RESEARCH ARTICLE

Functional network connectivity impairments and core cognitive deficits in schizophrenia

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Funding information

NIH Blueprint for Neuroscience Research, Grant/Award Numbers: T32MH067533, R01MH085646, R01DA027680, R01MH112180, 2R01EB015611, U01MH108148, U54EB020403

Abstract

Cognitive deficits contribute to functional disability in patients with schizophrenia and may be related to altered functional networks that serve cognition. We evaluated the integrity of major functional networks and assessed their role in supporting two cognitive functions affected in schizophrenia: processing speed (PS) and working memory (WM). Resting-state functional magnetic resonance imaging (rsfMRI) data, $N = 261$ patients and 327 controls, were aggregated from three independent cohorts and evaluated using Enhancing Neuroimaging Genetics through Meta Analysis rsfMRI analysis pipeline. Meta- and mega-analyses were used to evaluate patient-control differences in functional connectivity (FC) measures. Canonical correlation analysis was used to study the association between cognitive deficits and FC measures. Patients showed consistent patterns of cognitive and resting-state FC (rsFC) deficits across three cohorts. Patient-control differences in rsFC calculated using seed-based and dual-regression approaches were consistent (Cohen's d : 0.31 ± 0.09 and 0.29 ± 0.08 , $p < 10^{-4}$). RsFC measures explained 12–17% of the individual variations in PS and WM in the full sample and in patients and controls separately, with the strongest correlations found in salience, auditory, somatosensory, and default-mode networks. The pattern of association between rsFC (*within-network*) and PS ($r = .45$, $p = .07$) and WM ($r = .36$, $p = .16$), and rsFC (*between-network*) and PS ($r = .52$, $p = 8.4 \times 10^{-3}$) and WM ($r = .47$, $p = .02$), derived from multiple networks was related to effect size of patient-control differences in the functional networks. No association was detected between rsFC and current medication dose or psychosis ratings. Patients demonstrated significant reduction in several FC networks that may partially underlie some of the core neurocognitive deficits in schizophrenia. The strength of connectivity-cognition relationships in different networks was strongly associated with network's vulnerability to schizophrenia.

KEYWORDS

effect size, processing speed, resting-state functional connectivity, working memory

1 | INTRODUCTION

Schizophrenia is a neuropsychiatric disorder characterized by cognitive deficits and high rates of functional disability that contribute to its socioeconomic costs (Dickinson, Ramsey, & Gold, 2007; Faraone et al., 2000; Keefe et al., 2004; Keefe, Eesley, & Poe, 2005; Knowles, David, & Reichenberg, 2010; Reichenberg & Harvey, 2007). Fundamental cognitive impairments in schizophrenia include reduced information processing speed (PS) and working memory (WM) abilities that may also underwrite other higher level cognitive function (Barch & Ceaser, 2012; Bowie & Harvey, 2006; Kochunov et al., 2017). We hypothesized that these deficits may in part be caused by altered long-distance connectivity in functional networks that serve these cognitive functions (Bartzokis, 2012; Bartzokis, et al., 2010; Felts, Baker, & Smith, 1997; Waxman & Bennett, 1972). Magnetic resonance imaging (MRI) exploring the “resting-state” and “task-based” functionality of individuals with schizophrenia suggests reduced connectivity in networks that interconnect frontal, parietal, and temporal functions and are activated during tasks of higher cognitive function (Fornito & Bullmore, 2010; Godwin, Ji, Kandala, & Mamah, 2017; Kelly et al., 2018; Li et al., 2017; Liang et al., 2006; Whitfield-Gabrieli et al., 2009). Prior studies suggest that reduced functional connectivity (FC) is caused by complex interactions between brain maturation and genetic and environmental etiologies for schizophrenia (Blokland, 2017; Calhoun, Eichele, & Pearson, 2009; Karbasforoushan & Woodward, 2012; Whitfield-Gabrieli & Ford, 2012). However, the relationship between neurocognitive deficits and FC in schizophrenia remained unexplored in large inclusive samples. We hypothesized that FC deficits, particularly within and across resting-state networks may contribute to the cognitive deficits characterized by this disorder. Toward this aim, we used an analytical workflow developed for a cross-cohort meta-and-mega analysis of FC that uses the probabilistic regions of interest (ROIs) from the independent component analysis of the $N = 30,000$ functional experiments recorded in the BrainMap database (Smith et al., 2009). We ranked the statistical effect sizes (ESs) of FC deficits between patients and controls in major functional networks and then quantified the contribution of FC to individual variance related core cognitive deficits in PS and WM.

Deficits in PS and WM may underlie other neurocognitive deficits including attention, executive and other higher cognitive functions (Coyle, Pillow, Snyder, & Kochunov, 2011; Park & Holzman, 1992; Salthouse, 2009; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004). The cognitive disturbances might be caused by the abnormal connectivity between frontal, temporal, and parietal regions of individuals with schizophrenia (Farzan et al., 2010; Uhlhaas & Singer, 2010). In parallel, the onset, development, and severity of neurocognitive deficits imply impaired cerebral connectivity (Alba-Ferrara & de Erausquin, 2013; Ellison-Wright & Bullmore, 2009; Friedman et al., 2008; Glahn et al., 2013; Kubicki et al., 2007; Nazeri et al., 2012; Perez-Iglesias et al., 2011; Phillips, Rogers, Barrett, Glahn, & Kochunov, 2012; Wright et al., 2015). Specifically, individuals with schizophrenia have multimodal connectivity deficits that alter both functional and

structural connectivity outcomes (Bartzokis, 2012; Bartzokis, et al., 2010; Calhoun et al., 2009; Felts et al., 1997; Waxman & Bennett, 1972). Postmortem studies reveal widespread reductions in white matter myelin and glial density levels particularly in white matter regions that connect frontal areas with other parts of the brain (Kochunov, Rowland, et al., 2016; Kochunov et al., 2017). The reduced PS is correlated with widespread white matter abnormalities in diffusion MRI (Stotesbury et al., 2018), but deficits in WM, verbal memory, and executive functioning were not mediated by white matter integrity (Karbasforoushan, Duffy, Blackford, & Woodward, 2015). Previous research suggests that reduced FC strength may diminish coherence in long-distance cerebral networks that are active during rest and cognitive tasks (Bassett, Nelson, Mueller, Camchong, & Lim, 2012; Karbasforoushan & Woodward, 2012; Woodward, Rogers, & Heckers, 2011; Yu et al., 2012). However, research findings linking FC with cognitive deficits in this disorder have been inconsistent. For instance, a study in first-diagnosis subjects suggested that the deficits in PS are associated with *increased* connectivity between right central executive network and right ventral attention network (Attn) in patients (Anhoj et al., 2018). A study in chronic patients has failed to replicate that findings and instead linked cognitive deficits in PS, WM to *reduction* in thalamofrontal connectivity (Chen, Ye, Jin, Zhu, & Wang, 2018). For our study, we chose to use a data-driven approach and a large mega-analytical dataset to link FC deficits to cognition using meta-analytical sample design to reduce cohort-specific variances. The tests are known to measure PS deficits and WM abilities: the Digit Symbol Substitution Test (Dickinson et al., 2007; Knowles et al., 2010) and the Digit Sequencing Test (DST) (Keefe et al., 2004).

Meta-analytical studies reported moderate patient-control ESs for measurements of structural connectivity from white matter regions and cognition (WM) (Cohen's $d \sim 0.4$) (Kelly et al., 2018; Knowles et al., 2010). This necessitates the use of large samples to achieve statistical significance. We addressed this challenge by using a large mega-analytical sample and a standardized mega- and meta-analysis approach for assessing FC developed by the Enhancing Neuroimaging Genetics through Meta Analyses (ENIGMA) collaboration, which is focused on big data neuroimaging analysis (Jahanshad et al., 2013). Using datasets from three cohorts collected at a single site with the same recruitment criteria, neurocognitive and clinical assessments, followed by standardized workflows for meta-analytical estimates of group differences akin to larger studies enabled us to evaluate the reproducibility and robustness of our findings.

2 | METHODS

2.1 | Participants

The three cohorts comprised a total of 261 individuals with schizophrenia or schizoaffective disorder (patients) (161 males/100 females)—that were recruited from the outpatient clinics at the Maryland Psychiatric Research Center (MPRC) and the mental health clinics in greater Baltimore area between 2004 and 2016. $N = 327$ healthy controls (146 males/211 females), recruited through media

TABLE 1 Demographics for rsfMRI data for individuals with SCZ and HC groups. Values for age are in years. Symptom severity and medication measures are provided

	Cohort A		Cohort B		Cohort C		Mega-cohort	
	SCZ (n = 50)	HC (n = 64)	SCZ (n = 51)	HC (n = 81)	SCZ (n = 160)	HC (n = 182)	SCZ (n = 261)	HC (n = 327)
Mean age (SD) (years)	36.7 (11.8)	37.8 (13.2)	36.7 (11.8)	37.8 (13.2)	37.5 (14.4)	37.0 (16.1)	37.2 (13.5)	39.1 (15.2)
Age range (years)	18–56	18–62	18–56	18–62	18–63	18–65	18–63	18–65
Gender (M/F)	43/7	45/19	43/7	45/19	86/74	80/102	161/100	146/181
BPRS	30.7 ± 10.7	24.0 ± 5.0	30.7 ± 10.7	24.0 ± 5.0	31.2 ± 8.7	24.2 ± 6.9	30.8 ± 11.6	24.0 ± 5.0
CPZ	400.0 ± 352.9	NA	400.0 ± 352.9	NA	453.5 ± 367.9	NA	452.2 ± 416.9	NA
FTND	4.1 ± 2.2	4.2 ± 2.1	4.1 ± 2.2	4.2 ± 2.1	4.8 ± 2.5	4.5 ± 2.6	4.8 ± 2.3	4.5 ± 2.2
Age-of-onset (years)	18.5 ± 7.5	NA	18.9 ± 7.8	NA	18.1 ± 8.5	NA	18.3 ± 8.2	NA
Illness duration (years)	19.7 ± 13.6	NA	20.1 ± 13.7	NA	21.5 ± 15.1	NA	20.9 ± 14.6	NA

Abbreviations: BPRS, brief psychiatric rating scale, CPZ, chlorpromazine equivalence, FTND, Fagerstrom test for nicotine dependence; HC, healthy control; rsfMRI, resting-state functional magnetic resonance imaging; SCZ, schizophrenia.

advertisements from the same geographic area. The participants were required for a large ongoing study of the effects of cerebral dis-connectivity in the schizophrenia. Demographics of the samples along with the symptom severity and medication measures included in the current resting-state functional MRI (rsfMRI) study are reported in Table 1. Diagnoses were confirmed with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) in all participants. Major medical and neurological illnesses, history of head injury with cognitive sequelae, and diagnosis of intellectual disability were exclusionary. Control participants had no past or present DSM-IV Axis I psychiatric disorder and no family history of psychosis in the prior two generations. All participants gave written informed consent as approved by the local Institutional Review Board. The cohorts were collected using three 3 T Siemens scanners that constituted the progress in MRI technology. All subjects were assessed for research studies at MPRC using uniform recruitment criteria, neurological and clinical assessments, and inclusion of a control group were kept the same. Participants' demographic information and the image acquisition parameters for these three cohorts are provided in the Supporting Information. The aggregate rsfMRI data from these cohorts have not been published before; the aggregate cognitive data and the diffusion tensor imaging data from these cohorts has been published (Kochunov et al., 2017, 2018).

2.2 | Measures

All patients had undergone a uniform psychiatric interview that included Brief Psychiatric Rating Scale (BPRS) (Hedlund & Vieweg, 1980). The BPRS consists of 20 symptom constructs and each symptom is rated from 1 (not present) and 7 (extremely severe) and the total score of BPRS (Table 1) was used to represent overall clinical symptoms. Controls also had undergone BPRS tests. PS was assessed with the Digit Symbol Coding task of the WAIS-3 (Wechsler, 1997). The digit symbol test involves a key consisting of the numbers 1–9 paired with a unique, easy-to-draw symbol. The task requires the individual to scan the answer key, provided at the top of the page and then write the correct symbol by each number. The test taker is allowed for 90 s to fill in the corresponding symbol for each number. The number of correctly filled symbols is recorded. In meta-analyses of all cognitive domains affected by schizophrenia, the speed of information processing showed the largest patient-control differences, as measured by this task (Dickinson et al., 2007; Knowles et al., 2010). WM was assessed with the DST of the WAIS-3 (Keefe et al., 2004). It consisted of digits forward and digits backward subtasks. Examinee was asked to recall three to nine digits forward and two to nine digits backward. The number of successfully recalled digits within 90 s was recorded. Note that PS and WM are complex constructs, and a single task may not capture all aspects. However, as this was a large sample collected over many years, it would be difficult to maintain consistency if including a large battery; as such, we opted for testing only two of the most representative cognitive deficits for schizophrenia, while ensuring consistency. The current medication dose was recorded and converted to chlorpromazine equivalence (CPZ)

(Woods, 2003). CPZ was not significantly different among the three patient cohorts ($p = .20$, t test). Fagerstrom test for nicotine dependence (FTND) scores were recorded from the participants, yes/no items are scored 1/0 and multiple-choice items are scored from 0 to 3, yielding a total score of 0–10 (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). These FTND scores (Table 1) were not significantly different for controls and patients within cohorts and for mega-cohort ($p > .50$, t test). All participants with schizophrenia were evaluated for their capacity to provide informed consent.

2.3 | rsfMRI data processing and analysis

The three datasets were collected using phase array coils a 4-channel (Cohort A), a 12-channel head coil (Cohort B), and a 32-channel head coil (Cohort C), all manufactured by Siemens, Germany. The rsfMRI data included 150 volumes (Cohort A), 140 volumes (Cohort B), and 444 volumes (Cohort C). Resting-state data were obtained using a single-shot gradient-recalled, echo-planar imaging (EPI) pulse sequence with the following acquisition parameters: Cohort A: repetition time (TR): 2000 ms, echo time (TE): 27 ms, 64×64 matrix, 3.44×3.44 mm² in-plane resolution, 4 mm slice thickness, 39 axial slices; Cohort B: TR: 2210 ms, TE: 27 ms, 64×64 matrix, 3.44×3.44 mm² in-plane resolution, 4 mm slice thickness, 36 axial slices, and Cohort C: TR: 2000 ms, TE: 30 ms, 128×128 matrix, 1.72×1.72 mm² in-plane resolution, 4 mm slice thickness, 37 axial slices (more detail is provided in the Supporting Information). The ENIGMA resting-state analysis pipeline implemented in the Analysis of Functional NeuroImages (AFNI) software (Cox, 1996) was used to process the rsfMRI data. This single-modality resting-state analysis pipeline is an extension of the conventional AFNI rsfMRI pipeline (Figure S1) (Adhikari et al., 2018b). A principal component analysis-based denoising (Veraart, Fieremans, & Novikov, 2016; Veraart, Novikov, et al., 2016) approach is the first step implemented in this analysis pipeline to improve signal-to-noise ratio (SNR) and temporal SNR (tSNR) properties of the time series data. In the next step, a transformation is computed registering the base volume to the ENIGMA EPI template (Adhikari, et al., 2018) and this atlas is used for regression of the global signal, and as a common anatomical spatial reference frame (as detailed further in the Supporting Information).

Resting-state network templates were defined based on the probabilistic ROIs from the analysis of the BrainMap activation database and resting-state fMRI dataset (Smith et al., 2009). We defined the binary masks of the resting state template regions from the auditory network (AN), AttN, default mode network (DMN), executive control network (ECN), frontoparietal network (FPN), salience network (SN), sensorimotor network (SMN), and visual network (VN) (Figure S2; Adhikari et al., 2018a). Resting-state FC (rsFC) values were extracted from these template ROIs using seed-based and dual regression analysis approaches (more details are provided in the Supporting Information) and the subsequent analysis was performed using these measures (as detailed in the Supporting Information). Furthermore, AttN and FPN were divided into left and right subnetworks each (left AttN [lAttN], right AttN [rAttN] and left FPN [lFPN], right FPN

[rFPN]), the VN was divided into two subnetworks, and the DMN, SN, and SMN are divided into three subnetworks each (more detail is provided below and Supporting Information).

We further analyzed between-network FC using seed-based analysis. We extracted an average time series for each of these 24 ROIs and computed the correlation matrix for all ROIs for each control and schizophrenic participant. After the Fisher's r - to z -transformation, the FC between each pair of ROIs was calculated and compared using an independent sample t test, with multiple comparisons correction.

2.4 | Meta-analysis

A meta-analysis of patient-control ES measurements (Cohen's d -values) was performed in [R] software using the inverse variance method to compute the bias corrected standardized mean difference (ES) between individuals with schizophrenia and healthy controls, as implemented in the package, *meta* (www.meta-analysis-with-r.org).

2.5 | Mega-analysis

A "mega-analysis" of patient-control ES measurements (Cohen's d -values) was performed using "polyclass" function implemented in SOLAR-Eclipse software (www.solar-eclipse-genetics.org) (Jahanshad et al., 2013; Kochunov, Ganjgahi, et al., 2016). This function combines the data across the cohorts by fitting the covariate model consisting of sex, age, age², age $\times$ sex interaction, and age² $\times$ sex interaction for each cohort separately, that is followed by a per-site inverse Gaussian normalization of data (as detailed in Kochunov et al., 2014). Meta- and mega-analytical aggregation was used for both cognitive and connectivity measurements and produced residuals corrected for age and sex.

2.6 | Canonical correlation analysis between cognition and connectivity

Canonical correlation analysis (CCA) was performed to define a low dimensional representation of FC features following mega-analytical aggregation (using the function: "canoncorr.m"; <https://www.mathworks.com/>). The two cognitive measurements were used as the dependent variables and connectivity indexes served as predictors. CCA is a flexible and powerful multivariate statistical method to perform correlation analyses that allow for the linear relationship between dependent variables and predictors (Uurtio et al., 2017).

CCA was used to probe the pattern of FC measures that were related to cognitive deficits, as measured by PS and WM. To keep the number of connections, the same for each resting-state network under consideration and to minimize the possible overfitting effect by a network having a higher number of connections during CCA, we divided RSNs into the following 17 subnetworks: a network (sub-network) for AN and ECN each, two subnetworks for AttN (lAttN and rAttN), FPN (lFPN and rFPN), and VN (VN1, VN2) each and three subnetworks for DMN (DMN1, DMN2, DMN3), SN (SN1, SN2, SN3), and SMN (SMN1, SMN2, SMN3); keeping the functional connections from

FIGURE 1 Mega-analytic results. Mega-analytic Forest plots for group differences between individuals with schizophrenia and healthy controls, for resting-state functional connectivity (rsFC) measures, with (a) the seed-based analysis approach; and (b) the dual regression analysis approach, for each resting-state network's functional connections. Enclosed rectangular boxes, with different colors, separate the functional connections for each resting-state network. Abbreviations: AN, auditory network, a₁/a₂, left/right primary and association auditory cortices; Attn, attention network, f₁/f₂, left/right middle frontal gyrus, and p₁/p₂, left/right superior parietal lobule; DMN, default mode network, r₁, posterior cingulate/precuneus, r₂, bilateral temporal-parietal regions and, r₃, ventromedial frontal cortex; ECN, executive control network, r₁, anterior cingulate cortex and r₂, bilateral medial frontal gyrus; FPN, fronto-parietal network, f₁/f₂, left/right frontal area (inferior frontal gyrus) and p₁/p₂, left/right parietal area (inferior parietal lobule); SN, salience network, r₁, anterior cingulate cortex and r₂/r₃, left/right insula; SMN, sensorimotor network, m₁/m₃, left/right motor area and m₂, supplementary motor area; and VN, visual network, v₁, medial visual areas, v₂, occipital visual areas, and v₃, lateral visual areas [Color figure can be viewed at wileyonlinelibrary.com]

one ROI to next and the other way around for a subnetwork (more details are provided in the Supporting Information).

We also performed the CCA for rsFC measures computed between-networks analysis to investigate the pattern of association between cognitive deficits and these rsFC measures and hence, to derive relationship between cognitive measures (PS and WM) and the ES of the patient-control differences in the functional networks.

2.7 | Impact of symptom severity and medication

We studied whether the FC measures were associated with symptom severity and current antipsychotic medication dosages in schizophrenia in the resting-state functional connections between RSNs ROIs. We also performed CCA between BPRS scores and rsFC measures for each network/subnetwork to evaluate the correlation patterns

between them and then calculated the correlation of the BPRS with the ESs of diagnosis. This analysis was performed in both patients and controls to exclude any biasing effects of the diagnosis.

2.8 | Additional statistical procedures

We performed the correlation analysis between the FTND scores and rsFC values for each functional connection separately for both patients and controls.

The patient-control differences (ESs, Cohen's *d*-values) were calculated for individual functional connections in each cohort separately. Using these ES measures, the correlation analysis was performed between any two cohorts to evaluate the cognitive deficit patterns across three cohorts. Furthermore, the ESs measured from each cohort

Seed-based analysis approach					
Network	Connections	ES	95% CI	z-Value	p-Value
AN	a ₁ -a ₂	-0.54	[-0.70; -0.37]	-6.35	2.2E-10
	a ₂ -a ₁	-0.51	[-0.68; -0.34]	-6.04	1.5E-09
AttN	f ₁ -p ₁	-0.35	[-0.51; -0.18]	-4.15	3.3E-05
	p ₁ -f ₁	-0.35	[-0.51; -0.19]	-4.19	2.8E-05
	f ₂ -p ₂	-0.25	[-0.42; -0.09]	-3.03	.0025
	p ₂ -f ₂	-0.28	[-0.44; -0.11]	-3.33	.0009
DMN	r ₁ -r ₂	-0.25	[-0.41; -0.08]	-2.97	.0030
	r ₂ -r ₃	-0.23	[-0.39; -0.06]	-2.71	.0067
	r ₃ -r ₁	-0.27	[-0.43; -0.10]	-3.18	.0015
	r ₂ -r ₁	-0.21	[-0.37; -0.05]	-2.51	.0122
	r ₃ -r ₂	-0.19	[-0.36; -0.03]	-2.34	.0192
	r ₁ -r ₃	-0.27	[-0.44; -0.11]	-3.29	.0010
ECN	r ₁ -r ₂	-0.37	[-0.54; -0.21]	-4.46	8.1E-06
	r ₂ -r ₁	-0.21	[-0.38; -0.05]	-2.57	.0101
FPN	f ₁ -p ₁	-0.24	[-0.40; -0.08]	-2.86	.0042
	p ₁ -f ₁	-0.20	[-0.36; -0.03]	-2.37	.0178
	f ₂ -p ₂	-0.24	[-0.41; -0.08]	-2.94	.0033
	p ₂ -f ₂	-0.22	[-0.38; -0.06]	-2.64	.0084
SN	r ₁ -r ₂	-0.46	[-0.62; -0.29]	-5.46	4.7E-08
	r ₂ -r ₃	-0.40	[-0.56; -0.23]	-4.75	2.1E-06
	r ₃ -r ₁	-0.42	[-0.58; -0.25]	-4.97	6.8E-07
	r ₂ -r ₁	-0.49	[-0.65; -0.32]	-5.76	8.2E-09
	r ₃ -r ₂	-0.39	[-0.55; -0.22]	-4.63	3.6E-06
	r ₁ -r ₃	-0.43	[-0.60; -0.27]	-5.15	2.6E-07
SMN	m ₁ -m ₂	-0.29	[-0.45; -0.12]	-3.40	.0007
	m ₂ -m ₃	-0.26	[-0.42; -0.10]	-3.11	.0019
	m ₃ -m ₁	-0.35	[-0.52; -0.19]	-4.21	2.6E-05
	m ₂ -m ₁	-0.35	[-0.51; -0.18]	-4.16	3.1E-05
	m ₃ -m ₂	-0.21	[-0.38; -0.05]	-2.55	.0107
	m ₁ -m ₃	-0.33	[-0.49; -0.16]	-3.91	9.3E-05
VN	v ₁ -v ₂	-0.27	[-0.44; -0.11]	-3.27	.0011
	v ₂ -v ₃	-0.29	[-0.46; -0.13]	-3.51	.0005
	v ₃ -v ₁	-0.20	[-0.37; -0.04]	-2.45	.0144
	v ₂ -v ₁	-0.21	[-0.38; -0.05]	-2.56	.0106
	v ₃ -v ₂	-0.29	[-0.45; -0.13]	-3.46	.0005
	v ₁ -v ₃	-0.25	[-0.42; -0.09]	-3.04	.0024
Mean ES		-0.31	[-0.33; -0.28]	-19.5	<1.0E-04

TABLE 2 Mega-analytical statistics comparing groups of individuals with schizophrenia and healthy controls using FC measures from resting-state networks. ES values (in **bold font**) survived multiple comparison corrections (Bonferroni correction, $p < .05$)

Abbreviations: AN, auditory network, a₁/a₂, left/right primary and association auditory cortices; AttN, attention network, f₁/f₂, left/right middle frontal gyrus, and p₁/p₂, left/right superior parietal lobule; DMN, default mode network, r₁, posterior cingulate/precuneus, r₂, bilateral temporal-parietal regions and, r₃, ventromedial frontal cortex; ECN, executive control network, r₁, anterior cingulate cortex and r₂, bilateral medial frontal gyrus; ES, effect size; FC, functional connectivity; FPN, frontoparietal network, f₁/f₂, left/right frontal area (inferior frontal gyrus) and p₁/p₂, left/right parietal area (inferior parietal lobule); SN, salience network, r₁, anterior cingulate cortex and r₂/r₃, left/right insula; SMN, sensorimotor network, m₁/m₃, left/right motor area and m₂, supplementary motor area; and VN, visual network, v₁, medial visual areas, v₂, occipital visual areas, and v₃, lateral visual areas.

were assessed for correlation with the ESs derived from the mega-analysis approach.

3 | RESULTS

3.1 | Cognitive and functional connectivity deficits

Patients in all three cohorts showed reduced rsFC measures (Table S1 and Figure S5, see Supporting Information). The aggregated ESs performed using the mega-analysis and meta-analyses were highly correlated for both seed-based and dual regression approaches ($r > .90$ and $p < 10^{-13}$) (Figure S6a,b). All further analyses were performed in the full combined cohort using mega-analytical aggregation.

In the combined cohorts, patients demonstrated significantly lower average cognitive scores (Cohen's $d = 0.72 \pm 0.21$) and mega-analytical rsFC measures ($d = 0.31 \pm 0.09$, $p < 10^{-4}$ for seed-based approach (Figure 1a, Table 2), $d = 0.29$, $p < 10^{-4}$ for dual regression approach (Figure 1b). For subnetworks, the greatest rsFC deficits were observed for the SN3 ($d = 0.50 \pm 0.05$) followed by SN1 ($d = 0.48 \pm 0.05$); SMN1

($d = 0.34 \pm 0.05$); and AN ($d = 0.30 \pm 0.05$) (Figure 2). The meta-analytical analysis for rsFC measures produced similar deficit patterns (Table S2, Figure S3 (seed-based analysis), and Figure S4 (dual regression analysis) for meta-analysis, and Table 2 for mega-analysis).

Between-networks connectivity calculation using the seed-based analysis (Figure 3, Figure S8, and Table S5) showed 23 ROI pairs showed significant patient-control differences (still passing a corrected p -value of .05, after Bonferroni multiple comparisons correction, corresponding to an uncorrected $p < 1.8 \times 10^{-4}$). The significant differences indicated lower FC values in individuals with schizophrenia. Significant reductions in FC were found between the AN ROIs and the SN; DMN, ECN ROIs and the supplementary motor area (SMA) in SMN; between the DMN ROIs and SN ROIs; between SN ROIs and the SMA in SMN. We observed increases in FC between AttN ROIs and the AN, SMN, and DMN ROIs; between SMN ROIs and the ECN and FPN ROIs, but none of them were statistically significant, after Bonferroni multiple comparisons correction.

3.2 | Functional connectivity and cognition

CCA results for the two cognitive measures and FC measurements are shown in Table 3. We observed a significant positive correlation between rsFC and the two cognitive measurements ($r = .49$, $p = .002$ and $r = .46$, $p = .004$ for PS and WM, respectively) in the patients. A positive significant correlation was found between rsFC and PS when calculated in the full sample and control samples independently ($r = .36$, $p = .01$ for the full sample and $r = .34$, $p = .02$ for controls). Likewise, the correlation with WM was significant in the full sample and controls separately ($r = .35$, $p = .01$ for the full sample and $r = .45$, $p = .001$ for controls).

In the patient sample, the significant positive associations for PS were found for the AN ($r = .26$, $p = .01$) followed by SN3 ($r = .24$, $p = .01$); and SN1 ($r = .23$, $p = .02$) (Table S3). The significant associations for PS were observed for the SN3 ($r = .29$, $p = .002$) followed by SN1 ($r = .23$, $p = .01$); rAttN ($r = .23$, $p = .01$); and IFPN ($r = .22$, $p = .01$) for the full sample (Table S3). For the control sample, the significant association for PS was found for the VN2 ($r = .23$, $p = .002$) followed by SN1 ($r = .21$, $p = .007$); SMN3 ($r = .20$, $p = .009$); DMN3 ($r = .19$, $p = .01$); and rAttN ($r = .18$, $p = .02$) (Table S3).

Likewise, the significant positive association for WM was observed for the VN1 ($r = .25$, $p = .02$) followed by SN3 ($r = .25$, $p = .02$); and SMN1 ($r = .24$, $p = .02$) for the patient sample. For the full sample, SN3 ($r = .21$, $p = .002$) showed the significant associations with WM. None of the networks showed a significant association with WM performance in the sample of controls only (Table S3).

Table S6 showed the CCA results for the cognitive measures and rsFC for between-network calculations. We found a significant, positive correlation between rsFC and the two cognitive measurements ($r = .57$, $p = 8.0 \times 10^{-3}$ for PS and $r = .47$, $p = .04$ for WM) in the patients. The correlation between rsFC and PS remained significant when calculated in the full and control samples independently ($r = .41$, $p = 1.5 \times 10^{-3}$ for full sample and $r = .44$, $p = .02$ for controls). Likewise, the correlation with WM was significant in the full

FIGURE 2 Mega-analytic Forest plots for group differences between individuals with schizophrenia and healthy controls, from resting-state functional connectivity (rsFC) measures for resting-state subnetwork. Each subnetwork consisted of two functional connections between two regions of interest (connections from the first region to the second region and vice versa). The abbreviations used are the same as in Figure 1; additional prefixes (l/r: left/right) or suffixes (1, 2, 3) are used to represent the subnetwork components

FIGURE 3 The statistical *t*-map showing the patient-control differences in the functional connectivity (FC) for each pair of regions of interest (ROIs) in between-network connectivity analysis. The *t* values for the ROI pairs, statistically significant after Bonferroni multiple comparisons correction, were displayed. These ROI pairs showed reduced FC in patient sample [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Statistical measures from CCA. CCA was carried out between the rsFC from resting-state functional connections, as a set of variables with PS and working memory for the full sample, control sample, and patient sample

	Statistical measures from CCA (rsFC and processing speed)		Statistical measures from CCA (rsFC and working memory)	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Full sample	.36	.01	.35	.01
Control sample	.34	.02	.45	.003
Patient sample	.49	.002	.47	.002

Abbreviations: CCA, canonical correlation analysis; PS, processing speed; rsFC, resting-state functional connectivity.

sample ($r = .35, p = .03$), but it was not significant for controls ($r = .45$ and $p = .11$). The pattern of association between the rsFC and PS ($r = .52, p = 8.4 \times 10^{-3}$) and WM ($r = .47, p = .02$), derived from multiple networks was related to the ES of the patient-control differences in the functional networks.

3.3 | Overlap of networks in schizophrenia and cognitive deficits

The explanatory power of the associations between functional networks and cognitive measures (correlation coefficients) was plotted against Cohen's *d* ES with schizophrenia (Figure 4, Table 4). The functional networks that showed the strongest association with diagnosis (e.g., salience,

auditory, and default mode) were also those networks most positively associated with PS in the patient sample ($r = .64, p = .004$). The same trend was observed in the full sample ($r = .59, p = .01$) and the control ($r = .53, p = .03$), separately (Figure 4, first column). The same pattern was observed for WM in patients ($r = .55, p = .02$) and the full sample ($r = .56, p = .02$), but not for the control sample ($r = -.05, p = .84$) (Figure 4, second column). The functional networks showing association with diagnosis were also associated with PS corrected for WM, but not with WM corrected for PS (Table S4, Figure S7).

3.4 | Symptom severity and medication

The trending negative correlations between rsFC measures and the BPRS and CPZ equivalent were not statistically significant when applying multiple comparisons correction. There were no significant overlaps in the variance shared between rsFC and BPRS and the ESs with schizophrenia ($r = .38, p = .12$ for full sample, $r = .03, p = .9$ for control sample, and $r = .27, p = .27$ for the patient sample).

FTND scores were not statistically correlated to the rsFC measures for any of the resting-state connections, both for patients and control groups.

4 | DISCUSSION

Schizophrenia has been conceptualized as a disorder of cerebral disconnectivity (Baker et al., 2014; Meda et al., 2012). The findings of patient-control deficits on the rsFC and their impact on cognitive function are inconsistent, possibly due to small number of subjects

FIGURE 4 Correlation analysis between canonical correlation coefficients obtained using resting-state functional connectivity (rsFC) measures as a set of variables with cognitive measures as another set of variables versus Cohen's *d* effect size (ES) with schizophrenia. The first column shows the correlation between the canonical correlation coefficients obtained using rsFC measures with processing speed versus the ES (Cohen's *d*) for diagnosis. The second column shows the correlation between the canonical correlation coefficients obtained using rsFC measures with working memory versus ES (Cohen's *d*) of diagnosis. The first to third rows show information for the full combined sample (a,b), the control sample (c,d), and the patient sample (e,f) respectively. The correlation analysis was performed between 17 resting-state subnetworks, with each network comprising of two connections. Positive linear relationships were significant ($p < .05$), except for working memory in the control sample

and differences in the data analyses approaches (Adolphs, 2009; Calhoun & Hugdahl, 2012; Frith & Frith, 2007; Fryer et al., 2015; Geisler et al., 2015). We developed a large mega-analytic cohort to quantify patient-control differences in major functional networks. To help interpret our findings, we calculated the association between connectivity indices and performance in two fundamental neurocognitive domains impacted in schizophrenia: PS and WM. We replicated impaired rsFC in the salience, sensorimotor, auditory, default mode, and other functional networks that support cognitive function (Blokland, 2017; Calhoun et al., 2009; Karbasforoushan &

Woodward, 2012; Whitfield-Gabrieli & Ford, 2012) both for within-network and between-network resting-state connectivity. We found that lower rsFC measurements were consistent across three cohorts and two measurement approaches and that no rsFC showed a consistently higher connectivity in patients. The ES of patient-control differences (Cohen's *d* ~0.27–0.54) were comparable with ENIGMA's schizophrenia findings in diffusion tensor imaging fractional anisotropy measures (Cohen's *d* ~0.15–0.40) (Kelly et al., 2018); hippocampal volume (Cohen's *d* = 0.46) and volume of lateral ventricles (Cohen's *d* = 0.37) (van Erp et al., 2016). The association between

TABLE 4 Statistical measures from correlation analysis between rsFC measures with cognitive measures versus Cohen's *d* ES with schizophrenia. Canonical correlation coefficients were computed for rsFC measures with cognitive measures versus the ES of diagnosis represented by the rsFC measures. Seventeen resting-state subnetworks—each network comprising of two connections—were included in the analysis. Correlations were significant ($p < .05$), except for the case of working memory in the control sample

	Correlation between rsFC with PS versus Cohen's <i>d</i> ES with schizophrenia		Correlation between rsFC with WM versus Cohen's <i>d</i> ES with schizophrenia	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Full sample	.59	.014	.56	.019
Control sample	.53	.030	-.05	.842
Patient sample	.64	.004	.55	.020

Abbreviations: ES, effect size; PS, processing speed; rsFC, resting-state functional connectivity; WM, working memory.

rsFC, PS and WM were replicated in controls that were not ill or exposed to antipsychotic medication. In summary, the lower rsFC indices in patients were consistent, associated with cognitive function and have a potential use as endophenotypes in the imaging research in this disorder.

Our findings of reduced connectivity, both in within- and between-network computations, were consistent with the previous findings in the AN and SN (White, Joseph, Francis, & Liddle, 2010), the DMN (Repovs, Csernansky, & Barch, 2011; Whitfield-Gabrielia et al., 2009; Woodward et al., 2011). We observed significant reduction in within-network connectivity for AN and SN that were hypothesized to be associated with development of psychotic symptoms (White et al., 2010). The individuals with schizophrenia in this study exhibited overall decrease in rsFC measures, including the DMN, though hyperactivity and hyperconnectivity in the early stage of schizophrenia and in first-degree relatives of persons with schizophrenia in DMN has been reported, albeit in smaller cohorts (Fox et al., 2005; Karbasforoushan & Woodward, 2012; Whitfield-Gabrielia et al., 2009). Significant impairments in between-network FC, as observed for ROI pairs associated to the AN, SN, DMN, ECN, and SMN in our study, signify that the schizophrenia involves multiple networks (Baker et al., 2014; Li et al., 2018; Mamah, Barch, & Repovs, 2013; Tu, Lee, Chen, Li, & Su, 2013) and the findings of aberrant between-network connectivity have important implications in the search for the network endophenotype of neuropsychiatric disease (Greicius, Srivastava, Reiss, & Menon, 2004; Seeley et al., 2007).

We evaluated the rsFC underpinning of two neurocognitive functions that showed the largest patient-control differences in large meta-analytical studies: PS and WM (Dickinson et al., 2007; Knowles et al., 2010). Both PS and WM abilities rely on large-scale cerebral networks (Bartokis, 2012; Bartokis et al., 2010; Felts et al., 1997; Waxman & Bennett, 1972) and show consistent deficits in schizophrenia (Dickinson et al., 2007; Faraone et al., 2000; Keefe et al., 2004; Keefe et al., 2005; Knowles et al., 2010). We found significant

associations between rsFC measures and PS and WM performance, both in terms of the combined sample and in separate subsamples of controls and patients. We should note that the digit symbol task involves WM performance and likewise the digit sequencing task involves PS. The patterns of overlapping rsFC results are likely in part reflecting the overlapping in cognitive domains inherent in these neuropsychological tasks. The SN, AN, and DMN showed the strongest associations with diagnosis and were also the networks associated with PS and WM abilities within the patient sample. The observed a higher correlation in patients compared to controls, within- and between-network connectivity and cognitive measures, may indicate the connectivity is more involved in cognition in patients than in controls. We did not replicate the association between PS, WM, and rsFC measures for FPN although these findings were reported in unmediated first episode individuals with schizophrenia (Anhoj et al., 2018) nor were we able to link PS deficits to frontothalamic connectivity reported in (Chen et al., 2018).

We replicated our findings in controls without the disorder or antipsychotic medications where we found that associations with metrics of rsFC and cognition were network-specific and similar to the pattern observed in patients. RsFC abnormalities in schizophrenia were pervasive across multiple networks and consistent across three independent cohorts. Moreover, functional network measurements were significantly associated with PS and WM performance; those networks supporting PS and WM showed the largest vulnerability to schizophrenia. RsFC network deficits were not significantly related to medication dose or symptom severity or FTND score, although nicotine has been proved to reduce FC (Li et al., 2018) and affect network-level functions in schizophrenia (Liao et al., 2018). The overlap between the ES of disorder and the variance in rsFC in patients and controls highlight specific individual networks involved in cognition.

Replicable biological findings in complex disorders often require a large data sample to detect due to moderate ESs (Cohen's $d = 0.2$ – 0.6). We used an analytic workflow developed by the ENIGMA consortium to evaluate rsFC deficits in schizophrenia and link them to cognitive functions in a large and representative sample. ENIGMA rsfMRI workflow was developed to alleviate potential pitfalls such as variances in the quality of T1w data and registration biases that are common for data collected using different scanners and protocols. It uses the Marchenko-Pastur Principal Component Analysis (MPPCA) denoising to improve SNR/tSNR properties of time series data and rsFC measurements were shown to be consistently heritable across multiple cohorts (Adhikari, et al., 2018a).

This study has several limitations. We collected two neurocognitive measures that separate individuals with schizophrenia and controls, based on the pragmatic considerations of collecting a large sample of relevant data. The cognitive measures, PS and WM, were selected for empirical reasons because they showed the largest and the most consistent deficits in schizophrenia compared to controls in multiple meta-analyses. This may not capture all of the complex constructs involved in PS or WM. In addition, we did not detect correlations of CPZ with rsFC, yet chronic antipsychotic exposure may be a contributing factor.

In conclusion, we found consistent FC deficits across the three sample cohorts in schizophrenia; these rsFC measures are promising endophenotypes for future studies that may involve pharmacological interventions for cognitive enhancement efforts for schizophrenia. We found a significant association of rsFC measures with performance on two neurocognitive measurements: PS and WM in patients and in full sample and controls independently. Functional networks supporting PS and WM showed larger ESs in schizophrenia. Analysis involving large samples will be required for replicable findings.

ACKNOWLEDGMENT

Support was received from NIH Blueprint for Neuroscience Research grants U54EB020403, U01MH108148, 2R01EB015611, R01MH112180, R01DA027680, R01MH085646, and T32MH067533.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data can be made available upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Adhikari BM, Hong LE, Sampath H, et al. Functional network connectivity impairments and core cognitive deficits in schizophrenia. *Hum Brain Mapp*. 2019;40: 4593–4605. <https://doi.org/10.1002/hbm.24723>