



Differentiating implicit and explicit theory of mind and associated neural networks in youth at Clinical High Risk (CHR) for psychosis

Teresa Vargas^{a,*}, Katherine S.F. Damme^a, Christine I. Hooker^b, Tina Gupta^a, Henry R. Cowan^a, Vijay A. Mittal^{a,c,d,e,f}

^a Northwestern University Department of Psychology, USA

^b Rush University Medical Center, Department of Psychiatry, USA

^c Northwestern University Department of Psychiatry, USA

^d Northwestern University Department of Medical Social Sciences, USA

^e Northwestern University Institute for Innovations in Developmental Sciences, USA

^f Northwestern University Institute for Policy Research, USA

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ABSTRACT

Background: Theory of mind (ToM) has been shown to be impaired in Clinical High Risk (CHR) for psychosis populations and is linked to functional outcomes and symptom severity. Implicit versus explicit ToM has seldom been differentiated in this group, and underlying neural networks have also gone unexplored.

Methods: 24 CHR and 26 healthy volunteers (HV) completed a behavioral ToM measure called the Short Story Task (SST), as well as a resting state functional MRI scan. SST performance was correlated to attenuated psychosis symptoms. Interactions between group and ToM variables (implicit, explicit, and comprehension) on global efficiency in the Mentalizing (MENT) and Mirror Neuron System (MNS) were also examined.

Results: CHR individuals made significantly fewer spontaneous mental state inferences. There were trend-level associations between ToM variables and symptoms, such that greater ToM performance predicted less severe symptoms. There was an interaction of group by spontaneous mental state inference within MENT bilateral dorsomedial prefrontal cortex (dmPFC), such that CHR individuals that made spontaneous mental state inferences showed greater global efficiency within the MENT network's bilateral dmPFC.

Discussion: Findings suggest implicit ToM deficits are observable prior to psychotic disorder onset, and that these deficits implicate MENT network dmPFC efficiency. Explicit ToM performance was unaltered in the CHR group, and there were no interactions observed within MNS, suggesting specificity of implicit ToM associations with MENT network dmPFC global efficiency. Results identify potential treatment targets for the neural underpinnings of ToM, thus informing prevention and intervention efforts.

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1. Introduction

Theory of mind (ToM), constituting the ability to infer and understand others' mental states, such as their beliefs and emotions, is critical for navigating the social world. This ability has been found to be impaired in psychotic disorders and is also strongly linked to symptom severity and prognosis (Fett et al., 2011). However, it is unclear to what extent ToM deficits emerge across different stages of psychotic illness progression. One contributing issue relates to extant methodology, as common ToM paradigms have faced issues surrounding ceiling effects in populations that do not exhibit significant global cognitive impairment (Dodell-Feder et al., 2013). This lack of variability in ToM

performance may result in decreased sensitivity to the early emergence of ToM deficits that may occur prior to the onset of chronic illness. Further, previous ToM tasks have not often differentiated between implicit/spontaneous versus explicit/evoked ToM processes, decreasing specificity and sensitivity of measurement of this construct. Lastly, neural mechanisms underlying ToM ability in schizophrenia have been proposed and investigated; however these mechanisms have not often been examined early in disease course prior to neurotoxic effects of illness progression (Caspers et al., 2010; Schilbach et al., 2012a; Schurz et al., 2014; Kovacs et al., 2014; Schilbach et al., 2016; Kronbichler et al., 2017). Gaining a more thorough understanding of ToM deficits and possible neural underpinnings prior to psychosis onset would be instrumental in understanding the role that ToM plays in illness progression. These efforts would also aid in understanding shared etiological underpinnings of psychosis and ToM deficits as well as social cognition deficits more broadly.

* Corresponding author at: Northwestern University, Swift Hall 102, 2029 Sheridan Road, Evanston, IL 60201, USA.

E-mail address: teresavargas@u.northwestern.edu (T. Vargas).

ToM deficits have long been found in psychotic disorder patients (Fett et al., 2011; Bora and Pantelis, 2013). In these patients, the extent of social dysfunction has been closely tied to degree of ToM impairment (Fett et al., 2011; Kurtz and Richardson, 2012; Bora and Pantelis, 2013). ToM ability has also been shown to be impaired in those at Clinical High Risk (CHR) for developing psychosis (in addition to being linked to functional outcomes and symptom progression) (Stanford et al., 2011; Kim et al., 2011; Thompson et al., 2012; Bora and Pantelis, 2013; Healey et al., 2013). Stable deficits in ToM across psychotic stages of illness progression have also been reported (Green et al., 2012). Nonetheless, certain limiting methodological factors in assessing ToM have impacted the field's understanding of this construct and its relationship to psychosis. In cases of less severe ToM impairment, established measures may lack sensitivity to both nuanced individual differences and subtler clinical impairment (Dodell-Feder et al., 2013). For example, ceiling effects are often observed among healthy volunteers (HV) (and sometimes among clinical groups) in conventional ToM measures (Corcoran et al., 1995; Corcoran and Frith, 2003; Craig et al., 2004; Marjoram et al., 2005; Martino et al., 2007; Zhu et al., 2007; Bertrand et al., 2007; Bora et al., 2008; Pijnenborg et al., 2009; de Achaval et al., 2010; Hooker et al., 2011). CHR individuals are a highly heterogeneous group, with functional and cognitive deficits that, despite having significant implications for psychopathology risk, can often be subtle in presentation and difficult to detect (Bora and Pantelis, 2013; Dodell-Feder et al., 2013). Thus, using ToM measures that are able to detect a full range of the construct, including mild or subtle impairment, is critical for both early identification and prevention.

The Short Story Task (SST) was chosen as a ToM task sensitive to individual differences and subtle variation. Importantly, the task provides separate measures of implicit versus explicit ToM ability, and, to our knowledge, these dissociable components of ToM have not been studied in CHR populations. Implicit ToM ability constitutes the ability to spontaneously attribute mental state to others, thus making “mental state inferences” (Dodell-Feder et al., 2013). In contrast, explicit ToM ability would include “mental state reasoning” whereby an individual is able to think and reason about others' mental states when prompted (Dodell-Feder et al., 2013). This dissociation could be informative as, for example, research has shown that individuals with autism are able to make mental state inferences when prompted, though they are less likely to do so spontaneously (Senju et al., 2009; Moran et al., 2011). The SST has also proven promising in predicting individual differences in ToM correlates such as indirect request comprehension (Trott and Bergen, 2018).

Being able to engage in mental state reasoning when prompted is very different than spontaneously being prone to making these inferences. Understanding Implicit ToM ability thus could improve our ability to understand how likely CHR individuals are to spontaneously think about others' mental states, which could significantly impact their day-to-day functioning and quality of life (Dodell-Feder et al., 2013; Trott and Bergen, 2018). There are studies that suggest deficits in implicit ToM as psychotic illness progresses, though this has not yet been explored prior to psychotic illness onset (Bliksted et al., 2016; Langdon et al., 2017). Thus, determining possible trait-level differences in likelihood to make implicit versus explicit mental state inferences could lend useful information with regards to illness progression, symptom severity and social functioning. Ultimately, it could be informative to prediction models for risk of conversion to a psychotic disorder.

The literature has consistently found abnormalities in neural ToM processing in both CHR (Takano et al., 2017) and psychotic phases of illness (Kronbichler et al., 2017). Two neural networks that have been consistently associated with ToM processing in both healthy and psychotic disorder patients (Caspers et al., 2010; Schilbach et al., 2012a; Schurz et al., 2014). These distinct networks are referred to as the “mentalizing network” (MENT) and the “mirror neuron system” (MNS). The MENT is activated by tasks that explicitly require or implicitly elicit individuals to think about the mental states of others

(Schilbach et al., 2016). The MENT is also engaged during states of unconstrained cognition, which give rise to “social thoughts” (de Lange et al., 2008; Schilbach et al., 2008; Schilbach et al., 2010; Schilbach et al., 2012b). The MNS also plays a key role in social cognition through providing a pre-conscious sense of being and acting with others (Newman-Norlund et al., 2007; Gallese, 2009; Iacoboni, 2009; Rizzolatti and Sinigaglia, 2010; Shibata et al., 2011; Schilbach et al., 2016).

Recent investigations have discovered altered functional connectivity in schizophrenia patients in important network hubs of the MNS and MENT (Meda et al., 2012; Yu et al., 2012; Guo et al., 2014). Most recently, a study found decreased functional connectivity among the MENT and MNS networks in schizophrenia patients, which was linked to symptom severity (Schilbach et al., 2016). Exploring these resting state functional networks using brain graphs may be particularly important. Recent work strongly suggests that translating modality-specific connectivity statistics to topological measures on brain graphs may facilitate more reliable cognitive and clinical interpretations of neuroimaging systems (Bassett et al., 2009; Bullmore and Bassett, 2011). Brain graphs model the nervous system as nodes interconnected by a set of edges (Bullmore and Sporns, 2009). The edges can represent, for example, functional connections between cortical and subcortical regional nodes based on analysis of resting state data. Based on graph theory concepts, geometrical properties are estimated and related to network topology. Graph theory analyses allow us to compare across a variety of complex, information-processing systems (Bassett et al., 2009; Bullmore and Bassett, 2011). For example, it has been demonstrated across modalities (e.g. fMRI, EEG) that higher cognitive performance is associated with brain graphs globally configured for greater efficiency of parallel information transfer (Bassett et al., 2009; Bullmore and Bassett, 2011). Given compelling and widely accepted evidence that the brain supports massively parallel information processing, adapting efficiency metrics of brain functional network topology has been argued to be conceptually preferable to other methods (Achard and Bullmore, 2007). Further, among schizophrenia populations, alterations in topological measures of local information processing, such as efficiency, have been found in fMRI studies (Zalesky et al., 2010b; Zalesky et al., 2010a; Alexander-Bloch et al., 2010; Lynall et al., 2010; Fornito et al., 2012). Despite evidence that connectivity in the MENT and MNS networks is impaired in psychotic disorders, no studies, to date, have examined these networks in CHR populations. Thus, it is unclear which stage of illness progression these abnormalities emerge and what the link is between risk for psychosis, efficiency in these networks, and ToM performance.

The present investigation hypothesized that ToM performance would relate to positive and negative symptoms (Stanford et al., 2011; Kim et al., 2011; Thompson et al., 2012; Bora and Pantelis, 2013; Healey et al., 2013). It was also hypothesized that topological properties of the MENT and MNS networks (assessed by resting state fMRI) would be altered in CHR, especially in those with lower SST ToM performance (Carrington and Bailey, 2009; Schilbach et al., 2016; Kronbichler et al., 2017). Thus, analyses relating symptoms to ToM performance were undertaken in CHR individuals. In addition, neural analyses examined between-group (CHR versus HV) differences in addition to interactions of group by ToM variables within each network.

2. Participants

Participants included 50 adolescents and young adults (24 CHR and 26 HVs) recruited to the Adolescent Development and Preventive Treatment (ADAPT) research program at the University of Colorado, Boulder (Institutional Review Board approved protocol 10-0398). Ages 12–24 were eligible for inclusion. Exclusion criteria included history of head injury, history of a neurological disorder, MRI contraindications, and having an Axis I psychotic disorder or substance dependence according to the *Diagnostic and Statistical Manual of Mental Disorder* 4th ed., text rev. (American Psychiatric Association, 2000). In addition, presence of a

psychotic disorder in a first-degree relative or meeting for an Axis I disorder were exclusionary criteria for HVs. Participants 18 and older provided written informed consent. For participants under 18, parents or legal guardians additionally provided consent. After establishing eligibility, participants first completed clinical interviews. After, participants came back for another visit to complete the ToM task, and were additionally scheduled for an MRI session, which included a resting state scan (typically within a week of completing the clinical interviews and ToM task).

3. Measures and procedure

3.1. Short Story Task (SST)

In the SST participants are asked to read “The End of Something,” a short story by Ernest Hemingway. After reading the story, participants are asked a series of 14 questions to assess comprehension, explicit mental state reasoning (EMSR), and spontaneous mental state inference (SMSI). Comprehension items assess the participant's accurate understanding of non-mental state story content. Specifically, comprehension questions ask about factual information presented in the story, such as what object/item the character observed or what action they performed. Most importantly, accurate responses are based on available information and do not require inference or mental state understanding. As such, these questions assess the ability to comprehend concrete, factual information presented in narrative form. For purposes of task design, responses to comprehension questions help verify that the participant has sufficient cognitive capacity to complete the task and that they paid attention, understood instructions, and devoted adequate effort.

EMSR questions assess the accuracy of the mental state inference, number of character perspectives/emotions taken into account (i.e., second-order inferences generally received more points than first-order inferences), and understanding of non-verbal/indirect communications (e.g., sarcasm and body language). To assess SMSI, participants are asked a single question that simply asked them to summarize the story. Responses were coded for the presence or absence of a mental state inference (see Table 2 for sample questions). There were two raters, trained according to validated task guidelines (Dodell-Feder et al., 2013). Reliability was established for 5 subjects subsequently collected and coded. Kappas of at least 0.8 for SMSI and 0.9 for EMSR and Comprehension were obtained.

3.2. Structured Clinical Interviews and Assessment

Participants were administered the Structured Clinical Interview for DSM-IV Axis I disorders (SCID) (First et al., 2012). The SCID was administered to rule out psychosis diagnosis in the CHR and HV groups, as well as to assess history of mood and anxiety disorders. The Structured Interview for Prodromal Syndromes (SIPS) was administered to CHR and HV participants in order to identify CHR subjects and rule out symptoms in HVs (Miller et al., 1999). CHR inclusion criteria included Attenuated Positive Symptom Syndrome (APSS), APSS and schizotypal personality disorder prior to 18 years old, and Genetic Risk and Deterioration Syndrome (GRDS; see Table 1 for inclusion breakdown). All interviews were conducted by trained clinical doctoral students; Kappas of at least 0.8 for SIPS and 0.9 for prodromal (e.g. APSS, GRDS) and psychiatric diagnoses were obtained.

3.3. Imaging acquisition and processing

Scans were acquired using a 3 T Siemens Trio scanner. Resting-state blood oxygen level-dependent (BOLD) scans were acquired with a T2-weighted echo-planar functional protocol (number of volumes = 165; TR = 2000 ms; TE = 29 ms; matrix size = $64 \times 64 \times 33$; FA = 75° ; $3.8 \times 3.8 \times 3.5$ mm³ voxels; 33 slices; FOV = 240 mm). To investigate incidental pathology, a turbo spin echo proton density–T2 weighted acquisition (axial oblique aligned with anterior commissure-posterior

commissure line; TR = 3720 ms; TE = 89 ms; GRAPPA parallel imaging factor of 2; FOV = 240 mm; flip angle: 120° ; 0.9×0.9 mm² voxels; 77 interleaved 1.5-mm slices) was generated. Resting scans were 5 min and 34 s long. Participants were instructed to relax and keep their eyes closed. Previous studies have found that this functional connectivity MRI duration provides equal power to longer scan times (Van Dijk et al., 2010).

FSL Version 5 (Jenkinson et al., 2012) was used for data processing. This preprocessing involved motion correction, brain extraction, high-pass filtering (100 s), and spatial smoothing (6 mm FWHM). Functional images were aligned to the Montreal Neurological Institute (MNI) 2-mm brain template. Motion correction (Power et al., 2012) was carried out with the artifact detection software (ART; https://www.nitrc.org/projects/artifact_detect), which created confound regressors for motion parameters (three translation and three rotation parameters) and additional confound regressors for specific image frames with outliers based on brain activation and head movement. Mean global brain activity was calculated to identify outliers. Outliers were defined as frames where the global mean signal exceeded 3 SDs. Framewise measures of motion were used to identify any motion outliers/motion spikes. Motion outliers were defined as frames where motion exceeded 1 mm.

Functional connectivity analyses were performed using the *Conn Functional Connectivity Toolbox* (CONN), Version 17.b (Whitfield-Gabrieli and Nieto-Castanon, 2012) in SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). SPM12 was used to segment anatomical images into gray matter, white matter, and cerebrospinal fluid (CSF) and create masks for signal extraction. The *Conn Toolbox* extracts five temporal components from the segmented CSF and white matter, which were then entered as confound regressors in the subject-level general linear model (GLM). Motion from the ART toolbox was additionally included as a confound regressor.

The MNS was derived from a meta-analysis implicating this network in activation observation and action imitation (see Fig. 1, Table 3) (Caspers et al., 2010). The MENT network was derived from a meta-analysis of self-referential and social cognition, associating the network with introspective processes and socio-emotional function (see Fig. 1b, Table 3) (Schilbach et al., 2012a). Regions of Interest (ROI) were extracted using SPM toolbox. Seed-to-seed functional connectivity analyses were computed for the MENT and MNS networks (see Table 3) using CONN (Whitfield-Gabrieli and Nieto-Castanon, 2012).

3.4. Graph theory analysis

Global efficiency was calculated for the two networks. Global efficiency constitutes the average of the inverse shortest path lengths for all ROI-ROI pairs in the network, providing a measure of the network's overall connectedness, that is, how efficiently information is communicated between nodes (Bullmore and Bassett, 2011; Goparaju et al., 2014). Notably, global efficiency is a measure of the network's capacity for parallel information transfer between nodes (via several series of edges) (Achard and Bullmore, 2007). Given strong evidence of widespread brain parallel information processing, efficiency metrics of brain functional network topology are hypothesized to be particularly suited for interpreting these processes (Achard and Bullmore, 2007). In order to reduce the number of total comparisons in the current study, global efficiency was focused on, as it accounts for multiple graph features (described above) in a single metric.

3.5. Statistical analyses

Chi-square tests and *t*-tests, when appropriate, were used to test for differences in demographic characteristics. Within the CHR group, due to evidence of skew in symptom data, relationships between positive, negative and disorganized symptoms and ToM variables were tested using Spearman correlations in the case of EMSR and Comprehension, and Independent Samples Mann-Whitney *U* test in the case of SMSI. Global efficiency was extracted for MENT and MNS networks, with

Table 1
Demographic characteristics.

Demographics	CHR ¹ (n = 24) Mean (SD)	HV ² (n = 26) Mean (SD)	CHR Range	HV	Group diff.
Age	19.83 (2.22)	19.85 (2.72)	15–23	13–24	n.s.
Sex	41.67% female	50% female	–	–	n.s.
Cognitive function ^a	57.48 (9.06)	55 (8.98)	28–70	33–69	n.s.
Parental education ^b	15.48 (2.37)	16.30 (2.67)	10–20	10–20	n.s.
Self-identified race					
Black	0%	3.85%	–	–	–
Central/South American	16.67%	3.85%	–	–	–
East Asian	4.17%	7.69%	–	–	–
First Nations	8.33%	0%	–	–	–
Southeast Asian	0%	3.85%	–	–	–
White	70.83%	80.77%	–	–	–
Inclusion criteria met					
Attenuated Positive Symptom Syndrome (APSS)	79.17%	–	–	–	–
APSS and schizotypal personality disorder prior to 18 years old	4.17%	–	–	–	–
Genetic Risk and Deterioration Syndrome (GRDS)	16.67%	–	–	–	–
Symptoms ^c					
Positive	6.92 (5.08)	0.12 (0.33)	1–22	0–1	–
Negative	5.54 (5.79)	0.27 (0.53)	0–19	0–2	–
Disorganized	2.58 (2.24)	0.42 (0.81)	0–7	0–3	–
General	5.63 (3.84)	0.73 (1.40)	1–13	0–6	–
SST ^d performance					
SMSI ^e (yes/no)	29.17% (7/17)	69.23% (18/8)	0–1	0–1	1 < 2 ^{*,g}
EMSR ^f	8.83 (2.24)	8.54 (2.45)	4–13	2–12	n.s.
Comprehension	9.12 (1.23)	8.54 (1.53)	6–10	5–10	n.s.

Note: Mean (SD), 1 = Clinical High Risk, 2 = healthy volunteer.

^a MATRICS composite *t* score.

^b Averaged years of education of both parents.

^c Estimated by the SIPS interview.

^d Short Story Task.

^e Spontaneous Mental State Inference.

^f Explicit Mental State Reasoning.

^g Cramer's *V* = 0.40.

* *p* < .05.

network edges (adjacency matrix threshold) defined as *z* scores, using a two-sided FDR correction threshold of *p* < 0.05. For each network, group differences in global efficiency were tested. In addition, interactions of group by comprehension, EMSR, and SMSI were tested for each of the 2 networks.

4. Results

4.1. Demographics, symptoms and ToM

See Table 1 for demographic variables and group differences. A Pearson chi-square test of diagnosis by SMSI was significant [$\chi^2 = 8.01$, *p* = 0.01], whereby significantly less CHR individuals made a SMSI in their

story summary compared to HVs. There were no significant differences between groups with regards to both comprehension and EMSR (see Table 1). Relationships with symptoms are presented in Table 4. Trend-level associations were observed with symptoms, such that absence of SMSI was associated with greater positive and negative symptoms.

4.2. Graph theory analyses

There were no differences in global efficiency between groups for networks of interest (Table 5). In addition, interactions of group by Comprehension, EMSR, and SMSI were not found for the MNS network. However, an interaction of group by SMSI was found within the MENT

Table 2
Sample prompt and scoring criteria from the Short Story Task (SST) for Spontaneous Mental State Inference (SMSI), Explicit Mental State Reasoning (EMSR), and Comprehension. After reading Ernest Hemingway's short story, "The End of Something," participants are asked a set of questions. Responses are scored from 0 to 2, with 2 being the most accurate response.

	Prompt	2 score response	1 score response	0 score response
Spontaneous Mental State Inference	In just a few sentences, how would you summarize the story?	N/A	During the response, the participant makes a mental state inference (i.e. about a belief, thought, desire, intention, goal, emotion)	Participant does not make a mental state inference.
Explicit Mental State Reasoning	Why is Nick afraid to look at Marjorie?	Response needs to reference Marjorie's possible reaction to what he is saying; He knows she is hurt/upset by his comment, and he is afraid of her reaction/doesn't want to see the hurt in her face; is afraid of her judgment of him.	Some response that conveys his feelings without referencing how Marjorie's reactions affect his feelings; he is uncomfortable with the way the conversation is heading; he feels guilty/shameful/sad; he's about to break up with her and it's easier not to look at her; he's afraid he's making the wrong decision by breaking up with her.	He doesn't want Marjorie to see his reaction; none of the responses in 2 or 1.
Comprehension	Nick and Marjorie have a pail of perch for what purpose?	Bait; catching fish	Any response that conveys understanding of its use for some aspect of fishing without being explicit about its function as bait for catching fish.	Any response that doesn't convey understanding of its use for fishing.

Table 3
MNI coordinates for networks of interest.

Region	MNI coordinates		
	x	y	z
<i>MNS network</i>			
Right IFG (BA 44)	−56	8	28
Left IFG (BA 44)	58	16	10
Right SMA	10	−2	45
Left SMA	−1	16	52
Right IPL	51	−36	50
Left IPS/IPL	−38	−40	50
Right MTG	53	−45	5
Left MTG	−54	−50	10
Right V5	−52	−70	6
Left V5	54	−64	4
Right FG	44	−54	−20
Left FG	−28	−9	−38
<i>MENT network</i>			
Right PreC	10	−66	24
Left PreC	−6	−54	24
Right dmPFC	12	54	15
Left dmPFC	−2	52	14
Right TPJ	52	−62	16
Left TPJ	−46	−66	18

Note: cortex pMTG, posterior middle temporal gyrus; SMA, supplementary motor area (hidden within the interhemispheric fissure); IPS, intraparietal sulcus; MTG, middle temporal gyrus; FG, fusiform gyrus; PreC, precuneus; dmPFC, dorsomedial prefrontal cortex; TPJ, temporo-parietal junction; MENT, mentalizing network; MNS, mirror neuron system; IPL, inferior parietal lobe; V5, extrastriate visual area; BA 44, Broca's area; PCC, posterior cingulate cortex; mPFC, medial pre-frontal; MNI, Montreal Neurological Institute. All peaks are assigned to the most probable brain areas as revealed by the SPM Anatomy Toolbox.

network, such that bilateral dorsomedial prefrontal cortex (dmPFC) showed greater global efficiency within the MENT network for those CHR individuals that made SMSIs, relative to those that did not (see Fig. 2). This interaction was not observed in healthy individuals. Notably, interactions were not apparent within the MENT network for Comprehension or EMSR. The magnitude of the effects did not change when controlling for age and sex. Two CHR individuals eventually converted to a psychotic disorder. Running analyses without including these 2 individuals did not alter effect sizes.

5. Discussion

The present investigation used topographical functional resting state measures to explore the neural underpinnings of ToM in CHR individuals and HVs. First, behavioral differences between groups were examined. CHR individuals did not differ in explicit ToM ability, however they made significantly less SMSI, suggesting altered implicit and spontaneous ToM ability. Next, associations between ToM and symptoms in CHR were examined; there were trend-level relationships with positive and negative symptoms. Finally, topographical functional resting state measures were used to explore global efficiency (i.e. graph or network interconnectedness, or degree of global connectedness of a certain region

Table 5
Global efficiency statistics among networks of interest.

	ROI	Beta	T	<i>p</i> _{uncorrected}	<i>p</i> _{FDR}
<i>Mentalizing (MENT) network</i>					
Group	Network	−0.01	−0.16	0.87	–
Group by Comprehension	Network	−0.01	−0.23	0.82	–
Group by EMSR	Network	−0.00	−0.16	0.88	–
Group by SMSI	Network	0.15	1.67	0.10	–
	Right dmPFC	0.30	2.59	0.01	0.039
	Left dmPFC	0.27	2.67	0.01	0.039
<i>Mirror Neuron System (MNS) network</i>					
Group	Network	−0.03	−0.96	0.34	–
Group by Comprehension	Network	0.05	2.19	0.03	–
Group by EMSR	Network	0.02	1.52	0.14	–
Group by SMSI	Network	−0.10	−1.60	0.12	–

within the network) in well-established ToM networks. Network global efficiency differences between groups were not observed. We aimed to see how resting state function in these networks correlated with ToM performance outside the scanner. A relation was observed whereby group interacted with SMSI such that CHR individuals that made SMSIs showed greater global efficiency in bilateral dmPFC within the MENT network. Findings offer nuance to the extant literature of ToM deficits in CHR populations. They suggest that CHR individuals exhibit impairment in implicit ToM (implying less spontaneous thinking about others' mental states), while explicit ToM may be relatively more intact at this stage of illness progression (meaning CHR individuals are still able to exercise theory of mind and imagine others' mental states when explicitly prompted). Further, CHR individuals with intact spontaneous mental reference abilities may be aided by increased efficiency of dmPFC within the MENT (see Fig. 2). Taken together, results inform etiological models of ToM deficits and associated neural networks in psychotic disorders. In addition, findings offer specificity with regards to candidate neural mechanisms for treatment and intervention surrounding implicit ToM as well as with regards to what aspects of ToM may be more impaired prior to psychotic disorder onset.

The literature had yet to distinguish between implicit/spontaneous and explicit/evoked ToM ability in CHR populations, confounding understanding of specificity of neurocognitive function in this domain (Dodell-Feder et al., 2013). In this sample, there were no differences between CHR and HVs in story stimuli comprehension, nor were there differences in explicit/evoked mental state reasoning. However, compared to healthy individuals, CHR participants made significantly less SMSIs. This group difference suggests that implicit ToM may be particularly impacted in the CHR group, while explicit ToM remains relatively intact. This finding is consistent to what has been found in autism populations, who exhibit intact explicit ToM, but impaired implicit ToM function (Senju et al., 2009; Moran et al., 2011). However, given that previous meta analyses have found ToM deficits in CHR populations, future studies will be needed to replicate this finding using the SST (Bora et al., 2008). Further, there were trend-level associations between implicit ToM, positive and negative symptoms, such that those CHR participants

Table 4
Relationships of SST variables with symptoms in CHR.

	Positive symptoms ^a				Negative symptoms ^a				Disorganized symptoms ^a			
	<i>stat</i> ^b	<i>p</i>	Effect size ^c	95% CI	<i>stat</i> ^b	<i>p</i>	Effect size ^c	95% CI	<i>stat</i> ^b	<i>p</i>	Effect size ^c	95% CI
SMSI ^d	−1.6	0.11	0.11	−1.0–7.0	−1.25	0.21	0.07	−1.0–10.0	−0.58	0.56	0.01	−1.0–3.0
EMSR ^e	−0.17	0.44	0.17	−0.43–0.12	−0.09	0.69	0.09	−0.36–0.19	−0.03	0.88	0.03	−0.31–0.25
Comp ^f	0.08	0.72	0.08	−0.20–0.35	−0.25	0.25	0.25	−0.50–0.03	−0.18	0.40	0.18	−0.44–0.11

^a Estimated by the SIPS battery.

^b An Independent Samples Mann-Whitney *U* test was performed for SMSI, and Spearman correlations were performed for EMSR and Comp.

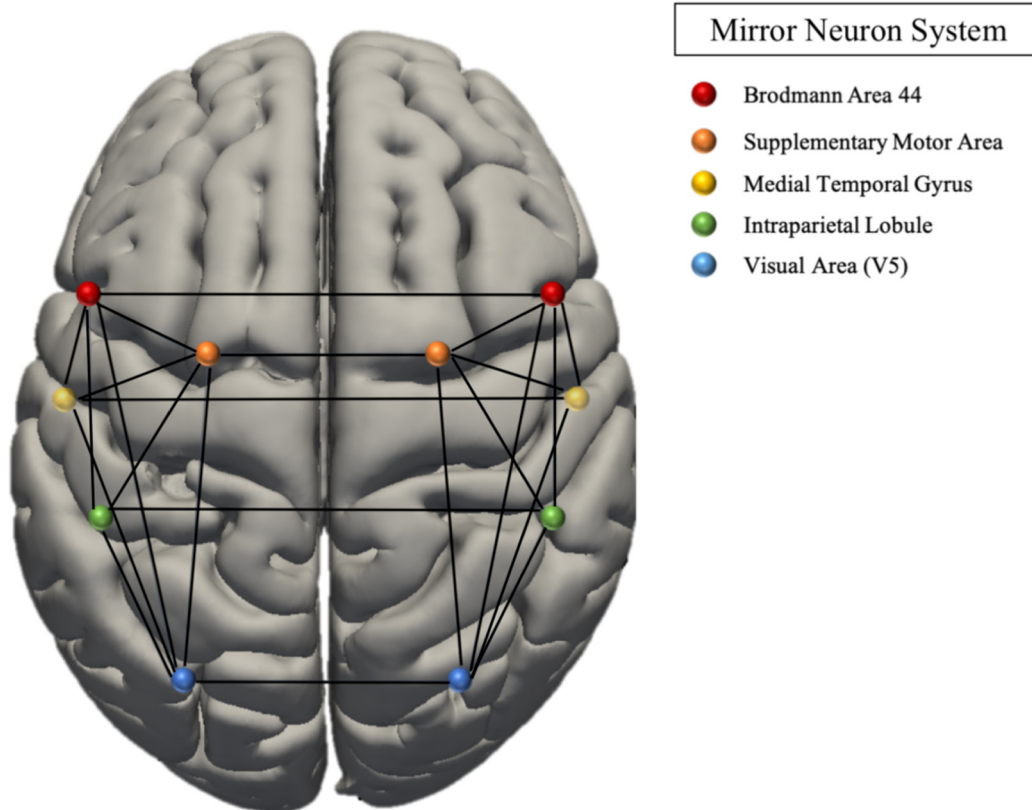
^c For SMSI, η^2 . For EMSR and Comp, $|r|$.

^d Spontaneous Mental State Inference.

^e Explicit Mental State Reasoning.

^f Comprehension.

(a). Graph Network Models: Mirror Neuron System (Caspers et al., 2010).



(b). Graph Network Models: Mentalizing Network (Schilbach et al., 2012a).

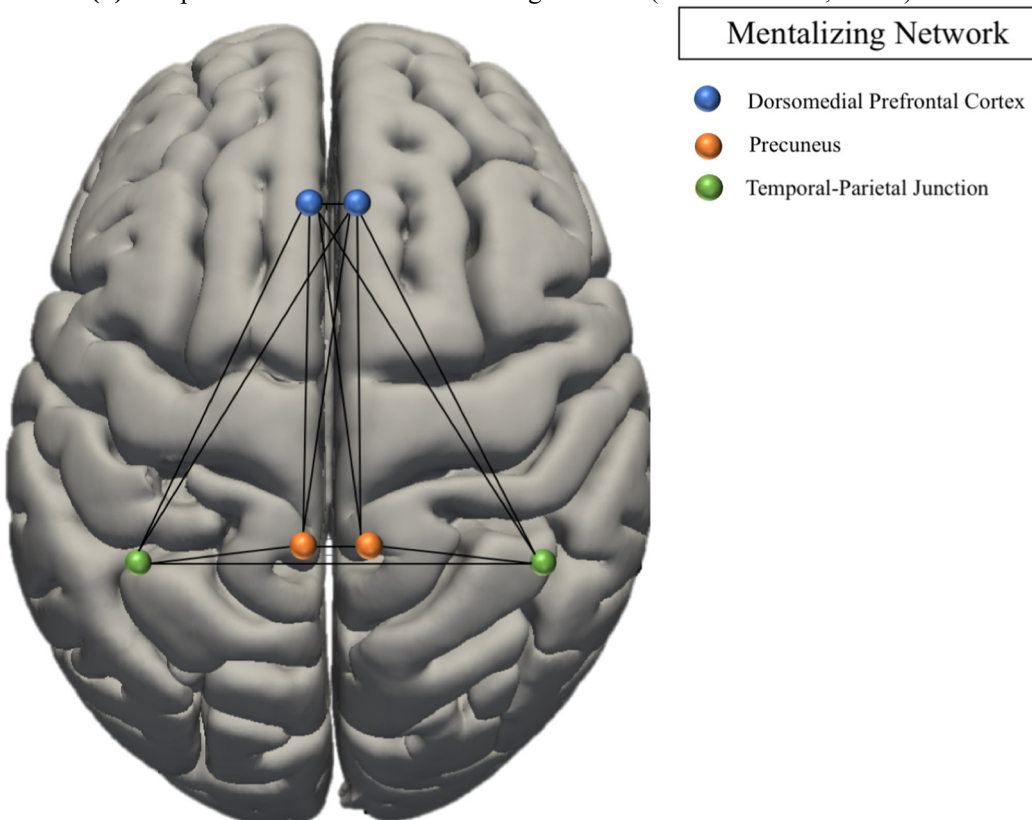


Fig. 1. (a). Graph network models: Mirror Neuron System (Caspers et al., 2010). (b). Graph Network models: Mentalizing Network (Schilbach et al., 2012a).

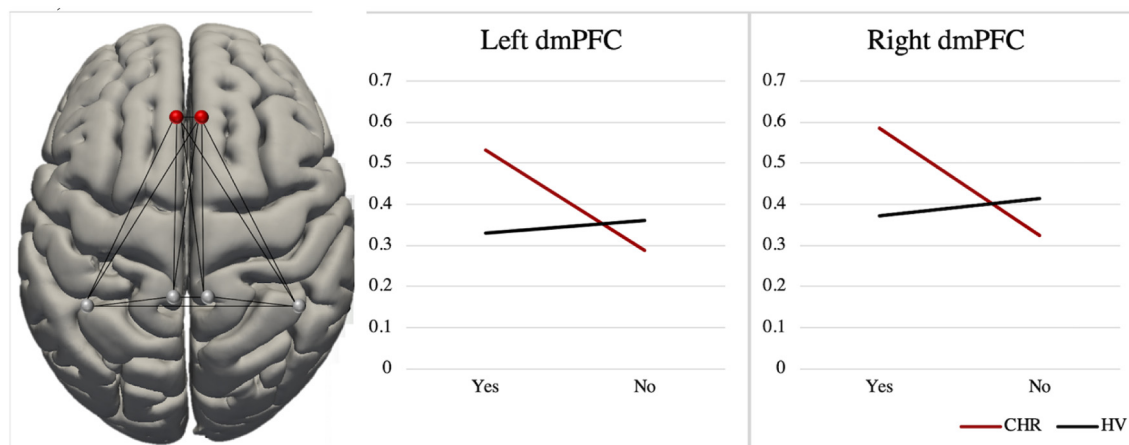


Fig. 2. MENT network global efficiency interaction of SMSI by Group in bilateral dmPFC. On the x-axis, “Yes” refers to having made a SMSI, and “No” refers to not having made a SMSI. Bilateral dmPFC global efficiency within the MENT network was extracted as eigen values (y-axis).

that made SMSI had less severe symptoms. These symptom associations partially supports previous studies linking ToM to functional outcome and illness severity (Pijnenborg et al., 2009; Bae et al., 2010; Fett et al., 2011), though limited power may have precluded observation of a stronger relationship.

Topographical measures of MENT and MNS network efficiency did not yield group differences. This null network wide finding suggests that across groups the networks are not distinguishable in terms of globally integrated, parallel information-processing capacity (Achard and Bullmore, 2007). This finding is contrary to study hypotheses, though it adds to a wide body of literature examining global efficiency at the whole-brain level as well as in particular networks in schizophrenia, which has thus far yielded mixed findings (Liu et al., 2008; Alexander-Bloch et al., 2010; Lynall et al., 2010; Becerril et al., 2011; Fornito et al., 2012; Wang et al., 2012). It is necessary, however, to keep in mind that lack of differences in these activation patterns at rest does not preclude there being activation differences during performance of ToM tasks (Van Overwalle and Baetens, 2009; Schilbach et al., 2012a; Schilbach et al., 2016). It is possible that there are differences in efficiency that are only apparent during active ToM processing. The present study aimed to explore individual-level differences in “resting-state” neural efficiency and correlates to behavioral implicit and explicit ToM measures. This is valuable in investigating possible “trait-level” differences in ToM network efficiency that co-occur with ToM behavioral measures. Future studies will be needed using task-based fMRI paradigms of implicit and explicit ToM to further explore and expand this work.

In examining the convergence of ToM performance and global efficiency in MENT and MNS networks, however, an interaction was observed of group by SMSI within the MENT bilateral dmPFC region. Within the MENT, interactions of group by EMSR and group by comprehension were not detected, lending evidence to specificity of implicit/spontaneous ToM capacity (versus explicit ToM or attention to task stimuli). Likewise, for MNS there were no group interactions across any ToM variables. In all, results are consistent with previous research implicating the MENT in states of unconstrained cognition, which give rise to spontaneous “social thoughts” (de Lange et al., 2008; Schilbach et al., 2008; Schilbach et al., 2010; Schilbach et al., 2012b). Perhaps the MENT specifically serves a role in spontaneous ToM.

It is striking that rather than observe a global efficiency interaction in the MENT network as a whole, the interaction was localized to global efficiency in bilateral dmPFC within the MENT network. There are several plausible interpretations for this observation. It is a possibility that the dmPFC is responsible to a sizable degree when it comes to spontaneous mentalizing. There is a large body of evidence supporting this interpretation. Most recently, for example, a task-based fMRI study implicated

the dmPFC in spontaneous mentalization specifically (Moessnang et al., 2017). Given the dmPFC has been found to be responsible for context-independent, flexible metacognitive representations of the social world, it may be particularly implicated in implicit ToM (Bzdok et al., 2013; Spunt and Adolphs, 2015).

CHR participants that made SMSI exhibited greater global efficiency in bilateral dmPFC (within the MENT network). This increased efficiency in dmPFC was not observed for HV individuals with SMSI. Again, there are several plausible interpretations for this finding. Previous investigations using brain graphs have found increased global efficiency in schizophrenia populations (Alexander-Bloch et al., 2010; Lynall et al., 2010). This increased global efficiency has been attributed to refined, subtle randomization of network topology (Fornito et al., 2012). It has also been hypothesized to contribute to robustness to random attacks of functional networks in schizophrenia, thus possibly providing a survival advantage (Lynall et al., 2010). That is, whole brain networks are less likely to break off into disconnected islands as regional nodes are removed at random (due to possible disease-caused multifocal brain lesions) (Lynall et al., 2010). This increased efficiency could be speculated to provide a survival advantage, lending greater resilience of global brain function in the face of possible multifocal brain lesions (Lynall et al., 2010). Thus, perhaps those CHR individuals that exhibit intact implicit ToM abilities, and that nonetheless experience clinical impairment and symptoms that put them at risk for psychosis, may develop compensatory neural mechanisms that serve as protective factors for conversion to a psychotic disorder. While this study is unique in linking global efficiency metrics within these networks to implicit ToM abilities, it will be essential for future studies to further delve into this question in order to determine whether global efficiency in these regions serves as a protective factor for at-risk individuals.

The current study elucidates multiple relevant etiological links that may serve to identify precursors of psychotic illness, as well as underlying biological factors. For example, research has shown that neural global efficiency is reduced in older individuals, and that these effects are largely localized to frontal cortical and subcortical regions (Achard and Bullmore, 2007). Perhaps the reduced global efficiency within dmPFC in the MENT network among those CHR individuals that exhibited impaired implicit ToM ability reflects deteriorating network function due to the same factors that put these individuals at risk (e.g. the latent or emerging pathophysiology of psychosis). Even more compelling, pharmacological blockade of dopamine transmission has also been shown to impair global and local efficiency of networks (Achard and Bullmore, 2007). Given widely observed cortical dopamine dysregulation in schizophrenia, this graph metric could serve as a candidate etiological factor informing risk for developing psychosis (Bauer et al., 2012; Bolton and Constantine-Paton, 2018; Gomes and Grace, 2018; Grace and Gomes, 2019).

There are several limitations that ought to be carefully considered when interpreting results. Most importantly, data is cross-sectional, thus causes of ToM deficits and neural underpinnings cannot be fully determined. Comparing CHR with psychotic disorder individuals in terms of implicit versus explicit ToM and involved networks would also be informative. Also, participants completed MRI scans in a separate visit than the SST task. We were interested in trait-level network features and relationships to ToM ability, which would, in theory, not be impacted by this delay in timing. It is also necessary to consider that there was high comorbidity of other Axis I disorders in our CHR sample, and it will be informative for future studies to compare to help-seeking controls with high incidence of Axis I disorders (in order to establish specificity to attenuated psychosis symptoms). Further, the study sample size was adequate but modest, and so lack of power may have precluded our finding of extant relationships with symptoms, for example. In addition, it would be beneficial for future explorations of this question to include multiple measures of social cognition, in order to establish convergence and divergence of social cognitive functions. Relatedly to the above point, limited power prevented us from undertaking a whole brain approach, as well as from exploring other networks that may have been differentially involved in implicit and explicit ToM (in the interest of limiting the number of comparisons). Future studies would benefit from exploring other networks of interest, such as the fronto-parietal and salience networks.

Conflicts of interest

There are no conflicts of interest.

Contributors

Teresa Vargas and Katherine Damme conducted analyses and drafted the manuscript. Vijay Mittal drafted the manuscript, aided in data analysis, interpretation and project conceptualization. Christine Hooker and Henry R. Cowan were consulted with regards to data analysis and result interpretation. Tina Gupta processed the data, including reliability analyses to ensure data quality, and provided feedback on result interpretation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2019.03.013>.

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