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Whole-brain intrinsic functional connectivity predicts symptoms and functioning in early psychosis

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Abstract

Theories of psychotic illness suggest that abnormal intrinsic functional connectivity may explain its characteristic positive and disorganization symptoms as well as lead to impaired general functioning. Here we used resting state functional magnetic resonance imaging (fMRI) to evaluate associations between these symptoms and the degree to which global connectivity is abnormal in early psychosis (EP). Eighty-six healthy controls (HCs) and 108 individuals with EP with resting state fMRI data were included in primary analyses. The EP group included 83 participants with schizophrenia-spectrum disorders and 25 with bipolar disorder type I with psychotic features. A global intrinsic connectivity "similarity index" for each EP individual was determined by calculating its correlation with the average HC connectivity matrix extracted using Schaefer atlases of multiple parcellations (100, 200, 300, and 400 region parcellations). As hypothesized, connectivity similarity with the average HC matrix was negatively associated with Brief Psychiatric Rating Scale total score, Scale for the Assessment of Positive Symptoms total score, and disorganization symptoms. Similarity was also positively associated with Global Assessment of Functioning score. Results were not driven by sex or diagnosis effects and were consistent across parcellation schemes. These results support the hypothesis that changes in whole-brain connectivity patterns are associated with psychosis symptoms and support the use of functional connectivity as a biomarker for these symptoms in EP.

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[1]These authors contributed equally to the manuscript.

Declaration of competing interest

The authors declare no conflicts of interest.

CRediT authorship contribution statement

Jason Smucny: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis. **Korey P. Wylie:** Writing – review & editing, Methodology. **Tyler A. Lesh:** Writing – review & editing, Data curation. **Cameron S. Carter:** Writing – review & editing, Supervision, Resources. **Jason R. Tregellas:** Writing – review & editing, Supervision, Software, Resources.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.05.042.

Keywords

Biomarker; Bipolar disorder; fMRI; Resting state; Schizophrenia

1. Introduction

One of the most fundamental hypotheses concerning the pathophysiology of psychotic illnesses such as schizophrenia-spectrum disorders (SZ) is that they are disorders of dysconnectivity caused by abnormal interactions between brain regions. The hypothesis was first proposed by Wernicke (1906) as a loss of fiber tract integrity he termed a "sejunction" and Bleuler's theoretical "loosening of associations" (1911). The theory was then reconceptualized later by Friston and Frith (1995) as a "disconnection syndrome" as evidenced from neuroimaging studies suggesting that loss of connectivity may result in loss of "intrinsically generated action" and "aberrant perception resulting from misattribution of a self-induced sensory change to external agencies." The hypothesis has since been frequently investigated using a wide range of imaging modalities, including structural and functional magnetic resonance imaging (fMRI) as well as diffusion tensor imaging (reviewed by Dong et al., 2018; Fitzsimmons et al., 2013; Kraguljac et al., 2021; Perry et al., 2019; Pettersson-Yeo et al., 2011; Wheeler and Voineskos, 2014). Overall, these studies suggests that these disorders are associated with widespread patterns of dysconnectivity between regions, in agreement with Wernicke's and Blueler's theories. Indeed, a 2018 meta-analysis of 52 studies by Dong et al. (2018) found reduced connectivity within the default mode, affective, ventral attention (VAN), thalamic, and somatosensory networks as well as between the VAN and thalamic, VAN and default mode, VAN and frontoparietal, frontoparietal and thalamic, and frontoparietal and default mode networks in SZ. Furthermore, evidence suggests the extent of functional dysconnectivity may also predict severity of positive symptoms in SZ (e.g., Damiani et al., 2022; O'Neill et al., 2019; Palaniyappan et al., 2013; Venkataraman et al., 2012). Importantly, identifying functional biomarkers that predict symptom severity is essential if psychiatric clinical research is to establish that investigational therapeutics are modifying their intended neuronal targets (Wylie et al., 2016).

Taken together, the results of previous studies suggest that abnormal functional connectivity may predict symptom severity in psychosis. One may additionally postulate that positive and disorganization symptoms (as well as general functioning) may be particularly affected by abnormal connectivity patterns in psychotic illness based on previous hypotheses. Here, we used resting state fMRI to examine the relationship between overall intrinsic functional connectivity and symptoms/functioning in early psychosis (EP). As we were broadly interested in relationships to psychosis symptoms, our EP group included individuals with schizophrenia-spectrum disorders as well as Type I bipolar disorder with psychotic features. To calculate global connectivity, we calculated a "similarity index," in which the connectivity matrix of an EP individual was correlated to the average matrix of a sample of healthy control (HC) participants. This index was thus considered a measure of how closely each EP participant's global connectivity matrix resembled that of the average unaffected individual. We hypothesized EP individuals with matrices less similar to the HC

average would show more severe positive and disorganization symptoms as well as lower functioning relative to those more similar to the HC average.

2. Material and methods

2.1. Sample

Neuroimaging data were available for 116 individuals with EP ("EPs"; 84 with SZ (including SZ, schizoaffective, and schizophreniform disorder) and 25 Type I bipolar disorder (BD) with psychotic features) and 86 HCs. EPs were recruited as outpatients from the University of California, Davis (UCD) Early Diagnosis and Preventive Treatment (of Psychosis) (EDAPT) research clinic (http://earlypsychosis.ucdavis.edu). The Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 2002) was used for diagnosis of psychopathology. Diagnoses were confirmed by a group of trained clinicians during case-conferences. EP participants reported psychosis onset within two years of the date of informed consent. BD individuals were typically scanned several weeks after their initial presentation for treatment and were not in an acute manic episode. In these participants, some residual psychotic symptoms were present, and some had residual mild hypomanic symptoms that did not compromise the collection of complete, high-quality data during the scanning sessions. EP individuals were excluded for a diagnosis of major medical or neurological illness, head trauma, substance abuse in the previous three months (as well as a positive urinalysis on the day of scanning), Weschler Abbreviated Scale of Intelligence-2 score (WASI-2) (Weschler, 1999) score <70, and magnetic resonance imaging (MRI) exclusion criteria (e.g. claustrophobia, metal in the body). HCs were excluded for all of the above as well as a history of Axis I mental illness or first-degree family history of psychosis. All participants provided written informed consent and were compensated for participation. The UCD Institutional Review Board approved the study. Medication regimen (type and chlorpromazine (CPZ)-equivalent dose) was assessed by clinical records at baseline and follow-up. Symptoms were ascertained using the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a), and Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b). Consistent with prior work (Barch et al., 2003), a "disorganization" score was also calculated that combined conceptual disorganization, mannerisms and posturing, and disorientation scores from the BPRS with attention score from the SANS as well as positive formal thought disorder, and bizarre behavior scores from the SAPS. This was done due to the lack of a separate scale to measure disorganization symptoms. Functioning was measured using total score from Global Assessment of Function instrument (First et al., 2002). Identical scales were used for participants with SZ and BD, consistent with prior work (Smucny et al., 2019; Smucny et al., 2020; Smucny et al., 2018; Smucny et al., 2021).

2.2. MRI acquisition

T1 weighted MPRAGE structural images were acquired for realignment and normalization during preprocessing. Structural imaging parameters were 2530 ms TR, 3.5 ms TE, flip-angle 7°, 256 mm^2 FOV, 1 mm isotropic voxels.

Resting state functional images were acquired on a 3 T MR scanner (Siemens Magnetom TimTrio) using a standard quadrature head coil. Images were acquired with the following parameters: 6 m scan time, 2000 ms TR, 28 ms TE, 220 mm^2 FOV, 3.4 × 3.4 × 4.0 mm voxel size, 33 slices, interleaved, anterior to posterior phase encoding, flip angle 75°, 180 volumes. Subjects were instructed to rest with eyes open while observing a fixation cross.

2.3. fMRI preprocessing

fMRI data were preprocessed using SPM12 (Wellcome Dept. Of Imaging Neuroscience, London). Briefly, images were realigned and then normalized to the Montreal Neurological Institute (MNI) template using a rigid-body transformation followed by non-linear warping to individual normalized, segmented T1 images. Data were not smoothed in accordance with CONN guidelines for ROI-to-ROI analysis (Nieto-Castanon, 2015).

2.4. Whole-brain connectivity calculation

Connectivity analysis was performed using the CONN v.21 toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). Prior to analysis, preprocessed fMRI images were scrubbed for movement and other artifacts using the ArtRepair toolbox implementation in CONN. Scrubbing thresholds were global-signal z-value >5 and interscan subject motion >0.9 mm, corresponding to the “intermediate” settings in CONN (97th percentiles in normative data). Two sets of analyses were performed: one in which individuals with >50% scans scrubbed were excluded, and one in which or individuals with >20% of scans scrubbed were excluded. Vectors constituting the 6 rigid body movement parameters (x, y, z, roll, pitch, yaw) as well as individual signal from white matter and cerebrospinal fluid (using Freesurfer-derived masks for each participant (Reuter et al., 2012)) were included as first-level nuisance regressors prior to calculating connectivity. Functional connectivity was then extracted using Schaefer atlas 100, 200, 300, or 400 region cortical parcellations (Schaefer et al., 2018) combined with the Wake Forest University Pickatlas ten region subcortical parcellation (Maldjian et al., 2003) to create whole-brain Fisher-transformed connectivity matrices. Multiple parcellations were used to determine if brain-behavior relationships were altered as a function of atlas scale. Connectivity was converted to absolute values.

After connectivity matrices were extracted for each participant that met quality control criteria, matrices for all HC individuals were combined to create an average HC connectivity matrix (Fig. 1, top half). A connectivity “similarity” index was then calculated for each EP individual by determining the Pearson’s correlation coefficient between all connectivity values of that individual’s matrix with the connectivity values of the mean HC matrix (Fig. 1, bottom half). This index captures to the degree to which the overall connectivity pattern of the EP individual mirrors that of the average HC individual in the sample.

2.5. Statistics

After similarity indices were determined, biological sex and diagnostic differences (BD vs. SZ) between these indices in the EP group were calculated using t-tests. We also examined the stability of the similarity index measure by determining the individual HC participant similarity indices from the HC mean matrix and then calculating the coefficient of variation (COV, i.e., standard deviation ÷ mean) and its 95% confidence interval (CI) from 1000

bootstrapped samples of these indices. Bootstrapped 95% COVs with upper bounds <15% were considered evidence of good stability of the measure, as suggested by the European Society of Radiology Statement on the Validation of Imaging Biomarkers (European Society of Radiology, 2020).

To determine relationships with symptoms, linear regression models were calculated in which similarity was set as the independent and symptom score as the dependent variable. Sex, antipsychotic medication dose (CPZ equivalents), and diagnosis were included as factors in initial regression models and removed if their effects were non-significant. Diagnosis was included as a factor as some evidence suggests that individuals with BD have less severe connectivity abnormalities than those with SZ (e.g., Argyelan et al., 2014; Rashid et al., 2014; Smucny et al., 2018). Significance was set to $p < 00.05$ for these analyses. All statistics were computed using SPSS v.29 (IBM, Armonk, NY).

3. Results

3.1. Demographics

Two individuals with EP ("EPs") were excluded for having >50% of their fMRI scans scrubbed, leaving 86 HCs and 114 EPs in the primary sample. A secondary analysis was also performed using more stringent criteria (having >20% of their scans scrubbed). Using these criteria an additional 3 HCs and 6 EPs were excluded. Demographic, clinical, and percent scans scrubbed information for HCs and EPs included in the primary analysis are presented in Table 1. Briefly, HCs and EPs did not significantly differ on age or parental education. The EP group was more predominantly male and had fewer years of education than the HC group. Total BPRS and SAPS scores were missing for 2 individuals.

3.2. Functional connectivity similarity with healthy controls: sex and diagnostic effects

Mean similarities (Pearson's correlation coefficients, see Methods and Fig. 1) between the connectivity matrix of an EP individual with the average HC functional connectivity matrix for each parcellation (Schaefer100, 200, 300, and 400 atlases + 10 subcortical regions) and percent scans scrubbed quality control (QC) threshold are presented in Table 2, Column 2. Mean similarities for males and females for each parcellation and QC threshold are also presented in Table 2. No significant differences were observed between the similarity of male EP vs. female EP individuals with the average HC matrix for any parcellation scheme/threshold. Mean similarities for EPs with BD and SZ for each parcellation are presented in Table 3. No significant diagnostic differences were observed in similarity values for each parcellation/threshold.

3.3. Similarity index stability in healthy controls: coefficient of variation analysis

Stability of the similarity index was examined by calculating COV values with associated 95% CIs of individual HC similarity indices from 1000 bootstrapped samples. 95% CIs of upper bounds of COV values were all <15%, suggesting the measure had good stability (Supplementary Table 1).

3.4. Functional connectivity similarity with healthy controls: relationships with symptoms/functioning

Next, we examined relationships between connectivity similarity with BPRS score, SANS score, SAPS score, disorganization symptoms, and GAF score in EP using linear regression models. Results of these models are presented in Table 4, and representative scatter plots of significant relationships between similarity and symptoms/functioning in EP are presented in Fig. 2. Summarizing these results, similarity was negatively associated with total SAPS score (standardized β′s from −0.22 to −0.25, p values from 0.007 to 0.026) and disorganization symptoms (standardized β′s from −0.21 to −0.28, p values from 0.004 to 0.037) and positively associated with GAF score (standardized β′s from 0.22 to 0.31, p values from <0.001 to 0.030) using all parcellation schemes and QC thresholds. Similarity was also negatively associated with total BPRS scores for the more lenient threshold (50% or less scans scrubbed) (standardized β′s from −0.19 to 0.23, p values from 0.017 to 0.047). Similarity showed no significant relationships with SANS symptoms using any parcellation or threshold. Sex and antipsychotic dose were not significant factors in any models and thus were not included in any of the full models presented in Table 4. Diagnosis was a significant factor in all models predicting total BPRS, SAPS and SANS scores as well as in one model predicting disorganization symptoms as participants with SZ had higher symptom scores than those with BD.

4. Discussion

In agreement with our hypothesis, an overall pattern of abnormal connectivity predicted greater positive and disorganization symptom severity as well as lower functioning in EP. These relationships were largely unaffected by the parcellation scheme or QC threshold, suggesting they were not artifacts of the atlas used or affected by motion-induced outliers. Furthermore, these relationships were not driven by sex or diagnosis (BD vs. SZ) effects, suggesting that they are not an artifact of sex or group differences in symptoms or functioning. Supporting its utility as a stable biomarker, the similarity measure also showed low variability in the HC sample as evidenced by upper bounds of bootstrapped 95% CIs of the HC COVs that were <15% for all parcellation schemes and scrubbing thresholds.

Overall, our results support the early ideas of Wernicke (1906), Bleuler (1911) and Friston and Frith (1995) in that abnormal connectivity may predict positive symptom severity and disorganization in the illness. The robust relationships observed here between connectivity, symptoms, and functioning over a fairly large sample (n > 100) suggest that intrinsic connectivity as captured by resting state fMRI may be a useful biomarker for clinical development in psychosis, in which therapeutic effects of investigational treatments may be evaluated neuronally by their effects on connectivity.

As a cross-sectional study, it is important to note that we cannot ascertain the directionality of these effects – i.e., it is unclear of intrinsic connectivity produces symptoms, or if symptoms result in disrupted connectivity. A longitudinal study in which connectivity is examined prior to illness onset (or even prodromal onset) is required to make such an assessment. Notably, however, a recent meta-analysis in individuals at clinical high risk for psychosis (CHRs) found reduced connectivity of the salience network in CHRs compared

to HCs (Del Fabro et al., 2021). Furthermore, several longitudinal studies of treatment response have found that individuals with more “healthy” patterns of connectivity at baseline show more symptom reductions at follow-up (e.g., Cadena et al., 2019; White et al., 2016), reviewed by Mehta et al. (2021). Some studies also have found that the degree to which connectivity normalizes over the course of treatment in psychosis predicts clinical response to that treatment (Cadena et al., 2019; Chopra et al., 2021; Yang et al., 2023). Taken together, these results suggest that not only are connectivity and symptoms associated with each other in psychosis, but that connectivity may also be causally linked to symptom presentation – an important factor to consider if connectivity is to be used as a biomarker in treatment studies in psychosis.

Although we did not observe significant differences in similarity index between BD and SZ, point estimates were in the direction of greater similarity in individuals with BD. This result is consistent with prior observations from neuroimaging studies that suggest SZ and BD lie on a functional linear continuum, with BD individuals showing less severe functional abnormalities compared to SZ (e.g., Argyelan et al., 2014; Rashid et al., 2014; Smucny et al., 2018). As the lack of a significant difference between SZ and BD may have been due to the low sample size in the BD group ($n = 25$), this preliminary finding requires further investigation in a larger sample. Importantly, relationships between symptoms and connectivity similarity persisted even while including group as a factor in regression models.

Our study had several limitations. First, we did not examine connectivity patterns between specific brain areas but rather used a whole brain approach to determine connectivity/clinical relationships. This was necessary as we did not have an *a priori* hypothesis as to what regions would be involved, and we did not have adequate statistical power to correct the number of comparisons that would be necessary to calculate these relationships post-hoc. Although a beyond the scope of the present study, a targeted network-based approach with fewer regions may therefore be used in future work. Second, the scanning time was relatively short for a resting state study (6 min). For this reason, we conducted analyses using two different QC thresholds (<50% of scans scrubbed – i.e., >3 min of scan time – and <20% of scans scrubbed, i.e., >4.8 min of scan time). Results mostly remained unchanged using these thresholds, although the exclusion of six more EP individuals under the more stringent threshold likely caused a sufficient loss of statistical power to where results fell just below significance thresholds for the regressions with total BPRS score. Future studies will examine these relationships under longer scanning times. Third, our EP group was relatively heterogenous, including individuals with BD and schizophrenia-spectrum disorders. Finally, although we did not observe any significant effects of antipsychotic dose on our regression models, we cannot rule out the possibility that antipsychotic use may have had an effect of the observed brain-behavior relationships. A separate analysis in a large unmedicated sample is necessary to rule out this possibility.

Overall, the results of this study support the hypothesis that disruptions in brain-wide connectivity patterns are robustly associated with the clinical presentation of psychotic illnesses, particularly for its positive and disorganization symptoms as well as general functioning. This study thus also presents a novel, straightforward, computationally non-demanding approach to utilizing an easily obtainable imaging modality (resting state fMRI)

for use as a biomarker in EP. Due to the methodological advantages of this approach and the resulting robust relationships to symptoms, it is plausible that it may be widely utilized as an indicator of treatment response in interventional studies involving participants with EP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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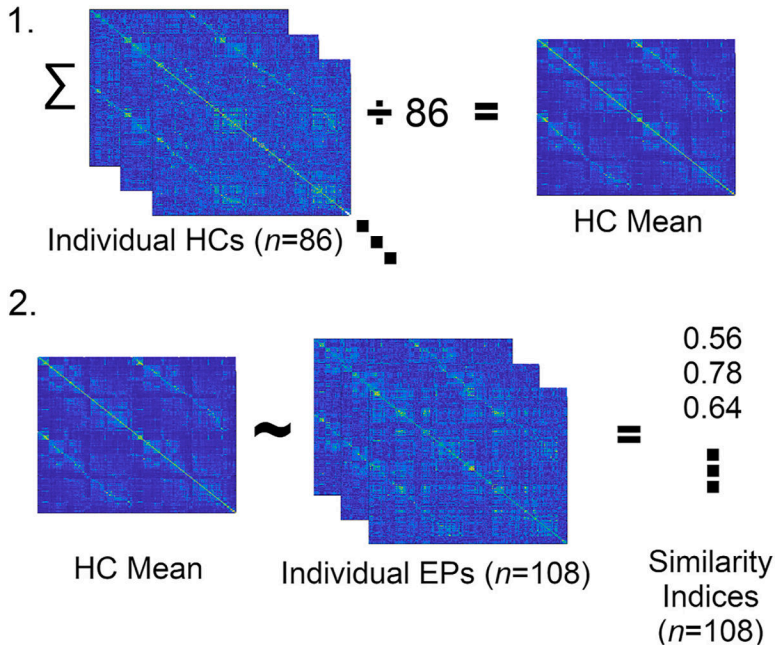

Fig. 1.

Similarity index calculation procedure. 1: Overall mean healthy control (HC) connectivity matrix is calculated. 2: The Pearson's *r* correlation coefficient against the mean HC matrix is calculated for each early psychosis (EP) individual. Sample displayed matrices are from the Schaefer200 atlas.

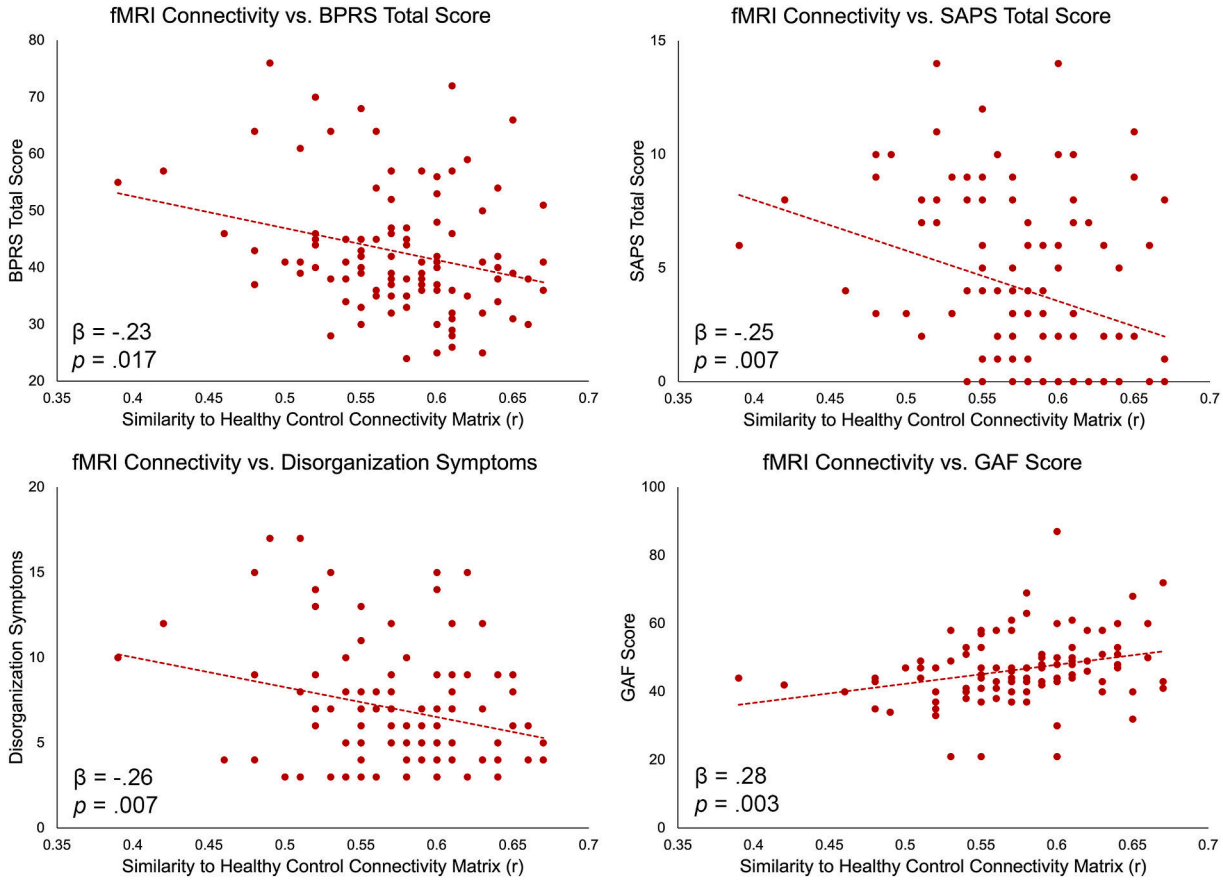

Fig. 2.

Representative scatter plots showing relationships between functional connectivity similarity (correlation with the average healthy control matrix) and symptoms/functioning. Similarity for these plots was calculated using a combination of the Schaefer200 atlas with the WFU PickAtlas ten region subcortical atlas. Only scans with <50% of volumes scrubbed were included. BPRS = Brief Psychiatric Rating Scale, GAF = Global Assessment of Functioning, SAPS = Scale for the Assessment of Positive Symptoms.

Table 1

Demographic, clinical, and resting state functional magnetic resonance imaging (fMRI) scrubbing information for all participants included in analyses.

Group	HC (SD)	EP (SD)	T or χ^2 (*p*)
n	86	108	–
***n* BD/SZ**	–	25/83	–
Age	20.13 (3.70)	20.48 (4.00)	− 0.18 (0.86)
Sex M/F	51/35	80/28	4.76 (0.029)
Handedness R/L/Ambidextrous	80/5/1	96/12/0	2.88 (0.24)
Years of Education	13.26 (3.20)	12.28 (2.20)	2.39 (0.018)
Parental Years of Education	14.57 (3.05)	14.45 (2.78)	0.27 (0.79)
Antipsychotic Treatment Y/N	–	99/9	–
Antipsychotics CPZ Equivalent Dose Mg/Day	–	224.32 (186.14)	–
BPRS Total Score	–	42.73 (1.83)	–
SANS Total Score	–	9.73 (4.16)	–
SAPS Total Score	–	4.10 (3.81)	
Disorganization Symptoms	–	6.94 (3.44)	–
GAF Score	–	46.56 (1.00)	–
%Resting State fMRI Frames Scrubbed	3.16 (5.81)	6.24 (7.87)	− 3.13 (0.002)

CPZ = chlorpromazine, BD = bipolar disorder, EP = early psychosis, GAF = global assessment of functioning, HC = healthy control, SD = standard deviation, SZ = schizophrenia-spectrum disorder.

Table 2

Functional connectivity matrix similarity with healthy controls: sex effects.

fMRI Scrubbing QC Threshold				
Parcellation				
All Scans < 50% Scrubbed	**All EP (SD) *n* = 108**	**M (SD) *n* = 84**	**F (SD) *n* = 30**	**M vs. F T (*p*)**
Schaefer100 + Subcortical	0.63 (0.05)	0.62 (0.05)	0.63 (0.05)	− 0.68 (0.50)
Schaefer200 + Subcortical	0.58 (0.05)	0.57 (0.05)	0.58 (0.05)	− 0.80 (0.43)
Schaefer300 + Subcortical	0.55 (0.05)	0.54 (0.06)	0.56 (0.04)	−1.20 (0.23)
Schaefer400 + Subcortical	0.53 (0.05)	0.52 (0.06)	0.54 (0.05)	−1.18 (0.24)
All Scans < 20% Scrubbed	**All EP (SD) *n* = 102**	**M (SD) *n* = 75**	**F (SD) *n* = 27**	**M vs. F T (*p*)**
Schaefer100 + Subcortical	0.63 (0.05)	0.63 (0.05)	0.63 (0.05)	−0.27 (0.79)
Schaefer200 + Subcortical	0.58 (0.05)	0.58 (0.05)	0.58 (0.05)	−0.30 (0.76)
Schaefer300 + Subcortical	0.55 (0.05)	0.55 (0.05)	0.56 (0.05)	−0.69 (0.49)
Schaefer400 + Subcortical	0.53 (0.05)	0.53 (0.05)	0.54 (0.05)	−0.61 (0.54)

The table is divided into two halves; the top half compares males (M) and females (F) including only participants with less than 50% of their scans scrubbed for movement and signal change, and the bottom half compares sexes including only participants with less than 20% of their scans scrubbed. fMRI = functional magnetic resonance imaging, QC = quality control, SD = standard deviation.

Table 3

Functional connectivity matrix similarity with healthy controls: diagnostic effects.

fMRI Scrubbing QC Threshold			
Parcellation			
All Scans < 50% Scrubbed	**BD (SD) *n* = 25**	**SZ (SD) *n* = 83**	**T (*p*)**
Schaefer100 + Subcortical	0.64 (0.05)	0.62 (0.05)	1.62 (0.11)
Schaefer200 + Subcortical	0.59 (0.05)	0.57 (0.05)	1.40 (0.17)
Schaefer300 + Subcortical	0.56 (0.05)	0.54 (0.06)	1.40 (0.16)
Schaefer400 + Subcortical	0.54 (0.05)	0.52 (0.06)	1.17 (0.25)
All Scans < 20% Scrubbed	**BD (SD) *n* = 25**	**SZ (SD) *n* = 77**	**T (*p*)**
Schaefer100 + Subcortical	0.64 (0.05)	0.62 (0.05)	1.37 (0.17)
Schaefer200 + Subcortical	0.59 (0.05)	0.58 (0.05)	1.11 (0.27)
Schaefer300 + Subcortical	0.56 (0.05)	0.55 (0.05)	1.10 (0.27)
Schaefer400 + Subcortical	0.54 (0.05)	0.53 (0.05)	0.86 (0.39)

The table is divided into two halves; the top half compares groups including only participants with less than 50% of their scans scrubbed for movement and signal change, and the bottom half compares groups including only participants with less than 20% of their scans scrubbed. BD = bipolar disorder, fMRI = functional magnetic resonance imaging, QC = quality control, SD = standard deviation, SZ = schizophrenia-spectrum disorder.

Table 4

Linear regression models examining relationships between intrinsic connectivity similarity index (calculated by correlating the connectivity matrix of an early psychosis individual with the average healthy control matrix (see Methods)) and symptoms/functioning.

Dependent Variable	Full Model			Diagnosis Effect			Similarity Index Effect		
fMRI Scrubbing Threshold									
Parcellation	**F**	**R^2**	***p***	**β**	**t**	***p***	**β**	**t**	***p***
Total BPRS Score									
QC Threshold: All Scans < 50% Scrubbed									
Schaefer100 + Subcortical	5.58	0.10	0.005	0.22	2.29	0.024	−0.19	−2.01	0.047
Schaefer200 + Subcortical	6.59	0.11	0.002	0.22	2.31	0.023	−0.23	−2.44	0.017
Schaefer300 + Subcortical	6.09	0.11	0.003	0.22	2.33	0.022	−0.21	−2.23	0.028
Schaefer400 + Subcortical	6.06	0.11	0.003	0.22	2.38	0.019	−0.21	−2.22	0.028
QC Threshold: All Scans < 20% Scrubbed									
Schaefer100 + Subcortical	4.03	0.08	0.021	0.22	2.19	0.031	−0.14	−1.46	0.15
Schaefer200 + Subcortical	4.79	0.09	0.010	0.22	2.20	0.030	−0.18	−1.89	0.062
Schaefer300 + Subcortical	4.40	0.08	0.015	0.22	2.22	0.029	−0.17	−1.68	0.096
Schaefer400 + Subcortical	4.45	0.08	0.014	0.22	2.27	0.026	−0.17	−1.71	0.090
Total SANS Score									
QC Threshold: All Scans < 50% Scrubbed									
Schaefer100 + Subcortical	5.55	0.10	0.005	0.31	3.27	0.001	−0.01	−0.08	0.94
Schaefer200 + Subcortical	5.96	0.10	0.004	0.30	3.19	0.002	−0.08	−0.86	0.39
Schaefer300 + Subcortical	6.12	0.11	0.003	0.30	3.17	0.002	−0.10	−1.01	0.31
Schaefer400 + Subcortical	6.12	0.11	0.003	0.30	3.20	0.002	−0.10	−1.02	0.31
QC Threshold: All Scans < 20% Scrubbed									
Schaefer100 + Subcortical	5.42	0.10	0.006	0.31	3.21	0.002	−0.03	−0.26	0.80
Schaefer200 + Subcortical	6.05	0.11	0.003	0.30	3.15	0.002	−0.11	−1.10	0.28
Schaefer300 + Subcortical	6.35	0.12	0.003	0.30	3.13	0.002	−0.13	−1.32	0.19
Schaefer400 + Subcortical	6.47	0.12	0.002	0.30	3.17	0.002	−0.13	−1.40	0.16
Total SAPS Score									
QC Threshold: All Scans < 50% Scrubbed									

Dependent Variable	Full Model			Diagnosis Effect			Similarity Index Effect		
fMRI Scrubbing Threshold									
Parcellation	**F**	**R^2**	***p***	**β**	**t**	***p***	**β**	**t**	***p***
Schaefer100 + Subcortical	7.72	0.13	<0.001	0.24	2.58	0.011	−0.23	−2.49	0.014
Schaefer200 + Subcortical	8.42	0.14	<0.001	0.24	2.63	0.010	−0.25	−2.74	0.007
Schaefer300 + Subcortical	8.26	0.14	<0.001	0.24	2.63	0.010	−0.25	−2.68	0.008
Schaefer400 + Subcortical	8.32	0.14	<0.001	0.25	2.70	0.008	−0.25	−2.70	0.008
QC Threshold: All Scans < 20% Scrubbed									
Schaefer100 + Subcortical	6.56	0.12	0.002	0.24	2.45	0.016	−0.22	−2.27	0.026
Schaefer200 + Subcortical	7.01	0.13	0.001	0.24	2.51	0.014	−0.23	−2.44	0.016
Schaefer300 + Subcortical	6.84	0.12	0.002	0.24	2.53	0.013	−0.23	−2.38	0.019
Schaefer400 + Subcortical	7.02	0.13	0.001	0.25	2.58	0.011	−0.23	−2.45	0.016
Disorganization Symptoms									
QC Threshold: All Scans < 50% Scrubbed									
Schaefer100 + Subcortical	5.97	0.05	0.016	*	*	*	−0.23	−2.44	0.016
Schaefer200 + Subcortical	7.51	0.07	0.007	*	*	*	−0.26	−2.74	0.007
Schaefer300 + Subcortical	8.77	0.08	0.004	*	*	*	−0.28	−2.96	0.004
Schaefer400 + Subcortical	6.22	0.11	0.003	0.19	2.01	0.047	−0.25	−2.64	0.010
QC Threshold: All Scans < 20% Scrubbed									
Schaefer100 + Subcortical	4.47	0.04	0.037	*	*	*	−0.21	−2.11	0.037
Schaefer200 + Subcortical	4.91	0.05	0.029	*	*	*	−0.22	−2.22	0.029
Schaefer300 + Subcortical	5.87	0.06	0.017	*	*	*	−0.24	−2.42	0.017
Schaefer400 + Subcortical	5.70	0.05	0.019	*	*	*	−0.23	−2.39	0.019
GAF Score									
QC Threshold: All Scans < 50% Scrubbed									
Schaefer100 + Subcortical	6.06	0.05	0.015	*	*	*	0.23	2.46	0.015
Schaefer200 + Subcortical	9.16	0.08	0.003	*	*	*	0.28	3.03	0.003
Schaefer300 + Subcortical	9.83	0.09	0.002	*	*	*	0.29	3.14	0.002
Schaefer400 + Subcortical	11.61	0.10	<0.001	*	*	*	0.31	3.41	<0.001
QC Threshold: All Scans < 20% Scrubbed									
Schaefer100 + Subcortical	4.83	0.05	0.030	*	*	*	0.22	2.20	0.030

Dependent Variable	Full Model			Diagnosis Effect			Similarity Index Effect		
fMRI Scrubbing Threshold									
Parcellation	**F**	**R^2**	***p***	**β**	**t**	***p***	**β**	**t**	***p***
Schaefer200 + Subcortical	7.67	0.07	0.007	*	*	*	0.27	2.77	0.007
Schaefer300 + Subcortical	8.46	0.08	0.004	*	*	*	0.28	2.91	0.004
Schaefer400 + Subcortical	10.34	0.09	0.002	*	*	*	0.31	3.22	0.002

Table is organized by type of symptom/functioning, quality control threshold (QC Threshold), and parcellation scheme (respectively). Beta values are standardized.

*Removed for being non-significant ($p > 00.05$).

BD = bipolar disorder, QC = quality control, SD = standard deviation, SZ = schizophrenia-spectrum disorder.