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Theory of Mind impairments in early course schizophrenia: An fMRI study

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ABSTRACT

Theory of Mind (ToM) refers to the ability to perceive others' mental states. Lower ToM has often been associated with poorer functional outcomes in schizophrenia, making it an important treatment target. However, little is known about the underlying neural mechanisms associated with ToM impairments in early course schizophrenia. This study aimed to validate the False Belief task to measure ToM in schizophrenia and to identify aberrant brain activity associated with impairments. 36 individuals with early course schizophrenia and 17 controls were administered the Hinting Task and performed a functional magnetic resonance imaging (fMRI) False Belief task. Between-group differences were examined in a priori regions of interest (ROIs) known to be associated with ToM tasks: medial prefrontal cortex, ventral medial prefrontal cortex, and both the left and right temporal parietal junction (TPJ). We observed a significant positive association between Hinting Task performance and False Belief accuracy, validating the False Belief task as a measure of ToM. Compared to controls, individuals with schizophrenia exhibited reduced brain activation in all four ROIs during the fMRI False Belief task. Furthermore, task-related activations in bilateral TPJs were shown to be positively associated with ToM abilities regardless of diagnosis. Individuals with schizophrenia with lower performance on the False Belief task showed significant reductions in task-related activation in the bilateral TPJ compared to controls, while reductions were not significant for those with higher performance. Our findings suggest that lower neural activity in the bilateral TPJ are associated with ToM impairments observed in individuals with early course schizophrenia.

1. Introduction

Social cognitive impairments are considered to be a core feature of schizophrenia (Green et al., 2015). Theory of Mind (ToM), a social cognitive domain particularly impaired in schizophrenia, refers to the ability to infer one's own and others' mental states such as thinking, believing, or pretending (Brüne, 2005; Green et al., 2008; Premack and Woodruff, 1978). ToM is considered to be a mediator between neurocognition and daily functioning (Couture et al., 2011; Schmidt et al., 2011); thus, lower ToM in schizophrenia is related to poorer social interactions and lower community functioning (Mehl et al., 2010; Mike et al., 2019; Roncone et al., 2002).

Although ToM impairments have been significantly documented in schizophrenia, they are not systematically assessed or treated in clinical settings (Bora et al., 2009). As ToM is an important treatment target to promote functional recovery in schizophrenia, a greater understanding of the neural mechanisms of ToM impairments is critical and may guide the development of more targeted interventions (Couture et al., 2006; Javed and Charles, 2018).

The neural basis of ToM has been well-characterized in healthy populations using functional magnetic resonance imaging (fMRI) studies. Healthy individuals tend to activate both the left and right temporal parietal junctions (TPJ) and the medial prefrontal cortex (mPFC) while performing a ToM task (Dodell-Feder et al., 2014; Mehl et al., 2010; Molenberghs et al., 2016; Schurz et al., 2014; Van Overwalle, 2009).

Previous studies investigating impaired ToM in schizophrenia have reported structural abnormalities in the mPFC (Benedetti et al., 2009; Brüne, 2005; Walter et al., 2009; Yamada et al., 2007), specifically in the ventral mPFC (vmPFC) (Hooker et al., 2011; Shamay-Tsoory et al., 2003,

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2009). Prior reports have also shown reduced functional activity in the mPFC and bilateral TPJ in schizophrenia compared to controls during various tasks assessing ToM performance (Das et al., 2012; Jáni and Kašpárek, 2018; Kronbichler et al., 2017; Lee et al., 2006, 2011; Russell et al., 2000; Walter et al., 2009). Conversely, one study reported increased activation in the mPFC and TPJ in individuals with schizophrenia in comparison to controls during a belief attribution task (Brüne et al., 2008).

Although these studies suggest that ToM impairments in schizophrenia are associated with aberrant brain activation, findings are somewhat inconsistent. Small sample sizes (schizophrenia, n = 5–22, healthy controls, n = 7–26), the diverse range of tasks utilized to measure ToM, and the lack of construct validity (as relatively few studies have assessed the psychometric properties of ToM tasks in general), may all contribute to these varying findings (Kronbichler et al., 2017). Furthermore, heterogeneous profiles of ToM abilities in schizophrenia populations represent a challenge for interpreting previous group comparison findings (Bechi et al., 2018); thus, more studies with larger sample sizes are needed.

Two recent meta-analyses report that overall, individuals with schizophrenia tend to show reduced brain activation in the mPFC and TPJ during tasks requiring ToM processes (Jáni and Kašpárek, 2018; Kronbichler et al., 2017). Kronbichler et al. (2017) specifically found that individuals with schizophrenia show reduced activation in the posterior TPJ but increased activation in the dorsal portion of the TPJ. Only two studies included in these meta-analyses have specifically assessed ToM using an fMRI False Belief task (Dodell-Feder et al., 2014; Lee et al., 2011). Both studies report that compared to controls, individuals with schizophrenia show reduced task-related activation in the mPFC during the False Belief task, but only Lee et al. (2011) consistently aligned with Jáni and Kašpárek (2018) and Kronbichler et al. (2017) by additionally showing reduced task-related activation in the TPJ. However, Lee et al. (2011) and Dodell-Feder et al. (2014) were both conducted in relatively small sample sizes (schizophrenia, n = 12/20, healthy controls, n = 13/18) which may contribute to the discrepancies in results. Furthermore, neither studies assess for individual variability in ToM performance nor associations between behavioral performance and brain activation.

The overall objective of this study is to investigate the neural mechanisms of ToM impairments in 36 individuals within the early course of schizophrenia during an fMRI False Belief task (Saxe and Kanwisher, 2003). We aimed to 1) determine the construct validity of the False Belief task with the well-validated ToM Hinting Task (Corcoran et al., 1995), 2) investigate whether individuals with schizophrenia show lower brain activation in regions supporting ToM while performing the False Belief task (i.e., mPFC and TPJ), 3) assess specific correlations between False Belief task performance and related brain activity, and 4) explore how individual variability in ToM abilities in schizophrenia affect brain activity. We hypothesized that 1) performance between the False Belief task and Hinting Task will be positively correlated to each other, 2) individuals with schizophrenia will display reduced recruitment of task-related activations in the mPFC and TPJ during the False Belief task in comparison to controls, 3) activity in the mPFC and TPJ will be associated with False Belief accuracy, and 4) greater abnormalities in brain activity will be seen in individuals with schizophrenia having lower performance during the False Belief task than in patients with a more normal ToM profile.

2. Materials and methods

2.1. Participants

A total of 48 individuals with a diagnosis of schizophrenia or schizoaffective disorder and 20 controls were recruited through the National Institute of Mental Health (NIMH) funded study: Brain Imaging, Cognitive Enhancement and Early Schizophrenia (BICEPS) from the Pittsburgh site. Participants were selected as part of a baseline (pre-treatment) assessment of a randomized-controlled study (NCT#01561859) investigating the effects of Cognitive Enhancement Therapy in schizophrenia. Inclusion criteria required participants to be between 18 and 45 years of age, have an IQ $\geq$ 80 (using the WASI-II) (Hays et al., 2002), ability to read at a 6th grade level or higher, and speak fluent English. Patients were included if they had a diagnosis of schizophrenia or schizoaffective disorder verified using the Structured Clinical Interview for the DSM-IV, duration of psychotic symptoms of 10 years or less, symptomatically stable on antipsychotic medication (assessed via SCID and medical history), and significant cognitive and social disability was assessed with the Cognitive Styles and Social Cognition Eligibility Interview (Hogarty et al., 2004). Controls were required to have no major psychiatric illness or family history of psychosis. Exclusion criteria for all participants consisted of reported history of significant neurological or medical disorders which may produce cognitive impairment (e.g., seizure disorder, traumatic brain injury), persistent suicidal or homicidal behavior, recent history of substance abuse or dependence (within the past 3 months), magnetic resonance imaging (MRI) contraindications, and decisional incapacity requiring a guardian.

This study received ethics committee approval from the University of Pittsburgh where data were collected and at Beth Israel Deaconess Medical Center where data were analyzed. The study was carried out in accordance with the latest version of the Declaration of Helsinki. All participants provided written, informed consent prior to participation. After quality control, 36 patients and 17 controls were included in this analysis.

2.2. Protocol

Clinical measures were first administered to patients to examine levels of positive and negative symptoms. All participants underwent cognitive testing in order to evaluate ToM abilities. Subsequently, a sequence of MRI scans was conducted for each participant, where they performed the computerized fMRI False Belief task to assess False Belief accuracy and task-related neural activity.

2.3. Clinical measures

Patients' negative and positive symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b), respectively. In addition, antipsychotic medication dosages were converted to chlorpromazine equivalents, calculated using methods described in detail by Woods (2003; http://www.scottwilliamwoods.com/files/Equivtext.doc).

2.4. Hinting Task

The Hinting Task (Corcoran et al., 1995) is a ToM measure with good psychometric properties in schizophrenia (Pinkham et al., 2016). During the Hinting Task, participants listen to a story presented verbally and are required to determine the intention of one character when the participant provides a verbal hint to another character. The task includes 10 short passages presenting an interaction between two characters which end with one of the characters dropping a hint. Afterwards, the participant is asked to determine what the character's intentions are. If the participant gives a correct response on the first attempt, a score of 2 is given. If the participant gives the correct response when prompted with paraphrasing of the hint, a score of 1 is given. If the participant fails to give a correct response, a score of 0 is given. The scores are then added for a total score ranging from 0 to 20.

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2.5. fMRI False Belief task

The False Belief task assesses participants' ability to predict behavior based on mental states (Dodell-Feder et al., 2011; Saxe and Kanwisher, 2003). Specifically, the task asks participants to read short stories classified under one of two conditions; (1) False Belief stories describe a false belief and actions based on the false belief (e.g., "*The morning of the high school dance, Sarah placed her high heel shoes under her dress and then went shopping. That afternoon, her sister borrowed the shoes and later put them under Sarah's bed.*"), and (2) False Photograph stories describe false physical states in the world through photographs and maps (e.g., "*The traffic camera snapped an image of the black car as it sped through the stoplight. Soon after, the car was painted red and the license plates were changed.*"). Both False Belief and False Photograph stories require representation of false content with the main difference being the type of false content represented. Thus, the False Photograph condition serves as a control as it uses reasoning processes similar to the False Belief task, but does not require inferring another person's mental representations. Each condition contains an equal number of questions referring to reality and false representation. Participants then respond to a true/false question pertaining to either a situation based in reality or false representation (e.g., False Belief: "*Sarah gets ready assuming her shoes are under the dress*"; False Photograph: "*According to the traffic camera, the car is black*").

During the fMRI task, participants completed two functional runs, lasting for a total of 5 min and 2 s. Each run included 5 stories from each condition. Stories were presented for 11 s, followed by a true/false question for 6 s, and then 12 s of fixation on a center cross.

2.6. MRI acquisition

MRI scans were acquired on a 3.0 T Siemens Magnetom Verio at the University of Pittsburgh. A T1-weighted 3D MPRAGE anatomical sequence was collected (voxel size of 1.0 × 1.0 × 1.2 mm, TR = 2300 ms, T1 = 900 ms, TE = 2.89 ms, flip angle = 90°, FOV = 256 mm, 256 × 256 matrix, 160 slices, slice thickness = 1.2 mm). fMRI images were acquired during the False Belief task using a gradient echo T2*-weighted sequence (voxel size of 3.2 × 3.2 × 3.2 mm, TR = 2000 ms, TE = 30 ms, bandwidth = 2298, flip angle = 79°, FOV = 205 mm (excluded part of the dorsal somatosensory-motor cortex), 64 × 64 matrix, 36 slices).

2.7. MRI preprocessing

All MRI preprocessing was done using modules from the Statistical Parametric Mapping 8 (SPM8, Welcome Department of Cognitive Neurology, London, UK) toolbox. The fMRI time series images were first realigned to the first volume to correct for interscan movement, and coregistered to the participants' own anatomical image. The deformation field map obtained from the "New Segment" segmentation of the anatomical image was applied to the fMRI images to normalize them from anatomical space into standard MNI space (voxel size 2 × 2 × 2 mm). Finally, fMRI images were smoothed with an isotropic 8-mm full width at half maximum Gaussian kernel. Low frequency drifts were removed through the application of a high-pass filter with a cut-off of 128 s.

Quality control was conducted by examining realignment measurements for all participants to ensure head motion did not exceed 4 mm in any direction during the fMRI acquisition. Consequently, 12 patients and 3 controls were excluded due to excess motion. For included participants, maximum absolute motion (in mm) for patients (mean = 1.00 mm, SD = .81) and controls (mean = .84 mm, SD = 1.01) as well as the mean translational relative motion for patients (mean = .09 mm, SD = .06) and controls (mean = .08 mm, SD = .05) did not significantly differ between the groups (all $p > .49$). All fMRI images were further quality checked visually to ensure correct transformation to MNI space.

2.8. fMRI processing

First-level analysis included a general linear model in which individual conditions were modeled with the canonical hemodynamic response function implemented in SPM8. Specifically, a subject-specific fixed-effects model was used to estimate the effect of each condition (i.e., Belief and Photograph) with six motion parameters entered as covariates in the model. Then, mean beta values were extracted using spheres of 10 mm within a priori regions of interest (ROI) using the WFU_PickAtlas (Maldjian et al., 2003, 2004). The ROIs were selected from regions known to be reliably recruited for ToM: mPFC, MNI coordinates: $x = 1, y = 58, z = 22$; vmPFC, MNI coordinates: $x = 2, y = 48, z = -18$; right TPJ (RTPJ), MNI coordinates: $x = 52, y = -52, z = 22$; and left TPJ (LTPJ), MNI coordinates: $x = -50, y = -58, z = 20$ (Dodell-Feder et al., 2014).

2.9. Statistical analysis

All behavioral analyses were conducted using R (version 3.5.1, https://www.r-project.org/). All *p*-values were corrected for multiple comparisons using False Discovery Rate (FDR) with an adjusted significance threshold of $q < .05$.

2.9.1. Demographic analysis

Demographic variables were assessed using *t*-tests (i.e., age and IQ) and chi-squared tests (i.e., sex and race).

2.9.2. Behavioral analysis

To assess the concurrent validity of the fMRI task, we performed a Spearman correlation between Hinting Task performance and False Belief accuracy in all participants. A *post hoc* linear model was used to further investigate group differences (i.e., interactions) on this association. A *t*-test was performed to investigate group differences on Hinting Task performance. Then, a linear model was used to assess for main group and a group by condition interaction on the False Belief task. A series of *post hoc t*-tests were performed to further investigate group differences on False Belief accuracy and False Photograph accuracy.

2.9.3. fMRI analysis

Linear mixed models (with random intercept) were performed in each group separately to investigate differences in brain activity between both conditions of the task (Belief versus Photograph) for each ROI. Between-group differences were then examined using a linear mixed model (with random intercept and interaction between conditions (Belief versus Photograph) and groups (schizophrenia versus control)) for each ROI. In addition, Spearman correlations were performed to investigate associations between changes in brain activity during the False Belief task (Belief > Photograph) and both False Belief task accuracy and Hinting Task performance in all participants. A *post hoc* linear model was used to further investigate group differences (i.e., interactions) on this association. The schizophrenia group was then divided into a high (n = 18) and low (n = 18) performance group based on performance above or below the median accuracy score. Interaction effects between conditions and performance groups (high performance, low performance, and control) for each ROI were then examined using a general linear model.

2.9.4. Symptom severity and medication analysis

Post hoc Spearman correlations were carried out to explore potential associations between clinical measures (SANS total scores, SAPS total scores, and antipsychotic medication) in patients and ToM performance. In addition, *post hoc* Spearman correlations were further conducted to assess potential associations between clinical measures in patients and changes in brain activity (Belief > Photograph) in the RTPJ and LTPJ.

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3. Results

3.1. Demographics results

As demonstrated in Table 1, no significant differences between patients and controls were reported for age, sex, race, and IQ (Table 1).

3.2. Behavioral results

3.2.1. False Belief task and Hinting Task association

Greater accuracy on the False Belief task significantly correlated with higher Hinting Task scores (Fig. 1, $r = .51$, $p < .001$), regardless of diagnosis ($F_{(3,49)} = 8.06$, $p = .90$).

3.2.2. Between-group differences

Individuals with schizophrenia displayed significantly lower performance on the Hinting Task ($t_{(51)} = 5.57$, $p < .001$) [(schizophrenia: mean = 14.1, SD = 3.6), (controls: mean = 18.1, SD = 1.6)] (Fig. 2). While a main group effect was observed for the False Belief task ($F_{(1,104)} = 19.86$, $p < .001$, $d = -.938$), no significant interaction effect was observed between groups for False Belief versus False Photograph conditions ($F_{(3,102)} = 7.39$, $p = .202$). Individuals with schizophrenia displayed significant reductions in both False Photograph ($t_{(31)} = 2.26$, $p < .031$) [(schizophrenia: mean = .74, SD = .10), (controls: mean = .84, SD = .10)] and False Belief accuracy ($t_{(38)} = 4.33$, $p < .001$) [(schizophrenia: mean = .74, SD = .10), (controls: mean = .91, SD = .10)] compared to controls.

3.3. fMRI results

3.3.1. Within-group results

For individuals with schizophrenia, significant brain activity differences were observed between the False Belief condition versus the False Photograph condition for all ROIs, with the exception of the vmPFC (mPFC, $F_{(1,35)} = 8.30$, $p = .007$, $q = .009$, $d = .360$; vmPFC, $F_{(1,35)} = .20$, $p = .656$, $q = .656$, $d = -.073$; RTPJ, $F_{(1,35)} = 65.46$, $p < .001$, $q < .001$, $d = .845$; LTPJ, $F_{(1,35)} = 24.02$, $p < .001$, $q < .001$, $d = .585$, see Fig. 3). For controls, significant brain activity differences were observed between the False Belief condition versus the False Photograph condition (mPFC, $F_{(1,16)} = 41.15$, $p < .001$, $q < .001$, $d = .863$; vmPFC, $F_{(1,16)} = 13.10$, $p = .002$, $q = .002$, $d = .532$; RTPJ, $F_{(1,16)} = 77.28$, $p < .001$, $q < .001$, $d = 1.418$; LTPJ, $F_{(1,16)} = 85.43$, $p < .001$, $q < .001$, $d = 1.007$, see Fig. 3).

Table 1
Demographic characteristics of schizophrenia and healthy control subjects.

Demographics	SZ (n = 36)		HC (n = 17)			
	N		N		X^2	p-value
Sex (Male/Female)	20/16		12/5		0.6	0.457
Race (CA/AA/OT)	24/9/3		13/3/1		0.5	0.769
	Mean	SD	Mean	SD	F	p-value
Age (years)	25.2	5.3	25.5	4.4	37.1	0.797
IQ	106.3	10.5	109.4	14.4	24.3	0.438
Age of Onset	21.2	4.4	–	–	–	–
Illness Duration	4.0	2.3	–	–	–	–
SANS Total Score	1.3	0.7	–	–	–	–
SAPS Total Score	0.3	0.4	–	–	–	–
Daily CPZ Equivalents (mg/day)	398.8	329.3	–	–	–	–

Notes: SZ = Schizophrenia; HC = Healthy Controls; SD = Standard Deviation; CA = Caucasian; AA = African American; OT = Other; IQ = Intelligence Quotient; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; CPZ = Chlorpromazine.

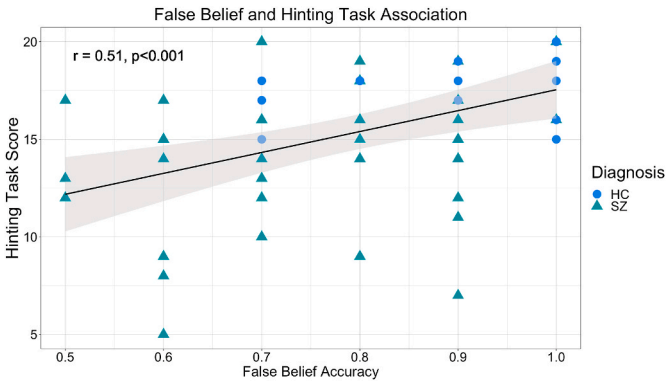

Fig. 1. False Belief and Hinting Task Association. False Belief accuracy was positively correlated with Hinting Task scores. HC = Healthy Controls, SZ = Schizophrenia.

3.3.2. Group interaction during the False Belief task

Individuals with schizophrenia displayed significant reductions in brain activity during the False Belief condition versus False Photograph condition when compared to controls in all 4 ROIs (mPFC, $F_{(1,51)} = 6.49$, $p = .014$, $q = .019$, $d = -.787$; vmPFC, $F_{(1,51)} = 10.37$, $p = .002$, $q = .009$, $d = -.949$; RTPJ, $F_{(1,51)} = 5.03$, $p = .029$, $q = .029$, $d = -.668$; LTPJ, $F_{(1,51)} = 7.33$, $p = .009$, $q = .018$, $d = -.848$, see Fig. 3).

3.3.3. Brain activity and performance association

During the False Belief condition of the False Belief task, only increased brain activation in the RTPJ ($r = .41$, $p = .002$, $q = .009$) and LTPJ ($r = .32$, $p = .018$, $q = .036$) were significantly associated with greater ToM performance (Fig. 4), regardless of group (RTPJ, $F_{(3,49)} = 3.44$, $p = .271$, $q = .710$; LTPJ, $F_{(3,49)} = 3.23$, $p = .412$, $q = .710$). No significant associations were observed for ToM performance and brain activation in the mPFC ($r = .22$, $p = .116$, $q = .154$) and vmPFC ($r = .15$, $p = .275$, $q = .275$). Furthermore, no significant associations were observed for Hinting Task performance and brain activation in all ROIs ($p > .146$).

3.3.4. Individual differences in schizophrenia group

We further explored individual differences in patients based on high and low performance groups in the RTPJ and LTPJ. After multiple comparisons, significant group interactions were only observed between the low-performance schizophrenia group and control group in the RTPJ ($F_{(2,50)} = 3.11$, $p = .016$, $q = .032$, $d = -.782$) and LTPJ ($F_{(2,50)} = 3.71$, $p = .013$, $q = .032$, $d = -.848$) (Fig. 5). No significant group difference was observed between the high-performance schizophrenia group and control group in the RTPJ ($F_{(2,50)} = 3.11$, $p = .161$, $q = .161$, $d = -.538$) and only a trend-related interaction was observed between both groups for the LTPJ ($F_{(2,50)} = 3.71$, $p = .040$, $q = .053$, $d = -.840$).

3.4. Symptom severity and medication results

To assess the potential impact of symptom severity and medication on ToM performance and TPJ neural activity (Belief > Photograph) in patients, additional *post hoc* analyses were carried out. For the RTPJ, increased brain activation was significantly associated with lower scores for both SAPS total scores ($r = -.42$, $p = .010$, $q = .032$) and SANS total scores ($r = -.42$, $p = .011$, $q = .032$). For the LTPJ, no significant association was observed between increased brain activation and SAPS total scores ($r = -.14$, $p = .416$, $q = .500$) and a trend-related association was observed between increased brain activation and lower SANS total scores ($r = -.34$, $p = .043$, $q = .086$). No significant associations were observed between antipsychotic medication and neural activity, $p > .14$. Finally, no significant associations were observed between clinical measures and ToM performance, $p > .15$.

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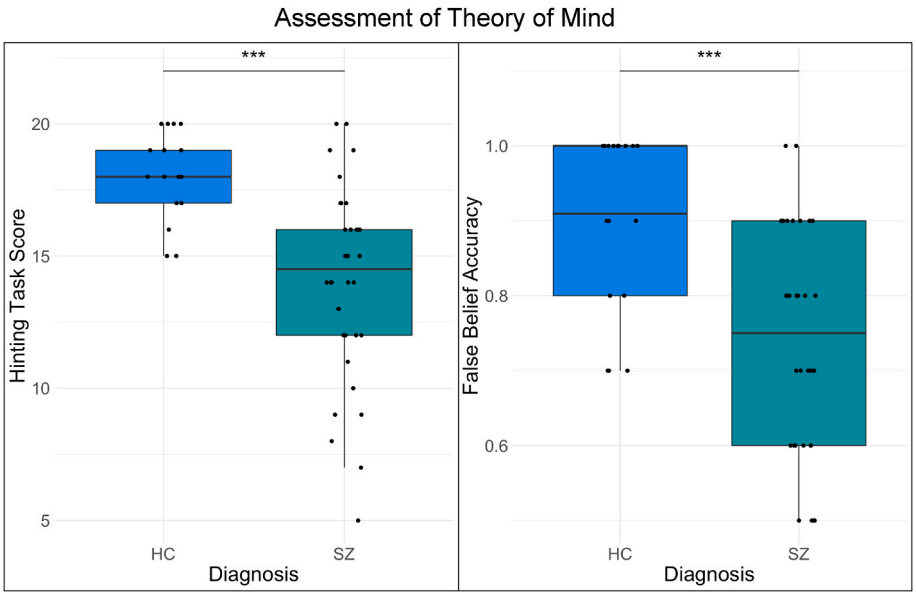

Fig. 2. Assessment of Theory of Mind. Hinting Task [(HC: mean = 18.1, SD = 1.6), (SZ: mean = 14.1, SD = 3.6)]. False Belief accuracy [(HC: mean = .91, SD = .10), SZ: mean = .74, SD = .10)]. ***($p < .001$). HC = Healthy Controls, SZ = Schizophrenia.

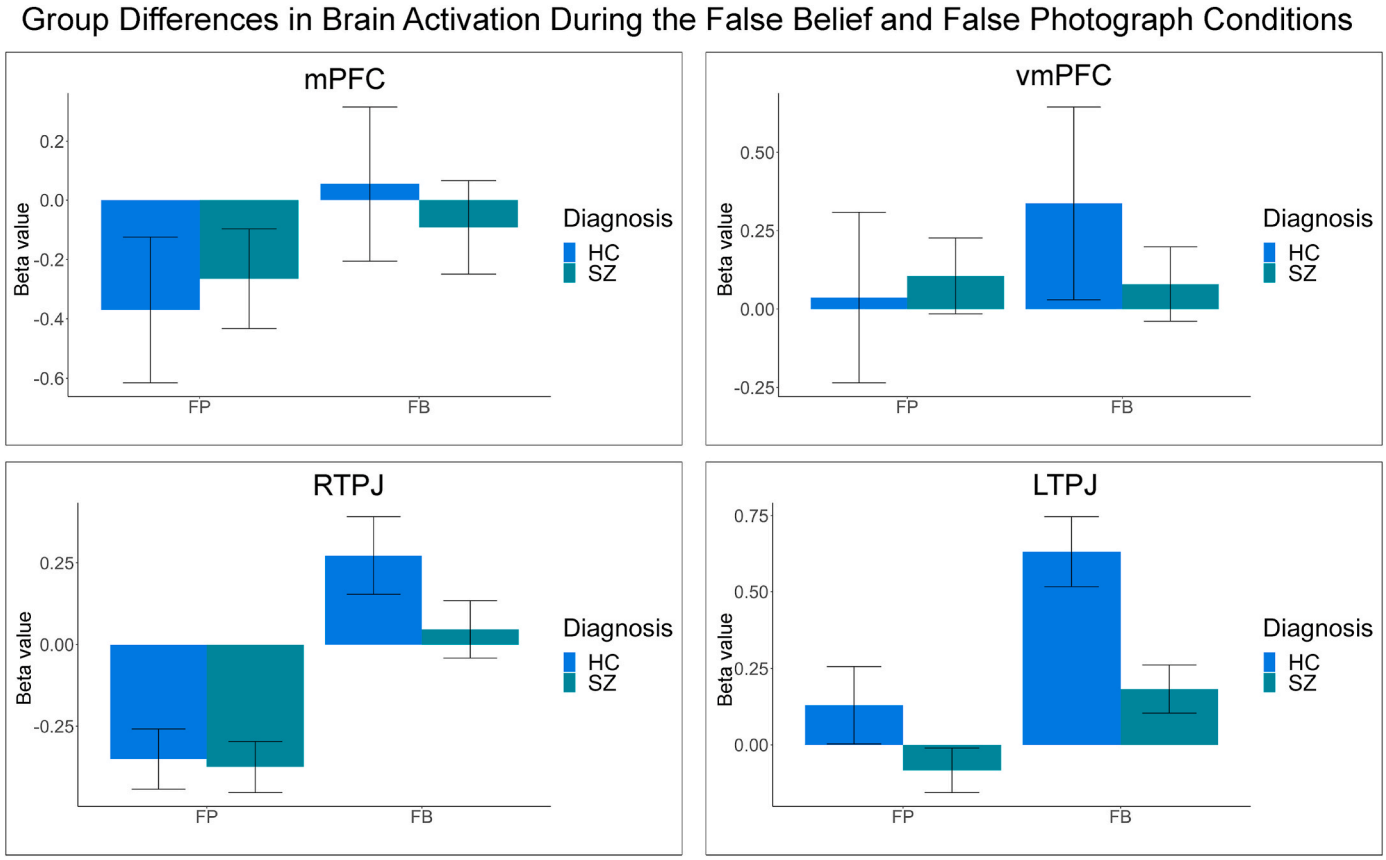

Fig. 3. Group Differences in Brain Activation During the False Belief and False Photograph Conditions. Error bars represent standard error of the mean. HC = Healthy Controls, SZ = Schizophrenia, FP = False Photograph condition, FB = False Belief condition, mPFC = medial prefrontal cortex, vmPFC = ventral medial prefrontal cortex, RTPJ = right temporal parietal junction, LTPJ = left temporal parietal junction.

4. Discussion

The goal of this study was to investigate the neural mechanisms of ToM impairments in early course schizophrenia by comparing the performance of patients and controls during an fMRI False Belief task. Specifically, we assessed the validity of the False Belief task as a measure of ToM, assessed correlations between brain activity and False Belief accuracy, and further examined the effects of individual variability in ToM abilities on brain activity.

Our results show that higher accuracy on the False Belief task was

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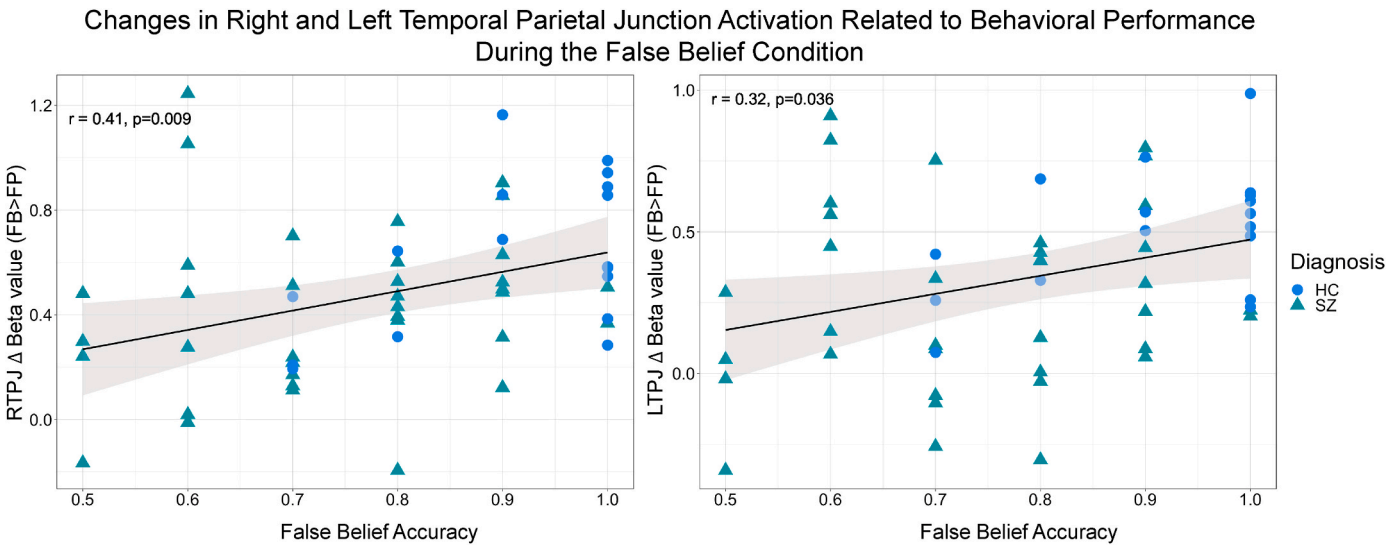

Fig. 4. Changes in Right and Left Temporal Parietal Junction Activation Related to Behavioral Performance During the False Belief Condition. Increased bilateral TPJ activation during the False Belief condition was positively correlated with False Belief accuracy regardless of diagnosis. Displaying FDR corrected p-values ($p < .05$). HC = Healthy Controls, SZ = Schizophrenia, FB = False Belief condition, FP = False Photograph condition, RTPJ = right temporal parietal junction, LTPJ = left temporal parietal junction.

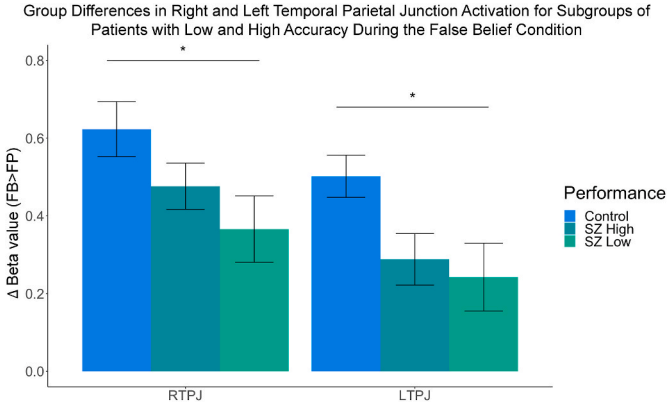

Fig. 5. Group Differences in Right and Left Temporal Parietal Junction Activation for Subgroups of Patients with Low and High Accuracy During the False Belief Condition. Error bars represent standard error of the mean. Displaying FDR corrected p-values (*$p < .05$). SZ = Schizophrenia, FB = False Belief condition, FP = False Photograph condition, SZ High = SZ FB high accuracy, SZ Low = SZ FB low accuracy, RTPJ = right temporal parietal junction, LTPJ = left temporal parietal junction.

significantly correlated with higher scores on the Hinting Task. The Hinting Task has been shown to be a good psychometric measure of ToM (Pinkham et al., 2016), but relatively few additional tests have been considered to be valid measures of ToM abilities (Sprong et al., 2007). Our finding provides concurrent validity for the False Belief task and suggests that it can measure ToM in individuals with schizophrenia as well as in healthy individuals. While the False Belief task has been used in previous publications (Dodell-Feder et al., 2011, 2014), to the best of our knowledge, this is the first time that a study establishes its concurrent validity with another ToM task.

We also observed significant differences between patients and controls for ToM abilities. As hypothesized, individuals within the early course of schizophrenia scored significantly lower for both the Hinting Task and False Belief task in comparison to controls. Our results further align with prior studies demonstrating lower performance on both the Hinting Task (Janssen et al., 2003; Lindgren et al., 2018; Raucher-Chéné et al., 2020) and False Belief task (Lee et al., 2011) for individuals with schizophrenia. Together, these findings provide strong evidence that ToM is impaired in schizophrenia.

In comparison to controls, patients also showed significantly abnormal task-related brain activation in all four selected ROIs during the False Belief task when comparing the False Belief and False Photograph conditions. Significant reductions in brain activity were observed for both the mPFC and vmPFC during the False Belief task for patients compared to controls. As the mPFC is considered to be a reliable brain region that healthy individuals significantly recruit during ToM tasks (Molenberghs et al., 2016; Schurz et al., 2014), our findings align with prior studies reporting significant reductions in mPFC activity for ToM in individuals with schizophrenia compared to controls (Dodell-Feder et al., 2014; Lee et al., 2006, 2011; Walter et al., 2009). Although the mPFC was implicated in abnormal brain activity during the False Belief task, this region was not related to ToM performance. Similar to Kronbichler et al. (2017), our results suggest that reduced activation in the mPFC region for patients compared to controls may be related to a general dysfunction across ToM tasks and may not be specifically associated with successful belief attribution abilities for individuals with schizophrenia.

Furthermore, we observed significant reductions in task-related brain activation in the TPJ region during the False Belief condition compared to the False Photograph condition in patients, aligning with previous ToM studies reporting reduced task-related activation in the TPJ for individuals with schizophrenia compared to controls (Das et al., 2012; Lee et al., 2011). Specifically for individuals with schizophrenia, Lee et al. (2011) similarly reported task-related reductions in the bilateral TPJ during the False Belief condition while Das et al. (2012) exclusively found task-related reductions in the RTPJ during an animated ToM task focused on implicit aspects of mentalizing. A recent meta-analysis by Molenberghs et al. (2016) observed consistent activation of the bilateral TPJ during several ToM tasks in healthy individuals. Thus, our results imply that the reduced task-related TPJ activation for patients compared to controls may be specific to ToM impairments in schizophrenia.

From all the regions implicated in the fMRI False Belief task, our results suggest that the bilateral TPJs are most related to successful ToM abilities, further supporting the crucial role of the TPJ region in ToM processes (Frith and Frith, 2006; Gallagher and Frith, 2003; Saxe and Kanwisher, 2003; Saxe and Powell, 2006). We report significant positive correlations between False Belief task accuracy and both RTPJ and LTPJ

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task-related brain activation in all participants. Amongst the ToM network, the TPJ region has been associated with belief attribution (Saxe et al., 2006; Saxe and Wexler, 2005; Van Overwalle, 2009) and has consistently been found to be active during ToM tasks in healthy control populations, specifically during the False Belief condition of the False Belief task (Döhnel et al., 2012; Saxe, 2010). Moreover, the TPJ region is known to be linked to implicit mentalizing processes (Perner et al., 2006; Perner and Leekam, 2008). Specifically, the RTPJ is known to be connected to the representation of beliefs (Saxe and Powell, 2006) and the LTPJ has been suggested to be responsible for processing perspective differences during mentalizing tasks (Perner et al., 2006). Although we found significant associations between task-related brain activation and the False Belief task, no significant associations between task-related brain activation and the Hinting Task were observed. Our results suggest that the task-related activity we report from the fMRI False Belief task may be specific only to False Belief accuracy. However, it is possible that the Hinting Task is considered to be a more generalized measure of ToM while the False Belief task is more specific to belief attribution. Another possibility is that the Hinting Task was not administered on the same day as the False Belief task, providing more variability and a less accurate representation of linking brain activity with behavioral performance.

Although patients demonstrated significantly lower ToM abilities, performance of several of the individuals with schizophrenia overlapped with the controls' performance in regards to False Belief accuracy. In an attempt to detect subtle differences which may be related to ToM impairments specifically in schizophrenia, individuals with schizophrenia were separated into a high and low performance group based on their False Belief accuracy performance. As expected, we specifically observed significantly greater abnormalities in TPJ neural activation for the low-performance schizophrenia group in comparison to controls. While we observed lower brain activity in the bilateral TPJ in the high-performance schizophrenia group who performed at a similar level to controls, this reduction was not significant. Similar to Lee et al. (2011), who report that patients showed lower accuracy on the False Belief condition, we were further able to associate low performance on the False Belief condition with neural activity. Our results suggest that reduced brain activity in the bilateral TPJ are associated with ToM impairments observed in individuals with schizophrenia. Furthermore, to our knowledge, this is the first study to report associations between individual differences in ToM performance and brain activity during a ToM task.

Although we did have a number of strengths to our study, such as including a relatively larger, well-characterized early course patient population, our results must be appreciated in the context of some limitations. Given the relatively young age of our sample (mean = 25.2 years) and the low average duration of illness (mean = 4 years), our study population is considered to be in the early course of schizophrenia; thus, our findings may only address ToM impairments in individuals within the early stages of schizophrenia and not in other stages of the illness. Although most patients were clinically stable with little variation in symptoms, we were unable to further assess the potential impact of patients' mood status on ToM performance. In addition, all patients were on antipsychotic medication, clinically stable, and had relatively high IQ levels, which further limits the generalization of our findings from unmedicated and higher symptomatology schizophrenia populations, in addition to lower IQ populations. Furthermore, the relatively small sample size of our control group is another potential limitation which may reduce the prospect of detecting subtle changes in brain activity between patients and controls. Finally, because we observed no associations between task-related brain activation and the Hinting Task, our significant correlations between task-related brain activation and ToM performance may only be specific to the False Belief condition of the False Belief task.

In conclusion, the present study reports that aberrant brain activation in the bilateral TPJ is significantly related to poorer ToM performance in schizophrenia. The current study links regional brain activity with behavioral data during a False Belief task in individuals within the early course of schizophrenia. To the best of our knowledge, it is also the first study to further explore individual differences in brain activity during a ToM task in an early course schizophrenia population. As ToM abilities correlate with greater neurocognitive capacity and reductions in negative symptom severity (Mike et al., 2019), early detection of these ToM impairments may help us identify patients who could benefit from targeted treatment of ToM difficulties; thus, improving quality of life for individuals with schizophrenia. Furthermore, our findings suggest that the bilateral TPJ may be proposed as a potential neural target for therapeutic intervention development aiming to improve ToM in schizophrenia.

Author contribution

MSK, SMH, and SG contributed to the design of the study. SP was involved in data collection. RRH, DB, VZ, and SG undertook fMRI and behavioral analysis and were involved in quality control. RRH wrote the manuscript with the help of SG. All authors provided feedback on data interpretation and have approved the final article.

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Declaration of competing interest

All authors approve the submission of this manuscript and have no conflicts of interest that may directly impact this work.

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References

Andreasen, N.C., 1984a. The Scale for the Assessment of Negative Symptoms (SANS). The University of Iowa.

Andreasen, N.C., 1984b. The Scale for the Assessment of Positive Symptoms (SAPS). The University of Iowa.

Bechi, M., Bosia, M., Agostoni, G., Spangaro, M., Buonocore, M., Bianchi, L., Cocchi, F., Guglielmino, C., Mastromatteo, A.R., Cavallaro, R., 2018. Can patients with schizophrenia have good mentalizing skills? Disentangling heterogeneity of theory of mind. Neuropsychology 32 (6), 746–753. https://doi.org/10.1037/neu0000456.

Benedetti, F., Bernasconi, A., Bosia, M., Cavallaro, R., Dallaspezia, S., Falini, A., Poletti, S., Radaelli, D., Riccaboni, R., Scotti, G., Smeraldi, E., 2009. Functional and structural brain correlates of theory of mind and empathy deficits in schizophrenia. Schizophr. Res. 114 (1), 154–160. https://doi.org/10.1016/j.schres.2009.06.021.

Bora, E., Yucel, M., Pantelis, C., 2009. Theory of mind impairment in schizophrenia: meta-analysis. Schizophr. Res. 109 (1–3), 1–9. https://doi.org/10.1016/j.schres.2008.12.020.

Brüne, M., 2005. "Theory of mind" in schizophrenia: a review of the literature. Schizophr. Bull. 31 (1), 21–42. https://doi.org/10.1093/schbul/sbi002.

Brüne, M., Lissek, S., Fuchs, N., Witthaus, H., Peters, S., Nicolas, V., Juckel, G., Tegenthoff, M., 2008. An fMRI study of theory of mind in schizophrenic patients with "passivity" symptoms. In: Part Special Issue: what Is the Parietal Lobe Contribution to Human Memory?, 46, pp. 1992–2001. https://doi.org/10.1016/j.neuropsychologia.2008.01.023, 7.

Corcoran, R., Mercer, G., Frith, C.D., 1995. Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. Schizophr. Res. 17 (1), 5–13. https://doi.org/10.1016/0920-9964(95)00024-g.

Couture, S.M., Granholm, E.L., Fish, S.C., 2011. A path model investigation of neurocognition, theory of mind, social competence, negative symptoms and real-world functioning in schizophrenia. Schizophr. Res. 125 (2–3), 152–160. https://doi.org/10.1016/j.schres.2010.09.020.

Couture, S.M., Penn, D.L., Roberts, D.L., 2006. The functional significance of social cognition in schizophrenia: a review. Schizophr. Bull. 32, S44–S63. https://doi.org/10.1093/schbul/sbl029. Suppl 1(Suppl 1).

Das, P., Lagopoulos, J., Coulston, C.M., Henderson, A.F., Malhi, G.S., 2012. Mentalizing impairment in schizophrenia: a functional MRI study. Schizophr. Res. 134 (2), 158–164. https://doi.org/10.1016/j.schres.2011.08.019.

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Dodell-Feder, D., Koster-Hale, J., Bedny, M., Saxe, R., 2011. FMRI item analysis in a theory of mind task. Neuroimage 55 (2), 705–712. https://doi.org/10.1016/j.neuroimage.2010.12.040.

Dodell-Feder, D., Tully, L.M., Lincoln, S.H., Hooker, C.I., 2014. The neural basis of theory of mind and its relationship to social functioning and social anhedonia in individuals with schizophrenia. NeuroImag. Clin. 4, 154–163. https://doi.org/10.1016/j.nicl.2013.11.006.

Döhnel, K., Schuwerk, T., Meinhardt, J., Sodian, B., Hajak, G., Sommer, M., 2012. Functional activity of the right temporo-parietal junction and of the medial prefrontal cortex associated with true and false belief reasoning. Neuroimage 60 (3), 1652–1661. https://doi.org/10.1016/j.neuroimage.2012.01.073.

Frith, C.D., Frith, U., 2006. The neural basis of mentalizing. Neuron 50 (4), 531–534. https://doi.org/10.1016/j.neuron.2006.05.001.

Gallagher, H.L., Frith, C.D., 2003. Functional imaging of "theory of mind. Trends Cognit. Sci. 7 (2), 77–83. https://doi.org/10.1016/s1364-6613(02)00025-6.

Green, M.F., Horan, W.P., Lee, J., 2015. Social cognition in schizophrenia. Nat. Rev. Neurosci. 16 (10), 620–631. https://doi.org/10.1038/nrn4005.

Green, M.F., Penn, D.L., Bentall, R., Carpenter, W.T., Gaebel, W., Gur, R.C., Kring, A.M., Park, S., Silverstein, S.M., Heinssen, R., 2008. Social cognition in schizophrenia: an NIMH workshop on definitions, assessment, and research opportunities. Schizophr. Bull. 34 (6), 1211–1220. https://doi.org/10.1093/schbul/sbm145.

Hays, J.R., Reas, D.L., Shaw, J.B., 2002. Concurrent validity of the wechsler abbreviated Scale of intelligence and the Kaufman brief intelligence test among psychiatric inpatients. Psychol. Rep. 90 (2), 355–359. https://doi.org/10.2466/pr0.2002.90.2.355.

Hogarty, G.E., Flesher, S., Ulrich, R., Carter, M., Greenwald, D., Pogue-Geile, M., Kechavan, M., Cooley, S., DiBarry, A.L., Garrett, A., Parepally, H., Zoretich, R., 2004. Cognitive enhancement therapy for schizophrenia: effects of a 2-year randomized trial on cognition and behavior. Arch. Gen. Psychiatr. 61 (9), 866–876. https://doi.org/10.1001/archpsyc.61.9.866.

Hooker, C.I., Bruce, L., Lincoln, S.H., Fisher, M., Vinogradov, S., 2011. Theory of mind skills are related to gray matter volume in the ventromedial prefrontal cortex in schizophrenia. Biol. Psychiatr. 70 (12), 1169–1178. https://doi.org/10.1016/j.biopsych.2011.07.027.

Jáni, M., Kašpárek, T., 2018. Emotion recognition and theory of mind in schizophrenia: a meta-analysis of neuroimaging studies. World J. Biol. Psychiatr. 19 (Suppl. 3), S86–S96. https://doi.org/10.1080/15622975.2017.1324176.

Janssen, I., Krabbendam, L., Jolles, J., van Os, J., 2003. Alterations in theory of mind in patients with schizophrenia and non-psychotic relatives. Acta Psychiatr. Scand. 108 (2), 110–117. https://doi.org/10.1034/j.1600-0447.2003.00092.x.

Javed, A., Charles, A., 2018. The importance of social cognition in improving functional outcomes in schizophrenia. Front. Psychiatr. 9, 157. https://doi.org/10.3389/fpsyt.2018.00157.

Kronbichler, L., Tschernegg, M., Martin, A.I., Schurz, M., Kronbichler, M., 2017. Abnormal brain activation during theory of mind tasks in schizophrenia: a meta-analysis. Schizophr. Bull. 43 (6), 1240–1250. https://doi.org/10.1093/schbul/sbx073. PubMed.

Lee, J., Quintana, J., Nori, P., Green, M.F., 2011. Theory of mind in schizophrenia: exploring neural mechanisms of belief attribution. Soc. Neurosci. 6 (5–6), 569–581. https://doi.org/10.1080/17470919.2011.620774.

Lee, K.H., Brown, W.H., Egleston, P.N., Green, R.D.J., Farrow, T.F.D., Hunter, M.D., Parks, R.W., Wilkinson, I.D., Spence, S.A., Woodruff, P.W.R., 2006. A functional magnetic resonance imaging study of social cognition in schizophrenia during an acute episode and after recovery. Am. J. Psychiatr. 163 (11), 1926–1933. https://doi.org/10.1176/ajp.2006.163.11.1926.

Lindgren, M., Torniainen-Holm, M., Heiskanen, I., Voutilainen, G., Pulkkinen, U., Mehtälä, T., Jokela, M., Kieseppä, T., Suvisaari, J., Therman, S., 2018. Theory of mind in a first-episode psychosis population using the Hinting Task. Psychiatr. Res. 263, 185–192. https://doi.org/10.1016/j.psychres.2018.03.014.

Maldjian, J.A., Laurienti, P.J., Burdette, J.H., 2004. Precentral gyrus discrepancy in electronic versions of the Talairach atlas. Neuroimage 21 (1), 450–455. https://doi.org/10.1016/j.neuroimage.2003.09.032.

Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19 (3), 1233–1239. https://doi.org/10.1016/s1053-8119(03)00169-1.

Mehl, S., Rief, W., Mink, K., Lüllmann, E., Lincoln, T.M., 2010. Social performance is more closely associated with theory of mind and autobiographical memory than with psychopathological symptoms in clinically stable patients with schizophrenia-spectrum disorders. Psychiatr. Res. 178 (2), 276–283. https://doi.org/10.1016/j.psychres.2009.10.004.

Mike, L., Guimond, S., Kelly, S., Thermenos, H., Mesholam-Gately, R., Eack, S., Keshavan, M., 2019. Social cognition in early course of schizophrenia: exploratory factor analysis. Psychiatr. Res. 272, 737–743. https://doi.org/10.1016/j.psychres.2018.12.152.

Molenberghs, P., Johnson, H., Henry, J.D., Mattingley, J.B., 2016. Understanding the minds of others: a neuroimaging meta-analysis. Neurosci. Biobehav. Rev. 65, 276–291. https://doi.org/10.1016/j.neubiorev.2016.03.020.

Perner, J., Aichhorn, M., Kronbichler, M., Staffen, W., Ladurner, G., 2006. Thinking of mental and other representations: the roles of left and right temporo-parietal junction. Soc. Neurosci. 1 (3–4), 245–258. https://doi.org/10.1080/17470910600989896.

Perner, J., Leekam, S., 2008. The curious incident of the photo that was accused of being false: issues of domain specificity in development, autism, and brain imaging. Q. J. Exp. Psychol. 61 (1), 76–89. https://doi.org/10.1080/17470210701508756, 2006.

Pinkham, A.E., Penn, D.L., Green, M.F., Harvey, P.D., 2016. Social cognition psychometric evaluation: results of the initial psychometric study. Schizophr. Bull. 42 (2), 494–504. https://doi.org/10.1093/schbul/sbv056.

Premack, D., Woodruff, G., 1978. Does the chimpanzee have a theory of mind? Behav. Brain Sci. 1 (4), 515–526. https://doi.org/10.1017/S0140525X00076512.

Raucher-Chéné, D., Lavigne, K.M., Makowski, C., Lepage, M., 2020. Altered surface area covariance in the mentalizing network in schizophrenia: insight into theory of mind processing. Biol. Psychiatr.: Cogn. Neurosci. Neuroimag. https://doi.org/10.1016/j.bpsc.2020.06.020.

Roncone, R., Falloon, I.R.H., Mazza, M., De Risio, A., Pollice, R., Necozione, S., Morosini, P.L., Casacchia, M., 2002. Is theory of mind in schizophrenia more strongly associated with clinical and social functioning than with neurocognitive deficits? Psychopathology 35 (5), 280–288. https://doi.org/10.1159/000067062.

Russell, T.A., Rubia, K., Bullmore, E.T., Soni, W., Suckling, J., Brammer, M.J., Simmons, A., Williams, S.C.R., Sharma, T., 2000. Exploring the social brain in schizophrenia: left prefrontal underactivation during mental state attribution. Am. J. Psychiatr. 157 (12), 2040–2042. https://doi.org/10.1176/appi.ajp.157.12.2040.

Saxe, R., Kanwisher, N., 2003. People thinking about thinking people. The role of the temporo-parietal junction in "theory of mind. Neuroimage 19 (4), 1835–1842. https://doi.org/10.1016/s1053-8119(03)00230-1.

Saxe, Rebecca, 2010. The right temporo-parietal junction: a specific brain region for thinking about thoughts. In: Handbook of Theory of Mind.

Saxe, Rebecca, Moran, J.M., Scholz, J., Gabrieli, J., 2006. Overlapping and non-overlapping brain regions for theory of mind and self reflection in individual subjects. Soc. Cognit. Affect Neurosci. 1 (3), 229–234. https://doi.org/10.1093/scan/nsl034.

Saxe, Rebecca, Powell, L.J., 2006. It's the thought that counts: specific brain regions for one component of theory of mind. Psychol. Sci. 17 (8), 692–699. https://doi.org/10.1111/j.1467-9280.2006.01768.x.

Saxe, Rebecca, Wexler, A., 2005. Making sense of another mind: the role of the right temporo-parietal junction. Neuropsychologia 43 (10), 1391–1399. https://doi.org/10.1016/j.neuropsychologia.2005.02.013.

Schmidt, S.J., Mueller, D.R., Roder, V., 2011. Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: empirical review and new results by structural equation modeling. Schizophr. Bull. 37 (Suppl. 2), S41–S54. https://doi.org/10.1093/schbul/sbr079.

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., Perner, J., 2014. Fractionating theory of mind: a meta-analysis of functional brain imaging studies. Neurosci. Biobehav. Rev. 42, 9–34. https://doi.org/10.1016/j.neubiorev.2014.01.009.

Shamay-Tsoory, S.G., Tomer, R., Berger, B.D., Aharon-Peretz, J., 2003. Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. J. Cognit. Neurosci. 15 (3), 324–337. https://doi.org/10.1162/089892903321593063.

Shamay-Tsoory, Simone, G., Aharon-Peretz, J., Perry, D., 2009. Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. Brain: J. Neurol. 132 (Pt 3), 617–627. https://doi.org/10.1093/brain/awn279.

Sprong, M., Schothorst, P., Vos, E., Hox, J., van Engeland, H., 2007. Theory of mind in schizophrenia: meta-analysis. Br. J. Psychiatr.: J. Ment. Sci. 191, 5–13. https://doi.org/10.1192/bjp.bp.107.035899.

Van Overwalle, F., 2009. Social cognition and the brain: a meta-analysis. Hum. Brain Mapp. 30 (3), 829–858. https://doi.org/10.1002/hbm.20547.

Walter, H., Ciaramidaro, A., Adenzato, M., Vasic, N., Ardito, R.B., Erk, S., Bara, B.G., 2009. Dysfunction of the social brain in schizophrenia is modulated by intention type: an fMRI study. Soc. Cognit. Affect Neurosci. 4 (2), 166–176. https://doi.org/10.1093/scan/nsn047.

Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J. Clin. Psychiatr. 64 (6), 663–667. https://doi.org/10.4088/jcp.v64n0607.

Yamada, M., Hirao, K., Namiki, C., Hanakawa, T., Fukuyama, H., Hayashi, T., Murai, T., 2007. Social cognition and frontal lobe pathology in schizophrenia: a voxel-based morphometric study. Neuroimage 35 (1), 292–298. https://doi.org/10.1016/j.neuroimage.2006.10.046.

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