Theory of mind skills are related to gray matter volume in the ventromedial prefrontal cortex in schizophrenia

Supplemental Information

Table of Contents

Behavioral Data

Table S1A. Participant demographics and clinical information

	Schizophrenia (SZ) Participants	Healthy Control Participants	Differences Between Groups
Gender (F/M)	4F/17M	4F/13M	U = 167.5, p = .982
Age: mean (SD), [range]	44.33 (10.18), [23-59]	43.75 (11.75), [23-59]	$t(35)$ = .164, p = .871
Education: mean (SD), [range]	13.05 (2.38), [9-20]	15 (1.15), [13-16]	$t(32)$ = 2.76, p = .010*
WASI: mean (SD), [range]	101.19 (19.42), [68-138]		
Diagnosis: *n* [%]			
Schizoaffective	9 [42.9%]	-	-
Schizophrenia	12 [52.4%]	-	-
SZ Subtypes	Paranoid 4/21	-	-
	Catatonic 1/21	-	-
	Undifferentiated 5/21	-	-
	Residual 2/21	-	-
Length of Illness: mean (SD), [range]	24.47 (11.77), [5-47]	-	-
Antipsychotic Medication: *n* [%]			
Typical	14 [66.6%]	-	-
Atypical	1 [4.8%]	-	-
Typical & Atypical	1 [4.8%]		
PANSS Symptoms : mean (SD), [range]			
Positive Symptoms	12.29 (5.19), [5-20]	-	-
Negative Symptoms	16.52 (5.87), [7-27]	-	-
Disorganized Symptoms	11.25 (3.39), [7-16]	-	-
MATRICS Scores (z scores): mean (SD), [range]			
Global Cognition	-.744 (.56), [-1.78-.41]	-	-

F, female; M, male; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; WASI, Wechsler Abbreviated Scale of Intelligence.

All p-values reported in the table are from two-tailed tests.

* significant at $p < .05$ (two-tailed).

Table S1B. Behavioral results for Theory of Mind (ToM) measures: Faux Pas Task, Interpersonal Reactivity Index (IRI) Perspective-Taking subscale, and Quality of Life Scale (QLS) - Empathy score. Results for all IRI subscales are also listed. Each participant's IRI score is the sum of ratings for items in that subscale. Group means (SD) and [range] are reported.

	SZ	Healthy	Difference between Groups
Faux Pas Task: mean % correct (SD), [range]			
Faux Pas Score (total for all scenarios)	70 (20), [33-98]	94 (9), [68-100]	$t(28.97) = -4.77$ $p = .000$*
Content Score (factual understanding; control condition)	93 (12), [50-100]	96 (5), [86-100]	$t(35) = -1.16$ $p = .248$
Faux Pas Task Repeated Measures 2 x 2 ANOVA: Group (SZ/Healthy Control) and Question Type (Faux Pas/Content)[b]			
Main Effect of Group (SZ/Healthy): $F(1, 35) = 14.83$, $p = .000$; $\eta^2_p = .30$[a]			
Main Effect of Question Type (Faux Pas/Content): $F(1, 35) = 22.87$, $p = .000$; $\eta^2_p = .40$[a]			
Group x Question Type Interaction: $F(1, 35) = 13.99$, $p = .001$*; $\eta^2_p = .29$[a]			
IRI[c] –Perspective-Taking: mean (SD), [range]	17.05 (4.68), [9-28]	19.73 (4.46), [13-28]	$t(33) = 1.71$ $p = .097$[#]
IRI –Empathic Concern: mean (SD), [range]	18.6 (5.87), [7-28]	20.6 (5.55), [7-27]	$t(33) = 1.0$, $p = .31$
IRI –Fantasy Scale: mean (SD), [range]	12.65 (5.87), [2-23]	18.27 (5.28), [8-27]	$t(33) = 2.9$, $p = .006$*
IRI –Personal Distress: mean (SD), [range]	10.7 (5.87), [1-20]	8.93 (4.83), [1-15]	$t(33) = .95$, $p = .35$
Quality of Life Scale - Empathy: mean (SD), [range]	4.14 (1.11), [2-6]		

All *p*-values reported in the tables are from two-tailed tests.
* significant at $p < .05$ (two-tailed).
[#] significant at $p < .05$ (one-tailed) (i.e. $p = .048$ with a one-tailed test).
[a] η^2_p = partial eta squared effect size.
[b] This analysis was also conducted using a 2 x 2 ANCOVA controlling for education. Education was significantly related to Faux Pas scores $F(1, 31) = 6.14$, $p = .019$; $\eta^2_p = .17$[a]. However, even when controlling for education, group is still a significant predictor of Faux Pas score $F(1, 31) = 6.83$, $p = .014$; $\eta^2_p = .18$.
[c] All IRI subscales are reported for the convenience of researchers interested in the different components of empathy.

Table S2. Correlations of behavioral data

2A. Correlations of behavioral data for schizophrenia group

	Faux Pas Score	IRI Perspective Taking	IRI Fantasy	IRI Empathic Concern	IRI Personal Distress	QLS Empathy	WASI	General Cognition
ToM Performance: Recognition of Faux Pas								
Faux Pas Total Score	1							
ToM Self Report: Interpersonal Reactivity Index								
Perspective Taking	.398	1						
Fantasy Scale	.079	-.118	1					
Empathic Concern	.169	.521*	-.079	1				
Personal Distress	.074	-.051	.724*	.167	1			
ToM Interview-based: Quality of Life Scale								
Empathy	.004	.354	-.135	.402	-.339	1		
Cognition								
WASI	.721*	.549*	.281	.298	.224	.252	1	
General Cognition	.572*	.314	.005	.247	.131	-.114	.584*	1

2B. Correlations of behavioral data for healthy control group

	Faux Pas Score	IRI Perspective Taking	IRI Fantasy	IRI Empathic Concern	IRI Personal Distress
Faux Pas Score	1				
Self Report: Interpersonal Reactivity Index					
Perspective Taking	-.369	1			
Fantasy Scale	-.154	.576*	1		
Empathic Concern	-.103	.629*	.634*	1	
Personal Distress	-.318	-.084	-.536*	-.289	1

IRI, Interpersonal Reactivity Index; QLS, Quality of Life Scale; WASI, Wechsler Abbreviated Scale of Intelligence.
* significant at $p < .05$ (two-tailed test).

Table S3. Correlations of ToM Measures with MATRICS Subscales in schizophrenia group

	Faux Pas Score	IRI Perspective Taking	IRI Fantasy	IRI Empathic Concern	IRI Personal Distress	QLS Empathy
General Cognition	.57*	.31	.01	.25	.13	-.11
Verbal Working Memory	.34	.17	-.27	.02	-.007	-.18
Visual Working Memory	.15	.08	.12	-.03	.10	-.07
Problem Solving	.24	.40	.15	.30	.24	-.05
Verbal Learning and Memory	.47*	-.11	-.06	.13	.05	-.19
Visual Learning and Memory	.23	.26	.26	.22	.20	.10
Processing Speed	.35	.22	-.19	-.01	-.15	-.01

IRI, Interpersonal Reactivity Index; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; QLS, Quality of Life Scale; ToM, theory of mind.

* significant at $p < .05$ (two-tailed test).

Voxel-Based Morphometry Regression Results for Schizophrenia Participants

Table S4. Among the schizophrenia group, regions showing a relationship between ToM skills and GMV, controlling for global cognition

Anatomical Region	R/L	BA	Volume in voxels (mm)	x	y	z[a]	T
ToM Performance: Recognition of Faux Pas Test and GMV controlling for global cognition							
Superior temporal sulcus; anterior portion	L	22	18 (144)	-52	-8	-12	5.02
Middle frontal gyrus	R	46	28 (224)	38	52	22	4.58
Superior temporal gyrus; posterior portion	R	22	7 (56)	66	-34	14	4.49
Superior parietal gyrus	R	7	7 (56)	28	-74	54	4.34
Middle frontal gyrus	R	46	8 (64)	20	44	22	4.12
Anterior cingulate cortex (VMPFC)∞	L	32, 10	11 (88)	-8	52	16	3.20
Anterior cingulate cortex (VMPFC)∞	L	32, 10	1 (8)	-8	44	2	3.04
ToM Self-Report: IRI Perspective-Taking and GMV controlling for global cognition							
Hippocampus	R	20	89 (712)	40	-16	-18	5.85
Lateral orbital gyrus	R	47	7 (56)	26	12	-20	4.99
Anterior cingulate cortex (VMPFC)*	L	10	40 (320)	-10	44	-2	4.70
Rolandic operculum (SRC)	L	48	24 (192)	-40	-14	20	4.33
Superior temporal gyrus	L	41, 48	6 (48)	-36	-28	8	4.30
Supplementary motor area	L	6	8 (64)	-16	-12	62	4.29
Middle occipital gyrus	R	19	7 (56)	34	-84	2	4.24
Inferior frontal gyrus - opercularis	L	44	4 (32)	-34	2	20	4.23
Supramarginal gyrus	L	2, 40	13 (104)	-36	-26	26	4.15
Rolandic operculum (SRC)	R	2, 48	5 (40)	42	-16	18	4.09
Middle cingulate cortex	L	32, 24	5 (40)	-8	28	30	3.87
ToM Interview-Rated: QLS Empathy and GMV controlling for global cognition							
Superior frontal gyrus	R	9	16 (128)	18	60	32	6.47
Middle frontal gyrus; anterior portion	R	46	39 (312)	26	52	20	5.83
Anterior orbital gyrus	R	11	21 (168)	34	58	-14	5.63
Middle cingulate cortex	R	32	45 (360)	10	14	40	5.53
Superior frontal gyrus – medial (VMPFC)*	L	10	40 (320)	-14	56	6	5.41

Supplementary motor area	R	6	7 (56)	8	-16	70	5.34
Precentral gyrus	L	6	19 (152)	-36	-18	66	5.26
Inferior frontal gyrus - triangularis	L	45	10 (80)	-46	30	16	5.24
Anterior cingulate/cingulate sulcus (VMPFC)*	R	10	12 (96)	10	58	4	5.10
Superior frontal gyrus; dorsal/anterior portion	L	9	21 (168)	-22	44	32	4.84
Middle cingulate cortex (VMPFC)	R	32	19 (152)	8	34	30	4.79
Supplementary motor area	L	6	6 (48)	-14	10	64	4.77
Middle frontal gyrus	L	46	13 (104)	-36	36	34	4.64
Anterior cingulate/supraorbital gyrus (VMPFC)	R	10	7 (56)	4	48	-8	4.19
Precentral gyrus	L	6	9 (72)	-32	-12	54	4.17
Middle frontal gyrus	R	46	5 (40)	46	46	20	4.12
Inferior frontal gyrus - triangularis	R	45	5 (40)	50	36	14	3.99

BA, Brodmann area; GMV, gray matter volume; IRI, Interpersonal Reactivity Index; L, left; QLS, Quality of Life Scale; R, right; SRC, somatosensory-related cortex; ToM, theory of mind; VMPFC, ventromedial prefrontal cortex.

Statistical threshold $p < .001$ (uncorrected); clusters not within VMPFC region of interest must exceed 5 voxels.

[a] Peak voxel x, y, z coordinates are in Montreal Neurological Institute (MNI) template space.

∞ significant at $p < .005$ (uncorrected).

* significant at $p < .05$, family wise error with small volume correction.

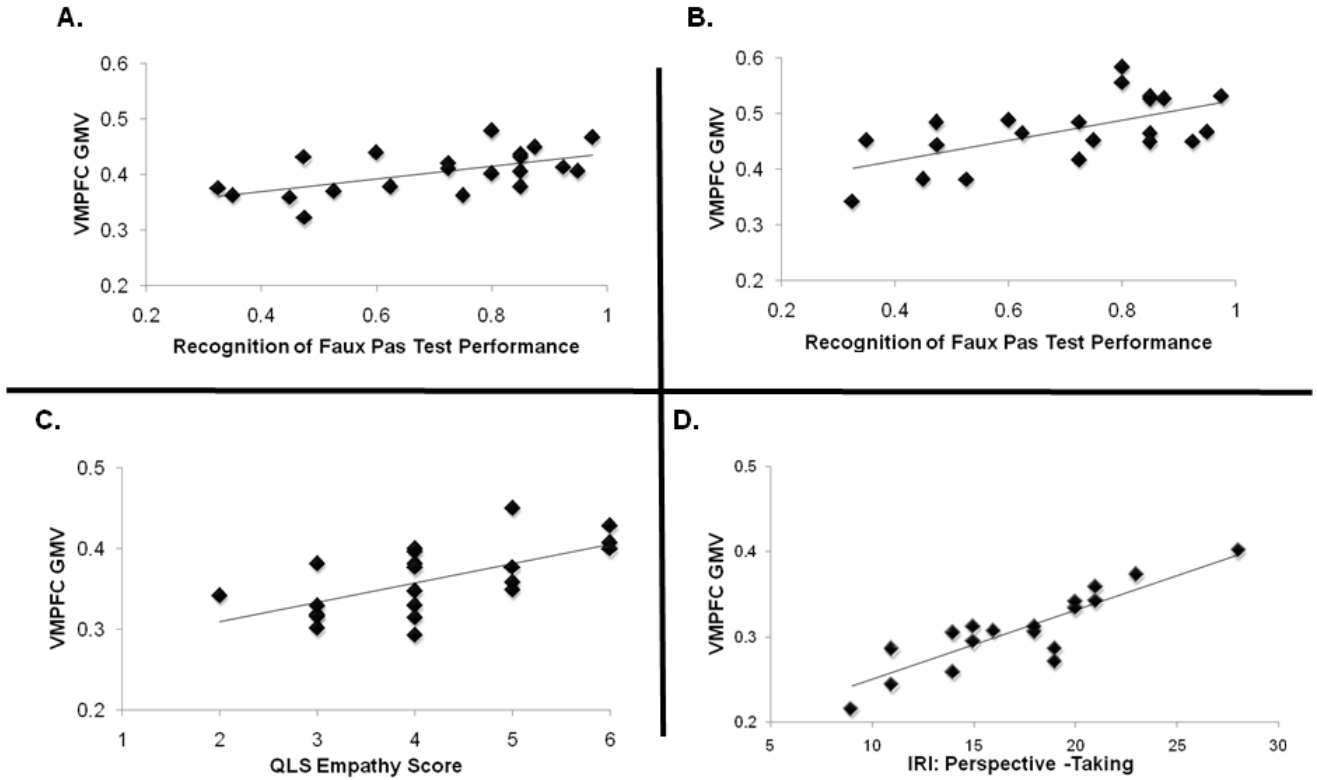

Figure S1. Scatter plots of regression results for each cluster shown on the sagittal slice (x = -8) in Figure 2 (main text). **(A)** Relationship between GMV and ToM Performance: Recognition of Faux Pas Test for cluster at MNI x, y, z coordinates: -8, 52, 16. **(B)** Relationship between GMV and ToM Performance: Recognition of Faux Pas Test for cluster at MNI x, y, z coordinates: -8, 44, 2. **(C)** Relationship between GMV and ToM Interview-Rated: QLS-Empathy for cluster at MNI x, y, z coordinates: -14, 56, 6. **(D)** Relationship between GMV and ToM Self-Report: IRI Perspective-Taking for cluster at MNI x, y, z coordinates: -10, 44, -2. GMV, gray matter volume; IRI, Interpersonal Reactivity Index; MNI, Montreal Neurological Institute; QLS, Quality of Life Scale; ToM, theory of mind; VMPFC, ventromedial prefrontal cortex.

Additional Information on Interpersonal Reactivity Index Subscales

Among the 4 IRI subscales (Perspective-Taking (PT), Empathic Concern, Fantasy Scale, and Personal Distress), both Perspective-Taking and Empathic Concern assess empathy in the context of interpersonal relationships. The Empathic Concern subscale assesses the self-reported tendency to feel sympathy or compassion for others in distress (e.g. "I am often quite touched by things that I see happen" and "I often have tender, concerned feelings for people less fortunate than me"). The Fantasy scale assesses tendency to relate to fictional characters (e.g. "I really get involved with the feelings of the characters in a novel"). Although this scale assesses capacity to imagine the lives of others, it does not directly pertain to a person's real interpersonal relationships. The Personal Distress subscale assesses the tendency to feel anxious and stressed during difficult situations (e.g. "In emergency situations, I feel apprehensive and ill-at-ease"), and does not pertain directly to empathic responding as it enhances relationships (see Davis, 1996 for more information (1-2)).

The current study focused on the IRI Perspective-Taking subscale as the self-reported ToM measure because the PT subscale specifically taps the use of ToM skills, perspective-taking, to understand others (also referred to as *cognitive empathy*). The IRI Empathic Concern subscale measures self-reported feelings of sympathy and compassion. This is a component of *affective empathy* which can occur automatically, does not require advanced ToM skills, and is usually found to be intact in schizophrenia participants whereas IRI PT (cognitive empathy) is more impaired (3-8). However, affective empathy does enhance social relationships, and it is an important component of successful social functioning (5-6, 8). Furthermore, because affective empathy involves generating and monitoring affective response, it is likely that affective empathy also relies on VMPFC function. Therefore, we conducted additional analyses to investigate the relationship between IRI Empathic Concern and GMV in schizophrenia participants.

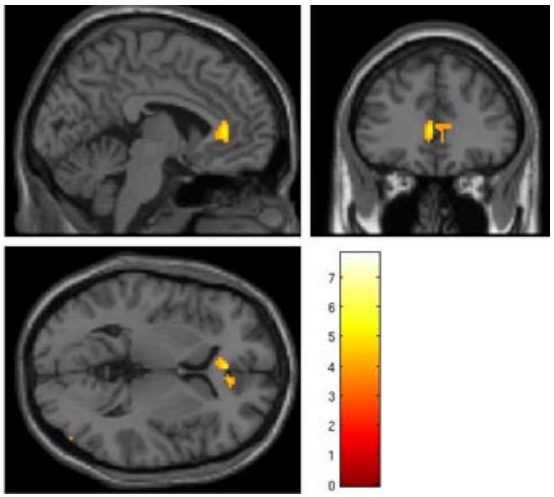

Figure S2. Whole-brain regression analysis of the relationship between IRI Empathic Concern and GMV among the schizophrenia group. Results show that greater IRI Empathic Concern is significantly related to more VMPFC GMV ($p < .001$ uncorrected). VMPFC cluster is centered in the anterior cingulate cortex (MNI coordinates: -4, 36, 4; results remain significant ($p < .05$, FWE) after small volume correction for multiple comparisons). FWE, family wise error; GMV, gray matter volume; IRI, Interpersonal Reactivity Index; MNI, Montreal Neurological Institute; VMPFC, ventromedial prefrontal cortex.

Table S5. Among schizophrenia participants, regions showing a relationship between IRI subscales Empathic Concern, Fantasy, and Personal Distress and GMV

Anatomical Region	R/L	BA	Volume in voxels (mm)	x	y	z[a]	T
TOM Self Report: IRI Empathic Concern and GMV							
Middle occipital gyrus	R	19	42 (336)	50	-74	10	7.79
Cingulate gyrus	L	24	31 (248)	-8	4	38	5.99
Precentral gyrus	R	6	60 (480)	36	-12	38	5.77
Precentral gyrus	L	6	47 (376)	-30	-12	48	5.59
Middle occipital gyrus	L	18	30 (240)	-24	-94	16	5.47
Insula	L	48	117 (936)	-40	-36	20	5.46
Cingulate gyrus	R	24	41 (328)	10	-2	38	5.21
Anterior cingulate cortex (VMPFC)*	L	25	151 (1208)	-4	36	4	5.18
Supramarginal gyrus	R	40	35 (280)	42	-28	30	4.97
Postcentral gyrus	L	3	12 (96)	-38	-12	38	4.90
Middle frontal gyrus	L	8	9 (72)	-26	18	48	4.36
Fusiform	R	20	6 (48)	38	-18	-24	4.24
Precentral gyrus	L	6	6 (48)	-14	-10	68	4.22
Superior frontal gyrus	R	8	11 (88)	20	4	48	4.18
Superior frontal gyrus (supplementary motor area)	R	6	6 (48)	10	-2	58	4.17
Posterior cingulate gyrus	R	26	7 (56)	18	-40	26	4.00
Inferior frontal gyrus	R	6	5 (40)	38	6	36	3.84
TOM Self Report: IRI Fantasy and GMV							
Postcentral gyrus	L	3	14 (112)	-24	-38	72	4.53
Middle temporal gyrus	R	21	7 (56)	48	-6	-16	4.49
Inferior frontal gyrus	R	6	9 (72)	58	6	10	4.39
TOM Self Report: IRI Personal Distress and GMV							
Inferior temporal gyrus	L	20	39 (312)	-56	-42	-14	5.33

BA, Brodmann area; GMV, gray matter volume; IRI, Interpersonal Reactivity Index; L, left; R, right; ToM, theory of mind; VMPFC, ventromedial prefrontal cortex.

Statistical threshold $p < .001$ (uncorrected); clusters not within VMPFC region of interest must exceed 5 voxels.

[a] Peak voxel x, y, z coordinates are in Montreal Neurological Institute (MNI) template space.

* significant at $p < .05$, family wise error with small volume correction.

Table S6. Among schizophrenia participants, regions showing a relationship between IRI subscales Empathic Concern, Personal Distress, Fantasy and GMV, controlling for global cognition

Anatomical Region	R/L	BA	Volume in voxels (mm)	x	y	z[a]	T
TOM Self Report: IRI Empathic Concern and GMV controlling for global cognition							
Middle temporal gyrus	R	19	85 (680)	50	-74	10	6.98
Inferior frontal gyrus	L	46	83 (664)	-48	48	-12	6.46
Superior frontal gyrus	R	6	213 (1704)	36	-12	36	6.46
Precentral gyrus	R	6	296 (2368)	6	4	50	6.09
Middle frontal gyrus	L	6	168 (1344)	-30	-12	46	6.02
Anterior transverse temporal gyrus	R		96 (768)	40	-28	28	5.95
Insula	L	48	88 (704)	-42	-36	22	5.49
Anterior cingulate cortex (VMPFC)*	L	24	133 (1064)	-2	36	6	5.36
Postcentral gyrus	L	3	8 (64)	-56	-18	48	5.13
Middle occipital gyrus	L	7	15 (120)	-24	-62	36	5.02
Middle occipital gyrus	L	18	59 (472)	-24	-94	18	4.97
Postcentral gyrus	L	3	26 (208)	-38	-14	36	4.82
Anterior thalamic nucleus	L		18 (144)	-2	-2	0	4.64
Middle frontal gyrus	L	8	10 (80)	-26	16	48	4.63
Superior parietal gyrus	L	7	8 (64)	-14	-74	58	4.6
Middle occipital gyrus	L	18	12 (96)	-20	-76	4	4.53
Inferior frontal sulcus	L	44	15 (120)	-48	28	28	4.5
Middle frontal sulcus	L	46	5 (40)	-36	46	8	4.19
Fusiform gyrus	R	20	5 (40)	38	-18	-26	4.19
Inferior frontal sulcus	R	6	7 (56)	38	6	36	4.11
Inferior frontal gyrus	R	45	12 (96)	42	36	14	4.06
Temporoparietal junction	R	21	6 (48)	54	-54	22	4.03
Anterior cingulate cortex (VMPFC)	R	32	1 (8)	10	38	10	3.77
TOM Self Report: IRI Fantasy and GMV controlling for global cognition							
Postcentral gyrus	L	3	8 (64)	-24	-38	72	4.84
Inferior frontal gyrus	R	6	7 (56)	58	8	10	4.62
Middle temporal gyrus	R	21	7 (56)	48	-6	-16	4.34

TOM Self Report: IRI Personal Distress and GMV controlling for global cognition							
Inferior temporal gyrus	L	20	25 (200)	-56	-42	-14	4.57

BA, Brodmann area; GMV, gray matter volume; IRI, Interpersonal Reactivity Index; L, left; R, right; ToM, theory of mind; VMPFC, ventromedial prefrontal cortex.

Statistical threshold $p < .001$ (uncorrected); clusters not within VMPFC region of interest must exceed 5 voxels.

[a] Peak voxel x, y, z coordinates are in Montreal Neurological Institute (MNI) template space.

* significant at $p < .05$, family wise error with small volume correction.

Table S7. Regions across the whole brain showing a relationship between theory of mind (ToM) and gray matter volume (GMV) among schizophrenia patients while controlling for age. Clusters designated as VMPFC are within the anatomically defined VMPFC region of interest (ROI). Regions are listed in the order they appear in the main analysis (Table 2, main text). All regions that were significant in the main analysis are listed. Symbols designate results after correcting for multiple comparisons within the VMPFC or STC using family wise error (FWE $p < .05$).

Anatomical Region	R/L	BA	Volume in voxels (mm)	x	y	z[a]	T
ToM Performance: Recognition of Faux Pas and GMV controlling for age							
Superior frontal gyrus (a portion is within VMPFC)	R	32, 9	35 (280)	20	46	22	5.15
Superior temporal gyrus	R	22	16 (128)	66	-34	14	5.04
Superior temporal sulcus	L	22	17 (136)	-52	-8	-12	4.80
Middle cingulate/Supplementary motor cortex	R	4, 23	11 (88)	12	-26	50	4.26
Superior frontal gyrus; anterior, dorsal portion	R	9	13 (104)	16	44	48	4.31
Superior parietal gyrus	R	7	5 (40)	30	-74	52	4.66
Anterior cingulate cortex (VMPFC)	L	32, 10	1 (8)	-8	44	2	3.97
Middle occipital gyrus	L	19	9 (72)	-28	-82	24	4.40
Anterior cingulate/cingulate sulcus (VMPFC)	L	32, 10	9 (72)	-8	52	14	4.43
Superior frontal gyrus/superior orbital gyrus	L	11	6 (48)	-14	54	-6	4.35
Anterior cingulate cortex (VMPFC)	R	32, 10	1 (8)	12	48	-2	3.75
ToM Self-report: IRI Perspective-Taking and GMV controlling for age							
Hippocampus	R	20	64 (512)	40	-16	-18	7.09
Anterior cingulate cortex (VMPFC)*	L	10	95 (760)	-10	44	-2	5.81
Supplementary motor area	L	6	37 (296)	-18	-10	62	5.57
Superior temporal gyrus/Heschl's gyrus	L	48	15 (120)	-36	-14	8	4.72
Rolandic operculum/Insula (SRC)	L	48	26 (208)	-40	-14	20	4.71
Middle occipital gyrus; posterior portion	R	18	28 (224)	26	-98	2	5.21
Precuneus	L	31	30 (240)	-24	-50	40	6.35
Rolandic operculum/Insula (SRC)	R	48	26 (208)	40	-14	20	4.71
Middle frontal gyrus; anterior	L	46	5 (40)	-32	42	20	4.28
Middle occipital gyrus; posterior portion	R	18	2 (16)	34	-84	4	4.12
Posterior cingulate cortex	R	17	9 (72)	22	-62	10	4.05

Additional regions that were not in the original analysis							
Superior frontal gyrus	R	32	12 (96)	16	24	40	5.33
Supplementary motor area	R	6	12 (96)	8	-14	64	4.83
Middle/Anterior cingulate cortex	L	32	7 (56)	-8	26	30	4.41
Rolandic operculum (SRC)	R	48, 44	14 (112)	50	-2	6	4.36
Angular gyrus	L	7	10 (80)	-34	-66	46	4.35
Insula/Rolandic operculum (SRC)	R	48	6 (48)	40	-14	18	4.09
ToM Interview-rated: QLS Empathy and GMV controlling for age							
Superior frontal gyrus	R	9	19 (152)	18	60	36	6.50
Middle frontal gyrus; anterior portion	R	46	35 (280)	26	52	20	5.71
Anterior orbital gyrus	R	11	9 (72)	32	58	-14	4.87
Middle cingulate gyrus	R	32	58 (464)	10	14	42	8.05
Precentral gyrus	L	6	13 (104)	-32	-12	54	4.59
Anterior cingulate gyrus (VMPFC)*	R	32	56 (448)	8	34	30	6.89
Supplementary motor area	L	6	11 (88)	-14	10	64	5.18
Inferior frontal gyrus - triangularis	L	45	11 (88)	-46	32	14	4.90
Posterior insula/Rolandic operculum	R	48	47 (376)	34	-28	26	4.77
Anterior cingulate/cingulate sulcus (VMPFC)* ¥	L	10	42 (336)	-8	52	6	5.15
Anterior insula (SRC)	R	48	50 (400)	24	28	0	5.40
Posterior insula/Rolandic operculum	L	48	25 (200)	-32	-30	24	4.32
Superior frontal gyrus; dorsal/anterior portion	L	9	6 (48)	-22	44	32	4.29
Orbital frontal gyrus; anterior portion	L	11	5 (40)	-8	66	-14	4.24
Anterior cingulate/Supraorbital sulcus (VMPFC)	R	10, 11	6 (48)	4	48	-8	4.13
Precentral gyrus	L	6	13 (104)	-32	-12	54	4.59
Middle frontal gyrus	L	46	4 (32)	-36	36	34	3.92
Anterior cingulate cortex (VMPFC)	R	32	6 (48)	8	44	8	4.15
Middle frontal gyrus	L	46	2 (16)	-32	46	20	3.72
Superior frontal gyrus/cingulate sulcus (VMPFC)	R	10	6 (48)	10	58	2	4.49
Additional regions that were not in the original analysis							
Precentral gyrus	L	4	9 (72)	-36	-18	66	4.92
Precuneus	R	23	10 (80)	16	-48	42	4.44
Inferior frontal gyrus - triangularis	R	45	14 (112)	56	28	2	4.30

Supplementary motor area	R	6	16 (128)	8	-16	70	4.16
Precuneus	R	23	5 (40)	12	-62	30	3.94

BA, Brodmann area; IRI, Interpersonal Reactivity Index; L, left; QLS, Quality of Life Scale; R, right; SRC, somatosensory-related cortices; STC, superior temporal cortex; VMPFC, ventromedial prefrontal cortex.

Statistical threshold $p < .001$ (uncorrected); clusters not within VMPFC region of interest must exceed 5 voxels.

[a] Peak voxel x, y, z coordinates are in Montreal Neurological Institute (MNI) template space.

* significant at $p < .05$, FWE with small volume correction.

¥ This region includes another peak in the superior frontal gyrus (VMPFC) at x, y, z coordinates: -14, 56, 6; $t = 5.14$. These two peaks were separate clusters in the original analysis.

Table S8. Regions across the whole brain showing a relationship between theory of mind (ToM) and gray matter volume (GMV) among schizophrenia patients when controlling for duration of illness. Clusters designated as VMPFC are within the anatomically defined VMPFC region of interest (ROI). Regions are listed in the order they appear in the main analysis (Table 2, main text). All regions that were significant in the main analysis are listed; those clusters that are no longer significant when controlling for duration of illness are shown in italics. Symbols designate results after correcting for multiple comparisons within the VMPFC or STC using family wise error (FWE $p < .05$).

Anatomical Region	R/L	BA	Volume in voxels (mm)	x	y	z[a]	T
ToM Performance: Recognition of Faux Pas and GMV controlling for duration of illness							
Superior frontal gyrus (a portion is within VMPFC)	R	32, 9	36 (288)	20	46	22	5.18
Superior temporal gyrus	R	22	14 (112)	66	-34	14	5.06
Superior temporal sulcus	L	22	21 (168)	-52	-8	-12	5.47
Middle cingulate/Supplementary motor cortex	R	4, 23	14 (112)	12	-26	50	4.33
Superior frontal gyrus; anterior, dorsal portion	R	9	12 (96)	16	44	48	4.20
Superior parietal gyrus	R	7	5 (40)	28	-72	52	4.22
Anterior cingulate cortex (VMPFC)	L	32, 10	3 (24)	-8	44	2	4.06
Middle occipital gyrus	L	19	8 (64)	-30	-84	26	3.96
Anterior cingulate/cingulate sulcus (VMPFC)	L	32, 10	3 (24)	-8	56	16	3.86
Superior frontal gyrus/superior orbital gyrus	L	11	4 (32)	-14	56	-6	3.96
Anterior cingulate cortex (VMPFC)	R	32, 10	10 (80)	12	50	0	4.37

ToM Self-report: IRI Perspective-Taking and GMV controlling for duration of illness							
Hippocampus	R	20	65 (520)	40	-18	-18	6.15
Anterior cingulate cortex (VMPFC)*	L	10	75 (600)	-10	44	-2	5.16
Supplementary motor area	L	6	20 (160)	-16	-10	64	4.95
Superior temporal gyrus/Heschl's gyrus	L	48	11 (88)	-36	-28	8	5.04
Rolandic operculum/Insula (SRC)	L	48	65 (520)	-40	-14	20	5.02
Middle occipital gyrus; posterior portion	R	18	19 (152)	28	-98	4	4.76
Precuneus	L	31	6 (48)	-20	-48	40	4.07
Rolandic operculum/Insula (SRC)	R	48	19 (152)	40	-14	18	4.75
Middle frontal gyrus; anterior	L	46	1 (8)	-32	42	20	3.81
Middle occipital gyrus; posterior portion	R	18	7 (56)	34	-84	4	4.20
Posterior cingulate cortex	*R*	*17*		*22*	*-60*	*10*	*ns*
Additional regions that were not in the original analysis							
Precuneus	L	31	15 (120)	-12	-50	44	4.92
ToM Interview-rated: QLS Empathy and GMV controlling for duration of illness							
Superior frontal gyrus - anterior	R	9	15 (120)	18	60	36	6.13
Middle frontal gyrus; anterior portion	R	46	26 (208)	26	52	22	5.65
Anterior orbital gyrus	R	11	6 (48)	32	58	-14	4.75
Middle cingulate gyrus	R	32	34 (272)	12	14	42	5.33
Precentral gyrus	L	6	9 (72)	-36	-18	66	4.89
Middle cingulate gyrus (VMPFC)	R	32	21 (168)	8	34	30	4.75
Superior frontal gyrus- medial portion (VMPFC)	L	10	10 (80)	-14	56	6	4.56
Supplementary motor area	L	6	5 (40)	-14	10	64	4.62
Inferior frontal gyrus - triangularis	L	45	5 (40)	-46	30	16	4.57
Posterior insula/Rolandic operculum	R	48	24 (192)	34	-28	26	4.59
Anterior cingulate/cingulate sulcus (VMPFC)	L	10	8 (64)	-8	52	4	4.32
Anterior insula (SRC)	R	48	47 (376)	26	28	0	4.75
Posterior insula/Rolandic operculum	L	48	15 (120)	-32	-30	24	4.37
Superior frontal gyrus; dorsal/anterior portion	L	9	12 (96)	-22	44	32	4.47
Orbital frontal gyrus; anterior portion	L	11	3 (24)	-8	66	-14	3.99
Anterior cingulate/Supraorbital sulcus	R	10, 11	6 (48)	4	46	-10	4.03

Precentral gyrus	L	6	2 (16)	-32	-12	54	3.97
Middle frontal gyrus	L	46	3 (24)	-36	36	34	3.76
Anterior cingulate cortex (VMPFC)	R	32	1 (8)	8	44	8	3.53
Middle frontal gyrus	L	46	12 (96)	-32	44	24	4.47
Superior frontal gyrus/cingulate sulcus (VMPFC)	*R*	*10*	-	*10*	*58*	*4*	*3.45, p = .002*
Additional regions that were not in the original analysis							
Inferior frontal gyrus	R	47,45	7 (56)	36	36	2	3.94

BA, Brodmann area; IRI, Interpersonal Reactivity Index; L, left; ns, not significant; QLS, Quality of Life Scale; R, right; SRC, somatosensory related cortices; STC, superior temporal cortex; VMPFC, ventromedial prefrontal cortex.

Statistical threshold $p < .001$ (uncorrected); clusters not within VMPFC region of interest must exceed 5 voxels.

[a] Peak voxel x, y, z coordinates are in Montreal Neurological Institute (MNI) template space.

* significant at $p < .05$, FWE with small volume correction.

Table S9. Regions across the whole brain showing a relationship between theory of mind (ToM) and gray matter volume (GMV) among schizophrenia patients when controlling for antipsychotic medication (quantified as chlorpromazine equivalents). Clusters designated as VMPFC are within the anatomically defined VMPFC region of interest (ROI). Regions are listed in the order they appear in the main analysis (Table 2, main text). All regions that were significant in the main analysis are listed; those clusters that are no longer significant when controlling for medication are shown in italics. Symbols designate results after correcting for multiple comparisons within the VMPFC or STC using family wise error (FWE $p < .05$).

Anatomical Region	R/L	BA	Volume in voxels (mm)	x	y	z[a]	T
ToM Performance: Recognition of Faux Pas and GMV controlling for medication dose (chlorpromazine equivalents)							
Superior frontal gyrus (a portion is within VMPFC)	R	32, 9	31 (248)	18	44	22	5.28
Superior temporal gyrus	R	22	11 (88)	66	-34	14	5.0
Superior temporal sulcus	L	22	11 (88)	-52	-8	-12	4.63
Middle cingulate/Supplementary motor cortex	R	4, 23	8 (64)	12	-26	50	4.14
Superior frontal gyrus; anterior, dorsal portion	R	9	7 (56)	16	44	48	4.08
Superior parietal gyrus	R	7	7 (56)	30	-74	52	4.51
Anterior cingulate cortex (VMPFC)	L	32, 10	1 (8)	-8	44	2	4.01
Middle occipital gyrus	L	19	12 (96)	-28	-80	22	4.26
Anterior cingulate/cingulate sulcus (VMPFC)	L	32, 10	7 (56)	-8	52	16	4.18

Superior frontal gyrus/superior orbital gyrus	L	11	3 (24)	-14	56	-6	3.94
Anterior cingulate cortex (VMPFC)	*R*	*32, 10*	-	*12*	*50*	*0*	*3.69, p = .002*
Additional regions that were not in the original analysis							
Precuneus	R	7, 31	35 (280)	14	-68	48	4.62
Postcentral gyrus	L	3,4	7 (56)	-24	-34	68	4.56
Inferior temporal gyrus	L	20	6 (48)	-60	-44	-14	4.21
ToM Self-report: IRI Perspective-Taking and GMV controlling for medication dose (chlorpromazine equivalents)							
Hippocampus	R	20	65 (520)	40	-16	-18	5.87
Anterior cingulate cortex (VMPFC)*	L	10	84 (672)	-10	44	-2	5.31
Supplementary motor area	L	6	27 (216)	-16	-12	62	4.86
Superior temporal gyrus/Heschl's gyrus	L	48	7 (56)	-36	-28	8	4.88
Rolandic operculum/Insula (SRC)	L	48	46 (368)	-40	-14	20	4.79
Middle occipital gyrus; posterior portion	R	18	20 (160)	26	-98	2	4.60
Precuneus	L	31	12 (96)	-22	-48	40	4.45
Rolandic operculum/Insula (SRC)	R	48	9 (72)	40	-14	18	4.19
Middle frontal gyrus; anterior	L	46	1 (8)	-32	42	20	4.08
Middle occipital gyrus; posterior portion	R	18	7 (56)	34	-84	4	4.32
Posterior cingulate cortex	R	17	10 (80)	24	-54	8	3.97
Additional regions that were not in the original analysis							
Inferior temporal gyrus	L	20	12 (96)	-40	-14	-26	4.46
Superior temporal gyrus	L	22	16 (128)	-36	-14	-6	4.37
Middle cingulate cortex	L	23	12 (96)	-14	-32	44	4.35
Inferior parietal lobule – angular gyrus	R	39,40	6 (48)	46	-54	48	4.27
Rolandic operculum	L	43, 48	5 (40)	-34	2	20	4.22
ToM Interview-rated: QLS Empathy and GMV controlling for medication dose (chlorpromazine equivalents)							
Superior frontal gyrus	R	9	17 (136)	18	60	36	6.31
Middle frontal gyrus; anterior portion	R	46	37 (296)	26	52	22	6.31
Anterior orbital gyrus	R	11	12 (96)	32	58	-14	4.89
Middle cingulate gyrus	R	32	40 (320)	12	14	42	5.48
Precentral gyrus	L	6	8 (64)	-36	-18	66	4.94
Middle cingulate gyrus (VMPFC)	R	32	22 (176)	8	36	30	5.01

Superior frontal gyrus- medial portion (VMPFC)	L	10	24 (192)	-14	56	6	4.80
Supplementary motor area	L	6	5 (40)	-14	10	64	4.81
Inferior frontal gyrus - triangularis	L	45	6 (48)	-46	30	16	4.74
Posterior insula/Rolandic operculum	R	48	29 (232)	34	-28	26	4.60
Anterior cingulate/cingulate sulcus (VMPFC)	L	10	23 (184)	-8	52	4	4.58
Anterior insula (SRC)	R	48	38 (304)	26	28	0	4.42
Posterior insula/Rolandic operculum	L	48	25 (200)	-32	-30	24	4.31
Superior frontal gyrus; dorsal/anterior portion	L	9	6 (48)	-22	44	32	4.33
Orbital frontal gyrus; anterior portion	L	11	4 (32)	-8	66	-14	4.20
Anterior cingulate/Supraorbital sulcus	R	10, 11	7 (56)	4	48	-8	4.21
Precentral gyrus	L	6	8 (64)	-32	-12	54	4.12
Middle frontal gyrus	L	46	10 (80)	-36	38	32	4.05
Anterior cingulate cortex (VMPFC)	R	32	6 (48)	8	46	6	4.29
Middle frontal gyrus	L	46	4 (32)	-32	44	24	4.03
Superior frontal gyrus/cingulate sulcus (VMPFC)	*R*	*10*	-	*10*	*58*	*2*	*3.61, p = .002*

BA, Brodmann area; IRI, Interpersonal Reactivity Index; L, left; QLS, Quality of Life Scale; R, right; SRC, somatosensory related cortices; STC, superior temporal cortex; VMPFC, ventromedial prefrontal cortex.

Statistical threshold $p < .001$ (uncorrected); clusters not within VMPFC region of interest must exceed 5 voxels.

[a] Peak voxel x, y, z coordinates are in Montreal Neurological Institute (MNI) template space.

* significant at $p < .05$, FWE with small volume correction.

Voxel-Based Morphometry Regression Results for Healthy Control Participants

Table S10. Among healthy participants, regions showing a relationship between ToM skills, IRI subscales and GMV. Italics indicate clusters in regions of interest that are below statistical threshold.

Anatomical Region	R/L	BA	Volume in voxels (mm)	x	y	z[a]	T
ToM Performance: Recognition of Faux Pas Test and GMV							
Inferior frontal gyrus	L	44	11 (88)	-34	18	18	5.49
Middle frontal sulcus	R	9	12 (96)	20	34	34	4.94
Superior frontal gyrus – medial (VMPFC)	R	32	2 (16)	16	40	28	4.90
ToM Self-Report: IRI Perspective-Taking and GMV							
Superior temporal gyrus (STC)*	L	22, 42	38 (304)	-54	-34	14	7.63
Inferior frontal gyrus	L	47	9 (72)	-48	22	0	5.13
Cingulate sulcus/supraorbital gyrus (VMPFC)∞	*R*	*10*	-	*-10*	*58*	*-2*	*3.50, p = .002*
ToM Self-Report: IRI Empathic Concern and GMV							
Inferior frontal gyrus	R	47	28 (224)	36	46	2	10.23
Medial orbital gyrus	L	11	12 (96)	-18	48	-14	6.08
Middle temporal gyrus	R	21	37 (296)	50	-36	-2	5.94
Hippocampus	L	37	10 (80)	-24	-34	0	5.67
Middle frontal gyrus	R	45, 46	25 (200)	36	40	14	5.6
Inferior occipital gyrus	L	37	7 (56)	-36	-60	-8	5.5
Caudate	R	n/a	40 (320)	10	14	-8	5.47
Caudate	L	n/a	26 (208)	-16	16	6	5.31
Middle frontal gyrus	R	46	11 (88)	36	32	28	5.21
Lingual gyrus	L	19	8 (64)	-22	-52	-2	4.95
Superior frontal gyrus (VMPFC)	R	11	5 (40)	14	54	-12	4.92
Inferior frontal gyrus	L	45	20 (160)	-40	34	20	4.91
Inferior frontal gyrus	L	47	23 (184)	-36	44	2	4.82
ToM Self-Report: IRI Fantasy Scale and GMV							
Postcentral gyrus	R	3	36 (288)	44	-20	52	7.27
Caudate	L	n/a	81 (648)	-20	10	18	7.2

Middle occipital gyrus	R	19	24 (192)	32	-74	20	6.62
Middle occipital gyrus	L	19	14 (112)	-32	-68	16	5.98
Inferior temporal gyrus	L	20	26 (208)	-42	-12	-30	5.95
Putamen	L	n/a	30 (240)	-26	-4	16	5.94
Putamen	R	n/a	45 (360)	14	14	0	5.90
Supramarginal gyrus (SRC)	L	48	11 (88)	-36	-34	28	5.15
Superior frontal gyrus	R	32, 9	5 (40)	18	38	40	5.00
Claustrum	R	48	15 (120)	32	-6	14	4.90
Inferior frontal gyrus/Rolandic operculum	R	6,44	6 (48)	52	4	12	4.85
Putamen	L	n/a	11 (88)	-26	-4	2	4.59
Subcallosal gyrus	L	25	6 (48)	-10	10	-16	4.57
Putamen	L	n/a	8 (64)	-28	6	2	4.43
ToM Self-Report: IRI Personal Distress and GMV							
Precuneus	R	30	33 (264)	20	-46	10	5.81
Middle frontal gyrus	R	46	19 (152)	44	42	32	5.43
Precentral gyrus	L	6	25 (200)	-38	0	64	5.41
Middle temporal gyrus	R	21	23 (184)	72	-30	-14	5.39
Superior frontal gyrus/Frontal pole	R	10	55 (440)	16	70	14	5.27
Superior temporal gyrus	R	22	17 (136)	70	-44	14	5.10
Temporal pole	L	38	13 (104)	-32	14	-24	4.88
Medial orbital gyrus	L	11	7 (56)	-2	58	-10	4.78
Middle occipital gyrus	R	39, 19	19 (152)	42	-86	26	4.49

BA, Brodmann area; GMV, gray matter volume; IRI, Interpersonal Reactivity Index; L, left; R, right; SRC, somatosensory related cortices; ToM, theory of mind; VMPFC, ventromedial prefrontal cortex.

Statistical threshold $p < .001$ (uncorrected); clusters not within VMPFC region of interest must exceed 5 voxels.

[a] Peak voxel x, y, z coordinates are in Montreal Neurological Institute (MNI) template space.

* significant at $p < .05$, family wise error with small volume correction.

∞ significant at $p < .005$ (uncorrected).

Between-Group Differences in the Relationship between ToM Skills and GMV

Table S11. Regions across the whole brain showing a significant interaction effect of Group (Schizophrenia/Healthy Control) and theory of mind (ToM) measure. For each ToM measure, interaction results for ventromedial prefrontal cortex (VMPFC) and superior temporal cortex (STC) regions of interest are listed first. All VMPFC and STC clusters that showed a significant relationship between ToM and GMV in the schizophrenia group (Table 2, Figure 2) are listed; those VMPFC and STC clusters that were significant within the schizophrenia group (Table 2, Figure 2) but not significant in the interaction are shown in italics. Small volume corrections (SVC) for multiple comparisons were applied to all clusters in the VMPFC and STC; clusters that are significant after SVC are designated with an asterisk (*).

Anatomical Region	R/L	BA	Volume in voxels (mm)	x	y	z [a]	T
ToM Performance: Recognition of Faux Pas and GMV							
Regions where correlation between Recognition of Faux Pas and GMV was stronger for Schizophrenia than Healthy Controls							
VMPFC and STC Clusters							
Anterior cingulate cortex (VMPFC)	L	32, 10	10 (80)	-6	36	12	3.70
Anterior cingulate cortex (VMPFC)	R	32, 10	24 (192)	8	40	-6	3.77
Paracingulate gyrus/supraorbital sulcus (VMPFC)	L	11	4 (32)	-10	56	-2	3.56
Anterior cingulate/cingulate sulcus (VMPFC)	*L*	*32, 10*	-	*-6*	*48*	*20*	*2.88, p = .004*
Superior temporal sulcus	L	22	47 (376)	-52	-6	-14	4.88
Superior temporal gyrus	*R*	*22*	-	*66*	*-26*	*12*	*2.83, p = .004*
All other regions							
Anterior insula	R	48	131 (1048)	32	18	-12	5.26
Lateral orbital gyrus	R	47	27 (216)	44	26	-10	4.84
Superior temporal gyrus	R	48,22	153 (1224)	58	-2	6	4.75
Temporal pole	R	38	41 (328)	46	14	-30	4.64
Inferior temporal gyrus	L	20	14 (112)	-40	-20	-28	4.35
Middle occipital	R	39	39 (312)	36	-68	14	4.34
Medial orbital gyrus	L	11	18 (144)	-24	44	-18	4.14
Superior temporal sulcus	R	48,22	40 (320)	58	-4	-12	4.12
Insula	L	48	113 (904)	-36	10	-2	4.11
Precentral gyrus	L	6	12 (96)	-24	6	32	4.02
Inferior frontal gyrus - opercularis	L	44,48	31 (248)	-46	14	4	4.00

Medial orbital gyrus	R	11	30 (240)	24	34	-20	3.95
Superior frontal gyrus/Supplementary motor area	L	6	8 (64)	-16	-8	56	3.92
Posterior insula	R	48	18 (144)	34	-14	0	3.86
Middle temporal gyrus	L	21	6 (48)	-66	-22	-10	3.66
Regions where correlation between Recognition of Faux Pas and GMV was stronger for Healthy Controls than Schizophrenia							
Middle frontal sulcus	L	6	13 (104)	-24	-6	48	4.12
ToM Self-report: IRI Perspective-Taking and GMV							
Regions where correlation between IRI Perspective Taking and GMV was stronger for Schizophrenia than Healthy Controls							
VMPFC and STC Clusters							
Anterior cingulate cortex (VMPFC)*	L	32, 10	38 (304)	-12	44	-2	5.21
All other regions							
Inferior occipital/Fusiform gyrus	L	16	37 (296)	-46	-74	-14	4.53
Inferior temporal gyrus/Temporal pole	R	20	29 (232)	48	10	-38	4.45
Precentral gyrus	R	6	12 (96)	32	-12	70	4.42
Cerebellum	L	n/a	26 (208)	-6	-86	-26	4.39
Inferior frontal gyrus – triangularis	R	45	41 (328)	34	18	22	4.35
Superior parietal gyrus	R	5	11 (88)	16	-50	62	4.02
Postcentral gyrus (SRC)	R	3	6 (48)	44	-28	64	3.90
Middle occipital gyrus	L	19	5 (40)	-38	-80	36	3.86
Middle occipital gyrus	R	18	8 (64)	40	-90	8	3.78
Regions where correlation between IRI Perspective Taking and GMV was stronger for Healthy Controls than Schizophrenia							
Supplementary motor area	L	6	23 (184)	-14	-12	52	4.58
Posterior hippocampus	L	37	16 (128)	-28	-34	-4	4.01
Postcentral gyrus (SRC)	L	3	12 (96)	-52	-12	32	4.07
Inferior frontal gyrus	R	45	9 (72)	46	24	4	3.83

GMV, gray matter volume; IRI, Interpersonal Reactivity Index; L, left; R, right; SRC, somatosensory related cortices.
Statistical threshold $p < .001$ (uncorrected); clusters not within VMPFC region of interest must exceed 5 voxels.
[a] Peak voxel x, y, z coordinates are in Montreal Neurological Institute (MNI) template space.
* significant at $p < .05$, family wise error with small volume correction in the ventromedial prefrontal cortex.

Supplemental References

1. Davis MH (1983): Measuring individual differences in empathy: Evidence for a multidimensional approach. *J Pers Soc Psychol*. 44:113-126.
2. Davis MH (1996): *Empathy: a social psychological approach*. Boulder, CO: Westview Press.
3. Montag C, Heinz A, Kunz D, Gallinat J (2007): Self-reported empathic abilities in schizophrenia. *Schizophr Res*. 92:85-89.
4. Shamay-Tsoory SG, Shur S, Harari H, Levkovitz Y (2007): Neurocognitive basis of impaired empathy in schizophrenia. *Neuropsychology*. 21:431-438.
5. Decety J (2010): The neurodevelopment of empathy in humans. *Dev Neurosci*. 32:257-267.
6. Decety J, Jackson PL (2004): The functional architecture of human empathy. *Behav Cogn Neurosci Rev*. 3:71-100.
7. Shamay-Tsoory SG (2011): The neural bases for empathy. *Neuroscientist*. 17:18-24.
8. Singer T (2006): The neuronal basis and ontogeny of empathy and mind reading: review of literature and implications for future research. *Neurosci Biobehav Rev*. 30:855-863.
9. Hooker CI, Verosky SC, Germine LT, Knight RT, D'Esposito M (2008): Mentalizing about emotion and its relationship to empathy. *Soc Cogn Affect Neurosci*. 3:204-217.