CNS Spectrums (2017), **22**, 450–462.
doi:10.1017/S1092852916000687

REVIEW ARTICLE

Clinical and therapeutic role of mentalization in schizophrenia—a review

Trisevgeni Dimopoulou,[1] *Frank I. Tarazi,*[2] *and Evangelia M. Tsapakis*[1,2]*

[1] 'Aghios Charalambos' Mental Health Center, Heraklion, Crete, Greece
[2] Department of Psychiatry and Neuroscience Program, Harvard Medical School and McLean Hospital, Boston, Massachusetts, USA

Recent empirical findings from clinical and genetic studies suggest that mentalization, a key area of social cognition, is a distinct construct, although it is closely related to the neurocognitive deficits and symptoms of schizophrenia. Mentalization contributes a great deal to impaired social functioning. Current measures often display methodological problems, and many aspects should be taken into account when assessing mentalization. Moreover, advances in cognitive and affective neurosciences have led to the development of more advanced behavioral methods to assess the relationship between cognitive functions, symptoms, and social cognition based on their underlying neural mechanisms. The development of assessment tools that better examine the neural circuitry of such relationships may lead to the development of new psychosocial and pharmacological treatments.

Received 14 July 2016; Accepted 1 September 2016; First published online 21 February 2017

Key words: First episode patients, mentalization, neurocognitive deficits, pharmacotherapy, schizophrenia, social functioning, theory of mind.

Introduction

Deficits in social functioning are common and prominent in schizophrenia spectrum disorders, and they often serve as predictors of outcome.[1] Impairment in social functioning in schizophrenia is best defined by social isolation and withdrawal, both aspects playing very important roles in the clinical profile of the disorder. Interpersonal functioning in schizophrenia remains essentially unexplored and awaits systematic investigation.[2] Targeting, therefore, proximal domains of social functioning has lately become front-line treatment for the illness.[3] Social cognition is a broad, multifaceted construct that refers to the mental processes that underlie interpersonal functioning and offers great conceptual proximity to social functioning.[4,5] Social cognition is one of the 7 domains of the National Institute of Mental Health (NIMH)-sponsored Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery, which involves 5 areas: theory of mind (ToM), emotion processing, social perception, social knowledge, and social attribution.[6,7] Empirical evidence has shown that social cognition is significantly impaired in individuals with schizophrenia, and is a better predictor of poor functional outcomes than symptoms and neurocognitive deficits.[8,9]

* Address for correspondence: Dr. Evangelia M. Tsapakis, 'Aghios Charalambos' Mental Health Center, 82, M. Alexandrou Street, 71305 Heraklion, Crete, Greece.
(Email: emtsapakis@doctors.org.uk)

Mentalization

Bateman and Fogany[10] defined mentalization as the capacity to conceive conscious and unconscious mental states in oneself and others. It is the person's ability to think about and reflect on personal experiences–to formulate interpretations about their own and others' behavior. Mentalization is a multidimensional construct that incorporates 3 dimensions: implicit and explicit mode of functioning, self/other-oriented mentalization, and cognitive/affective mentalization.[11] Mentalization deficits have been established in schizophrenia[12] as well as in other psychiatric and neurologic disorders, such as autism spectrum disorders,[13] mood disorders,[14] frontotemporal dementia,[15] and severe traumatic brain injury.[16]

Theory of Mind (ToM)

ToM is often used interchangeably with the term mentalization, but offers greater explanatory value as it provides the basis of the mentalization process. The term ToM refers to the cognitive ability to attribute mental states to self and others, as well as understanding the link between mental states and action.[17] ToM and emotion

perception are considered to be the most important processes for social behavior. Although there is a conceptual overlap between the two constructs, emotion perception is a low-level perceptual process that precedes ToM, whereas the latter requires higher-level processing.[18] This impressive human ability has an important social function: it allows us to navigate the personal and social world by explaining past behavior, and anticipating and predicting future actions. This review focuses on research findings related to the construct of ToM and critically presents current methods of ToM assessment and treatment, both pharmacological and psychosocial, using data retrieved from MEDLINE/PubMed, the Cochrane Database of Systematic Reviews, and the ClinicalTrials.gov databases.

Processes of ToM

Implicit and explicit ToM

Dual process theorists claim that there are 2 kinds of social mentalizing that work independently of one another and are served by exclusive neural networks: implicit (ie, fast and automatic) and explicit (ie, slow and controlled) ToM.[19] This claim is not, however, supported by empirical findings. A meta-analysis of 200 studies suggested that implicit and explicit ToM share the same early timing and the same core brain areas.[20] In addition, implicit processes may provide a quick default judgment to an assessment, which may later be either accepted or rejected by explicit reasoning.[21] Schneider *et al*[22] found that implicit mentalizing occurs in an uncontrollable and unintentional manner. Furthermore, implicit ToM appears to rely heavily on visual attention, and patients with schizophrenia are less likely to focus on the faces of others. ToM deficits in schizophrenia could, thus, be explained at least partly by impaired attention toward gaze orientation.[23]

Self and other referential processing

Perspective taking is the ability to see the world from another person's point of view. As such, it relies heavily on ToM abilities in order to understand other peoples' mental states, which may be different from one's own. It requires an implicit understanding of the behavior of others, while the person is still able to maintain a coherent sense of self to allow for self-other discrimination.[24] Deficits in perspective taking have long been considered central to both autism and schizophrenia.[25] In schizophrenia, the disrupted sense of self-other discrimination may result from malfunction of multisensory integration at the level of the ventral premotor cortex, which prevents a person from being able to control or switch between neural representations attributed to the self and to other people.[26]

Affective and cognitive ToM

Shamay-Tsoory *et al*[27] proposed the existence of cognitive and affective aspects of ToM. The cognitive construct involves inferring the mental states of other people, and the effectiveness of the actions controlled by this aspect are correlated to the functioning of cognitive abilities. On the other hand, the affective aspect involves the recognition of emotions based on facial expressions and movements. There seems to be an overlapping relationship between the affective process of ToM and emotion perception.[28] Findings from neuroimaging studies have shown some common identified regions, such as the medial prefrontal cortex and the temporal lobe areas. The main differences between them emerge from the perceptual, cognitive, and emotional demands of each process, where emotion perception is regarded as a low-level perceptual process necessary to decode affective cues, while ToM is usually seen as a higher-level cognitive process involving mental state deduction.[29] Cognitive ToM appears to involve the precuneus and cuneus, as well as regions in the temporal lobes bilaterally, whereas affective ToM involves the prefrontal cortical area and smaller regions in the posterior cingulate cortex and the basal ganglia.[30] The involvement of the basal ganglia in affective ToM could provide a motor control component that is known to influence reward learning and cognitive and reason functioning.[31,32]

Theories of ToM

The theories to account for the development of ToM are grouped into 3 major categories: theory-theory, simulation theory, and modularity theory.

Theory-theory

The term "theory-theory" postulates that knowledge about the mind derives from a kind of theory by which people try to predict and explain behavior in terms of its causation by beliefs, intentions, emotions, and traits of character.[33] In line with the theory-theory, conceptual change occurs during development, and that should be reflected in the brain. However, conceptual change at a neural level is difficult to examine. During infancy and early childhood, mentalizing takes an implicit form, such that information processing is spontaneous, automatic, and inaccessible to control and consciousness, whereas from late childhood onward, processing requires awareness, introspection, and control.[21] Based on the notion that implicit and explicit mentalizing are 2 distinct cognitive processes, some studies have found that the amygdala and the orbitofrontal cortex are linked to implicit social processes, and that the dorsolateral prefrontal cortex plays an important role in explicit

https://doi.org/10.1017/S1092852916000687 Published online by Cambridge University Press

social processes.[34,35] Nevertheless, a growing body of evidence has shown that there is a neural interaction between these social cognitive processes, and that this interaction has been associated with more effective cognitive performances.[36] In addition, the neural interactions involved during social cognitive processes are moderated by several genetic polymorphisms, such as those in brain-derived neurotrophic factor (BDNF), catechol-*O*-methyltransferase (COMT), and serotonin transporter genes.[34] A recent trend emerging from imaging studies is a common mentalizing neural network that is more prone to the content of a certain inference rather than the nature of the inference (ie, implicit or explicit).[37]

Simulation theory (ST)

Increasing attention has been given to an alternative account of mentalizing known as simulation theory (ST). It describes the ability to take the perspective of another person. ST relies on direct access to the individual's psychological states in order to make mental state attributions. ST suggests that people first inhibit their own perspectives to be able to infer about other peoples' perspectives. The problem may arise when self-inhibition fails and the simulated states are excessively influenced by egocentric tendencies. Deficits in perspective taking have long been considered central to schizophrenia.[25] According to ST, certain neural systems are responsible for imaginative processes during childhood, and these become more efficient during development.[36] Empirical data from studies utilizing different neuroimaging techniques have shown 2 major neural systems that are involved in mentalizing: the cortical midline structures and the mirror neuron system.[37] The mirror neuron system has been suggested as a deficient system underlying impairment of ToM in schizophrenia.[38] Nevertheless, others have argued that a more abstract neural mentalizing network may be necessary to efficiently process inner states.[39]

Modularity theory

Modularity theory postulates that ToM development is driven by an innate neural mechanism dedicated to mental state reasoning. Although experience may be important in triggering this mechanism, it cannot revise the mechanism's basic nature.[40] A particular brain region or a brain network would need to be consistently activated whenever individuals engage in mental state reasoning throughout their lifespan. More specifically, certain brain regions, such as the medial prefrontal cortex, the bilateral middle temporal gyrus, and the bilateral temporoparietal junction, respond selectively to ToM input.[41,42] The absence of robust neuroimaging evidence, however, does not allow for fully distinguishing between theories of ToM, and therefore further research is needed to investigate how ToM develops in the brain.[36]

Other Theories of ToM

Executive functions

It has been argued that information about mental states is processed entirely by executive functions (ie, higher-order cognitive processes, such as planning, shifting, and coordination of actions), and therefore, operation of implicit ToM is controlled by executive resources.[43] Bailey and Henry[44] examined the hypothesis that in order to take the perspective of another person, the self-perspective must first be inhibited, and as such, executive function failures may contribute to the ToM difficulties that have been observed in schizophrenia. The authors found that schizophrenia patients displayed impairment in ToM; however, this was not related to self-perspective inhibition but to another form of perspective taking.

Inflammation

Alterations in peripheral cytokines have been shown to play a role in the pathophysiology of schizophrenia, and therefore, inflammation could be held responsible for the impairment in social cognition processes.[45] The effects of acute peripheral inflammation on ToM abilities has been investigated in a double-blind, randomized, crossover functional magnetic resonance imaging (fMRI) study with healthy participants who were either injected with bacterial lipopolysaccharide or saline.[46] Findings showed that ToM performance was not worsened by acute inflammatory response, but it was linked to increased activation in relevant ToM brain regions. Similarly, Moieni *et al*[47] examined whether exposure to an experimental inflammatory challenge (ie, inflammatory-induced conditions via endotoxin) led to changes in ToM. Healthy participants were randomly assigned to receive either endotoxin or placebo, and then they complete the Reading the Mind in the Eyes test at baseline and at the peak of inflammatory response for the endotoxin group. Findings showed that the endotoxin group performed lower in ToM task compared to controls, indicating that inflammation can lead to impairment in inferring mental states.

Method of Assessment

Given the significance of ToM to social functioning, it is important that valid and reliable measures are utilized in clinical research. However, current measures often display methodological problems with lack of established psychometric properties.[8] In addition, several ToM tasks have been criticized for their low ecological validity.[48] Finally, many aspects and/or components

https://doi.org/10.1017/S1092852916000687 Published online by Cambridge University Press

TABLE 1. Methods of assessment of theory of mind

	Name of task	Reference(s)
Verbal tasks		
	False Belief Task	49, 50, 51, 52, 53
	Strange Stories Test	54, 55, 56, 57
	Hinting Task Test	58, 56, 59
	Faux Pas Recognition Test	60, 9, 38, 61
	Sarcasm Comprehension Test	62, 63
Visual Tasks		
	Reading the Mind in the Eyes Task	64, 65, 56, 66, 67
	Inference Intention Task	68, 69
	Moving Shapes Paradigm	70, 71, 72
Verbal–visual tasks		
	Picture Sequencing Task	73, 69, 74, 75
	Yoni Cartoon Eye Gaze Inference Task	27, 29, 76
	Inhibition of Imitation Tasks	77, 78
Audio-visual tasks		
	Movie for Assessing Social Cognition (MASC)	79, 80
	The Awareness of Social Inference Task	81, 82, 83, 67
	Director Task	84
Self-report and observer-based rating scales		
	Theory of Mind Assessment Scale	85
	Observable Social Cognition: A Rating Scale	86
	Metacognitive Assessment Scale	87, 88, 89

should be taken into account when measuring ToM (.., implicit/explicit form of reasoning, cognitive/affective process, self or others' mental states), as they may not be relevant in all clinical conditions or experimental purposes. See Table 1 for a list of methods of assessment for ToM.

Theory of Mind in Schizophrenia

Many studies that tried to evaluate the role of social cognition and mentalization in schizophrenia have focused on investigating ToM. The impaired ability of schizophrenia patients to evaluate and predict other people's mental states and/or their own is a well-established deficit in schizophrenia that might explain some aspects of the patients' social dysfunction and poor social outcomes.[90] The question arises: can mentalizing deficits in schizophrenia be considered a trait associated with the illness, or are they a state dependent on symptomatic exacerbation? Although some data support the notion that ToM deficits are heightened in acute phases of the illness, several lines of research have yielded evidence suggesting that the deficit is a trait.

State approach

Deficits in ToM (failure to monitor our own and other peoples' mental states and behaviors) may contribute to the positive and negative symptoms as well as social dysfunction in schizophrenia. For instance, schizophrenia patients, instead of taking beliefs as subjective representations of reality, often equate their representations with reality and may therefore experience difficulty at distinguishing between subjectivity and objectivity. They thus maintain false beliefs in the form of delusional convictions. Furthermore, failing to detect other people's social signals and intentions may lead to a breakdown of communication and eventually social isolation. Patients with psychotic symptoms may be aware of other people's mental states, but as they fail to use contextual information, they may be unable to make correct inferences about what these mental states are. They may, however, still be capable of compensating for their impaired ToM by using intelligence when not under pressure.[91] Moreover, patients with prominent negative symptoms exhibit the most impaired ToM, as they lack the capacity to represent mental states. Finally, patients whose symptoms are in remission and patients with passivity symptoms are predicted to have normal mentalizing abilities. Recent findings from patients with schizophrenia and matched controls showed that alterations in social interaction in patients with schizophrenia are related to oscillatory brain activity, suggesting maladjustment of expectation when patients face social and nonsocial agents.[92] Such alterations are related to psychotic symptoms and could guide further therapies for improving social functioning in patients with schizophrenia.

The relationship between clinical symptoms and ToM deficits was evaluated in patients with schizophrenia or schizoaffective disorder, and showed that

https://doi.org/10.1017/S1092852916000687 Published online by Cambridge University Press

overmentalizing was weakly associated with positive symptoms but disorganised symptoms were related to undermentalizing.[12] Another study showed that negative symptoms in schizophrenia were associated with lack of ToM, whereas positive symptoms were associated with "overmentalizing."[80] Moreover, a study in first episode psychosis (FEP) patients reported that metacognitive impairments of FEP were significantly correlated with greater negative symptoms and poorer functioning.[93] Lincoln *et al*[94] examined the hypothesis that social cognitive processes, including ToM, are involved in the formation and maintenance of negative symptoms in schizophrenia, and showed that impairment in ToM abilities was significantly associated with negative symptoms even after controlling for neurocognition and depression, but only in patients with lower self-esteem. These findings provide further support to the concept that the level of perceived criticism from family members can predict both the presence and the severity of negative symptoms.

Moreover, ToM ability in FEP patients was significantly related to the presence of positive symptoms but not alexithymia and empathy, and neurocognitive deficits appeared to have a moderate effect on ToM performance.[95] Another study[96] examined ToM ability and its relationship to symptoms in patients with psychosis, and found that schizophrenia patients exhibited impairment in ToM that was significantly associated with prominent negative but not with positive symptoms. Furthermore, the association between clinical symptoms and ToM abilities was examined in patients with schizophrenia, patients with affective disorder, and healthy controls.[97] Individuals with high levels of delusions and hallucinations performed significantly worse on ToM tasks, regardless of diagnosis, implying that ToM impairment is not exclusive to schizophrenia.

Trait approach

The trait approach suggests that ToM deficits exist prior to the onset of schizophrenia, and therefore the extent of ToM impairment depends on the level of abnormal development of ToM. Empirical evidence derived from comparison studies, studies of individuals with high risk of developing schizophrenia, family members of schizophrenia patients, and patients with FEP suggests that ToM is a trait of schizophrenia.

Comparison studies

The relationship between ToM, symptoms, and neurocognitive deficits was investigated in recent-onset, stabilized, schizophrenia patients compared to matched, healthy controls at baseline and after 6 months.[98] Schizophrenia patients scored significantly lower in ToM, and impairment in mentalizing was evident and stable in remitted patients as well. Moreover, ToM was significantly correlated with neurocognition, negative symptoms, and role functioning. The authors suggested that ToM possibly influences negative symptoms, which in turn impacts role functioning. Ioannidi *et al*[99] compared the level of ToM capacity in schizophrenia vs euthymic bipolar disorder patients. Schizophrenia patients exhibited impairment in both affective and cognitive ToM, but bipolar patients showed a specific deficit only in the cognitive domain of ToM. When the association of positive symptoms and ToM abilities was examined, patients with nonremitted schizophrenia were shown to perform significantly worse than patients with remitted schizophrenia and healthy controls.[52] It was, therefore, suggested that deficits in ToM might be state-dependent. In addition, schizophrenia patients were more impaired in social cognition tasks, whereas bipolar patients showed greater deficits in neurocognitive performance.[100] These results suggested that these two cognitive domains might play different roles in schizophrenia and bipolar disorder. Interestingly, ToM impairments in schizophrenia patients may be also detected during the remission phase of the disease.[101]

Clinical high-risk (CHR) individuals

Data from individuals at CHR for psychosis and healthy controls showed that individuals at CHR exhibited significant impairments in all domains of social cognition compared with healthy controls.[102] Moreover, in higher order theory of mind tasks, performance of CHR individuals did not seem to differ from the worse performance of patients with schizophrenia.[103]

Familial high risk

Several studies have examined deficits in ToM as potential biomarkers of vulnerability to psychosis in unaffected relatives. Moreover, the social consequences of ToM deficits in schizophrenia patients are thought to create further vulnerability for individuals at familial high risk. Cella *et al*[104] examined deficits in several aspects of social cognition including ToM in healthy siblings of schizophrenia patients, and found that siblings performed significantly worse in ToM tasks as well as in executive function, speed of processing, and IQ tests compared to healthy individuals, suggesting that ToM may be associated with a genetic vulnerability for schizophrenia. Similarly, Ho *et al*[76] found more impaired ToM in patients with FEP and unaffected siblings compared to healthy controls.[70] Imaging studies found that individuals at familial high risk demonstrated less neural activity in bilateral temporoparietal junction than controls, and the degree of deficit was related to day-to-day social functioning.[105] Montag *et al*[106] examined ToM ability in unaffected first-degree relatives of

https://doi.org/10.1017/S1092852916000687 Published online by Cambridge University Press

schizophrenia patients vs healthy controls and found subtle impairment in the cognitive but not the affective aspects of ToM in the relatives' group.

The extent to which deficits in ToM are shared by unaffected first-degree relatives and the nature of this relationship was explored in schizophrenia patients, unaffected first-degree relatives, and healthy subjects who underwent several tasks of social cognition including ToM measurements.[107] Results revealed that schizophrenia patients and first-degree relatives showed similar impairment in mentalizing, but nonidentical patterns of social cognition processing, as relatives showed deficits in emotion processing, but patients with schizophrenia did not. Cassetta and Goghari[82] examined ToM ability in terms of sarcasm comprehension in schizophrenia patients, their first-degree relatives and controls and reported that schizophrenia patients demonstrated impairments in sarcasm comprehension but relatives and controls had intact comprehension.

First episode psychosis (FEP)

The differences in social cognition, including ToM and metacognitive abilities, were investigated in FEP patients, patients with prolonged psychosis, patients with substance use disorder, and healthy controls.[108] Data analysis revealed that both psychotic groups performed similarly and worse in social cognition tasks when compared to controls. Metacognitive capabilities were, however, more impaired in FEP compared to prolonged psychosis. Bora and Pantelis[109] conducted a meta-analysis to investigate ToM as a vulnerability marker of schizophrenia. Data on ToM performance from individuals with FEP, individuals at ultra-high risk of psychosis (UHR), and unaffected relatives were compared to healthy controls. Analysis showed that ToM was substantially impaired in FEP, with a smaller effect size in UHR and unaffected relatives.

Schizotypy

Schizotypy is multidimensional trait organization that reflects psychosis-like symptoms and individual psychosis-proneness. One study recruited college students who undertook a comic strips functional imaging task to examine ToM and empathy.[110] Results showed that negative schizotypy was related to impairment in ToM as demonstrated by brain activity in regions typically involved in social cognition, such as the middle temporal gyrus and the medial prefrontal gyrus. Another study evaluated ToM abilities in 3 psychometrically identified schizotypes: only positive schizotypy (eg, perceptual distortions), negative schizotypy (eg, social anhedonia), and both positive and negative.[111] Results revealed that individuals with elevated positive schizotypy scores experience more difficulty inferring the meaning of others' mental states than negative schizotypy.

The Relationship Between the Neural Network of ToM and Schizophrenia

The neural basis of ToM in healthy adults is well documented and mainly involves disruption of neural activity in the medial prefrontal cortex (MPFC) and the right and left temporoparietal junctions (RTPJ/LTPJ).[112] Imaging studies have also identified the MPFC and the TPJ as prominent sites of abnormality in schizophrenia.[113,114] Such findings suggest an overlap in neural networks between ToM and schizophrenia. Indeed, when Dodell-Feder *et al*[115] examined, using fMRI, the neural basis of ToM in relation to social functioning and anhedonia in 20 individuals with schizophrenia and schizoaffective disorder and compared them to 18 healthy controls, they found that schizophrenia patients exhibited reduced neural activity in the MPFC in relation to matched controls. Reduction of neural activity in MPFC was associated with impairment in social functioning and social cognitive ability. Similarly, Lee *et al*[51] examined the neural network of 14 patients with schizophrenia and 14 matched healthy controls using fMRI during a ToM task, and found significantly less activation in the bilateral TPJ and right medial prefrontal cortex in individuals with schizophrenia compared to controls.

Relationship Between Neurocognitive Deficits and Mentalization in Schizophrenia

Cognitive deficits have been considered to be a core symptom of schizophrenia.[53] Neurocognition refers to the processes of linking and appraising information, and includes cognitive domains such as speed of processing, working memory, attention, memory, and executive functions. The relationship between ToM, neurocognitive deficits, negative symptoms, and functional outcome was investigated in FEP and healthy controls over 6 months.[98] ToM was assessed with a Social Animations Task, in which the participants' descriptions of scenes depicting abstract visual stimuli "interacting" in 3 conditions (ToM, goal-directed, and random) were rated for degree of intentionality attributed to the figures and for appropriateness. Results showed that FEP had lower scores than controls for both intentionality and appropriateness during ToM assessment. Moreover, ToM was significantly correlated with neurocognition and negative symptoms.

In addition, the relationship between ToM, executive functions, and negative attributions was assessed in schizophrenia patients with acute paranoia and remission compared with controls.[53] The authors found that patients following remission still exhibited greater levels of maladaptive attributional styles for negative events and poorer ToM performance than controls. Mehta *et al*[116] examined the relationship of ToM and social functioning and the role of symptoms. Data from schizophrenia patients showed that second-order ToM (ie, thinking about thinking) was

https://doi.org/10.1017/S1092852916000687 Published online by Cambridge University Press

significantly related to functional status, and that the relationship seemed to be mediated by the presence of negative symptoms. Koelkebeck *et al*[95] investigated ToM abilities in FEP vs healthy controls in relation to neuropsychological deficits. Patients showed significant impairment in ToM–a relationship that held true even after controlling for neuropsychological functioning and verbal IQ. Another study examined the relationship between ToM, neurocognitive deficits, IQ, and symptoms in FEP and healthy controls, and showed that neurocognitive deficits and symptoms explained a minor proportion of the variance in the patient group, and IQ was relevant to ToM only when the cognitive demands of the task were complex.[117] Metacognitive ability is viewed as a higher-order, more complex, and critical operation of ToM.

Genetic Considerations

The neural network supporting ToM has been well studied. What remains unclear is which neurotransmitter systems contribute to the reduction of ToM ability in schizophrenia. The dopamine mesocortical system that innervates the prefrontal cortex is a good candidate. Alfimova *et al*[118] examined the possible relationship between ToM abilities with COMT and DRD2 gene polymorphisms in 209 schizophrenia patients and 172 healthy individuals, and found an association between ToM performance and COMT Val158Met polymorphism. Walter *et al*[119] examined the hypothesis that activation of the ToM network is altered in healthy risk allele carriers of the single-nucleotide polymorphism rs1344706 in the gene ZNF804A that has been recently discovered to be a risk variant for psychosis. The risk carriers displayed neural activity in the medial prefrontal cortex and left temporoparietal cortex–both areas known to be associated with ToM processes. In addition, the association between the glutamatergic regulatory gene risk variant DAOA Arg30Lys and brain structure in people with schizophrenia and healthy controls was examined and revealed reduced cortical thickness in areas crucial for ToM functioning, namely the middle temporal, inferior parietal, and lateral occipital lobes, in schizophrenia patients only.[120] So far, research evidence suggest that ToM should be considered in future genetic studies in schizophrenia. However, the heritability of ToM functioning has not been sufficiently established, and more work is needed to confirm its status as a reliable endophenotype for schizophrenia research.[121]

Treatment

The NIMH MATRICS identified social cognition as one of the key targets for the development of new treatment interventions in schizophrenia and other psychoses.[6,7]

Pharmacological treatment

Pharmacological treatment research on social cognition of schizophrenia is limited. There are 2 main treatment strategies: (1) the use of antipsychotic medication to reduce symptoms and facilitate the patient's engagement in cognitive rehabilitation and (2) specific medication targeted at the social cognitive mechanisms related to the psychotherapeutic rehabilitation.

Antipsychotic drugs

Can standard pharmacotherapy repair social cognition and the dysfunctional social brain? Mizrahi *et al*[96] conducted a study with drug-free patients who received risperidone or olanzapine for a period of 6 weeks, and found that both positive symptoms and ToM improved with medication, particularly during the first 2 weeks of antipsychotic treatment, suggesting that antipsychotic treatment may be sufficient to improve ToM ability in FEP. Another study examined the impact of both typical and atypical antipsychotics on ToM, and showed that patients medicated with typical antipsychotics or risperidone performed worse in ToM tasks than patients receiving olanzapine and clozapine.[122] However, there was no significant difference in ToM performance between patients on olanzapine, clozapine, and healthy controls. Inconsistencies in study design, drug doses, and sample sizes produce inconclusive results regarding the influence of antipsychotics on ToM and other social cognitive aspects, and empirical evidence so far does not favor the use of antipsychotic medication for improving social cognition in schizophrenia.

Oxytocin (OT)

Recent evidence suggests that administration of OT targets complex social-cognitive circuitry and, therefore, may have clinical implications for the treatment of psychiatric disorders such as schizophrenia.[123] Interestingly, evidence suggests that OT may provide a useful biomarker for exploring mechanisms of change in social functioning in schizophrenia.[124] Current evidence on the role of OT in schizophrenia and its efficacy in improving mentalizing remains inconsistent but promising.

A randomized, placebo-controlled trial examined the efficacy of intranasal OT treatment and showed OT to diminish ToM deficits.[125] Using the MATRICS Consensus Cognitive Battery (MCCB), Frost *et al* examined whether endogenous peripheral OT levels would predict social cognition in schizophrenia patients and healthy controls. The 2 groups did not differ in plasma OT levels; however, schizophrenia patients demonstrated greater impairment in all 7 MCCB domains, including speed of processing, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition.[126] The efficacy of OT nasal spray treatment combined with social

https://doi.org/10.1017/S1092852916000687 Published online by Cambridge University Press

cognition training (SCT) was evaluated for its potential to improve ToM, clinical symptoms, and social functioning in early psychosis schizophrenia-spectrum illness, and was found to significantly improve negative symptoms of the disease.[127] A randomized, double-blind, placebo-controlled, cross-over study examined the effects of OT in several aspects of social cognition, including ToM, in schizophrenia patients vs healthy controls. The study reported that administration of intranasal OT significantly improved controlled (ability to comprehend emotions, thoughts, or intentions over longer time periods) but not automatic (rapid interpretation of emotional cues from the voice, face, and body) social cognition. Furthermore, healthy participants did not seem to benefit from OT administration.[128]

Psychological interventions

There are 2 types of interventions: (1) targeted interventions that seek to stimulate only 1 specific domain of social cognition and (2) broad-based interventions that incorporate multiple domains of social cognition.

Targeted interventions

Targeted interventions include Emotion and ToM Imitation Training (ETIT)[129] and mentalization-based therapy (MBT).[130] ETIT is a 12-week group-based intervention program involving observation of photos, paintings, figures, comic strips, and imitation of facial expression of emotions. MBT, which was initially developed for borderline personality disorder, is a psychodynamic psychotherapy intervention founded on the assumption that impaired mentalization is influenced by early attachment disruptions between the patient and the caregiver(s). Dismissing and disorganized forms of attachment have been associated with symptom development in schizophrenia, and insecure attachment has been linked with the development of maladaptive coping strategies in the recovery from psychosis.[131,132] MBT is a manualized, evidence-based treatment where active questioning about a patient's mental state and a "not-knowing" stance on behalf of the therapist are essential for the development of a collaborative mentalizing process. The MBT therapeutic approach may lead to improved clinical outcomes; however, future research is needed to further validate this intervention.

Broad-based interventions

Broad-based interventions include social cognition and interaction training (SCIT), integrated psychological therapy (IPT), social cognitive skills training (SCST), integrated neurocognitive therapy (INT), cognitive enhancement therapy (CET), and metacognitive training for schizophrenia (MTC).

SCIT. SCIT is a manual, group-based program that addresses a wide range of sociocognitive deficits in schizophrenia including ToM.[133] SCIT consists of 20 hour-long sessions of training that address emotion perception and social cognitive bias, such as "jumping to conclusions." A clinical trial showed that SCIT improved both social function and negative symptoms in schizophrenia patients.[134] Another trial showed improvement in social cognition abilities in schizophrenia patients after eight weeks of SCIT.[135] A third trial reported improvement in ToM in bipolar or schizoaffective disorder patients after an 18-week SCIT program. It is, however, unknown whether the effects of SCIT will persist over time due to the absence of follow-up assessment.[136] Delivery of SCIT is proved to be feasible and well received.

IPT. IPT is a cognitive behavioral therapy program for groups of 5–8 schizophrenia patients.[137] The IPT manual is based on the notion that cognitive deficits have a profound effect on social perception and social competence in schizophrenia. IPT is organized into 5 subprograms that target basic impairments in neurocognition and social cognition, and involves training in problem solving and interpersonal skills. A meta-analysis found that schizophrenia patients who underwent IPT showed significant improvement in social cognitive skills and functioning, as well as neurocognition and negative symptoms when compared to patients under different intervention programs or on standard care.[138]

SCST. SCST is a group-based intervention with 12 sessions that incorporates several skill-building strategies, such as breaking down complex social cognitive processes into their component skills. It targets 4 main domains: ToM, emotional processing, social perception, and attributional style.[139] Training includes analysis of complex videos, discussion of relevant material from participants' lives, and role-play exercises to practice obtaining additional information in socially ambiguous situations. One study administered SCST, computerized neurocognitive remediation, standard skills training, or a hybrid of SCST and neurocognitive remediation to a randomized group of schizophrenia patients, and found that SCST was more efficient in treating deficits in facial affect recognition than ToM or other domains of social cognition when compared with control groups.[140]

INT. INT is a broad-based, group remediation approach that consists of a total of 30 biweekly sessions, based on the MATRICS initiative, and includes 6 neurocognitive domains (speed of processing, attention, verbal and visual learning and memory, working memory, reasoning and problem solving) and 5 social cognitive domains, including emotion perception, social perception, ToM, social schema, and attribution style.[141] The authors

https://doi.org/10.1017/S1092852916000687 Published online by Cambridge University Press

evaluated the efficacy of the program in 169 schizophrenia outpatients who were compared with a control group that received treatment as usual. Results retrieved after therapy and at 1-year follow-up showed that the INT group showed better outcomes than the control group.

CET. CET is a developmental approach that integrates remediation in neurocognition and social cognition using multiple methods, including 60 hours of computer-assisted exercises (attention, memory, and problem solving; PSSCogRehab program) conducted in pairs.[142] It also includes 45 group-based, weekly training sessions in social cognitive skills (perspective-taking, social perception, managing emotions, and social context appraisal) that are taught and practiced in vivo via psychoeducation, role-playing, and experimental and homework exercises. CET is unique in that it is the only cognitive remediation approach that comprehensively addresses both neurocognition and social cognition. It aims to reinforce appraisal of social cues and interprets the perspectives or emotions of others, which both pertain to ToM. CET presents a significant advance in cognitive remediation for schizophrenia, as its approach extends beyond the traditional neurocognitive training offered in cognitive remediation interventions. In a sample of patients with schizophrenia and substance use, patients treated with CET for 18 months showed significant improvements in social cognition and social adjustment, as well as reduction in substance use.[143]

Metacognitive training for schizophrenia (MTC)

Metacognition can be simply defined as thinking about thinking. It consists of 2 processes: metacognitive knowledge and metacognitive regulation. Metacognition involves introspecting about one's own behavior, whereas ToM involves the perception of own and others' behaviour. Metacognition requires more complex verbal and linguistic operations, while ToM ability is associated with the representation and clear identification of self and others.[144] It is unclear whether ToM and metacognition are 2 independent mechanisms with distinctive seta of abilities that relate to different outcomes, or whether they share a common architecture that allows them to follow similar developmental paths and deliver similar inputs. Metacognitive training is based on the theoretical foundations of the cognitive-behavioral model of schizophrenia that targets cognitive (eg, jumping to conclusions) and problem solving (eg, poor memory recollection) errors and biases in schizophrenia, which in turn assist in the development of false beliefs to the point of delusions.[145] Since many of the cognitive biases observed in schizophrenia fall beyond conscious reflection, an intervention with metacognitive training may bring patients some awareness of all these biases to the patients. MCT is offered in a group format, which consists of 8 modules that cover the following 6 areas (jumping to conclusions bias, attributional biases, bias against disconfirmatory evidence, social cognition, overconfidence in errors, and depressive cognition).[146] A narrative review examined the efficacy of MCT in reducing delusions in schizophrenia from 16 trials and found that MCT is effective in addressing both symptoms and cognitive biases.[147] Like ToM, metacognitive abilities have been associated with poor functioning, even when neurocognitive deficits and symptoms are controlled for.

Ussorio *et al*[148] examined the effectiveness and the feasibility of a 4-month MCT training program to treat symptoms of the early phases of psychosis.[118] Data showed that there was significant improvement in positive symptoms, cognitive abilities, metacognitive functions, ToM abilities, and social perception. Another study examined whether metacognitive impairment can distinguish individuals with schizophrenia from others experiencing significant life adversity but without psychosis using the Metacognitive Assessment Scale Abbreviated (MAS-A).[149] Results showed that the MAS-A total score correctly classified 93% of the schizophrenia group, and as such the authors suggested that the abilities to synthesize thoughts about oneself and others into larger representations are a unique feature of schizophrenia. Indeed, when metacognitive abilities of individuals with schizophrenia were compared to those of patients with bipolar disorder (BD), domains of metacognition such as self-reflection and understanding of others' minds, were uniquely related to schizophrenia but not to bipolar disorder.[150]

Conclusions

Support for intervention at the level of theory of mind derives from recent empirical evidence. Research findings suggest that ToM seems to be a distinct construct, but related to neurocognitive deficits and clinical symptoms of schizophrenia. It possibly acts as a mediator in the relationship between symptoms, neurocognitive deficits, and functional outcome. Furthermore, impairment in ToM has been well documented across the psychosis spectrum, including individuals clinically at high risk or genetic risk for schizophrenia, individuals with schizotypy, first episode psychosis patients, and chronic schizophrenia patients. Such evidence suggests that ToM might be a prominent feature of psychotic disorders, associating psychotic symptoms with social cognitive deficits. Advances in cognitive and affective neurosciences seem to lead to the development of more advanced behavioral methods to assess the relationship between cognitive functions, symptoms, and social cognition based on their underlying neural mechanisms. Development of assessment tools that better examine the neural circuitry of such relationships may lead to the development of novel and improved pharmacotherapies for schizophrenia and other idiopathic psychotic disorders.

https://doi.org/10.1017/S1092852916000687 Published online by Cambridge University Press

Disclosures

The authors do not have anything to disclose.

REFERENCES:

1. Brissos S, Molodynski A, Dias VV, Figueira ML. The importance of measuring psychosocial functioning in schizophrenia. *Ann Gen Psychiatry*. 2011; **10**: 18.
2. Hooley JM. Social factors in schizophrenia. *Current Directions in Psychological Science*. 2010; **19**(4): 238–242.
3. Roberts DL, Velligan DI. Can social functioning in schizophrenia be improved through targeted social cognitive intervention? *Rehabil Res Pract*. 2012; **2012**: 742106.
4. Adolphs R. Cognitive neuroscience of human social behaviour. *Nat Rev Neurosci*. 2003; **4**(3): 165–178.
5. Couture SM, Penn DL, Roberts DL. The functional significance of social cognition in schizophrenia: a review. *Schizophr Bull*. 2006; **32**(Suppl 1): S44–S63.
6. Green MF, Nuechterlein KH, Gold JM, *et al*. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. *Biol Psychiatry*. 2004; **56**(5): 301–307.
7. Green MF, Penn DL, Bentall R, *et al*. Social cognition in schizophrenia: an NIMH workshop on definitions, assessment, and research opportunities. *Schizophr Bull*. 2008; **34**(6): 1211–1220.
8. Bora E, Yucel M, Pantelis C. Theory of mind impairment in schizophrenia: meta-analysis. *Schizophr Res*. 2009; **109**(1–3): 1–9.
9. Lam BY, Raine A, Lee TM. The relationship between neurocognition and symptomatology in people with schizophrenia: social cognition as the mediator. *BMC Psychiatry*. 2014; **14**: 138.
10. Bateman A, Fonagy P. *Psychotherapy for Borderline Personality Disorder: Mentalization-Based Treatment*. Oxford, UK: Oxford University Press; 2004.
11. Fonagy P, Bateman A, Bateman A. The widening scope of mentalizing: a discussion. *Psychol Psychother*. 2011; **84**(1): 98–110.
12. Fretland RA, Andersson S, Sundet K, Andreassen OA, Melle I, Vaskinn A. Theory of mind in schizophrenia: error types and associations with symptoms. *Schizophr Res*. 2015; **162**(1–3): 42–46.
13. O'Nions E, Sebastian CL, McCrory E, Chantiluke K, Happé F, Viding E. Neural bases of Theory of Mind in children with autism spectrum disorders and children with conduct problems and callous-unemotional traits. *Dev Sci*. 2014; **17**(5): 786–796.
14. Hoertnagl CM, Hofer A. Social cognition in serious mental illness. *Curr Opin Psychiatry*. 2014; **27**(3): 197–202.
15. Henry JD, Phillips LH, von Hippel C. A meta-analytic review of theory of mind difficulties in behavioral-variant frontotemporal dementia. *Neuropsychologia*. 2014; **56**: 53–62.
16. Robinson KE, Fountain-Zaragoza S, Dennis M, *et al*. Executive functions and theory of mind as predictors of social adjustment in childhood traumatic brain injury. *J Neurotrauma*. 2014; **31**(22): 1835–1842.
17. Premack D, Woodruff G. Does the chimpanzee have a theory of mind? *Behav Brain Sci*. 1978; **1**(4): 515–526.
18. Mitchell RL, Phillips LH. The overlapping relationship between emotion perception and theory of mind. *Neuropsychologia*. 2015; **70**: 1–10.
19. Strack F, Deutsch R. Reflective and impulsive determinants of social behavior. *Pers Soc Psychol Rev*. 2004; **8**(3): 220–247.
20. Van Overwalle F. Social cognition and the brain: a meta-analysis. *Hum Brain Mapp*. 2009; **30**(3): 829–858.
21. Evans JS. Dual-processing accounts of reasoning, judgment, and social cognition. *Annu Rev Psychol*. 2008; **59**(1): 255–278.
22. Schneider D, Nott ZE, Dux PE. Task instructions and implicit theory of mind. *Cognition*. 2014; **133**(1): 43–47.
23. Roux P, Forgeot d'Arc B, Passerieux C, Ramus F. Is the Theory of Mind deficit observed in visual paradigms in schizophrenia explained by an impaired attention toward gaze orientation? *Schizophr Res*. 2014; **157**(1–3): 78–83.
24. Ebisch SJH, Gallese VA. Neuroscientific perspective on the nature of altered self-other relationships in schizophrenia. *Journal of Consciousness Studies*. 2015; **22**(1–2): 220–240.
25. Abu-Akel AM, Wood SJ, Hansen PC, Apperly IA. Perspective-taking abilities in the balance between autism tendencies and psychosis proneness. *Proc Biol Sci*. 2015; **282**(1808): 20150563.
26. Sowden S, Shah P. Self-other control: a candidate mechanism for social cognitive function. *Front Hum Neurosci*. 2014; **8**: 789.
27. Shamay-Tsoory SG, Shur S, Barcai-Goodman L, Medlovich S, Harari H, Levkovitz Y. Dissociation of cognitive from affective components of theory of mind in schizophrenia. *Psychiatry Res*. 2007; **149**(1–3): 11–23.
28. Schlaffke L, Lissek S, Lenz M, *et al*. Shared and nonshared neural networks of cognitive and affective theory-of-mind: a neuroimaging study using cartoon picture stories. *Hum Brain Mapp*. 2015; **36**(1): 29–39.
29. Bodden ME, Kübler D, Knake S, *et al*. Comparing the neural correlates of affective and cognitive theory of mind using fMRI: involvement of the basal ganglia in affective theory of mind. *Adv Cogn Psychol*. 2013; **9**(1): 32–43.
30. Leisman G, Braun-Benjamin O, Melillo R. Cognitive-motor interactions of the basal ganglia in development. *Front Syst Neurosci*. 2014; **8**: 16.
31. Gopnik A. The theory theory as an alternative to the innateness hypothesis. In: Antony L, Hornstein N, eds. *Chomsky and His Critics*. New York: Basil Blackwell; 2003, 238–254.
32. Forbes CE, Poore JC, Barbey AK, *et al*. BDNF polymorphism-dependent OFC and DLPFC plasticity differentially moderates implicit and explicit bias. *Cereb Cortex*. 2012; **22**(11): 2602–2609.
33. Forbes CE, Cameron KA, Grafman J, *et al*. Identifying temporal and causal contributions of neural processes underlying the Implicit Association Test (IAT). *Front Hum Neurosci*. 2012; **6**: 320.
34. Siegel M, Donner TH, Engel AK. Spectral fingerprints of large-scale neuronal interactions. *Nat Rev Neurosci*. 2012; **13**(2): 121–134.
35. Ma N, Vandekerckhove M, Van Overwalle F, Seurinck R, Fias W. Spontaneous and intentional trait inferences recruit a common mentalizing network to a different degree: spontaneous inferences activate only its core areas. *Soc Neurosci*. 2011; **6**(2): 123–138.
36. Mahy CE, Voigt B, Ballhausen N, Schnitzspahn K, Ellis J, Kliegel M. The impact of cognitive control on children's goal monitoring in a time-based prospective memory task. *Child Neuropsychol*. 2015; **21**(6): 823–839.
37. Uddin LQ, Molnar-Szakacs I, Zaidel E, Iacoboni M. rTMS to the right inferior parietal lobule disrupts self-other discrimination. *Soc Cogn Affect Neurosci*. 2006; **1**(1): 65–71.
38. Mehta UM, Thirthalli J, Basavaraju R, Gangadhar BN, Pascual-Leone A. Reduced mirror neuron activity in schizophrenia and its association with theory of mind deficits: evidence from a transcranial magnetic stimulation study. *Schizophr Bull*. 2014; **40**(5): 1083–1094.
39. Suttrup J, Keysers C, Thioux M. The role of the theory of mind network in action observation–an rTMS study. *Brain Stimulation*. 2015; **8**(2): 415–416.
40. Leslie AM, Friedman O, German TP. Core mechanisms in "theory of mind." *Trends Cogn Sci*. 2004; **8**(12): 528–533.
41. van Veluw SJ, Chance SA. Differentiating between self and others: an ALE meta-analysis of fMRI studies of self-recognition and theory of mind. *Brain Imaging Behav*. 2014; **8**(1): 24–38.

https://doi.org/10.1017/S1092852916000687 Published online by Cambridge University Press

42. Schurz M, Radua J, Aichhorn M, Richlan F, Perner J. Fractionating theory of mind: a meta-analysis of functional brain imaging studies. *Neurosci Biobehav Rev*. 2014; **42**: 9–34.
43. Hardy-Bayle MC, Passerieux C, Claudel B, Olivier V, Chevalier JF. [Communication disorders in schizophrenic patients. Cognitive explanation and clinical reconsideration]. *Encephale*. 1994; **20**(4): 393–400.
44. Bailey PE, Henry JD. Separating component processes of theory of mind in schizophrenia. *Br J Clin Psychol*. 2010; **49**(Pt 1): 43–52.
45. Möller M, Swanepoel T, Harvey BH. Neurodevelopmental animal models reveal the convergent role of neurotransmitter systems, inflammation, and oxidative stress as biomarkers of schizophrenia: implications for novel drug development. *ACS Chem Neurosci*. 2015; **6**(7): 987–1016.
46. Kullmann JS, Grigoleit JS, Wolf OT, *et al*. Experimental human endotoxemia enhances brain activity during social cognition. *Soc Cogn Affect Neurosci*. 2014; **9**(6): 786–793.
47. Moieni M, Irwin MR, Jevtic I, Breen EC, Eisenberger NI. Inflammation impairs social cognitive processing: a randomized controlled trial of endotoxin. *Brain Behav Immun*. 2015; **48**: 132–138.
48. Couture SM, Penn DL. Introduction. In Roberts DL, Penn DL, eds. *Social Cognition in Schizophrenia*. New York: Oxford University Press; 2013, 1–16.
49. Wimmer H, Perner J. Beliefs about beliefs: Representation and constraining function of wrong beliefs in young children's understanding of deception. *Cognition*. 1983; **13**: 103–128.
50. Shryane NM, Corcoran R, Rowse G, Moore R, Cummins S, Blackwood N, *et al*. Deception and false belief in paranoia: modelling theory of mind stories. *Cogn Neuropsychiatry*. 2008; **13**(1): 8–32.
51. Lee J, Quintana J, Nori P, Green MF. Theory of mind in schizophrenia: Exploring neural mechanisms of belief attribution. *Soc. Neurosci.*. 2011; **6**: 569–581.
52. Wang Y, Roberts DL, Xu B, Cao R, Yan M, Jiang Q. Social cognition and interaction training for patients with stable schizophrenia in Chinese community settings. *Psychiatry Res*. 2013; **210**(3): 751–755.
53. Berry K, Bucci S, Kinderman P, Emsley R, Corcoran R. An investigation of attributional style, theory of mind and executive functioning in acute paranoia and remission. *Psychiatry Res*. 2015; **226**(1): 84–90.
54. Happé F. An advanced test of theory of mind: understanding of story characters' thoughts and feelings by able autistic, mentally handicapped, and normal children and adults. *J. Autism Dev. Disord*. 1994; **24**: 129–154.
55. Stanford AD, Messinger J, Malaspina D, Corcoran CM. Theory of Mind in Patients at Clinical High Risk for Psychosis. *Schizophr Res*. 2011; **131**(1-3): 11–17.
56. Scherzer P, Leveillé E, Achim A, Boisseau E, Stip E. A Study of Theory of Mind in Paranoid Schizophrenia: A Theory or Many Theories? *Front. Psychol*. 2012; **3**: 432.
57. Chung YS, Barch D, Strube M. A meta-analysis of mentalizing impairments in adults with schizophrenia and autism spectrum disorder. *Schizophr Bull*. 2014; **40**(3): 602–616.
58. Corcoran R, Mercer G, Frith CD. Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. *Schizophr Res*. 1995; **17**: 5–13.
59. Ng R, Fish S, Granholm E. Insight and theory of mind in schizophrenia. *Psychiatry Res*. 2015; **225**(1-2): 169–174.
60. Stone VE, Baron-Cohen S, Knight RT. Frontal lobe contributions to theory of mind. *J Cogn Neurosci*. 1998; **10**(5): 640–656.
61. Hasson-Ohayon I, Avidan-Msika M, Mashiach-Eizenberg M, Kravetz S, Rozencwaig S, Shalev H, Lysaker PH. Metacognitive and social cognition approaches to understanding the impact of schizophrenia on social quality of life. *Schizophr Res*. 2015; **161**(2-3): 386–391.
62. Channon S, Pellijeff A, Rule A. Social cognition after head injury: Sarcasm and theory of mind. *Brain and Language*. 2005; **93**: 123–134.
63. Rapp AM, Langohr K, Mutschler DE, Klingberg S, Wild B, Erb M. Isn't it ironic? Neural Correlates of Irony Comprehension in Schizophrenia. *PLoS ONE*. 2013; **8**(9): e74224.
64. Baron-Cohen S, Jolliffe T, Mortimore C, Robertson M. Another advanced test of theory of mind: Evidence from very high functioning adults with autism or Asperger syndrome. *J. Child Psychol. Psychiatry*. 1997; **38**: 813–822.
65. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "reading the mind in the eyes" test revised version: a study with normal adults, and adults with asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry*. 2001; **42**: 241–251.
66. Baker CA, Peterson E, Pulos S, Kirkland RA. Eyes and IQ: A meta-analysis of the relationship between intelligence and "Reading the Mind in the Eyes". *Intelligence*. 2014; **44**: 78–92.
67. Pinkham AE, Penn DL, Green MF, Harvey PD. Social Cognition Psychometric Evaluation: Results of the Initial Psychometric Study. *Schizophr Bull*. 2016; **42**(2): 494–504.
68. Sarfati Y, Hardy-Baylé MC, Besche C, *et al*. Attribution of intentions to others in people with schizophrenia: a non-verbal exploration with comic strips. *Schizophr Res*. 1997a; **25**: 199–209.
69. Brunet E, Sarfati Y, Hardy-Baylé MC. Reasoning about physical causality and other's intentions in schizophrenia. *Cogn Neuropsychiatry*. 2003; **8**(2): 129–139.
70. Castelli F, Happé F, Frith U, Frith C. Movement and Mind: A Functional Imaging Study of Perception and Interpretation of Complex Intentional movement patterns. *Neuroimage*. 2000; **12**: 314–325.
71. Pedersen A, Koelkebeck K, Brandt M, Wee M, Kueppers KA, Kugel H., *et al*. Theory of mind in patients with schizophrenia: is mentalizing delayed? *Schizophr Res*. 2012; **137**(1-3): 224–229.
72. Koelkebeck K, Hirao K, Miyata J, Kawada R, Saze T, Dannlowski U. Impact of gray matter reductions on theory of mind abilities in patients with schizophrenia. *Soc Neurosci*. 2013; **8**(6): 631–639.
73. Langdon R, Coltheart M. Mentalising, schizotypy, and schizophrenia. *Cognition*. 1999; **71**: 43–71.
74. Bechi M, Riccaboni R, Ali S, Fresi F, Buonocore M, Bosia M, *et al*. Theory of mind and emotion processing training for patients with schizophrenia: preliminary findings. *Psychiatry Res*. 2012; **198**(3): 371–377.
75. Langdon R, Connors MH, Still M, Ward PB, Catts S. Theory of mind and neurocognition in early psychosis: a quasi-experimental study. *BMC Psychiatry*. 2014; **14**(1): 316.
76. Ho KKY, Lui SSY, Hung KSY, *et al*. Theory of mind impairments in patients with first-episode schizophrenia and their unaffected siblings. *Schizophr Res*. 2015; **166**(1-3): 1–8.
77. Brass M, Bekkering H, Prinz W. Movement observation affects movement execution in a simple response task. *Acta Psychol* (Amst). 2001; **106**(1-2): 3–22.
78. Obhi SS, Hogeveen J. The controlled imitation task: a new paradigm for studying self-other control. *PeerJ*. 2013; **1**: e161.
79. Dziobek I, Fleck S, Kalbe E, Rogers K, Hassenstab J, Brand M, *et al*. Introducing MASC: a movie for the assessment of social cognition. *J Autism Dev Disord*. 2006; **36**(5): 623–636.
80. Montag C, Dziobek I, Richter IS, *et al*. Different aspects of theory of mind in paranoid schizophrenia: evidence from a video-based assessment. *Psychiatry Res*. 2011; **186**(2-3): 203–209.
81. McDonald S, Flanagan S, Rollins J. *The Awareness of Social Inference Test*. Suffolk, UK: Thames Valley Test Company, Ltd; 2002.

82. Cassetta B., Goghari V. Theory of mind reasoning in schizophrenia patients and non-psychotic relatives. *Psychiatry Res*. 2014; **218**(1-2): 12–19.
83. Barbato M., Liu L, Cadenhead KS, Cannon TD, Cornblatt BA, McGlashan TH. Theory of mind, emotion recognition and social perception in individuals at clinical high risk for psychosis: Findings from the NAPLS-2 cohort. *Schizophr Res Cogn*. 2015; **2**(3): 133–139.
84. Keysar B, Barr DJ, Balin JA, Brauner JS. Taking perspective in conversation: the role of mutual knowledge in comprehension. *Psychol Sci*. 2000; **11**(1): 32–38.
85. Bosco FM, Colle L, De Fazio S, Bono A, Ruberti S, Tirassa M. Th.o.m.a.s: an exploratory assessment of Theory of Mind in schizophrenic subjects. *Conscious Cogn*. 2009; **18**(1): 306–319.
86. Healey KM, Combs DR, Gibson CM, Keefe RSE, Roberts DL, Penn DL. Observable Social Cognition: A Rating Scale (OSCARS): An Interview-Based Assessment for Schizophrenia. *Cogn Neuropsychiatry* 2015; **20**(3): 198–221.
87. Semerari A, Carcione A, Dimaggio G, Falcone M, Nicolò G, Procacci M, Alleva G. How to evaluate metacognitive functioning in psychotherapy? The metacognition assessment scale and its applications. *Clin. Psychol. Psychother*. 2003; **10**: 238–261.
88. Lysaker P. H., Carcione A., Dimaggio G, Johannesen JK, Nicolò G, Procacci M, Semerari A. Metacognition amidst narratives of self and illness in schizophrenia: associations with neurocognition, symptoms, insight and quality of life. *Acta Psychiat. Scand*. 2005; **112**: 64–71.
89. Lysaker P.H., Dimaggio G, Daroyanni P, Buck KD, LaRocco VA, Carcione A, Nicolò G. Assessing metacognition in schizophrenia with the Metacognition Assessment Scale: associations with the Social Cognition and Object Relations Scale. *Psychol Psychother*. 2010; **83**: 303–315.
90. Sprong M, Schothorst P, Vos E, Hox J, Van Engeland H. Theory of mind in schizophrenia: meta-analysis. *Br J Psychiatry*. 2007; **191**(1): 5–13.
91. Pickup GJ, Frith CD. Theory of mind impairments in schizophrenia: symptomatology, severity and specificity. *Psychol Med*. 2001; **31**(2): 207–220.
92. Billeke P, Armijo A, Castillo D, *et al*. Paradoxical expectation: oscillatory brain activity reveals social interaction impairment in schizophrenia. *Biol Psychiatry*. 2015; **78**(6): 421–431.
93. Macbeth A, Gumley A, Schwannauer M, *et al*. Metacognition, symptoms and premorbid functioning in a first episode psychosis sample. *Compr Psychiatry*. 2014; **55**(2): 268–273.
94. Lincoln TM, Mehl S, Kesting ML, Rief W. Negative symptoms and social cognition: identifying targets for psychological interventions. *Schizophr Bull*. 2011; **37**(2): S23–S32.
95. Koelkebeck K, Pedersen A, Suslow T, Kueppers KA, Arolt V, Ohrmann P. Theory of Mind in first-episode schizophrenia patients: correlations with cognition and personality traits. *Schizophr Res*. 2010; **119**(1–3): 115–123.
96. Mizrahi R, Korostil M, Starkstein SE, Zipursky RB, Kapur S. The effect of antipsychotic treatment on theory of mind. *Psychol Med*. 2007; **37**(4): 595–601.
97. Marjoram D, Gardner C, Burns J, Miller P, Lawrie SM, Johnstone EC. Symptomatology and social inference: a theory of mind study of schizophrenia and psychotic affective disorder. *Cogn Neuropsychiatry*. 2005; **10**(5): 347–359.
98. Ventura J, Ered A, Gretchen-Doorly D, *et al*. Theory of mind in the early course of schizophrenia: stability, symptom and neurocognitive correlates, and relationship with functioning. *Psychol Med*. 2015; **45**(10): 2031–2043.
99. Ioannidi N, Konstantakopoulos G, Ploumpidis D, *et al*. Cognitive and affective theory of mind in schizophrenia and euthymic bipolar disorder. *Eur Psychiatry*. 2014; **29**(Suppl 1): 1.
100. Lee J, Altshuler L, Glahn DC, Miklowitz DJ, Ochsner K, Green MF. Social and nonsocial cognition in bipolar disorder and schizophrenia: relative levels of impairment. *Am J Psychiatry*. 2013; **170**(3): 334–341.
101. Herold R, Tényi T, Lénárd K, Trixler M. Theory of mind deficit in people with schizophrenia during remission. *Psychol Med*. 2002; **32**(6): 1125–1129.
102. Lee TY, Hong SB, Shin NY, Kwon JS. Social cognitive functioning in prodromal psychosis: a meta-analysis. *Schizophr Res*. 2015; **164**(1–3): 28–34.
103. Stanford AD, Messinger J, Malaspina D, Corcoran CM. Theory of mind in patients at clinical high risk for psychosis. *Schizophr Res*. 2011; **131**(1–3): 11–17.
104. Cella M, Hamid S, Butt K, Wykes T. Cognition and social cognition in non-psychotic siblings of patients with schizophrenia. *Cogn Neuropsychiatry*. 2015; **20**(3): 232–242.
105. Dodell-Feder D, DeLisi LE, Hooker CI. Neural disruption to theory of mind predicts daily social functioning in individuals at familial high-risk for schizophrenia. *Soc Cogn Affect Neurosci*. 2014; **9**(12): 1914–1925.
106. Montag C, Neuhaus K, Lehmann A, *et al*. Subtle deficits of cognitive theory of mind in unaffected first-degree relatives of schizophrenia patients. *Eur Arch Psychiatry Clin Neurosci*. 2012; **262**(3): 217–226.
107. de Achával D, Costanzo EY, Villarreal M, *et al*. Emotion processing and theory of mind in schizophrenia patients and their unaffected first-degree relatives. *Neuropsychologia*. 2010; **48**(5): 1209–1215.
108. Vohs JL, Lysaker PH, Francis MM, *et al*. Metacognition, social cognition, and symptoms in patients with first episode and prolonged psychoses. *Schizophr Res*. 2014; **153**(1–3): 54–59.
109. Bora E, Pantelis C. Theory of mind impairments in first-episode psychosis, individuals at ultra-high risk for psychosis and in first-degree relatives of schizophrenia: systematic review and meta-analysis. *Schizophr Res*. 2013; **144**(1–3): 31–36.
110. Wang Y, Liu W, Li Z, *et al*. Dimensional schizotypy and social cognition: an fMRI imaging study. *Front Behav Neurosci*. 2015; **9**: 133.
111. Pflum MJ, Gooding DC, White HJ. Hint, hint: theory of mind performance in schizotypal individuals. *J Nerv Ment Dis*. 2013; **201**(5): 394–399.
112. Molenberghs P, Johnson H, Henry JD, Mattingley JB. Understanding the minds of others: a neuroimaging meta-analysis. *Neurosci Biobehav Rev*. 2016; **65**: 276–291.
113. Pomarol-Clotet E, Canales-Rodríguez EJ, Salvador R, *et al*. Medial prefrontal cortex pathology in schizophrenia as revealed by convergent findings from multimodal imaging. *Mol Psychiatry*. 2010; **15**(8): 823–830.
114. Jimenez AM, Lee J, Wynn JK, *et al*. Abnormal Ventral and Dorsal Attention Network Activity during Single and Dual Target Detection in Schizophrenia. *Frontiers in Psychology*. 2016; **7**: 323.
115. Dodell-Feder D, Tully LM, Lincoln SH, Hooker CI. The neural basis of theory of mind and its relationship to social functioning and social anhedonia in individuals with schizophrenia. *Neuroimage Clin*. 2014; **4**: 154–163.
116. Mehta UM, Thirthalli J, Kumar CN, Kumar JK, Gangadhar BN. Negative symptoms mediate the influence of theory of mind on functional status in schizophrenia. *Soc Psychiatry Psychiatr Epidemiol*. 2014; **49**(7): 1151–1156.
117. Bliksted V, Fagerlund B, Weed E, Frith C, Videbech P. Social cognition and neurocognitive deficits in first-episode schizophrenia. *Schizophr Res*. 2014; **153**(1–3): 9–17.
118. Alfimova MV, Golimbet VE, Korovaĭtseva GI, *et al*. [The association of COMT and DRD2 gene polymorphisms with a cognitive ability to understand others in schizophrenic patients]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2013; **113**(8): 50–56.

119. Walter H, Schnell K, Erk S, *et al*. Effects of a genome-wide supported psychosis risk variant on neural activation during a theory-of-mind task. *Mol Psychiatry*. 2011; **16**(4): 462–470.
120. Schultz CC, Nenadic I, Koch K, *et al*. Reduced cortical thickness is associated with the glutamatergic regulatory gene risk variant DAOA Arg30Lys in schizophrenia. *Neuropsychopharmacology*. 2011; **36**(8): 1747–1753.
121. Martin AK, Robinson G, Dzafic I, Reutens D, Mowry B. Theory of mind and the social brain: implications for understanding the genetic basis of schizophrenia. *Genes Brain Behav*. 2014; **13**(1): 104–117.
122. Savina I, Beninger RJ. Schizophrenic patients treated with clozapine or olanzapine perform better on theory of mind tasks than those treated with risperidone or typical antipsychotic medications. *Schizophr Res*. 2007; **94**(1–3): 128–138.
123. Wigton R, Radua J, Allen P, *et al*. Neurophysiological effects of acute oxytocin administration: systematic review and meta-analysis of placebo-controlled imaging studies. *J Psychiatry Neurosci*. 2015; **40**(1): E1–E22.
124. Gumley A, Braehler C, Macbeth A. A meta-analysis and theoretical critique of oxytocin and psychosis: prospects for attachment and compassion in promoting recovery. *Br J Clin Psychol*. 2014; **53**(1): 42–61.
125. Pedersen CA, Gibson CM, Rau SW, *et al*. Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. *Schizophr Res*. 2011; **132**(1): 50–53.
126. Frost K, Keller W, Buchanan R, *et al*. Plasma oxytocin levels are associated with impaired social cognition and neurocognition in schizophrenia. *Arch Clin Neuropsychol*. 2014; **29**(6): 577–578.
127. Cacciotti-Saija C, Langdon R, Ward PB, *et al*. A double-blind randomized controlled trial of oxytocin nasal spray and social cognition training for young people with early psychosis. *Schizophr Bull*. 2014; **41**(2): 483–493.
128. Woolley JD, Chuang B, Lam O, *et al*. Oxytocin administration enhances controlled social cognition in patients with schizophrenia. *Psychoneuroendocrinology*. 2014; **47**: 116–125.
129. Mazza M, Lucci G, Pacitti F, *et al*. Could schizophrenic subjects improve their social cognition abilities only with observation and imitation of social situations? *Neuropsychol Rehabil*. 2010; **20**(5): 675–703.
130. Fonagy P, Bateman A. Mechanism of change in mentalization based treatment of borderline personality disorder. *J Clin Psychol*. 2006; **62**(4): 411–430.
131. Harder S. Attachment in schizophrenia–implications for research, prevention, and treatment. *Schizophr Bull*. 2014; **40**(6): 1189–1193.
132. Korver-Nieberg N, Berry K, Meijer CJ, de Haan L. Adult attachment and psychotic phenomenology in clinical and non-clinical samples: a systematic review. *Psychol Psychother*. 2014; **87**(2): 127–154.
133. Combs DR, Adams SD, Penn DL, Roberts D, Tiegreen J, Stem P. Social Cognition and Interaction Training (SCIT) for inpatients with schizophrenia spectrum disorders: preliminary findings. *Schizophr Res*. 2007; **91**(1–3): 112–116.
134. Roberts DL, Combs DR, Willoughby M, *et al*. A randomized, controlled trial of Social Cognition and Interaction Training (SCIT) for outpatients with schizophrenia spectrum disorders. *Br J Clin Psychol*. 2014; **53**(3): 281–298.
135. Taylor R, Cella M, Csipke E, Heriot-Maitland C[1], Gibbs C[1], Wykes T. Tackling social cognition in schizophrenia: a randomized feasibility trial. *Behav Cogn Psychother*. 2016; **44**(3): 306–317.
136. Lahera G, Benito A, Montes JM, *et al*. Social cognition and interaction training (SCIT) for outpatients with bipolar disorder. *J Affect Disord*. 2013; **146**(1): 132–136.
137. Brenner HD, Hodel B, Roder V, Corrigan P. Treatment of cognitive dysfunctions and behavioral deficits in schizophrenia. *Schizophr Bull*. 1992; **18**(1): 21–26.
138. Roder V, Mueller DR, Schmidt SJ. Effectiveness of integrated psychological therapy (IPT) for schizophrenia patients: a research update. *Schizophr Bull*. 2011; **37**(2): S71–S79.
139. Horan WP, Kern RS, Shokat-Fadai K, *et al*. Social cognitive skills training in schizophrenia: an initial efficacy study of stabilized outpatients. *Schizophr Res*. 2009; **107**(1): 47–54.
140. Horan WP, Kern RS, Tripp C, *et al*. Efficacy and specificity of social cognitive skills training for outpatients with psychotic disorders. *J Psychiatr Res*. 2011; **45**(8): 1113–1122.
141. Roder V, Mueller DR, Schmidt SJ. A broad-based remediation approach: the integrated neurocognitive therapy (INT). *Eur Psychiatry*. 2011; **26**(Suppl 1): 2159.
142. Hogarty GE, Greenwald DP. *Cognitive Enhancement Therapy: The Training Manual*. Pittsburgh, PA: University of Pittsburgh Medical Center; 2006.
143. Eack SM, Hogarty SS, Greenwald DP, *et al*. Cognitive Enhancement Therapy in substance misusing schizophrenia: results of an 18-month feasibility trial. *Schizophr Res*. 2015; **161**(2–3): 478–483.
144. Buck KD, Warman DM, Huddy V, Lysaker PH. The relationship of metacognition with jumping to conclusions among persons with schizophrenia spectrum disorders. *Psychopathology*. 2012; **45**(5): 271–275.
145. Peters E, Garety P. Cognitive functioning in delusions: a longitudinal analysis. *Behav Res Ther*. 2006; **44**(4): 481–514.
146. Moritz S, Veckenstedt R, Bohn F, Köther U, Woodward TS. Metacognitive training in schizophrenia. Theoretical rationale and administration. In Roberts DL, Penn DL, eds. *Social Cognition in Schizophrenia: From Evidence to Treatment*. New York: Oxford University Press; 2013: 358–383.
147. Moritz S, Andreou C, Schneider BC, *et al*. Sowing the seeds of doubt: a narrative review on metacognitive training in schizophrenia. *Clin Psychol Rev*. 2014; **34**(4): 358–366.
148. Ussorio D, Giusti L, Wittekind CE, *et al*. Metacognitive training for young subjects (MCT young version) in the early stages of psychosis: is the duration of untreated psychosis a limiting factor? *Psychol Psychother*. 2015; **89**(1): 50–65.
149. Lysaker PH, Vohs J, Hamm JA, *et al*. Deficits in metacognitive capacity distinguish patients with schizophrenia from those with prolonged medical adversity. *J Psychiatr Res*. 2014; **55**: 126–132.
150. Tas C, Brown EC, Aydemir O, Brüne M, Lysaker PH. Metacognition in psychosis: comparison of schizophrenia with bipolar disorder. *Psychiatry Res*. 2014; **219**(3): 464–469.