Mapping neural circuit biotypes to symptoms and behavioral dimensions of depression and anxiety

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ABSTRACT

Background: Despite tremendous advances in characterizing human brain circuits that govern emotional and cognitive functions that are impaired in depression and anxiety, we lack a circuit-based taxonomy that captures transdiagnostic heterogeneity and informs clinical decision making.

Methods: We develop and test a novel system for quantifying six brain circuits reproducibly and at the individual patient level. We implement standardized circuit definitions relative to a healthy reference group, and algorithms to generate circuit function and dysfunction scores for the overall circuit and its constituent regions.

Outcomes: In primary and generalizability samples of depression and anxiety (n=251) we demonstrate that overall disconnections within task-free salience and default mode circuits map onto symptoms of anxious avoidance, loss of pleasure, threat dysregulation, and negative emotional biases – core characteristics that transcend diagnoses – and poorer daily function. Regional dysfunctions within task-evoked cognitive control and affective circuits implicate more specific cognitive symptoms and valence-congruent behavioral disruptions. Circuit dysfunction scores also predict response to pharmacological and behavioral therapies in an independent sample (n=207).

Interpretation: Our findings articulate circuit dimensions that parse the heterogeneity of depression and anxiety and have direct clinical translational significance. Our novel system offers a foundation for deploying standardized circuit assessments across research groups, trials and clinics to advance more precise classifications and treatment targets for psychiatry.

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INTRODUCTION

Depression and accompanying anxiety disorders are responsible for more years of disability than any other disease,[1] but we have no objective tests for detection, treatment choice, or the mechanistic understanding of disease progression. Recent advances in non-invasive functional brain imaging provide insights into brain circuit dysfunctions that underlie depression and anxiety. Still, we currently have no method for quantifying profiles of brain circuit dysfunction for each patient in a standardized manner to facilitate actionable clinical decisions. Connecting patient-level brain dysfunction profiles with clinical phenotypes and treatment outcomes is crucial for developing a new taxonomy of depression and anxiety anchored in an understanding of the brain.

We have put forward a theoretical taxonomy based on a synthesis of existing knowledge about brain circuits relevant in depression and anxiety disorders.[2] Well-powered studies[3,4] and meta-analyses[5,6] implicate large-scale circuits in key aspects of human function: the default mode circuit in self-directed reflection, the salience circuit in detecting and orienting to noticeable changes, the negative affect circuit in reacting to threat and negative emotion, the positive affect circuit in responding to rewards, the frontoparietal attention circuit in maintaining attention, and the cognitive control circuit in response inhibition.[2] Dysfunctions in these brain circuits and their accompanying symptoms have been implicated in depression and anxiety.[7-9] Testing this taxonomy and developing its utility for clinical action requires addressing the limitations of prior imaging studies of functional brain dysfunction in depression and anxiety. Previous studies are limited by case:control designs that assume within-group homogeneity rather than parsing heterogeneity, small sample sizes, and/or not connecting symptom profiles to specific circuit dysfunctions. A major barrier to clinical translation is the lack of a validated circuit framework connected to validated symptom phenotypes and clinical treatment outcomes. Overcoming this barrier requires standardized circuit definitions and protocols for quantifying circuit dysfunction relative to standardized norms that are reproducible, generalizable and clinically interpretable.

In this study, we systematically imaged six brain circuits and profiled clinical symptoms, behaviors and daily function in multiple samples of adults with a broad range of depression and anxiety pathologies (total n=251), and in a sample of patients treated for depression (n=207). The study objectives were five-fold. First, we derived and validated the six circuits of interest and

established their canonical properties based on convergence with established meta-analytic functional databases. Second, we developed protocols for quantifying circuit dysfunction scores, expressed in standardized units of measurement relative to healthy norms for each circuit and its constituent regions, and evaluated each circuit dysfunction score for psychometric properties including internal consistency and construct validity. Third, we derived and validated clinical phenotypes representative of depression and anxiety. Our phenotypes span symptoms, behavior, and daily function. Fourth, we evaluated the ability of circuit dysfunction scores to predict specific phenotype profiles across multiple independent samples. Fifth, we examined how circuit dysfunction scores relate to response to pharmacological and behavioral antidepressant therapies.

METHODS

Summary of Research Design and Cohorts

A primary sample of 160 adults with symptoms of depression and anxiety (Supplementary Figure 1, Supplementary Table 1) was randomly stratified into training (n=112) and test (n=48) sub-samples (Supplementary Table 2). Three additional samples were included in the analysis and underwent similar assessments: 1) an independently recruited generalizability sample (n=91) with similar characteristics as the primary sample (Supplementary Table 3), 2) a treatment sample from randomized controlled trials of pharmacological (n=137) or behavioral (n=70) treatment for major depression (Supplementary Table 4) and, 3) healthy adults recruited at each of the two sites at which the treatment sample was acquired (n=40 at Stanford, n=41 at Sydney; (Supplementary Table 5).

Each sample was assessed using functional imaging to quantify circuit function and dysfunction and on self-report and behavioral measures to quantify clinical phenotypes (Figure 1 and Supplementary Methods Section 1). All procedures were approved by the Stanford University Institutional Review Board (IRB 27937 and 41837) or Western Sydney Area Health Service Human Research Ethics Committee. All participants provided written informed consent prior to study procedures. Details of task-free and task-evoked conditions for engaging circuits, as well as imaging acquisition and preprocessing can be found in Supplementary Methods Section 2-4.

FIGURE 1 ABOUT HERE

Derivation of Canonical Circuit Function

To derive valid canonical circuits suited to standardized quantification, we followed a systematic procedure (Figure 2a).

FIGURE 2 ABOUT HERE

Meta-Analytic Search

We identified six target circuits of interest relevant to depression and anxiety based on our prior synthesis of existing knowledge:[2] default mode, salience, attention, negative affect, positive affect, and cognitive control (Supplementary Figure 2). To operationalize these circuits for quantification, we first leveraged the meta-analytic database Neurosynth.org.[10] Nodes within each circuit were defined by combining spheres centered on local peaks of the meta-analytic maps with anatomical masks (see Supplementary Methods Section 5a).

Applying Regional Masks in Task-Elicited and Intrinsic Connectivity Conditions

We quantified intrinsic connectivity for all pairs of regions in the default mode, salience, and attention circuits after extracting task effects.[11] For negative affect, positive affect, and cognitive control circuits, we quantified average activation in each region, as well as functional connectivity via psychophysiological interaction for all pairs of regions within each circuit (Supplementary Figure 4). The negative affect circuit was examined during viewing of sad and threat faces, the positive affect circuit was examined during viewing of happy faces, and the cognitive control circuit was examined during a cognitive inhibition task (Supplementary Methods Section 5b).

Quality Evaluation

We refined the selection of regions to ensure good quality data, based on temporal signal-to-noise and overlap with gray matter (Supplementary Methods Section 5c, Supplementary Figure 3). In addition, intrinsic connectivity pairs were refined to ensure greater average within-circuit relationships than between-circuit relationships (Supplementary Figure 4). Details of final circuit features are in Supplementary Figure 5 and Supplementary Table 6. The circuit features were then averaged to a single score per circuit to characterize circuit function; Pearson correlation analysis verified that these scores were largely statistically independent (86% of score pairs with $R^2 < 0.1$, Supplementary Figure 6).

Derivation of Circuit Dysfunction Scores

Key Regions of Dysfunction

Following the definition of each circuit in healthy subjects as described above, we then computed circuit *dysfunction* scores for each of seven hypothesized types of circuit dysfunction[2]

for each individual (Figure 2b). To do this we first identified regions for which there is robust evidence for dysfunction of activation and/or connectivity in depression and/or anxiety in meta-analyses or at least two well-powered studies, as outlined in our prior theoretical synthesis (Supplementary Methods Section 6, Supplementary Table 7).[2]

Addressing Standardization and Directionality

We expressed each activation and connectivity feature in standard deviation units relative to our healthy reference sample (Supplementary Methods Section 6c) in order to interpret circuit dysfunction in clinical participants relative to a healthy reference group. We then ensured that the directionality of each dysfunction feature was oriented so that greater scores always indicated greater dysfunction, according to our theoretical framework (Figure 2b).[2]

Creating Circuit Dysfunction Scores

Following standardization and directionality adjustment, features were averaged within each circuit to form circuit dysfunction scores for each individual. These scores showed adequate psychometric properties, including independence across scores (91% of pairs of scores with $R^2 < 0.1$; Supplementary Figure 6) and internal consistency (Cronbach's alpha = .53-.84; Supplementary Figure 7).

Content and Construct Validation of Clinical Phenotypes

Symptom Phenotypes

We followed a content validation procedure[12] to operationalize the clinical phenotypes from our theoretical circuit taxonomy[2] using items from self-report questionnaires (Supplementary Methods Section 7 and Supplementary Table 8).[13] Questionnaire items were assigned to phenotypes[2] first by expert consensus (authors ANGP, TMB, ZS, LMW) and then refined by a principal component analysis (PCA) on the primary sample. Primary analyses focus on six target symptom phenotypes (rumination, anxious avoidance, threat dysfunction, anhedonia, negativity bias, and inattention-cognitive dyscontrol). Secondary analyses explore additional phenotypes (e.g., tension, suicidality, subcomponents of anxious avoidance; Supplementary Table 10). We constructed composite scores for each participant by averaging the standardized item-level data assigned to each of these constructs and use these composites in all subsequent analyses.

Behavioral Phenotypes

We similarly pursued a content validation procedure to operationalize behavioral phenotypes based on computerized tests assessing general and emotional cognition (Supplementary Methods Section 8).[14] For general cognition, we identified five constructs that aligned with a prior PCA conducted during the development of the test battery:[14] sustained attention (N-back Continuous Performance Test), response inhibition (Go-NoGo), information processing speed (Stroop Verbal Interference and Trails-B), executive function (Maze) and working memory (Digit Span), and a sixth component defined by interference measures available in our sample but not during initial test development (Supplementary Table 11). We constructed composite scores for each participant by averaging the standardized data assigned to each of these six constructs and used these composites in all subsequent analyses.

For emotional cognition we identified eight constructs that aligned with those identified during test development:[14,15] speed for explicit identification of sad, threat (fear and anger), disgust, and happy expressions; and implicit priming of face recognition biased by these same four expressions (Supplementary Table 12). We also explored two additional PCA-identified constructs representing the accuracy for identifying individual positive and negative emotions. We constructed composite scores for each participant by averaging the standardized data assigned to each of these ten constructs and used these composites in all subsequent analyses.

Daily Function Phenotypes

We explored relationships between circuit dysfunction scores and two measures of daily function: the self-reported Satisfaction With Life Scale[16] and the observer-rated Social and Occupational Functioning Assessment Scale (Supplementary Methods Section 9, Supplementary Table 9).[17]

Circuit Dysfunction Relations with Clinical Phenotypes

Our first-order analyses characterized the relations between circuit dysfunction and clinical phenotypes (Supplementary Methods Section 10a). We utilized a false discovery rate (FDR) threshold using the Benjamini-Hochberg procedure[18] within each family of tests (i.e., separately for primary symptom measures, general cognition, emotional cognition). Analyses were conducted on the primary training sample, then replicated in the test sample and generalizability

sample. To unpack the circuit dysfunction score findings, our second-order analyses examined relations between clinical phenotypes and the constituent regional dysfunctions that make up each circuit dysfunction score (Supplementary Methods Section 10b). Meaningful effects were defined in the training sample by 95% bootstrapped confidence interval that did not contain zero, without FDR correction. For both global and regional circuit dysfunction scores, we evaluated the consistency of our effects by examining whether the beta coefficient of the test and/or generalizability sample was contained within the 95% bootstrapped confidence interval of the training sample. In exploratory analyses we modeled circuit dysfunction scores and their pair-wise interactions simultaneously as predictors of clinical phenotypes (Supplementary Methods Section 10d).

Proof-of-Concept Analysis of Treatment Response Profiles Based on Circuit Dysfunction Profiles

We explored whether our circuit dysfunction scores are associated with treatment outcomes from two randomized controlled trials: of three first-line antidepressant pharmacotherapies (n=137),[19,20] and of behavioral therapy versus treatment as usual (n=70)[21] for major depression. In each sample, we defined response as $\geq$50% reduction in patient-reported symptom severity following treatment.

We implemented a model comparison approach using logistic regression with binary treatment response as the dependent variable and modeled separately for each circuit and for each treatment sample. We used $p<.05$ uncorrected due to the proof-of-concept nature of these analyses. First, we tested whether circuit dysfunction scores predict general treatment response, over and above baseline symptom severity. Next, we evaluated circuit dysfunction as a differential response predictor based on treatment arm by adding interactions between circuit dysfunction scores and treatment to the model. In the pharmacotherapy sample treatment was defined as SSRI (sertraline or escitalopram) vs SNRI (venlafaxine), and in the behavioral sample treatment was defined as behavioral therapy vs treatment as usual. Finally, after the above models were run using the circuit dysfunction scores, we re-ran analyses entering all regional constituent inputs to the scores instead of the scores themselves, with follow-up t-tests for coefficients to identify whether specific regional inputs were especially relevant for treatment outcome prediction (Supplementary Methods Section10e).

RESULTS

Default Mode Circuit

In the primary training sample, lower default mode circuit (DMN) dysfunction scores (reflecting relative hypo-connectivity of the DMN) predicted more severe symptoms of negativity bias, anhedonia, and tension (Table 1a; Figure 3) as well as greater general negative affect (Supplementary Table 14a).

TABLE 1 and FIGURE 3 ABOUT HERE

With respect to the constituent regional parts of the DMN dysfunction score, lower connectivity between the anterior medial Prefrontal Cortex (amPFC) and angular gyrus (AG) was associated with more severe rumination in our planned second-order analyses (Table 1c; Figure 4). In post-hoc analyses, lower DMN amPFC-AG connectivity was also associated with more severe negativity bias, anhedonia, and social and occupational dysfunction (Table 1d). Lower connectivity of the DMN posterior cingulate cortex (PCC) and AG, conversely, was associated with more severe tension symptoms (Table 1d).

FIGURE 4 ABOUT HERE

In exploratory interaction analyses, DMN and salience circuit dysfunction scores combined to predict more severe symptoms of threat dysregulation and sleep loss (uncorrected, Supplemental Table 13). DMN dysfunction scores also combined with attention circuit dysfunction scores to predict fear and threat bias. These exploratory circuit interaction analyses similarly suggest that sad-evoked negative affect dysfunction combines with global DMN dysfunction to predict inattention/cognitive dyscontrol (uncorrected, Supplementary Table 13).

Salience Circuit

Higher salience circuit dysfunction scores (reflecting hypothesized hypo-connectivity within this circuit) predicted more severe symptoms across most symptom domains and across samples, including anxious avoidance, negativity bias, threat dysregulation, anhedonia, and inattention/cognitive dyscontrol (Table 1a; Figure 3). In a secondary analysis, salience circuit dysfunction scores were also related to the dizzy/faint sub-components of anxious avoidance symptoms (Table 1b) and to general negative affect (Supplementary Table 14a). Greater salience circuit dysfunction scores also predicted worse satisfaction with life (Table 1a; Supplementary Figure 9).

When we parsed the salience circuit into its constituent regional parts, the relationship between hypo-connectivity and anxious avoidance was specific to hypo-connectivity of the left anterior insula and left amygdala (Table 1c; Figure 4). In post-hoc analyses, left anterior insula-amygdala hypo-connectivity was additionally associated with more severe threat dysregulation symptoms and left-right insula hypo-connectivity, with more severe negativity bias and anhedonia symptoms (Table 1d). The left anterior insula-amygdala hypo-connectivity was also associated with the autonomic, homeostasis, and faint/dizzy sub-components of anxious avoidance symptoms (Supplemental Table 14c). Finally, both left anterior insula-amygdala and left-right insula hypo-connectivity were associated with worse satisfaction with life (Table 1d).

In exploratory interactions, salience circuit dysfunction combined with positive affect circuit dysfunction to predict the secondary anger identification construct (uncorrected, Supplementary Table 13).

Attention Circuit

For the attention circuit, associations with phenotype profiles were observed for constituent regions and not for global circuit dysfunction scores. Specifically, greater intrinsic connectivity between lateral prefrontal cortex (PFC) and medial superior PFC was associated with more severe symptoms of inattention/cognitive dyscontrol (Table 1c; Figure 4).

Negative Affect Circuit

For the task-evoked negative affect circuit, associations with phenotype profiles were similarly observed for constituent regions only. In response to sad face stimuli, hypo-activation in the

anterior insula, both left and right-sided, predicted more severe symptoms of negativity bias (Table 1c; Figure 4). Complementing this association, exploratory analyses suggest that left anterior insula hypo-activation also relates to altered sad and disgust identification (Supplemental Table 12; Supplementary Table 14c). Conversely, hyper-activation in right amygdala when viewing threat-related faces predicted accelerated responses to identifying these faces (Table 1c; Figure 4).

Positive Affect Circuit

The positive affect circuit probed by happy stimuli did not show relationships between clinical phenotypes and global circuit dysfunction scores or constituent regional parts. In exploratory interaction analyses, positive affect circuit dysfunction scores combined with DMN dysfunction scores to predict more severe symptoms of threat dysregulation (uncorrected, Supplementary Table 13).

Cognitive Control Circuit

As with the other task-evoked circuits, we observed relations between constituent regions of the cognitive control circuit and specific phenotypes, but no associations with global circuit dysfunction scores. Hypo-activation of the dorsal anterior cingulate cortex (dACC) and greater connectivity between dACC and right dorsolateral PFC were predictive of more severe symptoms of inattention/cognitive dyscontrol (Table 1c; Figure 4).

Circuit Dysfunction Profiles and Treatment Outcomes

The salience circuit dysfunction score was a general predictor of response in the pharmacotherapy sample, with responders to all medications exhibiting greater pre-treatment dysfunction than non-responders (Table 2a; Figure 5a; Supplementary Figure 11). Additionally, the attention circuit dysfunction score was a general predictor of response in the behavioral therapy sample, with responders exhibiting greater pre-treatment dysfunction than non-responders (Table 2b; Figure 5b; Supplementary Figure 11).

With respect to differential prediction, positive affect circuit dysfunction differentiated responders to behavioral therapy such that greater circuit dysfunction predicted non-response to the behavioral intervention, but not treatment as usual (Table 2b; Supplementary Figure 12).

TABLE 2 AND FIGURE 5 ABOUT HERE

We then modeled these effects using all regional parts of each circuit rather than the global dysfunction scores. For the pharmacotherapy sample, hyper-connectivity between the PCC and right angular gyrus within the DMN predicted response to SSRIs but non-response to the SNRI (Table 2c; Figure 5c; Supplementary Figure 12). In addition, responders to SSRIs were distinguished from responders to SNRI by constituent regions of the negative affect circuit elicited by threat. Specifically, SSRI responders showed hyper-connectivity of the left amygdala and dACC and hypo-connectivity of right amygdala and dACC elicited by conscious threat, along with hypo-connectivity of the left amygdala and sgACC elicited by nonconscious threat. Responders to the SNRI, on the other hand, showed hypo-activation of the right amygdala to nonconscious threat (Table 2c; Figure 5c; Supplementary Figure 12).

For the behavior therapy sample, hyper-connectivity connectivity between the left insula and left amygdala within the salience circuit was a general predictor of response across both therapy and treatment as usual (Table 2d; Figure 5d). In addition, responders to the behavioral intervention were distinguished from responders to treatment as usual by regions of the attention circuit: responders to behavioral therapy were characterized by lower connectivity between left anterior inferior parietal lobule and left prefrontal cortex, relative to responders in the treatment as usual arm (Table 2d; Figure 5d; Supplementary Figure 12). Within the positive affect circuit, responders to behavioral therapy also showed lower activation in the ventromedial prefrontal cortex compared to responders to treatment as usual (Table 2d, Figure 5d; Supplementary Figure 12).

DISCUSSION

In this study, we show that distinct profiles of dysfunction within human neural circuits that support self-reflection, emotion, and cognition relate to the phenotypic heterogeneity of depression and anxiety as well as treatment outcomes for pharmacotherapy and behavioral therapy. We developed a novel standardized and reproducible approach for quantifying profiles of neural circuit dysfunction, connected patient-level circuit dysfunction with clinical symptoms, behaviors and social-occupational function, and illustrated potential applications for treatment choices. Imaging has played a central role in precision health advances and our approach facilitates these advances for mental health, specifically for depressive and anxiety disorders that contribute disproportionately to illness burden and suicide.

Our novel precision image processing system integrates three key features: standardized definitions of six functional brain circuits spanning task-free and task-evoked contexts, validation of the neuroanatomical basis and consistency of each circuit, and reproducible procedures for quantifying the activation and connectivity of these circuits. This approach incorporates algorithms for computing summary circuit dysfunction scores for each patient standardized to a healthy reference cohort, along with scores for each constituent region of the circuits that make up these summary scores.

We applied this imaging methodology in three samples of adults with a broad range of depression and anxiety symptoms and systematically targeted brain circuit-phenotype relations that build on our theoretical framework,[2] and led to new clinically relevant discoveries about circuit-phenotype relations. A striking finding was of global dysfunction of intrinsic circuits accompanied by phenotype profiles that transcend diagnostic categories of depression and anxiety. Specifically, dysfunction of salience circuit, especially hypo-connectivity between the insula and amygdala, contributed to symptoms of anxious avoidance, consistent with our theoretical framework.[2] Salience circuit dysfunction also contributed broadly to symptoms of anhedonia, negativity bias, threat dysregulation inattention/cognitive dyscontrol, and general negative affect, and predicted lower life satisfaction. Thus, we consider salience circuit dysfunction to be akin to a global “g” factor in neuropsychological testing that manifests as difficulty with anxiety and related emotional states, with accompanying effects on cognitive and functional capacity. Notably, salience circuit dysfunction also predicted treatment response to

first line antidepressant medications, over and above pre-treatment depression symptom severity, consistent with previous work implicating resting metabolism in the insula, a core node of the salience network, in antidepressant medication response.[22,23]

Overall default mode network (DMN) dysfunction was also associated with more severe symptoms of anhedonia and negativity bias, which is consistent with observations that this network reflects severity of depression-related phenomenology[24] but is in contrast to the common view that DMN dysfunction uniquely relates to rumination and brooding.[25] We found DMN dysfunction to be independent of salience circuit dysfunction and thus, disruptions in these circuits may each make unique contributions to phenotypes of depression and anxiety.

Although our findings for global circuit dysfunction scores were specific to intrinsic circuits, several important associations in constituent regions were found for task-evoked circuits. For example, consistent with the amygdala's role in detecting and responding to threatening stimuli,[26] and with the transdiagnostic role of amygdala reactivity in depression and anxiety,[27] hyper-activation of this region within the negative affect circuit was associated with accelerated detection of threat-related facial expressions. In addition, lower activation but increased connectivity in frontal regions of the cognitive control and attention circuits was associated with more severe self-reported symptoms of inattention and cognitive dyscontrol.

We focused on the mapping between dysfunction within circuits and phenotypic profiles to demonstrate the clinical utility of our standardized circuit quantification approach. However, due to the highly interconnected nature of the brain, we also explored statistical interactions between circuit dysfunction scores. We found that the majority of these interactions involved the DMN, which highlights the need for future systematic investigations of the DMN and its interactions with other large-scale brain circuits in depression and anxiety.

Our circuit dysfunction profiling system offers a standardized patient-level tool for using brain insights to help inform treatment choices. By deploying our standardized circuit scores in well-characterized treatment cohorts, we highlight the promise of a standardized imaging tool for clinical use and for advancing precision medicine for psychiatry. Using circuit dysfunction scores, in addition to the pharmacotherapy finding for the salience circuit discussed above, we found that pre-therapy hypo-connectivity within the attention circuit characterized patients who subsequently responded to behavioral therapy compared to treatment as usual. This observation

accords with independent reports that intrinsic hypo-connectivity of attention networks could identify who may benefit from cognitive behavior therapy.[28] We also found that responders to SSRIs had greater right amygdala connectivity with regions of the anterior cingulate in response to threat stimuli, consistent with findings from effective connectivity analyses in independent studies.[29] Although we emphasize that these treatment outcome relationships need to be confirmed in independent samples, they do offer a rich foundation for guiding future prospective biomarker trials grounded in our standardized quantification of circuit dysfunction at the individual patient level. Future prospective trials will be necessary to accelerate the translation of circuit dysfunction insights into real-world practice, and to facilitate a precision medicine approach to mental health care based on an understanding of neural circuits.

Given that circuit-informed precision psychiatry is a newly emerging field, this study should be considered within the context of its limitations. Our samples were transdiagnostic but likely on the less severe end of the clinical spectrum and had a strong representation of anxiety features. We have applied our methodology to a specific set of circuit dysfunction patterns that are relevant for mood and anxiety disorders and are informed by a particular theoretical perspective.[2] Nonetheless, our system is designed to be flexibly applied to quantify any pattern of relevant circuit dysfunction, enabling the potential for future expansion and refinement. An important area of future research would be to ultimately quantify the complex links between circuits (e.g., via DMN[3]) and to delineate underlying mechanisms, including with functional localizers for more precise accounting of inter-individual differences in functional brain architecture[30] and with prospective assignment of patients to treatments based on targeted circuit dysfunction profiles.

Our vision of the mental health clinic of the future is one in which practitioners can complement the traditional clinical interview by ordering tests of functional brain circuitry. Rather than require all mental health practitioners to become fully competent to analyze and interpret functional imaging results, our methodology is designed to deliver interpretable circuit dysfunction profiles into clinical settings. In sum, our methodology and insights offer a path for advancing the application of quantifiable neural circuit metrics that aid in personalized diagnoses of mood and anxiety biotypes, and for informing treatment decisions based on neurobiology rather than on the need to wait and see.

Data Availability: The datasets for the primary sample analyzed during the current study are made available through the National Institutes of Health Database, NDA, https://nda.nih.gov/user/dashboard/collections.html, collection number C2100. The datasets for the generalizability sample analyzed during the current study will be made available from the corresponding author on reasonable request. Patients' whole-brain correlation matrices and our full analysis codes for the primary and generalizability samples are available from the corresponding author on reasonable request. The datasets for the treatments sample analyzed during the current study will be made available from the corresponding author on reasonable request. For the pharmacotherapy data, reasonable requests will also require the permission of the study sponsor, Brain Resource Ltd. For the behavioral therapy data, study measures will be made available through the National Institutes of Health Science of Behavioral Change repository, https://scienceofbehaviorchange.org/measures/.

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Author Contributions: LMW designed the study, imaging and conceptualized the image processing system and theoretically motivated analytic approach. ANG-P, TMB, and ZS implemented the theoretically motivated analytic approach. ANG-P and BRS implemented the image processing system. SLF designed and implemented the interaction analysis. KAG with LMW implemented the phenotype battery for the primary sample. KAG and BHG collected data for the primary and generalizability samples. LMW designed and oversaw the pharmacotherapy treatment study design, JM and LMW designed and oversaw the behavioral therapy treatment study design and BRS and ASK implemented the treatment illustration. ANG-P, TMB, ZS, BRS, KAG, SLF, and LMW analyzed data. ANG-P, TMB, ZS, KAG, SLF, BRS, ASK, BHG, and LMW wrote the paper.

Competing Interests: LMW declares US Pants. App. 10/034,645 and 15/820,338: Systems and methods for detecting complex networks in MRI image data. ANG-P, TMB, ZS, KAG, SLF, ASK, BRS, and BHG declare no competing interests.

Figure 1

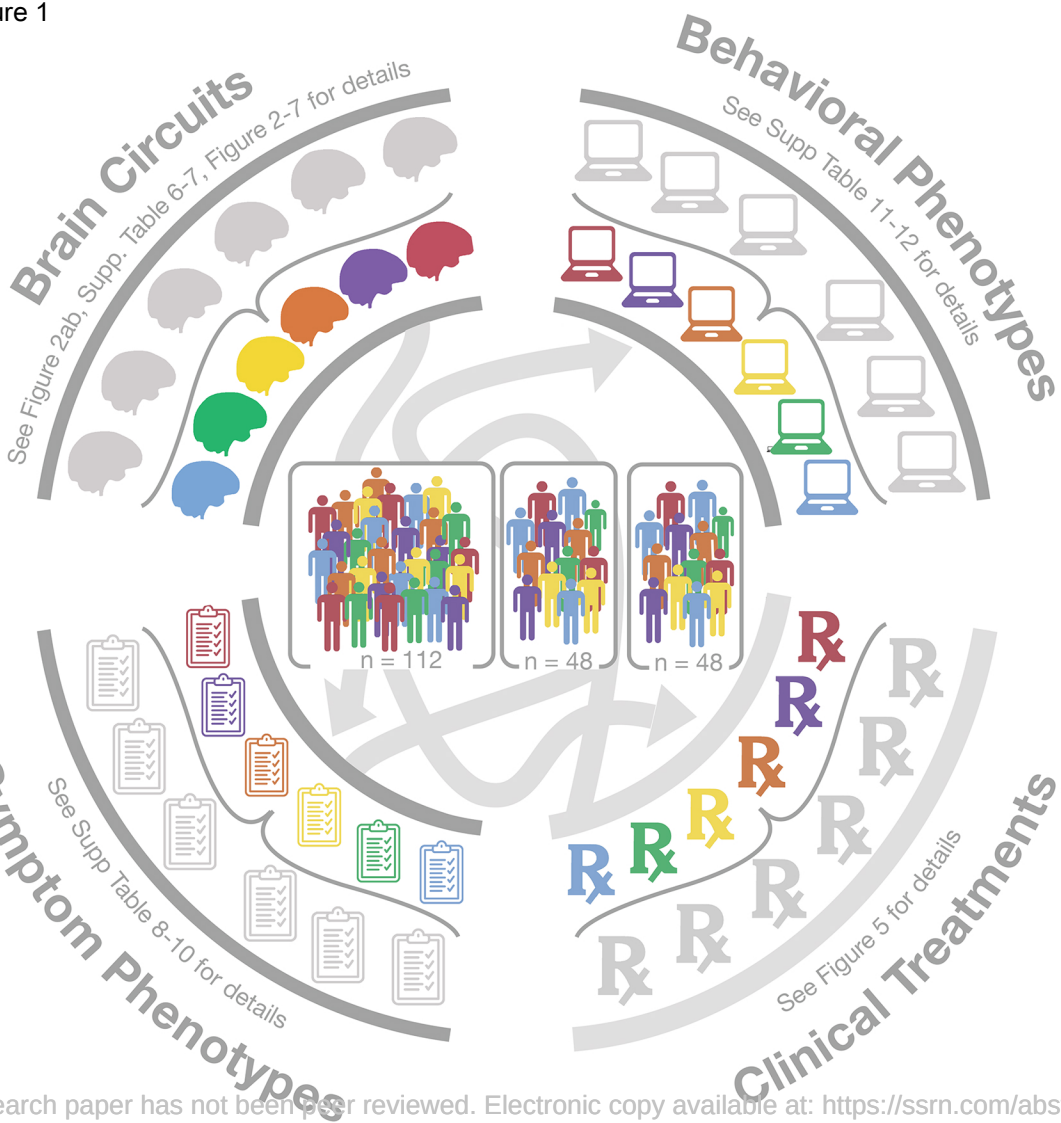


Figure 2

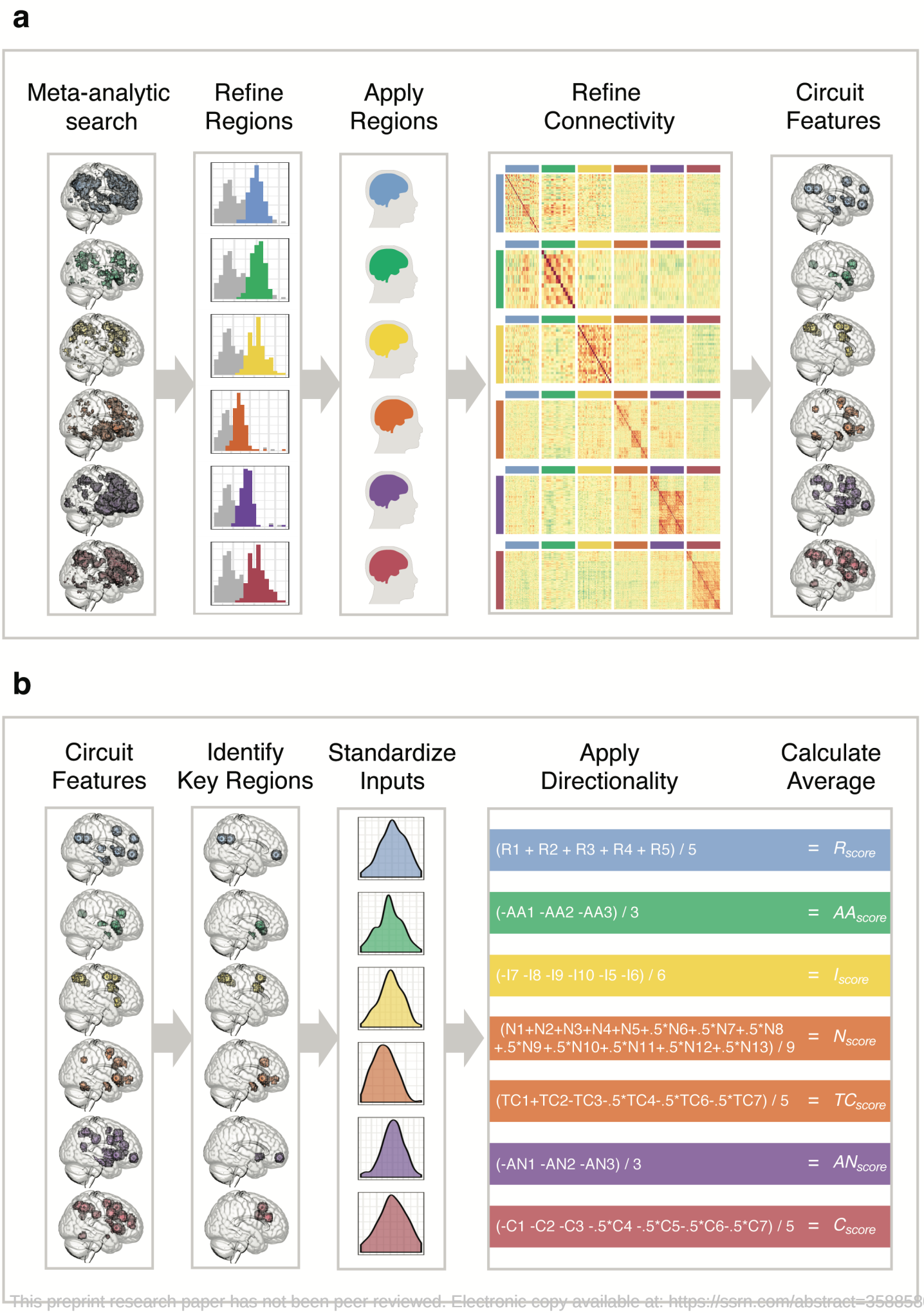


Figure 3

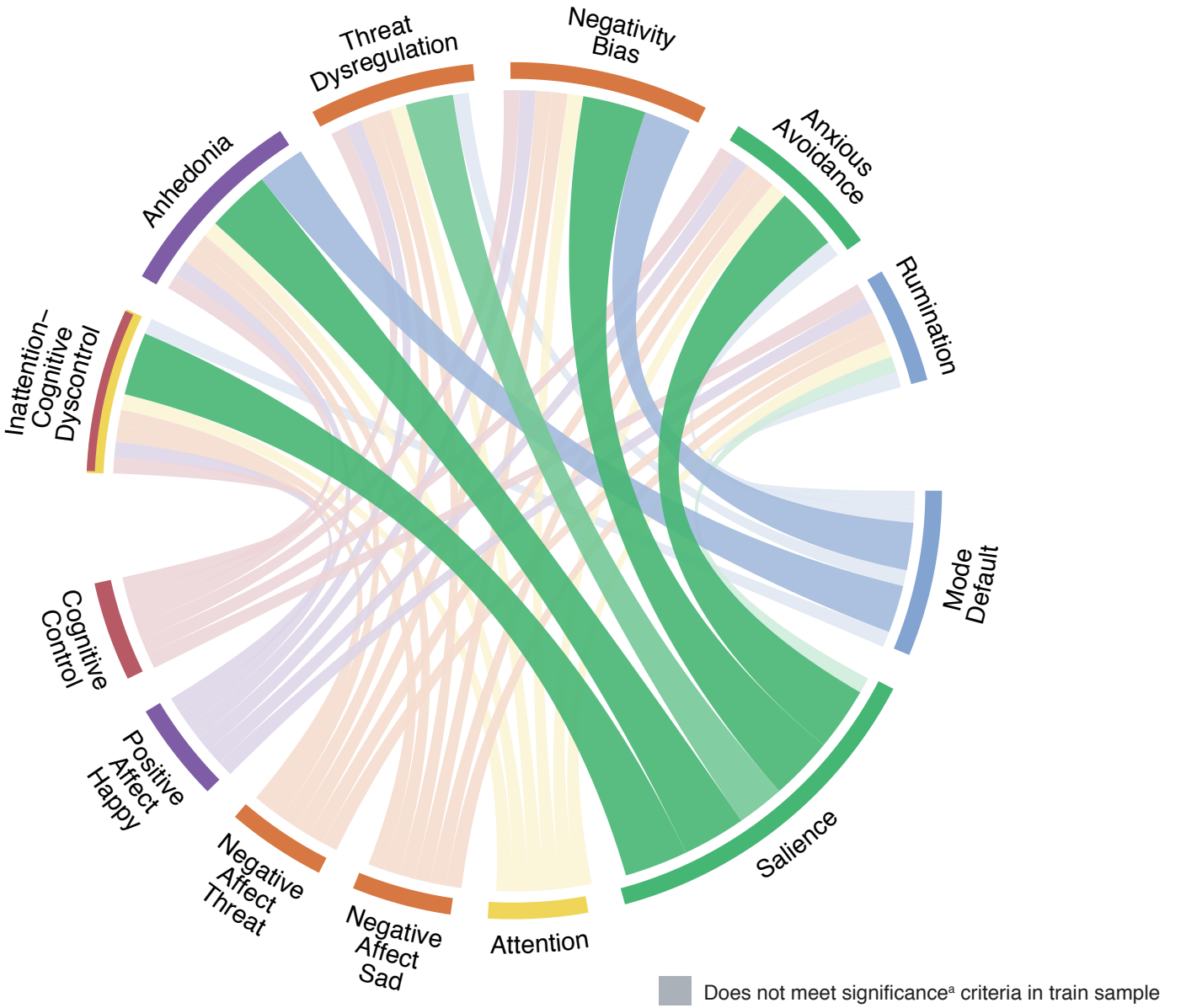
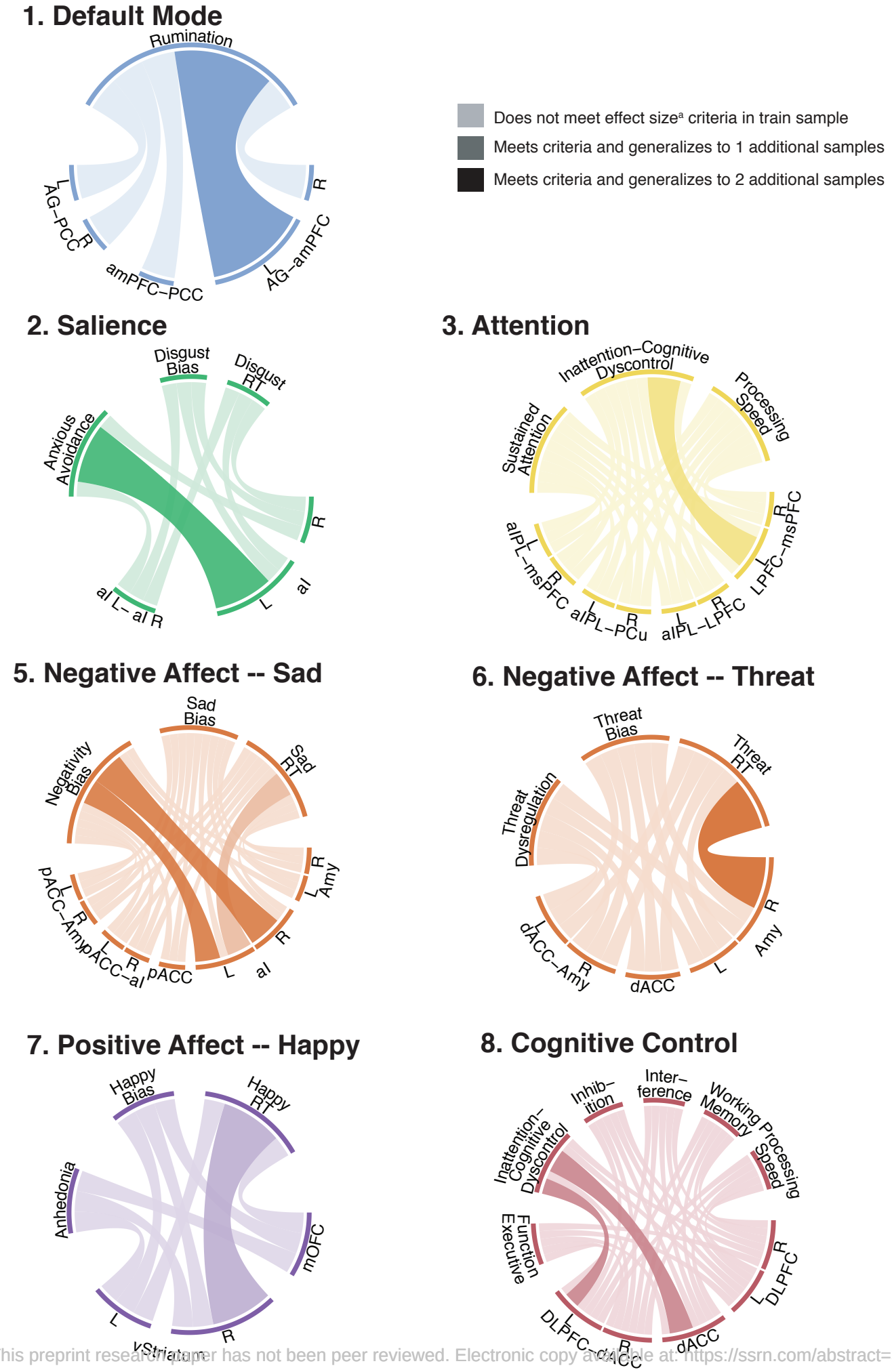
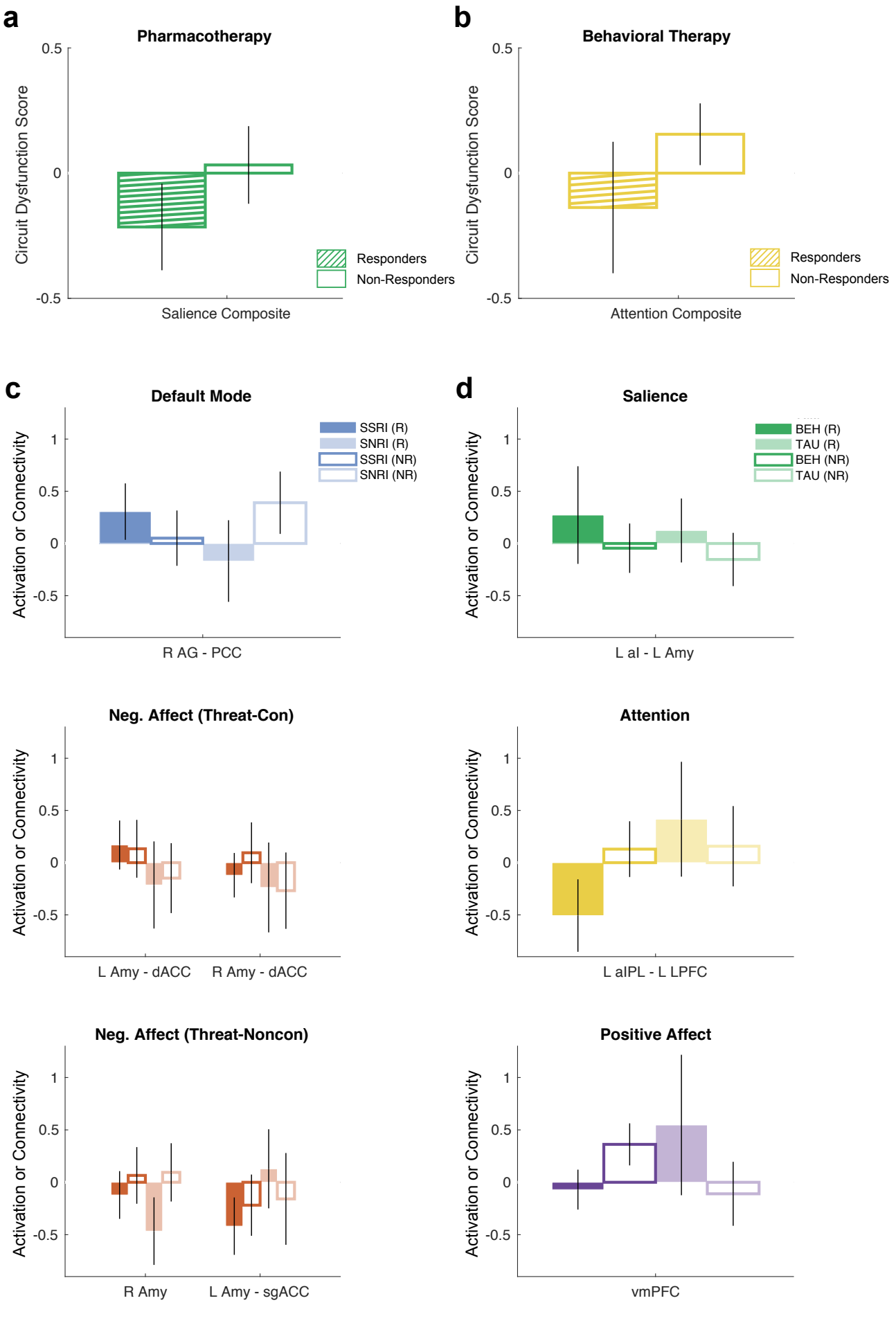


Figure 4




a
Pharmacotherapy
Circuit Dysfunction Score
0.5
0
-0.5
Salience Composite
Responders
Non-Responders
b
Behavioral Therapy
Circuit Dysfunction Score
0.5
0
-0.5
Attention Composite
Responders
Non-Responders
c
Default Mode
Activation or Connectivity
1
0.5
0
-0.5
R AG - PCC
SSRI (R)
SNRI (R)
SSRI (NR)
SNRI (NR)
d
Salience
Activation or Connectivity
1
0.5
0
-0.5
L aI - L Amy
BEH (R)
TAU (R)
BEH (NR)
TAU (NR)
Neg. Affect (Threat-Con)
Activation or Connectivity
1
0.5
0
-0.5
L Amy - dACC
R Amy - dACC
Attention
Activation or Connectivity
1
0.5
0
-0.5
L aIPL - L LPFC
Neg. Affect (Threat-Noncon)
Activation or Connectivity
1
0.5
0
-0.5
R Amy
L Amy - sgACC
Positive Affect
Activation or Connectivity
1
0.5
0
-0.5
vmPFC