Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Scanning Factors

fMRI	TR (ms)	TE (ms)	FA (degree)	Slices (N)	slice order	Acq matrix (mm)	Voxel Size (mm)	Vendor
Baltimore	2210	30	70	36	Interleaved ascending	64x64	3.4x3.4x3	Siemens Triotim
Hartford	1500	27	70	29	Sequential ascending	64x64	3.4x3.4x5	Siemens Allegra
Detroit	1570/1720	22	60	29	Sequential ascending	64x64	3.4x3.4x4	Siemens TrioTim
Dallas	1500	27	60	29	Sequential ascending	64x64	3.4x3.4x4	Philips
Chicago	1775	27	60	29	Sequential ascending	64x64	3.4x3.4x4	GE Signa HDX
Boston	3000	27	60	30	Sequential ascending	64x64	3.4x3.4x5	GE Signa HDX
T1-Weighted Structural	**TR (ms)**	**TE (ms)**	**FA (degree)**	**Slices (N)**	**slice order**	**Acq matrix (mm)**	**Voxel Size (mm)**	**Vendor**
Baltimore	2300	2.91	9	160	N/A	256x240	1x1x1.2	Siemens Triotim
Hartford	2300	2.91	9	160	N/A	256x240	1x1x1.2	Siemens Allegra
Detroit	2300	2.94	9	160	N/A	256x240	1x1x1.2	Siemens TrioTim
Dallas	6.6	2.8	8	170	N/A	256x256	1x1x1.2	Philips
Chicago	6.98	2.84	8	166	N/A	256x256	1x1x1.2	GE Signa HDX
Boston	6.98	2.84	8	166	N/A	256x256	1x1x1.2	GE Signa HDX

Reproduced based on Meda et al., 2015

eTable 2. Associations Between Covariates and Variables of Interest

	Cognition Factor Score	Cingulo-Opercular Network Global Efficiency	Subcortical Network Global Efficiency
Age	##	r=.11, p=.007	r=-.11, p=.011
Head Motion	r=-.18, p<.001	r=-.01, p=.81	r=.03, p=.473
Sex	F(1,561)=5.80, p=.02	F(1,591)=4.18, p=.04	F(1,591)=2.79, p=.095
Race	F(2,560)=21.72, p<.001	F(2,591)=3.89, p=.02	F(2,591)=.25, p=.78
B-SNIP Site	F(6,556)=1.29, p=.259	F(6,587)=9.82, p<.001	F(6,587)=6.60, p<.001
CON Global Efficiency	r=.15, p<.001	-	r=.18, p<.001
Subcortical Global Efficiency	r=.15 p<.001	r=.18, p<.001	-

Appendix. Supplementary Methods

Inclusion/Exclusion Criteria

Inclusion/exclusion criteria for all participants included: no history of seizures or head injury resulting in >10 minutes loss of consciousness, negative drug screen on the day of testing, no diagnosis of substance abuse in the past 30 days or substance dependence in the past 6 months, no history of serious medical or neurological disorder that would likely affect cognitive functioning, sufficient fluency in English, and an age-corrected Wide-Range Achievement Test (4^{th} edition) reading test standard score >65. Additionally, participants could not have had a medication change, and needed to be clinically stable over the past month.

Brief Assessment of Cognition in Schizophrenia (BACS)

The BACS takes approximately 30 minutes to complete in healthy subjects, and involves assessment of cognitive ability in the domains of working memory, processing speed, motor speed, executive functions, verbal fluency, and verbal memory[1]. Working memory is assessed through a digit sequencing task, processing speed is measured through a symbol coding task lasting 90 seconds, and motor speed is measured through a token motor task where subjects are given 100 plastic tokens and are asked to rapidly pick up one token at time, with each hand simultaneously, for 60 seconds. Executive functions are assessed through a tower test, verbal fluency is assessed through both category and letter fluency over the course of 60 seconds, and verbal memory is assessed through a list learning task that includes 15 words.

fMRI Data Preprocessing

Participants were instructed to keep their eyes focused on a crosshair during the 5-minute resting state scan. Structural scans were segmented through FreeSurfer53[2].

To further improve signal-to-noise ratio, additional preprocessing steps were applied to functional images based on published recommendations[3]: data were voxel-wise demeaned and detrended, followed by nuisance regression including 24 motion parameters (six rigid body estimates, their preceding timepoints, and their squares), and whole brain, white matter, ventricle signals and their temporal derivatives. Frequency filtering was applied, retaining frequencies in the $0.009 < f < 0.08$ Hz band. Data were additionally spatially smoothed with a Gaussian kernel (6mm FWHM in all directions). Additional motion-correction was applied based on procedures suggested by Power and colleagues[3], in which frames exceeding a frame displacement (fd)>0.4mm were excluded from that subject's data. Subjects with <50 total frames following data scrubbing were removed from all analyses. Based on this criteria, 116 participants (18 HC, 37 schizophrenia, 26 schizoaffective, and 35 bipolar) were removed from the original BSNIP dataset, due to excessive motion. These individuals did not significantly differ from those who passed motion scrubbing on age, personal education, parental education, SES, or BACS composite.

The Power atlas was selected for network assignment and graph creation due to the robustness of its networks across both resting-state and task data, indicating good reliability[4], and because we have previously shown relationships between the Power-designated FPN and CON efficiency and cognitive ability, allowing us to test for

reproducibility[5]. BOLD timecourses were averaged across all voxels within the ROIs, and the resulting timeseries were correlated to create a 264x264 correlation matrix of functional connectivity values. Power atlas ROI assignments for the fronto-parietal network (FPN, 25x25), cingulo-opercular network (CON; 14x14), and auditory network (AUD; 13x13) were used to construct network graphs, in addition to the 264x264 whole brain graph.

Graphs were thresholded to preserve the 5%-10% strongest positive connections, in 1% increments. This thresholding range was selected for several reasons: 1) Power and colleagues[6] identified this range as most appropriate for isolating meaningful networks, with higher thresholds resulting in noisy and fragmented graphs, 2) Bassett and colleagues[7] have shown this range best differentiates between schizophrenia and healthy subjects' whole brain networks. Because there is no "correct" threshold, CON and FPN global efficiency are presented at every threshold in the supplement (eFigure1), revealing a stable pattern of group differences across thresholds.

Motion

Head movement for each subject was quantified as the total (sum) root mean square of the incremental movement between all frames in the resting-state scan (rms_totalframe). One-way ANOVA revealed a significant omnibus difference between groups ($F(3,571)=2.81$, $p=.04$) in rms_totalframe, and post-hoc comparisons using LSD showed that only the healthy controls and schizophrenia patients significantly differed on motion ($p=.005$, Cohen's $d = .280$; all other group difference p's>.09).

Importantly, when this rms_totalframe variable was included as a covariate in our main analyses, our findings were unchanged. In the MANOVA analysis comparing global efficiency across groups, we continued to observe a significant omnibus difference between groups ($F(12, 1701)=2.755$, $p=.001$) and a significant difference in CON global efficiency ($F(3,568)=6.33$, $p<.001$). The same was true for local efficiency, with the omnibus test ($F(12, 1701)=2.37$, $p=.005$) and CON ($F(3, 568)=4.81$, $p=.003$). Additionally, CON global efficiency continued to significantly predict general cognition ($\beta=.848$, $t=2.929$, $p=.004$) and was also still a significant mediator of the relationship between diagnostic status and general cognition (95% CI [-.0662, -.0122]). The same was true for CON global efficiency's significant mediation of diagnostic group and processing speed (95% CI [-.0939, -.0200]), executive functioning (95% CI [-.1083, -.0210]), and verbal fluency (95% CI [-.0935, -.0116]).

Differences in BACS Scores Between Groups

General cognition was measured by the factor score of the first (and only factor with an eigenvalue >1) from a principal axis factor analysis that included all BACS subtests. Groups significantly differed from one another overall ($F(3,559)=66.39$, $p<.001$), and post-hoc LSD tests revealed significantly reduced cognitive ability in all clinical groups compared to healthy controls (all p's<.001). Additionally, both schizophrenia and schizoaffective patients were significantly impaired on general cognition compared to the bipolar group (p's<.001), but did not significantly differ from one another (p=.403). All groups significantly differed in cognitive ability for all cognitive domains. All four groups significantly differed on working memory ability ($F(3,559)=31.28$, $p<.001$). The

same pattern of group differences as seen in general cognition (healthy controls> bipolar> schizoaffective/ schizophrenia) were observed for processing speed ($F(3,559)=65.03$, $p<.001$), motor speed ($F(3,559)=51.51$, $p<.001$), executive functioning ($F(3,559)=15.75$, $p<.001$), and verbal memory ($F(3,559)=26.64$, $p<.001$). For verbal fluency ($F(3,559)=18.23$, $p<.001$), schizophrenia subjects were significantly impaired compared to the other three groups.

CON and Subcortical Global Efficiency and Specific Cognitive Domains

To unpack the observed association with general cognition, we assessed relationships between CON and subcortical network global efficiency and the specific cognitive domains that comprise our general cognition measure. CON global efficiency was significantly positively associated with processing speed ($\beta=.113$, $p=.003$), executive functioning ($\beta=.120$, $p=.004$), and verbal fluency ($\beta=.107$, $p=.012$), but not with any other cognitive domains. We did not find significant group interactions in the prediction of these cognitive variables. Further, mediation analyses revealed that CON global efficiency significantly mediated the relationship between psychotic disorder status and processing speed (95% CI [-.0917, -.0178]), executive function (95% CI [-.1126, -.0254]), and verbal fluency (95% CI [-.1009, -.0157]).

Subcortical network global efficiency was also significantly associated with processing speed ($\beta=.084$, $p=.024$), but not with any other specific domain. Subcortical global efficiency was also a significant mediator in the relationship between psychotic disorder status and processing speed (95% CI [-.0710, -.0072]).

Relationships with Symptoms

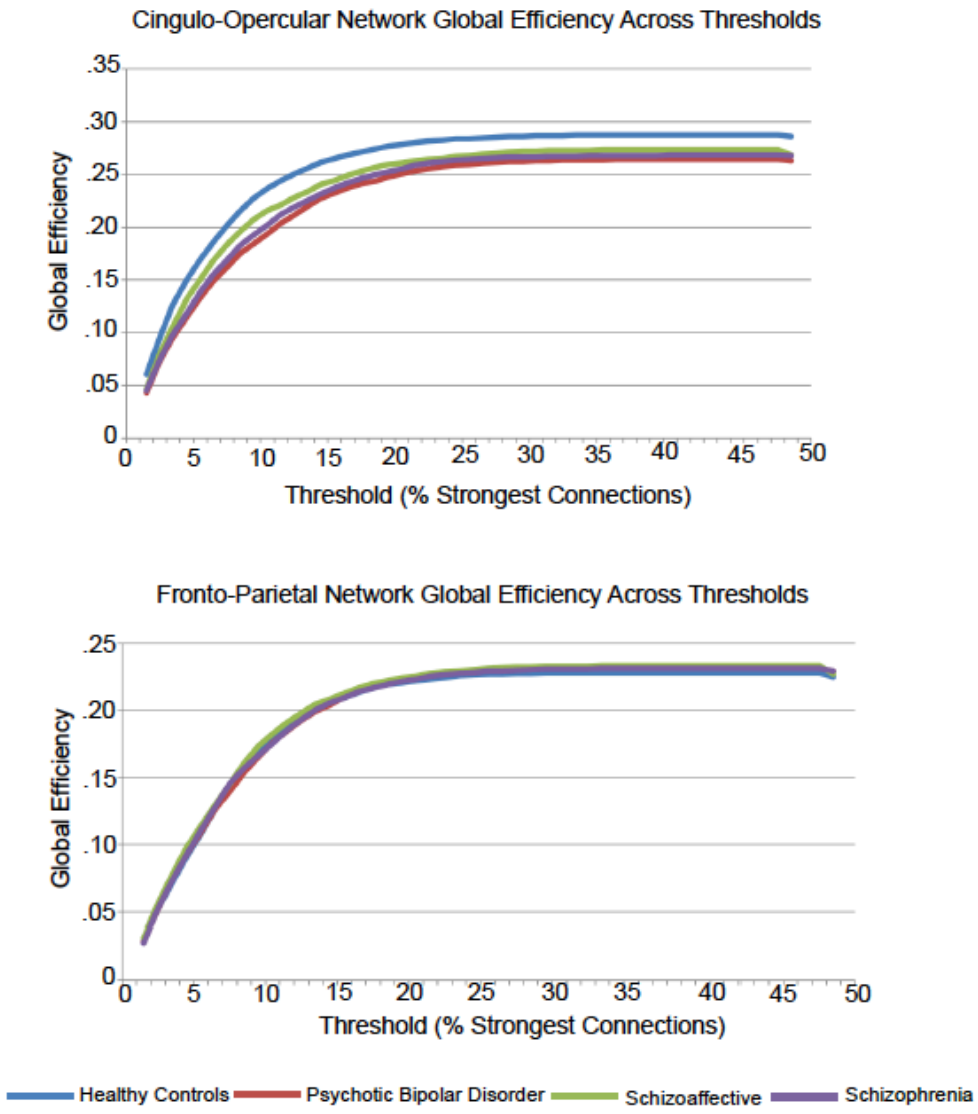
Using partial correlation analyses controlling for sex and race, we observed no significant associations between any of our clinical variables and global or local efficiency of our *a priori* networks or the subcortical network. We did observe some significant associations between clinical symptoms and cognitive ability, however the effect sizes were small and would likely not survive stringent multiple comparisons tests. Relationships with a significance level of $p<.02$ included: general cognition and negative symptoms ($r=-.159$, $p=.003$), general cognition and PANSS total ($r=-.144$, $p=.007$), motor speed and general psychopathology ($r=-.162$, $p=.002$), motor speed and PANSS total ($r=-.170$, $p=.001$), verbal fluency and negative symptoms ($r=-.188$, $p<.001$), verbal memory and negative symptoms ($r=-.146$, $p=.006$), and verbal memory and PANSS total ($r=-.137$, $p=.011$). Despite the small effect sizes, all relationships were negative, suggesting that more severe symptoms were associated with worse cognitive ability across all psychotic disorders.

Sex Differences in Graph Metrics

All results presented in the manuscript control for sex, however given recent work showing sex differences in nodal degree and nodal efficiency in healthy individuals (Rubin et al., 2016), we explored sex differences in our graph metrics, within diagnostic groups. We completed MANOVA analyses within each diagnostic group, controlling for race. For global efficiency, we observed a significant omnibus main effect of sex across all networks in the healthy controls ($F(4, 201)=2.846$, $p=.025$), which was being driven by significantly higher CON global efficiency in healthy men than women ($F(1,207)=4.797$, $p=.03$). We also observed significant differences in global efficiency in

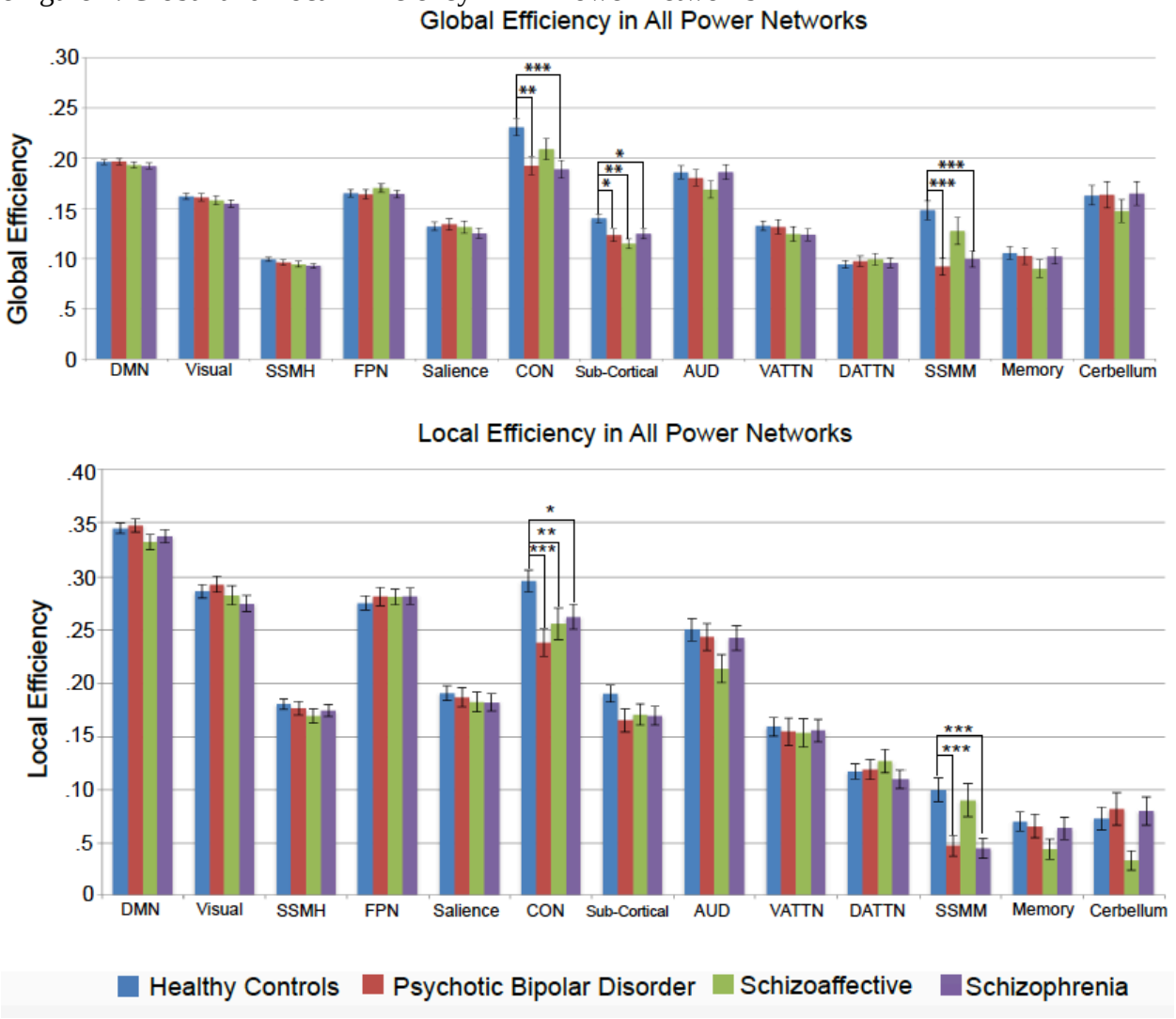
psychotic bipolar disorder ($F(4,123)=3.045$), which was driven by significantly increased whole brain global efficiency in the men compared to the women ($F(1,126)=6.056$, $p=.012$). No significant sex differences were seen in local efficiency or participation coefficient, for any of the diagnostic groups. Given the relatively small effect sizes of these exploratory analyses, we cannot make any strong conclusions on sex differences in this sample, although they were notably absent from the schizophrenia and schizoaffective groups.

eFigure 1. CON and FPN Global Efficiency Across Graph Thresholds



Global efficiency of the cingulo-opercular network and fronto-parietal network at each graph threshold, from the top 1% - top 49% strongest connections. Beyond the 49% threshold, networks begin including negative correlations, which are difficult to interpret in network science, in terms of how they contribute to graph metrics. Although presented analyses only include data from the top 5-10% strongest connections, as described in the Methods section, we observe a consistent trend of group differences across thresholds.

eFigure 2. Global and Local Efficiency in All Power Networks



Group differences in average global and local efficiency within all networks identified in the Power atlas. Networks are ordered from largest (DMN: 55 nodes) to smallest (Cerebellum: 4 nodes). DMN=Default Mode Network; SSMH = Somatosensory Hand; FPN = Fronto-Parietal Network; CON= Cingulo-Opercular Network; AUD = Auditory Network; VATTN= Ventral Attention Network; DATTN= Dorsal Attention Network; SSMM = Somatosensory Motor. *p<.05, **p<.01, ***p<.001

eReferences

1. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophrenia research.* 2004;68(2-3):283-297.
2. Fischl B. FreeSurfer. *NeuroImage.* 2012;62(2):774-781.
3. Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage.* 2014;84:320-341.
4. Cole MW, Bassett DS, Power JD, Braver TS, Petersen SE. Intrinsic and task-evoked network architectures of the human brain. *Neuron.* 2014.
5. Sheffield JM, Repovs G, Harms MP, et al. Fronto-parietal and cingulo-opercular network integrity and cognition in health and schizophrenia. *Neuropsychologia.* 2015;73:82-93.
6. Power JD, Cohen AL, Nelson SM, et al. Functional network organization of the human brain. *Neuron.* 2011;72(4):665-678.
7. Bassett DS, Nelson BG, Mueller BA, Camchong J, Lim KO. Altered resting state complexity in schizophrenia. *NeuroImage.* 2012;59(3):2196-2207.