Published in final edited form as:
Biol Psychiatry. 2013 September 15; 74(6): 458–466. doi:10.1016/j.biopsych.2013.04.024.

Is Aberrant Functional Connectivity A Psychosis Endophenotype? A Resting State Functional Magnetic Resonance Imaging Study

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Abstract

Background—Schizophrenia and bipolar disorder share overlapping symptoms and risk genes. Shared aberrant functional connectivity is hypothesized in both disorders and in relatives.

Methods—We investigated resting state functional MRI (fMRI) in 70 schizophrenia and 64 psychotic bipolar probands, their respective first-degree relatives (N = 70 and 52) and 118 healthy subjects. We used independent component analysis (ICA) to identify components representing various resting state networks and assessed spatial aspects of functional connectivity within all networks. We first investigated group differences using five-level, one-way analysis of covariance (ANCOVA), followed by post-hoc t-tests within regions displaying ANCOVA group differences

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This data was presented at the 14th International Congress On Schizophrenia Research, Grand Lakes, Florida, 21-25 April, 2013.

Financial Disclosures

John Sweeney is a consultant to Pfizer and has a research grant from Janssen. Carol Tamminga has the following disclosures to make: Intracellular Therapies (ITI, Inc.) - Advisory Board, drug development >$10,000; PureTech Ventures- Ad Hoc Consultant <$10,000; Eli Lilly Pharmaceuticals – Ad Hoc Consultant < $ 10,000; Sunovion – Ad Hoc Consultant < $10,000; Astellas – Ad Hoc Consultant < $10,000; Cypress Bioscience – Ad Hoc Consultant < $10,000; Merck – Ad Hoc Consultant < $10,000; International Congress on Schizophrenia Research - Organizer; Unpaid volunteer; NAMI – Council Member; Unpaid Volunteer; American Psychiatric Association - Deputy Editor >$10,000.

Conflicts of Interest:

Other authors report no biomedical financial interests or potential conflicts of interest.

and correlation of such functional connectivity measures with symptom ratings to examine clinical relationships.

Results—Seven different networks revealed abnormalities (five-level one-way ANCOVA, family-wise error correction $p < 0.05$): (A) fronto-occipital, (B) midbrain/cerebellum, (C) frontal/thalamic/basal ganglia, (D) meso/paralimbic, (E) posterior default mode network, (F) fronto-temporal/paralimbic and (G) sensorimotor networks. Abnormalities in networks B and F were unique to schizophrenia probands only. Furthermore, abnormalities in networks D and E were common to both patient groups. Finally, networks A, C and G showed abnormalities shared by probands and their relative groups. Negative correlation with Positive and Negative Syndrome Scale (PANSS) negative and positive scores were found in regions within network C and F respectively, and positive correlation with PANSS negative scores was found in regions in network D among schizophrenia probands only.

Conclusion—Schizophrenia, psychotic bipolar probands and their relatives share both unique and overlapping within-network brain connectivity abnormalities, revealing potential psychosis endophenotypes.

Keywords

Bipolar; endophenotype; relatives; resting state; schizophrenia; within-network connectivity

Introduction

Whether schizophrenia and bipolar disorder share important features or are independent disorders is the subject of perennial debate [1,2,3]. Traditionally, schizophrenia (SZ) is viewed as a chronic psychotic disorder with altered perception, cognition, thought processes and behaviors while bipolar (BP) illness is an episodic mood disorder characterized by discrete episodes of mania and depression [4]. However, psychotic features occur in 60% of bipolar I patients and both disorders share other clinical [5,6], neurocognitive [7] and neuroanatomic [8] characteristics. Their common features suggest overlapping genetic risk factors for SZ and BP [9], as confirmed by studies including genome-wide association analysis (GWAS) that revealed overlapping shared genetic determinants [10,11]. In addition family and genetic linkage studies support shared genetic risk [1,12]. Consistent with the above, neurocognitive, neurophysiological and neuroanatomic abnormalities [13,14,15,16,17] are seen in SZ and BP, and consistent with shared familial risk, unaffected relatives show similar illness-related dysfunctions to those detected in affected probands [11,18,19]. However, other studies show neuroanatomic distinctions between schizophrenia and bipolar disorder [8], revealing findings specific to SZ [20,21] or BP [22], or that SZ show severe neurocognitive deficits compared to BP [23,24]. Some of these differences may be ascribed to different medications used to treat the two disorders [25].

Resting state functional MRI (rs-fMRI) is used extensively to assess regional interactions of brain circuits, including studies of clinical populations. Several analytic approaches are used to assess rs-fMRI data [26,27,28]; all focus on temporally coherent fMRI time-courses (TCs) that reflect functionally relevant activity [26] and have specific strengths and weaknesses. Some methods utilize time courses derived from a pre-defined voxel or region of interest; such functional brain connectivity results can be biased by the selection of seed voxel or region [29]. In contrast, independent component analysis (ICA) is a data driven, multivariate method that identifies spatially independent components with strongly temporally coherent hemodynamic signal change over time [26,30] thus defining brain regions that are functionally connected [31,32,33]. These spatially independent components may exhibit temporal dependency (i.e. temporal correlation across components), even when they are weaker than those between regions within a given component [34,35]. Thus, ICA

allows one to assess functional connectivity (FC) flexibly, either (a) comparing voxel-wise spatial differences within a component, or (b) evaluating temporal connectivity across pairs of spatially independent ICA components, often termed functional network connectivity (FNC) [36].

In a prior study using the current dataset, we reported the results of pairwise FNC across components [35]. In the current study we focused our analysis on comparison of voxel-wise FC findings within each component in a distinct but complementary manner to our previous analysis. One aim of the present study was to detect whether aberrant functional connectivity in delineated networks would be specific to SZ or BP disorder, or shared by SZ and BP probands. We hypothesized that shared FC abnormalities would be evident in some brain networks, such as the default mode network ((DMN [37]) while disease-specific differences would manifest in circuits associated with emotion and/or cognitive function. Furthermore, we hypothesized that some abnormal FC findings would be shared by both probands and their relatives, constituting potential psychosis endophenotypes.

Methods and Materials

Subjects

The study sample consisted of 118 healthy controls (HC, age 21-66), 70 SZ (age 17-61) and 64 BP probands (age 17-60), first-degree relatives of person with schizophrenia (70 SZ-Relative, age 16-63) and bipolar disorder (52 BP-Relative, age 16-63) who participated in the study at Hartford Hospital as part of the Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study [38]. Details of the study population are reported elsewhere [38]. The current study population contains subsample of B-SNIP subjects whose demographic information is shown in Table 1. All probands met Structured Clinical Interview for DSM IV (SCID, [39,40]) criteria for SZ or BP I disorder with psychosis [40]. Clinical symptom determinations and structured clinical diagnostic interviews [40] were conducted by trained clinical raters and senior diagnosticians; inter-rater reliability was > . 90. Additionally, on the day of scanning probands were assessed with the Positive and Negative Syndrome Scale (PANSS), Montgomery-Asberg Depression Rating Scale (MADRS), Young Mania Scale (YMS) and Brief Assessment of Cognition in Schizophrenia (BACS). These scores were available in subset of probands only (PANSS: 60 SZ, 48 BP;; MADRS: 30 SZ; 25 BP; YMS: 32 SZ; 27 BP; BACS: 32 SZ; 27 BP). All probands were clinically stable with consistent medication doses for ≥ 4 weeks; [mood stabilizers (19 SZ; 44 BP), typical antipsychotics (7 SZ; 2 BP), atypical antipsychotics (58 SZ; 36 BP), benzodiazepines (13 SZ; 11BP), anticholinergics (11 SZ; 4 BP), SSRIs (18 SZ; 16 BP), tricyclics or monoamine oxidase inhibitors (9 SZ; 13 BP), and psychostimulants (2 SZ; 4 BP)]. Relatives were free of DSM-IV Axis 1 psychopathology (but could posses non-psychotic Axis 1 disorders, e.g. major depression, phobia or anxiety disorder) and not taking any antipsychotic medications. After a complete description of the study, all participants gave written informed consent approved by Hartford Hospital and Yale University.

All bipolar subjects had a prior psychotic episode based on criteria of Strasser et al [41]. Psychotic symptoms and current manic or depressive episodes of all probands were assessed using SCID by clinicians. Additionally, psychotic symptoms were assessed with the positive subscale of the PANSS [42], comprising delusions, conceptual disorganization, hallucinations and suspiciousness/persecutory items. 50% of the samples had current psychotic symptomatology (based on scores of ≥ 3 on any PANSS positive subscale). Also, BP probands were assessed for current manic and depressive episodes using MADRS > 32 and YMS > 20, [43,44] respectively; consequently 3 of 64 BP subjects met criteria for major depressive episode and 8 of 64 met criteria for manic episode. The Structured Interview for Disorders of Personality [45] was used to assess presence or absence of DSM-IV-TR Cluster

A personality disorders; only 3 SZ and 4 BP relatives so qualified. Relatives with cluster A personality disorder were retained in our analysis.

MRI Data Acquisition and Pre-Processing

FMRI images were acquired at the Institute of Living, Hartford, CT, USA, on a Siemens Allegra 3T system. Functional scans were acquired with gradient-echo echo planar imaging with the following parameters: repetition time (TR) = 1.5 sec, echo time (TE) = 28 msec, flip angle = 65°, voxel size = 3.4 mm × 3.4 mm × 5 mm, slice thickness = 5 mm, number of slices = 30. A custom-built head coil cushion was used to minimize head motion. During data acquisition subjects were asked to fixate on a cross presented on the monitor, remain alert with eyes open and keep their head still. A total of 210 time points were acquired, out of which six initial images were discarded. Data pre-processing used SPM2 software (http://www.fil.ion.ucl.ac.uk/spm2/). Images were realigned using INRIAlign [46]. Each participant's interscan motion were assessed with translation/rotation and an exclusion criteria (translation >3 mm, rotation >3°; in each direction) was set. No subjects met exclusion criteria. Data were then spatially normalized to Montreal Neurological Institute (MNI) space, resampled to 2 mm × 2 mm × 2 mm voxels and spatially smoothed using a 9 mm × 9 mm × 9mm full width at half-maximum Gaussian kernel.

Group ICA

The temporally distinct resting state components were determined with all subjects (118 HC, 64 BP probands, 70 SZ probands, 54 bipolar relatives (BP-Relative) and 70 schizophrenia relatives (SZ-Relative)) using the group ICA toolbox (http://mialab.mrn.org/software/gift). Dimension estimation to determine number of components were estimated using modified minimum description length (MDL) algorithm [26,34,47,48] that accounts for spatial correlation [48]. The number of independent components estimated among across all subjects in average was 19. The stability of independent components was investigated with using ICASSO [49]; all components were highly stable ($Iq > 0.95$). Data were then reduced using principal components analysis (PCA), followed by independent component estimation with the infomax algorithm [30]. The IC's spatial maps and time courses were back-reconstructed for each subject using a method based on PCA compression and projection [26,50] and image distribution centered to a mode of zero [51].

Identifying resting state networks (RSNs)

To identify valid RSNs, network components were examined visually to determine obvious artifacts and correlated spatially with a-priori probabilistic gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) templates using multiple regressions. Components with low association ($|\beta| < 0.5$) with GM and high association ($|\beta| > 2$) with WM and CSF were identified as artifacts. Statistical maps were created with voxel-wise one sample t-tests for each component and thresholded with t-value > 20. Three ICA components were regarded as noise, leaving 16 ICs as RSN's of interest, that were considered for further analysis, as illustrated in Supplement: Figure S1. The likely function of each network was determined by voxel-wise spatial correlation with functional maps produced by Laird et al [52] as shown in Supplement: Table S1.

Statistical comparisons

Spatial maps of all diagnostic groups were entered into a five-level one-way ANCOVA in SPM8 (http://www.fil.ion.ucl.ac.uk/spm8/) for each of the 16 networks separately, with age and sex as covariates. To ensure only highly-connected regions were analyzed, we used an explicit mask created with voxel-wise one-sample t-test ($t > 20$). The significance level for each network was adjusted for $p < 0.05$ (family wise error (FWE) correction). Regions

showing main effect of group difference in ANCOVA model were further evaluated by pairwise t-test between probands plus their relatives and HCs ($p < 0.0125$, accounting for 4 pairwise comparisons). Mean loading coefficient of all voxels within the region showing group difference in ANCOVA model was extracted into SPSS v19.0 (SPSS Inc., Chicago, Illinois) for post-hoc t-test.

Relationships to PANSS symptom scores

Bivariate correlations (limited to aberrant networks) were conducted between mean loading coefficients in regions showing a main effect of group difference and PANSS positive, negative and general scores in both groups separately. The significance level for each network was adjusted for $p < 0.05$/number of regions showing main effect of group difference for each network.

Results

Among the 16 networks of interest, seven (fronto-occipital, cerebellum/midbrain, frontal/thalamic/basal ganglia, meso/paralimbic, posterior default mode, fronto-temporal/paralimbic and sensorimotor networks) showed significant group differences (ANCOVA F (4, 362), FWE-corrected $p < 0.05$); these networks and their component regions are summarized in Table 2 and shown in Figure 1.

Mean z-scores among all voxels within regions showing main effects of group difference were calculated and averaged across each group. Figure 2 shows bar graphs representing the mean loading coefficient of HC, BP, SZ, BP-Relative and SZ-Relative for all regions within each component.

Fronto-occipital network (A)

ANCOVA group main effects showed significant differences in left cuneus and right lingual gyrus, with peak F (4, 362) = 9.74 and 9.46 respectively (Figure 1A). Post-hoc t-test revealed that both BP, SZ probands showed decreased connectivity in cuneus (cluster A(ii)). Also, these abnormalities were shared by both BP-Relative and SZ-Relative in cuneus (Table 3, figure 2 A(ii)). Furthermore, only SZ probands showed decreased connectivity in right lingual gyrus (cluster A(i)) (Table 3, figure 2 A(i)).

Cerebellum/midbrain network (B)

ANCOVA group main effects showed significant differences in left brainstem (cluster B(i)) with peak F (4, 362) = 8.57 and right brainstem (cluster B(ii)) with peak F (4, 362) = 7.86 (Figure 1B). Post hoc t-test revealed that SZ probands showed decrease in connectivity right brainstem only when compared to HC (Table 3, Figure 2 B(ii)). Post-hoc t-test did not reveal any group differences in left brainstem (Table 3, Figure 2 B(i)). Also, BP probands did not show abnormalities in this network.

Frontal/thalamic/basal ganglia network (C)

ANCOVA group main effects showed significant differences in right thalamus (cluster C(i)) with peak F (4, 362) = 9.08 and right putamen (cluster C(ii)) with peak F(4, 362) = 7.73 (Figure 1C). Post-hoc t-test revealed both BP, SZ probands and their relatives showed decrease in connectivity in right thalamus (Table 3, Figure 2 C(i)). Furthermore SZ and SZ-Relative showed decreased connectivity in right putamen when compared to HC (Table 3, Figure 2 C(ii)). BP probands did not show abnormality in right putamen; however BP-Relative when compared to HC showed decrease in connectivity. Exploratory analysis with the Caucasian sample only revealed that all four groups (BP, SZ, BP-Relative and SZ-

Relative) showed the same thalamus abnormality but only SZ and SZ-Relatives showed the putamen abnormality. Thus putamen results must be considered cautiously.

Meso/paralimbic network (D)

ANCOVA group main effects showed significant differences in left superior temporal gyrus (STG)/Uncus (cluster D) with peak F (4, 362) = 9.59 (Figure 1D). Post-hoc t-test showed both BP and SZ probands when compared with HC showed increase in connectivity (Table 3, Figure 2D). No abnormalities were seen in relatives.

Posterior default mode network (E)

ANCOVA group main effects showed significant differences in posterior cingulate gyrus (cluster E) with F (4, 362) = 8.2 (Figure 1E). Post-hoc t-test revealed BP and SZ probands showed decrease in connectivity when compared with HC (Table 3, Figure 2E). No abnormalities were seen in relatives.

Fronto-temporal/paralimbic network (F)

ANCOVA showed significant difference in main effect of group in the left medial temporal gyrus (MTG)/inferior temporal gyrus (ITG) (cluster F) with peak F (4, 362) = 11.59 (Figure 1F). Post-hoc t-test showed only SZ probands showed increase in connectivity when compared with HC (Table 3, Figure 2F). No abnormalities were seen in BP probands in this network.

Sensorimotor network (G)

ANCOVA revealed main effect of group differences in right superior frontal gyrus (SFG)/ medial frontal gyrus (MFG) (cluster G(i)) with peak F (4, 362) = 9.3, right MFG/right precentral gyrus (cluster G(ii)) with peak F (4, 362) = 12.7 and right supplementary motor area (SMA)/right SFG (cluster G(iii)) with peak F (4, 362) = 9.3 (Figure 1G). BP, SZ probands plus their relatives showed increase in connectivity in SFG/MFG (cluster G(i)) when compared with HC (Table 3, Figure 2 G(i)). Only SZ probands showed increased connectivity in right MFG/precentral gyrus (cluster G(ii)) and, right SMA/SFG (cluster G(iii)) when compared to HC (Table 3, Figure 2 G(ii) and G(iii) respectively).

An exploratory analysis removing subjects with cluster A personality disorders from sample was carried out. Results remained the same as reported.

Relationship between connectivity measures and PANSS scores

FC measures in component C, cluster C(ii) were correlated negatively with PANSS negative scores in SZ only (r = -0.3, p = 0.01). Furthermore, FC in component D positively correlated with PANSS negative score in SZ only (r = 0.3, p = 0.02). PANSS positive score were negatively correlated with network F's FC measures (r = -0.3, p = 0.01). Also, bivariate correlation between FC and MADRS, YMS and BACS composite Z-score was done as an exploratory analysis (Supplement: Table S2).

Discussion

In contrast to our prior study in this population that examined pairwise correlational abnormalities across networks using functional network connectivity [35], the current investigation used multi-variate ICA-based method to assess functional connectivity within all plausible RSNs, in psychotic bipolar and schizophrenia probands along with their respective first degree relatives and HCs. This approach delineated both common and unique

within-network FC abnormalities in probands and determined which of these were detectable in their relatives, thereby examining their possible genetic origin.

The numbers of IC decomposed is highly debated. Recently, studies have adopted high-order ICA to decompose refined separation of brain regions [31,53,54]. However, low order ICAs are used extensively in previous studies and components are highly reproducible across studies [34,52,55,56]. In this current study low order ICA (determined by MDL [48]) was chosen so as to be able to compare networks with those in other ICA studies. Of 16 networks, (all of which resembled previously identified networks in other ICA resting state studies [34,52,55,56]), seven showed abnormal functional connectivity. In three such networks, FC abnormalities were shared between both probands and their relatives, in addition to abnormalities that were common to both probands only and/or unique to given proband group. These results suggest SZ and BP disorder possess some common and disorder specific abnormalities (SZ only in current analysis). The abnormalities shared by both patient groups and their relatives are likely underpinned by genetic factors.

In this current study, confounding effects of medication on aberrant FC could not be assessed as we did not collect probands at a drug free baseline. A few studies have suggested that medications alter FC in SZ probands [57,58]. To our knowledge, this is the first within-network study to compare BP, SZ along with their first degree relatives with HC comprehensively across multiple RSNs.

Aberrant functional connectivity unique to SZ probands

The fronto-temporal/paralimbic network (F) was abnormal in SZ probands, who showed increased connectivity in left medial temporal gyrus (MTG)/inferior temporal gyrus (ITG) (cluster F). The abnormal fronto-temporal FC in SZ might be due to the inability of prefrontal cortex to control temporal lobe activity [59]. A previous seed-based FC study in SZ showed abnormal connectivity in left ITG, consistent with our findings [60]. SZ probands also showed decreased connectivity in pons (cluster B(ii)) in the cerebellum/midbrain (B) network. Prior studies reported dysfunction of pons to be associated with SZ [61,62]. However, the role of pons in SZ is not well established, thus functional dysconnectivity in pons in SZ must be looked into cautiously. Further studies are required for validation and replication. In contrast, no circuit showed abnormalities unique to BP probands.

Aberrant functional connectivity shared by SZ and BP probands only

Both meso/paralimbic (D) and posterior DMN (E) networks exhibited abnormal functional connectivity common to both SZ and BP probands. In network D, both SZ and BP probands showed increased functional connectivity in left STG/Uncus (cluster D). The limbic system is involved in emotional regulation/processing and memory. A prior study reported decreased activation for SZ but increased activation for BP in left STG in response to emotional prosody [63]. The direction of change in activation for SZ reported in that study was opposite in direction compared with our results; however that study used task-based as opposed to resting state fMRI, a likely reason for difference in results. Also, the current study comprised a much larger sample size. Thus, our results implicate abnormal emotional regulation/processing as common to both SZ and psychotic BP disorder.

Both the probands showed abnormal functional connectivity in the posterior DMN (Network E). DMN is most often identified as comprising brain regions active during the resting state and suppressed during task engagement [37]. Both BP and SZ probands showed decreased functional connectivity in right precuneus/cingualte gyrus (cluster E). A recent study revealed DMN to have a key role in distinguishing BP and SZ patients from each other and

from HC [53]. Earlier studies reported overactive DMN [53,64] in SZ. Although those studies derived DMN from auditory oddball task data as opposed to our resting state, results were consistent which reported BP and SZ to show increased connectivity in cingulate gyrus [53].

Aberrant functional connectivity shared by SZ, BP probands and their relatives

As risk genes are shared by probands and their first-degree relatives, we predicted that some fMRI network abnormalities common to both patient groups would be shared by their relatives but not healthy controls, representing potential risk endophenotypes. We detected common abnormalities across all four groups in three such RSNs, namely fronto-occipital (A), frontal/thalamic/basal ganglia (C) and sensorimotor (G) networks.

We found decreased connectivity in left cuneus (cluster A(ii)) in the fronto-occipital network across all four groups. This circuit has been implicated in higher-order visual processing [53,65], which is reported to be impaired both in BP and SZ [66,67]. A prior study reported early visual sensory deficits in SZ and their first-degree relatives [68]. Another previous study reported deficits in visuospatial abilities in BP and their first-degree relatives [69] indicating it as a neurocognitive endophenotype. Thus aberrant functional connectivity in visual processing network might constitute neurocognitive endophenotype for both SZ and psychotic BP. Also, we found abnormal functional connectivity in the frontal/thalamic/basal ganglia network (C) in all four groups. This network has been linked as transitional circuit linking cognition and emotion/interoception [52]. All four groups showed decreased connectivity in right thalamus (cluster C(i)). Thalamus is considered as a relay station between many subcortical regions and cerebral cortex. Among other functions, thalamus has been implicated in emotion processing [70] and has been reported to show lack of connectivity in both SZ and BP probands [71,72,73]. Prior studies suggest that abnormal functional connectivity in thalamus might be attributable to shared risk genes in SZ and BP disorder [74]. In addition, we found abnormal functional connectivity in the sensorimotor network (G) in all four groups who showed increased connectivity in SFG/MFG area. Interestingly results in SFG/MFG (cluster G(i)) indicate greater FC abnormality in SZ-Relative and BP-Relative than their probands when compared to HC. One would expect relatives to be less abnormal than patient groups. The likely explanation might be the abnormality is attenuated by current medication (e.g. Lithium) in proband groups even though abnormality is shared by both probands and their relatives. This network has been reported to show abnormality in both BP and SZ in prior studies [75,76,77]. The aberrant FC in thalamic and SFG/MFG regions that are common to BP, BP-Relative, SZ and SZ-Relative might represent potential psychosis endophenotypes.

Comparison to our prior FNC study [35]

In this current within-network analysis, compared to healthy controls, persons with SZ or BP and their relatives all showed reduced connectivity in networks A and C and increased connectivity in network G. Resting state network F showed increased connectivity in SZ probands only. In our prior across-network (FNC) study [35] we found abnormal inter-network connectivity in C-G and C-F. C-G showed reduced inter-network connectivity in SZ along with BP-Relative and SZ-Relative while C-F showed increased inter-network connectivity in BP probands only. In addition we detected inter-network disconnectivity between network A and anterior DMN (no abnormality in this network was reported in current within-component analysis). Our current results suggest that within-network abnormalities in A, C, F and G might influence the across-network disconnectivity we observed previously.

Advantages and Limitations

The present study had several advantages over prior, similar investigations: 1) the largest single-site resting state fMRI study of these diagnostic groups, 2) global analysis including all RSNs rather than limited to *a priori* networks (e.g., DMN), 3) we directly compared RSNs in SZ and BP, and 4) examined whether disorder-specific abnormalities also occurred in relatives to explore potential endophenotypic status. This study also had limitations: 1) it was limited to comparing spatial maps and not the spectral power of components and 2) medications taken by probands may have influenced our results and confounded interpretation. Because relatives were not taking antipsychotic medications however, only proband comparisons could be influenced by such drugs. Several studies have indicated that medications can alter functional connectivity in SZ probands [57,58], 3) The numbers of relatives with cluster A personality disorders was small, precluding any analysis of psychosis continuum effects.

Conclusion

We identified several abnormal resting state networks unique to SZ and other abnormalities shared by both SZ and BP disorders including a subset shared by both proband groups and their first-degree relatives. Functional connectivity anomalies shared by both proband groups and their relatives constitute candidate psychosis endophenotypes. Also, such abnormalities might help suggest the pathophysiology of the disorder(s) and identify genetic effects common to probands and their relatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was funded by NIMH grants R37MH43375 and R01MH074797 (GP), the von Humboldt Foundation & NIMH MH077862 (JS), NIH/NIBIB: 2R01 EB000840 & NIH/NCRR: 5P20RR021938 (VDC), NIMH MH 78113 (MSK), NIMH MH077851 to Carol Tamminga, NIMH5R01 MH077945-03 to Gunvant Thaker, Carol Tamminga, Godfrey Pearlson, Matcheri Keshavan, and John Sweeney.

Godfrey Pearlson and Sabin Khadka have had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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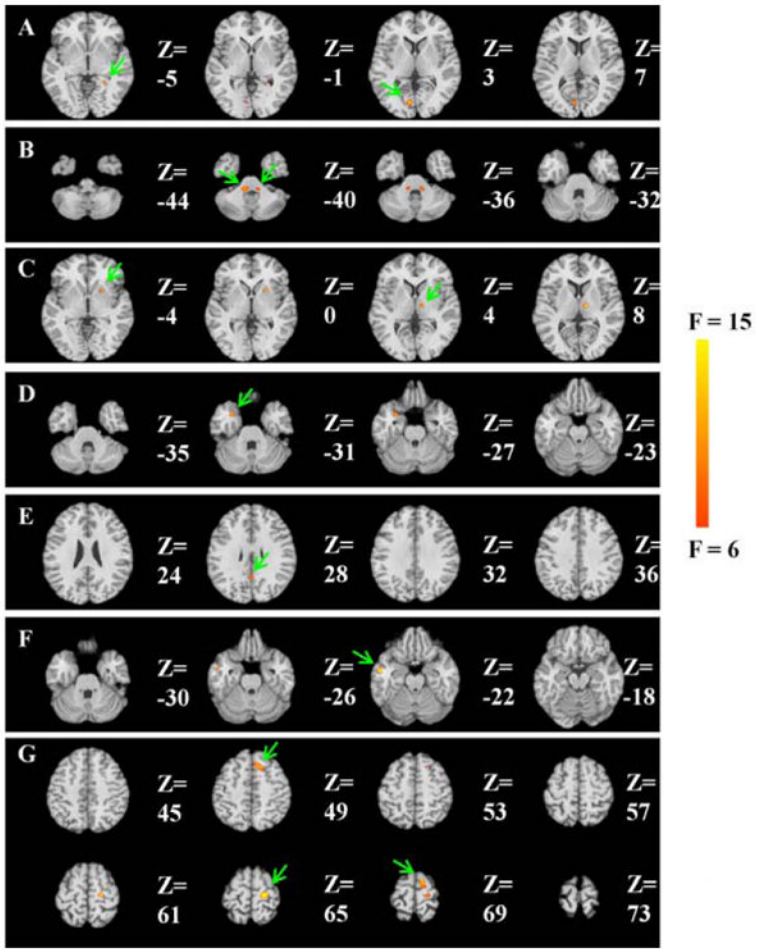

Figure 1.

One-way ANCOVA main effect of group difference ($p < 0.05$, Family-wise error corrected, cluster threshold $k = 10$ voxels): (A) fronto-occipital, (B) cerebellum/midbrain, (C) fronto-limbic, (D) meso/paralimbic, (E) posterior default mode network, (F) fronto-temporal/ paralimbic and (G) sensorimotor network. All the brain slices are in transverse view with their corresponding MNI slice in mm.

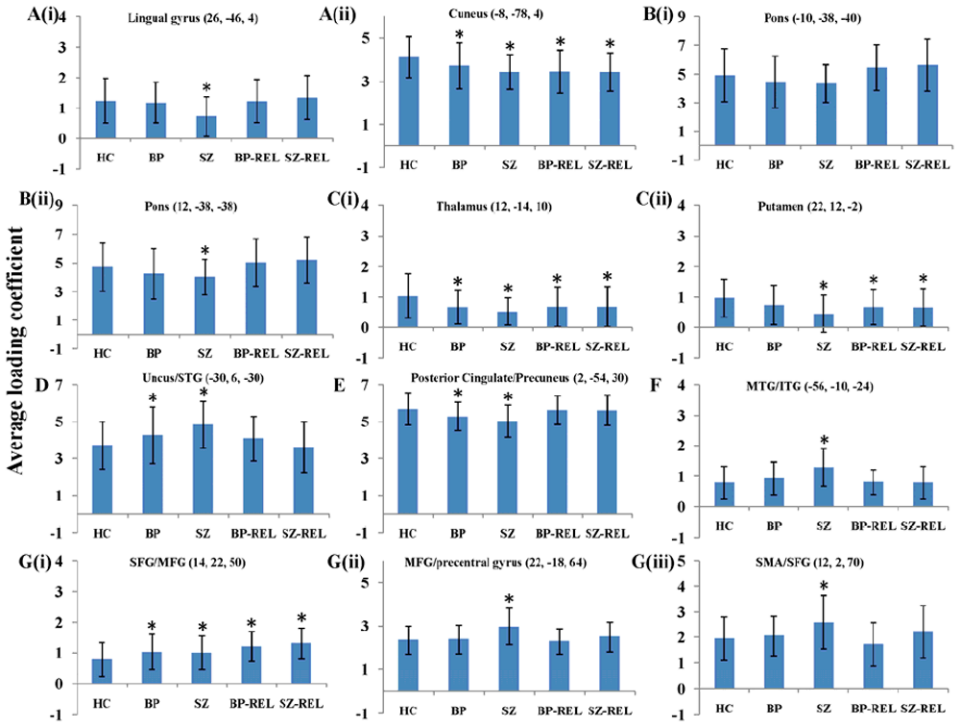

Figure 2.

Bar plot of mean loading coefficients in HC, BP, SZ, BP-Relative (BP-REL) and SZ-Relative (SZ-REL) in fronto-occipital network: A(i) lingual gyrus with peak at (26, -46, -4), A(ii) cuneus with peak at (-8, -78, 4), cerebellum/midbrain network: B(i) left pons with peak at (-10, -38, -40), B(ii) right pons with peak at (12, -38, -38), fronto-limbic network: C(i) right thalamus with peak at (12, -14, 10), C(ii) right putamen with peak at (22, 12, -2), meso/paralimbic network: (D) uncus/superior temporal gyrus with peak at (-30, 6, -30), posterior default mode network: (E) posterior cingulate gyrus/precuneus with peak at (2,-54, 30), fronto-temporal/paralimbic network: (F) medial temporal gyrus/inferior temporal gyrus with peak at (-56, -10, -24), sensorimotor network: G(i) superior frontal gyrus/medial frontal gyrus with peak at (14, 22, 50), G(ii) medial frontal gyrus/precentral gyrus with peak at (22, -18, 64) and G(iii) supplementary motor area/superior frontal gyrus with peak at (12, 2, 70). Coordinates reported here are in MNI. Error bar represents standard error of mean. *Groups with significant aberrant functional connectivity when compared to HC ($p < 0.0125$). BP: Bipolar probands, SZ: Schizophrenia probands, BP-REL: Relatives of bipolar probands, SZ-REL: Relatives of schizophrenia probands, HC: Healthy controls.

Table 1

Demographic and clinical information.

	HC N=118		BP N=64		SZ N=70		BP-Relative N=52		SZ-Relative N=70		Statistics	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F**	**p**
Age(yrs)	36.4	10.8	35.1	11.2	37.4	12.8	40.6	13	40.8	15.6	2.4	0.03*
PANSS	-	-	N=48	-	N=60	-	-	-	-	-	-	-
Positive	-	-	13.27	4.5	16.02	5.5	-	-	-	-	-	-
Negative	-	-	11.8	4.9	16.32	5.9	-	-	-	-	-	-
General	-	-	27.7	6.9	32.7	7.8	-	-	-	-	-	-
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	χ^2	**p**
Sex												
Male	55	46.6	35	54.6	43	61.4	18	34.6	26	37.1	13.6	0.01
Female	63	53.3	29	45.3	27	38.5	34	65.3	44	62.8		
Ethnicity												
Caucasian	78	66.1	48	75	51	72.8	46	88.4	52	74.2	20.9	0.05
Hispanic	13	11.0	6	9.3	5	7.1	1	1.9	1	1.4	-	-
African-American	21	17.8	5	7.8	12	17.1	4	7.6	13	18.5	-	-
Asian	6	5.08	0	0	1	1.4	1	1.9	2	2.8	-	-

HC: Healthy controls; BP: Bipolar; SZ: Schizophrenia; BP-Relative: Bipolar relatives; SZ-Relative: Schizophrenia relatives subjects; SD: standard deviation; PANSS: Positive and Negative and Syndrome Scale.

*Post-hoc t-test revealed non-significant p-values when SZ, BP, SZ-Relative, BP-Relative when compared to HC.

Table 2

Peak F-values in region showing main effect of group difference, its corresponding MNI coordinated in mm and volume in mm^3.

IC Network	Cluster	Volume (mm^3)	Regions (L/R)	Peak (x,y,z)	F-value
Fronto-occipital (A)	**A(i)**	152	Lingual gyrus (R)	(26, -46, -4)	9.7
	A(ii)	536	Cuneus (L), Lingual gyrus (L)	(-8, -78, 4)	9.4
Midbrain/cerebellum (B)	**B(i)**	456	Brainstem (L), Pons (L)	(-10, -38, -40)	8.5
	B(ii)	248	Brainstem (R), Pons (R)	(12, -38, -38)	7.8
Frontal/thalamic/basal ganglia (C)	**C(i)**	200	Thalamus (R)	(12, -14, 10)	9.1
	C(ii)	88	Putamen (R)	(22, 12, -2)	7.7
Meso/paralimbic (D)	**D**	320	STG (L), Uncus (L)	(-30, 6, -30)	9.5
Posterior default mode (E)	**E**	176	Cingulate gyrus (L,R), Precuneus (L/R)	(2, -54, 30)	8.2
Fronto-temporal/paralimbic (F)	**F**	528	MTG (L), ITG (L)	(-56, -10, -24)	11.5
Sensorimotor (G)	**G(i)**	648	SFG (R), MFG (R)	(14, 22, 50)	9.3
	G(ii)	800	Precentral gyrus (R), MFG (R)	(22, -18, 64)	12.7
	G(iii)	384	SMA (R), SFG (R)	(12, 2, 70)	9.3

L/R: Left/Right; STG: superior temporal gyrus; MTG: medial temporal gyrus; ITG: inferior temporal gyrus; SFG: superior frontal gyrus; MFG: medial frontal gyrus; SMA: supplementary motor area. Cluster column corresponds to regions within network as shown in figure 2.

Table 3

Post-hoc pairwise group comparison in regions showing main effect of group difference. Only regions with significant differences ($p < 0.125$) are reported.

IC Network	Results	Cluster	Regions (L/R)	t-value
Fronto-occipital	HC>BP	A(ii)	Cuneus (L), Lingual gyrus (L)	2.5
	HC>SZ	A(i)	Lingual gyrus (R)	4.61
		A(ii)	Cuneus (R), Lingual gyrus (R)	5.9
	HC>BP-Relative	A(ii)	Cuneus (L), Lingual gyrus (L)	3.9
	HC>SZ-Relative	A(ii)	Cuneus (L), Lingual gyrus (L)	4.4
Midbrain/Cerebellum	HC>SZ	B(ii)	Pons (R)	3.02
Frontal/thalamic/basal ganglia	HC>BP	C(i)	Thalamus (R)	3.3
		C(ii)	Putamen (R)	2.3
	HC>SZ	C(i)	Thalamus (R)	5.1
		C(ii)	Putamen (R)	5.5
	HC>BP-Relative	C(i)	Thalamus (R)	2.9
		C(ii)	Putamen (R)	2.9
	HC>SZ-Relative	C(i)	Thalamus (R)	2.9
		C(ii)	Putamen (R)	2.9
Meso/paralimbic	HC<BP	D	STG/Uncus (L)	2.5
	HC<SZ	D	STG/Uncus (L)	5.7
Posterior default mode	HC>BP	E	Cingulate Gyrus (L/R), Precuneus (L/R)	3.04
	HC>SZ	E	Cingulate Gyrus (L/R), Precuneus (L/R)	4.9
Fronto-temporal/paralimbic	HC<SZ	F	MTG (L), ITG (L)	5.8
Sensorimotor	HC<BP	G(i)	SFG (R), MFG (R),	-2.8
	HC<SZ	G(i)	SFG (R), MFG (R),	-2.6
		G(ii)	Precentral (R), MFG (R)	-5.66
		G(iii)	SMA (R), MFG (R)	-4.6
	HC<BP-Relative	G(i)	SFG (R), MFG (R)	-4.7
	HC<SZ-Relative	G(i)	SFG (R), MFG (R)	-6.5

All abbreviations represent same as in table 2.