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Prefrontal cortical dysfunction during visual perspective-taking in schizophrenia

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ABSTRACT

Schizophrenia is characterized by marked impairments in a broad and diverse array of social–cognitive domains. Fundamental deficits in the ability to visualize and shift to the perspectives of others and the neural networks that support this ability may contribute to many of these impairments. This study sought to investigate deficits in prefrontal brain function and connectivity in patients with schizophrenia during visual perspective-taking, and the degree to which such deficits contribute to higher-order impairments in social cognition. A total of 20 outpatients with schizophrenia and 20 age- and gender-matched healthy volunteers completed a basic, visual perspective-taking task during functional magnetic resonance imaging, along with a behavioral assessment of theory of mind after neuroimaging. Results revealed hypoactivity in the medial prefrontal (anterior cingulate) and orbitofrontal cortices during perspective-taking trials compared to control trials in schizophrenia patients relative to healthy controls. In addition, patients demonstrated significant deficits in negative connectivity between medial prefrontal and medial-temporal regions during perspective-taking, which fully mediated behavioral impairments observed in theory of mind. These findings suggest that disruptions are present in the most fundamental aspects of perspective-taking in schizophrenia, and that these disruptions impact higher-order social information processing.

1. Introduction

Schizophrenia is characterized by pervasive deficits in cognitive function (Heinrichs and Zakzanis, 1998), which place significant limitations on the ability of individuals to recover from the disorder (Green et al., 2000). Impairments in social cognition, or the ability to process and interpret socio-emotional information in oneself and others (Newman, 2001), are among the most disabling cognitive deficits individuals with schizophrenia experience and represent some of the strongest predictors of functional outcome (Fett et al., 2011). Central to these deficits in social information processing may lie in an inability to shift from one's own perspective to the perspective of others, which we have postulated as a critical treatment target for social–cognitive interventions (Hogarty et al., 2004; Eack, 2012).

The neural basis of higher-order perspective-taking deficits in theory of mind has been extensively investigated in schizophrenia and studies have often identified deficiencies in medial prefrontal networks such as the ventromedial prefrontal, anterior cingulate, and orbitofrontal cortices during such tasks (Brunet et al., 2003; Brüne, 2005; Andreasen et al., 2008; Brüne et al., 2008; Hirao et al., 2008; Benedetti et al., 2009). While this research has helped elucidate abnormalities in brain function during perspective-taking tasks that require making social and emotional inferences, few investigations have examined whether similar deficits in perspective-taking exist at the most fundamental visual levels in schizophrenia. Studies have suggested that similar brain regions may be involved in visual and higher-order perspective-taking (David et al., 2006; Carrington and Bailey, 2009), and the presence of deficits in some of these regions during basic visual perspective-taking tasks that are not confounded by strong social or emotional stimuli could help identify abnormalities in the most central neural pathways that contribute to perspective-taking deficits in schizophrenia. In the only study to date to examine basic visual perspective-taking in schizophrenia, Langdon et al. (2001) used an array rotation task with 32 individuals with schizophrenia and 24 healthy volunteers and found significant deficits in the ability of patients to accurately visualize different perspectives of the array. Further, the pattern of errors made by patients was not consistent with random responding, but indicated a difficulty in shifting from their own egocentric visual perspective. These findings have suggested that deficits in perspective-taking in schizophrenia may be present even at the most fundamental levels, and may give rise to impairments in theory of mind and other

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deficits patients experience in taking the perspectives of others. However, the neural basis of these impairments in schizophrenia has not been investigated.

This study sought to examine differences in prefrontal brain function during the completion of a visual perspective-taking paradigm commonly employed in the developmental psychology field in patients with schizophrenia matched with healthy volunteers. We hypothesized that relative to healthy controls, patients with schizophrenia would demonstrate reduced BOLD-signal activity in the medial prefrontal and orbitofrontal cortices during visual perspective-taking, and that hypofunction in these areas would be associated with behavioral deficits in theory of mind.

2. Method

2.1. Participants

Participants included 20 outpatients diagnosed with schizophrenia ($n = 9$) or schizoaffective disorder ($n = 11$) and 20 age- and gender-matched healthy volunteers. Individuals with schizophrenia were included if they were between the ages of 18 and 50, had a diagnosis of schizophrenia or schizoaffective disorder verified by the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002), were psychiatrically stable and adherent to prescribed antipsychotic medications, and had an IQ ≥ 80. Healthy volunteers were included if they did not have a current psychiatric disorder according to the SCID and reported no family history of psychosis. Exclusion criteria for both groups included MRI contraindications, significant neurological conditions, a history of medical disorders producing cognitive impairment, persistent suicidal/homicidal behavior, or significant substance abuse problems. As can be seen in Table 1, the study sample was young, the majority of individuals were male, and most had attended some college. Healthy controls were significantly more likely to be white and had higher IQ scores than patients with schizophrenia.

2.2. Perspective-taking task

A visual perspective-taking task was developed for this study based on a looking-time paradigm commonly employed to measure perspective-taking and egocentricity in developmental psychology (Epley et al., 2004). Participants were instructed that they were going to play a game in the MRI scanner with a research assistant, where the assistant was going to identify an object placed in a 5 × 5 grid array that she/he wanted (see Fig. 1). The virtual grid array was two-sided, with the participant facing the front side and the assistant facing the back. Within the array, four blockers were placed in fixed positions on the back side that occluded the assistant's view of objects, but not that of the participant. Instructions were given to the participant that the assistant was going to play the game with him/her virtually 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/his perspective. Multiple ($n = 8$) distractor objects were placed in the array in addition to the target object. Prior to entering the MRI scanner and completing the task all individuals were provided with standardized instructions describing the task, were asked to practice the task to ensure they had an understanding of its requirements, and were shown both perspectives of the grid array (the front they would see and the back that the assistant would see).

The task was constructed as a block design with seven trials per block, and three blocks per run consisting of 1 of 3 conditions: a simple perspective-taking condition, a complex perspective-taking condition, and a non-perspective taking control condition. The basic task of the perspective-taking conditions was for the participant to select an item from the array based on an instruction that was ambiguous, because multiple items in the array resembled the instruction (*e.g.*, “hand me the cupcake” when two cupcakes were present in the array), and to properly select the item that the assistant could see from her/his perspective. In the simple perspective-taking condition, two similar items were presented in the grid array, one which was occluded and one which was not. In the more difficult complex perspective-taking condition, three similar items of varying sizes were presented in the array and the participant was tasked with selecting the largest or smallest item based on what the assistant could see (*e.g.*, “hand me the large book”). Non-perspective taking control trials asked the participant to select an unambiguous item that was not occluded from the view of the assistant. A total of three runs of the task were completed for each participant, with the order of block conditions within each run counterbalanced. Within blocks, trials were randomly intermixed to include 5 condition trials (*e.g.*, simple perspective-taking) and 2 non-condition trials (*e.g.*, control) to avoid habituation effects. Trials consisted of a 2.5 s instruction image (*e.g.*, “hand me the large book”) and a 3.5 s task image displaying the grid array and selection options, with a 2 s interstimulus interval during which a blank screen was presented. A 15 s fixation period displaying a blank grid array was inserted at the beginning and end of the first and last run, respectively, with no fixation period present during the second run of the task. Total task time was 8 min 54 s.

Table 1
Demographic and clinical characteristics of patients with schizophrenia and healthy volunteers.

Variable	Healthy volunteer ($n = 20$)	Schizophrenia ($n = 20$)	p[a]
	M (SD)/n (%)	M (SD)/n (%)	
Age	26.50 (5.82)	27.80 (6.61)	.513
Male	13 (65%)	14 (70%)	1.000
White	16 (80%)	7 (35%)	.010
Attended college	18 (90%)	15 (75%)	.407
IQ	106.55 (6.67)	97.90 (8.11)	.001
SCID diagnosis			
Schizophrenia	–	9 (45%)	–
Schizoaffective disorder	–	11 (55%)	–
Illness duration (years)	–	4.85 (3.18)	–
Receiving atypical antipsychotic	–	19 (95%)	–
Antipsychotic dose (CPZ)	–	308.08 (235.89)	–
BPRS total	21.90 (1.59)	38.05 (10.42)	<.001
GAS	86.35 (6.67)	54.30 (11.85)	<.001
Theory of mind–hinting task	17.35 (1.63)	14.68 (3.83)	.007

Note. BPRS = Brief Psychiatric Rating Scale, CPZ = Chlorpromazine equivalent dose, GAS = Global Assessment Scale, SCID = Structured Clinical Interview for DSM-IV.
[a] Results of χ^2 or independent sample t-tests (two-tailed) for significant differences between patients with schizophrenia and healthy volunteers.

2.3. Theory of mind and symptom measures

Measures of theory of mind and psychopathology were collected to examine the associations between BOLD-signal response during the perspective-taking task and social–cognitive and symptom outcomes. These measures included the Hinting Task (Corcoran et al., 1995) and the Brief Psychiatric Rating Scale (Overall and Gorham, 1962).

2.4. Image acquisition and processing

Structural and functional MR data were collected on a 3 T Siemens Tim Trio whole-body scanner with a 12-channel head coil. Functional MR data were acquired using an echo T2*-weighted sequence with real-time motion correction (voxel size of 3.2 × 3.2 × 3.1 mm, TR = 2000 ms, TE = 28 ms, bandwidth = 3004 Hz/px, flip angle = 90°, echo spacing = .47 ms, FOV = 205 mm, 64 × 64 matrix, 39 slices, slice thickness = 3.1 mm). High resolution structural MR data were collected using a 3D MPRAGE sequence in the axial orientation (voxel size of 1.0 mm, TR = 2200 ms, TI = 1000 ms, TE = 3.31 ms, flip

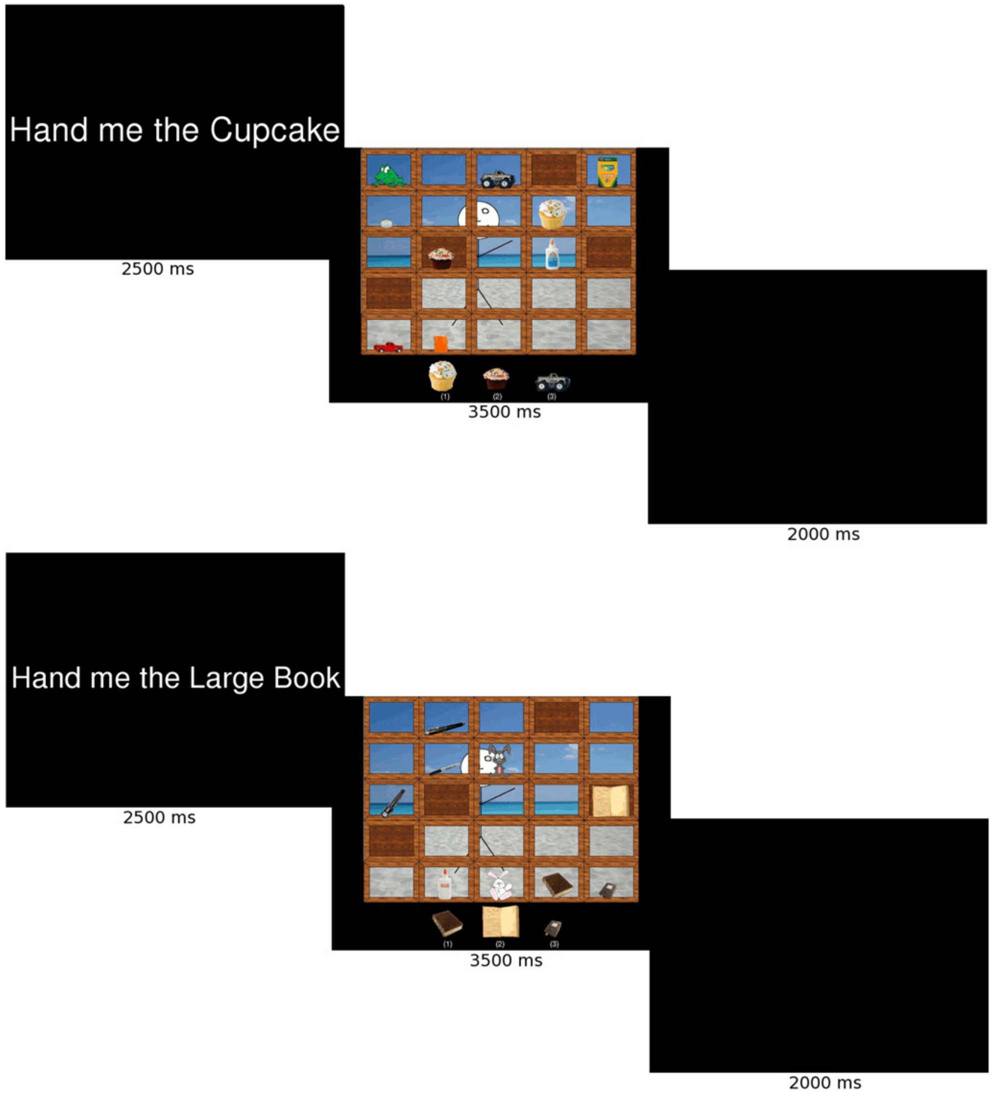

Fig. 1. Visual perspective-taking task.

angle = 90°, FOV = 256 mm, 256 × 192 matrix, 192 slices, slice thickness = 1.0 mm). After collection, images were inspected for significant motion or other artifacts and preprocessed in Statistical Parametric Mapping software, version 8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). All preprocessed functional data were smoothed using an 8 mm Gaussian kernel.

2.5. Procedures

Participants were recruited from community clinics, advertisements, support groups, and other studies from Pittsburgh, PA and surrounding areas. Upon recruitment, individuals were screened for eligibility using the SCID and Ammon's Quick Test. Participants were then administered the aforementioned perspective-taking task while in the MRI, and on a separate day administered the theory of mind and symptom measures by trained research technicians. 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.

2.6. Data analysis

Behavioral data were analyzed using a series of linear mixed-effects models adjusting for potential demographic (age, sex, race) and IQ confounders to investigate group differences in the accuracy and latency of responses. Functional MR data were analyzed using region-of-interest mixed-effects models in SPM8. First-level models used a block design and examined the effect of task condition compared to fixation on BOLD-signal activity for each participant, and included artifact and motion parameters as covariates (Whitfield-Gabrieli, 2011). Second-level models examined the effect of task condition, group status, and their interaction on first-level BOLD-signal response, and adjusted for the potential confounding effects of demographics (age, sex, race) and IQ. Because there were no *a priori* hypotheses regarding systematic differences in brain function between the simple and complex perspective-taking conditions, these trials were collapsed into a single perspective-taking condition to conserve statistical power. Regions of interest for second-level models were restricted to the lateral and medial prefrontal cortices, consisting of the anterior cingulate and orbitofrontal cortices, and the dorsolateral prefrontal cortex (Brodmann areas 9 and 46) based on previous literature (*e.g.*, Carrington and Bailey, 2009). Regions of interest were defined using atlases outlined by Tzourio-Mazoyer et al. (2002) in the Wake Forest University PickAtlas toolbox for SPM8 (Maldjian et al., 2003). Type I error rates for voxel-wise comparisons in second-level models were maintained at .05 using a voxel-extent threshold of 95 and uncorrected alpha threshold of .01 from AlphaSim (Ward, 2000). Exploratory whole-brain functional connectivity analyses were then conducted using the Functional Connectivity Toolbox (Nieto-Castanon and Whitfield-Gabrieli, 2009) based on seed regions identified from second-level BOLD-signal activity analyses that demonstrated significant abnormalities in patients. These connectivity analyses conducted simultaneous whole-brain correlations between BOLD-signal activity in seed regions of interest with every other non-seed voxel in the brain for perspective-taking *versus* control trials. The resulting differential correlation coefficients between task conditions were then compared directly between participant groups, after adjusting for demographic and IQ characteristics, with corrected Type I error rates held to .05 using a combined voxel-extent and uncorrected alpha threshold of 92 and .001, respectively. Finally, mediator analyses based on Baron and Kenny's (1986) framework were constructed using separate general linear models predicting Hinting Task performance from group status through BOLD signal activity or connectivity. Indirect effects were calculated using the product of coefficients method, and their statistical significance tested using MacKinnon et al. (2002) asymptotic z' test for indirect effects.

3. Results

3.1. Behavioral results during perspective-taking

Behavioral data on 38 of the 40 participants (behavioral responses were not recorded for 2 patients due to a device malfunction, although these individuals are included in all fMRI analyses) indicated lower accuracy rates for schizophrenia patients, with no significant interaction observed between group and task condition (see Table 2). In addition, the reaction time of patients was slightly slower than healthy controls across all trials. However, there was a significant group by task condition interaction indicating that the difference in response time for control *vs.* perspective-taking trials was significantly less for patients, suggesting that individuals with schizophrenia spent less time shifting to the other person's perspective than healthy individuals. No significant associations were observed between accuracy or reaction times during perspective-taking trials and performance on the Hinting Task (all $p > .339$).

3.2. Brain function during perspective-taking

Results of region-of-interest analyses of task-related BOLD-signal activity are presented in Table 3. Across both patients with schizophrenia and healthy volunteers, greater functional activity was observed in the bilateral dorsolateral prefrontal cortex during perspective-taking *vs.* control trials. In addition, during perspective-taking participants selectively deactivated the anterior cingulate cortex to a greater degree than during control trials. Significant group by condition interactions were observed indicating hypofunction in the left orbitofrontal and bilateral anterior cingulate cortices in patients with schizophrenia during perspective-taking trials (see Fig. 2 and Table 3). Specifically, when shifting to trials that required taking the perspective of others, patients failed to activate the left orbitofrontal cortex to the same degree as healthy volunteers and demonstrated a differentially greater deactivation of the bilateral anterior cingulate cortex. No significant associations were observed between behavioral measures of theory of mind, psychopathology, or medication dose and brain activity in these regions.

3.3. Functional connectivity during perspective-taking

Exploratory whole-brain functional connectivity analyses were conducted using seeds in the left orbitofrontal and bilateral anterior cingulate cortical regions that demonstrated functional abnormalities during perspective-taking in patients with schizophrenia. Although no significant differences were observed in orbitofrontal connectivity, those with schizophrenia demonstrated significantly less negative connectivity between the anterior cingulate cortex and right fusiform/parahippocampal area during perspective-taking. As can be seen in Fig. 3, while the deactivation of the anterior cingulate cortex was associated with an increase in activation in the right fusiform and parahippocampal gyri among healthy controls, patients with schizophrenia showed the opposite pattern of neural coordination. Furthermore, after adjusting for IQ, a positive correlation between activity in these regions was associated with reduced theory of mind ability on the Hinting Task ($\beta = -.40$, $p = .014$). Patients with schizophrenia demonstrated significantly worse performance on the Hinting Task compared to controls (see Table 1), and the impairments observed in fronto-temporal functional connectivity fully mediated this behavioral deficit in theory of mind ($z' = -1.81$, $p = .049$).

4. Discussion

Social–cognitive impairment is increasingly recognized as a significant aspect of schizophrenia and a critical domain for treatment development (Green et al., 2008). A deficit in the ability to take the perspective of other people could give rise to some of the most functionally disabling aspects of these impairments. This study examined the neurobiologic impairments of individuals with schizophrenia during a basic visual perspective-taking task. Results revealed that patients spent less time shifting to another person's visual perspective and that they demonstrated reduced BOLD-signal response in the left orbitofrontal and bilateral anterior cingulate cortices during perspective-taking compared to healthy individuals. Further, those with schizophrenia exhibited deficits in negative functional connectivity between the anterior cingulate and fusiform/parahippocampal gyrus, and these abnormalities in the coordination of fronto-temporal systems fully accounted for higher-order perspective-taking deficits in theory of mind observed on the Hinting Task.

The results of this investigation support the behavioral findings of Langdon et al. (2001), and increasingly suggest that impairments in the neural basis of perspective-taking may be present in schizophrenia at even the most fundamental levels. It is interesting that the anterior

Table 2
Behavioral results during visual perspective-taking in patients with schizophrenia and healthy volunteers.

Outcome	Group				Analysis		
	Healthy volunteer ($n = 20$)		Schizophrenia ($n = 18$)		Condition	Group	Group × condition
	M	*SE*	*M*	*SE*	*p*	*p*	*p*
Accuracy (%)					.018	<.001	.234
Control	92.65	1.90	85.98	2.76			
Simple perspective-taking	77.51	4.13	71.21	4.54			
Complex perspective-taking	68.87	5.09	52.53	5.65			
Latency (ms)					.296	<.001	<.001
Control	1513.57	100.39	1760.90	100.32			
Simple perspective-taking	2202.20	101.37	2278.60	101.44			
Complex perspective-taking	2539.81	103.05	2484.20	103.61			

Note. Two participants were excluded from behavioral analyses due to missing behavioral data from a recording device malfunction.

Table 3
Prefrontal functional activation during visual perspective-taking in patients with schizophrenia and healthy volunteers.

MNI coordinates (x, y, z)	Cluster size	Location	BA	*t*	*p*	Direction
Condition: perspective-taking vs. control						
0, 36, −4	242	Anterior cingulate cortex	24/32	3.23	.001	Perspective-taking < control
−46, 4, 30	197	Left dorsolateral prefrontal cortex	9/46	4.32	<.001	Perspective-taking > control
50, 38, 20	128	Right dorsolateral prefrontal cortex	46	5.03	<.001	Perspective-taking > control
46, 4, 28	128	Right dorsolateral prefrontal cortex	9	4.50	<.001	Perspective-taking > control
−52, 32, 20	108	Left dorsolateral prefrontal cortex	46	4.07	<.001	Perspective-taking > control
Group × condition						
−8, 40, 0	114	Anterior cingulate cortex	32	3.24	.001	Patient < control
−30, 24, −20	104	Left orbitofrontal cortex	47	3.34	.001	Patient < control

Note. BA = Brodmann Area.

cingulate cortex was selectively deactivated during perspective-taking *vs.* control trials in both participant groups in this study, and that this selective deactivation was stronger in schizophrenia. With regard to social cognition, others have found the anterior cingulate cortex to be particularly involved in self-processing (Northoff and Bermpohl, 2004) and first-person perspective-taking (David et al., 2006), and have found the deactivation of this region when shifting to the third-person perspective (Lamm et al., 2007). Many investigators view taking the perspective of another person as an inhibitory process that requires an explicit shift from the self to other perspective (Epley et al., 2004), and the deactivation of the anterior cingulate during visual perspective-taking may reflect this shift. The excessive inhibitory response in the anterior cingulate in schizophrenia patients may further reflect the greater effort experienced by these individuals in inhibiting an egocentric response, as well as difficulty in coordinating anterior cingulate inhibition with the activation of medial-temporal social–cognitive networks.

These findings should be considered in the context of several limitations. All patients were receiving antipsychotic medication, which could have affected neural responses, and this could not be reasonably

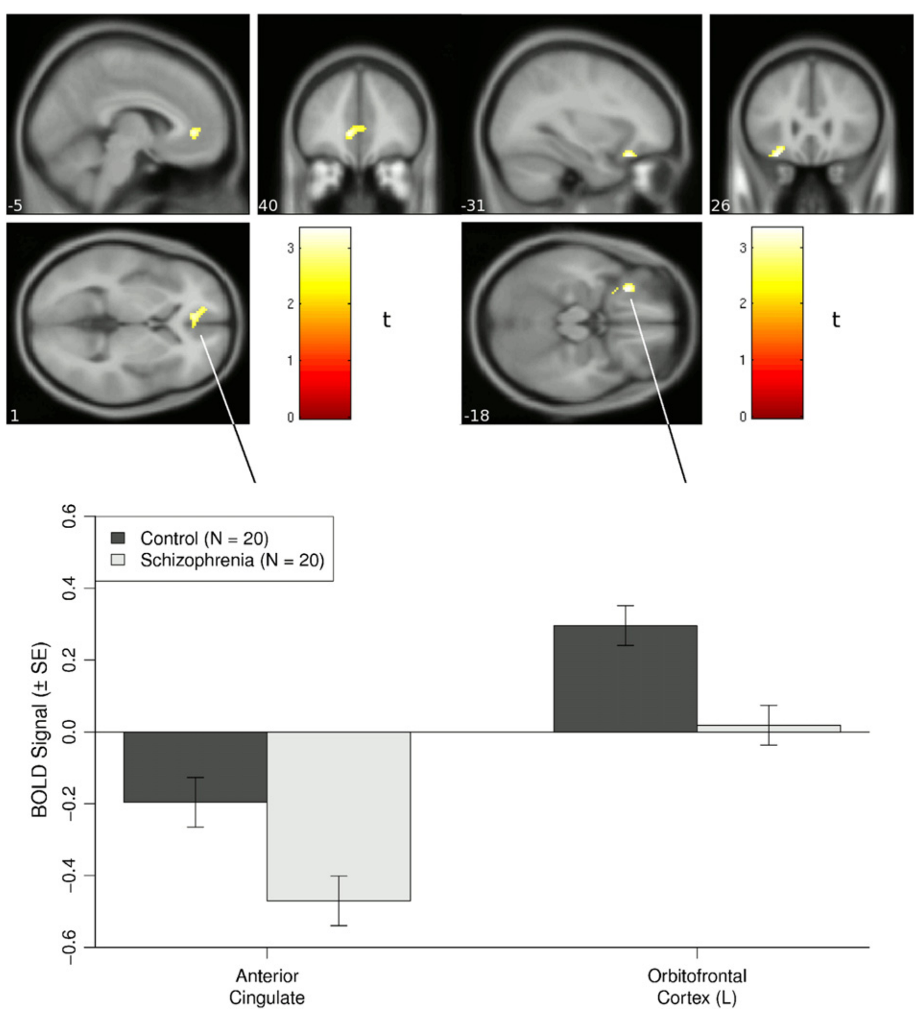

Fig. 2. Prefrontal functional activity during visual perspective-taking in patients with schizophrenia compared to healthy volunteers.

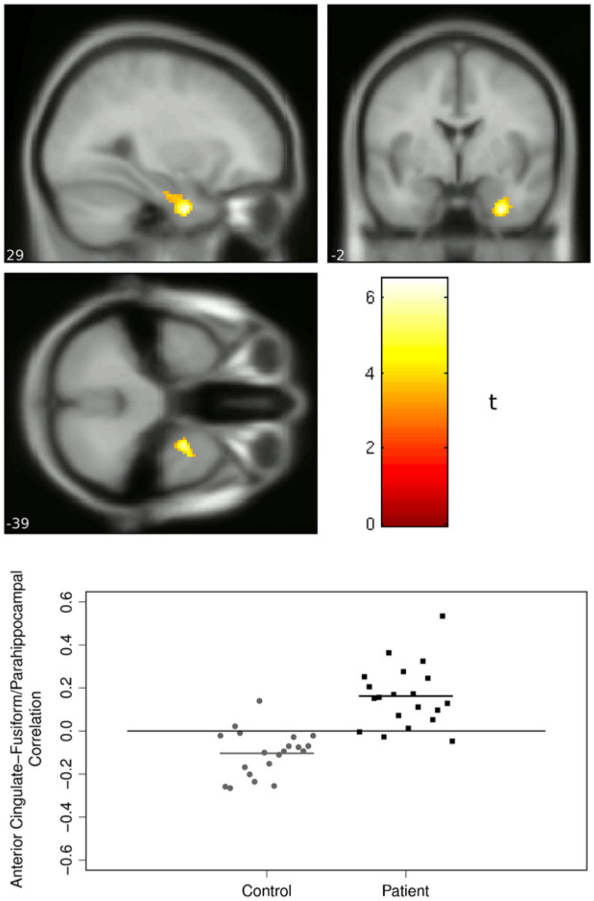

Fig. 3. Anterior cingulate and medial-temporal functional connectivity during visual perspective-taking in patients with schizophrenia and healthy volunteers.

adjusted for in analyses, although neither BOLD-signal activity nor functional connectivity in affected regions were associated with antipsychotic dose or psychopathology. In addition, a relatively focused set of regions of interest was chosen to examine group differences in brain function in this study based on previous evidence (*e.g.*, Carrington and Bailey, 2009), and it is possible that broader deficits are present during visual perspective-taking in schizophrenia than those observed in the anterior cingulate and orbitofrontal cortices. Furthermore, first-level task contrasts were made against a modest number of fixation blocks, which could have limited statistical power for detecting task-related effects. Finally, similar to the work of Korver-Nieberg et al. (2013) with adolescents with various psychotic conditions, greater behavioral impairments in accuracy were not observed during visual perspective-taking in this study, although patients spent less time shifting to the third-person perspective. The lack of differential impairments in accuracy may reflect our effort to construct a task that patients could feasibly complete, and suggests that the neural deficits observed in those with schizophrenia are not attributable to a poorer understanding or greater difficulty with the task. Despite these limitations, this study is the first to demonstrate neurobiologic abnormalities during the most fundamental aspects of perspective-taking in schizophrenia, and suggests that these abnormalities may contribute to broader social–cognitive impairments in the disorder.

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Contributors

This study was designed by Drs. Eack, Phillips, Keshavan, and Newhill. Dr. Eack wrote the initial draft of the manuscript, Drs. Newhill, Keshavan, and Phillips, along with Ms. Wojtalik provided critical revisions and feedback on both the manuscript and analyses. 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.

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