net formulation, S-GIMME first looks across individuals to detect signal from noise and arrive at a map of lagged and contemporaneous directed connections that exist for the majority (“group-level map”). Next, S-GIMME arrives at a similarity matrix using the individual-level estimates of these group-level connections as well as anticipated estimates for candidate connections. Walktrap (33), an ‘unsupervised’ (see **Supplement**) community detection algorithm found to be robust across many issues common in clustering [e.g., unequal cluster sizes; (34)], is conducted on this matrix to arrive at subgroups who have shared connectivity patterns (similar strength and direction of connectivity paths). Having arrived at robust subgroups, S-GIMME then searches for subgroup-level paths, using the group-level search described above. Finally, S-GIMME robustly identifies individual-level connections using group-derived temporal patterns as a starting point.

Characterization of subgroup connectivity

S-GIMME generated group-level, subgroup-specific, and individual (per-participant) connectivity maps. Subgroups were characterized using subgroup-specific maps and by comparing the strength of each path present at the group-level (excluding auto-regressive paths) via unpaired t-tests comparing beta weights from individual-level maps, with False Discovery Rate (FDR) correction.

External variables

Subgroups were compared across levels of analysis on five indices of affective processing: diagnostic status; factor scores representing severity of self-reported affective dysregulation across 13 validated scales (**Supplement**); average affect rating during minutes 2-7 of the induction—a marker of sustained moment-to-moment positive affect which strongly differentiated patients from controls (29); biases in reaction times when asked to rate the self-relevance of negative, neutral, and positive words—a behavioral marker of affective information processing [Personal Relevance Rating Task, PRRT (e.g., 35); negative bias=mean neutral RT – mean negative RT; positive bias=mean neutral RT – mean positive RT]; and beta weights representing connectivity from PCC->pgACC during a distinct resting state task (see **Supplement**). A single index was desired per level of analysis to limit multiple comparisons. The PCC->pgACC pathway was selected *a priori* as the external neurobiological index because it represents two primary nodes of the DMN (36), and this directed path was significant at the group level (i.e., was present in every individual in the sample) when identical GIMME methods were applied to the resting state data, enabling parallel analysis on a continuously distributed external outcome. For continuous variables, main and interacting effects of diagnosis and subgroup were explored in ANCOVAs (controlling for scanner), allowing us to test whether anticipated main effects of diagnosis were moderated by connectivity subgroup (as indicated by hypothesized diagnosis*subgroup interactions). *Post hoc* comparisons then quantified effects of subgroup within-diagnosis.

As a comparison, external variables were compared across symptom-based (clinician-rated/self-report) subgroups within the depressed participants (+/− melancholic depression, +/− comorbid anxiety, median split on the BDI anhedonia subscale).

Results

Connectivity maps

Group-level: At the group level, connectivity paths depicted in **Figure 2** were present, in addition to lagged autocorrelations at every ROI. ROIs behaved as a strongly interconnected network, including numerous ipsilateral and within-network (e.g., VAN->VAN) connections. Subgroups. Based on unsupervised search for the optimal number of subgroups, two subgroups emerged (see **Supplement** for subgroup quality analyses**)**. Subgroup was unrelated to the scanner where data were acquired (χ^2=0.97, p=.324). In t-tests, Subgroup B exhibited stronger connectivity than Subgroup A in numerous group-level paths (**Figure 2;** FDR p<.05); no group-level paths were stronger in Subgroup A. In paths unique to each subgroup (**Figure 3**), *post hoc* comparisons (detailed in **Supplement**) suggested greater overall connectivity in Subgroup B, specifically in VAN->VAN (t(90)=−3.83,p<.001) and

VAN->DMN (t(90)=−5.60,p<.001) pathways and in all 3 types of CCN-driven paths (*p*'s<.001). Subgroup A had less than half as many specific paths (4 vs. 9); these included increased DMN->VAN (t(90)=3.31,p<.005) and DMN->DMN paths (t(90)=2.29,p=< .05).

External variables

Scanner was included as a covariate in all analyses. **Diagnosis.** Depressed patients were more likely to be classified in Subgroup B (80.9% of patients), while controls were equally split (50%) between the two subgroups (χ^2=8.6,*p*=.003;**Figure 4A**). **Symptom severity.** Patients in Subgroup B had higher symptom severity than their counterparts in Subgroup A, while the effect was absent among controls (diagnosis*subgroup interaction: $F_{1,71}$=6.50,*p*=.013;**Figure 4B**). **Concurrent affect.** Patients in Subgroup B had lower positive mood during the induction than Subgroup A, while the effect was absent in controls (diagnosis*subgroup interaction: $F_{1,80}$=4.36,*p*=.040;**Figure 4C**). **Affective information processing.** Patients in Subgroup B had increased negative bias in reaction times (i.e., were faster to rate the personal relevance of negative descriptors relative to neutral words) compared to Subgroup A. A marginal interaction suggested no corresponding effect in controls (diagnosis*subgroup interaction: $F_{1,86}$=3.77,*p*=.055;**Figure 4D**). No main or interaction effects were observed for reaction time bias towards positive (relative to neutral) words (*p*'s>.30). **Resting state connectivity.** During the distinct resting state task, Subgroup B exhibited decreased PCC->pgACC connectivity compared to Subgroup A ($F_{1,83}$=7.8,*p*=.007). A marginal interaction ($F_{1,83}$=3.1,*p*=.083) reflected decreased connectivity specifically in *controls* in Subgroup B compared to all other groups (*p*'s <.05;**Figure 4E**). An additional *post hoc* analysis further suggested decreased PCC->pgACC connectivity was useful in distinguishing which Subgroup B members were controls rather than depressed (**Supplement).**

In aggregate, analyses suggested connectivity-based subgroups had external clinical, behavioral, and biological relevance.

Symptom-category-based subgroups

No external variable in **Figure 4** showed a significant difference across depressed participants with (n=20) and without (n=46) melancholia, with (n=15) and without (n=51) comorbid anxiety diagnosis, or with high (n=34) vs. low (n=26) levels of self-reported anhedonia (*p*'s>.16). Symptom-category-based subgroups were also unrelated to connectivity subgroup (χ^2's<1.7,*p*'s>.19).

Discussion

Using a robust method to characterize individuals' directed connectivity paths (20,27), we identified two brain-based subgroups of individuals completing a positive mood induction. Pervasive hyperconnectivity (i.e., relative to other individuals in the sample) emerged as a functional connectivity-based biomarker that characterized many (81%)—but not all—depressed participants in the sample, as well as 50% of controls. Brain-based categorization thus traveled with psychiatric syndrome-based nosology, but did not map perfectly onto it, suggesting diagnostic categorization collapses across empirically detectable heterogeneity in

both depressed and never-depressed individuals. Directed functional connectivity maps offer a novel possibility for parsing this biological heterogeneity. Across multiple external variables and levels of analysis, the hyperconnectivity profile proved clinically relevant, differentiating depressed participants with a more severely impaired presentation, while the traditional symptom-category-based (DSM, severity of anhedonia) subgroups we tested failed to do so. Subgroups were also predictive of an external neurobiological variable. The hyperconnectivity profile was associated with *decreased* DMN node connectivity (particularly for healthy controls) during a distinct, resting state task.

Broadly speaking, findings support the utility of accounting for biological heterogeneity in order to fully understand both adaptive and maladaptive patterns of functioning. A diagnostic group comparison would have overlooked both the 19% of depressed participants who do not show hyperconnectivity and the 50% of controls who do, implying a unitary pathway to depression. The inclusion of healthy controls in the clustering algorithm clarified that the depression-heavy subtype did not appear inherently pathological. Findings suggest that biological diversity within healthy samples (here, rigorously screened, psychopathology-free controls) overlaps substantially with patient profiles.

Our findings appear consistent with two conclusions: 1) there are two subtypes present within the population at large (in equal proportions within healthy individuals), one of which is characterized by relatively increased connectivity during positive mood induction (e.g., among VAN regions); 2) depression is more highly represented in the hyperconnectivity subtype—particularly, a form of depression characterized by higher severity of self-reported symptoms, moment-to-moment positive affect disruption, and negative information processing patterns. As causality cannot be disentangled with the present design, severe depression may push individuals towards the hyperconnectivity profile, or the profile may represent risk for severe depression that has either not manifested yet among healthy controls, or is being successfully compensated for in the context of other protective factors. In either case, the hyperconnectivity profile suggests a biomarker that is not pathological in and of itself, yet tracks with psychopathology, consistent with numerous temperamental and trait-like individual difference dimensions that vary across the population (37). Indeed, connectivity patterns tend to exhibit trait-like stability over time within specific task states [e.g., at rest (38)] and are posited to represent neural “functional architecture” that might be re-purposed for both adaptive and maladaptive thought processes. As an example of such a “double-edged sword,” creativity characterizes many healthy individuals, yet is over-represented among individuals with psychopathology (including unipolar and bipolar depression)(39). Given recent evidence linking creativity to increased coordination/connectivity across DMN, CCN, and VAN (40), it is possible that hyperconnectivity while recalling a positive autobiographical memory is a substrate for greater propensity to creatively “think outside the box” (or beyond the task), which would be detrimental to affect regulation only to the extent that the content of such divergent thinking is less positive. Given that regions in our network do not serve unitary (e.g., exclusively negative or positive) emotional functions (41-43), the content resounding within an identical hyperconnected network might therefore differ in healthy individuals, e.g., being full of pleasant, fulfilling memories.

With regard to the “depression-heavy” subgroup (Subgroup B), current findings appear consistent with neurocognitive models emphasizing hyperconnected ventral affective and self-referential processing mechanisms in depression (44-46), and extend these models to a positive mood induction. While Subgroup A had few unique paths, Subgroup B had increased VAN->VAN and VAN->DMN paths, as well as increased connectivity in nearly half of the group-level paths. Both unique and increased (group-level) paths followed a primarily ventral-to-dorsal gradient (**Figures 2-3**), suggesting depression is typified by ventrally-driven spreading activation within the VAN and DMN when reading, listening to, and continuously rating positive content. Similar hyperconnectivity patterns observed in depressed individuals at rest have been framed as either a cause or an effect of habitual perseverative cognition patterns such as negative rumination, and correlate with these cognitive habits (47). Together with previously established increased baseline activity in these networks (48,49), these hyperactive pathways could thus drive interference from spreading activations representing over-learned negative processing patterns and cognitions (e.g., unfavorable comparisons between the past and present), consistent with cognitive theories emphasizing spontaneously emerging negative thoughts (e.g., 50,51). If observed hyperconnectivity patterns indeed represent a ventrally-driven ‘downward spiral’ of negative thoughts, this interpretation could explain all three behavioral patterns observed in the patients in Subgroup B--difficulty sustaining positive affect during the task, difficulty regulating affect in daily life, and a bias towards negative self-representations. This interpretation generates the hypothesis, testable in future studies, that similar hyperconnectivity would extend to other sustained affective tasks (e.g., processing of negative stimuli, auditory/pictorial stimuli).

Select CCN->VAN and CCN->DMN paths were also unique to Subgroup B, consistent with studies linking frontostriatal hyperconnectivity during reward processing to adolescent depression risk (52,53). Such hyperconnectivity has been suggested to index unhelpful attempts to ‘dampen down’ positive affect. No markers of decreased top-down control (e.g., CCN->VAN *hypo*connectivity) were found; instead, hyperconnectivity was also present across spatially distal, anterior-to-posterior connections within the CCN, suggesting hyperconnectivity extended to all depression-relevant networks examined.

More broadly, findings indicate that connectivity and disease states interact, suggesting the depressive context alters the meaning and/or consequences of a unitary neural pattern. As psychiatry research advances towards a greater appreciation of nuances introduced by within-group heterogeneity, it may be useful to explore additional factors that differentiate healthy and ill individuals in cases where they share an overlapping data-driven biological signature on one or more dimensions of interest. In the present analyses, one external variable provided a clue: resting state connectivity across two DMN nodes (PCC->pgACC). Individuals high on network-wide connectivity (during positive mood), but *low* on DMN connectivity at rest, were likely to be healthy, while individuals high on both connectivity measures were likely to be depressed (**Supplement)**. This could suggest healthy individuals who share the “depresso-typic” profile during the positive task have a unique ability to flexibly down-regulate connectivity in the absence of task demands, consistent with greater neural adaptability to context (54) and, possibly, decreased self-focus at rest (55).

Generating such *flexibility* in DMN connectivity could constitute a novel treatment target. As we did not replicate DMN hyperconnectivity previously observed in depression, this preliminary finding may be specific to our particular directed connectivity approach. Comprehensive, well-powered characterization of resilient individuals who are biologically classified as being similar to patients is an important and novel avenue for future research, with the potential to reveal new intervention targets based on a model of successful compensation or "balancing," rather than strict remediation of deficits.

Findings have possible clinical implications for personalized medicine. For instance, one specific directed path found in Subgroup B alone, sgACC->pgACC, is notable in light of findings from Deep Brain Stimulation (DBS) studies in depression, where throughput from the sgACC to pgACC and other medial PFC areas is implicated as a critical pathway that must be modulated if DBS is to be successful (56). Our findings suggest the same pathway is relevant in positive affective function, but also highlights individual differences. Future work could test whether this functional pathway, and the broader network-level patterns that traveled with it, might be relevant to individual differences in response to DBS targeting sgACC. Incorporating additional tasks and indices would likely extend clinical utility, capturing further depressive heterogeneity beyond the two subgroups reported here.

Limitations

S-GIMME relies on accurate specification of a relevant network of ROIs, necessitating a balance between under-inclusion (which risks omission of key regions that would alter results) and over-inclusion (which reduces interpretability and parsimony of models and increases processing time). Results may have differed with the inclusion of different regions, as many potentially relevant regions (e.g., dorsomedial PFC beyond the ACC boundaries; additional reward circuitry) were omitted in favor of the present set. The specific subgroup connectivity maps and point estimates of subgroup prevalence we obtained require replication, as they may depend upon sample characteristics—for example, healthy and depressed sample sizes were uneven and the two samples were recruited to be highly divergent on symptomatology. Findings may have differed (e.g., additional subgroups) if individuals at moderate levels on an affective continuum were included. The healthy sample was small and recruited to be homogeneous on clinical variables, hindering comprehensive characterization of healthy controls as a function of subgroup. Clinical translation of findings (e.g., patient subclassification for treatment assignment) will likely require the use of less expensive, more widely available techniques than fMRI, and would require assessing the robustness of these subgroups in additional samples, and across time. The use of external indicators, as we have begun to do, to construct phenotypic profiles associated with neural endophenotypes is a potential first step in this direction.

Conclusions

Using data-driven, brain-based categorization, severe depression was associated with a more ventrally-driven, hyperconnected functional connectivity profile during positive processing. DSM-based (melancholia, comorbid anxiety) and anhedonia-based subgroups did not predict any external variable examined, while brain-based subgroups did, suggesting the connectivity subgroups provided unique, clinically relevant information that was evident

across symptoms, affect, behavior, and a discrete marker of neurobiology. However, our findings simultaneously argue that patient-reported experiences (i.e., depressive symptoms) qualify the meaning and impact of functional connectivity patterns that are routinely shared in common by both healthy and depressed individuals. Connectivity-based subgrouping, a novel extension of biological subtyping, could provide new insights into the non-unitary neural conditions that promote both vulnerability and resilience. Intervention development may benefit from a) seeking to address diverse pathways to depression through a precision medicine approach and b) identifying compensatory mechanisms present in resilient individuals, who remain depression-free in spite of sharing concurrent biological features with patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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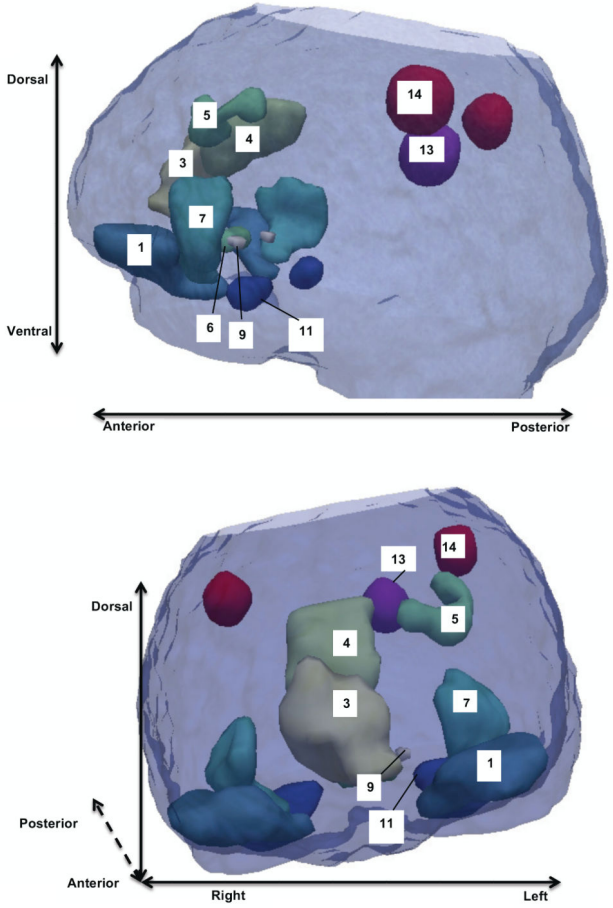

Figure 1.

3d renderings of region of interest (ROI) locations in template space. For ROIs that are bilateral, a uniform color is used to label both hemispheres and regions are numerically labeled on the left hemisphere only. 1=left ventrolateral PFC (L VLPFC); 2=R VLPFC; 3=perigenual anterior cingulate cortex (pgACC); 4=dorsal ACC (dACC); 5=L dorsolateral PFC (L DLPFC); 6=subgenual ACC (sgACC); 7=L Insula; 8=R Insula; 9=L nucleus accumbens (NucAcc); 10=R NucAcc; 11=L Amygdala; 12=R Amygdala; 13=posterior cingulate cortex (PCC); 14=left posterior parietal cortex (L Parietal); 15=R Parietal.

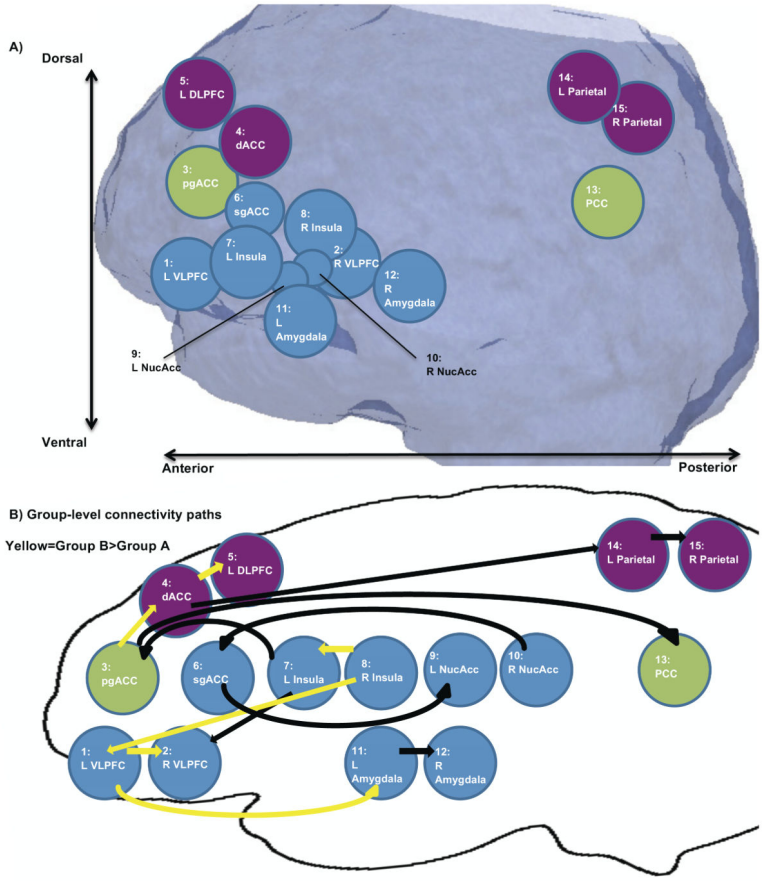

Figure 2.

(A) Regions of interest represented as nodes in rough anatomical space. Nodes of the ventral affective network (VAN) are presented in blue; default mode network (DMN) in green; cognitive control network (CCN) in purple.

(B) Group-level directed connectivity paths between regions of interest (flattened to two dimensions and stretched in space to facilitate visualization of all significant paths). Beta weights for all paths are positive (see **Supplement** for further discussion of group paths). Paths present in the whole group, but significantly stronger in Subgroup B, are indicated in yellow.

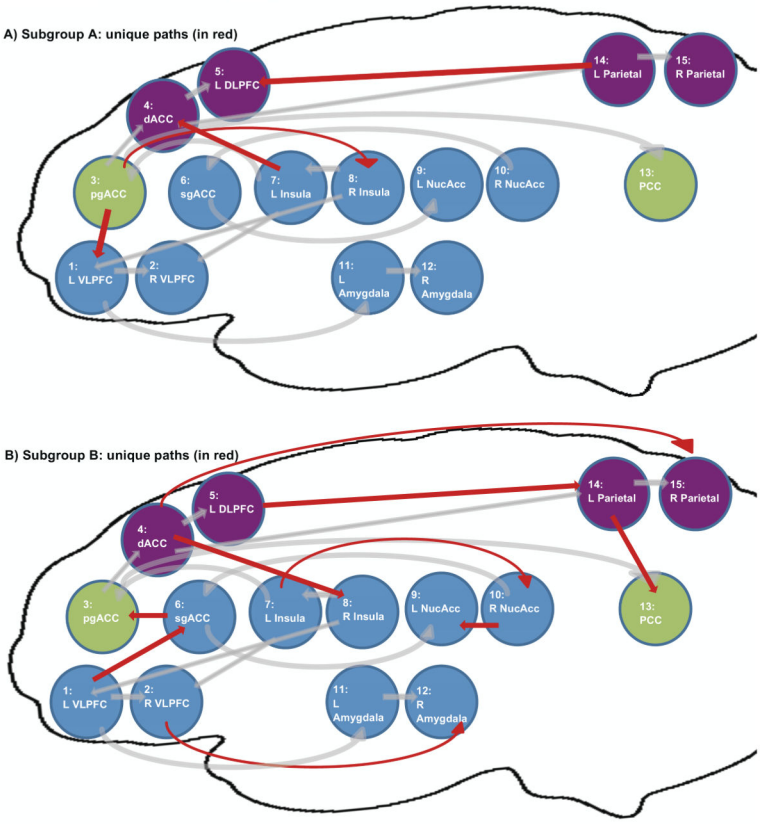

Figure 3.

(A)Directed connectivity paths unique to subgroup A (in red), superimposed on group-level connectivity map (in grey).

(B) Directed connectivity paths unique to subgroup B (in red), superimposed on group-level connectivity map (in grey).

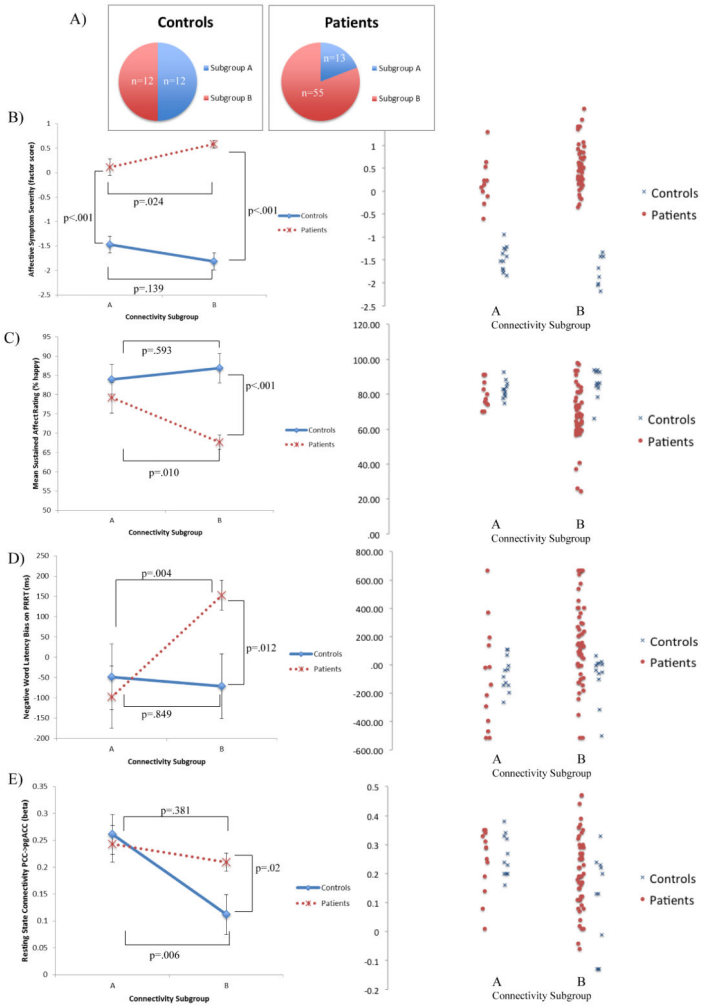

Figure 4.

External variables associated with connectivity-based subgroups. Left-most panels display group means and SDs; right-most panels display individual data points for the same variables. (A) Clinical diagnosis. (B) Symptom severity factor scores. (C) Sustained positive affect during mood induction. (D) Bias in reaction times during Personal Relevance Rating Task responses to negative (relative to neutral) words. (E) Resting state directed connectivity path strength from the posterior cingulate cortex (PCC) to the perigenual anterior cingulate (pgACC).

Table 1

Sample Characteristics

	Controls (n=24)	Depressed (n=68)	Statistic testing group differences	Statistical significance (p)
Mean Age (SD)	33.38 (9.67)	34.90 (10.85)	t(90)=.61	.545
Sex (% Female)	76% (n=19)	73.1% (n=49)	Fisher's exact	1.00
Ethnicity (% Caucasian)	87.5% (n=21)	76.5% (n=52)	Fisher's exact	.380
BDI (SD)[a]	1.04 (1.49)	30.54 (9.38)	t(80)=14.96	<.0001
HAM-D (SD)	---	18.28 (5.06)	---	---

Note: BDI=Beck Depression Inventory; HAM-D=Hamilton Rating Scale for Depression (depressed participants only)