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Archival Report

Aberrant Effective Connectivity During Eye Gaze Processing Is Linked to Social Functioning and Symptoms in Schizophrenia

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ABSTRACT

BACKGROUND: Patients with schizophrenia show abnormal gaze processing, which is associated with social dysfunction. These abnormalities are related to aberrant connectivity among brain regions that are associated with visual processing, social cognition, and cognitive control. In this study, we investigated 1) how effective connectivity during gaze processing is disrupted in schizophrenia and 2) how this may contribute to social dysfunction and clinical symptoms.

METHODS: Thirty-nine patients with schizophrenia/schizoaffective disorder (SZ) and 33 healthy control participants completed an eye gaze processing task during functional magnetic resonance imaging. Participants viewed faces with different gaze angles and performed explicit and implicit gaze processing. Four brain regions—the secondary visual cortex, posterior superior temporal sulcus, inferior parietal lobule, and posterior medial frontal cortex—were identified as nodes for dynamic causal modeling analysis.

RESULTS: Both the SZ and healthy control groups showed similar model structures for general gaze processing. Explicit gaze discrimination led to changes in effective connectivity, including stronger excitatory, bottom-up connections from the secondary visual cortex to the posterior superior temporal sulcus and inferior parietal lobule and inhibitory, top-down connections from the posterior medial frontal cortex to the secondary visual cortex. Group differences in top-down modulation from the posterior medial frontal cortex to the posterior superior temporal sulcus and inferior parietal lobule were noted, such that these inhibitory connections were attenuated in the healthy control group but further strengthened in the SZ group. Connectivity was associated with social dysfunction and symptom severity.

CONCLUSIONS: The SZ group showed notably stronger top-down inhibition during explicit gaze discrimination, which was associated with more social dysfunction but less severe symptoms among patients. These findings help pinpoint neural mechanisms of aberrant gaze processing and may serve as future targets for interventions that combine neuromodulation with social cognitive training.

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Individuals with schizophrenia exhibit pervasive social cognitive deficits (1,2), which are resistant to treatment (3) and contribute to poor functional outcomes (4,5). Understanding mechanisms that contribute to these deficits is crucial to developing novel treatments that improve outcomes. One component of social cognition is the ability to accurately perceive social cues including the eye gaze direction of others (6,7). The ability to accurately perceive gaze is important for interpreting the mental/emotional states of others, which in turn contributes to adaptive behavior (6,7). Individuals with schizophrenia show less precise gaze perception and enhanced self-referential bias compared with healthy control (HC) participants (8–14), and these abnormalities contribute to functional impairment (15). During social cognition, people with schizophrenia show altered patterns of activity in brain regions associated with visual perception, salience detection, face processing, mentalizing, and cognitive control (1,16). In addition to regional abnormalities, functional disconnection is well documented in schizophrenia; nonetheless, how brain regions dynamically interact to facilitate psychological processes such as gaze perception is not well understood (10,17–19). Understanding the neural architecture of aberrant gaze processing in schizophrenia would improve our understanding of core disease mechanisms and help guide our choice of therapeutic targets in future translational research. Thus, the current study applied dynamic causal modeling (DCM) to characterize aberrant brain network dynamics during gaze processing in schizophrenia and their relationship to social dysfunction.

Prior research on the neural correlates of social cognitive processes (e.g., emotion perception or mentalizing) in schizophrenia has provided insights into the underlying neural mechanisms of social cognitive deficits (1). Gaze processing

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has been studied less often, but a limited body of research has shown evidence of frontal, occipital, and limbic hypoactivation along with sensorimotor hyperactivation in schizophrenia (14,20,21). Nonetheless, a comprehensive account of the neural mechanisms of gaze processing in schizophrenia must consider how regional abnormalities dynamically interact to collectively contribute to altered gaze processing and social cognition. Prior studies suggest that gaze processing abnormalities in schizophrenia are a consequence of alterations in bottom-up processes—such as encoding and integrating visual stimuli, which are associated with occipital and parietal association regions—and top-down processes—such as cognitive control and mentalizing, which are associated with medial frontal regions (20,22–27). However, most previous functional magnetic resonance imaging (fMRI) studies have relied on regional activation or correlation-based indices of functional connectivity. Functional connectivity allows researchers to identify shared variation in activations between brain regions, but it does not allow conclusions to be drawn about the direction of information flow. This leaves key questions unanswered. Is abnormal gaze processing in schizophrenia due to abnormalities in bottom-up processes that stem from visual processing deficits, top-down processes such as biased prior beliefs, or both? By studying effective connectivity, we can examine how bottom-up and top-down connections differ between people with schizophrenia and HC participants and evaluate their functional significance.

One method for quantifying effective connectivity is DCM. DCM estimates underlying neural dynamics in terms of excitatory and inhibitory connections between regions, self-inhibition parameters that account for natural decay over time within regions, and changes in connections as a function of experimental contexts, such as task conditions (28–30). DCM has been used in schizophrenia research to understand the role of functional dysconnectivity in altered working memory, attention, prediction, and visual illusions (22,31–34). In addition, our research group previously used DCM to investigate gaze processing in schizophrenia using a sample of 27 patients and 22 control participants (10). We found that patients and control participants showed similar model structure, but patients showed altered self-connections (i.e., local cortical dysfunction), reduced excitatory bottom-up connections during general gaze processing (i.e., weaker data-driven gaze processing), and stronger inhibitory top-down connections during both general and explicit gaze discrimination (i.e., overreliance on prior beliefs). Altered effective connectivity was significantly associated with poorer social cognition/functioning. These results provided preliminary insight into the brain dynamics that underlie gaze processing abnormalities in schizophrenia but warrant replication given the small sample size.

In the current study, we sought to replicate our previous work and further investigate the relevance of eye gaze processing to functioning and clinical symptoms. Patients and control participants completed a gaze processing task during fMRI. DCM was applied to quantify effective connectivity during general gaze processing, as well as modulation of connectivity during explicit gaze discrimination. We anticipated that—mirroring our previous results (10)—patients and control participants would show similar model structures characterized by a combination of excitatory bottom-up connections during general gaze processing, as well as excitatory and inhibitory top-down connections. We anticipated that explicit gaze discrimination (compared with general gaze processing) would lead to stronger excitatory bottom-up and inhibitory top-down connections across groups. In addition, we expected the schizophrenia group to show altered self-connections, reduced excitatory bottom-up connections during general gaze processing, and stronger inhibitory top-down connections during both general and explicit gaze discrimination compared with control participants. Finally, we hypothesized that connectivity would be associated with individual differences in social cognition/functioning and symptom severity.

METHODS AND MATERIALS

Participants

Thirty-nine patients with schizophrenia (n = 15) or schizoaffective disorder (n = 24) (SZ group) and 33 matched HC participants completed the study. No participants overlapped with those in our previous report (10). Diagnoses were established using the Structured Clinical Interview for DSM-IV Axis I Disorders (35). Participants completed several measures of social cognition/functioning, which are documented in Table 1, along with demographic variables. In terms of race, participants included 5 Asian, 23 Black, 2 multiracial, 1 Native American, and 41 White individuals; 5 individuals identified as Hispanic/Latino.

fMRI Task, Acquisition, and Preprocessing

Participants completed an eye-contact detection task during fMRI, details of which are shown and described in Figure 1. MRI scanning occurred on a 3.0T GE MR Discovery scanner, using a multiband echo planar imaging sequence for functional images. Data were processed using typical methods in Statistical Parametric Mapping (36); after slice-time correction, functional volumes were coregistered with a high-resolution T1 image, spatially normalized to the Montreal Neurological Institute 152 brain, and spatially smoothed with an 8-mm isotropic Gaussian kernel.

Behavioral Analyses

Two psychophysical metrics were derived from participants' behavioral responses on the explicit gaze discrimination task (Figure 1C): slope (indexing perceptual precision) and threshold (indexing self-referential bias). Hierarchical Bayesian modeling was used to derive individual and group estimates of these metrics (see the Supplement for details).

Effective Connectivity Analysis

Identification of Nodes. We applied a general linear model to the fMRI time-series data to identify DCM nodes. Individual blood oxygen level–dependent signals were regressed to 2 boxcar regressors of interest (gaze and gender) along with nuisance regressors (6 runs, 6 motion parameters, 6 squared motion parameters, and 12 motion parameter derivatives) convolved with a hemodynamic response function. Then, to identify regions that played a significant role in explicit gaze

Table 1. Participant Characteristics

Variable	SZ Group, *n* = 39	HC Group, *n* = 33	*t* or χ^2	*p* Value	Cohen's *d*
Demographics					
Age, years	33.2 ± 10.3	33.5 ± 9.3	0.12	.902	0.03
Sex, female/male	20/19	16/17	0.06	.813	–
Education, years	14.3 ± 2.1	16.3 ± 2.0	4.30	<.001	1.01
Parental education, years	15.5 ± 2.0	15.7 ± 3.2	0.34	.732	0.08
Clinical Assessments					
CPZeq, mg daily	363.1 ± 396.8	–	–	–	–
SAPS	23.9 ± 20.5	–	–	–	–
SANS	34.7 ± 16.6	–	–	–	–
Socioemotional Functioning					
MSCEIT perception	0.60 ± 0.15	0.64 ± 0.09	1.70	.094	0.39
MSCEIT using	0.44 ± 0.09	0.49 ± 0.05	2.99	.004	0.68
MSCEIT understanding	0.53 ± 0.16	0.66 ± 0.10	4.14	<.001	0.95
MSCEIT managing	0.41 ± 0.10	0.46 ± 0.06	2.89	.005	0.66
Gaze threshold	0.74 ± 0.15	0.77 ± 0.07	0.84	.403	0.19
Gaze slope	2.6 ± 0.6	3.4 ± 0.4	6.64	<.001	1.53
SSPA	4.3 ± 0.4	4.8 ± 0.2	6.17	<.001	1.49
UPSA communication	38.1 ± 5.5	41.4 ± 6.1	2.36	.021	0.57
RME	0.69 ± 0.12	0.79 ± 0.10	3.79	<.001	0.92
ER-40	30.6 ± 6.2	34.2 ± 2.8	3.26	.002	0.76
QCAE	88.2 ± 14.6	94.9. ± 13.0	1.99	.051	0.48
General Cognitive Ability					
MATRICS memory	44.8 ± 11.5	51.6 ± 8.8	2.76	.007	0.66
MATRICS reasoning	48.3 ± 9.9	51.4 ± 11.2	1.23	.222	0.29
MATRICS composite	40.1 ± 12.1	54.4 ± 10.0	5.28	<.001	1.29

Values shown are mean ± SD or *n* unless otherwise specified. Measures of social cognition included the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) (76); Reading the Mind in the Eyes (RME) Task (77); and Penn Emotion Recognition Task (ER-40) (78). In addition, the Questionnaire for Cognitive and Affective Empathy (QCAE) (79), Social Skills Performance Assessment (SSPA) (80), and University of California, San Diego Performance-Based Skills Assessment (UPSA) communication scale (81) were administered to assess broader social and adaptive functioning. General cognitive ability was assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery (82). Finally, the Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms (SAPS/SANS) were used to assess clinical symptoms of schizophrenia (83).

CPZeq, antipsychotic dose in chlorpromazine equivalent; HC, healthy control; SZ, schizophrenia or schizoaffective disorder.

discrimination, individual beta estimates of the gaze-gender contrast were forwarded to second-level analysis (Figure 2A).

We selected 4 regions of interest relevant to gaze processing, mirroring our original study (10): the secondary visual cortex (Vis) for early visual processing, the inferior parietal lobule (IPL) for social cognition and visuospatial processing (37), the posterior superior temporal sulcus (pSTS) for encoding of gaze direction (38–44), and the posterior medial frontal cortex (pMFC) for cognitive control (45–47). For each region of interest, the first principal component of a 5-mm radius sphere centered at the individual's peak coordinate within a 10-mm radius of the group peak was extracted as the time-series data for DCM.

Dynamic Causal Modeling. DCM uses differential equations to model effective connectivity among given neuronal populations of interest (nodes) (28). Connectivity parameters are represented using 3 matrices: matrix A representing intrinsic (i.e., baseline or reference) connectivity within and between nodes, matrix B representing changes in connectivity due to specific experimental conditions, and matrix C representing external driving inputs (i.e., experimental stimuli) (48). Relationships among these matrices, observed blood oxygen level–dependent response at nodes of interest (z), and experimental conditions of interest (u) are modeled using equation 1:

$$\frac{dz}{dt} = \left(A + \sum_{j=1}^{m} u_j B^j\right) z + Cu \quad (1)$$

The neuronal model in equation 1 is coupled to the Balloon-Windkessel hemodynamic model to predict observed blood oxygen level–dependent response from underlying connectivity. Model estimation was completed using SPM12 (36), and our model is visually represented in Figure 2C. The model paralleled the one that we used in our previous study (10) and consisted of 4 nodes: the Vis, IPL, pSTS, and pMFC. For each node, we included a self-connection parameter that models natural decay of activity over time. We also included bidirectional connections among all nodes but omitted feedforward connections from the Vis to the pMFC and connections between the IPL and the pSTS based on the visual processing

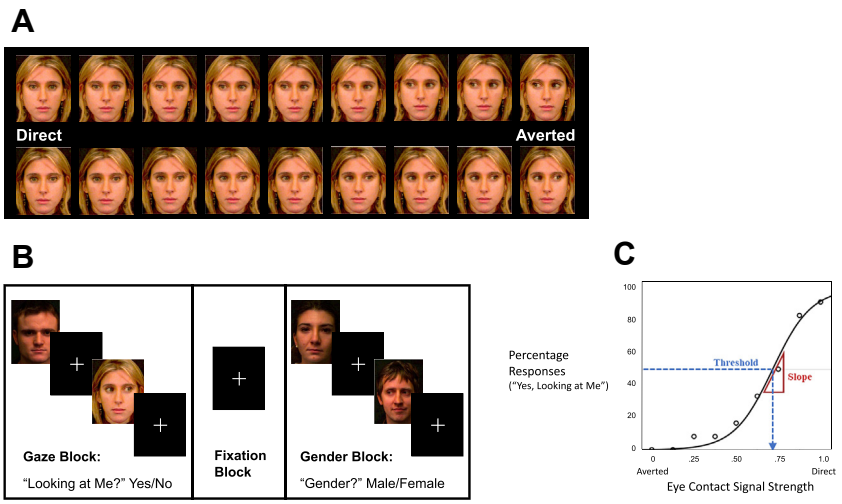

Figure 1. Face stimuli and design of the gaze processing task. Participants completed an eye-contact detection task in which they determined whether individuals pictured in a series of face stimuli were looking at them or not (i.e., explicit gaze discrimination). **(A)** Color photographs of 6 actors with 9 different gaze angles were used. Angles represent levels of eye-contact signal strength: 0° (direct), 3.75°, 7.5°, 11.25°, 15°, 18.75°, 22.5°, 26.25°, 30° (most averted). **(B)** As a control task that involved implicit gaze processing, participants determined whether faces were male or female. Eyes and gender trials were presented in alternating blocks with a fixation block between each task block. The task was organized into 6 runs, with each run containing 6 task blocks (3 gaze and 3 gender) and 5 fixation blocks. Within each block, the gaze angle and gender of face stimuli were pseudorandomized. Each face was presented for 1.5 seconds and separated from the next face by a random jitter (1.6–3.9 seconds). There was a total of 216 trials (6 runs × 3 blocks × 2 conditions × 6 trials). **(C)** After psychophysical curve-fitting based on task performance data, 2 metrics were obtained for each participant: threshold and slope. Face images were taken from George *et al* (84). The procedure to generate stimuli for various gaze angles is described in Lasagna *et al* (85).

literature (49) and our previous study (10). In terms of driving input, we assumed that face stimuli would enter the neural system through the visual cortex, and we used a boxcar regressor to model activity in the Vis as a function of each face presentation. Finally, we modeled the modulatory effects of explicit gaze discrimination on the bottom-up connections from the Vis to the IPL and pSTS and the top-down connections from the pMFC to the Vis, IPL, and pSTS.

In this study, we labeled matrix A as general gaze processing because its elements represent connectivity across both explicit (i.e., gaze trials) and implicit (i.e., gender trials) gaze processing trials. We labeled matrix B as explicit gaze discrimination because its elements represent changes in connectivity as a function of explicit gaze discrimination (i.e., gaze trials). Elements in the matrix diagonals represent self-connections, or strength of connectivity within nodes (with positive values representing stronger self-inhibition), whereas elements in the off-diagonals represent directed (inhibitory or excitatory) influences between nodes.

Parameter Estimation. Rather than estimating separate model structures for the HC and SZ groups, our analyses focused on identifying quantitative differences in effective connectivity between groups. We focused on connectivity during general gaze processing (matrix A) and modulation of connectivity during explicit gaze discrimination (matrix B). First, individual-level parameter estimates were obtained (variance explained: HC group = 10.91%, SD = 6.34%; SZ group =

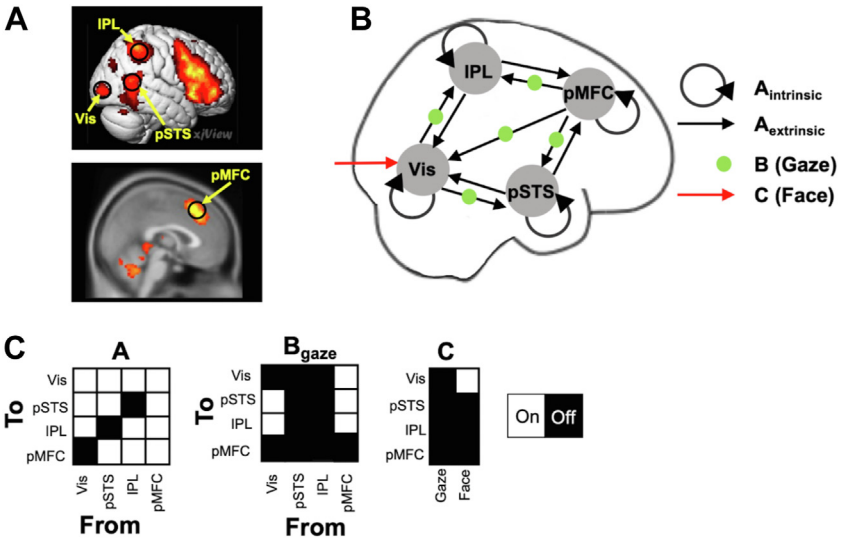

Figure 2. Brain nodes and our model for dynamic causal modeling (DCM). **(A)** Based on the general linear model results for our gaze-gender contrast across all participants, 4 nodes were selected for subsequent DCM analysis: V2 visual cortex (Vis), posterior superior temporal sulcus (pSTS), inferior parietal lobule (IPL), and posterior medial frontal cortex (pMFC). **(B)** The model used for DCM. Black arrows indicate connections during all face events (matrix A), while green dots indicate the connections that were allowed to be modulated by explicit gaze discrimination (matrix B). The red arrow indicates driving input (matrix C). **(C)** The dynamic causal model in terms of on/off parameters specified in matrices A, B, and C.

13.72%, SD = 9.13%). We then used the parametric empirical Bayes (PEB) method—a hierarchical Bayesian modeling technique that estimates group-level parameters accounting for uncertainty in the individual-level estimates—to obtain group-level estimates of our DCM parameters for the HC and SZ groups (48,50). Finally, we performed a PEB-of-PEB to quantify group communalities and differences.

Functional Relevance

To investigate functional relevance of effective connectivity, canonical correlation analyses (CCAs) were conducted. One set of variables included DCM parameters that showed >75% credible group differences; the other set consisted of social cognition/functioning measures. Next, we conducted a second CCA to quantify associations between DCM parameters and symptoms (i.e., Scale for the Assessment of Positive Symptoms/Scale for the Assessment of Negative Symptoms) in the SZ group. Finally, we conducted follow-up analyses to assess robustness, which are documented in the Supplement.

RESULTS

Behavioral Data

Compared with the HC group, the SZ group showed lower slope (i.e., lower perceptual precision; posterior probability > 99.99%). The SZ group also showed a lower threshold (i.e., higher self-referential bias), but the difference was not credible (posterior probability = 69%) (see Figure 3).

Effective Connectivity

No clusters differed significantly in activation between the SZ and HC groups. PEB results are illustrated in Figure 4 and Table 2 together with estimates from our previous work (10) for comparison. The SZ and HC models showed many similarities. During general gaze processing (matrix A), both groups showed excitatory bottom-up connectivity throughout the system and inhibitory top-down influences of the pMFC and IPL on the Vis. For both groups, explicit gaze discrimination (matrix B) strengthened the excitatory bottom-up connections from the Vis to the IPL and pSTS and strengthened inhibitory top-down influences of the pMFC on the Vis.

Despite similarities, there were also several credible group differences (>95% posterior probability). Specifically, the self-connection parameter of the pMFC was increased in the SZ group compared with the HC group, suggesting greater self-inhibition of the pMFC in the SZ group. In terms of interregional connections, the SZ group showed stronger inhibitory top-down influence of the IPL on the Vis compared with the HC group. In terms of explicit gaze discrimination (matrix B) (Figure 4), the SZ and HC groups differed strongly in patterns of top-down modulation from the pMFC to the pSTS;

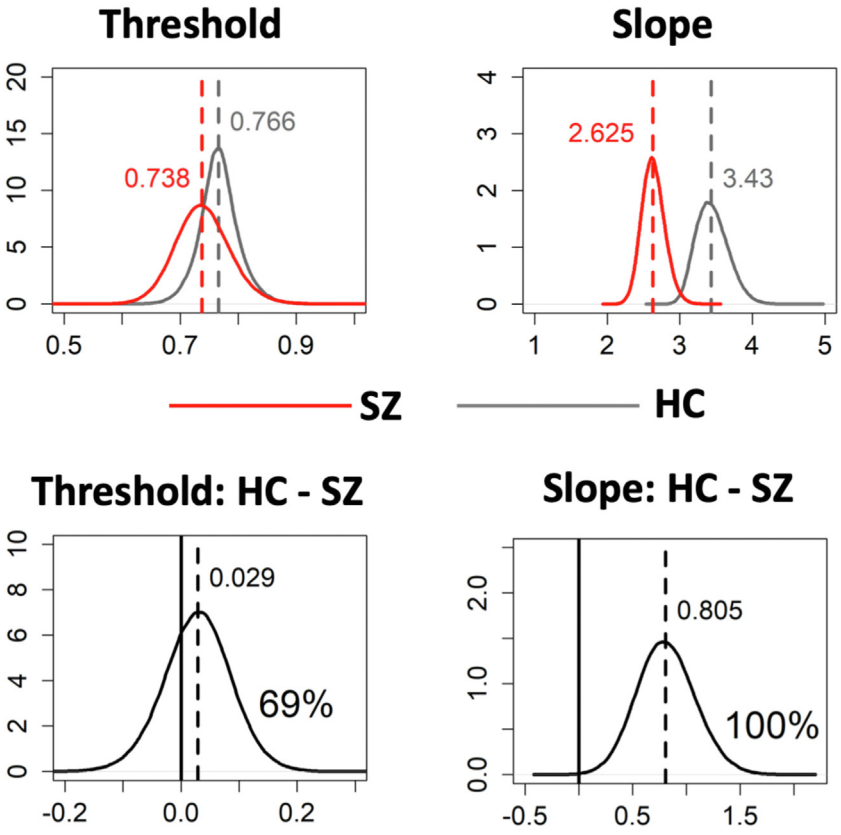

Figure 3. Posterior probability density plots of the psychophysical gaze perception metrics. Dashed vertical lines and numbers at the top indicate median values of Markov Chain Monte Carlo samples. Numbers at the bottom right (bottom panel) indicate the posterior probability of the healthy control (HC)—schizophrenia or schizoaffective disorder (SZ) group difference > 0. This probability is represented by the area under the curve to the right of the solid vertical line.

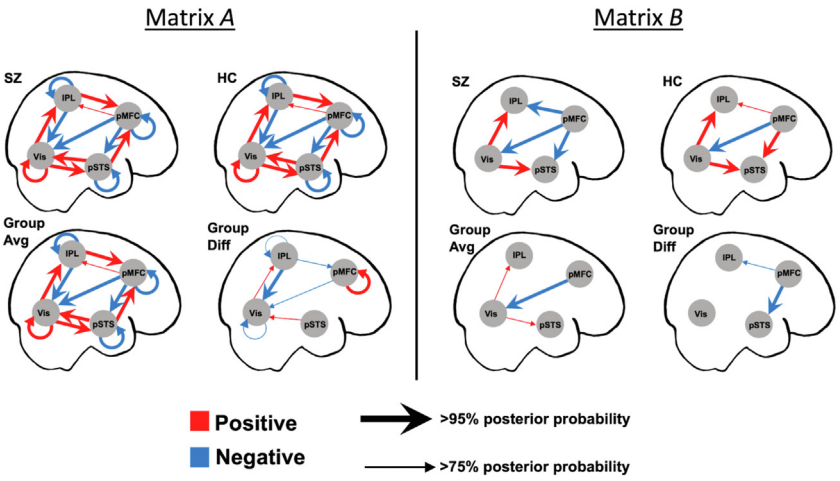

Figure 4. Effective connectivity parameters. Matrix A represents connectivity during all face events. Matrix B represents connectivity changes due to explicit gaze discrimination. For group differences, red indicates parameters that are greater in the schizophrenia or schizoaffective disorder (SZ) group (vs. the healthy control [HC] group), whereas blue indicates parameters with lower values in the SZ group. For clarity, only parameters with values that are nonzero with posterior probability > 75% are shown. IPL, inferior parietal lobule; pMFC, posterior medial frontal cortex; pSTS, posterior superior temporal sulcus; Vis, V2 visual cortex.

specifically, whereas inhibitory connections were attenuated in the HC group during explicit gaze discrimination compared with general gaze processing, these connections were further strengthened in the SZ group. Additional parameters that differed using a criterion of >75% posterior probability are noted in Table 2 and Figure 4.

Functional Relevance of Effective Connectivity

The CCA model examining the relationships between DCM parameters and social cognition/functioning yielded 1 significant canonical function (Wilks' Λ = 0.109, $p < .001$) (Figure 5A). The canonical function suggested that poorer social cognition/functioning was particularly related to stronger self-inhibition of the pMFC, weaker self-inhibition of the IPL, and stronger inhibition of the pSTS by the pMFC during explicit gaze discrimination. The same finding was seen when examined only in the SZ group (r = 0.536, $p < .001$) but was not significant in the HC group (r = 0.197, p = .272), suggesting that the association between connectivity and social cognition was stronger in the SZ group (Figure 6A).

Our second CCA yielded 1 significant canonical function (Wilks' Λ = 0.541, p = .006) (Figures 5B and 6B). A higher level of symptoms was particularly associated with weaker self-inhibition in the IPL and Vis, less inhibition of the Vis by the IPL/less excitation of the Vis by the pSTS during general gaze processing, and less inhibition of the IPL by the pMFC during explicit gaze discrimination. Importantly, while self-connection parameters in the direction of alterations found in the SZ group were largely associated with higher symptom levels, interregional parameters in the direction of alterations found in the SZ group were largely associated with lower symptom levels.

Follow-up analyses showed that the CCA results remained significant when controlling for potential confounds. See the Supplement for these results and for bivariate correlations among DCM parameters, social cognition/functioning, and symptoms.

DISCUSSION

This study aimed to replicate and extend our previous work (10), identifying patterns of altered effective connectivity during gaze processing in schizophrenia. As in our previous study, the SZ and HC groups showed similar DCM structures during general gaze processing. In both studies, general gaze processing in both groups was characterized by excitatory bottom-up influences of the visual cortex on temporoparietal regions (i.e., IPL and pSTS) and of temporoparietal regions on the medial frontal cortex. Moreover, in both groups in both studies, the medial frontal and parietal regions exerted inhibitory top-down influences on the visual cortex. Finally, explicit gaze discrimination strengthened excitatory bottom-up connections from the visual cortex to temporoparietal regions and inhibitory top-down connections from the medial frontal cortex to the visual cortex. These patterns of effective connectivity are consistent with a scientific understanding of gaze processing because accurate gaze discrimination depends on both bottom-up processing of sensory information from the eye regions and top-down regulation based on one's prior expectations of gaze direction.

As in our previous study, there were group differences in self-connection strength across several regions during general gaze processing. Specifically, the pMFC was more inhibited in the SZ group than in the HC group (>95% posterior probability) while the IPL and Vis were less inhibited in the SZ group (>75% posterior probability in the current study, >95% posterior probability in the previous study). These abnormal self-connections suggest aberrant excitatory-inhibitory balance in schizophrenia (48,51), which may originate from the abnormalities in glutamatergic and GABAergic (gamma-aminobutyric acidergic) function that have been observed in schizophrenia and have significant implications for social cognitive dysfunction (52–55). Similar to our original study, minimal group differences were seen for interregional connections during general gaze processing. Only 1 parameter showed >95% posterior probability—stronger top-down inhibitory connections from the IPL to the Vis in the SZ

Table 2. Dynamic Causal Modeling Parameter Estimates

	From							
	Vis		pSTS		IPL		pMFC	
To	Current	2021	Current	2021	Current	2021	Current	2021
Matrix A (Connections During All Face Events)								
Vis								
HC	0.43[a]	0.43[a]	0.22[a]	0.24[a]	−0.14[a]	−0.57[a]	−0.19[a]	−0.10[b]
SZ	0.36[a]	0.63[a]	0.35[a]	−0.02	−0.46[a]	−0.54[a]	−0.30[a]	−0.34[a]
All	0.43[a]	0.56[a]	0.31[a]	0.13[a]	−0.34[a]	−0.62[a]	−0.28[a]	−0.24[a]
SZ-HC	−0.05[b]	0.10[a]	0.07[b]	−0.14[a]	−0.19[a]	0.00	−0.06[b]	−0.13[a]
pSTS								
HC	0.16[a]	0.02[b]	−0.17[a]	−0.62[a]	–		−0.11[a]	−0.01
SZ	0.19[a]	0.05[a]	−0.14[a]	−0.51[a]	–		−0.11[a]	0.00
All	0.17[a]	0.03[b]	−0.16[a]	−0.60[a]	–		−0.11[a]	−0.01
SZ-HC	0.00	0.01	0.00	0.07[b]	–		0.00	0.01
IPL								
HC	0.17[a]	0.27[a]	–		−0.13[a]	0.06[b]	0.04[b]	0.19[a]
SZ	0.20[a]	0.18[a]	–		−0.19[a]	−0.14[a]	0.03[b]	0.01
All	0.18[a]	0.22[a]	–		−0.17[a]	−0.04[b]	0.03[b]	0.10[a]
SZ-HC	0.02[b]	−0.05[a]	–		−0.03[b]	−0.11[a]	0.00	−0.10[a]
pMFC								
HC	–		0.21[a]	0.34[a]	0.18[a]	0.26[a]	−0.23[a]	0.30[a]
SZ	–		0.26[a]	0.30[a]	0.08[a]	0.22[a]	−0.09[a]	−0.07[b]
All	–		0.24[a]	0.34[a]	0.13[a]	0.25[a]	−0.16[a]	0.14[a]
SZ-HC	–		0.00	−0.03	−0.05[b]	−0.02	0.07[a]	−0.21[a]
Matrix B (Changes in Connections Due to Gaze Discrimination)								
Vis								
HC	–		–		–		−0.61[a]	−0.01
SZ	–		–		–		−0.46[a]	−0.30[a]
All	–		–		–		−0.50[a]	−0.15[b]
SZ-HC	–		–		–		0.07	−0.13[b]
pSTS								
HC	0.20[a]	0.25[a]	–		–		0.33[a]	−0.14[b]
SZ	0.21[a]	0.21[a]	–		–		−0.44[a]	−0.12[b]
All	0.20[b]	0.22[b]	–		–		−0.05	−0.12
SZ-HC	0.00	−0.02	–		–		−0.37[a]	0.01
IPL								
HC	0.22[a]	0.19[a]	–		–		0.08[b]	−0.27[a]
SZ	0.08[a]	0.24[a]	–		–		−0.31[a]	−0.40[a]
All	0.14[b]	0.20[b]	–		–		−0.11	−0.31[a]
SZ-HC	−0.06	0.03	–		–		−0.18[b]	−0.06
pMFC								
HC	–		–		–		–	
SZ	–		–		–		–	
All	–		–		–		–	
SZ-HC	–		–		–		–	

Values to the left in each column represent parameter estimates in the current dataset, whereas values to the right represent parameter estimates from Tso *et al.* (10,12).

HC, healthy control; IPL, inferior parietal lobule; pMFC, posterior medial frontal cortex; pSTS, posterior superior temporal sulcus; SZ, schizophrenia or schizoaffective disorder; Vis, secondary visual cortex.

[a]Parameter value is nonzero with posterior probability > 95%.

[b]Parameter value is nonzero with posterior probability > 75%.

group. Stronger inhibition of the visual cortex by the IPL in schizophrenia may underlie the difficulties with perceptual organization and visual integration that have been reported consistently in schizophrenia (24), which have been shown in previous studies to rely on coordination between the visual cortex and regions such as the IPL (37). Because these basic

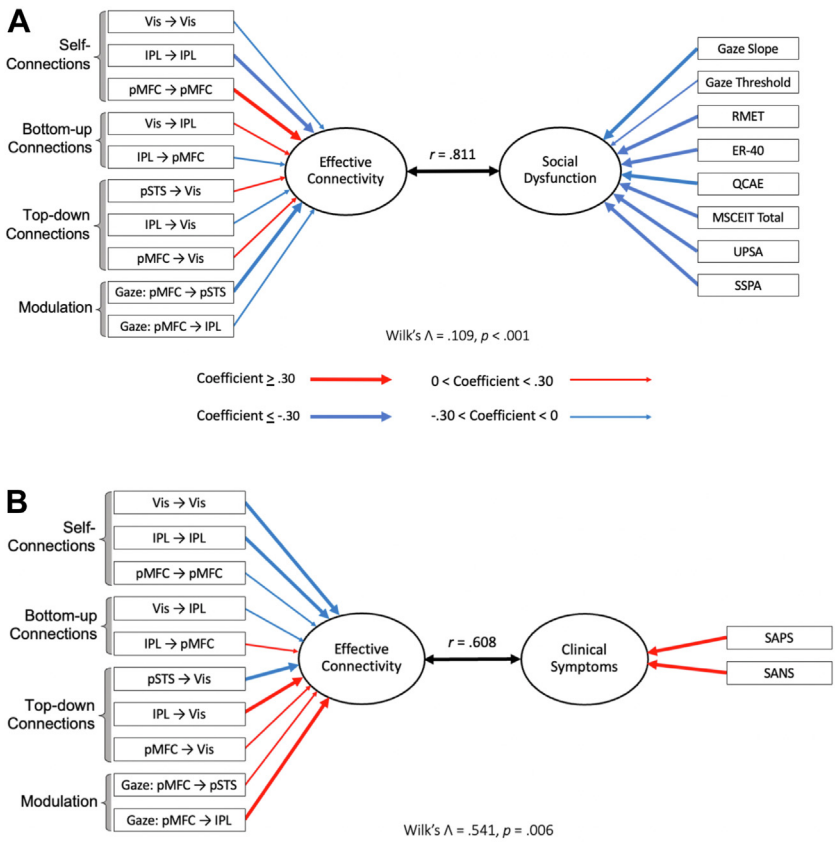

Figure 5. Canonical correlation between effectivity connectivity and **(A)** social dysfunction or **(B)** symptoms. Sample for the social dysfunction canonical correlation analysis (CCA) included both schizophrenia or schizoaffective disorder (SZ) and healthy control (HC) groups, whereas the symptom severity CCA included only the SZ group. Ovals represent predictors (left) and criterion variables (right). ER-40, Penn Emotion Recognition Task accuracy; IPL, inferior parietal lobule; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test; pMFC, posterior medial frontal cortex; pSTS, posterior superior temporal sulcus; QCAE, Questionnaire for Cognitive and Affective Empathy; RME; Reading the Mind in the Eyes Task accuracy; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SSPA, Social Skills Performance Assessment; UPSA, University of California, San Diego Performance-Based Skills Assessment; Vis, V2 visual cortex.

visual processes contribute to social cognitive functioning (11), future work using noninvasive brain stimulation to modulate this pathway could provide confirmation of its role and direct the development of targeted interventions.

During explicit gaze discrimination, the SZ group showed differential top-down inhibitory connections from the pMFC compared with the HC group. Specifically, whereas inhibitory connections from the pMFC to the IPL and pSTS during explicit gaze discrimination were attenuated in the HC group (i.e., connections that were inhibitory during general gaze processing became more excitatory), these connections were further strengthened in the SZ group (i.e., connections that were inhibitory during general gaze processing became even more inhibitory). Given that determining gaze direction requires coordination of higher-level self-referential processing, social cue detection, and visual integration, it is logical that the HC group would rely on higher-level cognition (related to the pMFC) to engage and upregulate lower-level processes

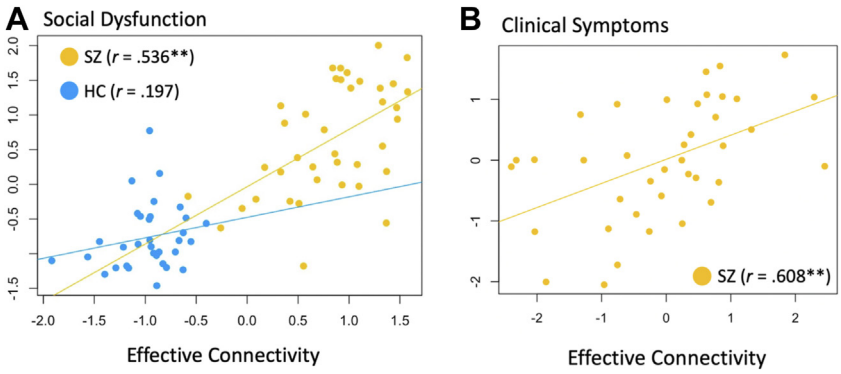

Figure 6. Scatter plot visualizations of the canonical correlations between effective connectivity and **(A)** social dysfunction or **(B)** symptoms. Dynamic causal modeling connections that differentiated the 2 diagnostic groups were also significantly associated with **(A)** social dysfunction and **(B)** clinical symptom severity in the schizophrenia or schizoaffective disorder (SZ) group. $^{**}p < .01$. HC, healthy control.

(related to the pSTS and IPL). Stronger downregulating influences of the pMFC in schizophrenia could reflect an overreliance on prior beliefs when processing gaze, perhaps due to compromised quality of sensory information that results from basic visual perceptual deficits (24,56). This is consistent with observations of stronger self-referential bias in schizophrenia (13–15) and findings of a stronger tendency to perceive gaze as self-directed when self-related beliefs are experimentally manipulated in healthy individuals (57). However, it is important to note that overreliance on prior beliefs may be inappropriate in the context of gaze perception, even if it relies on higher-level cognitive processing; indeed, people with schizophrenia show prominent prefrontal dysfunction and associated impairments in higher-level cognition (58,59). Alternatively, it is possible that the enhanced top-down inhibition in schizophrenia reflects top-down mediated disengagement from the task during the more demanding explicit gaze perception condition. Each of these possible explanations warrants further investigation.

Consistent with previous findings (10), DCM parameters that were altered in the SZ group were associated with social dysfunction. We found a significant canonical correlation between social cognition/functioning and DCM parameters that differentiated the groups; this association was also significant when examined within the SZ group alone. This suggests that abnormal effective connectivity found in schizophrenia contributes to more severe dysfunction and that this was not an artifactual finding due to group differences in both effective connectivity and social cognition/functioning. The presence of large canonical loadings across a range of measures—spanning gaze processing, emotion recognition, perceptual theory of mind, self-reported empathy, and interview-based social functioning—suggests that aberrant connectivity during gaze processing is associated with broad rather than merely narrow social dysfunction. This is consistent with evidence that individual differences in neural activity that underlie gaze processing were related to broad social cognitive functioning in schizophrenia (14).

The results of our CCA for clinical symptoms were more nuanced. Greater symptoms were associated with decreased self-inhibition of the Vis and IPL, decreased excitation of the Vis by the pSTS, decreased inhibition of the Vis by the IPL, and decreased inhibition of the IPL by the pMFC during explicit gaze discrimination. As with our findings for social dysfunction, self-connection parameters that were altered in the SZ group were associated with more dysfunction (in this case, greater symptoms). Counterintuitively, though, interregional connections that were altered in the SZ group were largely associated with lower schizophrenia symptom severity. This effect was particularly strong for top-down inhibition of the IPL by the pMFC during explicit gaze discrimination and suggests that this altered connection in schizophrenia may serve as a compensatory mechanism among at least some individuals with the disorder. As mentioned earlier, the need for such top-down inhibitory processing may arise from unreliable sensory processing (11,24,56). Thus, leveraging top-down processing in the context of gaze perception (which, as mentioned earlier, could be related to a reliance on prior beliefs or to top-down mediated disengagement from the task) may protect the individual from developing more severe symptoms, which is consistent with previous studies suggesting over-recruitment of prefrontal resources in some patients with schizophrenia (60,61). However, specific compensatory pathways remain speculative and warrant future research that incorporates longitudinal methods or neuromodulation to provide convergent evidence.

Overall, there were several consistencies between the current findings and our 2021 study (10)—for example, we found similar models for general gaze processing, abnormal self-connections, and top-down inhibition in the SZ group and robust associations between DCM parameters and functioning. Nonetheless, some of the new findings were not consistent with our previous work—for example, the current study found faster pMFC self-inhibition in the SZ group (vs. slower decay in the previous study) and abnormal top-down inhibition from the pMFC to the IPL and pSTS (rather than to the Vis as in the previous study) during explicit gaze processing. There are several potential explanations for these inconsistencies. First, the current study used multiband fMRI data acquisition, which allows for greater temporal and spatial resolution and can increase the precision and reliability of statistical metrics estimated using the data (62–65). We also used a different set of face stimuli for the current study (i.e., higher resolution face images and color rather than black/white). Previous research suggests that reduced visual noise leads to increased perceptual certainty during gaze processing (66). The fact that participants in the current study had a higher median slope parameter for the gaze task compared with the participants in our 2021 study (10) suggests that the new task stimuli were more easily discriminable, which could lead to corresponding changes in brain activity and connectivity. For example, when images are noisier, healthy participants may rely more strongly on inhibitory top-down processing to inform decision making; this would be consistent with the cross-study differences that we saw for DCM parameters during explicit gaze discrimination. Taken together, the improvements in fMRI data acquisition, study design/stimuli, and the larger sample size suggest that the current study's parameter estimates are likely to be more reliable. However, it is also worth noting that large samples are often needed to reliably detect whether original results have been replicated (67); thus, future studies with even larger samples would be useful to better assess the robustness of our current results and previous findings.

A few specific limitations and future directions are worth noting. First, although CCA is a powerful multivariate tool, it tends to overestimate correlations between the predictor and criterion variables. This is especially true with a low sample-size-to-number-of-variables ratio. Therefore, when interpreting CCA results, it is advisable to focus on the meaning of the dimensions (i.e., how the variables load onto variates) rather than specific magnitudes. It is also worth noting more broadly that CCA solutions may not achieve stable estimates in datasets with the current sample size (68), so further investigation and replication of our reported effects is warranted. Second, we cannot rule out the potential confounding effects of antipsychotic medication use (though chlorpromazine dose equivalents were not significantly associated with DCM parameters in the current sample). Third, although we used a 4-node model to remain consistent with our original DCM study, there are likely other important regions that are involved

in gaze processing. Alternative methods could be used to explore effective connectivity in complex brain networks (69,70). Fourth, all the actors used for our current task stimuli were White—limited by the face image set that was available at the time of the study—which could influence performance among non-White participants, given past research suggesting effects of race and ethnoracial matching on social cognition (71,72); future research should use more racially diverse stimuli. Finally, we did not detect a significant between-group difference for self-referential bias, likely due to sample size; this should not take away from our DCM findings given that 1) the groups did differ in perceptual precision, 2) a lack of behavioral group differences in the presence of neural differences is relatively common, and 3) in our work with larger samples, we found a group difference in self-referential bias (14).

Future research should consider incorporating additional tests of social cognition. This would allow us to examine whether the neural dynamics that underlie aberrant gaze processing overlap with those that contribute to higher-level social cognitive processes such as mentalizing. Such an approach could eventually inform interventions that lead to improvements across multiple levels of functioning. Future studies could also further explore the mechanisms of aberrant gaze perception in schizophrenia by integrating the current methods with approaches such as eye tracking. Previous research suggests that dwell time for faces (and gaze in particular) is reduced in schizophrenia and related to symptom severity (73–75). Integrating eye tracking with fMRI could allow us to determine whether processes such as gaze avoidance drive the link between brain connectivity and social cognition/functioning in schizophrenia.

Conclusions

Using DCM, we attempted to replicate and extend our previous research showing altered effective connectivity in schizophrenia during gaze processing. Results suggest that abnormal excitatory-inhibitory balance and top-down inhibition during social perception are plausible mechanisms of social dysfunction in schizophrenia. However, abnormal top-down inhibition may also serve compensatory functions given its association with lower symptom severity. Given our finding of group differences in effective connectivity despite a lack of regional activation abnormalities, our work provides further support for the central role of functional dysconnectivity in schizophrenia (18,19). Taken together, our findings help pinpoint plausible neural mechanisms underpinning gaze processing abnormalities that may serve as future targets for intervention.

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The study was conducted in accordance with the protocol approved by the institutional review board of the University of Michigan Medical School (HUM00080457, "Neural Mechanisms of Gaze Perception in Psychosis"), and written informed consent was obtained from each participant. Data are available upon reasonable request by contacting SDB or IFT.

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REFERENCES

1. Green MF, Horan WP, Lee J (2015): Social cognition in schizophrenia. Nat Rev Neurosci 16:620–631.
2. Penn DL, Sanna LJ, Roberts DL (2008): Social cognition in schizophrenia: An overview. Schizophr Bull 34:408–411.
3. Harvey PD, Patterson TL, Potter LS, Zhong K, Brecher M (2006): Improvement in social competence with short-term atypical antipsychotic treatment: A randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. Am J Psychiatry 163:1918–1925.
4. Couture SM, Penn DL, Roberts DL (2006): The functional significance of social cognition in schizophrenia: A review. Schizophr Bull 32(suppl 1):S44–S63.
5. Fett AK, Viechtbauer W, Dominguez MD, Penn DL, van Os J, Krabbendam L (2011): The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. Neurosci Biobehav Rev 35:573–588.
6. Emery NJ (2000): The eyes have it: The neuroethology, function and evolution of social gaze. Neurosci Biobehav Rev 24:581–604.
7. Farroni T, Csibra G, Simion F, Johnson MH (2002): Eye contact detection in humans from birth. Proc Natl Acad Sci USA 99:9602–9605.
8. Hooker C, Park S (2005): You must be looking at me: The nature of gaze perception in schizophrenia patients. Cogn Neuropsychiatry 10:327–345.
9. Rosse RB, Kendrick K, Wyatt RJ, Isaac A, Deutsch SI (1994): Gaze discrimination in patients with schizophrenia: Preliminary report. Am J Psychiatry 151:919–921.
10. Tso IF, Angstadt M, Rutherford S, Peltier S, Diwadkar VA, Taylor SF (2021): Dynamic causal modeling of eye gaze processing in schizophrenia. Schizophr Res 229:112–121.
11. Tso IF, Carp J, Taylor SF, Deldin PJ (2014): Role of visual integration in gaze perception and emotional intelligence in schizophrenia. Schizophr Bull 40:617–625.
12. Tso IF, Taylor SF, Johnson TD (2021): Applying hierarchical Bayesian modeling to experimental psychopathology data: An introduction and tutorial. J Abnorm Psychol 130:923–936.
13. Yao B, Mueller SA, Grove TB, McLaughlin M, Thakkar K, Ellingrod V, *et al.* (2018): Eye gaze perception in bipolar disorder: Self-referential bias but intact perceptual sensitivity. Bipolar Disord 20:60–69.

14. Blain SD, Taylor SF, Rutherford SE, Lasagna CA, Yao B, Angstadt M, *et al.* (2023): Neurobehavioral indices of gaze perception are associated with social cognition across schizophrenia patients and healthy controls. J Psychopathol Clin Sci 132:733–748.
15. Tso IF, Mui ML, Taylor SF, Deldin PJ (2012): Eye-contact perception in schizophrenia: Relationship with symptoms and socioemotional functioning. J Abnorm Psychol 121:616–627.
16. Dong D, Wang Y, Jia X, Li Y, Chang X, Vandekerckhove M, *et al.* (2018): Abnormal brain activation during threatening face processing in schizophrenia: A meta-analysis of functional neuroimaging studies. Schizophr Res 197:200–208.
17. Friston KJ, Brown HR, Siemerkus J, Stephan KE (2016): The dysconnection hypothesis (2016). Schizophr Res 176:83–94.
18. Friston KJ, Frith CD (1995): Schizophrenia: A disconnection syndrome? Clin Neurosci 3:89–97.
19. Pettersson-Yeo W, Allen P, Benetti S, McGuire P, Mechelli A (2011): Dysconnectivity in schizophrenia: Where are we now? Neurosci Biobehav Rev 35:1110–1124.
20. Kohler CG, Loughead J, Ruparel K, Indersmitten T, Barrett FS, Gur RE, Gur RC (2008): Brain activation during eye gaze discrimination in stable schizophrenia. Schizophr Res 99:286–293.
21. Pinkham AE, Loughead J, Ruparel K, Overton E, Gur RE, Gur RC (2011): Abnormal modulation of amygdala activity in schizophrenia in response to direct- and averted-gaze threat-related facial expressions. Am J Psychiatry 168:293–301.
22. Dima D, Dietrich DE, Dillo W, Emrich HM (2010): Impaired top-down processes in schizophrenia: A DCM study of ERPs. NeuroImage 52:824–832.
23. Earls HA, Curran T, Mittal V (2016): Deficits in early stages of face processing in schizophrenia: A systematic review of the P100 component. Schizophr Bull 42:519–527.
24. Silverstein SM, Keane BP (2011): Perceptual organization impairment in schizophrenia and associated brain mechanisms: Review of research from 2005 to 2010. Schizophr Bull 37:690–699.
25. Sugranyes G, Kyriakopoulos M, Corrigall R, Taylor E, Frangou S (2011): Autism spectrum disorders and schizophrenia: Meta-analysis of the neural correlates of social cognition. PLoS One 6:e25322.
26. Taylor SF, Chen AC, Tso IF, Liberzon I, Welsh RC (2011): Social appraisal in chronic psychosis: Role of medial frontal and occipital networks. J Psychiatr Res 45:526–538.
27. van Veen V, Carter CS (2002): The anterior cingulate as a conflict monitor: fMRI and ERP studies. Physiol Behav 77:477–482.
28. Friston KJ, Harrison L, Penny W (2003): Dynamic causal modelling. NeuroImage 19:1273–1302.
29. Friston KJ, Preller KH, Mathys C, Cagnan H, Heinzle J, Razi A, Zeidman P (2019): Dynamic causal modelling revisited. NeuroImage 199:730–744.
30. Friston KJ, Litvak V, Oswal A, Razi A, Stephan KE, van Wijk BCM, *et al.* (2016): Bayesian model reduction and empirical Bayes for group (DCM) studies. NeuroImage 128:413–431.
31. Dima D, Roiser JP, Dietrich DE, Bonnemann C, Lanfermann H, Emrich HM, Dillo W (2009): Understanding why patients with schizophrenia do not perceive the hollow-mask illusion using dynamic causal modelling. NeuroImage 46:1180–1186.
32. Fogelson N, Litvak V, Peled A, Fernandez-del-Olmo M, Friston KJ (2014): The functional anatomy of schizophrenia: A dynamic causal modeling study of predictive coding. Schizophr Res 158:204–212.
33. Roiser JP, Wigton R, Kilner JM, Mendez MA, Hon N, Friston KJ, Joyce EM (2013): Dysconnectivity in the frontoparietal attention network in schizophrenia. Front Psychiatry 4:176.
34. Zhou Y, Zeidman P, Wu S, Razi A, Chen C, Yang L, *et al.* (2018): Altered intrinsic and extrinsic connectivity in schizophrenia. NeuroImage Clin 17:704–716.
35. First MB, Spitzer RL, Gibbon M, Williams JBW (1995): Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition. (SCID-P), Version 2.0. New York State Psychiatric Institute, New York, NY: Biometrics Research.
36. Ashburner J, Barnes G, Chen C-C, Daunizeau J, Flandin G, Friston KJ, *et al.* (2021): SPM12 Manual. London: Wellcome Trust Centre for Neuroimaging.
37. Itier RJ, Batty M (2009): Neural bases of eye and gaze processing: The core of social cognition. Neurosci Biobehav Rev 33:843–863.
38. Boyarskaya E, Sebastian A, Bauermann T, Hecht H, Tüscher O (2015): The Mona Lisa effect: Neural correlates of centered and off-centered gaze. Hum Brain Mapp 36:619–632.
39. Burra N, Baker S, George N (2017): Processing of gaze direction within the N170/M170 time window: A combined EEG/MEG study. Neuropsychologia 100:207–219.
40. Carlin JD, Calder AJ, Kriegeskorte N, Nili H, Rowe JB (2011): A head view-invariant representation of gaze direction in anterior superior temporal sulcus. Curr Biol 21:1817–1821.
41. Caruana F, Cantalupo G, Lo Russo GL, Mai R, Sartori I, Avanzini P (2014): Human cortical activity evoked by gaze shift observation: An intracranial EEG study. Hum Brain Mapp 35:1515–1528.
42. Sato W, Kochiyama T, Uono S, Toichi M (2016): Neural mechanisms underlying conscious and unconscious attentional shifts triggered by eye gaze. NeuroImage 124:118–126.
43. Schobert AK, Corradi-Dell'Acqua C, Frühholz S, van der Zwaag W, Vuilleumier P (2018): Functional organization of face processing in the human superior temporal sulcus: A 7T high-resolution fMRI study. Soc Cogn Affect Neurosci 13:102–113.
44. Steuwe C, Daniels JK, Frewen PA, Densmore M, Pannasch S, Beblo T, *et al.* (2014): Effect of direct eye contact in PTSD related to interpersonal trauma: An fMRI study of activation of an innate alarm system. Soc Cogn Affect Neurosci 9:88–97.
45. Calder AJ, Lawrence AD, Keane J, Scott SK, Owen AM, Christoffels I, Young AW (2002): Reading the mind from eye gaze. Neuropsychologia 40:1129–1138.
46. Schilbach L, Wohlschlaeger AM, Kraemer NC, Newen A, Shah NJ, Fink GR, Vogeley K (2006): Being with virtual others: Neural correlates of social interaction. Neuropsychologia 44:718–730.
47. Urakawa S, Takamoto K, Ishikawa A, Ono T, Nishijo H (2015): Selective medial prefrontal cortex responses during live mutual gaze interactions in human infants: An fNIRS study. Brain Topogr 28:691–701.
48. Zeidman P, Jafarian A, Corbin N, Seghier ML, Razi A, Price CJ, Friston KJ (2019): A guide to group effective connectivity analysis, part 1: First level analysis with DCM for fMRI. NeuroImage 200:174–190.
49. Gilbert CD, Li W (2013): Top-down influences on visual processing. Nat Rev Neurosci 14:350–363.
50. Zeidman P, Jafarian A, Seghier ML, Litvak V, Cagnan H, Price CJ, Friston KJ (2019): A guide to group effective connectivity analysis, part 2: Second level analysis with PEB. NeuroImage 200:12–25.
51. Bastos AM, Usrey WM, Adams RA, Mangun GR, Fries P, Friston KJ (2012): Canonical microcircuits for predictive coding. Neuron 76:695–711.
52. Krystal JH, Anticevic A, Yang GJ, Dragoi G, Driesen NR, Wang XJ, Murray JD (2017): Impaired tuning of neural ensembles and the pathophysiology of schizophrenia: A translational and computational neuroscience perspective. Biol Psychiatry 81:874–885.
53. Lee J, Green MF (2016): Social preference and glutamatergic dysfunction: Underappreciated prerequisites for social dysfunction in schizophrenia. Trends Neurosci 39:587–596.
54. Taylor SF, Tso IF (2015): GABA abnormalities in schizophrenia: A methodological review of in vivo studies. Schizophr Res 167:84–90.
55. Tso IF, Fang Y, Phan KL, Welsh RC, Taylor SF (2015): Abnormal GABAergic function and face processing in schizophrenia: A pharmacologic-fMRI study. Schizophr Res 168:338–344.
56. Butler PD, Abeles IY, Weiskopf NG, Tambini A, Jalbrzikowski M, Legatt ME, *et al.* (2009): Sensory contributions to impaired emotion processing in schizophrenia. Schizophr Bull 35:1095–1107.
57. Stoyanova RS, Ewbank MP, Calder AJ (2010): You Talkin' to Me?": Self-relevant auditory signals influence perception of gaze direction. Psychol Sci 21:1765–1769.

58. Perlstein WM, Carter CS, Noll DC, Cohen JD (2001): Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. Am J Psychiatry 158:1105–1113.
59. Shelton RC, Karson CN, Doran AR, Pickar D, Bigelow LB, Weinberger DR (1988): Cerebral structural pathology in schizophrenia: Evidence for a selective prefrontal cortical defect. Am J Psychiatry 145:154–163.
60. Ramsey NF, Koning HAM, Welles P, Cahn W, van der Linden JA, Kahn RS (2002): Excessive recruitment of neural systems subserving logical reasoning in schizophrenia. Brain 125:1793–1807.
61. Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR (2003): Complexity of prefrontal cortical dysfunction in schizophrenia: More than up or down. Am J Psychiatry 160: 2209–2215.
62. Boyacioğlu R, Schulz J, Koopmans PJ, Barth M, Norris DG (2015): Improved sensitivity and specificity for resting state and task fMRI with multiband multi-echo EPI compared to multi-echo EPI at 7 T. NeuroImage 119:352–361.
63. Demetriou L, Kowalczyk OS, Tyson G, Bello T, Newbould RD, Wall MB (2018): A comprehensive evaluation of increasing temporal resolution with multiband-accelerated protocols and effects on statistical outcome measures in fMRI. NeuroImage 176:404–416.
64. Liao XH, Xia MR, Xu T, Dai ZJ, Cao XY, Niu HJ, *et al.* (2013): Functional brain hubs and their test–retest reliability: A multiband resting-state functional MRI study. NeuroImage 83:969–982.
65. Preibisch C, Castrillón GJG, Bührer M, Riedl V (2015): Evaluation of multiband EPI acquisitions for resting state fMRI. PLoS One 10: e0136961.
66. Mareschal I, Calder AJ, Dadds MR, Clifford CWG (2013): Gaze categorization under uncertainty: Psychophysics and modeling. J Vis 13:18.
67. Simonsohn U (2015): Small telescopes: Detectability and the evaluation of replication results. Psychol Sci 26:559–569.
68. Helmer M, Warrington S, Mohammadi-Nejad A-R, Ji JL, Howell A, Rosand B, *et al.* (2023): On stability of canonical correlation analysis and partial least squares with application to brain-behavior associations. bioRxiv. https://doi.org/10.1101/2020.08.25.265546.
69. Frässle S, Lomakina EI, Kasper L, Manjaly ZM, Leff A, Pruessmann KP, *et al.* (2018): A generative model of whole-brain effective connectivity. NeuroImage 179:505–529.
70. Rajapakse JC, Zhou J (2007): Learning effective brain connectivity with dynamic Bayesian networks. NeuroImage 37:749–760.
71. Dodell-Feder D, Ressler KJ, Germine LT (2020): Social cognition or social class and culture? On the interpretation of differences in social cognitive performance. Psychol Med 50:133–145.
72. Elfenbein HA, Ambady N (2002): On the universality and cultural specificity of emotion recognition: A meta-analysis. Psychol Bull 128:203–235.
73. Patel GH, Arkin SC, Ruiz-Betancourt DR, DeBaun HM, Strauss NE, Bartel LP, *et al.* (2021): What you see is what you get: Visual scanning failures of naturalistic social scenes in schizophrenia. Psychol Med 51:2923–2932.
74. Jeon G, Choi HS, Jung DU, Moon S, Kim G, Kim SJ, *et al.* (2022): Evaluation of the correlation between gaze avoidance and schizophrenia psychopathology with deep learning-based emotional recognition. Asian J Psychiatr 68:102974.
75. Jang SK, Kim S, Kim CY, Lee HS, Choi KH (2016): Attentional processing of emotional faces in schizophrenia: Evidence from eye tracking. J Abnorm Psychol 125:894–906.
76. Mayer JD, Salovey P, Caruso DR (2012): Mayer-Salovey-Caruso Emotional Intelligence Test. American Psychological Association. Available at: https://doi.org/10.1037/t05047-000. Accessed June 15, 2016.
77. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I (2001): The "Reading the Mind in the Eyes" test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry 42:241–251.
78. Gur RC, Ragland JD, Moberg PJ, Bilker WB, Kohler C, Siegel SJ, Gur RE (2001): Computerized neurocognitive scanning: II. The profile of schizophrenia. Neuropsychopharmacology 25:777–788.
79. Reniers RLEP, Corcoran R, Drake R, Shryane NM, Völlm BA (2011): The QCAE: A questionnaire of cognitive and affective empathy. J Pers Assess 93:84–95.
80. Patterson TL, Moscona S, McKibbin CL, Davidson K, Jeste DV (2001): Social skills performance assessment among older patients with schizophrenia. Schizophr Res 48:351–360.
81. Patterson TL, Goldman S, McKibbin CL, Hughs T, Jeste DV (2001): UCSD performance-based skills assessment: Development of a new measure of everyday functioning for severely mentally ill adults. Schizophr Bull 27:235–245.
82. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, *et al.* (2008): The MATRICS consensus cognitive battery, Part 1: Test selection, reliability, and validity. Am J Psychiatry 165:203–213.
83. Andreasen NC, Grove WM (1986): Evaluation of positive and negative symptoms in schizophrenia. Psychiatr Psychobiol 1:108–122.
84. George N, Driver J, Dolan RJ (2001): Seen gaze-direction modulates fusiform activity and its coupling with other brain areas during face processing. Neuroimage 13:1102–1112.
85. Lasagna CA, McLaughlin MM, Deng WY, Whiting EL, Tso IF (2020): Deconstructing eye contact perception: Measuring perceptual precision and self-referential tendency using an online psychophysical eye contact detection task. PloS One 15(3):e0230258.