

## **Theory of Mind in the Early Course of Schizophrenia**

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## **ABSTRACT**

Theory of mind deficit is a core feature of schizophrenia and is considered a vulnerability marker of the disorder. The majority of studies measuring theory of mind in schizophrenia involve multiple-episode or chronic schizophrenia patients, and therefore it is important to delineate whether these deficits occur before or following illness-onset by assessing high-risk subjects (clinical high risk and ultra-high risk), early-onset psychosis, and first-degree relatives. We address the question of whether theory of mind impairment is specific or a facet of general cognitive impairment in these clinical populations, and incorporate genetic and neuroimaging studies on theory of mind. The review provides a succinct evaluation of the literature, discusses current limitations and proposes future directions.

**Key words:** theory of mind, adolescence, neuroimaging, social cognition, unaffected relatives; high risk, endophenotype; mentalising.

## INTRODUCTION

Schizophrenia is a complex psychiatric disorder with a strong genetic predisposition [1]. Cognitive dysfunction is a well-established feature of schizophrenia, with moderate to severe deficits across a range of domains, including attention, verbal learning and memory, working memory and executive functions [2, 3, 4]. Neurocognitive deficits have consistently been shown to be associated with functional outcome, such as social functioning, social skills, and independent living skills in schizophrenia [5, 6]. Social cognition has been argued to have a strong relationship with work-related social skills and occupational outcome than neurocognition outcome [7].

A key element of social cognition is Theory of Mind (ToM), which refers to the ability of an individual to represent and make attributes about the mental state of another [8]. It has been shown that this capacity is in deficit in psychotic illnesses from the ultra-high risk and first episode stages [9] through to established illness such as schizophrenia [8, 10]. Theory of mind deficits has been shown to be highly associated with community functioning in people with psychosis [9].

A number of different tasks have been developed over the years in order to assess ToM [10]. False belief tasks require the participant to understand that other people with different information about a situation may have other beliefs about the situation. A second order false belief task assesses whether the individual is able to understand that a character in the story has a belief about the beliefs of another character. An intention-inferencing task requires an individual to infer the intention of a character from information provided in a short story. Other tasks examine the capacity of individuals to derive meaning from indirect speech such as irony and metaphors [10].

Theory of mind is a capacity that develops normally through childhood. Children develop the capacity to understand first order false belief (i.e. that other people have different views about a situation from themselves) about the age of 4 years, and second order false belief (that people can have mental representations of the mental states of others) by 6 years of age [11]. As noted, deficits of ToM become apparent before the onset of psychotic disorder [9] and are also present in a variety of other neurodevelopmental disorders including bipolar disorders [12], autism spectrum disorders [13, 14], attention-deficit/hyperactivity disorder [15, 16] and specific language impairment [17, 18].

Over the last two decades there has been an upsurge of research interest in understanding ToM in schizophrenia. In this brief, not exhaustive review, we provide an evaluation of the literature on ToM deficits in children and adolescents with schizophrenia, clinical high risk (CHR) and ultra-high risk (UHR) populations, and first-degree relatives. We discuss the association of ToM with other cognitive processes, and broadly identify the genetic basis of ToM deficits in schizophrenia. A selection of key neuroimaging studies using MRI and functional neuroimaging techniques are described and evaluated. Finally, we provide conclusions and suggestions for future work.

## **2. THEORY OF MIND STUDIES**

### ***2.1 Children and adolescents with schizophrenia***

Early onset schizophrenia (EOS) presents in childhood or adolescence typically before the age of 18, is a relatively rare, clinically severe and chronic form of the illness [19, 20]. EOS is associated with greater disease severity [21-24], developmental delays [25-28], higher rates of chromosomal abnormalities and greater burden of copy number variants [29-33], and poor prognosis [34-36] compared with the adult onset counterpart. Furthermore, patients with EOS demonstrate significant cognitive impairments in specific domains, mainly general intellectual ability [36-42], memory [43-47], attention [43, 48, 49], and executive function [46, 48, 50, 51]. Studying early-onset cases may provide important insights into the etiopathogenesis of the disorder [50-51]. However, there has been limited research addressing impairments in social cognition in young people with schizophrenia.

Over the past several decades, ToM deficits were considered unique to autism spectrum disorder [52], however subsequent research revealed that ToM deficits also appear to develop in schizophrenia [53, 54]. Frith [53] suggested that schizophrenia may represent a disorder of mental state representations, based on evidence that ToM deficits are related to positive symptoms. Langdon and coworkers stated that the positive symptoms are a form of hyper-mentalizing, and ToM in schizophrenia appears to be unsynchronized either as an impairment or inflexibility of understanding social interactions and over-attribution of mental states and the intentions of others [55]. Pilowsky et al. [56] compared ToM abilities in COS patients, children with high-

functioning autism and typically developing (TD) children using a ToM test battery, specifically the fact and value belief task, deception task, and false belief task. The results showed that compared with TD children, COS patients showed no difference on the fact and value tasks, and performance was significantly better on the deception task. However, patients with COS performed significantly worse on the false belief task compared with TD children. Additionally the study revealed that both clinical groups showed ToM deficits in measures underpinning first- and second-order task demands. Some authors have argued that patients with COS may have intact ToM abilities until their first psychotic episode [53].

## ***2.2 First-episode psychosis***

Several studies have consistently reported that first-episode psychosis present with social cognitive impairments, suggesting that these impairments may be an underlying trait at the time of illness onset [57, 58]. A few studies that have examined social cognition in first-episode psychosis report deficits in facial affect recognition compared with non-psychiatric controls [58-61]. Inoue and colleagues [62] investigated ToM ability in first-episode schizophrenia in remission and matched controls, using a cartoon picture story which comprised of a first-order and second-order false belief, a reality question and a tactical deception. There was a significant difference between groups on sequencing of the cartoon story. Additionally, patients in remission underperformed on the second order false belief task compared with controls, and the sum score of all outcome variables showed that the first-episode group performed significantly less well than controls. Another study used the Reading the Mind in the Eyes Test Revised to measure ToM in first-episode schizophrenia compared with outpatients with non-psychotic major depressive disorder, individuals in the general community, and students from an undergraduate university course [63]. Patients with schizophrenia showed a poor total accuracy compared with community controls and university controls but no difference compared with the depression group. The findings support the notion that first-episode patients show specific first-order ToM impairments, which has been reported in previous studies [64, 65].

Several lines of evidence demonstrate ToM deficits in patients with first-episode psychosis [62, 66]. Studying this population is particularly fruitful in understanding the precise illness process when ToM impairments occurs since there are fewer effects of

long-term medication use and prolonged duration of psychosis. Achim and colleagues [67] investigated ToM using a combination of mentalizing stories (hinting task, false belief task, faux-pas test and the strange stories test) in 31 first-episode psychosis patients and 31 matched controls. Compared with other tasks which measured social cue recognition and social knowledge, the greatest impairments in first-episode psychosis patients were reported in mentalizing tasks. Similar findings have been reported in a study utilising the Hinting task and the interpretation of visual jokes task to measure ToM in first-episode psychosis, which showed the largest effect size for the ToM tasks [68].

A recent study used a variety of measures of social cognition, namely the Bell-Lysake Emotional Recognition Task, Hinting Task [53], and the Reading the Mind in the Eyes Test, in a group of first episode psychosis (n=26), participants with prolonged psychosis (n=72), and a psychiatric normal controls group (n=14) [69]. The results showed no difference on any measures between first-episode and prolonged psychosis cohort, however first-episode patients performed significantly less well than psychiatric controls on the eyes test (total score) and hinting task. Langdon and co-workers [70] studied mentalising in first-episode patients (n=23) and matched controls (n=19) using three measures: non-verbal picture-sequencing task, joke appreciation task, and story comprehension task. The authors reported large deficits in ToM (among other neurocognitive measures such as verbal memory and semantic fluency) in first-episode patients compared with healthy controls. These findings harmonize with evidence that ToM impairments occur in the early stages of illness [71]. Adopting a family-based case-control design, Ho and colleagues [72] measured first-episode schizophrenia and healthy controls using the (a) Chinese version of the computerized Yoni Task, which consists of first- and second-order mental state inferences (cognitive ToM, affective ToM, and physical inference); (b) Faux Pas task developed from the Faux Pas Recognition test. Contrary to previous studies [73, 74], this study showed no group differences in the first-order ToM tasks, however patients performed less well on cognitive and affective components of the second-order mentalisation task compared with controls. Additionally, first-episode patients performed significantly less well on the faux pas recognition and understanding questions (no difference on control questions) in comparison with healthy controls [72].

First-episode schizophrenia patients show first-order ToM deficits, however there are some discrepancies in the findings. The evidence suggests ToM deficits might be a

trait marker for schizophrenia. An important question is whether ToM impairments are attributed to deficits in other neurocognitive functions, such as verbal learning and memory, attention, and executive function.

### ***2.3 Clinical High Risk and Ultra-High Risk for Psychosis***

There has been an upsurge of research interest in studying “ultra-high risk” (UHR) and “clinical high risk” (CHR) populations. Cognitive deficits are reported in individuals who are at CHR for psychosis [75-77], however there are relatively few studies on social cognitive deficits or the relative degree of impairments between first-episode and UHR and CHR populations [78]. Stanford and colleagues [79] measured ToM using the first and second-order false belief cartoon tasks and two higher-order task (‘Strange Stories Task’ and the ‘Reading the Mind in the Eyes’ task) in a group of 63 CHR and 24 healthy youths, and 13 schizophrenia patients and 14 adult controls. They reported significant errors in the first- and second-order ToM task in schizophrenic patients compared with controls. There was no difference in ToM performance between CHR patients and the matched youth comparison group. Further, the authors found that performance on the high-order ToM tasks was ‘undeveloped’ in the high risk group and normal youths, suggesting that higher-order cognitive processes and executive function develops after a full transition from adolescence to adulthood. Another study used three different measures of social cognition (emotion processing was measured using the Mayer-Salovey-Caruso Emotional Test, ToM was assessed using the Awareness of Social Inference Test, and social relationships measured using the Relationships Across Domains Test) in three independent groups, namely (a) 50 UHR for psychosis and 34 matched controls, (b) 81 first-episode schizophrenia patients, and 46 matched controls; (c) 53 chronic schizophrenia patients versus 47 matched normal volunteers [5]. The results showed poor performance across all social cognitive measures in all clinical groups, however group differences were found to be similar regardless of phase of illness [5]. On the contrary, Thompson and coworkers [68] used three specialized measures of social cognition, including ToM (hinting task and interpretation of visual jokes), facial and vocal recognition (Diagnostic Assessment of Nonverbal accuracy) and social perception (Mayer-Salovey-Caruso Emotional Intelligence Test) in a group of UHR subjects, first-episode psychosis patients and normal controls, where the authors found that UHR patients performed at an intermediate level on all social cognition tasks,

with first-episode psychosis patients performing worse compared with controls. Further research is required on ToM performance in CHR and UHR subjects to delineate whether ToM is a risk (predictor) factor for those who make a transition to psychosis.

#### ***2.4 First-degree relatives of schizophrenia***

Over the last decade there is been an upsurge of research interest in studying non-psychotic relatives of patients to evaluate whether they have a genetic predisposition to impairments in ToM, which are comparable to reported evidence of cognitive impairments in first-degree relatives of schizophrenia [76, 80, 81].

Versmissen and colleagues investigated mentalising, using the Hinting Task, in varying levels of psychosis vulnerability groups, namely 40 patients with psychosis, 49 nonpsychotic biological relatives (familial risk), 41 controls with high levels of psychotic experiences and 54 healthy controls, to assess the degree of ToM impairments [82]. The authors found that relatives performed at an attenuated level compared with controls, while there was a strong association between task performance and clinical patient group. A study by Anselmetti et al. [83] assessed relatives of schizophrenia patients and healthy controls using the ToM picture sequencing task, and reported ToM deficits in parents (separate score for mother and father) of patients with schizophrenia. Similarly, other studies have found genetic liability effects in first-degree relatives [84-88]. Montag and colleagues reported impairments in ToM reasoning in parents and siblings of schizophrenic patients (not explained by other aspects of neurocognitive measures) using the 'Movie for the Assessment of Social Cognition' video-based task [87]. de Achával and colleagues [89] found that unaffected first-degree relatives showed underperformance on the Faces Test, Reading the Mind in the Eyes Test and the detection of social Faux Pas. Similar to previous studies, as above, ToM impairments were reported independent of performance in general cognitive processes.

Although there are numerous studies reporting ToM impairments in first-degree relatives, some studies have shown no differences in ToM reasoning between non-psychotic first-degree relatives and controls. Some studies measuring the ability to identify mental states of a person through the images (depicted in a photograph) of eyes [90] and the Hinting task (comprehension Hinting statements) [91] showed no impairments in ToM in non-psychotic relatives of patients with schizophrenia compared with controls. Pentaraki and colleagues [92] measured ToM using the first-order and



second-order ToM stories, and the Revised Eyes Test in patients with schizophrenia, their unaffected parents (separate score for father and mother), compared with matched healthy controls according to group. They reported significant deficits in first-order ToM tasks (but not second-order ToM), however these were related to deficits in general intellectual ability.

The evidence suggests that unaffected relatives perform significantly less well than controls on ToM performance, and these differences appear to be intermediate to individuals with schizophrenia. Furthermore, the magnitude of deficits appear to be similar to numerous cognitive studies reported in relatives [80, 81]

### **ASSOCIATION OF THEORY OF MIND WITH OTHER COGNITIVE DOMAINS**

First-episode psychosis patients demonstrate deficits in ToM tasks compared with healthy controls [62, 63 66]; however it is unclear whether ToM impairments interact with or is explained by general cognitive deficits found in schizophrenia. A quantitative review of 204 studies yielding 22 mean effect sizes was carried out by Heinrichs and Zakzanis [93] to measure global cognitive function and selective measure of specific cognitive domains. They reported moderate to large effect size for all neurocognitive measures, where mentalizing impairments were ranked fourth. Several studies reviewed above co-varied for age, symptoms, general intellectual ability and other cognitive variables, and point out that patients with schizophrenia show specific ToM impairments. Koelkebeck and colleagues [94] investigated ToM ability in relation to other cognitive functions and clinical measures in 23 first-episode schizophrenia patients and matched healthy controls, and underlined previous studies suggesting a moderate influence of general cognitive deficits and limited influence of clinical symptoms, empathy or conditions of alexithymia on ToM performance. In a recent study on first-episode schizophrenia (n=36) and a matched control group, Bliksted et al. [95] showed that social cognition contributed to 24% of the variance, and theory of mind performance were the other multivariate variability, while cognition and symptom scores contributed to a small proportion of the patient group, suggesting that impairments in social cognition may have two subtypes: one type may be associated with general intellectual ability, while the second version may contribute to less complex forms of social cognition not influenced by IQ. The studies shed light on the complex nature of social cognition in

schizophrenia, and its relation with intelligence. There is a need to investigate both versions of this distinct pattern in a larger more-focused study.

## **GENETIC CONTRIBUTION OF THEORY OF MIND DEFICITS**

There is a relative paucity of studies of the genetic contribution to ToM deficits in schizophrenia. Several studies have investigated the influence of single nucleotide polymorphisms (SNP) for the development ToM deficits in schizophrenia. Evidence suggests a role of the serotonergic and dopaminergic system in mentalizing ability. Abnormalities in the serotonergic system in schizophrenia lead to cognitive deficits in schizophrenia which influence ToM performance, argued to be mediated by executive function abilities [96-99].

The serotonin receptor 1A (*5HT1A-R*) has been associated with several cognitive domains, including executive control, information processing, and episodic memory [100, 101], and activation of the 5HT1A receptors increases dopamine release in the prefrontal cortex [102, 103]. In a sample of 118 patients with schizophrenia, Bosia and colleagues [103] investigated the effect of *5HT1A-R* -1019 C/G functional polymorphism on ToM performance, as measured using the ToM picture sequencing task, and reported that CC genotype carriers performed significantly better on the picture sequencing task compared with CG and GG genotypes. The study confirmed the influence of 5HT1A-R on cognitive function and its role in the ability to mentalize [103]. Several lines of evidence support a dysregulation of subcortical dopamine system as an etiology of schizophrenia [104-106]. The role of dopamine transmission in impairments in the ToM in schizophrenia has been explored between genes encoding dopamine receptor D2 (*DRD2*) and the enzyme of catecholamine metabolism, catechol-O-methyltransferase (*COMT*). Alfimova et al. [107] investigated the association between ToM, as measured using the second-order false beliefs task, and *DRD2* receptor and *COMT* Val158Met polymorphism in 209 individuals with schizophrenia and 172 healthy controls. The authors reported a significant gender effect and an association between the *COMT* gene and effective performance in solving the false beliefs tasks in schizophrenia. Females who were Met158 allele carriers underperformed on the task compared with Val/Val genotype, while males with the Val/Val genotype showed marked

impairments on the task compared with the Met158 allele group [107]. The evidence suggests that the coupling between the serotonergic and dopaminergic system is critical for the development of ToM.

Several studies have reported that the SNP rs1344706 of the zinc-finger protein gene (*ZNF804A*) is strongly implicated in schizophrenia [108-110]. Hargreaves et al. [111] studied the association between performance on two mental state reasoning tasks (Eyes of the Mind and Hinting tasks) and a common variant within *ZNF804A* in patients with schizophrenia and healthy controls. Contrary to a previous study from the same group in healthy volunteers [112], the authors did not find an association between the risk allele in either group, however healthy controls (not schizophrenia patients) with the A risk allele at rs1344706 showed greater personalizing bias scores compared with non-carriers [111]. The study underlines the differences in gene by cognitive (ToM) phenotype results between schizophrenia patients and controls, and emphasizes the need to exercise caution in applying findings based on healthy participants to exploring the neural mechanisms in clinical patients, particularly concerning the influence of *ZNF804A*.

Evidence suggests that individual genes have been associated with ToM in schizophrenia. However, the precise influence of gene expression on mentalizing ability in this heterogeneous and complex disorder has not been fully explored. Further research is warranted to confirm ToM as a cognitive endophenotype for schizophrenia.

## **NEUROIMAGING STUDIES OF THEORY OF MIND DEFICITS IN SCHIZOPHRENIA**

Neuroimaging studies in healthy population has suggested a ToM brain network, of which the medial prefrontal region (mPFC) and the temporo-parietal junction (TPJ) have been found to be the most robust regions involved in mentalizing processing [113-115]. Different paradigms have been adopted in previous fMRI studies to examine the neural correlates of ToM and different types of the stimuli have been used, such as cartoon stories, video of the biological animation, and mind in the eyes. The common feature of such tasks is asking participants to “referring others’ mental state”. For example, in a cartoon mentalizing task, a series of comic strips were presented and participants were asked to choose an appropriate ending for the story

with referring the intentions of the characters [116, 117]. Most recently, a meta-analysis reviewed imaging studies adopted different ToM tasks and evidenced a core network including mPFC and posterior TPJ which is commonly activated during the mentalising across different tasks or stimuli types [118].

Both brain structural and functional abnormalities associated with the ToM deficits have been reported in patients with schizophrenia. For example, impaired ToM performance in schizophrenia patients were found to be associated with the reduction of grey matter volume in the ventral medial prefrontal cortex [119] and the superior temporal sulcus (STS) [120-121]. In addition, adopting the functional imaging tasks, previous studies also found the reduced brain activities in the mPFC and the TPJ in patients with schizophrenia [122]. An imaging study adopted a false belief task in patients with schizophrenia or schizoaffective disorders and healthy controls, and requests participants to read the stories on the screen, understand the false content and then metallize the mental states to the characters in the story. The results showed that, compared to controls, patients with schizophrenia had reduced activity in mPFC during the ToM task; in addition, further analysis also showed that the reduced activity in mPFC is related to the social anhedonia and social functioning [123]. Lee et al. [124] conducted an fMRI study in patients with schizophrenia during an acute episode and after recovery. The results showed that the brain activity in mPFC of schizophrenia patients increased after recovery compared to their acute episode [124]. On the contrary, previous studies have found increased brain activation in individuals at-risk (prodromal) of developing schizophrenia [125] as well as individuals with psychosis proneness [126]. The former study was conducted in prodromal individuals for psychosis (n=10, mean age = 25.5 years) using the mental states attribution task presented using cartoons [125]. The results showed that prodromal individuals showed greater activation in the ToM neural network [including prefrontal cortex, the posterior cingulate and temporo-parietal cortex] than healthy controls. Modinos and colleagues [126] examined the neural correlates of ToM in individuals with high psychosis proneness (n=18, mean age 19.8, range from 18 to 24 years) measured by the positive subscale of the Community Assessment of Psychic Experiences questionnaire (CAPE). They adopted the Yoni task developed by Shamay-Tsoory et al. [127] which presents a face in the middle and four figures of objects in the corners of the screen and consists of first- and second- order attributions of the cognitive and affective mental states. The results showed that

individuals with high psychosis proneness had stronger activations in dorsomedial and lateral prefrontal regions than the matched controls during the second order mentalizing. Most recently, researchers have also reported positive correlations between negative schizotypy measured by the Chapman Social Anhedonia Scale [128] and brain activation changes during a cartoon mentalising task in the mPFC and the TPJ in a college sample [129]. These findings suggest an important role of the mPFC during the mentalising for the development of the schizophrenia which might be a compensation mechanism in high risk population and also an indicator for the schizophrenia patients.

Although behavioural studies have shown that first-degree relatives of patients with schizophrenia also have deficits on ToM, imaging studies in this sample are quite scarce. Marjoram et al. [88] conducted the first neuroimaging study in relatives of schizophrenia patients and they used a visual joke paradigm with one condition requires mentalizing ability to understand jokes or another condition does not. The results showed that relatives who were symptomatic showed less activation in bilateral prefrontal regions than symptomatic relatives as well as controls [88]. Adopting a false belief imaging task, the reduced brain activation in the TPJ was also observed in 19 individuals with familial high risk (with at least two affected relatives) [130].

Differentiating self and others is another important component during the mentalising. Recently, an fMRI study examined the neural correlates of the self-inhibition in ToM in eighteen individuals with high psychosis proneness measured by the positive subscale of CAPE [131]. The task consists of the movie clips presenting the false belief situation between two real persons and manipulated to be high and low inhibition conditions or control condition. The results showed that individuals with high psychosis proneness showed greater activation in inferior frontal gyrus during the self-perspective inhibition but not during the stop signal task than individuals with low psychosis proneness. The researchers suggest that individuals with high psychosis proneness need more resources for inhibiting the self-perspective when they mentalized to others [131].

The fMRI studies of ToM in early stage of the schizophrenia spectrum, such as individuals with psychosis proneness, prodromal and first episode patients, and the unaffected relatives are still limited. There is a pressing need for more research to assess the degree of social impairment and their neural correlates in various clinical

groups to understand the neurodevelopmental features related to the ToM deficits of schizophrenia. Particularly, the reverse activation pattern of the mPFC in established schizophrenia patients and high-risk populations calls for further investigation. In addition, the associations between dimensions of symptoms, executive functions and neural correlates of the ToM need to be extensively examined in future studies.

## **CONCLUSIONS**

Theory of mind impairments in first episode schizophrenia appear to be similar to chronic schizophrenia [132, 133], and the studies suggest that these patients show specific deficits in ToM in the early stages of illness and are not influenced by symptom severity, course of illness, long-term exposure to medication, or other potential predictors of ToM. Unaffected relatives of schizophrenia patients, including parents, display deficits in ToM and other social cognitive measures, performing at an intermediate level to patients and normal controls. The findings suggest that the familial traits are rather specific, and are not explained by additional factors such as age, years of education, IQ, and general cognitive abilities. Future work should focus on longitudinal investigation of ToM impairments in first-degree relatives. Additionally it is important to discover the neuropsychometric properties of the various ToM measures used in this field. Further research is likely to improve early detection and prediction of schizophrenia, by understanding the developmental trajectories of the mentalising process in those who make a transition to psychosis.

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