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Differences in resting-state fMRI functional network connectivity between schizophrenia and psychotic bipolar probands and their unaffected first-degree relatives

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Abstract

Background—Schizophrenia and bipolar disorder share overlapping symptoms and genetic etiology. Functional brain dysconnectivity is seen in both disorders.

Methods—We compared 70 schizophrenia and 64 psychotic bipolar probands, their respective unaffected first-degree relatives (N= 70 and 52) and 118 healthy subjects, all group age-, sex- and ethnicity-matched. We used functional network connectivity (FNC) analysis to measure differential connectivity among 16 fMRI RSNs. First, we examined connectivity differences between probands and controls. Next, we probed these dysfunctional connections in relatives for potential endophenotypes. Network connectivity was then correlated with PANSS scores to reveal clinical relationships.

Results—Three different network pairs were differentially connected in probands (FDR-corrected $q < 0.05$) involving 5 individual resting-state networks: (A) Fronto/Occipital, (B) anterior Default Mode/Prefrontal, (C) Meso/Paralimbic, (D) Fronto-Temporal/Paralimbic & (E) Sensory-motor. One abnormal pair was unique to schizophrenia, (C-E), one unique to bipolar, (C-D) and one (A-B) shared. Two of these 3 combinations (A-B, C-E) were also abnormal in bipolar relatives, but none in schizophrenia relatives (non-significant trend for C-E). The Paralimbic circuit (C-D), that uniquely distinguished bipolar probands, contained multiple mood-relevant regions. Network relationship C-D correlated significantly with PANSS negative scores in bipolar probands and A-B was correlated to PANSS positive and general scores in schizophrenia.

Conclusions—Schizophrenia and psychotic bipolar probands share several abnormal RSN connections, but there are also unique neural network underpinnings between disorders. We identified specific connections and clinical relationships that may also be candidate psychosis endophenotypes, although these do not segregate straightforwardly with conventional diagnoses.

Keywords

resting state; default mode; schizophrenia; bipolar; functional connectivity; gene; relatives

Schizophrenia (SZ) and bipolar disorder (BP) are ostensibly separate clinical entities with distinct clinical courses and outcomes, but substantial overlap in phenomenology (1), cognition (2-4), brain structure (5-8), brain function (9, 10) and disease risk genes (11-14), especially for SZ and the psychotic subtype of BP (5-8). Approximately 60% of Bipolar I patients display psychotic symptoms (15, 16), suggesting that the psychosis domain represents a useful starting point to compare commonalities and differences between these disorders. Similarities may originate in similarly disturbed neurophysiology, (17, 18).

Both disorders are heritable. Large meta-analytic linkage studies based on clinical SZ and BP phenotypes report several overlapping genetic risk loci (12, 13, 19). SZ and affective psychoses co-occur within kindreds, suggesting shared familial risk, consistent with shared genes conferring risk for both disorders (11, 20, 21), again especially for SZ and psychotic BP (15, 22). Finally, psychotic symptoms aggregate familially in BP (23). Thus, some disease risk genes and associated physiologic processes appear common across disorders; others may be unique.

If genetic factors are associated with neurophysiological dysfunction in both illnesses, one would anticipate both common aberrant brain function and illness-specific impairment. Schizophrenia endophenotype research has identified several putative functional and anatomical neural risk markers. Endophenotypes (24) are operationalized as measurable, trait-related, heritable, illness-associated biological features, co-segregating with disease in families and over-represented in unaffected relatives of probands compared to the general population (25-27). Because illness risk genes are necessarily present in unaffected relatives,

one expects them to exhibit some of these neurophysiological dysfunctions. This is true for particular brain imaging and cognitive deficits in both disorders (2, 28, 29).

Functional dysconnectivity models of SZ suggest that several brain regions subserving different cognitive functions interact abnormally to generate the SZ phenotype (30, 31). Empirical support for dysconnection can be found by examining strength of structural or functional connections between different brain regions, which informs understanding organized behavior of cortical functions, either during task-driven cognition or when the brain is at “rest.” Functional connectivity (FC) identifies distinct sets of brain regions that are functionally coupled over time, measured as synchronous co-activation of distal neuronal assemblies (30, 31). Particular attention has focused on SZ and BP brain activity and FC during “resting” or “baseline” states. At least a dozen distinct, functionally connected resting state networks (RSNs) have been identified, generally reproducible across different study populations and methodologies. These networks comprise regions mediating motor, visual, executive, auditory and memory functioning and the so-called default-mode network (DMN); these RSN patterns are genetically influenced (32-35).

An informative variation of FC, “functional network connectivity” (FNC) (36-38) evaluates functional coupling or coherence among large-scale distributed networks. Few studies have examined *interactions* amongst different resting networks in SZ or BP (37, 39-42). Zhou et al. first examined functional connections between different RSNs in SZ (41), finding significant connectivity differences within and between resting state fMRI networks, notably those associated with dorsal prefrontal, lateral parietal, inferior temporal, dorsolateral prefrontal and dorsal premotor cortices. Jafri et al. (37) examined FNC in SZ, employing the same method as the current study, reporting several abnormally higher connections, primarily between DMN, fronto-parietal and basal ganglia networks. Ongur et al (43) compared DMN (derived from resting state fMRI) in SZ and BP; both had less DMN connectivity in medial prefrontal cortex; abnormal recruitment in BP involved parietal cortex; in SZ frontopolar cortex/basal ganglia. Patients had significantly higher frequency fluctuation than controls, suggesting abnormal functional organization of the core RSN circuit and implicating dysfunction in how broad networks engage/disengage relative to one another over time. Therefore, FNC techniques provide a means to quantify how overall engagement of broad networks is influenced by other large neural systems and permits testing hypotheses about abnormalities in clinical disorders. Evidence for FNC deficits could indicate abnormal mechanisms mediating inter-cellular signaling. Because they affect large-scale network engagement, these mechanisms would likely be found consistently across many brain structures having diverse structure and functional specialization. If FNC abnormalities represent general psychosis intermediate phenotypes (26, 44, 45), or even unique SZ or BP markers, inquiry could turn towards generalized neuronal signaling mechanisms, ideally related to specific, measureable genetic risk factors and etiological pathways. It therefore is important to study unmedicated and unaffected relatives of probands to detect psychosis endophenotypes.

We used a dysconnectivity model to investigate how these different RSNs interact in SZ and BP, to better understand such large scale systems interactions and better delineate their underlying pathology. We expected that such analyses would highlight commonalities and differences in neural systems integration between disorders. Our goals were to: 1) delineate common and unique FNC profiles in SZ and BP, and 2) determine which abnormalities occur in their unaffected relatives, suggesting strong genetic influence. We first used group ICA to identify RSNs in all subjects. We then employed a two-stage analytic approach to find connectivity differences among resting state components using our previously published FNC methods (37, 46). Our data-driven FNC approach provides a unique, means to test brain connectivity focusing on naturally-occurring large scale networks versus pre-

specifying regions or seeds that impose more assumptions and possible bias on the data examined. We hypothesized that both SZ and BP probands would exhibit different FNC between components, including those representing both DMN and other networks (37). We additionally predicted reduced FNC between network pairs supporting cognitive functions impaired in the disorders, e.g. fronto-parietal (SZ) and fronto-temporal (BP) systems. Consistent with cognitive dysmetria hypotheses, we predicted abnormalities in cerebellar, sensori-motor and related subcortical structures in SZ (41). For BP we hypothesized FNC differences in limbic circuits (47), spatial memory/attention and emotional regulatory areas (42, 48, 49). Finally, we hypothesized that subsets of aberrant connections in probands would also be observed in their unaffected relatives due to shared genetic risk.

Methods and Materials

Subjects

We assessed 118 normal controls, 70 first-degree relatives of SZ, 52 BP first-degree relatives, 64 psychotic BP and 70 SZ patients (age, sex and ethnicity matched to controls; Table 1). DSM IV (50) consensus diagnoses were established by trained clinical raters and senior diagnosticians using all clinical data and structured clinical interviews for DSM diagnoses (SCID (51)) interviews: inter-rater reliability was $>.90$ among raters. Probands were clinically stable with constant medication doses for 4 weeks as follows (N of 70 SZ/ 64 BP): mood stabilizers (19/44), typical antipsychotics (7/2), atypical antipsychotics (58/36), benzodiazepines (13/11), anticholinergics (11/4), SSRIs (18/16), tricyclics or monoamine oxidase inhibitors (9/13) and psychostimulants (2/4). Relatives of probands were free of Axis I psychopathology and not taking psychoactive medications. Participants were recruited via word of mouth and advertisements at the Olin Neuropsychiatry Research Center (ONRC); all provided written informed consent approved by Hartford Hospital's and Yale's IRBs. Participants were drawn from BSNIP and other ongoing ONRC studies, independent from samples in previous publications.

Bipolar subjects all had a lifetime diagnosis of psychosis, based on the presence of hallucinations/delusions during at least one episode (within or distinct from an affective episode) in their illness course, described in (52); each was assessed additionally for current psychosis on day of scanning based on scores ≥ 3 , in one or more of the following PANSS positive subscales: delusions, conceptual disorganization, hallucinations and suspiciousness/persecutory. Based on these criteria, 50% of bipolar probands had current psychosis. BP probands were assessed on scan day using commonly-employed cutoff scores for manic and depressive episodes respectively: Montgomery/Asberg Depression Rating Scale >32 and Young Mania Scale >20 (53, 54). Thus defined, 3/64 BP subjects met criteria for major depressive and 8/64 for manic episode. Relatives were further classified for presence or absence of DSM-IV-TR Cluster A personality disorders, based on the Structured Interview for Disorders of Personality (SIDP-IV) (55); there were only 3 SZ and 4 BP relatives respectively.

Data pre-processing

fMRI images were collected on ONRC's Siemens Allegra 3T system. The echo planar image gradient-echo pulse sequence (TR/TE 1500/28 ms, flip angle 65° , 3.4 by 3.4 mm in plane resolution, 5 mm effective slice thickness, 30 slices) effectively covered the entire brain. Head motion was restricted using a custom-built head-coil cushion. During scanning, participants were asked to fixate on a small cross presented on the screen, remain alert with eyes open and head still. These instructions helped reduce head motion, prevented subjects from falling asleep and served as an experimental control over visual input. All participants were judged as awake and alert at the fMRI session's start and conclusion. The stimulus run

consisted of 210 time-points. The initial six images during which T2 effects stabilized were discarded. Remaining images were reconstructed offline and each run separately realigned using INRIAlign (56) as implemented in statistical parametric mapping ((SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/>)). Each participant's translation/rotation corrections were examined to exclude excessive head motion ($> 3\text{mm}$ in each direction). A mean functional image volume was constructed for each session from the realigned image volumes to determine parameters for spatial normalization into Montreal Neurological Institute standardized space (<http://www.mni.mcgill.ca/>). Normalization parameters determined for the mean functional volume were applied to each participant's corresponding functional image volumes, which were smoothed with a $9\times 9\times 9\text{ mm}$ Gaussian filter.

Independent Component Analysis (ICA)

The GIFT group ICA toolbox (<http://icatb.sourceforge.net/>, version 1.3g) (57) was used to identify temporally distinct resting state components. Using data from all subjects, nineteen spatially independent components were determined using the minimum description length (MDL) criteria (29, 37, 57). An initial data reduction step used principal component analysis followed by an IC estimation that produced time-courses and spatial maps using the Fast-ICA algorithm. Estimated ICs at the group level (both spatial maps and time courses) were then back-reconstructed for each subject yielding subject specific spatial maps and time courses for each estimated component. This specific back reconstruction feature of the GIFT algorithm allows analysis of all subjects simultaneously as part of a large ICA group matrix (58). Each component's time course therefore represented a pattern of synchronized brain activity, whose coherency pattern across voxels was represented in the associated spatial map. Component intensity values were then Z-scaled to provide a form of normalization across subjects. Icaso software determined the stability of the derived networks based on a random initiation method (59).

Identifying valid RSNs

We employed standard methods of rejecting artifactual ICA networks. Network components were examined visually to eliminate those clearly representing artifacts, then spatially correlated to *a priori* probabilistic gray, white matter and CSF templates (in SPM2) using multiple regression; components having low associations ($|\text{beta}| < 0.5$) with gray matter and high association ($|\text{beta}| > 2$) with white matter and CSF were discarded. Thus, 3 components were removed and 16 deemed valid RSNs. Statistical parametric maps using 1-sample t-tests were created for each remaining component at the group level to further examine validity (networks shown in Figure 1 and Figure S1 in the Supplement).

Functional network connectivity (FNC) analysis

Timecourse data were band-pass filtered using a Butterworth filter with cut-off frequencies of 0.008 - 0.15 Hz (60-62) and each network's timecourses subjected to a recently developed FNC analysis (<http://mialab.mrn.org/software>). Although individual ICA-derived components are maximally spatially independent, significant temporal coherence can exist among the different networks. FNC analysis examines this specific temporal correlation in a non-parametric pairwise manner using a maximal lagged correlation approach. Timecourses of all ICA networks were initially interpolated to detect finer and sub-TR hemodynamic differences. Then all 16 resting networks, taken two-at-a-time, yielded 120 total pairwise combinations per group. Each pairwise correlation coefficient (representing magnitude/extent of network connection) within all groups was extracted into SPSS v15.0. Resulting correlation data were transformed to Fisher's Z-values and subjected to a two-stage analysis: Stage1: A one-way ANOVA model with controls, SZ probands and BP probands as the three independent factors identified significantly anomalous correlations (FDR corrected

$q < 0.05$) for all 120 component combinations across probands. Stage 2: Only connections thus identified as abnormal were carried forward to test for similar differences in relatives. We also conducted an exploratory analysis to probe connectivity differences in relatives not limited to relationships affected in probands, using a one-way ANOVA similar to stage 1 above, but including only controls and relatives as fixed factors.

Relationship to PANSS scores

Supplementary correlations (limited to significantly dysfunctional networks) were conducted between variations in network connectivity coefficients and PANSS scores within proband groups separately.

Results

ICA identified sixteen independent RSNs of interest, yielding 120 different pair-wise network connections/subject. A detailed region list (with cluster spans) within each significantly modulated functional network is provided in Table S1 Figure S1 in the Supplement. Icasso determined that all networks were highly stable ($iq > 0.95$).

Network Connections Anomalous in SZ/BP (Stage 1)

From 120 pairwise network combinations tested using one-way ANOVA for a main effect of FC modulation among probands, three survived multiple corrections in initial analysis. These three network pairs contained five different resting networks: (A) Fronto/Occipital, (B) anterior Default Mode (aDMN)/Prefrontal, (C) Meso/Paralimbic, (D) Fronto-Temporal/Paralimbic and (E) Sensory-Motor. Combination A-B had reduced connectivity in both SZ and BP probands. Combination C-E had a lower connectivity coefficient only in SZ but not BP probands. Combination C-D was unique to BP probands, with increased connectivity compared to controls. Figure 2 depicts all three connections and their mean network connectivity strength for each group (including relatives). Spatial layouts of networks in Figure 1 were derived from a random effects one-sample t-test ($p < 1e-4$ FWE corrected) computed across all subjects in SPM2.

Network Connections Anomalous in Relatives of SZ/BP Probands (Stage 2)

Subsequent testing for significant differences in relatives revealed reduced connectivity between networks A-B in relatives of BP but not of SZ. Network combination C-E, showed reduced connectivity in BP relatives with a strong trend in SZ relatives. Combination C-D was unaffected in both relative groups. Table 2 summarizes findings from both stages. Exploratory stage-1 ANOVA including all network pairs and relatives revealed no additional group differences.

Although we sought to examine whether these network abnormalities in first-degree relatives were more marked in those with DSM-IV-TR Cluster A personality disorders, as noted earlier, there were insufficient such relatives to assess this. We also tested FNC values among currently psychotic versus lifetime history of psychosis BP probands (based on PANSS criteria at time of scan); FNC between-network pairs were not significantly different between these subgroups.

Relationship between connectivity measures and PANSS scores

Correlations between the above dysfunctional networks and PANSS scores revealed that schizophrenia probands showed positive relationships between network A-B and PANSS positive ($r = 0.373$; $p = 0.004$) and general ($r = 0.421$; $p = 0.001$) scores. Bipolar probands', network C-D correlated positively with PANSS negative symptoms ($r = 0.297$; $p = 0.047$); p values unadjusted $\alpha = 0.05$.

Discussion

We sought to delineate common and unique functional network connectivity abnormalities in SZ and psychotic BP and to determine which of these were detectable in these probands' unaffected relatives, thereby examining their possible genetic origin. Using a combination of ICA and a validated lagged correlation FNC technique on component time course data, we extracted spontaneous low-frequency resting state hemodynamic fluctuations in sixteen independent brain circuits, all of which resembled previously identified networks in other ICA resting state studies (32, 33, 37, 63), underscoring their reproducibility. We identified several abnormal inter-connections in SZ and in BP probands and detected disorder-specific patterns of familial abnormality. To our knowledge this study is the first to report a large-scale connectivity analysis comparing FNC data between SZ and specifically psychotic BP subjects that also shows brain connection differences across multiple resting state functional networks among their non-ill relatives.

To better interpret the identified aberrant networks, we compared them to those in a recent article by Laird et al. who used a BrainMap-based neuroinformatics meta-analytic approach on behavioral taxonomy to derive behavioral interpretations of ICA-derived RSNs (63). Interpreting our networks in this context (actual spatial correlation values between networks found in this study and component data reported in Laird et al are provided in parenthesis), Network A ($r=0.75$) was linked to visual perception and higher-order visual processing, our Network B ($r=0.52$) highly resembled the anterior portion of the default mode network (aDMN), primarily associated with theory of mind/social cognition tasks and episodic recall,. Network C ($r=0.8$) was linked to discrimination of emotional faces and pictures and to interoceptive processing, Network D ($r=0.43$) sub-clustered into networks that contained portions of Network C and was associated with complex language, executive function, affective and interoceptive processes (i.e. a transitional network linking cognition and emotion), Network E ($r=0.5$) was linked to cognitive control, motoric action and preparation.

Commonly affected abnormal network connection(s) in SZ and BP probands

Because SZ and BP share overlapping putative genetic risk and pathophysiology, we predicted similarly-affected inter-network connections in both diseases. Consistent with this, we found a specific connection between Fronto-occipital network (A) and aDMN/prefrontal network (B) with shared abnormalities in BP and SZ probands, suggesting that this connection might play a common role in psychosis and share a similar genetic vulnerability. This reduced connectivity was greater in SZ than BP. A shared candidate symptom linking social cognition to higher-order visual processing is paranoia (64, 65). A recent diffusion tensor study (66) showed fronto-occipital tract abnormalities associated with positive symptoms in unmedicated SZ, consistent with functional disintegration of resting-state fMRI connectivity between medial-frontal/prefrontal and parietal networks in SZ (41). Disturbed long-distance fronto-occipital network EEG gamma coherence characterizes BP (67). Abnormal affective and directed visual processing in BP support disturbed functional responses in higher-order visual areas and lateral frontal cortex (68, 69). This abnormal connection resembles a recent report using FNC to explore medication effects on RSN connectivity in SZ (70). This network connectivity was identified as abnormal, but opposite in direction to a previous resting state study using FNC to examine network correlations in SZ; however, that study measured connectivity differences over a larger frequency range (0.03-0.37 Hz) compared to the current one, (we examined conventionally very low-medium order resting-state fluctuations in the 0.008-0.15Hz range), suggesting a primary reason for different connectivity results between the two studies. Other explanations for the different findings could be our substantially higher sample size and probands that were likely taking different medications (37). Although we attempted to address connectivity-related

medication effects in previous studies (70), these involved additional differences in imaging parameters and additional illness attributes (e.g. first episode vs chronic) making it difficult to compare among studies employing different samples.

Overall, the above functional network(s) are associated with self-referential processing, executive attention, orientation and mediate goal-directed top-down processing (63, 71), all of which are compromised in both SZ and BP (4, 64, 65).

Uniquely affected network connection(s) in SZ and BP probands

One network combination (C-D) was modulated differently (significantly increased connectivity) only in BP, consisting primarily of meso/paralimbic regions (mesial temporal cortex, amygdala, parahippocampus, hippocampus), with other mood-regulatory regions (subgenual cingulate, ventrolateral pre-frontal cortex, orbitofrontal cortex, insula). This network is likely linked to emotional regulation/expression and memory, all affected in BP (68, 72, 73, 74, 75).

We also identified connections between fronto-premotor and meso/paralimbic networks (C-E) with significantly reduced connectivity only in SZ. This network likely relates to multiple domains, including affective flattening, abnormal goal-directed planning, mediation, emotional processing and cognitive control. Altered core regions in this circuit were associated with psychiatric symptoms in PINK1 gene mutation carriers (76). Disordered connectivity of large-scale brain networks in SZ is associated with significantly reduced integration of several local networks comprising the C-E combination (77).

We also demonstrated specific abnormal connectivity patterns related to different PANSS domains consistent with the existing literature (e.g. emotional withdrawal and reduced empathy with inter-limbic connections), helping underpin the overall findings (78), consistent with a general hypothesis that psychotic symptoms derive from functionally disconnected brain circuits.

Network connections affected in relatives of probands

Compared to controls, endophenotypes are more likely expressed in unaffected relatives, who importantly have no systematic treatment with medications potentially altering brain function. Seeking endophenotypic markers in unaffected relatives, we found A-B network connectivity significantly altered in BP relatives only; this network pair demonstrated reduced connectivity in both proband groups and primarily consisted of aDMN, frontal and higher-order visual regions. DMN regions are richly connected to other prefrontal cortical areas and likely involved in emotional regulation, social cognition and reward-related feedback; lesions in these regions affect decision-making and emotional control (79). Connection C-E that was reduced only in SZ, showed a non-significant trend of reduced connectivity in SZ relatives, but surprisingly differed significantly in BP relatives compared to controls.

What are possible shared pathophysiological abnormalities linking psychotic bipolar illness and schizophrenia? One possibility is that there are similarities in underlying pathophysiology, e.g. neurotransmitter (80) dysfunctions that could plausibly affect resting state activity via modulating the default mode (81-83). Reduced aDMN–Fronto-Occipital (A-B) connectivity in our sample characterized both schizophrenia and bipolar probands and bipolar relatives. Several recent papers suggest possible roles for anterior DMN. As attentional and working memory problems characterize both SZ and BP (3, 4), Mayer et al. (84) investigated task-induced deactivations within DMN regions, segregating those deactivated by high attentional demand, working memory load or both. Multiple frontal areas corresponding to those in our network B (more anterior DMN, e.g. BA 9, 10, 46)

influenced many regions commonly deactivated during both attention and WM encoding in (84), corresponding to those in our network A (e.g. BA 13, 22, 31). Koshino et al. (85) determined that anterior-medial PFC (medial BA10) plays a role in task set formation. Frontal DMN areas were associated with neural activity that predicted forgetting in a meta-analysis of memory studies (86). Finally, a "resting state hypothesis" of auditory hallucinations implicates abnormal auditory cortex modulation by anterior midline DMN regions (87).

Other hypothesized shared pathogenetic mechanisms (12) could be investigated for possible effects on fMRI resting state patterns. Finally, similar genetic mechanisms could explain the above findings; e.g. reduced prefrontal DMN connectivity is related to familial genetic loading in schizophrenia (88).

Both BP (especially the psychotic form) and schizophrenia are treated with similar medications. As noted, these affect resting state fMRI patterns, although clearly not those shared with unaffected, unmedicated relatives as was the case in our study. Two paradoxical findings potentially attributable to psychopharmacologic medications affecting FNC differently across disorders and endophenotypes, included 1) The positive relationship between PANSS and A-B network connectivity and 2) Connection C-E being non-compromised in SZ relatives but affected in BP relatives.

Study Limitations and Conclusions

The present study had several advantages over prior, similar investigations: 1) the largest single-site resting state fMRI study (unconfounded by scanner and site differences), 2) global analysis including all RSNs rather than limited to *a priori* networks (e.g., DMN), 3) we directly compared FNC in SZ and BP, and 4) examined whether disorder-specific abnormalities also occurred in unaffected relatives to explore potential endophenotypic status. This study also had limitations: 1) it only investigated connectivity modulation across RSNs and not within each network (this could be performed straightforwardly, but was beyond the focus of this study and cannot be accommodated in a single manuscript), 2) the analytic approach limited us from identifying connectivity differences absent in probands but present in relatives (i.e., potential protective markers) although exploratory analyses showed no such effects, 3) using lagged correlations to interpret causality could be potentially problematic because they are based on slower hemodynamic activity (89, 90) 4) medication differences across groups could confound interpretation. Because relatives were not taking antipsychotic medications, only proband comparisons could be influenced by such drugs. We compared our findings with the Lui et al. study (70) investigating modulation of RSN connections in SZ using FNC before and after antipsychotic administration. A connection similar to A-B in our study did not differ at baseline but was reduced post-medication; the other two network connections in our study were not significantly different. This could result from different sample characteristics and a different range of RSN frequencies interrogated in Lui et al. Even though this is only partly consistent with our findings, it is nevertheless noteworthy.

In conclusion, we identified several abnormal low-frequency RSN interactions in two major psychiatric diseases and shed light on possible interactions among these baseline networks that might both extend our understanding of the pathophysiology of the disorder(s) and reflect their common genetic basis. Overall, these connectivity abnormalities may pinpoint underlying diverse effects seen in disease conditions and similar, more subtle effects seen in their unaffected relatives using a brief baseline (non-overt) scan in an effort to capture intermediate phenotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Godfrey Pearlson and Shashwath Meda 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. Analysis stage 1: Depicts a map of low-frequency connections between resting state networks that were significantly different ($q < 0.05$ FDR corrected for multiple comparisons) between controls, schizophrenia and bipolar probands. Behavioral interpretation of networks was based on Laird, A et. al. In press.

Figure 2. Shows the mean correlation coefficient (with standard error of mean) across each significant network pairs among all five diagnostic groups.

Table 1

Enumerates the basic demographic and clinical information for the different groups investigated in the study.

Demographic/Clinical Characteristics	Controls (N=118)		Bipolar (N=64)		Schizophrenia (N=70)		Schizophrenia Relatives (N=70)		Bipolar Relatives (N=52)		Statistic	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p value
Age (years)	36.4	10.8	35.19	11.2	37.4	12.8	40.8	15.6	40.6	13.0	2.4	NS
PANSS												
Positive	-	-	13.9	5.3	16.4	5.5	-	-	-	-	-	-
Negative	-	-	11.4	4.4	15.3	5.7	-	-	-	-	-	-
General	-	-	27.8	8.0	32.3	8.3	-	-	-	-	-	-
Total	-	-	53.7	14.4	64.8	16.5	-	-	-	-	-	-
	N	%	N	%	N	%	N	%	N	%	Chisquare	p value
Gender												
Male	55	46.61	35	54.69	43	61.43	26	37.14	18	34.62	13.3	NS
Female	63	53.39	29	45.31	27	38.57	44	62.86	34	65.38		
Ethnicity												
Caucasians	78.0	66.10	48.00	75.00	51.00	72.86	52.00	74.29	46.00	88.46	20.9	NS
Hispanics	13.00	11.0	6.00	9.38	5.00	7.14	1.00		1.00			
African Americans	21.00	17.80	5.00	7.81	12.00	17.14	13.00	18.57	4.00	7.69		
Asians	6.00	5.08	0.00	0.00	1.00	1.43	2.00	2.86	1.00	1.92		
No Data	0.00	0.00	5.00	7.81	1.00	1.43	2.00	2.86	0.00	0.00		

Table 2

Represents a summary of connectivity analysis performed in stage 1 (differences in connectivity strengths among probands) and stage 2 (differences in connectivity strengths in unaffected relatives).

STAGE 1			STAGE 2	
Component combination	Main effect of abnormal connectivity in probands (FDR corrected)	Significant post-hoc difference in probands	Increase or decrease in connectivity?	Significant abnormal connectivity in relatives?
A-B	0.03	SZ, BP	↓	BP REL
C-E	0.01	SZ	↓	BP REL, Strong trend in SZ REL
C-D	0.05	BP	↑	None