Resting-state connectivity biomarkers define neurophysiological subtypes of depression

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Biotypes and biomarkers for depression.

(a) In a discovery sample, Drysdale et al. identified fMRI-imaging depression biotypes on the basis of patterns of functional connectivity, first by using canonical correlation analysis (CCA) to relate patterns of brain connectivity with symptom profiles, and then by clustering these individuals according to these connectivity patterns or components. The biotypes were further optimized and accuracy was tested through cross-validated analysis \( (n = 711) \) and in an independent replication sample \( (n = 477) \). (b) Biotypes predicted response to dorsomedial prefrontal cortex (dmPFC) transcranial magnetic stimulation (TMS) treatment for 154 individuals with depression. (c) Biotypes of depression (dep.) overlapped with generalized anxiety disorder (GAD) but not schizophrenia (Sz.).

To identify reliable, depression-related connectivity patterns, Drysdale et al. use machine learning, a family of pattern-recognition techniques that is increasingly used in many fields, ranging from cancer genomics to consumer behavior and aerospace engineering (9). They developed the four biotypes of depression in a closely matched, multisite sample of individuals clinically diagnosed with major depression (\(n = 220\)). They optimized the biotypes in a larger training sample that consisted of patients with depression (\(n = 333\)) and healthy controls (\(n = 378\)) and tested how accurately patients with each biotype were differentiated from controls. Impressively, they tested the final model prospectively in a separate replication sample (\(n = 477\))


The biotypes included a common core of altered connectivity in prefrontal, orbitofrontal, posterior cingulate and parahippocampal cortices, and in the thalamus, nucleus accumbens and pallidum. Each biotype was associated with a distinct pattern of symptoms and functional connectivity.

Biotypes 1 and 2 are highest in anergia and fatigue, and as compared to healthy controls, they show reduced connectivity with anterior cingulate and orbitofrontal cortex.

Biotypes 3 and 4 are high in anhedonia and psychomotor slowing and show increased thalamic and frontostriatal connectivity.

Biotypes 1 and 4 are high in anxiety and abnormal in fronto-amygdala connectivity.
BOLD signal time series were extracted from 258 spherical regions of interest (ROIs) distributed across the cortex and subcortical structures. The schematics (top) show lateral (left) and medial (right) views of right-hemisphere ROIs projected onto an inflated cortical surface and colored by functional network (lower left). Left-hemisphere ROIs (data not shown) were similar. For each subject, whole-brain functional-connectivity matrices were generated by calculating pairwise BOLD signal correlations between all ROIs, as in this example of correlated signals ($r^2 = 0.88$) for DLPFC (solid line) and PPC (dashed line) nodes of the FPTC network in a representative subject.
Whole brain $258 \times 258$ functional-connectivity matrix averaged across all healthy controls ($n = 378$ subjects). $z =$ Fischer transformed correlation coefficient.

| ACC | anterior cingulate cortex; | amyg, amygdala; | antPFC, anterior prefrontal cortex; | a.u., arbitrary units; | AV, auditory/visual networks; | CBL, cerebellum; | COTC, cingulo-opercular task-control network; | D/VAN, dorsal/ventral attention network; | DLPFC, dorsolateral prefrontal cortex; | DMN, default-mode network; | DMPFC, dorsomedial prefrontal cortex; | FPTC, frontoparietal task-control network; | GP, globus pallidus; | LIMB, limbic; | MR, memory retrieval network; | NAcc, nucleus accumbens; | OFC, orbitofrontal cortex; | PPC, posterior parietal cortex; | precun, precuneus; | sgACC, subgenual anterior cingulate cortex; | SS1, primary somatosensory cortex; | SN, salience network; | SSM, somatosensory/motor networks; | subC, subcortical; | thal, thalamus; | vHC, ventral hippocampus; | VLPFC, ventrolateral prefrontal cortex; | VMPFC, ventromedial prefrontal cortex; | vStr, ventral striatum |
CCA was used to define a low-dimensional representation of depression-related connectivity features and identified an “anhedonia-related” component (canonical variate; c).

The scatterplots in c and d illustrate the correlation between low-dimensional connectivity scores and low-dimensional clinical scores for the anhedonia-related ($r^2 = 0.91$) and anxiety-related components ($r^2 = 0.95$), respectively ($P < 0.00001$).

ACC, anterior cingulate cortex; amyg, amygdala; antPFC, anterior prefrontal cortex; a.u., arbitrary units; AV, auditory/visual networks; CBL, cerebellum; COTC, cingulo-opercular task-control network; D/VAN, dorsal/ventral attention network; DLPFC, dorsolateral prefrontal cortex; DMN, default-mode network; DMPFC, dorsomedial prefrontal cortex; FPTC, frontoparietal task-control network; GP, globus pallidus; LIMB, limbic; MR, memory retrieval network; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; PPC, posterior parietal cortex; precun, precuneus; sgACC, subgenual anterior cingulate cortex; SS1, primary somatosensory cortex; SN, salience network; SSM, somatosensory/motor networks; subC, subcortical; thal, thalamus; vHC, ventral hippocampus; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; vStr, ventral striatum.
anxiety-related” component (d), represented by linear combinations of connectivity features that were correlated with linear combinations of symptoms.

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(e) Hierarchical clustering analysis. The height of each linkage in the dendrogram represents the distance between the clusters joined by that link. For reference, the dashed line denotes 20 times the mean distance between pairs of subjects within a cluster.

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(f) Scatterplot for four clusters of subjects along dimensions of anhedonia- and anxiety-related connectivity. Gray data points indicate subjects with ambiguous cluster identities (edge cases, cluster silhouette values < 0; $n = 15$, or 6.8% of all subjects)
A common neuroanatomical core of pathology underlying all four biotypes and encompassing areas spanning the insula, orbitofrontal cortex, ventromedial prefrontal cortex and multiple subcortical areas.

Of the 17 symptoms quantified by the HAMD, three were present in almost all patients with depression (>90%): mood (“feelings of sadness, hopelessness, helplessness,” 97.1%), anhedonia (96.7%) and anergia or fatigue (93.9%).


(a) Neuroanatomical distribution of the 25 ROIs (top 10%) with the most abnormal connectivity features shared by all four biotypes (summed across all connectivity features for a given ROI), identified using Wilcoxon rank–sum tests to test for connectivity features that were significantly abnormal in all four biotypes relative to healthy controls in data set 1 (n = 378).
(b) Heat maps depicting a pattern of abnormal connectivity ($P < 0.05$, false-discovery rate (FDR) corrected) shared by all four biotypes for the top 50 most abnormal ROIs, colored on the basis of Wilcoxon rank–sum tests comparing patients and controls, as in a. Warm colors represent increase and cool colors decrease in depression as compared to controls.

Across subjects, regardless of biotype, abnormal connectivity in this shared neuroanatomical core (as indexed by the first principal component in a principal-component analysis (PCA)) was correlated with severity scores on these three symptoms \( r = 0.72–0.82 \).

(c) Correlations \( r = 0.72–0.82, ***P < 0.001, \) Spearman) between shared abnormal connectivity features (as indexed by the first principal component (PC) of the features depicted in b and the severity of the core depressive symptoms. Insets depict the prevalence of each symptom. Symptom severity measures are z-scored with respect to controls and plotted as the mean for each quartile, ± s.e.m.
Superimposed on this shared pathological core, distinct patterns of abnormal functional connectivity differentiated the four biotypes (d, e) and were associated with specific clinical-symptom profiles (f).

(d) Neuroanatomical distribution of dysfunctional connectivity features that differed by biotype, as identified by Kruskal–Wallis analysis of variance (ANOVA) \((P < 0.05, \text{FDR corrected})\), summarized for the 50 ROIs (top ~20%) with the most biotype-specific connectivity features (i.e., the 50 ROIs with the largest test statistic summed across all connectivity features, showing cluster specificity at biotype with a threshold of \(P < 0.05, \text{FDR corrected}\)). Nodes (ROIs) are colored to indicate the most abnormal connectivity features and scaled to indicate how many connectivity features exhibited significant effects of biotype.
Reduced connectivity in frontoamygdala networks, which regulate fear-related behavior and reappraisal of negative emotional stimuli, was most severe in biotypes 1 and 4, which were characterized in part by increased anxiety.

(e) Heat maps depicting biotype-specific patterns of abnormal connectivity for the functional nodes illustrated in d, plus selected limbic areas, colored as in b. Green boxes highlight corresponding areas in each matrix discussed in the main text.
(f) Biotype-specific clinical profiles for the six depressive symptoms that varied most significantly by cluster ($P < 0.005$, Kruskal–Wallis ANOVA). Symptom severities (HAMD) are z-scored with respect to the mean for all patients in the cluster-discovery set.  

(g) Boxplot of biotype differences in overall depression severity (total HAMD score), in which boxes denote the median and interquartile range (IQR) and whiskers the minimum and maximum values. In f and g, asterisk (*) indicates significant difference from mean symptom severity rating for all patients ($z = 0$) at $P < 0.05$; error bars depict s.e.m.; n.s., not significant. Aud, auditory cortex; HC, hippocampus; lat PFC, lateral prefrontal cortex; lat OFC, lateral orbitofrontal cortex; MTG, middle temporal gyrus; PHC, parahippocampal cortex; PCC, posterior cingulate cortex; SSM, primary sensorimotor cortex (M1 or S1); STG, superior temporal gyrus; vis, visual cortex. Other abbreviations are as in Figure 1.
Depression biotypes transcend conventional diagnostic boundaries

GAD was associated with widespread connectivity differences in resting-state networks (Fig. 5a–c) that overlapped significantly with those in depression (χ² = 5,457; P < 0.0001; Fig. 5a–c)
Although none of the patients with GAD in this analysis met clinical criteria for a diagnosis of depression, 69.2% of them were nevertheless classified as belonging to one of the depression biotypes, and a majority of these (59.3%) were assigned to the anxiety-associated biotype 4 (Fig. 5d).
Although major depressive depression—is up to 45% heritable, identifying genetic risk factors has proven challenging, even in extremely large genome-wide association studies. Likewise, efforts to develop new treatments have slowed, owing in part to a lack of physiological targets for the assessment of treatment efficacy and the selection of individuals who are most likely to benefit.


.....inform recent initiatives to rethink our system for diagnosing psychiatric disorders and investigating their neuro-physiological and genetic basis, by stratifying subjects into subgroups defined by shared neurobiological substrates. They might also guide optogenetic and other circuit neuroscience approaches to investigating how dysfunction in specific circuits contributes to depression- and anxiety-related behaviors in experimentally tractable animal models.


Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers

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A large biomarker panel (neuropsychological, stop signal, saccadic control, and auditory stimulation paradigms) characterizing diverse aspects of brain function was collected on individuals with schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis (N=711), their first-degree relatives (N=883), and demographically comparable healthy subjects (N=278). Biomarker variance across paradigms was exploited to create nine integrated variables that were used to capture neurobiological variance among the psychosis cases.

Multivariate taxometric analyses identified three neurobiologically distinct psychosis biotypes that did not respect clinical diagnosis boundaries. The same analysis procedure using clinical DSM diagnoses as the criteria was best described by a single severity continuum (schizophrenia worse than schizoaffective disorder worse than bipolar psychosis); this was not the case for biotypes. The external validating measures supported the distinctiveness of these subgroups compared with clinical diagnosis, highlighting a possible advantage of neurobiological versus clinical categorization schemes for differentiating psychotic Disorder.

FIGURE 1. Group Separations on Biomarker Composite Variables for Probands With Psychosis and Their First-Degree Relatives, by Proband Biotype⁹

Resting-state fMRI (rsfMRI) is an especially useful modality because it can be used easily in diverse patient populations to quantify functional network connectivity in terms of correlated, spontaneous MR signal fluctuations. Depression is associated with dysfunction and abnormal functional connectivity in frontostriatal and limbic brain networks (15–20), in accordance with morphological and synaptic changes in chronic stress models in rodents (21–24).

Defining depression subtypes by clustering subjects according to distinct, whole-brain patterns of abnormal functional connectivity in resting-state networks, **unbiased by assumptions about the involvement of particular brain regions**, and tested it in a large, multisite data set.
5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression

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**Figure 4** Functional connectivity between the subgenual cingulate and amygdala is dissociated by genotype and significantly explains harm avoidance scores, whereas other functional or structural measures do not. (a) Short allele carriers show significantly reduced functional connectivity compared to l/l genotype (n = 94). Plot represents extracted peak results normalized to the mean absolute functional connectivity, relative to the l/l genotype group. (b) Only functional connectivity between subgenual cingulate and amygdala explains (Bonferroni corrected, P < 0.05) harm avoidance scores, in contrast to other structural and functional measures (n = 26 subjects with both functional and structural data). Amygdala was used as reference for connectivity measures. A small vertical line indicates values close to zero. Error bars, s.e.m.
Anhedonia and Reward-Circuit Connectivity Distinguish Nonresponders from Responders to Dorsomedial Prefrontal Repetitive Transcranial Magnetic Stimulation in Major Depression

Treatment response was strongly bimodal, with individual patients showing either minimal or marked improvement. **Compared with responders, nonresponders showed markedly higher baseline anhedonia symptomatology (including pessimism, loss of pleasure, and loss of interest in previously enjoyed activities) on item-by-item examination of Beck Depression Inventory-II and Quick Inventory of Depressive Symptomatology ratings.** Congruently, on baseline functional magnetic resonance imaging, nonresponders showed significantly lower connectivity through a classical reward pathway comprising ventral tegmental area, striatum, and a region in ventromedial prefrontal cortex. Responders and nonresponders also showed opposite patterns of hemispheric lateralization in the connectivity of dorsomedial and dorsolateral regions to this same ventromedial region.

Figure 1. (A) Demonstration of placement of repetitive transcranial magnetic stimulation coil for dorsomedial prefrontal cortex stimulation with orientation of current flow to achieve preferential stimulation of the left hemisphere. In this series, 3000 pulses of 10 Hz stimulation at 120% resting motor threshold were applied to left then right hemisphere at each session. (B) T1 anatomical magnetic resonance imaging scan with small white square indicating the positioning of the coil vertex in a representative subject. To achieve dorsomedial prefrontal cortex coverage, the coil was placed at a scalp location corresponding to the Talairach coordinate (x 0, y +60, z +60), corresponding to ~25% of the nasion-inion distance.
Neuroimaging correlates of response to dorsomedial prefrontal cortex (DMPFC)-repetitive transcranial magnetic stimulation. A comparison of betweenness centrality values in nonresponders versus responders to treatment revealed a single region whose betweenness centrality was significantly higher in nonresponders (A). This region lay in left ventromedial prefrontal cortex (VMPFC), at a location similar to that observed in previous metaanalyses of reward- versus loss-related activation in healthy control subjects (B) [reprinted from Diekhof et al. (53)]


Figure 3. (A) Trajectories of improvement in responder and nonresponder subpopulations. Responders showed a steady improvement to meet the remission criterion of 17-item Hamilton Rating Scale for Depression (HAMD-17) score ≤7 over the course of treatment, while nonresponders showed minimal improvement. (B) The normalized product of pretreatment scores on three anhedonia-related items (Beck Depression Inventory-II item 2, Beck Depression Inventory-II item 4, and Quick Inventory of Depressive Symptomatology item 13) was a strong negative predictor of percentage improvement in HAMD-17 score from pretreatment to posttreatment.
Original Investigation

Toward a Neuroimaging Treatment Selection Biomarker for Major Depressive Disorder

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A, Scatterplot of insular activity from individual subjects in the remitter (REM) and nonresponders (NR) groups. Note: the anterior insula is the only region where the interaction subdivides patients into hypermetabolic (region/whole-brain mean >1.0) and hypometabolic region/whole-brain mean <1.0) subgroups.

B, Correlations of insula activity with percentage of change in Hamilton Depression Rating Scale (HDRS) Score in the full cohort of subjects treated with cognitive behavior therapy (CBT) and escitalopram oxalate.


