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Social-Cognitive Brain Function and Connectivity During Visual Perspective-Taking in Autism and Schizophrenia

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Abstract

Background—Autism spectrum disorder (ASD) and schizophrenia are neurodevelopmental conditions that are characterized by significant social impairment. Emerging genomic and neurobiological evidence has increasingly pointed to shared pathophysiologic mechanisms in the two disorders. Overlap in social impairment may reflect similar underlying neural dysfunction in social-cognitive brain networks, yet few studies have directly compared brain function and communication between those with ASD and schizophrenia.

Methods—Outpatients with schizophrenia ($n = 36$), ASD ($n = 33$), and healthy volunteers ($n = 37$) completed a visual perspective-taking task during functional neuroimaging at 3T to assess similarities and differences in fronto-temporal brain function and connectivity during social-cognitive processing. Analyses employed general linear models to examine differences in amplitude of BOLD-signal response between disorder groups, and computed functional connectivity coefficients to investigate differences in the connectivity profiles of networks implicated in social cognition.

Results—Despite similar behavioral impairments, participants with ASD and schizophrenia evidenced distinct neural abnormalities during perspective-taking. Functional activation results indicated reduced temporo-parietal junction and medial prefrontal activity in ASD compared to

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Contributors

This study was designed by Drs. Eack, Minshew, and Keshavan. Dr. Eack wrote the initial draft of the manuscript, Drs. Minshew and Keshavan and Ms. Wojtalik provided critical revisions and feedback on both the manuscript and analyses. Dr. Minshew contributed to autism data collection and analysis, and Dr. Keshavan contributed to schizophrenia data collection and analysis. Dr. Eack oversaw all data collection and analysis aspects of the study. All authors contributed to and have approved the final manuscript.

Conflict of Interest

The authors report no conflicts of interest. Dr. Keshavan reports a grant from Sunovion within the past two years, and is a consultant for Forum Pharmaceuticals. The remaining authors have no financial interests to disclose.

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schizophrenia (all $P_{uncor} < .002$). Functional connectivity analyses further revealed significantly greater local orbitofrontal connectivity in ASD than schizophrenia (all $P_{FDR} < .028$) during perspective-taking. Differences in brain activation and connectivity were unrelated to antipsychotic medication dose.

Conclusions—Autism and schizophrenia are characterized by similar social-cognitive impairments that may stem from different underlying abnormalities in the functional organization and communication of the social brain.

Keywords

fmri; functional connectivity; autism; schizophrenia; social cognition; RDoC

1. Introduction

Autism spectrum disorder (ASD) and schizophrenia are neurodevelopmental conditions that share similarities in some of their cognitive and behavioral manifestations (Kanner, 1965). Although the two disorders emerge at different developmental periods, both are characterized by significant impairments in social behavior and understanding (American Psychiatric Association, 2013). Individuals with these conditions often spend the majority of their adult lives socially isolated (Harrow, Grossman, Jobe, & Herbener, 2005; Howlin, Moss, Savage, & Rutter, 2013), have few to no significant friendships (Macdonald, Hayes, & Baglioni, 2000; Orsmond, Shattuck, Cooper, Sterzing, & Anderson, 2013), and a poor quality of life (Mazurek, 2014; Eack, Newhill, Anderson, & Rotondi, 2007). Brain-based impairments in social cognition, e.g., those abilities that support the processing and interpretation of socio-emotional information in oneself and others (Newman, 2001), have been shown to contribute to some of the interpersonal challenges that characterize ASD and schizophrenia (Wallace et al., 2011; Fett et al., 2011). Further, direct comparisons of social cognition deficits across the two disorders have yielded analogous profiles and impairments of similar magnitude in many (Couture et al., 2010; Eack et al., 2013; Sasson, Pinkham, Weittenhiller, Faso, & Simpson, 2016), but not all cases (Sasson et al., 2007), increasingly suggesting the possibility of common underlying mechanisms contributing to social disability in ASD and schizophrenia.

Emerging biological evidence has supported the notion of shared genetic and neural mechanisms across autism and schizophrenia spectra (Cheung et al., 2010; Guilmatre et al., 2009; Radeloff et al., 2014). With respect to studies of brain functions supporting social cognition, a recent meta-analysis of the separate social neuroscience literatures in ASD and schizophrenia indicated that both conditions were characterized by medial-temporal and ventrolateral prefrontal hypoactivity during social-cognitive processing (Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011). Pinkham, Hopfinger, Pelphrey, Piven, and Penn (2007) found similarly reduced brain activity in the amygdala, fusiform gyrus and ventrolateral prefrontal cortex in 12 adults with ASD and 12 adults with paranoid schizophrenia during a trustworthiness task. Ciaramidaro et al. (2015) also found comparable reductions in superior temporal sulcus and ventromedial prefrontal cortex activity during a mentalizing task relative to healthy volunteers among 23 individuals with ASD and 18 patients with paranoid schizophrenia. Furthermore, they extended this work to

examine functional connectivity, and found that both autism and schizophrenia were characterized by reduced fronto-temporal (superior temporal sulcus to ventromedial prefrontal cortex) connectivity.

This growing literature suggests that the behavioral overlap in social-cognitive deficits present in ASD and schizophrenia may be due to shared neural mechanisms reflecting reduced coordination and activation of fronto-temporal systems. However, few studies have directly compared social-cognitive brain function in the two disorders, particularly in adequately powered samples. This study sought to examine fronto-temporal brain function and connectivity during a visual perspective-taking task among individuals with ASD, schizophrenia, and healthy volunteers. It was hypothesized that relative to healthy individuals, participants with ASD and schizophrenia would evidence similar reductions in fronto-temporal activity in social-cognitive brain networks during perspective-taking. Further, it was hypothesized that both patient groups would demonstrate reduced functional connectivity between prefrontal and temporal networks previously shown to support perspective-taking in healthy individuals.

2. Method

2.1. Participants

Participants consisted of 36 individuals with schizophrenia or schizoaffective disorder, 33 individuals with ASD, and 37 healthy volunteers. Participants were recruited for brain imaging studies at the University of Pittsburgh and generally included if they were age 18 years or older, had an IQ ≥ 80 , and were free from any MRI contraindications. Individuals with schizophrenia ($n = 31$) or schizoaffective disorder ($n = 5$) were required to be receiving antipsychotic medication and have their diagnosis verified by the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 2002). Individuals with ASD were required to meet criteria for autism ($n = 17$) or autism spectrum disorder ($n = 15$) based on the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1989). Healthy individuals were included if they were free from a current psychiatric diagnosis as evaluated using the SCID.

Table 1 provides an overview of demographic and clinical characteristics for the sample. Participants were mostly young adults and predominantly male. No significant differences were observed between study groups with regard to age, race, or IQ. However, fewer individuals with ASD were female, and healthy volunteers had attended more years of education than both patient groups (all $p < .001$), with no difference between patients ($p = .679$). All individuals with schizophrenia were receiving antipsychotic medication, by design, and 3 individuals with ASD were receiving antipsychotic treatment as part of their routine care. Psychiatric symptomatology was low for all groups, significantly lower for healthy individuals than patients (all $p < .001$), and not significantly different between ASD and schizophrenia ($p = .580$).

2.2. Visual Perspective-Taking Task

Brain functions supporting visual perspective-taking ability were assessed using a novel paradigm based on a looking-time task developed by Epley and colleagues (Epley, Morewedge, & Keysar, 2004) and previously described elsewhere (Eack, Wojtalik, Newhill, Keshavan, & Phillips, 2013). The task requires participants to identify items in a 5×5 virtual grid array (see Figure 1) from the perspective of a confederate (the research assistant). The virtual grid array contains two sides with four occluders, such that items visible from the participant's perspective are not always in view from the perspective of the assistant. Participants were instructed that the research assistant was going to play the game with them from the MRI control room and that because the assistant would only be able to see the back of the array, the participant had to be sure to only select objects that the assistant could see from her perspective. The target object and 8 distractor objects, randomly interspersed, then appeared in the array for each trial. Trials were 8000 ms in length and consisted of a 2500 ms instruction image (e.g., "hand me the bottle"), a 3500 ms task image displaying the grid array and selection options, and a 2000 ms fixed inter-trial interval during which a blank fixation screen was presented. A total of 63 trials were administered in blocks of 7 trials each, which consisted of either randomly interspersed control ($k = 27$) or perspective-taking trials ($k = 36$). Although the task was administered in blocks, it was modeled using an event-related design because of the random interspersed control and perspective-taking trials within a single block. All conditions asked the participant to complete the same task: select an item in the grid array from the visual perspective of the assistant. During control trials, this item was unambiguous and not occluded from the view of the assistant. For perspective-taking trials, either two similar items were presented in the grid array and one was occluded (simple trials) or three similar items of varying sizes, with one occluded, were presented and the participant was tasked with selecting the largest or smallest item based on what the assistant could see (complex trials). For the purposes of this research, simple and complex perspective-taking trials were aggregated, as we have not previously observed an empirical distinction between these two types of perspective-taking trials (Eack, Wojtalik, Newhill, Keshavan, & Phillips, 2013).

2.3. Image Acquisition and Processing

Magnetic resonance imaging data were collected on a 3T Siemens Verio whole-body scanner with a 12-channel head coil at the Scientific Imaging and Brain Research Center, Carnegie Mellon University. Functional MR data were acquired using an echo T2*-weighted sequence with real-time motion correction (voxel size of 3.2 mm, TR = 2000 ms, TE = 30 ms, flip angle = 79° , 64×64 matrix, 36 slices). High resolution anatomical data were collected using a standard 3D MPRAGE sequence for the purposes of individual subject normalization. All images were visually inspected for quality assurance, assessed for significant motion or signal artifacts, and preprocessed in Statistical Parametric Mapping (SPM) software, version 12 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Preprocessing consisted of a standard indirect normalization pipeline, where functional MR data were aligned, normalized based on high-resolution anatomical data, and smoothed using an 8mm Gaussian kernel.

Motion and signal outliers were infrequent ($M = 1.57\%$, $SD = 3.69\%$) and did not differ significantly between groups, $F(2, 103) = 1.63$, $p = .201$. Average normalized movement was also minimal ($M = .19\text{mm}$, $SD = .14\text{mm}$). However, healthy individuals did display less in-scanner motion than participants with ASD and schizophrenia, $F(2, 103) = 6.18$, $p = .003$, who did not differ significantly from each other, $t(67) = -.61$, $p = .544$. To address the impact of motion on functional connectivity estimates, which are particularly sensitive to head displacement (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), an aCompCor approach was taken to connectivity estimation (Behzadi, Restom, Liau, & Liu, 2007), which has been shown to adequately remove motion and other physiological artifacts (Power, Schlaggar, & Petersen, 2015). Movement parameters obtained during realignment were also included as nuisance variables in all first-level models. Finally, second-level between-group functional activation and connectivity analyses also included average normalized movement as a confounding covariate.

2.4. Procedures

Participants were recruited from the University of Pittsburgh Center for Excellence in Autism Research, Western Psychiatric Institute and Clinic schizophrenia outpatient programs, and the local community. Upon recruitment, participants were screened using the SCID or ADOS, and standardized IQ assessments by a trained clinical interviewer and neuropsychological tester. Eligible participants then completed a series of cognitive and clinical batteries, along with neuroimaging data collection on a separate day. The study was reviewed and approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent prior to study participation.

2.5. Data Analysis

Behavioral performance on the visual perspective-taking task was examined using a series of linear mixed-effects models predicting accuracy and response latency from task condition, group status, and their interaction. Functional neuroimaging data were first analyzed to investigate group differences in task-related brain activity using a series of general linear models implemented in SPM12. First-level models predicted blood-oxygen-level-dependent (BOLD) response from task condition (perspective-taking vs. control), adjusting for motion and timeseries outliers using the Artifact Detection Tools (Whitfield-Gabrieli, 2011). Second-level models predicted perspective-taking BOLD contrasts [perspective-taking - control] from group status, and contrasted the three study groups using a pairwise approach. Type I error was maintained at .05 using a combined voxel-extent threshold of 82 and uncorrected α threshold of .005 based on 10,000 Monte Carlo simulations using the August 25, 2016 complied version of 3dClustSim that implements several changes to maintain better control over false positives (Ward, 2000; Eklund, Nichols, & Knutsson, 2016). Subsequently, seed-based connectivity models were implemented in the Functional Connectivity Toolbox (Nieto-Castanon & Whitfield-Gabrieli, 2009) for SPM12 to examine between-group differences in brain connectivity. These models predicted differential regional connectivity values during perspective-taking - control conditions from group status, and employed a false discovery approach of $p_{FDR} = .05$ at the seed level to maintain Type I error at acceptable levels. A whole-brain analysis was considered, but given the growing number of studies indicating specific regional involvement in social-cognitive processing, particularly

theory of mind and perspective-taking (Carrington & Bailey, 2009), a region of interest approach was used. Regions of interest were specified *a priori*, were identical for activation and connectivity analyses, and included the dorsolateral prefrontal cortex, medial prefrontal cortex, orbitofrontal cortex (subdivided into superior, middle, inferior, and medial [x centered] components), ventromedial prefrontal cortex, anterior cingulate cortex, and temporo-parietal junction based on previous literature (Carrington & Bailey, 2009). Regional definitions were obtained using the automated anatomical labeling atlas by Tzourio-Mazoyer and colleagues (2002) and temporo-parietal junction empirical masks from Dufour and colleagues (2013). A combined region of interest mask was used for all analyses, rather than analyzing each region independently, and analyzed voxels were restricted to those included in this mask. Connectivity seed regions were defined using the same combined region of interest mask employed in activation analyses, with each anatomical region representing a seed, whose BOLD signal time courses were correlated with all other seed regions of interest in the mask. Seeds were defined by averaging activation timeseries across each entire anatomical region, rather than defining seeds by arbitrarily selecting a single voxel within the region of interest. Between-group functional activation and connectivity analyses adjusted for the potential confounding effects of gender and normalized in-scanner movement. Finally, correlation analyses examined the association between extracted BOLD signal activity/connectivity data showing significant between-group differences and chlorpromazine equivalent antipsychotic medication dose to assess the impact of medication on the study findings.

3. Results

3.1. Visual Perspective-Taking Task Performance

Behavioral performance data during the visual perspective-taking task among participants with ASD, schizophrenia, and healthy volunteers are presented in Table 2. As expected, accuracy was reduced during perspective-taking trials in both ASD and schizophrenia, compared to healthy individuals. Latency of response was also decreased for control trials versus perspective-taking trials across all groups, although both participants with ASD and schizophrenia showed increased reaction times during control trials relative to healthy individuals. No significant differences were observed in latency of response between groups during perspective-taking trials.

3.2. Brain Activation During Visual Perspective-Taking in ASD and Schizophrenia

Figure 2 presents BOLD signal activation during perspective-taking versus control trials across the three study groups. Consistent with previous literature (Carrington & Bailey, 2009), regional patterns of activation during perspective-taking included broad areas of the medial and orbito prefrontal cortex, as well as the temporo-parietal junction and superior temporal gyrus. Participants with ASD displayed less bilateral temporo-parietal junction activity than healthy individuals (see Table 3). Conversely, individuals with schizophrenia demonstrated greater medial prefrontal and anterior cingulate activity during perspective-taking than healthy volunteers. When comparing patient groups directly, participants with schizophrenia evidenced significantly greater ventromedial prefrontal and left temporo-parietal junction activity than participants with ASD.

3.3. Brain Connectivity During Visual Perspective-Taking in ASD and Schizophrenia

As shown in Figure 3, seed-based connectivity analyses revealed significantly different patterns of brain connectivity between participants. Findings are organized around hubs of network connectivity, which represented seed regions with the highest number of connections to other region of interest seeds (Bullmore & Sporns, 2009). Healthy individuals displayed a single robust hub of coordination in the right temporo-parietal junction, which was consistently synchronized with medial prefrontal/orbitofrontal brain activity. In contrast, individuals with ASD demonstrated a densely connected medial prefrontal circuit, as well as bilateral connections between the temporo-parietal junction and the medial prefrontal cortex. When examining the sample of participants with schizophrenia, only a single local positive connection between the left dorsolateral prefrontal and right ventromedial prefrontal cortices persisted after correction.

Direct comparisons of connectivity strength between study groups indicated that individuals with ASD had significantly greater connectivity between the left orbitofrontal cortex and bilateral medial prefrontal cortices, as well as the left temporo-parietal junction, compared to healthy participants (see Table 4). In contrast, patients with schizophrenia demonstrated reduced connectivity between the right temporo-parietal junction and medial prefrontal cortex relative to controls. However, individuals with schizophrenia also displayed significantly greater orbitofrontal and anterior cingulate connectivity with the medial prefrontal cortex during perspective-taking compared to healthy individuals. Only two significant connectivity differences between individuals with ASD and schizophrenia were observed, indicating increased bilateral orbitofrontal connectivity in participants with ASD.

4. Discussion

Autism and schizophrenia are neurodevelopmental conditions characterized by significant social disability that may reflect similar underlying neural dysfunction in social-cognitive brain networks (Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011; Pinkham, Hopfinger, Pelphrey, Piven, & Penn, 2007; Ciaramidaro et al., 2015). This study examined fronto-temporal brain activity and connectivity during visual perspective-taking in a well-characterized sample of individuals with ASD, schizophrenia, and healthy volunteers to investigate the degree to which brain functions supporting social cognition are similarly altered across autism and schizophrenia spectra. Findings regarding brain activation indicated greater ventromedial prefrontal and temporo-parietal junction activity in schizophrenia relative to ASD. Differences in patterns of functional connectivity indicated that participants with ASD displayed significantly increased orbitofrontal connectivity compared to patients with schizophrenia. These findings suggest that local social-cognitive networks may be significantly over-connected in ASD, as others have noted (Supekar et al., 2013), which could contribute to inefficient and reduced activation of broader fronto-temporal systems involved in social cognition. Although direct evidence for differentially reduced fronto-temporal connectivity in schizophrenia compared to ASD was not observed, it is interesting that comparisons with healthy individuals indicated less fronto-temporal connectivity in schizophrenia and greater connectivity in autism, lending some support to previous studies of fronto-temporal disconnection in schizophrenia (Mukherjee et al., 2014,

Leitman et al., 2008, Das, Calhoun, & Malhi, 2012). Overall, these findings suggest that unique neural mechanisms may underlie similar patterns of social impairment in autism and schizophrenia.

These findings contribute to a growing understanding of social brain processes in autism and schizophrenia, and diverge some from the small number of previously conducted studies. Pinkham and colleagues (2007) and Ciaramidaro and colleagues (2015) both found reduced prefrontal and medial-temporal brain activity in schizophrenia and ASD during social-cognitive processing relative to healthy individuals, which we did not observe. Patients with schizophrenia showed increased in medial prefrontal cortical activity, and participants with ASD displayed reduced temporal-parietal junction activity during perspective-taking. Variation in brain activation results may be due to methodological differences in the particular social-cognitive construct under study, as these investigations each assessed putatively different aspects of social cognition. While participation of similar brain networks may be likely for various social-cognitive processes (Van Overwalle, 2009), far more research is needed to understand the neural basis of these constructs and their comparability across autism and schizophrenia spectra.

Although this research holds implications for understanding the neural basis of social impairments in autism and schizophrenia, there are several limitations that temper our conclusions. First, participants were not matched on medication characteristics, although antipsychotic dose was unrelated to activation and connectivity values showing between-group differences (see Table S1). Second, our sample size was not large enough to permit meaningful subgroup analyses. Both ASD and schizophrenia are highly heterogeneous conditions, and it will be important for future research to pool larger samples that can perform meaningful subgroup analyses to parse this heterogeneity. In addition, our study is limited in that it did not conduct autism diagnostic assessments in patients with schizophrenia or vice versa, and such information will be important to collect in future studies seeking to understand heterogeneity and overlap between these conditions. Finally, while this research documents diverging abnormalities in brain function and connectivity in ASD and schizophrenia, it does not indicate what mechanisms may give rise to these changes. Previous studies have found evidence for excessive synaptic pruning in schizophrenia (Keshavan, Anderson, & Pettegrew, 1994), which may give rise to the generally under-connected nature of social-cognitive and other brain networks in that disorder. Conversely, ASD appears to be characterized, in some cases, by reduced pruning of dendritic spines, possibly leading to hyper-connectivity (Tang et al., 2014). Future research might profitably investigate these differences in neurodevelopmental mechanisms and integrate functional and structural imaging data to arrive at a better understanding of the factors that contribute to altered functional connectivity during social-cognitive processing in autism and schizophrenia.

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Figure 1.
Visual Perspective-taking Task.

Figure 2.

Regional Activation Maps During Visual Perspective-Taking in Autism Spectrum Disorder, Schizophrenia, and Healthy Volunteers.*

ASD = autism spectrum disorder; SZ = schizophrenia

*Images displayed in neurological convention and thresholded at uncorrected $p < .005$ and $k > 5$ voxels

Figure 3.
Regional Connectivity Maps During Visual Perspective-Taking in Autism Spectrum Disorder, Schizophrenia, and Healthy Volunteers.*
ASD = autism spectrum disorder; SZ = schizophrenia
*Images displayed in neurological convention

Table 1

Demographic and Clinical Characteristics of Individuals with Autism Spectrum Disorder, Schizophrenia, and Healthy Volunteers.

	HC (N = 37)	ASD (N = 33)	SZ (N = 36)	
Variable	<i>M</i> (<i>SD</i>)/ <i>N</i> (%)	<i>M</i> (<i>SD</i>)/ <i>N</i> (%)	<i>M</i> (<i>SD</i>)/ <i>N</i> (%)	<i>p</i> ^a
Age	25.41 (4.71)	23.91 (6.05)	26.25 (6.83)	.257
Female	8 (22%)	3 (9%)	14 (39%)	.014
Non-White	7 (19%)	4 (12%)	10 (28%)	.261
Years of Education	16.16 (2.70)	14.06 (1.78)	13.83 (2.18)	< .001
IQ	106.70 (10.81)	108.36 (14.13)	107.25 (11.90)	.849
BPRS Total	20.38 (2.45)	32.82 (10.41)	33.86 (8.80)	< .001
Anxiety/Depression	1.30 (.39)	2.45 (1.25)	2.53 (.91)	< .001
Withdrawal/Motor Retardation	1.11 (.24)	2.09 (.70)	1.63 (.88)	< .001
Thought Disorder	1.17 (.23)	1.71 (.64)	2.05 (.75)	< .001
Hostility	1.01 (.06)	1.36 (.52)	1.82 (.74)	< .001
ADOS				
Communication	-	3.39 (1.17)	-	-
Reciprocal Social Interaction	-	7.21 (2.38)	-	-
Stereotyped Behavior	-	2.36 (1.34)	-	-
Receiving antipsychotic medication	-	3 (9%)	36 (100%)	-
Receiving second-generation	-	3 (100%)	33 (92%)	-
Chlorpromazine equivalent dose	-	104.17 (83.23)	416.92 (295.26)	.079

Note. BPRS = Brief Psychiatric Rating Scale (Overall & Gorham, 1962), HC = Healthy control, ASD = autism spectrum disorder, SZ = schizophrenia, ADOS = Autism Diagnostic Observation Schedule

^a χ^2 test or analysis of variance, two-tailed, for significant differences between study groups

Table 2

Behavioral Performance During Visual Perspective-Taking in Autism Spectrum Disorder, Schizophrenia, and Healthy Volunteers.

	HC (<i>N</i> = 37)	ASD (<i>N</i> = 38)	SZ (<i>N</i> = 41)	
Variable	<i>M</i> (<i>SE</i>)	<i>M</i> (<i>SE</i>)	<i>M</i> (<i>SE</i>)	Direction ^a
Accuracy (% correct)				
Control	95.44 (2.97)	89.49 (2.96)	92.95 (2.69)	-
Simple Perspective-Taking	87.47 (2.97)	72.39 (2.96)	81.38 (2.69)	HC, SZ > ASD
Complex Perspective-Taking	77.02 (2.97)	59.86 (2.96)	60.73 (2.69)	HC > ASD, SZ
Reaction Time (ms)				
Control	1555.30 (49.54)	1697.96 (49.43)	1732.96 (44.97)	HC < ASD, SZ
Simple Perspective-Taking	2176.47 (49.54)	2303.04 (49.43)	2270.73 (44.97)	-
Complex Perspective-Taking	2585.30 (49.54)	2616.52 (49.43)	2577.72 (44.97)	-

Note. HC = Healthy control, ASD = autism spectrum disorder, SZ = schizophrenia

^aResults of pairwise comparisons from mixed-effects models with multiplicity adjustment applied using the Benjamini and Hochberg (Benjamini & Hochberg, 1995) approach.

Table 3
Brain Activation During Visual Perspective-Taking in Autism Spectrum Disorder, Schizophrenia, and Healthy Volunteers.

Coordinates	k	BA	Label	z	p ^a	Direction
HC						
6, 64, 14	612	9, 10	Medial prefrontal cortex	3.85	< .001	PT < Control
46, 36, 26	128	10, 46	Ventromedial prefrontal cortex, dorsolateral prefrontal cortex	3.72	< .001	PT > Control
56, -36, 10	113	22	Superior temporal gyrus, temporo-parietal junction	3.72	< .001	PT < Control
26, 6, 50	103	6	Middle frontal gyrus	3.28	.001	PT > Control
-42, 36, 28	101	46	Ventromedial prefrontal cortex, dorsolateral prefrontal cortex	3.50	< .001	PT > Control
ASD						
-44, -56, 18	512	39, 22	Superior temporal gyrus, temporo-parietal junction	4.09	< .001	PT < Control
8, 34, -8	406	32	Anterior cingulate cortex	3.98	< .001	PT < Control
52, -56, 20	301	39	Superior temporal gyrus	4.05	< .001	PT < Control
8, 28, 34	133	9, 32	Medial prefrontal cortex	3.93	< .001	PT > Control
SZ						
2, 28, 40	396	32	Medial prefrontal cortex, anterior cingulate cortex	3.90	< .001	PT > Control
44, 38, 26	386	10, 46	Ventromedial prefrontal cortex, dorsolateral prefrontal cortex	4.63	< .001	PT > Control
-44, 42, 18	328	10	Ventromedial prefrontal cortex, dorsolateral prefrontal cortex	4.71	< .001	PT > Control
28, 8, 56	129	6	Middle frontal gyrus	3.96	< .001	PT > Control
HC vs. ASD						
-50, -50, 14	226	22	Temporo-parietal junction	3.49	< .001	HC > ASD
52, -56, 20	213	39	Temporo-parietal junction, angular gyrus	3.66	< .001	HC > ASD
HC vs. SZ						
12, 66, 12	145	10	Medial prefrontal cortex	3.82	< .001	HC < SZ
8, 40, 22	82	9, 32	Anterior cingulate, medial prefrontal cortex	3.33	< .001	HC < SZ
ASD vs. SZ						
-40, 16, 24	132	9, 46	Ventromedial prefrontal cortex	3.82	< .001	ASD < SZ
-52, 28, -2	106	47	Ventromedial prefrontal cortex, orbitofrontal cortex	3.89	< .001	ASD < SZ
-60, -42, 8	94	22	Temporo-parietal junction, superior temporal gyrus	3.20	.001	ASD < SZ

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Note: ASD = autism spectrum disorder, HC = healthy control, PT = perspective-taking, SZ = schizophrenia

^aUncorrected p -values. Type I error was maintained at $p < .05$ using a combined uncorrected α threshold of .005 and voxel-extent threshold of 82 based on Monte Carlo simulations.

Table 4

Fronto-Temporal Functional Connectivity Differences During Visual Perspective-Taking Between Adults with Autism Spectrum Disorder, Schizophrenia, and Healthy Volunteers.

Seed ROI	Target ROI	β	p_{FDR}	Direction
HC vs. ASD				
Hub #1: Middle orbitofrontal cortex (L)	Medial prefrontal cortex (L)	.14	.013	HC < ASD
	Medial prefrontal cortex (R)	.10	.047	HC < ASD
	Temporo-parietal junction (L)	.10	.047	HC < ASD
HC vs. SZ				
Hub #1: Medial prefrontal cortex (R)	Middle orbitofrontal cortex (R)	.12	.047	HC < SZ
	Anterior cingulate (L)	.10	.047	HC < SZ
Hub #2: Temporo-parietal junction (R)	Medial orbitofrontal cortex (L)	-.14	.014	HC > SZ
ASD vs. SZ				
Hub #1: Middle orbitofrontal cortex (L)	Medial orbitofrontal cortex (R)	.14	.004	ASD > SZ
	Medial orbitofrontal cortex (L)	.13	.027	ASD > SZ

Note. ASD = autism spectrum disorder, HC = healthy control, SZ = schizophrenia