



Functional connectomics of affective and psychotic pathology

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Converging evidence indicates that groups of patients with nominally distinct psychiatric diagnoses are not separated by sharp or discontinuous neurobiological boundaries. In healthy populations, individual differences in behavior are reflected in variability across the collective set of functional brain connections (functional connectome). These data suggest that the spectra of transdiagnostic symptom profiles observed in psychiatric patients may map onto detectable patterns of network function. To examine the manner through which neurobiological variation might underlie clinical presentation, we obtained fMRI data from over 1,000 individuals, including 210 diagnosed with a primary psychotic disorder or affective psychosis (bipolar disorder with psychosis and schizophrenia or schizoaffective disorder), 192 presenting with a primary affective disorder without psychosis (unipolar depression, bipolar disorder without psychosis), and 608 demographically matched healthy comparison participants recruited through a large-scale study of brain imaging and genetics. Here, we examine variation in functional connectomes across psychiatric diagnoses, finding striking evidence for disease connectomic “fingerprints” that are commonly disrupted across distinct forms of pathology and appear to scale as a function of illness severity. The presence of affective and psychotic illnesses was associated with graded disruptions in frontoparietal network connectivity (encompassing aspects of dorsolateral prefrontal, dorsomedial prefrontal, lateral parietal, and posterior temporal cortices). Conversely, other properties of network connectivity, including default network integrity, were preferentially disrupted in patients with psychotic illness, but not patients without psychotic symptoms. This work allows us to establish key biological and clinical features of the functional connectomes of severe mental disease.

functional connectome | schizophrenia | major depressive disorder | bipolar disorder | resting-state connectivity

Recent progress in the neurosciences has provided unprecedented opportunities for advancing our understanding of the etiology and pathogenesis of psychiatric illness. At the same time, the gradual reification of diagnostic categories has hampered our ability to take full advantage of these innovations (1–4). To date, the vast majority of research on the biological origins of psychopathology has focused on discrete illness categories, studied in isolation. Although modern psychiatric diagnoses provide advantages to the field in terms of diagnostic reliability, their construct validity and utility for understanding brain circuit dysfunction has been challenged (2, 3). Converging epidemiologic, genetic, and neuroscientific research suggests that populations of psychiatric patients are not separated by clear neurobiological borders between diagnostic categories or across health and disease. There is evidence, for example, of substantial overlap in the genetic factors that increase risk for both affective and psychotic illness (5–7). Consistent with shared heritability, partially overlapping patterns of brain network dysfunction mark a broad range of mental diseases (8–10), indicating that their breakdown can lead to diverse forms of psychopathology. However, despite a flurry of important scientific

advances, we still remain far from a mechanistic understanding of how the functioning of large-scale brain networks might serve to influence suites of behaviors within, or across, psychiatric illnesses.

Identifying signatures of pathology across the functional connectome could provide a framework for researchers to study neurobiological contributions to the onset and maintenance of clinically relevant symptoms, informing the development of novel treatments and future classification schemes. Emerging evidence in healthy populations suggests that individual differences in behavior may be reflected in variability across the collective set of functional brain connections (11–13) (functional connectome) (14). Work from our group and others indicate that the unique connectome architecture of an individual’s brain serves as a stable and reliable “fingerprint” (12, 13, 15–17), likely influenced by genetic variation (18–20). The spectra of symptom profiles observed in patient populations may arise through detectable patterns of network function (1, 21, 22). In particular, the disturbance of individual networks might preferentially contribute to domain-specific (e.g., executive, affective, and

Significance

Historically, most research on the biological origins of psychiatric illness has focused on individual diagnostic categories, studied in isolation. Mounting evidence indicates that nominally distinct psychiatric diagnoses are not separated by clear neurobiological boundaries. Here, we derive functional connectomic signatures in over 1,000 individuals, including patients presenting with different categories of impairment (psychosis), clinical diagnoses, and severity of illness as reflected in treatment seeking. Our analyses reveal features of connectome functioning that are commonly disrupted across distinct forms of pathology, scaling with clinical severity. Conversely, other aspects of network connectivity were preferentially disrupted in patients with psychotic illness. These data have important implications for the establishment of functional connectome fingerprints of severe mental disease.

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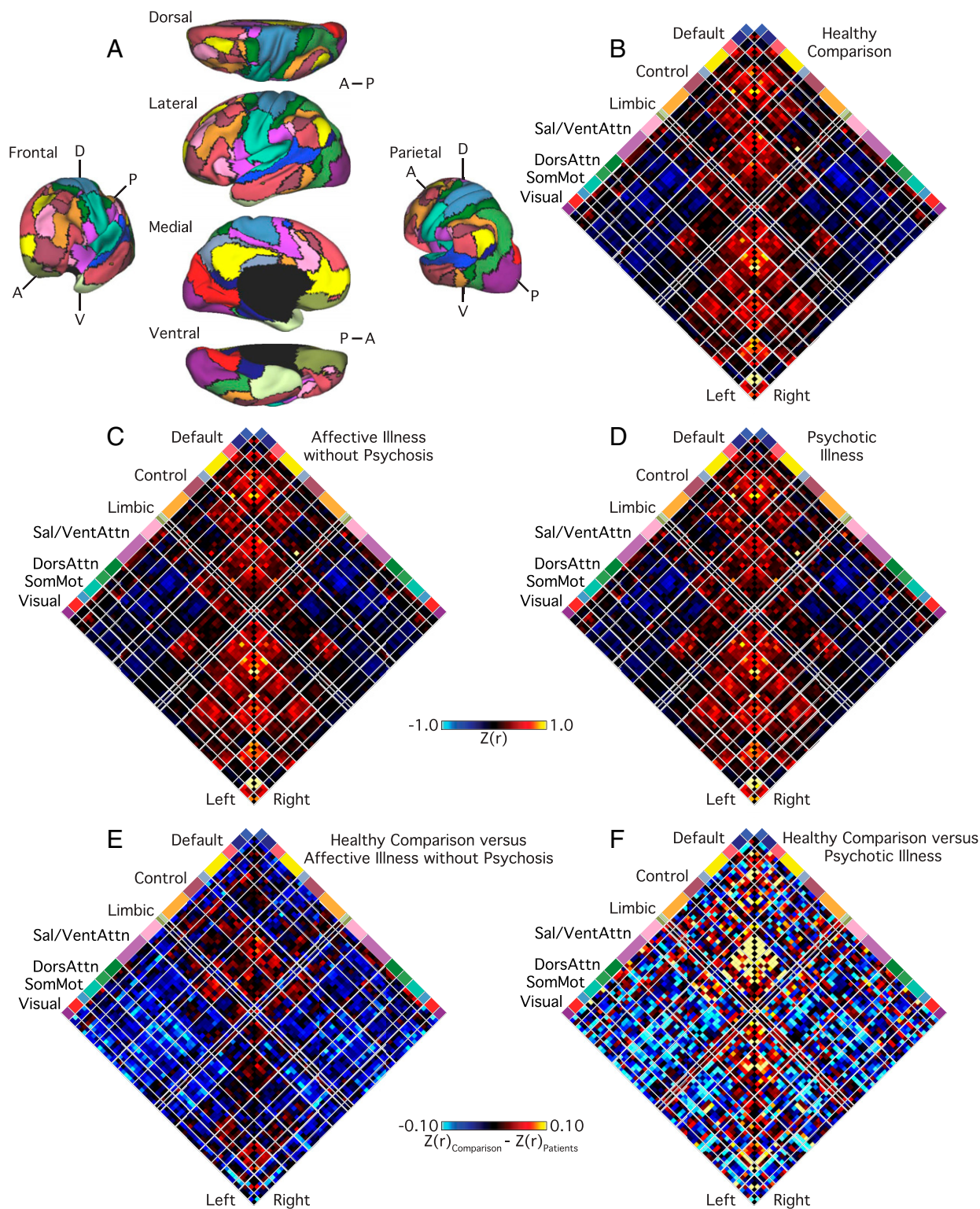


Fig. 1. Cortical network connectivity in patients and healthy comparison participants. (A) The functional network organization of the human cerebral cortex revealed through intrinsic functional connectivity. Colors reflect regions estimated to be within the same network. Regions determined based on the 17-network solution from Yeo et al. (34). The approach groups similar correlation profiles based on a winner-take-all solution, with every surface vertex assigned to its best-fitting network. The 2D grids (B–D) display the complete coupling architecture of the cerebral cortex measured at rest for (B) the healthy comparison participants, (C) patients with affective illnesses without psychosis, and (D) patients with psychotic illnesses. Values reflect z-transformed Pearson correlations between every region and every other region, after accounting for the effects of coil, scanner, console software version, age, sex, race, ethnicity, and handedness. Within-network correlations fall along the center diagonal. Between-network correlations are plotted away from the diagonal and reveal both positive (red) and negative (blue) correlations. (E and F) The 61×61 grids show the differences in resting BOLD correlation between controls and (E) patients with affective illnesses without psychosis, as well as (F) patients with psychotic illnesses, for each intrahemispheric regional pair. Differences were obtained by an analysis of variance of z-transformed Pearson correlation values, adjusting for nuisance variables. White lines represent network boundaries. DorsAttn, dorsal attention; Left, left hemisphere; Right, right hemisphere; Sal, salience; SomMot, somatomotor; and VentAttn, ventral attention.

in individuals presenting to the emergency room seeking care for schizophrenia or related diagnoses, even before starting psychiatric medication (57). Moreover, connectomic changes are apparent in early phases of antipsychotic treatment (58). This literature suggests that differences in symptom severity, rather than medication per se, may underlie the extent and degree of changes observed in our present analyses. However, future longitudinal research designs will be critical for fully disentangling the effects of treatment, fluctuating symptom-severity, and illness course on brain function.

The unprecedented growth of big data in neuroscience provides opportunities for researchers seeking to understand how brain functions influence suites of behaviors and associated illness risk. In the present analyses we make use of a large sample of individuals with imaging data, spanning domains of psychopathology, levels of acuity, and engagement with care. This heterogeneous sample of participants represented a broad range of symptom profiles and illness severity, including individuals with self-reported mental health, nontreatment-seeking forms of depression, and treatment-seeking forms of unipolar depression, bipolar disorder, and severe psychotic illness. Our analyses revealed aspects of the frontoparietal control network that are commonly disrupted across diagnostically distinct forms of severe pathology, whether psychotic or nonpsychotic affective in nature. In addition, we established both shared and unique functional alterations in affective and psychotic illnesses. For example, a preferential reduction in default network integrity was evident in patients with psychotic illness, but absent in affective illnesses without psychosis. These analyses highlight the potential to discover individualized network profiles that are predictive of symptom-relevant cognitive domains, both within and across diagnostic boundaries, as exemplified in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) effort (59) and our own ongoing work. In conclusion, this study provides a comprehensive characterization of connectomic dysfunction in a range of psychopathological conditions that matches well with the core deficits observed in these populations. These data have important implications for the future creation of connectome-based models that predict behavior, an approach with the potential to account for symptom comorbidity while simultaneously explaining the biological process that give rise to the diversity of clinical presentations.

Methods

Between November 2008 and June 2017, fMRI data were collected from a total of 1,010 individuals, including 210 diagnosed with a primary psychotic disorder (137 meeting criteria for schizophrenia or schizoaffective disorder, 73 with bipolar disorder with psychosis), 192 presenting with a primary affective disorder without psychosis (26 with bipolar disorder without psychosis, 57 treatment-seeking individuals with unipolar depression, 109 nontreatment-seeking individuals with unipolar depression), and 608 demographically matched healthy comparison participants recruited through an ongoing, large-scale study of brain imaging and genetics (30). Diagnosis was determined using the Structured Clinical Interview for the DSM-IV (60). Details regarding participant recruitment and characterization, as well as the demographic and clinical characteristics of the patient and matched healthy comparison samples, are available in *SI Appendix, Table S1*. In brief, patients were recruited from clinical services at MGH or McLean Hospital through the procedures detailed in Baker et al. (23). Nontreatment-seeking individuals who met diagnostic criteria for unipolar depression were recruited from the surrounding Boston area using the procedures detailed in Dillon et al. (61).

Healthy comparison participants were selected from an existing database of adults (aged 18–83 y) (30), scanned previously using identical pulse sequences on identical scanners, and selected to match patients on the basis of age, gender, race, handedness, as well as a mean slice-based signal-to-noise ratio (SNR) derived from the participant's blood oxygenation level-dependent (BOLD) T2* image series. In this context, SNR is calculated as the mean/SD of the mean slice intensity time series. Using this strategy, we were able to ensure statistically matched distributions for both demographic variables and comparable data quality (as well as head movement metrics).

The reported experiments were approved by the Partners HealthCare Institutional Review Board and the Harvard University Committee on the Use of Human Subjects in Research McLean Hospital Institutional Review Board, and all participants gave written informed consent before participating in the study.

MRI Data Acquisition. Imaging data were collected on 3T Tim Trio scanners (Siemens) using either 12- or 32-channel phased-array head coils at Harvard University, MGH, or McLean Hospital as detailed in Holmes et al. (30). Briefly, structural data included a high-resolution, multiecho T1-weighted magnetization-prepared gradient-echo image [144 slices, repetition time (TR) = 2,200 ms, inversion time (TI) = 1,100 ms, echo time (TE) = 1.54 ms for image 1 to 7.01 ms for image 4, flip angle = 7°, voxels = 1.2 mm³, field-of-view (FOV) = 230]. Functional data were acquired using a gradient-echo echoplanar imaging sequence (47 axial slices, interleaved with no gap), 124 time points (TR = 3000 ms, TE = 30 ms, flip angle = 85°, voxels = 3 mm³, FOV = 216). Participants were instructed to remain still and keep their eyes open, while blinking normally. Although no fixation image was used, participants with psychotic illness were monitored via eye-tracking video to ensure compliance during functional scans. Software upgrades (VB13, VB15, VB17) occurred during data collection. All results are reported after partialing out variance associated with coil, scanner (Harvard Bay 1, McLean Bay 1, MGH Bay 4, MGH Bay 8, and so forth), and software upgrade, as well as age, sex, handedness, race, and ethnicity. All treatment-seeking patient samples were collected on a 12-channel coil. In the healthy comparison, participants and nontreatment-seeking individuals with unipolar depression 78.5 and 36.7% of the data were collected on a 12-channel coil, respectively. All reported analyses are consistent when separately considering only 12-channel and 32-channel coil data. The patient and healthy comparison samples did not differ in mean slice-based signal-to-noise [all patients: 172.4 ± 66.8; healthy comparison: 175.3 ± 51.2; $F_{(1, 1,008)} = 0.61, P = 0.43$]. Patients displayed a significantly greater number of micromovements (translations > 0.1 mm) during data collection [all patients: 25.5 ± 27.2; healthy comparison: 20.3 ± 24.7; $F_{(1, 1,008)} = 9.89, P \leq 0.005$]. The reported group-level effects are consistent when incorporating mean slice-based SNR and micromovement counts as model covariates.

Preprocessing. Data were analyzed with a series of steps common to intrinsic connectivity analyses (31–33) and further elaborated in Holmes et al. (30) and Yeo et al. (34). Preprocessing included discarding the first four volumes of each run to allow for T1-equilibration effects, compensating for slice acquisition-dependent time shifts per volume, and correcting for head motion using rigid body translation and rotation. Additional steps involved the removal of constant offset and linear trends over each run and the use of a temporal filter to retain frequencies below 0.08 Hz. Sources of spurious variance, along with their temporal derivatives, were removed through linear regression. These included six parameters obtained by correction for rigid-body head motion, the signal averaged over the whole brain, the signal averaged over the ventricles, and the signal averaged over the deep cerebral white matter. Functional data were first aligned to the structural image using the FreeSurfer software package, smoothed using a 6-mm kernel applied in surface space, and down-sampled to a 4-mm mesh Yeo et al. (34).

Functional Parcellation. Cortical functional coupling matrices were computed for each participant, across all available regions within the 17 network functional parcellation of Yeo et al. (34) (Fig. 1A). This parcellation consisted of 122 cortical regions composed of 61 roughly symmetric territories in the left and right hemispheres (23). Correlation matrices were constructed to include all regional pairs arranged by network membership. Pearson correlation coefficients were computed between each regional fMRI time course, averaged across all vertices within the region, and the mean fMRI time course for every other region (Fig. 1B–D). Correlation values were z-transformed to increase normality of the correlation distribution and compared across groups using an ANOVA after linear regression of nuisance variables. Reported tests survived correction for multiple comparisons using a family-wise error rate (Bonferroni procedure) of $P \leq 0.05$ or FDR of $q \leq 0.05$. Readers should note that caution is warranted when interpreting group differences in within-network connectivity for subnetworks with limited numbers of parcels (e.g., frontoparietal control C and default D).

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