Archival Report

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Resting-State Connectivity Biomarkers of Cognitive Performance and Social Function in Individuals With Schizophrenia Spectrum Disorder and Healthy Control Subjects

Joseph D. Viviano, Robert W. Buchanan, Navona Calarco, James M. Gold, George Foussias, Nikhil Bhagwat, Laura Stefanik, Colin Hawco, Pamela DeRosse, Miklos Argyelan, Jessica Turner, Sofia Chavez, Peter Kochunov, Peter Kingsley, Xiangzhi Zhou, Anil K. Malhotra, and Aristotle N. Voineskos, for the Social Processes Initiative in Neurobiology of the Schizophrenia(s) Group

ABSTRACT

BACKGROUND: Deficits in neurocognition and social cognition are drivers of reduced functioning in schizophrenia spectrum disorders, with potentially shared neurobiological underpinnings. Many studies have sought to identify brain-based biomarkers of these clinical variables using a priori dichotomies (e.g., good vs. poor cognition, deficit vs. nondeficit syndrome).

METHODS: We evaluated a fully data-driven approach to do the same by building and validating a brain connectivity–based biomarker of social cognitive and neurocognitive performance in a sample using resting-state and task-based functional magnetic resonance imaging (n = 74 healthy control participants, n = 114 persons with schizophrenia spectrum disorder, 188 total). We used canonical correlation analysis followed by clustering to identify a functional connectivity signature of normal and poor social cognitive and neurocognitive performance.

RESULTS: Persons with poor social cognitive and neurocognitive performance were differentiated from those with normal performance by greater resting-state connectivity in the mirror neuron and mentalizing systems. We validated our findings by showing that poor performers also scored lower on functional outcome measures not included in the original analysis and by demonstrating neuroanatomical differences between the normal and poorly performing groups. We used a support vector machine classifier to demonstrate that functional connectivity alone is enough to distinguish normal and poorly performing participants, and we replicated our findings in an independent sample (n = 75).

CONCLUSIONS: A brief functional magnetic resonance imaging scan may ultimately be useful in future studies aimed at characterizing long-term illness trajectories and treatments that target specific brain circuitry in those with impaired cognition and function

Keywords: Biomarker, Functional outcomes, Imaging, Machine learning, Resting-state fMRI, Schizophrenia

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Social cognitive and neurocognitive (SC/NC) deficits are associated with real-world functioning impairment in individuals with schizophrenia spectrum disorders (SSDs): schizophrenia, schizoaffective disorder, or schizophreniform disorder. However, these deficits can range from mild to severe, and some individuals with an SSD perform just as well or even better than matched controls (1,2). Past attempts to understand SC/NC deficits through separation into subtypes [e.g., type 1 vs. type 2 (3), good vs. poor outcomes (4), deficit vs. nondeficit (5–9)] are based on clinical characterization rather than data-driven approaches. Additionally, while DSM-IV subtypes have demonstrated separable domains of psychopathology in schizophrenia (negative symptomatology, psychosis, and disorganization) (10–16), they failed to produce distinct groups of SC/NC performers or help uncover biomarkers of reduced functioning (17). The variability in SC/NC function, social impairment, and brain circuitry among people with SSDs may explain why standard univariate or case-control approaches have not translated well to biomarker identification.

Data-driven approaches that group individuals into neurophysiological subtypes, or "biotypes," have been applied to persons with psychosis and depression, producing novel subgroups with distinct biomarkers (18–20). These approaches

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can uncover distinct biological factors that give rise to overlapping clinical presentations in disease. In SSDs, intact SC/NC processes are important for real-world function, and deficits in these domains are predictive of one's ability to form or sustain relationships, one's probability of gaining and maintaining employment, and long-term outcomes (15,21–28). Social cognitive processes have recently emerged as particularly strong determinants of functional outcome (25,29,30), and studies have identified the frontoparietal, corticomidline, and temporoparietal (or "mirror neuron") circuitry (31) as important for imitation, empathy, theory of mind, and perspective taking. Smaller functional magnetic resonance imaging (fMRI) studies have focused on case-control differences in these regions (32–39), and such differences have not clearly translated to real-world function.

We assessed the utility of resting-state and task-based functional connectivity, and task activations for two social fMRI tasks, for identifying biologically different groups with differences in SC/NC performance. We first aimed to identify the fMRI data type (comparing task activations and/or connectivity from the tasks and resting-state data) that produced biotype groupings with the largest differences in SC/NC performance between groups using canonical correlation analysis (CCA), followed by hierarchical clustering that grouped the participants into biotypes based on these brain features (19). We validated our findings by comparing the identified groups on symptom, functional outcome, and structural neuroimaging measures (subcortical volumes, cortical thickness, and diffusion-based white matter metrics) not included in the original biotyping. We also tested whether the biotype of held-out participants could be correctly identified by a support vector machine classifier (SVC) trained using fMRI features, similar to a diagnostic test, and ranked the utility of each fMRI input by SVC classification accuracy. As control analyses, we compared these accuracies with those from SVCs trained to distinguish participants with normal or poor SC/NC scores, and diagnosis (SSD cases vs. controls) using the same input fMRI data. We hypothesized that SVCs trained to distinguish biotypes (i.e., groups informed by neurobiology) would achieve higher scores on held-out participants than would classifiers trained on cognitive score–based groups or diagnostic groups. We finally repeated our analyses in an independent sample.

METHODS AND MATERIALS

We analyzed participant data from the three-site Social Processes Initiative in Neurobiology of the Schizophrenia(s) study (N = 188, mean age ± SD = 33.0 ± 10.2 years; participants with SSD = 114, mean age ± SD = 34.3 ± 10.2 years; control subjects = 74, mean age ± SD = 31.0 ± 10.1 years). Demographics are summarized in Table 1; see Supplemental Table S5 for demographics at each site split by diagnosis. See the Supplement for inclusion and exclusion criteria. All participants signed an informed consent agreement, and the study was approved by institutional ethics boards at all participating institutions. All participants completed multiple assessments out of the MRI scanner. SC/NC functioning was assessed via the Penn Emotion Recognition Task (40), Reading the Mind in the Eyes Test (41), Relationships Across Domains (42), the three scales from the Awareness of Social Inference Test Revised (43), and six neurocognitive domains of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (44). Social functioning and quality of life were assessed via the Birchwood Social Functioning Scale (45) and Quality of Life Scale (46). Psychiatric symptom burden was assessed via the Brief Psychiatric Rating Scale (47) and Scale for the Assessment of Negative Symptoms (48). Two additional measures of diminished emotional expression and poor motivation that were based on the Scale for the Assessment of Negative Symptoms were included, as they relate to functional outcomes in SSD (16,49). Extrapyramidal symptoms were assessed via the Simpson–Angus Scale (50), general medical burden via the Cumulative Illness Rating Scale for Geriatrics (51), and antipsychotic medication exposure via chlorpromazine equivalents (52,53).

All sites used weekly phantom scans to ensure the stability of the T1-weighted, diffusion tensor imaging–based, and functional magnetic resonance imaging–based sequences over time. At all sites, we implemented standardized operating

Table 1. Demographics From the Three Sites of Data Collection

	Site CAMH	Site MPRC	Site ZHH
Group, n_{SSD}:n_{HC}	44:29	43:26	27:19
Sex, n_F:n_M	27:46	20:49	23:23
Ethnicity, n_{nh}:n_h	65:7	66:3	34:11
Language, n_{efl}:n_{esl}	62:11	66:3	44:2
Marital Status, n_m:n_d:n_s	11:2:60	13:6:50	6:5:33
Special Education, n_Y:n_N	6:67	11:58	12:34
Age, Years, Mean ± SD	27.81 ± 7.70	36.20 ± 10.67	34.42 ± 9.04
Education, Years, Mean ± SD	14.40 ± 2.43	14.33 ± 2.37	14.33 ± 2.54
Mother's Education, Years, Mean ± SD	14.28 ± 2.93	14.36 ± 2.80	14.31 ± 3.30
Father's Education, Years, Mean ± SD	15.02 ± 3.38	14.56 ± 2.67	13.89 ± 3.49
Handedness (Left = 0, Right = 1), Mean ± SD	0.65 ± 0.49	0.63 ± 0.41	0.55 ± 0.62
IQ, Mean ± SD	112.13 ± 12.45	107.04 ± 15.95	101.58 ± 15.31

CAMH, Centre for Addiction and Mental Health; d, divorced; efl, English as a first language; esl, English as a second language; F, female; h, Hispanic; HC, healthy control; M, male; m, married; MPRC, Maryland Research Centre; N, no; nh, not Hispanic; s, single; SSD, schizophrenia spectrum disorder; Y, yes; ZHH, Zucker Hillside Hospital.