Social Cognitive Networks and Social Cognitive Performance Across Individuals With Schizophrenia Spectrum Disorders and Healthy Controls

Supplementary Information

Supplemental Methods and Materials

Participants

Participants were recruited for SPINS from the Centre for Addiction and Mental Health (CAMH; Toronto, Canada), Zucker Hillside Hospital (ZHH; New York, USA), and the Maryland Psychiatric Research Center (MPRC; Maryland, USA). Data for this study included participants recruited from December 2014 to March 2018 (time of CAMH scanner upgrade). Of 180 participants with SSDs and 126 healthy individuals who completed all study visits and met eligibility requirements throughout, 164 participants with SSDs and 117 healthy individuals (cases:controls by site: CAMH 66:42; ZHH 42:34; MPRC 56:41) were included in data analyses after quality control. Participants with SSDs met DSM-5 diagnostic criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified, assessed using the Structured Clinical Interview for DSM (SCID-IV-TR), and had no change in antipsychotic medication or decrement in functioning/support level in the 30 days prior to enrollment. Controls did not have a current or past Axis I psychiatric disorder, excepting adjustment disorder, phobic disorder, and past major depressive disorder (over two years prior; presently unmedicated), or a first degree relative with a history of psychotic mental disorder. Additional exclusion criteria included a history of head trauma resulting in unconsciousness, a substance use disorder (confirmed by urine toxicology screening), intellectual disability, debilitating or unstable medical illness, or other neurological diseases. Participants also had normal or corrected-to-normal vision.

Clinical and Cognitive Assessment

Data collection occurred across three visits within a one-month period (Visit 1: Consent, screening, clinical scales; Visit 2: Magnetic resonance imaging (MRI); Visit 3: Non-social cognitive and social cognitive testing).

Administered social cognitive tasks ranged from basic emotion recognition to complex mental state inference, and were selected based on findings from the Social Cognition Psychometric Evaluation (SCOPE) study (1) and the Social Cognition and Functioning in Schizophrenia project (2). These included the Penn Emotion Recognition Test (ER40; 3), which assesses basic emotion recognition from static images, the Reading the Mind in the Eyes test (RMET; 4), involving mental state inference from the eye region of faces, and the Empathic Accuracy (EA) task (2, 5). Participants also completed The Awareness of Social Inference Test - Revised (TASIT; 6), which involves viewing social video clips and includes three subtests (TASIT 1: Identifying emotions; TASIT 2 and 3: Social inference, including detection of lies and sarcasm).

All participants also completed the Wechsler Test of Adult Reading (7) as a measure of premorbid IQ. Non-social cognition was evaluated using the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB; 8), which includes tests of processing speed, reasoning and problem solving, attention/vigilance, working memory, and verbal and visual learning. Psychiatric symptoms were assessed in the SSD sample only using the Brief Psychiatric Rating Scale (BPRS; 9) and the Scale for the Assessment of Negative Symptoms (SANS; 10). Functioning was evaluated using the Birchwood Social Functioning Scale (BSFS; 11) across groups, and the Quality of Life Scale (QLS; 12) in the SSD group only.

MRI Data Acquisition

MRI scans were collected using harmonized scanning parameters on 3T scanners with multichannel head coils, including a General Electric Discovery (N=108; CAMH), a General Electric Signa (N=33; ZHH) and Siemens Prisma (N=43; ZHH), and a Siemens Tim Trio (N=55; MPRC) and Siemens Prisma (N=42; MPRC).

Empathic Accuracy (EA) Task

The EA task was completed during functional MRI. Prior to scanning, participants were trained using a practice version of the task in a mock scanner. During the task, participants watch 9 videos in a set order of individuals (5 females, 4 males) discussing emotional (4 positive, 5 negative) autobiographical events, such as taking a trip to Spain, seeing their favorite comedian, getting a part in a movie, not being paid on time, an uncle passing away, and having their truck broken into. This version of the EA task was designed to include adults varying in age, race, and ethnicity. The details of the video development are presented elsewhere (2, 13). Throughout the videos, participants provide continuous ratings of how positive or negative the individual in the video is feeling, on a 9-point scale (1 = extremely negative to 9 = extremely positive) using a button box. Thus, they provide a valence rating rather than having to explicitly infer higher-level, more complex mental states. EA was calculated for each participant by correlating their ratings with self-ratings provided by the individuals in the videos. These values were then Fisher r-to-z transformed. The task is presented in three runs (~10 mins/run) with three EA videos (120-150 s each) and two interleaved control videos (40 s each) per run. During the control condition, participants provide continuous ratings of the relative light or darkness of a greyscale circle as it changes shades, on a 9-point scale. This condition is included to ensure that participants are engaged in the task (controlling for avolition) and comprehend it.

fMRI Preprocessing

All scans were preprocessed using an in-house pipeline system, epitome [https://github.com/josephdviviano/epitome], which uses FSL and AFNI. All scans had the first 4 TRs removed and were slice-time corrected. Time series outliers were removed using despiking and each run was scaled to have a global mean of 1000. Linear registrations were calculated between the EPI image and each subject's T1 image using FLIRT, and the T1 and MNI space, followed by a non-linear warp to MNI space using FNIRT.

For each participant, TRs with framewise displacement > .5 mm were censored (14), along with the preceding and trailing TR, and replaced with a linear interpolate to perform confound regression. A nuisance regression model was then applied to the data, including regressors for the

6 head motion correction parameters, a 2nd order detrend, mean white matter (WM) signal, mean cerebral spinal fluid (CSF) signal, the square, derivative, and square of the derivative for each of these regressors, and the top three principal components of the WM and CSF signals (aCompCor). This approach combines thorough regression of head motion parameters (15) and tissue-specific regressors (16). The data was then smoothed to a full width half maximum of 8 mm (17, 18) using 3dBlurToFWHM, and warped into MNI space using the previously calculated transform.

Following mean residual time series generation for selected regions of interest, censored TRs were then dropped, and participants were excluded if more than 30% of their time points were dropped across all three runs.

Data-Driven Social Cognitive Subnetwork Detection

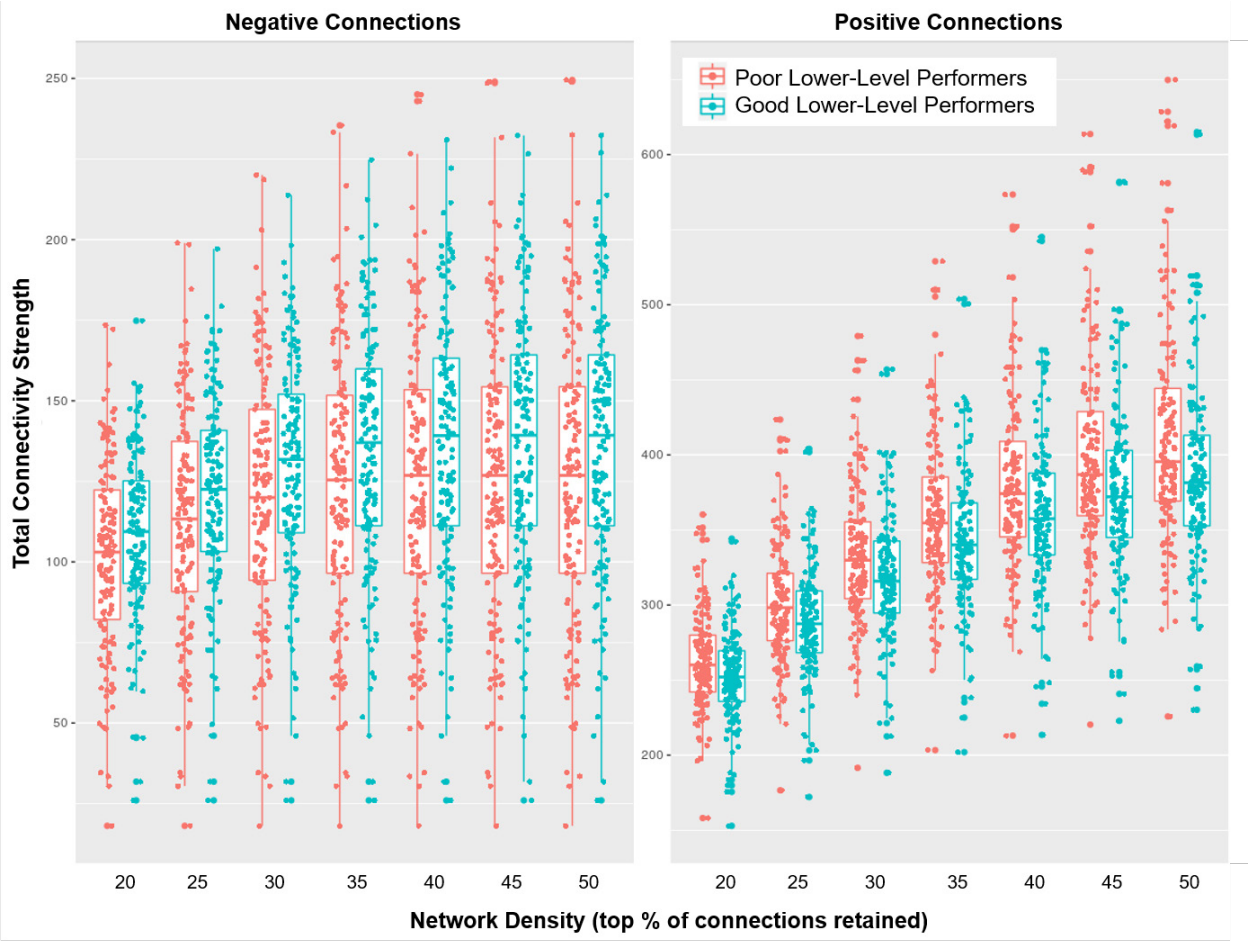
Community detection is a data-driven method of defining densely connected subgroups of nodes, or modules, which have high intramodular connectivity and lower intermodular connectivity (19). Social cognitive subnetworks (or communities) were identified for each participant using the Louvain community detection algorithm for signed networks (positive and negative weights) from the Brain Connectivity Toolbox (20), which divides nodes into modules while maximizing within-module connections and minimizing between-module connections. This was done at network densities ranging from the top 20-70% of connections (5% intervals). To generate consensus partitions for each participant at each density, this algorithm was run 100 times per participant at each density, after which consensus clustering was performed using the Louvain algorithm (1000 iterations; 21) across the 100 partitions per participant at agreement thresholds of 30, 40, 50, and 60% (19), at each density. A group-level partition was then generated by performing the same consensus clustering procedure across the individual partitions at each density. Consensus clustering produces an agreement matrix based on the individual partitions (indicating the proportion of partitions where a pair of nodes were assigned to the same module). The agreement matrix is then thresholded by a given level of agreement and consensus partitions are created by running the algorithm iteratively on the agreement matrix, and repeating this until a single representation is achieved. The consistency of these consensus partitions was then examined across the 11 densities at each of the four agreement thresholds, and an overall parcellation was generated based on the most frequently assigned module across all consensus partitions.

Division of Sample Based on Social Cognitive Performance

The lower- and higher-level social cognition factor scores were estimated for each participant using multiple regression in the R package lavaan (22), based on our previous two-factor model of social cognition which demonstrated very good fit across individuals with SSDs and healthy controls (CFI = 1.00, RMSEA = 0.00; 23). We also tested this two-factor model in the current sample using confirmatory factor analysis, confirming good fit for the data across participants (CFI = .990, RMSEA = .042). Model fit was assessed using ranges of acceptable fit values outlined by Hu and Bentler (24), including comparative fit index (CFI) $\geq .95$ and root mean square error of approximation (RMSEA) $\leq .06$ to suggest that the hypothesized model fits the observed data relatively well.

Statistical Analysis

Figure S1: Representative example of total connectivity strength across network densities demonstrating consistent patterns by lower-level social cognitive performance group and connection-type



Supplemental Results

Table S1: Participant demographic and clinical characteristics by lower-level social cognitive performance group

	Poor Lower-Level Social Cognition (N = 141)		Good Lower-Level Social Cognition (N = 140)		
	N	**%**	**N**	**%**	***p***
Diagnostic Group (control)	31	22.0	86	61.4	< .001
Higher-Level Social Cognition Group (good)	22	15.6	118	84.3	< .001
Gender (male)	94	66.7	80	57.1	.128
	Mean	**SD**	**Mean**	**SD**	***p***
Age	33.09	9.99	30.71	9.72	.044
Education (highest grade)	13.51	2.18	15.31	1.96	< .001
WTAR (standard score)	102.81	13.92	116.55	8.39	< .001
BSFS Total	143.20	29.92	163.39	27.07	< .001
Lower-Level Social Cognition Score	-0.67	0.65	0.74	0.33	< .001
Higher-Level Social Cognition Score	-0.61	0.80	0.69	0.39	< .001

SD = standard deviation, WTAR = Wechsler Test of Adult Reading, BSFS = Birchwood Social Functioning Scale

Table S2: Participant demographic and clinical characteristics by higher-level social cognitive performance group

	Poor Higher-Level Social Cognition (N = 141)		Good Higher-Level Social Cognition (N = 140)		
	N	**%**	**N**	**%**	***p***
Diagnostic Group (control)	31	22.0	86	61.4	< .001
Lower-Level Social Cognition Group (good)	22	15.6	118	84.3	< .001
Gender (male)	90	63.8	84	60.0	.590
	Mean	**SD**	**Mean**	**SD**	***p***
Age	33.14	9.46	30.65	10.22	.035
Education (highest grade)	13.61	2.21	15.21	2.02	< .001
WTAR (standard score)	103.23	14.31	115.82	8.78	< .001
BSFS Total	142.43	29.20	164.16	27.26	< .001
Lower-Level Social Cognition Score	-0.57	0.78	0.63	0.45	< .001
Higher-Level Social Cognition Score	-0.69	0.70	0.76	0.29	< .001

SD = standard deviation, WTAR = Wechsler Test of Adult Reading, BSFS = Birchwood Social Functioning Scale

Network Connectivity

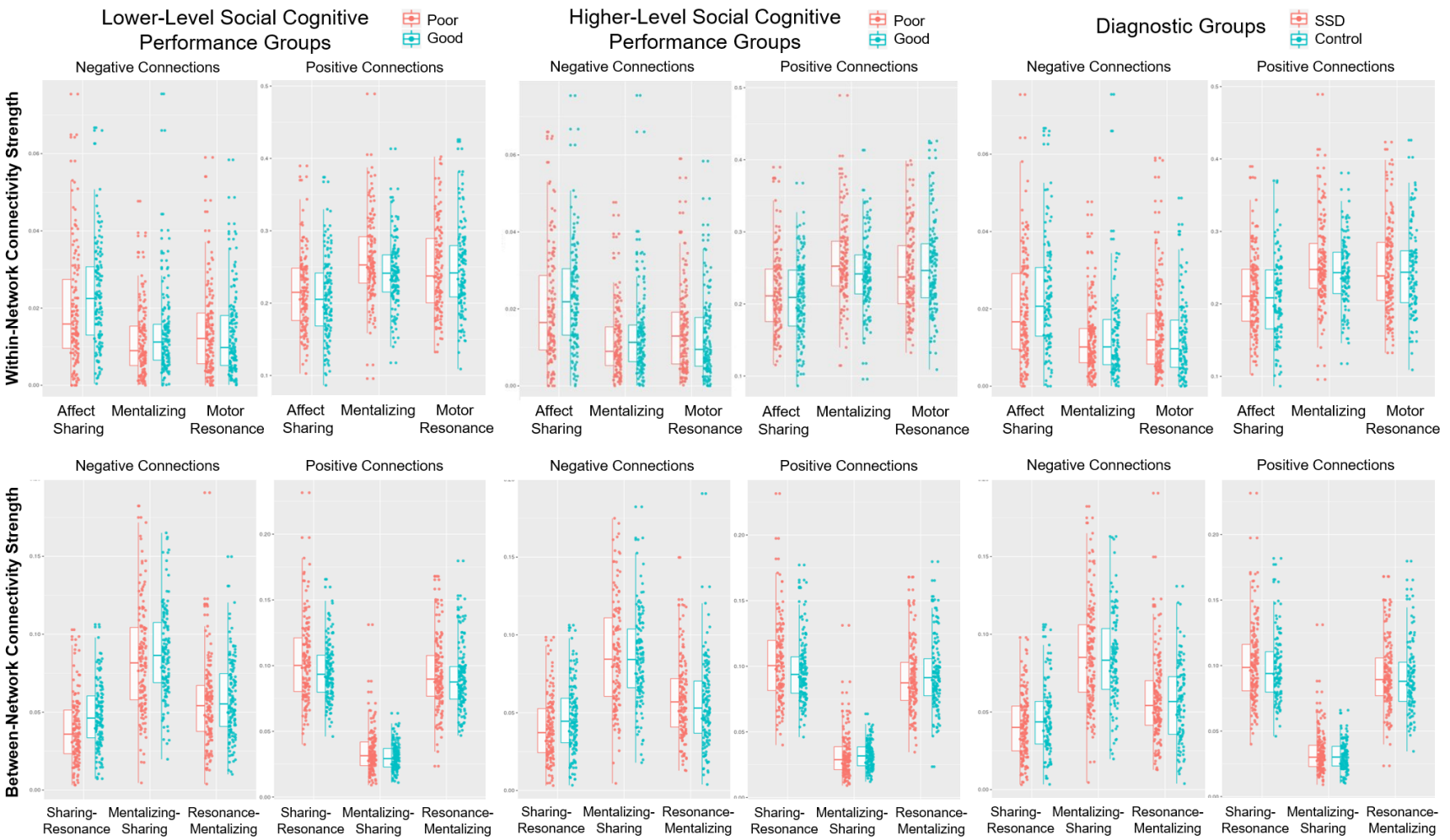
Within-Network Connectivity (Table 2)

The ANCOVAs comparing within-network connectivity values between groups all demonstrated a main effect of network (Table 2). Pairwise comparisons revealed that overall within-network connectivity was significantly greater in the mentalizing ($t(546) = 8.11$, $p < .0001$) and motor resonance ($t(546) = 6.84$, $p < .0001$) networks than the affect sharing network, but there was no difference between the mentalizing and motor resonance networks ($t(546) = 1.27$, $p > .1$). There was also a main effect of connection-type, driven by greater within-network positive connectivity than negative connectivity ($t(273) = 80.25$, $p < .0001$). Further, there was a significant network x connection-type interaction. This was characterized by greater positive within-network connectivity in the mentalizing ($t(1055) = 12.8$, $p < .0001$) and motor resonance ($t(1055) = 10.9$, $p < .0001$) networks than the affect sharing network, and marginally greater positive within-network connectivity in the mentalizing than the motor resonance network ($t(1055) = 1.95$, $p = .052$). In contrast, greater negative within-network connectivity was seen in the affect sharing network than both the mentalizing ($t(1055) = 2.52$, $p = .036$) and motor resonance ($t(1055) = 2.19$, $p = .043$) networks, but there was no difference between the mentalizing and motor resonance networks ($t(1055) = -.325$, $p > .1$).

Between-Network Connectivity (Table 2)

Across group comparisons of between-network connectivity, there was a significant main effect of network (Table 2). This was driven by greater mentalizing-motor resonance connectivity, than both motor resonance-affect sharing ($t(546) = 2.90$, $p = .004$) and mentalizing-affect sharing connectivity ($t(546) = 16.7$, $p < .0001$) and greater motor resonance-affect sharing connectivity than mentalizing-affect sharing ($t(546) = 13.8$, $p < .0001$). A main effect of connection-type was also observed, characterized by greater positive versus negative between-network connectivity ($t(273) = 7.77$, $p < .0001$). Additionally, there was a significant network x connection-type interaction. Motor resonance-affect sharing positive connectivity was greater than both mentalizing-motor resonance ($t(843) = 4.19$, $p < .0001$) and mentalizing-affect sharing ($t(843) = 34.7$, $p < .0001$) positive connectivity, and mentalizing-motor resonance positive connectivity was greater than mentalizing-affect sharing ($t(843) = 30.5$, $p < .0001$). The opposite pattern was seen for negative between-network connectivity, with lower motor resonance-affect sharing than mentalizing-motor resonance ($t(843) = -6.96$, $p < .0001$) and mentalizing-affect sharing ($t(843) = -21.45$, $p < .0001$) negative connectivity, and lower mentalizing-motor resonance than mentalizing-affect sharing negative connectivity ($t(843) = -14.49$, $p < .0001$).

Figure S2: Within- and between-network connectivity strength by connection-type and lower-level social cognitive performance, higher-level social cognitive performance, and diagnostic groups



Prisma Subsample Connectivity

Regression analyses including positive and negative within- and between-network connectivity strengths in the Prisma subsample revealed that increased motor resonance-affect sharing negative connectivity was significantly associated with greater lower-level social cognition factor scores (β=0.44, p=.045, R^2=0.250), as in the full sample, though this was not a significant predictor of higher-level social cognition factor scores in the subsample (β=0.30, p=.26, R^2=0.219).

The same ANCOVA analyses in the Prisma subsample also revealed very similar effects to those found in the full sample (Table S3). Significant main effects and interactions coincided with findings in the full sample for between-network connectivity, including a significant connection-type x lower-level social cognitive performance group interaction and a network x connection-type x higher-level social cognitive performance group interaction. For within-network connectivity, though lower- and higher-level social cognitive performance group effects and interactions were not statistically significant, the network x connection-type x higher-level social cognitive performance group interaction effect size was larger than that in the full sample. There also remained to be no significant main effects of, or interactions with, diagnostic group for within- or between-network connectivity.

Table S3: Prisma subsample within- and between-network connectivity results by lower-level social cognitive performance, higher-level social cognitive performance, and diagnostic groups

	df	F	*p*	partial eta^2
Within-Network Connectivity				
Lower-Level Social Cognitive Performance Group Comparisons				
Network	2.00, 159.61	13.52 ***	<.0001	.145
Connection-type	1, 80	2281.77 ***	<.0001	.966
Group	1, 80	0.25	.616	.003
Network x Connection-type	2.00, 159.84	17.33 ***	<.0001	.178
Network x Group	2.00, 159.61	0.29	.748	.004
Connection-type x Group	1, 80	0.62	.435	.008
Network x Connection-type x Group	2.00, 159.84	0.28	.754	.004
Higher-Level Social Cognitive Performance Group Comparisons				
Network	2.00, 159.72	13.74 ***	<.0001	.147
Connection-type	1, 80	2264.35 ***	<.0001	.966
Group	1, 80	0.02	.900	.000
Network x Connection-type	2.00, 159.97	17.64 ***	<.0001	.181
Network x Group	2.00, 159.72	1.62	.201	.020
Connection-type x Group	1, 80	0.00	.997	.000
Network x Connection-type x Group	2.00, 159.97	1.68	.190	.021
Diagnostic Group Comparisons				
Network	1.99, 159.38	13.60 ***	<.0001	.145
Connection-type	1, 80	2267.47 ***	<.0001	.966
Group	1, 80	0.37	.543	.005

Network x Connection-type	2.00, 159.83	17.28 ***	<.0001	.178
Network x Group	1.99, 159.38	0.76	.470	.009
Connection-type x Group	1, 80	0.11	.741	.001
Network x Connection-type x Group	2.00, 159.83	0.05	.953	.001
Between-Network Connectivity				
Lower-Level Social Cognitive Performance Group Comparisons				
Network	1.97, 157.43	63.83 ***	<.0001	.444
Connection-type	1, 80	20.64 ***	<.0001	.205
Group	1, 80	2.51	.117	.030
Network x Connection-type	1.62, 129.31	215.54 ***	<.0001	.729
Network x Group	1.97, 157.43	0.85	.426	.011
Connection-type x Group	1, 80	6.49 *	.013	.075
Network x Connection-type x Group	1.62, 129.31	1.05	.341	.013
Higher-Level Social Cognitive Performance Group Comparisons				
Network	1.96, 157.12	63.21 ***	<.0001	.441
Connection-type	1, 80	19.13 ***	<.0001	.193
Group	1, 80	0.01	.910	.000
Network x Connection-type	1.64, 131.49	223.96 ***	<.0001	.737
Network x Group	1.96, 157.12	0.08	.923	.001
Connection-type x Group	1, 80	0.17	.686	.002
Network x Connection-type x Group	1.64, 131.49	4.22 *	.023	.050
Diagnostic Group Comparisons				
Network	1.96, 156.63	64.25 ***	<.0001	.445
Connection-type	1, 80	19.09 ***	<.0001	.193
Group	1, 80	0.05	.815	.001
Network x Connection-type	1.61, 128.85	214.42 ***	<.0001	.728
Network x Group	1.96, 156.63	1.39	.252	.017
Connection-type x Group	1, 80	0.01	.915	.000
Network x Connection-type x Group	1.61, 128.85	0.63	.503	.008

Nodal Connectivity (Table S4)

Regions exhibiting greater positive within-network connectivity in poor versus good lower-level social cognitive performers (Figure 2) included the left dorsal anterior cingulate cortex (ACC) and posterior temporoparietal junction (TPJ; mentalizing network). Greater positive between-network connectivity was demonstrated in poor performers in bilateral inferior parietal lobule (IPL) nodes (affect sharing network), whereas greater negative between-network connectivity was seen in good performers in the right IPL/intraparietal sulcus (affect sharing network) and bilateral supplementary motor area (SMA) and inferior frontal gyrus (IFG; motor resonance network).

Fewer nodes showed higher-level social cognitive performance group-based differences (Figure 3), though greater positive within-network connectivity in poor versus good performers was also

seen in left posterior TPJ (mentalizing network), and between-network negative connectivity was greater in right IPL/intraparietal sulcus (affect sharing network) in better performers.

No nodes demonstrated significant diagnostic group differences in positive or negative within-network connectivity strength. However, cases showed greater between-network positive connectivity in bilateral IPL nodes (affect sharing network) than controls, whereas the right IPL (affect sharing network) exhibited greater between-network negative connectivity in controls (see Table S4 for details).

Table S4: Nodal connectivity results by lower-level social cognitive performance, higher-level social cognitive performance, and diagnostic groups

	t	*p FDR*		Direction of Effect	Network
Lower-Level Social Cognitive Performance Group Comparisons					
Positive Within-Network Connectivity Strength					
L dACC	-3.23	.036	*	Poor > Good	Mentalizing
L pTPJ	-3.74	.012	*	Poor > Good	Mentalizing
Negative Within-Network Connectivity Strength					
No regions with significant differences					
Positive Between-Network Connectivity Strength					
R SMG	-4.50	.001	**	Poor > Good	Affect Sharing
L IPL/SMG	-3.98	.002	**	Poor > Good	Affect Sharing
L IPS	-3.46	.011	*	Poor > Good	Affect Sharing
Negative Between-Network Connectivity Strength					
R SMA	3.71	.007	**	Good > Poor	Motor Resonance
L SMA	4.62	.0003	***	Good > Poor	Motor Resonance
R IFG BA44	3.02	.029	*	Good > Poor	Motor Resonance
L IFG BA45 1	3.19	.020	*	Good > Poor	Motor Resonance
R IPL/IPS	3.34	.017	*	Good > Poor	Affect Sharing
Higher-Level Social Cognitive Performance Group Comparisons					
Positive Within-Network Connectivity Strength					
L pTPJ	-3.51	.028	*	Poor > Good	Mentalizing
Negative Within-Network Connectivity Strength					
No regions with significant differences					
Positive Between-Network Connectivity Strength					
R SMG	-3.60	.019	*	Poor > Good	Affect Sharing

Negative Between-Network Connectivity Strength					
R IPL/IPS	3.25	.034	*	Good > Poor	Affect Sharing
R mPFC/ACC	-3.39	.034	*	Poor > Good	Mentalizing

Diagnostic Group Comparisons

Positive Within-Network Connectivity Strength

No regions with significant differences

Negative Within-Network Connectivity Strength

No regions with significant differences

Positive Between-Network Connectivity Strength					
R IPL/IPS	-3.23	.036	*	Case > Control	Affect Sharing
R SMG	-4.63	.0003	***	Case > Control	Affect Sharing
Negative Between-Network Connectivity Strength					
R IPL/IPS	3.72	.013	*	Control > Case	Affect Sharing

R = right, L = left, Good = good social cognitive performance group, Poor = poor social cognitive performance group, BA = Brodmann area, dACC = dorsal anterior cingulate cortex, pTPJ = posterior temporoparietal junction, SMG = supramarginal gyrus, IPL = inferior parietal lobule, IPS = intraparietal sulcus, SMA = supplementary motor area, IFG = inferior frontal gyrus, mPFC = medial prefrontal cortex

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