

Alterations in Brain Activation During Cognitive Empathy Are Related to Social Functioning in Schizophrenia

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Impaired cognitive empathy (ie, understanding the emotional experiences of others) is associated with poor social functioning in schizophrenia. However, it is unclear whether the neural activity underlying cognitive empathy relates to social functioning. This study examined the neural activation supporting cognitive empathy performance and whether empathy-related activation during correctly performed trials was associated with self-reported cognitive empathy and measures of social functioning. Thirty schizophrenia outpatients and 24 controls completed a cognitive empathy paradigm during functional magnetic resonance imaging. Neural activity corresponding to correct judgments about the expected emotional expression in a social interaction was compared in schizophrenia subjects relative to control subjects. Participants also completed a self-report measure of empathy and 2 social functioning measures (social competence and social attainment). Schizophrenia subjects demonstrated significantly lower accuracy in task performance and were characterized by hypoactivation in empathy-related frontal, temporal, and parietal regions as well as hyperactivation in occipital regions compared with control subjects during accurate cognitive empathy trials. A cluster with peak activation in the supplementary motor area (SMA) extending to the anterior midcingulate cortex (aMCC) correlated with social competence and social attainment in schizophrenia subjects but not controls. These results suggest that neural correlates of cognitive empathy may be promising targets for interventions aiming to improve social functioning and that brain activation in the SMA/aMCC region could be used as a biomarker for monitoring treatment response.

Key words: empathy/social functioning/functional neuroimaging/schizophrenia

Introduction

Empathy can be defined as sharing and understanding the emotional experiences of others¹ by cognitively processing the behaviors and cues displayed during social encounters.² These empathic processes can be separated into “affective” and “cognitive” subcomponents^{2,3}; sharing the emotions of others is critical to affective empathy, whereas understanding the emotional perspective of others and maintaining a distinction between one’s own feelings and the experiences of others is critical for cognitive empathy.⁴

Research suggests that affective empathy is generally supported by activation of the inferior frontal gyrus (IFG), anterior insula, anterior cingulate cortex, and supplementary motor area (SMA), while cognitive empathy is supported by activation of the IFG, anterior insula, and the anterior midcingulate cortex (aMCC).^{5,6} The activation of the IFG and anterior insula during cognitive empathy performance suggests that cognitive empathy may require affective processing.^{7,8} Cognitive empathy may also be supported by activation in regions associated with the mentalizing network such as the medial prefrontal cortex (mPFC),^{9–12} right temporoparietal junction (TPJ),^{12–14} and precuneus.^{9,15,16} These same regions subserve theory-of-mind processes (ie, mentally representing the nonemotional beliefs and intentions of others).^{17–19} Thus, cognitive empathy appears to use neural

regions associated with both affective processing and theory-of-mind.^{3,20}

Recent studies suggest that schizophrenia subjects demonstrate hypoactivation of brain regions related to empathy.^{21–24} Moreover, cognitive empathy is particularly impaired in schizophrenia subjects,^{25–27} while self-reported and performance-based measures of cognitive empathy explain unique variation in measures of social functioning after accounting for neurocognitive deficits and clinical symptoms.^{28,29} Hence, cognitive empathy may be a critical target for developing interventions aimed at improving social functioning in this population. For instance, a recent finding suggests that cognitive empathy in schizophrenia subjects may be enhanced with oxytocin treatment.³⁰ Although multiple studies investigated the neural correlates associated with impaired cognitive empathy in schizophrenia, they have not yet examined whether these neural correlates might also be related to social functioning.

Schizophrenia subjects have been characterized by alterations in frontotemporoparietal brain activation when making judgments related to cognitive empathy.^{21–23} Some studies found that schizophrenia subjects had hypoactivation of the mPFC and right TPJ as compared with healthy subjects during cognitive empathy performance,^{22,31} while others found that schizophrenia subjects had hypoactivation of the IFG, mPFC, aMCC, and precuneus during cognitive empathy performance.²¹ Overall, the results suggest that schizophrenia subjects may have generalized hypoactivation across multiple regions involved in empathic decision making. Although some studies demonstrated that brain activation during social cognitive task performance (ie, facial affect perception, theory-of-mind) was associated with social functioning,^{32,33} the relationship between neural activation underlying cognitive empathy and social functioning among schizophrenia subjects has not been examined.

The current study used an event-related design with whole-brain analysis to examine the brain activation in schizophrenia subjects and healthy controls during a cognitive empathy paradigm and the associations between empathy-related brain activation, and measures of cognitive empathy and social functioning. Based on our review of the literature, we hypothesized that schizophrenia subjects would: (1) demonstrate poorer cognitive empathy and social functioning as compared with control subjects, (2) be characterized by hypoactivation in anterior insula, IFG, mPFC, aMCC, TPJ, and precuneus as compared with control subjects, and (3) exhibit brain-behavior correlations between empathy-related brain activation and measures of cognitive empathy and social functioning.

Methods

Subjects

Clinically stable schizophrenia subjects ($n = 30$) and healthy controls ($n = 24$), group-matched for age

(18–50 years old), gender, race, parental socioeconomic status,³⁴ and handedness (table 1), participated in the study, which was approved by the institutional review board at Northwestern University Feinberg School of Medicine. These subjects are a subset from a larger study on empathy among individuals with schizophrenia who returned to complete neuroimaging procedures.²⁹ Schizophrenia subjects were recruited from advertisements at local outpatient treatment centers, surrounding neighborhoods, and the National Alliance for Mental Illness. Control subjects were recruited from neighborhoods near the service providers and via online advertisements. Subjects were excluded if they (1) met Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV) criteria for current substance abuse or dependence within the past 6 months, (2) had a severe medical disorder, (3) had a head injury with neurological sequelae, or (4) met criteria for mental retardation. Control subjects were further excluded if they had a lifetime history of any DSM-IV axis I disorder or a first-degree relative with a psychotic disorder. Written informed consent was obtained after a complete description of the study was provided to subjects.

Demographic and Clinical Measures

Demographic and clinical measures were collected using the Structured Clinical Interview for DSM-IV (SCID),³⁵ which was administered by Master- and PhD-level research staff who regularly participated in training and reliability sessions. Diagnosis was validated from a consensus between a semistructured psychiatrist interview and the SCID. Antipsychotic medication dosages were converted into chlorpromazine equivalents using a standardized method.³⁶ Psychopathology was assessed in schizophrenia subjects using the global ratings from the Scale for the Assessment of Positive Symptoms³⁷ and the Scale for the Assessment of Negative Symptoms.³⁸ Self-reported empathy was assessed using the interpersonal reactivity index (IRI),³⁹ which includes subscales for fantasy, perspective-taking, empathic concern, personal distress, and an IRI total score.

Social Functioning

Social functioning was assessed using validated measures of social competence and social attainment.^{40,41} Social competence was assessed using the social skills performance assessment, a video-recorded test comprised of 2 role-play scenes involving meeting a new neighbor and requesting help from a landlord.⁴² Each scene was rated on a 5-point scale across 8 criteria for the first scene and 9 criteria for the second scene⁴² and a final score was calculated by averaging the 2 role-play scores (intraclass correlation coefficient = 0.92 for 2 blinded raters on 25% of the videos). Social attainment was assessed using the total score from the Specific Levels of Functioning

Table 1. Demographic and Clinical Characteristics of Study Groups

	Between-Group Differences, Mean (SD)				χ^2 Statistic	P Value
	Control Subjects (<i>n</i> = 24)		Schizophrenia Subjects (<i>n</i> = 30)			
	<i>N</i>	%	<i>N</i>	%		
Demographic						
Gender (% male)	14	58.3	18	60.0	0.1	.90
Race					0.5	.79
Caucasian	12	50.0	13	43.3		
African American	9	37.5	14	46.7		
Other	3	12.5	3	10.0		
	Mean	SD	Mean	SD	<i>F</i> Statistic	
Age (years)	34.4	8.9	33.6	7.1	0.1	.72
Handedness	0.9	0.3	0.9	0.4	0.5	.57
Mean parental SES ^a	26.0	10.5	22.6	10.9	1.3	.24
Clinical						
SAPS global ratings						
Hallucinations	—	—	2.8	2.1	—	—
Delusions	—	—	3.3	1.9	—	—
Bizarre behavior	—	—	1.7	1.9	—	—
Positive formal thought disorder	—	—	2.2	1.6	—	—
SANS global ratings						
Affective flattening	—	—	3.2	1.6	—	—
Alogia	—	—	2.3	1.6	—	—
Avolition	—	—	3.4	1.5	—	—
Anhedonia	—	—	3.1	1.5	—	—
Attention	—	—	3.1	1.5	—	—
Duration of illness (years)	—	—	13.6	7.5	—	—
Chlorpromazine equivalent	—	—	362.8	237.7	—	—

Note: Parental socioeconomic status (SES), Scale for the assessment of positive symptoms (SAPS), Scale for the assessment of negative symptoms (SANS).

^aCompleted by *n* = 23 control subjects and *n* = 29 schizophrenia subjects.

Scale, which measures interpersonal relationships, social acceptability, daily living activities, and work skills.⁴³

Cognitive Empathy Task

Cognitive empathy was assessed using an emotional perspective-taking (EPT) event-related paradigm adapted from Derntl et al⁴⁴ and administered while subjects underwent functional magnetic resonance imaging (fMRI). Participants completed 2 runs and each run consisted of 2 blocks of EPT trials and 2 blocks of control trials. The run order was counterbalanced across participants. In each trial, one of 70 static scenes of 2 people engaged in an emotional interaction with the face of one person masked was presented (see online [supplementary figure 1](#)). For EPT trials, subjects viewed the static scene and were then presented with 2 emotional (or neutral) faces from which they were instructed to choose the best option that characterized the emotion of the masked face (eg, fear, anger, sadness, disgust, or happiness).⁴⁴ For control trials, subjects viewed the static scene and were asked to choose whether the masked face was on the left

or right. The locations of the response labels were counterbalanced across trials (eg, “left” on right side of the screen, thus requiring a right button press). Stimuli were presented in blocks of 7 trials; each block was preceded by directions indicating whether the block included emotion or control trials. The face stimuli were taken from a standardized stimulus set.⁴⁵ Static scenes were presented at fixed intervals of 4000 ms followed by a pseudorandom fixation period (0, 550, 1100, or 1650 ms) after which the response stimuli were presented for ≤ 4000 ms. Responses triggered progression to the next intertrial interval displaying a central cross-hair for 8–12 s. Accuracy and response times were recorded for each trial.

fMRI Acquisition and Processing

MR scanning was performed on a 3T TIM Trio system (Siemens Medical Systems) at Northwestern University's Center for Translational Imaging. Anatomical MRI was collected using a high-resolution 3D T1-weighted MPRAGE sequence optimized for gray-white contrast (echo time (TE) = 3.16 ms, repetition time (TR) = 2400 ms,

1 × 1 × 1 mm voxels, time = 8.09 min). During each functional run, 360 volumes were collected consisting of 40 contiguous axial images acquired parallel to the anterior-posterior commissure plane using an echo-planar sequence contrast (T2*) (TR = 2200 ms, TE = 20 ms, field of view (FOV) = 220 × 206 mm, flip = 80°, 1.7 × 1.7 × 3.0 mm voxels). Each run lasted 13:12 min and the first 3 volumes of each run were excluded to account for nuclear magnetic resonance and eddy-current equilibrium.

Functional data preprocessing, individual subject, and group-level fMRI analyses were conducted using Analysis of Functional NeuroImages (AFNI).⁴⁶ The data were slice-timing and motion corrected, volume registered, spatially smoothed to have a Gaussian blur of 8 mm and aligned to a common Talairach-Tournoux template. First-level modeling used multiple linear regression to model our stimuli of interest with the functional time series to yield least squares estimates of the linear regression coefficients and the *T*-statistics for significance of the coefficients using 3dDeconvolve within AFNI. A model hemodynamic response function and its temporal derivative modeled the onset of directions displayed prior to each block, the duration of scene presentation for correct and incorrect EPT and control trials separately, the trials in which a response was not made, and correct and incorrect responses. Timepoints with excessive motion (>1 mm) were not analyzed and no subject had >25% of their timepoints discarded. Groups did not differ with respect to the number of timepoints censored ($T = 0.3$, $df = 52$, $P > .10$).

Demographic and Behavioral Analyses

Group differences on demographic variables as well as measures of self-reported empathy, task accuracy and response time, and social functioning were evaluated with ANOVA for continuous variables and chi-square (χ^2) tests for categorical variables.

Group Analyses Using Functional Imaging

Mixed-effects meta-analysis, which uses group-level variation and a precision estimate of the effect of interest from individual participants,⁴⁷ was used in the whole-brain analysis of the event-related paradigm to examine the main effect of group for the activation throughout the duration of the emotional scene displayed to participants. There were not enough incorrect trials to independently model the activation during the viewed scenes with an incorrect response and thus these trials were excluded from imaging analyses. Control trial data were not included in the imaging analyses due to the emotional nature of the control trial scenes. This approach is consistent with prior work using this same paradigm.²¹

The differential blood-oxygen-level-dependent (BOLD) response during correct EPT scenes was

evaluated between schizophrenia subjects and control subjects via a whole-brain analysis. In prior studies, the differentiation between correctly and incorrectly performed trials is often not made which can complicate interpretation of differences in regional activation between groups who differ in performance. By analyzing only correctly performed trials, we can identify differences in regional activation between groups when they are engaged in the same behavior (ie, accurate empathic decision making). To correct for multiple comparisons, an alpha probability simulation was used to compute the probability that a random field of noise would produce a cluster of a given size. With an individual voxel threshold of $P < .001$ and a minimum cluster size of ≥ 65 voxels, the clusters of significant difference between the 2 groups are corrected for multiple comparisons to have a corrected P value of $\leq .05$.

Correlation Analyses

The correct EPT trial BOLD response from each functionally defined cluster (derived from between-group differences in brain activation) in regions hypothesized to be involved in cognitive empathy were used for subsequent correlation analyses including the anterior insula, IFG, SMA/aMCC, mPFC, right TPJ, and precuneus. We examined whether the mean activation across each cluster was associated with measures of empathy and social functioning using 2-tailed Pearson partial correlations that covaried for the number of censored timepoints and task response time. We applied a false discovery rate to adjust for multiple comparisons in these correlation analyses at a value of 0.05.⁴⁸

Exploratory Analyses

We generated exploratory 2-tailed Pearson partial correlations (uncorrected with censored timepoints and task reaction time as covariates) between the clusters of brain activation in non-hypothesized neural regions and measures of empathy, social functioning, clinical symptoms, duration of illness, and medication use.

Results

Demographic, Empathy, and Social Functioning

Means and SDs using ANOVA and χ^2 analyses for demographic and clinical data can be found in [table 1](#). Tests of between-group effects revealed schizophrenia subjects had significantly lower accuracy ($F = 6.2$, $df = 1,52$, $P < .05$) and slower response times ($F = 3.5$, $df = 1,52$, $P = .07$) at the trend level as compared with control subjects on EPT trials. Schizophrenia subjects did not differ from control subjects with respect to accuracy ($F = 2.2$, $df = 1,52$, $P > .10$) and response time ($F = 2.8$, $df = 1,52$, $P > .10$) on the control trials. Schizophrenia subjects scored

lower than controls on measures of social competence ($F = 18.8$, $df = 1,43$, $P < .001$), social attainment ($F = 17.2$, $df = 1,52$, $P < .001$), IRI perspective taking ($F = 9.3$, $df = 1,52$, $P < .01$) and higher on the IRI personal distress ($F = 17.3$, $df = 1,52$, $P < .001$). Groups did not differ on measures of IRI fantasy and empathic concern. See [table 2](#) for means and SDs for empathy and social functioning data.

Between-Group Differential Activation

Between-group analyses determined that schizophrenia subjects hypoactivated a network of brain regions that may be involved with cognitive empathy as compared with control subjects. Clusters of peak activation difference included bilateral IFG, right SMA (extending to the aMCC), the right TPJ (including the superior temporal sulcus), and the right precuneal sulcus. We did not find between-group differences in activation of the anterior insula, while schizophrenia subjects deactivated the left mPFC and right visual posterior region of the precuneus to a greater extent than controls.

In addition to the hypothesized regions involved in cognitive empathy, we found that schizophrenia subjects hypoactivated the dorsolateral PFC (dlPFC) and caudate nucleus as well as hyperactivated the lingual gyrus and cuneus as compared with control subjects. Lastly, we found that schizophrenia subjects deactivated the left posterior cingulate cortex (PCC) during accurate EPT trial performance to a greater extent than control subjects. The percent signal change for all clusters (by group)

are presented in [figure 1](#), while Montreal Neurological Institute coordinates for all peak activations can be found in [table 3](#).

Brain-Behavior Correlations

In schizophrenia subjects, the cluster with peak activation in the right SMA (extending to the aMCC) was correlated with social competence ($r = .46$, $P < .05$), social attainment ($r = .46$, $P < .05$), and accuracy during EPT performance ($r = .41$, $P < .05$) ([figure 2](#)). The right visual posterior region of the precuneus negatively correlated with self-reported cognitive empathy ($r = -.45$, $P < .05$), and the right precuneal sulcus correlated with social attainment ($r = .35$, $P = .07$) and IRI fantasy ($r = .36$, $P = .06$) at the trend level. In control subjects, we found that the right visual posterior region of the precuneus was negatively correlated with IRI personal distress ($r = -.49$, $P < .05$). The remaining pairwise correlations between the regions hypothesized to be involved with cognitive empathy (ie, IFG, mPFC, SMA/aMCC, right TPJ, and precuneus) and all study measures completed by schizophrenia and control subjects did not attain significance.

Exploratory Correlations

The following exploratory correlations were found to be significant for schizophrenia subjects: right cuneus with social competence ($r = -.40$, $P < .05$), left lingual gyrus with the chlorpromazine equivalent at the trend level ($r = .37$, $P = .054$). No other correlations between brain

Table 2. Mean (SD) of Empathy and Social Functioning Measures

	Between-Group Differences				F Statistic	P Value
	Control Subjects (n = 24)		Schizophrenia Subjects (n = 30)			
	Mean	SD	Mean	SD		
Empathy measures						
Interpersonal reactivity index						
Fantasy	14.54	6.65	14.46	6.24	<0.01	.97
Perspective taking	20.58	4.65	16.67	4.72	9.29	.004
Empathic concern	20.33	4.66	18.83	5.09	1.25	.27
Personal distress	8.33	4.20	13.43	4.69	17.30	<.001
Total score	63.79	11.99	63.40	13.96	<0.01	.91
EPT trial accuracy	0.92	0.09	0.84	0.13	6.52	.01
EPT reaction time, correct trials (s)	1.34	0.36	1.52	0.36	3.47	.07
Control trial accuracy	0.91	0.10	0.85	0.16	2.20	.14
Control trial reaction time, correct trials (s)	1.04	0.36	1.26	0.55	2.76	.10
Social functioning						
Social competence ^a	4.36	0.61	3.23	0.84	24.29	<.001
Social attainment	141.79	13.17	127.20	12.62	17.15	<.001

Note: EPT, emotional perspective-taking.

^aCompleted by $n = 18$ control subjects and $n = 25$ schizophrenia subjects.

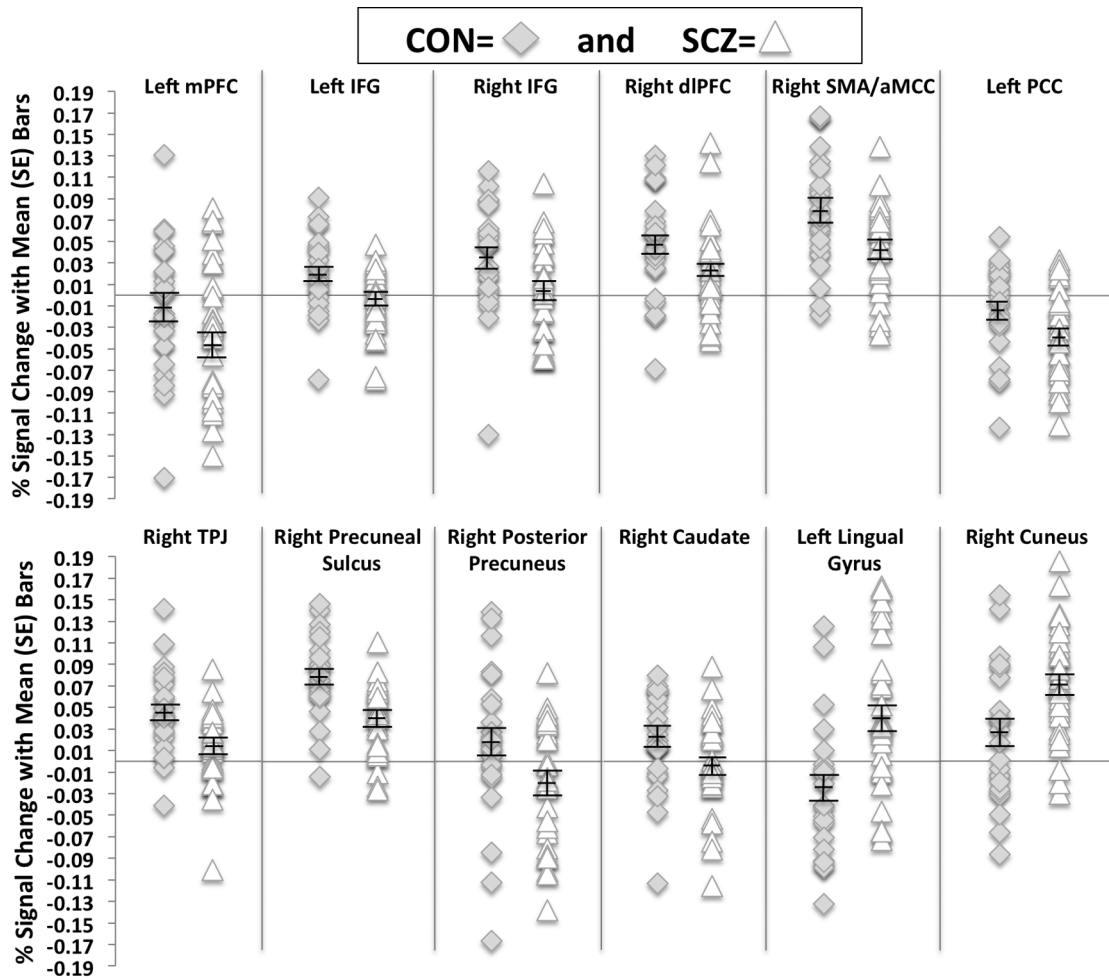


Fig. 1. Percent signal change during accurate emotional perspective-taking (EPT) trials within schizophrenia subjects and control subjects. Plots include mean and SE bars. Medial prefrontal cortex (mPFC); inferior frontal gyrus (IFG); dorsolateral PFC (dlPFC); supplementary motor area (SMA); anterior midcingulate cortex (aMCC); posterior cingulate cortex (PCC); temporoparietal junction (TPJ).

activation and the remaining study measures were significant for either group (including clinical symptoms and duration of illness for schizophrenia subjects). Among the empathy and social functioning measures completed by the schizophrenia subjects, we found that EPT trial accuracy correlated with self-reported cognitive empathy ($r = .40, P < .05$), social competence ($r = .47, P < .05$), and social attainment ($r = .35, P = .07$) at the trend level, while self-reported cognitive empathy correlated with social attainment ($r = .59, P < .001$) and social competence at the trend level ($r = .33, P = .09$). Social competence and social attainment were not correlated ($r = .26, P = .18$).

Discussion

We examined whether brain activation associated with accurate performance during a cognitive empathy task differed between schizophrenia subjects and control subjects and whether empathy-related brain activation was correlated with measures of empathy and social functioning. Our results suggest that schizophrenia

subjects, as compared with controls, were characterized by hypoactivation in a network of brain regions known to support empathic processing as well as hyperactivation in occipital regions during accurate performance on a cognitive empathy task. Among schizophrenia subjects, task activation in the right SMA extending to the aMCC was correlated with measures of social competence and social attainment. These findings extend our previous work demonstrating that schizophrenia subjects have deficits in self-reported and performance-based cognitive empathy that were associated with social functioning.^{28,29}

Empathy and Social Functioning

Schizophrenia subjects demonstrated reduced accuracy on the cognitive empathy task performed in the scanner, which is consistent with prior studies using the fMRI version and full versions of this task.^{21,25,29} The schizophrenia subjects also demonstrated lower social competence and social attainment than control subjects, which is

Table 3. Peak % Change in BOLD Activation in Study Participants

Region With Peak Activation	Hem	“BA”	Peak Coordinates			Peak <i>T</i> Value	Cluster Size
			L/R	A/P	S/I		
Control subjects > schizophrenia subjects							
Frontal regions							
mPFC	L	9	−0	54	32	4.82	96
IFG	L	11,47	−35	35	−8	6.17	176
	R	47	52	32	−2	7.35	165
dIPFC	R	9	38	24	30	6.84	88
SMA (including aMCC)	R	6,32	2	6	52	7.56	253
PCC	L		−0	−36	48	5.88	104
Temporoparietal regions							
TPJ (including STS)	R	22,40	68	−34	28	8.53	531
Parietooccipital regions							
Precuneal sulcus	R	7	18	−64	32	6.56	300
Posterior precuneus	R		2	−64	30	7.63	90
Subcortical region							
Caudate nucleus	R		8	10	2	5.37	82
Schizophrenia subjects > control subjects							
Occipital regions							
Lingual gyrus	L		−0	−72	−2	−6.36	133
Cuneus	R	17	10	−96	4	−7.54	128

Note: Blood oxygenation level dependent (BOLD), hemisphere (Hem), left (L), right (R), Brodmann’s area (BA), medial prefrontal cortex (mPFC), inferior frontal gyrus (IFG), dorsolateral PFC (dIPFC), supplementary motor area (SMA), anterior midcingulate cortex (aMCC), posterior cingulate cortex (PCC), temporoparietal junction (TPJ), superior temporal sulcus (STS).

expected given the current participants were a subsample from a prior studying reporting on measures of social functioning.²⁹

Neural Alterations in Cognitive Empathy

Schizophrenia subjects hypoactivated several regions (ie, bilateral IFG, right TPJ, and right precuneal sulcus) involved in cognitive empathy during accurate task performance. Specifically, we found bilateral hypoactivation in Brodmann’s area (BA) 47 within the IFG of schizophrenia subjects and a recent meta-analysis supports the involvement of BA 47 in empathy.⁴⁹ IFG activation has also been observed during affective mentalizing and the processing of emotions,^{49–51} while the right TPJ has been implicated in distinguishing one’s own emotional state from the feelings and perspectives of others.⁵² Research suggests the precuneus is associated with self-reflection, perspective-taking, and the default mode network (DMN).⁵³ Overall, the observed hypoactivation in this region was consistent with recent studies on the neural correlates of cognitive empathy in schizophrenia.^{21,22,31}

Our results showed some divergence from prior studies of cognitive empathy. First, schizophrenia subjects in the present study were characterized by hyperactivation of the lingual gyrus and cuneus, while prior research did not observe empathy-related hyperactivation in any region.²¹ Although these findings were unexpected, a recent study

of adolescents with traumatic brain injuries to the IFG and other prefrontal regions found that participants hyperactivated both the lingual gyrus and cuneus during perspective-taking task performance.⁵⁴ Thus, our observation of hyperactivation in these regions could suggest a potential compensatory mechanism for accurate task completion. This interpretation would be consistent with prior studies implicating activity in the cuneus as a compensatory region associated with emotional processing.⁵⁵ However, cuneus hyperactivation in schizophrenia subjects was associated with poorer social competence, which suggests this additional activation could be interfering with social functioning. The observed hyperactivation in this study compared with prior research could be explained by greater statistical power given the much larger sample size in this study compared with prior studies.^{21–23}

We found that schizophrenia subjects deactivated the mPFC, PCC, and right visual posterior regions of the precuneus (extending into PCC) during task performance. Due to the role of these regions in the DMN,^{56–58} this pattern of activation could potentially be explained as the schizophrenia subjects needing to “turn off” the DMN to a greater extent in order to engage in task performance for which they still had poorer accuracy than controls.^{59,60} Also, we observed that schizophrenia subjects were characterized by hypoactivation in the dIPFC and caudate nucleus, which are regions involved in working memory⁶¹ and typically hypoactive during

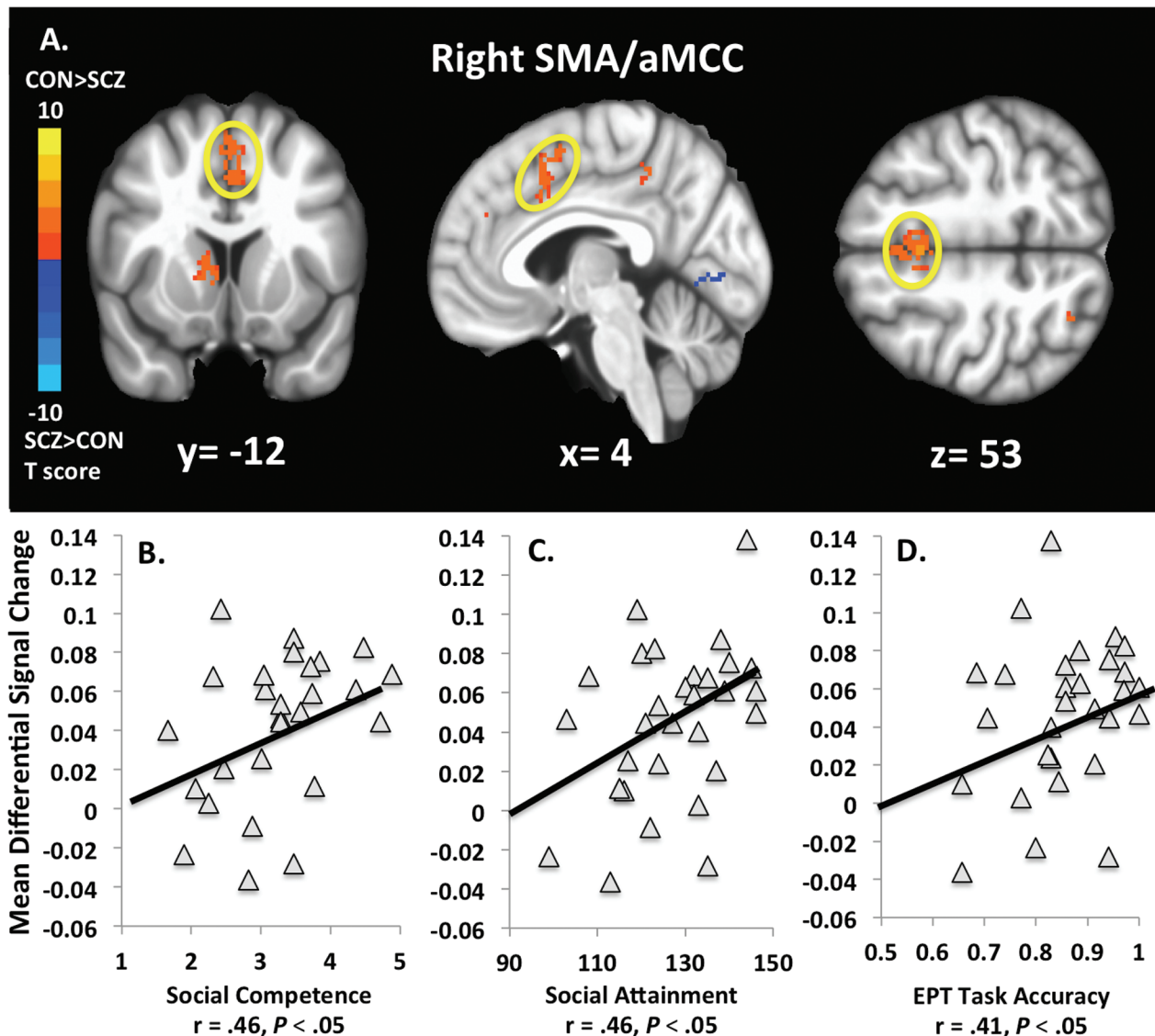


Fig. 2. Activation maps displaying the blood-oxygen-level-dependent (BOLD) change within the right SMA/aMCC cluster during accurate emotional perspective-taking (EPT) trials between schizophrenia (SCZ) subjects and control (CON) subjects (A). Right SMA/aMCC activation was greater in CON as compared with SCZ ($T = 2.58$, $df = 29$, $P < .05$). CON > SCZ activation is reflected by warmer colors ($T > 0$), while SCZ > CON is reflected by cooler colors ($T < 0$). Activation in this region in SCZ was correlated with higher levels of social competence (B), social attainment (C), and EPT task accuracy (D).

working memory performance in this population.^{62,63} Prior research suggests that working memory performance is correlated with accuracy on a lab-based version of the EPT task.²⁹ Thus, the observed hypoactivation in these regions suggests that schizophrenia subjects had difficulty engaging this working memory circuitry to complete the task (eg, maintain contents of stimulus, retrieve and maintain prior memories to help interpret the stimulus).

Correlations With Neural Alterations

In addition to being characterized by hypoactivation in schizophrenia subjects, the cluster with peak activation in

the SMA extending to the aMCC was significantly correlated with social competence, social attainment, and task accuracy in this group. A recent meta-analysis suggests that the SMA and aMCC are core regions of an empathy neural network.⁵ Furthermore, the cytoarchitecture and primate literature suggest the aMCC extends to the SMA and that the SMA may be vulnerable to impairments in aMCC function.^{64,65} Specifically, the aMCC has been implicated in emotion and pain discrimination, empathy for pain, and the preparation of behavioral responses to stressful events.^{7,66–68} Similarly, the SMA has been implicated in empathic responding, the perception and mental imagery of action, and mobilizing behavioral responses to aversive stimuli.^{5,7,69–73} These processes might

be involved when someone cognitively empathizes with emotional scenes referenced with action-based content and images of full-body social interactions as presented by the stimuli in this study.

The observed correlations involving the SMA/aMCC cluster are consistent with prior studies of schizophrenia suggesting that higher-level social cognitive brain activation correlates with measures of empathy and social functioning.^{13,33} Also, our results contrast a recent finding that brain activation during performance on a theory-of-mind task was negatively associated with social functioning in schizophrenia subjects.³² The emphasis on nonemotional mental states in the theory-of-mind task as opposed to EPT could possibly explain this divergence in the findings.

We found a significant negative correlation between self-reported cognitive empathy and activation in the right visual posterior region of the precuneus. Given the potential involvement of this region in the DMN,⁵⁸ this relationship could suggest that schizophrenia subjects who have difficulty deactivating the DMN may have greater impairments in cognitive empathy. However, future research using resting-state data would need to examine this relationship more carefully. Also, we did not observe any significant correlations between empathy-related brain activation and self-reported cognitive empathy. Given that the correlation between self-reported cognitive empathy and the SMA/aMCC cluster trended toward significance ($r = .31, P = .11$), it is possible that we did not have the statistical power to observe this particular effect. We did not observe any significant correlations between brain activation and social functioning measures in control subjects. These non-findings could be explained by a lack of variability in the control subjects' social functioning measures, which were designed to capture deficits related to schizophrenia and were typically at ceiling in the controls.

Study Implications

Our results suggest that cognitive empathy could be a critical treatment target for improving social functioning in schizophrenia subjects, which is an important consideration for the field as interventions targeting social cognition continue to be developed.^{74–76} Based on the observed brain-behavior correlations in the present study, clinical interventions that increase SMA/aMCC activation or increase accurate cognitive empathy may help facilitate improved social functioning for schizophrenia subjects living in the community. Future research could examine the association between treatments targeting empathic behavior and empathy-related brain activation. For instance, recent work by Davis et al³⁰ suggests that treatment with oxytocin is related to improved performance on the same cognitive empathy task used in the current study. Thus, additional research is needed to understand the neural mechanisms contributing to this change.

Our findings also suggest that SMA/aMCC activation could potentially be used as biomarkers to monitor the success of treatment. For example, the observed SMA/aMCC activation during an empathic task could be used as neurofeedback to improve empathic abilities or to monitor the effectiveness of cognitive behavioral therapy. There is evidence that treatment with repetitive transcranial magnetic stimulation can increase SMA and aMCC activity.⁷⁷ Alternatively, interventions aimed at improving social cognition could also be examined in this context, as some of the resultant benefits could generalize to empathic behavior.^{78–80}

Limitations

Although our findings provide insight into the relationship between cognitive empathy brain activation and social functioning, they must be interpreted in the context of some limitations. First, the results may not generalize to individuals during the prodromal or first-episode stages of schizophrenia given an illness duration of more than 10 years in our sample. Second, recent studies suggest that lower-level auditory processing deficits (ie, cue and pitch detection) may have an important role in higher-level social cognitive tasks assessing prosody and sarcasm.^{81–83} Similarly, mentalizing processes rely on intact lower-level visual processing.^{84,85} The current study did not account for potential lower-level visual processing contributions to cognitive empathy, and future research might consider evaluating this relationship in the context of social functioning. Third, there was limited specificity regarding the relationship between empathy and social functioning given that we did not examine the neural correlates of affective empathy and their association with social competence and social attainment. Future research examining the neural correlates of these processes might further inform our understanding of how empathy is associated with social functioning.

Conclusions

Schizophrenia subjects were characterized by hypoactivation in neural regions known to support empathic behavior, which were associated with poor social functioning. Thus, cognitive empathy is a potential treatment target that may be contributing to everyday functioning. As such, measures of SMA/aMCC activation could be used as biomarkers to help guide future research to improve treatment and outcome. Altogether, these findings suggest that the poor everyday functioning observed for decades in individuals with schizophrenia could be influenced by alterations in the neurobiological substrates for empathy.

Supplementary Material

Supplementary material is available at <http://schizophreniabulletin.oxfordjournals.org>.

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