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Highlights

- Functional significance of Theory of Mind in schizophrenia is supported
- ToM interventions produced more improvement in ToM assessments
- more realistic learning environments may facilitate the development
- immersive Virtual Reality might be a promising tool for future development

Interventions for the treatment of Theory of Mind deficits in Schizophrenia:

Systematic Literature Review

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Abstract:

Theory of Mind (ToM) plays a central role in regulating social interactions and its impairment is consistently reported in schizophrenia. Regarding schizophrenia, ToM is usually discussed as a sub-domain of social cognition. Since social cognitive deficits have drawn the attention of researchers, a variety of novel treatment techniques and approaches targeting social cognitive deficits have been developed. Encouraging results have repeatedly been reported on the modifiability of social cognitive impairment through these techniques. However, emotional perception seems to be over-represented in these approaches at the expense of other areas, such as ToM.

This article presents a systematic review on the social cognitive interventions of the last 10 years, which focused on the remediation of ToM or used techniques primarily focusing on one or more social cognitive domains other than ToM, but with hypothetical effects on it. The aim of our systematic review was to compare these intervention techniques in order to see how effective they are in the remediation of ToM, and to find the best techniques to ameliorate ToM deficits in schizophrenia. According to our findings targeted ToM intervention produced more improvement in ToM tasks, while data regarding non-ToM interventions showed contradictory results with limited effects on ToM.

Keywords: Theory of Mind, Schizophrenia, Virtual Reality

Abbreviations: Theory of Mind (ToM), randomized controlled trial (RCT), Treatment as Usual (TAU), Theory of Mind Intervention (ToMI), Social Cognitive Training (SCT), Emotion and ToM Imitation Training (ETIT), Cognitive-Emotional Rehabilitation (REC), Social Cognition Interaction Training (SCIT), Social Cognitive Skills Training (SCST), Treatment of Affect Recognition (TAR), Social Cognition Enhancement Training (SCET), “Schizophrenia – Facial Affects Recognition Cognitive Enhancement” (GAIA’s-face) virtual reality (VR), Problem Solving Skills Training (PST)

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1. Introduction

Theory of Mind (ToM) refers to the ability to consider various viewpoints in the process of attributing mental states (e.g. emotions, intentions) to others, based on available social context and social cues (Allen et al., 2008)□. Understanding and conceptualizing other peoples' mental states is a key aspect in the regulation of social interactions (Brüne, 2005), and its impairment can lead to incompetent social judgements.

Since the first proposition of the concept of ToM, it has been well acknowledged that its impairment might have an important role in the explanation of several psychopathological symptoms in certain psychiatric disorders (Brüne and Brüne-Cohrs, 2006; Premack and Woodruff, 1978). Regarding schizophrenia Minkowski (1927) and Cameron (1944) might have been the first two authors who have suggested that failure in making appropriate social judgements are core feature of schizophrenia. However, the importance of ToM deficit in schizophrenia was first acknowledged several years later by Frith (Frith and Corcoran, 1996), followed by numerous studies supporting that ToM is typically impaired in this disease (Abu-Akel and Shamay-Tsoory, 2013; Bora et al., 2009; Brüne, 2005; Langdon et al., 2006; Sprong et al., 2007).

Although ToM impairment appears to be an important feature of schizophrenia, it is still not clear whether it is a specific deficit or it is a consequence of the general cognitive impairment in schizophrenia. Earlier evidence mainly supported neurocognitive impairment as a core predictor of social functioning (Kurtz and Tolman, 2011), however social cognition and its subdomains, such as ToM became the focus of researchers' attention, in the last decades. To identify specific domains as best possible targets for new interventions, it is crucial to explore the differential associations between neurocognitive impairment, impaired ToM and social functioning.

Regarding the mentioned relationship Couture (Couture et al., 2011) showed that in schizophrenia ToM might be an important mediator and moderator between neurocognition (working memory, executive functions, verbal and visual memory and learning) and social competence. According to

their model neurocognition explained 17.3% of the variance of ToM, while neurocognition and ToM was accounted for 20% of the variance in social competence. Their results, along with previous findings support that there is a specific ToM deficit in schizophrenia, where ToM may explain approximately 15-40% of the variance of social functioning in schizophrenia (Bora et al., 2006; Brüne, 2005, 2006; Couture et al., 2011; Harrington et al., 2005; Roncone et al., 2002). In order to help understanding the role of ToM deficits in schizophrenia, several theories have been proposed. Frith suggests that ToM develops normally before the manifestation of the illness, and the development of schizophrenic symptoms can be understood through the later impairment of ToM (Corcoran et al., 1995; Frith, 2000; Frith and Corcoran, 1996)□. According to his model, schizophrenic symptoms can be explained as cognitive misinterpretations of others' mental states and can be traced back to impaired monitoring of one's own and others' behavior and mental states (Corcoran et al., 1995; Frith, 2000; Pickup and Frith, 2001)□. For example, patients' inability to taking into account that others not necessarily share common knowledge with them (and therefore neglecting their social cues) may result in formal thought disorder, while the difficulties of monitoring others' mental states, (in this case monitoring refers to the impaired process of gathering information which guides the patient to inadequate judgement about other's mental states) may result in delusions of persecution (Frith, 2004)□.

Other authors say that the problem is not only the insufficient monitoring of one's actions, but also the inadequate representations of others' mental states, and the inability to integrate relevant information from the context. This conception assumes that ToM deficit in schizophrenia can be primarily associated with impaired planning and executive functions and mainly resulted in language and thought disorganization (Hardy-Bayle et al., 2003).

Besides the above-mentioned conceptions simulation theory suggests that ToM relates to the ability of imaginatively modeling others' observed behaviors. (Gallese, 2005). Regarding schizophrenia in the theoretical concept of simulation theory, impaired ToM might be the result of the patient's

inability to imaginatively mimicking or replicating others' mental states, where the success of the process based on the memories of past experiences. This conception suggests that ToM impairment in schizophrenia is mainly associated with impaired mnemonic system and can be resulted in negative symptoms (Park et al., 2008).

Another interesting theory proposed by Abu-Akel argues that not only the above described deficits of ToM may occur in schizophrenia, but “Hyper ToM” is also a possibility, where the patient “over-attributes” intentions, desires or feelings to someone else. According to the authors (Abu-Akel and Bailey, 2000) this kind of ToM impairment may relate to pragmatic language impairment, where the patients have difficulties in following pragmatic rules of language during social interactions, and as a result they cannot express intentions or perceive others expressed intentions properly. Delusions might be good examples of this form of the impairment. Furthermore, Abu-Akel places ToM deficits along a continuity model. Specifically, this conception suggests that from the complete loss of ToM to “Hyper ToM”, patients with schizophrenia might be characterized by different degree of ToM deficit. (Abu-Akel and Shamay-Tsoory, 2013)□.

While the significance of ToM in schizophrenia is well documented (Brüne, 2006; Roncone et al., 2002)□, it seems to be underrepresented in the development of new forms of therapeutic interventions. A variety of novel remediation strategies have been developed in the last decades in order to ameliorate social cognition deficits in schizophrenia. Emotion perception seems to be over-represented among these new techniques at the expense of other areas, such as ToM. Previous meta-analyses showed encouraging results on the modifiability of all sub-domains of social cognition, and on the improvement of social functioning. However, the contribution of the targeted sub-domains to the final results on social functioning remains unclear, as well as the results on the effectiveness of the different interventions on ToM impairment are contradictory (for example, great variance in effect sizes) (Kurtz and Richardson, 2012; Kurtz et al., 2016; Statucka and Walder, 2013; Tan et al., 2016).

Considering the mentioned research directions, our review aimed to explore the currently existing methods for improving ToM in schizophrenia, compare these methods along their effectiveness in the remediation of ToM, and identify the best existing techniques to improve ToM deficits in schizophrenia.

2. Methods

2.1. Search strategy

In this review we attempt to summarize existing social cognitive interventions that focus on the remediation of ToM or use techniques targeting at least one area of social cognition other than ToM (social perception, attributional style, emotional perception), but with hypothetical effects on the ability to infer others' mental states. We used a computer-based search of PubMed, Cochrane, Scopus and Ebsco databases from 2006-2017.01.01. to identify relevant articles and systematized manually. The following keywords were used: schizophrenia AND Theory of Mind OR mentalization AND remediation OR training OR intervention. We also used the term Virtual Reality, since the rapid development of computer techniques have been successfully infiltrating medical treatment and have become very popular also among the developers of new cognitive and social cognitive interventions. We also studied the reference sections of the identified articles for relevant literature. A 10-year cut-off was used because comprehensive reviews (highlighting the interventions' effects on ToM) have been published for earlier studies (Kurtz and Richardson, 2012).

Our study followed PRISMA guidelines for systematic reviews.

2.2. Study selection

The inclusion criteria were that studies had to use social cognitive interventions, defined as methods that were developed to improve areas of social cognition within broad psychosocial approaches. A

combination with training of neurocognition was allowed, but the majority of interventions had to aim at social cognition, or the effect of neurocognitive intervention had to be ruled out (a) (Bechi et al., 2015, 2013, 2012)□. The included studies also had to: be written in English (b), be a randomized controlled trial (RCT) (c), have the majority of the sample with a diagnosis of schizophrenia spectrum disorder (d), and use at least one ToM outcome measure (e).

Some of the interventions, based on the Shamay-Tsoory model (Abu-Akel and Shamay-Tsoory, 2013)□, highlight the multidimensional nature of ToM, where cognitive ToM refers to the process of attributing intentions to other people, while affective ToM is about attributing feelings to others. Affective ToM assumes intact empathy, which raises the possibility of using empathy tests in the assessment of ToM. We included studies using these kinds of assessments only if the authors tagged these tools as ToM tasks (Bechi et al., 2015, 2013, 2012; Pino et al., 2015).

Study selection (Fig.1. 2.) was made along the following steps: The first two authors reviewed each record independently from each other. In case of any disagreement between the two authors, another author was involved in a common decision-making process. Based on the described methods, 7462 articles were identified. After the exclusion of duplications, 7005 further studies were excluded, based on their titles or abstracts. After reading the full-texts of the remaining 47 articles, 30 more were excluded. Therefore, based on inclusion and exclusion criteria, 17 studies were found eligible for inclusion (Table 1, and Table 2).

3. Results

Among the 17 included papers, 10 studies used non-ToM interventions (techniques targeting at least one of the following areas of social cognition: social perception, attributional style and/or emotional perception, and the authors hypothesizes that these techniques might have generalized effects on ToM) (See Table 1, and Table 2) (Choi and Kwon, 2006; Gaudelus et al., 2016; Horan et al., 2011, 2009; Roberts et al., 2014; Roberts and Penn, 2009; Tas et al., 2012; Taylor et al., 2016; Wang et al.,

2013; Wölwer and Frommann, 2011). We also reviewed targeted ToM interventions, which used techniques defined by the authors as interventions specifically aimed at ToM deficits. Seven studies met these criteria (See Table 2) (Bechi et al., 2015, 2013, 2012; Kayser et al., 2006; Mazza et al., 2010; Pino et al., 2015; Veltro, 2011)□. The reviewed studies included 681 patients. Twelve studies reported results on social functioning besides ToM. There were 14 different ToM assessment tools, and 11 different social functioning scales used in the reviewed 17 papers.

3.1. Targeted ToM interventions

Targeted ToM interventions were specifically designed to improve the patients' ability to attribute mental states to others. These types of interventions have some characteristics in common. They use vignettes, comic strip tasks or short video scenes as training materials to present social interactions, where the patients are asked to identify and analyze the characters' mental states. Their specificity is given by the intensity of the training, the content of the presented situation and the characteristics of the therapeutic interventions. The included targeted interventions are presented below.

Kayser et al. (Kayser et al., 2006)□ developed a training technique using short video scenes (20-70 sec) to incite chronic schizophrenic patients to explore others' minds, and to help them better understand them. The training consisted of two weekly sessions. Six video scenes were presented in each session. The approach of the training can be understood in the theory of Hardy-Bayle, as it aims to incite chronic schizophrenic patients to explore (monitor) others' minds, help them make more adequate representations of those, and integrate these with relevant contextual information. Despite the short length of the treatment, the video group showed significant improvement in inference of mental states of others after treatment, while no improvement was found in the Treatment as Usual (TAU) group. Although between-group comparison didn't show any significant differences, the results are encouraging and hold the promise of direct improvement of ToM (pre- to

posttreatment comparison: $d=0.6$, $p<0.05$). Kayser's experiences and results led other authors to design specific training materials using videos for schizophrenic patients.

For example, Bechi et al. (Bechi et al., 2015, 2013, 2012) developed two different methods. One of them used comic strips, and the other used video scenes. They also used neurocognitive training before these interventions, but due to accurate methodological design, the effect of the social cognitive interventions could still be evaluated independently. One of the mentioned methods is Theory of Mind Intervention (ToMI) (Bechi et al., 2012)□, which uses comic strips to educate patients on how to identify and reach out for relevant details from the context, and how to recognize hidden meanings during a conversation. This treatment provides one-hour long group sessions. Two sessions were held for nine weeks. On the other hand, they used Social Cognitive Training (SCT) (Bechi et al., 2013), which uses short video scenes (30-70s) about social interactions. Initial videotapes focus on the display of basic emotions. Through the process these scenes display more complex interactions with ToM-specific content in focus (e.g. irony). Both techniques focused not only on the monitoring process during mentalization, but also on the integration of the gained information with relevant contextual clues. Therefore, their approach can be linked to the conception of Hardy-Bayle (Hardy-Bayle et al., 2003). SCT includes three-month weekly sessions lasting about one hour, their results support the feasibility and efficacy of both techniques in amelioration of ToM and social functioning. Statistical analysis supported a significant pre- to posttreatment improvement on all ToM tasks (except third order beliefs) with medium to large effect size for both ToMI ($d=0.61-0.71$), and SCT ($d=0.64-0.91$). When compared to the active control group (newspaper discussion, standard social cognitive training or standard rehabilitation treatment program) greater progress was found (ToMI: $p=0.037-0.042$; SCT: $p=0.002-0.008$). They also compared the two treatment groups where no significant differences were found (Bechi et al., 2015)□. The results also supported the independence of ToM performance after these treatments from the effect of cognitive remediation.

Another treatment approach was designed under the influence of the “simulation” theory (Gallese, 2005). This theory led Mazza et al (Mazza et al., 2010) to the assumption that the process of mental state attribution may be improved by using imitation and observation. They developed the Emotion and ToM Imitation Training (ETIT), which guides the patients through four phases as follows: phase 1: observation of eye direction of other people. phase 2: observation and imitation of facial expressions phase 3-4: attribution of mental states, using the gained information on other’s observed actions in comic strip tasks (Mazza et al., 2010). The tasks were presented to the patients in two sessions per week for three months, where one meeting lasted about fifty minutes. According to their results, after the ETIT, increased performance was detected in false belief understanding, and emotion and intention attributing compared to Problem Solving Skills Training (PST) (between-group difference: $\eta^2=0.64-0.98$; $p<0.002$). Another research study, using the same control group (PST) confirmed these results. Pino (Pino et al., 2015) reported that patients in the ETIT group showed better performance on ToM tasks (both on cognitive and affective aspects) compared to the control group (between-group difference: $p=0.05-0.03$). Both the treatment and the control conditions showed significant effect on social functioning, with no significant between group differences. Their results suggest that imitation can be a good technique to help patients become more able to correctly infer intentions.

Finally, Cognitive-Emotional Rehabilitation (REC) is a structured method that mainly focuses on affect recognition, but specifically addresses ToM as well. REC primarily uses psychoeducation and other cognitive-behavioral techniques (Veltro, 2011), but unlike previously described methods, in this training no specific training materials were used; the patients had to observe and analyze other patients’ facial expressions with the guidance of a conductor. The training consisted of six months weekly group sessions, with 8-12 patients per group. Compared with PST, both the treatment and control groups showed improved performance on emotion perception and social functioning tasks, however, according to the statistics, REC showed greater improvement. It is also pointed out that

only subjects in the REC group showed significantly better performance on first-order ToM (between-group difference: $F(1,22) = 7.3, p < 0.05$). These results provide further evidence that ToM can be directly modified through targeted interventions, even though in this case REC did not show significant effect on higher-order false belief tasks.

3.2. Non-ToM interventions

3.2.1. Broad based non-ToM interventions

Non-ToM interventions usually focus on more subcomponents of Social Cognition. In these approaches the focus is more on general amelioration, without any particular attention to one area. Among these interventions, Social Cognition Interaction Training (SCIT) is one of the most generally used (Roberts et al., 2014; Roberts and Penn, 2009; Taylor et al., 2016; Wang et al., 2013). SCIT guides the patients through three phases. The first phase attempts to improve handling of emotions, the second phase addresses attributional style and ToM, and the goal of the third phase is the integration of the learned skills. SCIT provides five-months weekly sessions, where the duration of one session is 60 minutes. Four of the included studies used this type of intervention. Three of them used SCIT with outpatients (Roberts et al., 2014; Roberts and Penn, 2009; Wang et al., 2013)□, and one of them used its modified version with forensic patients (shorter version with the same structure) (Taylor et al., 2016). These efforts to improve ToM displayed mixed results. Only one of them could show ToM improvement related to SCIT, with a medium to large effect size (between--group effect sizes regarding ToM measurements: $p < 0.001, \eta^2 > 0.24$) (Wang et al., 2013), while the other three were not able to show any significant advantages of SCIT over TAU in ToM assessments (Roberts et al., 2014; Roberts and Penn, 2009; Taylor et al., 2016). However, three studies reported significant progress on social functioning scales (within group effect sizes regarding SCIT: $p < 0.05; d = 0.31-1.17$). One possible explanation of the contradictory results on ToM performance is the diversity of assessment tools. Some of the used assessments aimed at the cognitive component of ToM (Roberts et al., 2014; Roberts and Penn, 2009), while others were

developed to assess the affective component (Wang et al., 2013)□. With this in mind, the results showed more effect on affective component in one case (between group effect size: $p < 0.001$, $\eta^2 > 0.24$) (Tas et al, 2012). Finally, as the authors raise the possibility that increasing the training intensity could likely be associated with more promising results. SCIT became the basis of other interventions, such as F-SCIT, which is a family-assisted version of SCIT (Tas et al., 2012)□, or Social Cognitive Skills Training (SCST) (Horan et al., 2011, 2009). The development of F-SCIT is based on the presupposition that active cooperation of family members or close friends may help patients in transferring the learned skills from an artificial learning environment to real life interactions. To test this hypothesis, Tas et al. (Tas et al., 2012) have extended the original SCIT program. They kept the main structure of the program, but they modified the proportion of sessions among the three main phases. They also added one individual session to the phase of integration. Both modifications were intended to help patients use the learned skills more effectively in everyday life. The whole training contained 80 minutes long weekly sessions for three-months. In addition, each patient chose a close friend or a family member who participated in a four-session long training. (each session lasted one hour) Compared with the active control condition, F-SCIT was found to be highly significant in the development of social functioning (on all sub-scales of the Social Functioning Scale except the independence and employment sub-scales between group effect size was: $d = 0.22-0.79$; $p < 0.05$), and the cognitive component of ToM, where between-group effect sizes were large ($d = 1.16$; $p < 0.001$), and within-group effect sizes were in the range of small to medium ($\eta^2_p = 0.54$, $p < 0.001$). Contrary to previously described results on the effectiveness of SCIT, F-SCIT did not show significant improvement in the affective aspect of ToM (between group effect size: $d < 0$), however they used the same tool to assess this component, and used the intervention among outpatients, like in previous studies with SCIT. Small sample sizes may at least partially explain the differences.

As mentioned above, developers of SCST also used SCIT as a basis. Horan et al. (Horan et al., 2011, 2009) combined successful elements of SCIT with elements of Treatment of Affect Recognition (TAR) (Wölwer and Frommann, 2011) and with some novel techniques. SCST dedicates one module to each domain of social cognition as follows: The first module addresses the identification of emotions in the voice and on the face of others, the second attempts to improve the understanding of non-verbal social cues and contextual information, the goal of the third is to make the complex nature of suspiciousness more understandable, while the fourth focuses on the integration of the previously learned skills in order to improve mental state attribution. (Horan et al., 2011, 2009) □. In SCST each session lasts one hour, and the whole training takes four months, where two sessions are held weekly. Studies on the efficacy of SCST were able to present stable results of beneficial effects over control conditions only for affect recognition. SCST did not show any significant improvement in ToM tasks (within SCST group; $d=0.19$; $p>0.05$; between group $\eta^2p=0.005$, $p>0.05$). The authors published two RCTs in this field, but only one of them included assessment of social functioning. In this case, SCST did not show any significant improvement in performance on social functioning scales. Considering the previously described experiences with SCIT or F-SCIT, these results are quite confusing. The authors suggest that small sample size, low intensity of training or unknown psychometric properties of commonly used social cognition assessment tools may be responsible for the inconsistency with previous findings.

Another interesting approach, the Social Cognition Enhancement Training (SCET) uses comic strips as training material (Choi and Kwon, 2006). In this training, patients were encouraged to recognize and use relevant social cues on the pieces of a cartoon, try to arrange these pieces in the right order based on the extracted information, and explain the displayed social situation coherently. The training consisted of two, one and a half hour long sessions every week for six months. According to their findings, the SCET group showed significant improvement only on one ToM outcome measure (Picture Arrangement Test) (between-group difference: $F(3,16) = 3.40$, $p<0.05$),

while on the other ToM or emotion perception tasks no improved performance was detected. The psychometric characteristics of the applied assessments in this study are less known, which may at least partially explain the weak effect of the treatment (Choi and Kwon, 2006).

3.2.2. Targeted non-ToM interventions

Some targeted methods were also included in the “non-ToM intervention” category. These programs primarily focused on one social cognitive domain other than ToM (social perception, attributional style or emotional perception), but investigated the generalized effect of these trainings on the inference of mental states (at least one ToM outcome measure was used). Both of these targeted non-ToM interventions primarily addressed affect recognition. One of them was the TAR (Wölwer and Frommann, 2011). The program comprises of strategies such as approach of error-less learning or self-instructions, and guides the patients through three modules, characterized by increasing complexity, from discrimination of basic emotions to recognition of emotions in social interactions. Although TAR was mainly designed to improve affect recognition, according to the Shamay-Tsoory model, attribution of emotions to other people can be defined as affective ToM, which may explain the significant improvement observed in ToM measures in the treatment group, compared to the control group (between -group difference: $d=0.89-1.14$; $p<0.004$). However, TAR-associated changes in the performance of social functioning tasks were not as stable. Pre- to post treatment comparisons showed significant improvements ($d=0.58-0.75$; $p=0.019$), but the authors did not report any significant differences over the cognitive remediation training (Wölwer and Frommann, 2011).

Gaudelus et al. (Gaudelus et al., 2016) used another targeted social cognitive remediation that also aimed at facial affect recognition. “Schizophrenia – Facial Affects Recognition Cognitive Enhancement” (GAIA’s-face) guides the patients through three phases from the recognition and discrimination of basic emotions to understanding of dynamic, complex social situations. The

training contains one hour long weekly sessions for ten weeks. Contrary to previously mentioned results, participants in cognitive remediation group (focusing on selective attention) were superior in the performance of Hinting Task ($p=0.01$) compared to social cognitive intervention group, while the authors did not report any significant differences in other ToM tasks (between group difference: $p=0.086$; Reading the mind in the eyes test, Versailles-Situational Intention Reading). However, on one of the social functioning scales, the superiority of the GAIA group could be proven. Inconsistent findings may be interpreted by the approach underlying the cognitive remediation program. Supported by previous findings on the association between attentional deficits and facial emotion recognition, cognitive remediation group mainly focused on selective attention to improve the ability of focusing on relevant facial features (Gaudelus et al., 2016). According to the literature, another possible explanation of the inconsistent results may be that different ToM tasks may aim at different aspects of ToM (e.g. affective or cognitive aspects) (Abu-Akel and Shamay-Tsoory, 2013; Bora et al., 2006).

4. Discussion

To our knowledge this is the first study to review RCTs of ToM intervention possibilities. Our experiences are in line with the results of a previous meta-analysis of social-cognitive trainings in schizophrenia (Kurtz and Richardson, 2012)□. Its findings support the modifiability of the ability of mental state attribution, with small to moderate weighted mean effect size ($d: 0.46$, 95% CI: 0.15-0.78). They also reported significant heterogeneity between the overall effect sizes of the studies, however they focused on the nature of the ToM measures but did not consider the type of intervention. Contrary to this approach, we distinguished between “Targeted ToM” and “Non-ToM” interventions, depending on whether they focused specifically on ToM amelioration or not. This current review of the relevant findings in the literature support our expectation that targeted ToM interventions produced more improvement in ToM assessments, while data regarding non-ToM interventions showed contradictory results, with limited effect on ToM (both for targeted and broad-

based interventions). These inconsistent findings may reflect the unknown psychometric properties of some ToM measurements (e.g. ceiling effect or reliability). In some cases, ToM results were contradictory even within the same study (Roberts et al., 2014; Roberts and Penn, 2009) raising the possibility that these ToM measuring tools (See Table 1, and, Table 2) evaluate different aspects (and/or levels) of this construct. The Shamay-Tsoory model supports this interpretation (Shamay-Tsoory et al., 2010). According to their model, ToM includes multiple processes. These processes can be divided into at least two subcomponents: affective (inferring others' emotions) and cognitive subcomponents (inferring others' thoughts and intentions), where intact ToM ability requires the integration of both mentioned subcomponents. This approach suggests that both aspects need to be considered during the development of new training programs or assessment tools.

Some other factors may also contribute to poor and inconsistent outcomes, such as small sample sizes or the heterogeneity of the samples (e.g. illness duration, inpatient vs outpatient subjects). A previously reported meta-analysis suggested the possibility that there may be some connection between illness duration and the efficacy of social cognition training, as they found that longer illness duration led to better performance in social cognition interventions (Kurtz and Richardson, 2012). In this review only two of the included non-ToM intervention studies reported results on the duration of the illness. Some authors also claim that increasing the training intensity could likely be associated with more promising results. Finally, although non-ToM interventions usually use interactive computer-assisted techniques, the learning environments are still far from real-life interactions, which may contribute to the possibility of less successful adaptation of the acquired skills.

Contrary to non-ToM interventions, ToM interventions usually use training materials, such as video tapes or comic strips, making the learning environment more similar to real-life situations, and therefore holds the possibility to the transfer of the learned skills easier for the participant. Our findings strengthen the probability of that relationship, since results regarding targeted ToM

interventions consistently support the supposition that these techniques, specifically aimed at mental state attribution may be more effective in the remediation of ToM than non-ToM approaches. Both video-based and comic strip-based interventions were associated with greater improvement on ToM tasks usually with medium to large effect sizes. These conditions also had detectable superiority over control conditions and seem to be able to take into account both affective and cognitive aspects of ToM, however, third order false beliefs remained challenging for the patients. According to the authors, the lack of improvement of third order beliefs could be due to basal neurocognitive deficits associated with schizophrenia, which makes the understanding of tasks with higher complexity harder for the participants (Bechi et al., 2015, 2012). On the other hand, the improvement in performance on second order beliefs indicates the modifiability of complex mentalizing abilities. In addition, exploration of targeted ToM interventions suggests that techniques such as forcing the manipulation of others' mental state, using verbalization during the training, or using imitation and observation, may contribute to the effectiveness of these interventions (Bechi et al., 2015, 2013, 2012; Kayser et al., 2006; Mazza et al., 2010).

Twelve out of the 17 studies (7 non-ToM interventions, and 5 ToM interventions) reported results on social functioning. Interventions for both groups had an effect on social functioning, and almost all intervention techniques showed advantages over the control condition. However, results of the included studies do not make it possible to draw conclusions about the relative efficacy of these training programs, as most of them use only one score to describe overall social functioning. Social functioning is a broader construct, with many components, such as employment or personal autonomy. It's possible that these aspects have different sensitivity with respect to the type of intervention. More studies are needed to reveal these connections.

Included interventions mainly focus directly on social cognitive processes, with less attention to making patients aware of these dysfunctions. The use of meta-cognitive strategies could overcome this limitation. Although several studies showed encouraging results of meta-cognitive strategies in

social cognitive remediation, none of them met our inclusion criteria (Moritz et al., 2011; Rocha and Queirós, 2013).

Interestingly, contrary to our expectations, we did not find any studies that used VR to improve ToM in schizophrenia and fulfilled the inclusion criteria at the same time. However, a recent review (Tan et al., 2016) on social cognitive interventions, with less strict inclusion criteria, managed to include two studies using VR. According to their findings, VR-assisted training programs were associated with improved performance in social functioning tasks in patients with schizophrenia. However, these training programs did not specifically aim at social cognition, and therefore the effect of VR interventions on social cognitive assessments was not examined. They also reported high satisfaction among the patients who participated in VR groups. Other studies evaluating the feasibility of VR in psychosis also reported that patients' positive attitude towards participating in VR environments, even if they knew that it involved confrontation with fearful situations (Cobb et al., 1999; Da Costa and De Carvalho, 2004; Pot-Kolder et al., 2016)□. Due to the revealed unique motivational effect of VR environments, this technology may contribute to the success of future interventions, as lack of motivation is often a major obstacle to the effective delivery of treatment in schizophrenia (Freeman et al., 2016).

Focusing on ToM, in commonly used social cognitive interventions, patients usually analyze presented situations (e.g. using vignettes) (Gaudelus et al., 2016; Mazza et al., 2010). In virtual environments, patients can get inside such situations, and learn mentalizing skills in real-time interactions with an avatar□. Reactions of the patient are recordable, directly observable, and analyzable, which may form the basis of the clinician's (or the avatar's) feedback. Virtual situations are repeatable and therefore allow the participant to practice and incorporate these feedbacks. It provides a safe learning zone, making it possible to keep a social situation entirely under control, be interrupted if necessary and avoid harm, such as the stigma of mental illness (Freeman, 2008; Freeman et al., 2016; Rus-Calafell et al., 2014).

In summary, our review suggests that targeted ToM interventions may be effective in improving ToM in schizophrenia. The use of training materials sufficiently similar to real-life situations may facilitate the transfer between learning environment and real-life interactions. Thus, although no VR studies were included in our review, the related and already reported advantages of VR technology makes it a possible and promising future direction in treatment development and assessment for ToM in schizophrenia

Finally, certain limitations of our review should be noted. First, non-English and unpublished work were excluded. Thus, publication bias cannot be avoided. Unpublished negative results may affect our conclusions and lead to overestimation of the effectiveness of targeted ToM interventions. Second, due to the cultural specificity of social cognitive domains, the low number of studies from areas other than Europe and the USA limits the generalizability of our findings to other regions. Third, this review only studied the effect of social cognitive interventions on ToM and Social Functioning, however the generalization effect of targeted ToM interventions to symptomatology or other social cognitive or neurocognitive domains would be an interesting question. Fourth, as we noted, important sample information is often not reported, which also limits to draw firm conclusions. Fifth, in many cases, psychometric characteristics of the used assessments are not known, and this fact limits the possibilities for interpretation and conclusions.

New ToM and social cognitive interventions are under development or research, which means that our understanding of the relationship between ToM and schizophrenia, as well as our possibilities to improve ToM in schizophrenia shall further improve in the near future (Fekete et al., 2016; Peyroux and Franck, 2016; Vázquez-Campo et al., 2016).

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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Figure 1 Flowchart of study selection process

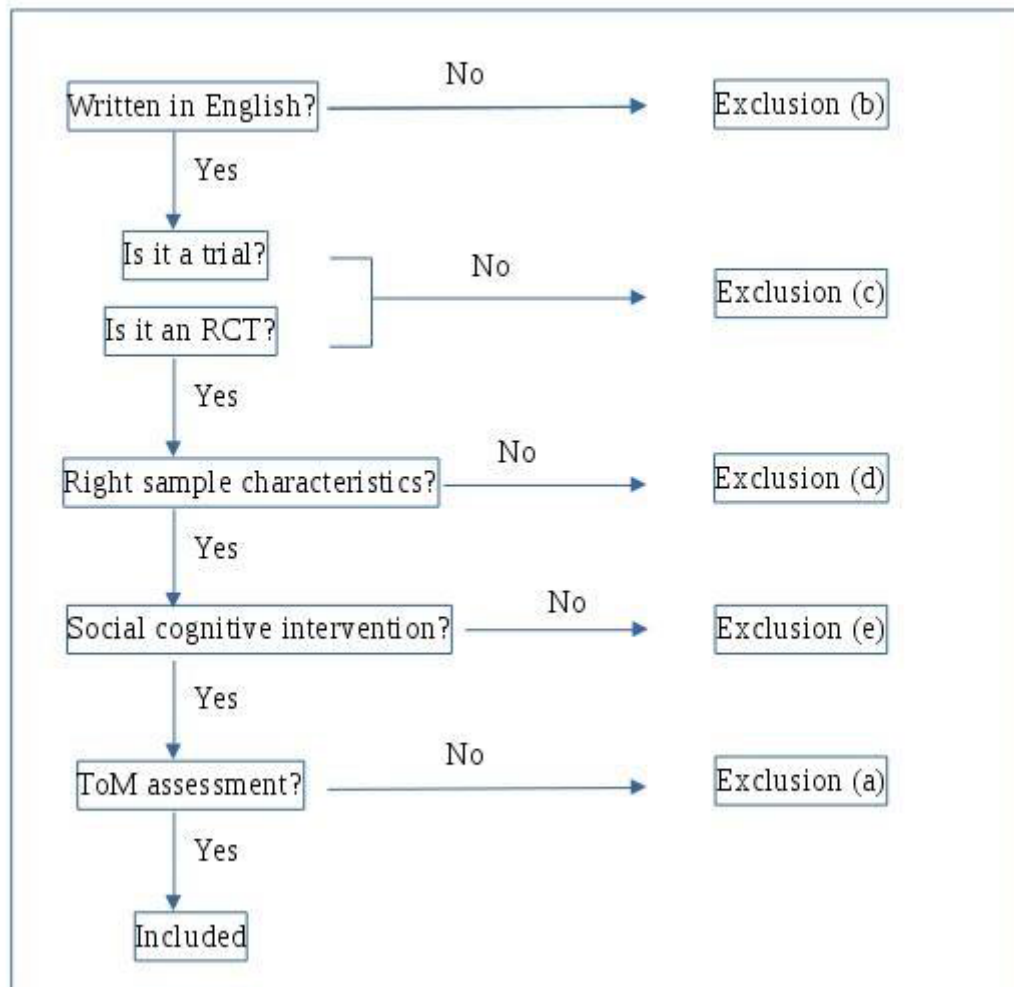


Figure 2 Flowchart of study selection

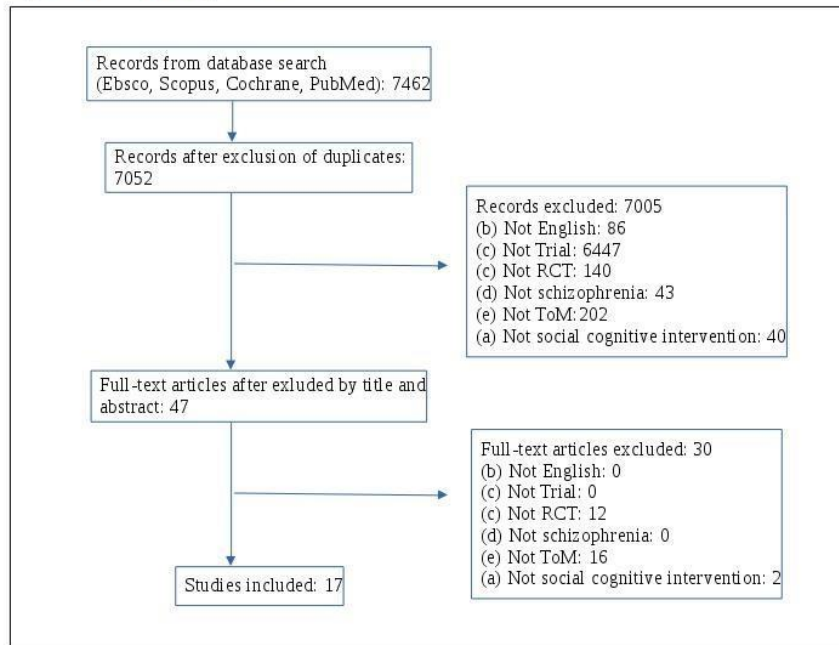


Table 1. Studies of Non-ToM interventions in Schizophrenia included in the review (n: 9)

Author	Sample size and diagnosis (N)	Mean Age (years)	Gender (Male %)	Duration of Illness (years)	Social cognition intervention	Control Condition	Intensity of Intervention	ToM Outcome Measures	Social Functioning Measures	Major Findings (ToM and social functioning if reported)
Choi et al. (2006)	N:34 (schizophrenia or schizoaffective disorder)	SCE T: 20.8, CG: 34.0	55.38 %	29	Social Cognition Enhancement Training (SCET) (n:17)	Standard Psychiatric Rehabilitation Training (CG=Control Group) (n:17)	1.5 h sessions, 2 sessions/week for 6 months	Picture Arrangement (PA), Social Behavior Sequencing Task (SBST)	Not Reported	The SCET group, showed significant improvements on PA ($F(3,16) = 3.40, p < .05$) over CG, no interaction effects were found for SBST.
Gaudelus et al. (2001)	N:40 (schizophrenia)	GAI A: 31.7, RE CO S: 33.7	GAIA : 81% REC OS: 79%	Not Reported	GAIA' s-face (Schizophrenia-Facial Affects Recognition Cognitive Enhancement) (n:21)	RECOS (neurocognitive remediation) (n: 19)	Three 1 h sessions/week for 10 weeks	Eyes Test, Versailles-Situational Intention Reading, Hinting Task	Echelle Social Autonomy Scale (EAS)	No improvement was found on the Hinting Task in the GAIA group, while the scores of the RECOS group showed a significant effect (T2-T1 mean, $p: 0.01$). no improvement on any other ToM tasks. Significant improvement on EAS in the GAIA group (T2-T1 $p: 0.086$).
Horton et al. (2009)	N:31 (schizophrenia or schizoaffective disorder)	SCS T: 50.7, CG: 45.9	SCST : 87%, CG: 100%	Not Reported	Social Cognition Skills Training (SCST) (n:15)	"Illness self-management and relapse prevention skills training" (ISF) (n: 16)	group interventions, 1 h /session, 2 sessions/week for 6 weeks	The Awareness of Social Inference Test (TASIT)	Not Reported	No significant improvement on TASIT in SCST.
Horton et al. (2011)	N:68 (primary psychotic disorders, 89.7% schizophrenia or schizoaffective disorder)	SCS T: 51, NR: 46.6, ST: 45.1, H: 50.4	88.24 %	Not Reported	SCST(n:16)	Cognitive remediation, (CRT) (n: 19) illness management skills training, (ST) (n:19) hybrid treatment (CRT + SCST) (H) (n:14)	1 h sessions, 2 sessions/week for 12 weeks	TASIT	UCSD Performance-based skills assessment, (UPSA), Maryland Assessment of Social Competence (MASC)	No significant improvement for ToM or for social skills

Table 1. Continued

Author	Sample size and diagnosis (N)	Mean Age (years)	Gender (Male %)	Duration of Illness	Social cognition intervention	Control Condition	Intensity of Intervention	ToM Outcome Measures	Social Functioning Measures	Major Findings (ToM and social functioning if reported)
Roberts et al. (2009)	N:31 (schizophrenia)	SCI T: 36.9, TAU: 41.4	SCIT: 55% TAU: 64%	Not Reported	Social Cognition Training (SCIT) +TAU (n: 20)	Treatment as Usual (TAU) (n:11)	1 h sessions/week for 20 weeks	Hinting Task, TASIT	Social Skills Performance Assessment (SSPA)	In SCIT group no significant improvement on the Hinting Task, but approached significance in TASIT. (F=4.24, P=0.07, d: .05). SCIT group showed improvement in social skills (p: 0.024, d: 1.17).
Roberts et al. (2014)	N:66 (schizophrenia or schizoaffective disorder)	SCI T: 40, TAU: 39.4	66.66%	Not Reported	SCIT (n: 33)	(TAU) (n:33)	1 session /week for 6 months	Hinting Task, TASIT – Social Inference Enriched Subtest	SSPA, Global Social Functioning Scale (GSFS), Quality of Life Scale - Social and Work subscales (QLS-S, QLS-W)	No significant advantage of SCIT could be shown over TAU in any ToM tasks. SCIT group showed improvement on GSFS (post treatment: p<.07 d=.38, follow-up. P<.05, d: .43), and on SSPA (post treatment: p=.07, d=.31, at follow up, no significant differences).
Tas et al. (2012)	N:49 (schizophrenia)	F-SCI T: 33.3, SS: 34.6	F-SCIT: 57.9%, SS: 46.2%	F-SCIT: 12.63, SS: 11.85	Family-assisted Social Cognition and Training (F-SCIT) (n:19)	Social Stimulation (n: 26)	80 min/week for 14 weeks for the patients, and 60 min/week for four weeks	Hinting Task, Eyes Task	Quality of Life Scale (QLS), Social Functioning Scale (SFS)	A significant improvement on nearly all social functioning subscales (SFS, QLS)(within group effect sizes: d:0.22-0.79, p<0.05 between-group effect sizes: n^2_p :0.08-0.42, p<0.05). (Except Employment and Independence subscales) . Significant effect on cognitive aspects of ToM (within group effect sizes: d:1.16, p<0.001 between-group effect sizes: n^2_p :0.54, p<0.001), less effects on perceptual (or affective) aspects of

ToM (within group
effect sizes: d:-0.02,
between-group
effect sizes:
 η^2_p :0.02).

Table 1. Continued

Author	Sample size and diagnosis (N)	Mean Age (years)	Gender (Male%)	Duration of Illness	Social cognition intervention	Control Condition	Intensity of Intervention	ToM Outcome Measures	Social Functioning Measures	Major Findings (ToM and social functioning if reported)
Taylor et al. (2016)	N: 36 (schizophrenia spectrum)	SCIT : 40.7, TAU : 39.2	100%	Not Reported	Modified SCIT for forensic inpatients (n: 21)	Treatment as Usual (TAU) (n:15)	2 session/week for 8 weeks	Hinting Task,	Not Reported	No significant improvement for ToM in SCIT group.
Wang et al. (2013)	N:39 (schizophrenia)	SCIT : 43.8, TAU : 40.8	51.28%	Not Reported	SCIT + TAU (n: 22)	TAU (n:17)	1 session/week for 20 weeks	Eyes Task	Social Performance Scale (PSP)	Significant improvement was found in ToM over TAU and social functioning (in all tests: between group effect size: $p < 0.001$, $\eta^2 > 0.24$, between group effect size was significant, with smaller effect size).
Wölwer et al. [40]	N:38 (schizophrenia or schizoaffective disorder)	36.7	68.42%	Not Reported	Training of Affect Recognition (TAR) (n:20)	CRT (n:18)	45-60 min/session, 2 sessions/week for 6 weeks	Cartoon Test	Social and Occupational Functioning Assessment Scale (SOFAS)	No effect was found in the CRT group for ToM or social competence, while the TAR group showed a significant pre-post improvement (between-group effect sizes for pre-post improvement: facial affect recognition: $d = 1.2$, ToM: $d = 1.14$, $p = 0.01$ prosody: $d = 0.89$, $p = 0.04$ social functioning: $d = 0.58 - 0.75$). The difference between CRT and TAR was significant for ToM but not for social competence.

Table 2. Studies of ToM interventions in Schizophrenia included in the review (n: 7)

Author	Sample size and diagnoses (N)	Mean Age	Gender (Male %)	Duration of Illness	Social cognition intervention	Control Condition	Intensity of Intervention	ToM Outcome Measures	Social Functioning Measures	Major Findings (ToM)
Bechi et al. (2013)	N:30 (schizophrenia)	ToMI: 37.68, ACG: 37.73	ToMI: 42%, ACG: 54%	ToMI: 10.76, ACG: 15.44 (years)	Theory of Mind Intervention (ToMI) (n:19)	newspaper discussion group (ACG) (n:11)	1h/sessions, 2 sessions/week for 18 sessions, prior to the group session all patients started a CRT (Cognitive Remediation Training)	Theory of Mind Picture Sequencing Task (PST-A-B), ToM Questionnaire	UCSD Performance-based skills assessment-Brief, (UPSA-B)	Significant pre-to post test improvement in the ToMI group (PST total score, $d=.61$, second order beliefs, $d=.71$). Significant difference between ToMI and ACG in ToM scores except third order beliefs (PST: $F(1,18)=4.55$, $p=.042$; second order beliefs: $F(1,28)=4.79$, $p=0.037$) significant correlation between PST and UPSA-B ($p=.013$, $r=.46$).
Bechi et al. (2012)	N:76 (schizophrenia spectrum disorder)	SRT: 38, SCT: 37.14, NT:40.2	SRT: 63%, SCT: 68%, NT:67%	SRT: 15.4, SCT: 14, NT: 16.62 (years)	CRT + video-based social cognitive traing (SCT) (n: 28)	1, CRT+ standard social cognitive training (SRT)(n: 24), 2, No treatment group (NT) (n: 24)	SCT group interventions , 1h sessions/ week for 3 months. Prior to the social cognitive intervention, CRT lasted for 3 months.	PST, ToM Questionnaire (first order beliefs, second order beliefs, third order beliefs, cheat detection)	Not Reported	Significant improvement in the SCT group from pre- to post test for ToM tests (effect sizes: 0.64-0.91, first order beliefs: $d= 0.64$, second order beliefs: $d= 0.73$, ToM Questionnaire: $d=0.74$, cheating detection: $d=0.91$) except PST and third order false beliefs. SRT showed significant improvements over the SCT group in more ToM tasks ($P= 0.02$ -0.008). Between groups effect size: 0.07

										In ToMI and SCT groups significant improvement on ToM tests (ToMI effect size: d= 0.65 - 0.74, SCT effect sizes: d= 0.16-0.6). Differences between ToMI and SCT were not significant. No improvement for ToM in ACG group. ToMI and SCT showed significant improvements in social functioning (p<0.009). No statistically significant differences were found between paranoid and non-paranoid groups.
Be chi et al. (2 01 5)	N:75 (schizop hrenia)	ToMI: 40.34, SCT: 38.08, ACG:37.2 1	ToMI: 53.13 %CST: 66.67 ACG: 52.63 %	(years) ToMI: 16.25, SCT: 13.87, ACG: 14.94	ToMI (n:32)	SCT (n:24), Newspape r discussion group (ACG) (n:19)	ToMI: 1h /session, 2 sessions /week for 18 weeks, SCT: 1h /session/wee k for 12 weeks, prior to the group session all patients started a CRT.	PST-A-B, ToM Questionnaire	Quality of Life Scale (QLS)	

Table 2. Continued

Author	Sample size and diagnosis (N)	Mean Age	Gender (Male %)	Duration of Illness (years)	Social cognition intervention	Control Condition	Intensity of Intervention	ToM Outcome Measures	Social Functioning Measures	Major Findings (ToM)
Kayser et al. (2006)	N:14 (chronic schizophrenia)	VG: 32.4, TAU: 38.2	Not Reported	12.3, TAU: 11.5	Video group (VG) (n:8)	Treatment as Usual (TAU) (n:6)	1h session/week for 2 weeks	Comic strips task (Attribution of intentions)	Not Reported	No improvements were found in the TAU group. Video group showed significant differences pre- to post test on ToM task (d=0.6; p<0.05).
Mazza et al. (2010)	N:16 (schizophrenia)	ETIT: 24.37, PST: 24.71	Not Reported	(months) ETIT: 6.3, PST: 6.5	Emotion and ToM Imitation Training (ETIT) (n:16)	Problem Solving Training (PST) (n:17)	50 min /session, 2 /week for 12 weeks	Advanced Theory of Mind Scale, First and Second Order ToM Tasks, Emotion Attribution Task	Personal and Social Performance Scale (PSP)	ETIT group showed significant improvement on ToM tests (advanced ToM, p=.000, η^2 p=.98; second level ToM, p=.002, η^2 p=.64) over the control group.
Maria C. Pino et al. (2015)	N:14 (schizophrenia)	ETIT: 16.91, PST: 42.25	50,00%	(months) ETIT: 17, PST: 14.5	ETIT (n:7)	PST (n:7)	50 min /session, 2 /week for 12 weeks	Advanced Theory of Mind Scale, Emotion Attribution Task, Social Situation Task (SST), Eyes Task	PSP, Social and Occupational Functioning Assessment (SOFA S)	ETIT showed significant improvement on cognitive and affective Theory of Mind over the control group, except SST (cognitive ToM; $t_{1,12}=3.705$; p=.003, affective ToM; $t_{1,12}=3.437$; p=.005). Both conditions showed significant improvements in social functioning (PSP; ETIT: $t_{1,12}=5$; p=.004, PST $t_{1,12}=11.13$; p=.0001).

									REC was more effective on first order ToM tasks ($F(1,22)=7.3$, $p<.05$) and emotion perception ($F(1,22)=13.69$, $p<.05$) over PST. Both groups showed improvement in social function (PSP; $F(1,22)=7.06$, $p<.05$).
Veltro et al. (2011)	N:24 (schizophrenia)	38.8	Not Reported	Not Reported	Cognitive Emotional Rehabilitation (REC) (n:12)	PST (n:12)	75-90 min /group session. 1 session /week for 6 months	Advanced Theory of Mind Scale, First and Second Order ToM Tasks, Emotion Attribution Task	PSP