



Have We Been Comparing Theory of Mind in High-Functioning Autism to Patients with Chronic Schizophrenia: a Systematic Review and Meta-Analysis

Lotte Veddem^{1,2,3} · Vibeke F. Bliksted^{1,2,4}

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Abstract

Introduction Autism spectrum disorders (ASD) and schizophrenia represent different mental disorders, but intriguing similarities seem to appear.

Objective In the present meta-analysis, we examined theory of mind (ToM) impairments in adults with ASD or schizophrenia based on studies that have compared the two patient groups directly by using the same test-battery at the same time point.

Results Ten studies were included with a total of 344 ASD patients and 339 schizophrenia patients. We found no significant difference in ToM, but patient characteristics such as severity of mental illness and disorder heterogeneity may have influenced the results.

Conclusions The limited number of studies emphasizes the need for further direct comparisons of ToM in ASD and schizophrenia with awareness of social cognitive subgroups in both disorders.

Keywords Social cognition · Theory of mind · Mentalizing · Autism spectrum disorder · Schizophrenia · Psychosis

Introduction

Theory of mind (ToM) deficits have long been recognized as common symptoms in autism spectrum disorders (ASD) (Association, 2013; Baron-Cohen 2000; Lombardo et al. 2011). Chris D. Frith defined ToM as “our belief that other people have minds different from our own and also our ability to infer beliefs, wishes, and intentions of other people in order to predict their behaviour” (Frith 1992). ToM is considered to be identical to mentalizing, mental state attribution, and cognitive empathy (Shamay-Tsoory 2011). Today, ToM

impairments are well documented in both ASD and schizophrenia (Bora and Pantelis 2013a; Bora et al. 2008; Frith and Frith 1991; Green et al. 2015; Lombardo et al. 2011; Savla et al. 2013; Sprong et al. 2007; Yirmiya et al. 1998). ToM is a developmental construct changing and evolving progressively throughout childhood and adolescence (Wellman et al. 2001). Most scientific research indicate that the most simple aspects of ToM develop already in infancy and early childhood, whereas the developmental onset of more complex aspects occurs in middle childhood and adolescence (Astington and Hughes 2013; Weimer et al. 2017).

ASD are pervasive developmental disorders that exist from birth and persist throughout life (Brugha et al. 2011; Frith 1996). Based on diagnostic criteria, ASD are characterized by impairments in social interaction and communication as well as stereotyped and repetitive behaviors and interests (American Psychiatric Association 2013; W.H.O. 1993). As such, impairments in abilities regarding social interactions stand as a key diagnostic criterion in ASD. The ToM hypothesis provides a cognitive explanation positing that ASD patients are impaired in the ability to understand and interpret mental states. This is argued to underlie both the social cognitive deficits and communicative difficulties of the disorder

✉ Lotte Veddem
lotved@clin.au.dk

¹ The Psychosis Research Unit, Aarhus University Hospital, Palle Juul-Jensens Boulevard 175, 8200 Aarhus, Denmark

² Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

³ The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus, Denmark

⁴ Interacting Minds Centre, Aarhus University, Aarhus, Denmark

(Baron-Cohen 1988; Eack et al. 2017; Frith et al. 1991; Lombardo et al. 2011).

Interestingly, the term “autism” was originally coined by Eugen Bleuler to describe the urge of schizophrenia patients to live their lives in an inner fantasy world separating them from the real world (Bleuler 1983). In contrast to ASD, social cognitive deficits are not part of the diagnostic features in schizophrenia despite the essential relevance for prognosis, psychopathology, and daily functioning. The diagnostic features of schizophrenia involve a range of cognitive, behavioral, and emotional dysfunctions or distortions such as hallucinations and delusions. However, in recent years, an increasing interest in social cognition in schizophrenia has emerged. In 2004, the MATRICS-initiative (Measurement and Treatment Research to Improve Cognition in Schizophrenia, National Institute of Mental Health, USA) specified social cognition as one out of seven neurocognitive domains of importance for clinical trials (Green et al. 2004). In continuation of this, in 2008, the CNTRICS-initiative (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia, National Institute of Mental Health, USA) identified five social cognitive domains as particularly affected in schizophrenia: (1) ToM, (2) social perception, (3) social knowledge, (4) attributional bias, and (5) emotion processing (Green et al. 2008). Thereby, social cognitive deficits were pointed out as important features of schizophrenia, although not being part of the diagnostic criteria. A meta-analysis of the abovementioned social cognitive domains concluded that ToM and social perception are the domains most severely affected in schizophrenia patients compared to healthy controls (Savla et al. 2013). Moreover, strong associations have been found between ToM and functional outcome (Fett et al. 2011).

Some suggest that the ToM deficits in schizophrenia are similar to those found in ASD (Chung et al. 2014; Corcoran et al. 1995; Fernandes et al. 2018; Mazza et al. 2001). Others report that the ToM deficits in schizophrenia are less severe than those in ASD (Pickup and Frith 2001; Pilowsky et al. 2000). A recent meta-analysis revealed no significant differences between ASD and schizophrenia regarding verbal and visual ToM abilities (Chung et al. 2014). However, patients with schizophrenia showed a trend towards larger impairments with regard to verbal ToM tests compared to visual ToM tests. In patients with ASD, results were similar in the visual and verbal ToM tests. Importantly, the majority of the included studies in the meta-analysis by Chung et al. did not directly compare the two patient groups, but instead, it consisted of ToM research in ASD and compared these results to ToM research in schizophrenia, respectively. This entails important issues since ToM was examined by using different tasks in the two patient groups, and patients were tested in different countries by different researchers at different times. Nevertheless, the results indicate that the two disorders may

share some social cognitive deficits (Chung et al. 2014; Frith and Frith 1991). Another review compared ToM in ASD and schizophrenia patients who had been tested with the same tasks as part of the same research projects (Fernandes et al. 2018), but similarly, no differences were found. This study included both children and adults with either ASD or schizophrenia. However, the highest incidence of first-episode schizophrenia is around age 22 (Bergen et al. 2014; Pedersen et al. 2014). Besides, early onset schizophrenia (EOS) (age 14–18) is very rare, has a more severe prognosis, and many EOS patients are re-diagnosed later in life (Clemmensen et al. 2012; Driver et al. 2013). Furthermore, as previously described, ToM evolves from early childhood until adolescence in typically developing children (Osterhaus et al. 2016; Wellman and Liu 2004), and this ToM development is delayed in children and adolescents with ASD (Peterson and Wellman 2018; Pino et al. 2018; Pino et al. 2017). This makes it complicated to conclude if the observed ToM deficits in children and adolescents with ASD are final, or if further development could be expected. Thereby, it is of high relevance to examine and directly compare social cognitive domains such as ToM in adults with ASD or schizophrenia, which was the aim of the present literature review and meta-analysis. In other words, we aimed at including studies that have examined both patient groups as well as a group of healthy controls. This helps to ensure that the same behavioral test has been applied by the same researcher at the same time point in both patient groups. Based on the reviewed findings of ToM in ASD and schizophrenia, respectively, we expected to find significant differences between healthy controls compared to ASD as well as between healthy controls compared to schizophrenia with the probability of the patient groups performing more poorly on the ToM tasks. Despite the findings from the meta-analyses by Chung et al. (Chung et al. 2014) and Fernandes et al. (Fernandes et al. 2018), we expected to find a significant difference between the two patient groups anticipating the ASD patients to perform more poorly on the ToM tasks compared to the schizophrenia patients. This latter expectation was based on the fact that ASD is diagnosed in childhood, while schizophrenia primarily is diagnosed in early adulthood indicating that their ToM difficulties might occur at some more advanced developmental levels of ToM (Bergen et al. 2014; Osterhaus et al. 2016; Pedersen et al. 2014; Peterson and Wellman 2018; Wellman and Liu 2004).

Materials and Methods

This meta-analysis was performed according to the Preferred Reporting Items for a Systematic Review and Meta-analysis, the PRISMA statement (Stewart et al. 2015).

Data Sources and Search Strategy

LV and a research assistant (CBK) conducted systematic MeSH and free text searches independently in PubMed, PsycINFO and EMBASE up to the 21st of August 2020. Search terms were (((((((("mentalisation") OR "mentalization") OR "mentalising") OR "mentalizing") OR "Theory of Mind") OR "Theory of Mind"[Mesh]) OR "social cognition"))) AND ((Schizophreni*) OR "Schizophrenia"[Mesh]) AND (((("autism" OR "autistic"))) OR "Autistic Disorder"[Mesh]) OR "Autism Spectrum Disorder"[Mesh]). In EMBASE, we used the following filters: English, age 18–64 years, article, review, article in press; in PsycINFO, we applied peer-review, English, and age-group (18–60 years) as filters, while we used English language and age 18+ years as filters in PubMed. We decided to include literature reviews and meta-analyses to ensure awareness of all available and relevant studies in the field.

Reference lists of all included publications were reviewed for additional publications. Full-texts were obtained for the publications that were assessed for eligibility. Inclusion criteria were written in English, peer-reviewed, case-control study comparing ASD and schizophrenia and healthy controls, adults (age 18–60), diagnoses based on DSM-IV, DSM-V, and ICD-10, or Wing's clinical definition (Wing 1981). IQ estimates had to be evident, and finally a behavioral test assessing ToM had to be applied in the study, and results should be presented with mean scores and standard deviations. Exclusion criteria were drug or alcohol dependency, neurological disorder, or severe head trauma based on DSM-IV, DSM-V, or ICD10 criteria (American Psychiatric Association 1994, 2013; W.H.O. 1993).

Selection Process

LV and CBK did the selection process independently, and in cases of disagreement, the matter was discussed with VB until consensus was reached. Of the 43 publications assessed for eligibility, 33 publications were excluded: seven studies did not provide behavioral data, e.g., due to being a fMRI study, three studies were meta-analyses, three studies examined subjects under age 18, nine studies were out of scope, e.g., examining another social cognitive domain, subjects from one study were included in a newer and larger sample, and finally, five studies lacked either healthy controls or one of the clinical groups (see supplementary materials, Table S1). Moreover, one study did not present the standard deviations for their mean ToM scores, and for that reason, the authors were contacted, but we were not able to receive any further data. Reviewing the reference lists of all included publications for additional publications resulted in no further inclusions. Finally, 10 studies comparing ToM in

both ASD and schizophrenia were included and applied in the present meta-analysis (see the flow chart of the literature search in Fig. 1).

Data Extraction

To be able to perform the planned meta-analyses, we only employed results from one ToM task in each study. In order to ensure validity, we aimed at including as comparable results as possible, inducing that we included results from the same ToM task in each study if possible. We prioritized tasks that were validated for schizophrenia ToM research (Pinkham et al. 2013). Seven of the included studies used the Reading the Mind in the Eyes Test (RME), in which the minimum score is 0 and the maximum score is 36 (Baron-Cohen et al. 2001). However, Lugnegaard and colleagues used a modified Swedish version of RME (score range 0–24) (Lugnegård et al. 2013), and the Couture et al. study administered the test twice (score range 0–72) (Couture et al. 2010). The RME consists of 36 pictures of eye regions. Based on this, subjects are asked to choose among four words, which one most accurately describes the thought or feeling being portrayed. One study measured ToM by using a False Belief Test (FBT) (score range 0–2) (Baron-Cohen 1989; Perner and Wimmer 1985), where a story describing social interaction among two persons was read out loud and at the same time the plot was enacted. Finally, two studies used the intentionality score from the ToM animations of the Animated Triangles Task (ATT) (score range 0–20) (Abell et al. 2000). The ATT consists of small movie clips where a large and a small triangle are moving around. In four of the clips, the triangles move around randomly with no intentional interaction. In the four other clips, also referred to as the ToM condition, the animated triangles are intended to interact in a socially meaningful way, in order to prompt the viewer to attribute that the intention of one of the triangles is to influence the mental state of the other. To ensure concordance, data from the included studies were extracted by both of the authors.

Meta-Analysis

Meta-analyses were performed with Stata IC 16 software for Windows. Effect sizes were calculated based on means and standard deviations for each between-group comparison on the ToM subtests. Chi-squared tests (χ^2) were used to test the heterogeneity of the resulting mean-weighted effect sizes. I^2 -tests were used to measure the percentage of variation across studies in standardized mean difference (SMD) attributable to heterogeneity. A value of 0.25% corresponds to low, 0.50% to moderate, and 0.75% to high heterogeneity. Effect sizes were estimated using Hedges' g . In Hedges' method, the differences in means are divided by an estimate of the standard deviation. Moreover, a small sample bias correction factor is

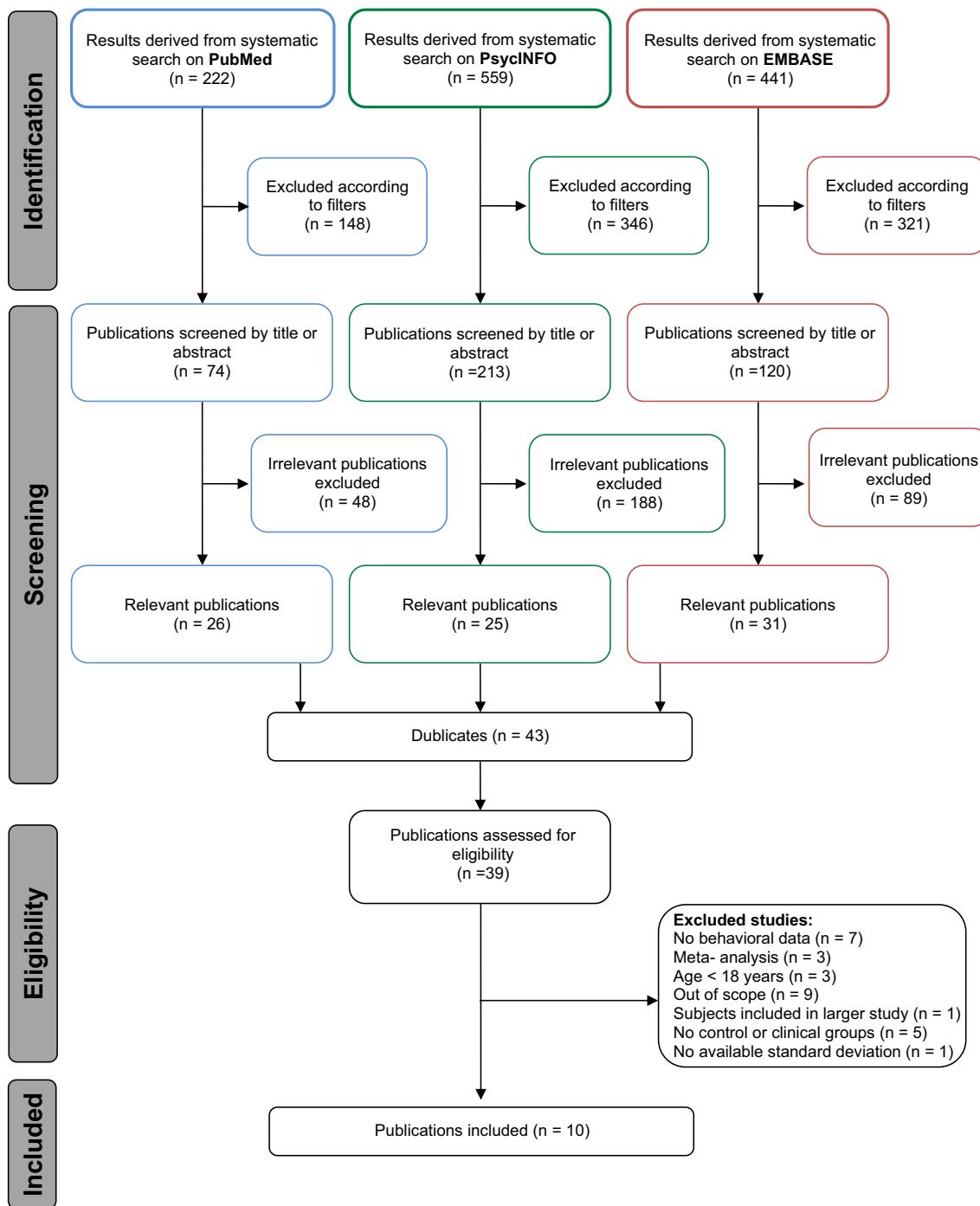


Fig. 1 Flow chart illustrating the search strategy and the inclusion/exclusion criteria

incorporated in the calculations of Hedges’ *g*. Random-effects models as well as Hedges’ *g* were used for the meta-analysis due to large heterogeneity. *Tau*²-tests were used in the meta-analysis with random-effects models to find an estimate of between-study variances. The effect of potential moderators (age and IQ) was examined by random-effects meta-regressions. Publication bias, which is a widespread problem when conducting meta-analyses, was examined visually by funnel plots.

Results

As clarified above, the main aim of the present meta-analysis was to compare ToM deficits in ASD and schizophrenia, and only 10 studies met the inclusion criteria. In generally, the aim of the included studies was to compare social cognitive abilities or impairments in ASD and schizophrenia due to possible overlaps between these two mental disorders. Five of the 10 included studies solely focused on ToM, while the remaining

Table 1 Sample characteristics of patients with autism spectrum disorders (ASD), schizophrenia patients (SZ), and healthy controls (HC)

Author (year)	N (female) (ASD)	N (female) (SZ)	N (female) (HC)	Age (ASD)	Age (SZ)	Age (HC)	IQ (ASD)	IQ (SZ)	IQ (HC)	Duration of illness (SZ)
Bowler (1992)	15 (2)	15 (8)	15 (8)	26.67 (8.42)	45.92 (11.92)	N.A.	86.8 (11.41)	84.73 (9.92)	N.A.	> 3 years
Couture et al. (2010)	36	44	41	20.9 (5.7)	27.5 (6.3)	22.9 (5.6)	101.3 (13.93)	98.8 (15.8)	109.4 (15.1)	5.5 (5.9) years
Craig et al. (2004)	17 (2)	16 (5)	16 (5)	24.12 (6.72)	31.69 (9.85)	29.44 (8.41)	104.76 (7.11)	105.14 (8.42)	110.25 (9.89)	N.A.
Hyatt et al. (2020)	30 (4)	30 (11)	30 (8)	21.7 (3.4)	26.0 (3.5)	24.3 (3.6)	110 (14.4)	101 (13.8)	115 (12.8)	N.A.
Krawczyk et al. (2014)	15 (4)	13 (6)	15 (9)	21.73 (4.39)	30.00 (5.72)	23.44 (4.00)	107.50 (14.07)	101.67 (12.84)	120.44 (9.20)	N.A.
Lugnegard et al. (2013)	55 (27)	36 (14)	50 (31)	27.3 (4.1)	28.8 (4.1)	28.8 (9.3)	104.4 (2.3) ^b	9.4 (2.2) ^b	9.9 (2.1) ^b	7.3 (4.8) years (men) 6.1 (4.3) years (women)
Martinez et al. (2019)	32	51	23	22.62 (3.50)	23.35 (3.60)	23.26 (3.10)	100.60 (14.60)	98.10 (13.10)	105.40 (10.40)	19.9 (3.3) years ^c
Pinkham et al. (2019)	101 (11)	92 (27)	101 (16)	24.23 (6.18)	27.77 (7.28)	24.62 (5.82)	106.1 (11.58)	104.23 (10.69)	106.62 (10.67)	N.A.
Radeloff et al. (2014)	34 (3)	21 (5)	26 (4)	19.06 (5.12)	24.67 (5.2)	19.54 (3.46)	105.73 (12.92)	103.33 (11.21)	107.75 (11.97)	67 (45) months
Veddum et al. (2019)	11 (7)	21 (11)	32 (18) ^a	25.09 (6.43)	40.48(12.38)	sz:40.33 (12.76) ^a ASD:25.45 (6.19) ^a	104.55 (22.97)	98.14 (20.46)	sz:110.52 (15.08) ^a ASD:108.09 (12.67) ^a	N.A.

N.A. not available

Results are reported with mean and standard deviation

^a Patients and controls were matched one to one. ^b Cognition score based on WAIS-III Vocabulary, scaled score (SS). ^c Number of years refers to age at onset of first psychotic episode

five studies also examined other social cognitive areas such as persecutory beliefs (Craig et al. 2004), emotion perception and social judgements (Couture et al. 2010), relational reasoning (Krawczyk et al. 2014), and social perception (Veddum et al. 2019; Pinkham et al. 2013). Of note, the main aim of the included studies by Radeloff and colleagues as well as Hyatt and colleagues was to examine structural alterations or neural mechanisms in the social brain by using magnetic resonance imaging data from patients with ASD or schizophrenia (Hyatt et al. 2020; Radeloff et al. 2014). These studies were thus included, because behavioral data from the applied ToM tests were reported. Table 1 lists the sample characteristics of included studies. In total, our meta-analyses included 344 patients with ASD, 339 patients with schizophrenia, and 349 healthy controls. The ASD patients had an age range from 19.06 to 27.3 years, while patients with schizophrenia were from 23.4 to 45.92 years old, and healthy controls were between 19.54 to 40.33 years old. Duration of schizophrenia illness ranged from 3–19.9 years. In all of the three groups, more males than females participated; however, two studies did not provide gender ratios. Table 2 shows the ToM test scores and overall results from the included studies.

Risk of Bias Across Studies

Study quality was evaluated using the Cochrane Risk of bias tool (Higgins and Green 2011). Main findings are summarized below.

Internal Validity

Only one study matched the patients and controls one to one (Veddum et al. 2019). Two of the included studies matched the two patient groups regarding age and/or IQ (Bowler 1992; Craig et al. 2004). All subjects (schizophrenia, ASD, and healthy controls) were tested using the same tasks administered by the same staff, which is an advantage. Five studies used the RME task; however, the test was administered in three different ways. The applied tasks differed in complexity making it questionable, whether results across studies can be directly compared. All studies reported estimated IQ scores, but one study reported this as scaled scores based on the WAIS-III Vocabulary subtest (Lugnegård et al. 2013). One study did not report the age of the control subjects (Bowler 1992). The schizophrenia patients differed in mean IQ among studies ranging from 84.73 to 105.14. Similar differences in mean IQ were observed in the ASD samples with the lowest mean IQ score of 86.8 and the highest mean IQ score of 105.7.

External Validity

The studies suffer from selection bias since data only are reported for patients who in fact were able to understand and

Table 2 ToM tests, mean scores, standard deviation and overall results of patients with autism spectrum disorders (ASD), schizophrenia patients (SZ), and healthy controls (HC)

Author (year)	ToM test used	ToM score for ASD (SD)	ToM score for SZ (SD)	ToM score for HC (SD)	Overall results
Bowler (1992)	False belief Test	1.47 (0.64)	1.20 (0.68)	1.67 (0.49)	No significant differences in ToM between any of the three groups (based on the Test Questions score).
Couture et al. (2010)	Reading the Mind in the Eyes Test	58.7 (15.8)	60.9 (16.1)	69.5 (11.9)	No significant differences in ToM between groups after controlling for IQ. However, large effect sizes between both clinical groups and HC, but not between ASD and SZ, when comparing mean ToM scores of the three groups
Craig et al. (2004)	Reading the Mind in the Eyes Test	19.88 (6.10)	18.19 (6.65)	27.63 (4.33)	Significant differences in ToM between both clinical groups and HC, but no significant difference between ASD and SZ. This effect remained significant when controlling for IQ
Hyatt et al. (2020)	Reading the Mind in the Eyes Test	24.4 (3.51)	24.3 (4.24)	27.0 (3.22)	No significant difference in ToM between ASD and SZ, but significant difference between both clinical groups compared to HC
Krawczyk et al. (2014)	Reading the Mind in the Eyes Test	20.64 (4.96)	23.67 (4.05)	28.33 (2.73)	HC performed better than ASD and SZ
Lugnegard et al. (2012)	Reading the Mind in the Eyes Test	18.2 (2.5)	17.2 (3.2)	18.9 (2.4)	No significant difference in ToM between clinical groups or between ASD and HC, but significant difference between SZ and HC
Martinez et al. (2019)	Animated Triangles Task	12.62 (3.08) ^a	12.10 (3.25) ^a	14.95 (1.79) ^a	ASD and SZ scored significant lower than HC. No difference between clinical groups
Pinkham et al. (2013)	Reading the Mind in the Eyes Test	25.45 (6.51)	22.80 (6.88)	22.84 (6.02)	No significant difference in ToM between ASD and SZ, but significant difference between both clinical groups compared to HC
Radeloff et al. (2014)	Reading the Mind in the Eyes Test	16.74 (4.25)	20.57 (2.27)	21.15 (2.74)	Significant differences in ToM between clinical groups as well as between ASD and HC, but no significant differences between SZ and HC
Veddum et al. (2019)	Animated Triangles Task	12.78 (3.01)	9.84 (3.52)	14.33 (2.69) ^b	ASD and SZ scored lower than HC. No difference were found between clinical groups when controlling for age and neurocognition

^aThe intentionality score of the ToM animations; ^b Total number of HC (matched one to one to the ASD and SZ patients)

complete the social cognitive tests. This for example leaves out a large group of patients with ASD and intellectual disability. Patients with schizophrenia who, e.g., are very paranoid or suffers from severe negative symptoms such as blunted affect and poverty of speech might also not have been able to participate in the studies. Furthermore, patients were recruited from mental health hospital units, implying that the participating patients were receiving or in need of some kind of psychiatric treatment. This leaves out patients in remission or patients who are able to cope with their mental illness.

Investigation of Publication Bias

We found no signs of publication bias, indicating that the results of the meta-analyses are reflecting actual state of the art within this research area (for supplemental materials, see Figure S2, S3, and S4).

ToM in ASD, Schizophrenia, and Healthy Controls

We performed three separate meta-analyses comparing the mean and SD ToM scores of the three groups: (1) healthy controls compared to ASD patients, (2) healthy controls compared to schizophrenia patients, and (3) schizophrenia patients compared to ASD patients. In addition, we performed meta-

regression analyses examining if the results were moderated by age and IQ.

Healthy Controls Compared to ASD

When comparing the ToM scores of healthy controls and the ASD sample, statistical tests showed large heterogeneity between the included studies ($\chi^2 = 67.42$, $p < 0.001$; $I^2 = 86.7\%$; $\text{Tau}^2 = 0.45$). As expected, the meta-analysis revealed a significant difference between the two groups (Fig. 2). More specifically, the ASD sample had substantial ToM deficits compared to the healthy controls (SMD = 0.74; $z = 3.16$ and $p = 0.002$). We examined if the results were moderated by age or IQ. However, we found no effect of either age (coef. = -0.13 , SE = 0.08, $z = -1.64$, $p = 0.10$) or IQ (coef. = 0.006, SE = 0.007, $z = 0.85$, $p = 0.40$).

Healthy Controls Compared to Schizophrenia

When comparing the ToM scores of the healthy controls and the schizophrenia sample, statistical tests showed that the ten studies were heterogeneous ($\chi^2 = 34.13$, $p < 0.001$; $I^2 = 73.6\%$). Again, as expected, the meta-analysis revealed a significant difference between the two groups regarding their ToM abilities (Fig. 3). The schizophrenia sample had substantial ToM deficits compared to the healthy controls (SMD =

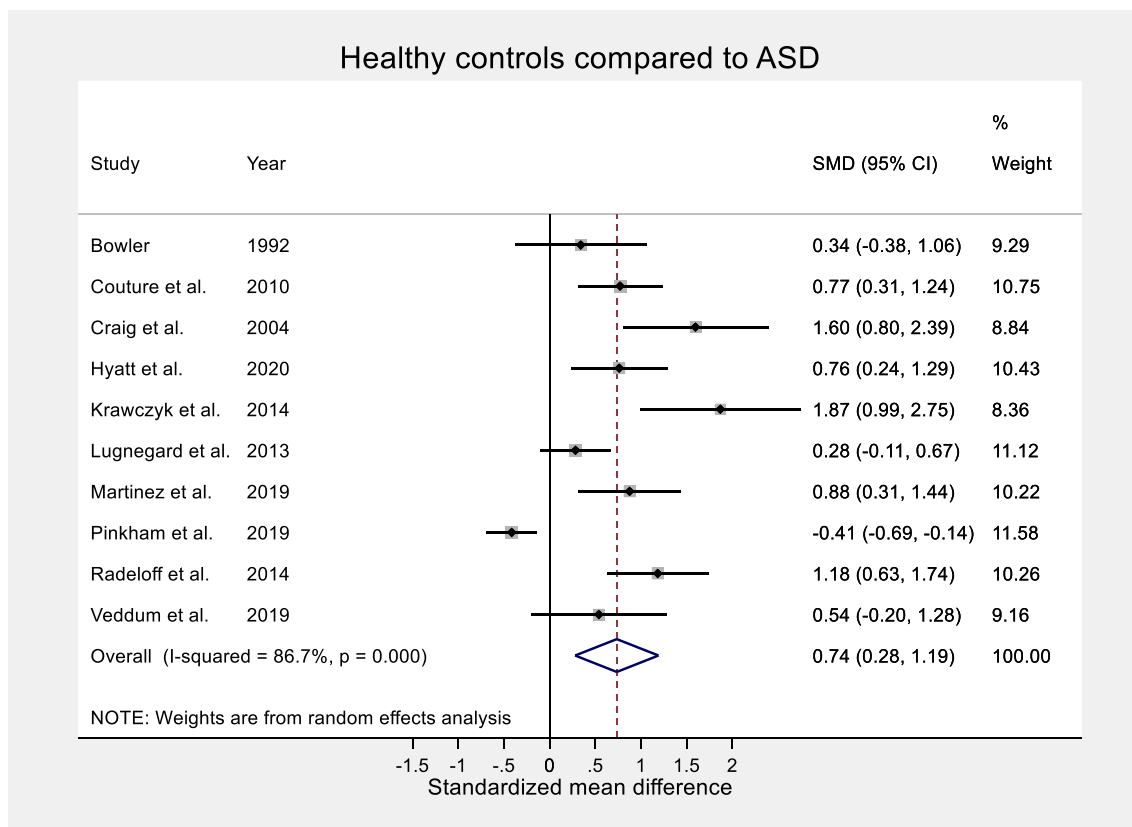


Fig. 2 Forest plot of ToM in ASD compared to healthy controls

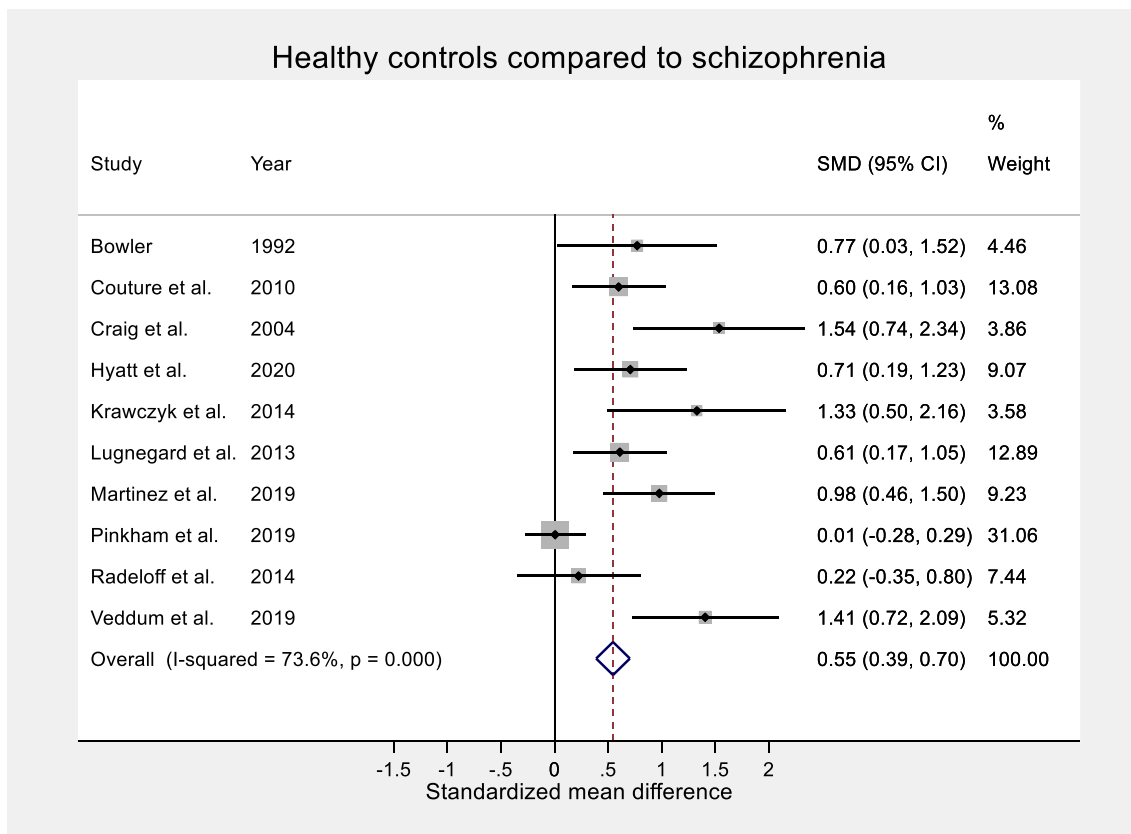


Fig. 3 Forest plot of ToM in schizophrenia compared to healthy controls

0.55; $z = 6.80$ and $p < 0.001$). We examined if the results could be explained by differences in age or IQ. However, moderator analyses showed no effect of age (coef. = 0.03, SE = 0.02, $z = 1.16$, $p = 0.25$) or IQ (coef. = 0.001, SE = 0.006, $z = 0.24$, $p = 0.81$).

Schizophrenia Compared to ASD

When comparing the ToM scores of the two patient groups, statistical tests revealed that the results from the ten included studies showed large heterogeneity ($\chi^2 = 30.64$, $p < 0.001$; $I^2 = 70.6\%$; $\text{Tau}^2 = 0.16$). The meta-analysis revealed no significant difference in ToM abilities between ASD and schizophrenia (SMD = -0.025 ; $z = 0.16$ and $p = 0.87$) (Fig. 4). We again examined if differences in age or IQ in the two patient groups could be an explanation of this result. However, moderator analyses showed no effect of age (coef. = 0.04, SE = 0.02, $z = 1.48$, $p = 0.14$) or IQ (coef. = -0.005 , SE = 0.006, $z = -0.90$, $p = 0.37$).

Discussion

The main aim of the present literature review and meta-analysis was to compare ToM deficits in adults with ASD or schizophrenia measured by the same behavioral test at the

same time point by the same researchers. Previous meta-analyses comparing ToM deficits in these two disorders primarily rely on case-control studies, which have focused on either ASD or schizophrenia (Chung et al. 2014) respectively, as well as studies that have compared a mixture of adults and children (Fernandes et al. 2018). In the present meta-analysis, 10 studies were included, revealing sparse availability of research directly comparing ToM abilities in these two mental disorders.

We only included adults above age 18, since the highest incidence of first-episode schizophrenia is around age 22 (Bergen et al. 2014; Pedersen et al. 2014), and early onset schizophrenia is considered rare having a more severe prognosis or being re-diagnosed later on (Clemmensen et al. 2012; Driver et al. 2013). Furthermore, advanced aspects of ToM is developing throughout childhood and adolescence (Osterhaus et al. 2016; Wellman and Liu 2004), and ASD subjects have a delayed ToM development compared to typically developing subjects (Peterson and Wellman 2018).

Our results indicate that ASD patients and schizophrenia patients both have substantial ToM deficits compared to healthy controls. This confirms earlier research findings (Bora and Pantelis 2013a; Bora et al. 2008; Savla et al. 2013; Song et al. 2015; Sprong et al. 2007; Yirmiya et al. 1998). However, in direct comparison of the two patient groups, we found no significant difference, which reflects

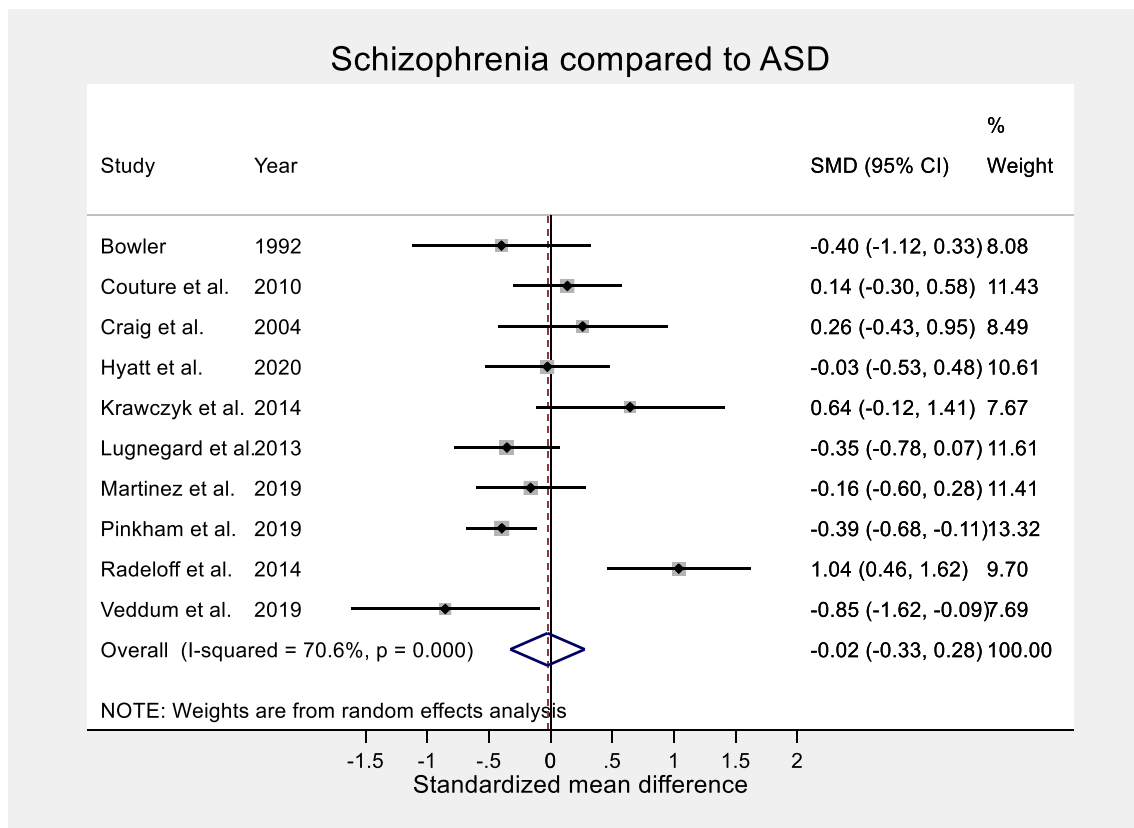


Fig. 4 Forest plot of ToM in schizophrenia compared to ASD

mixed results in the included studies. Some of the included studies showed that patients with schizophrenia performed more poorly on ToM tasks than ASD patients, while others found the opposite result. We also found mixed results when comparing healthy controls to ASD or schizophrenia, respectively. Although it is evident that both of the two patient groups have substantial ToM deficits compared to healthy controls in all of the included studies, not all of these differences were significant (see Table 2). These mixed findings may reflect essential differences between patient groups from study to study.

Subgroups of ASD and Schizophrenia Patients

A distinction between high-functioning autism (HFA) and low-functioning autism (LFA) is commonly based on daily functioning and intelligence level. ToM deficits in HFA seem to be less severe than those in LFA with some HFA patients performing comparably to healthy controls (Begeer et al. 2010; Roeyers and Demurie 2010). Research findings indicate that ToM deficits in ASD are a significant predictor of the severity of the diagnosis (Tager-Flusberg 2003). The ASD sample in the present meta-analysis had an average IQ estimate above 85, which seem to place the ASD sample in the HFA category, which is assumed to have a high IQ compared to an average ASD sample. Further, three of the included

studies only involved patients diagnosed with Asperger syndrome (Bowler 1992; Craig et al. 2004; Lugnegard et al. 2012), which is an ASD diagnosis characterized to be less severe. Moreover, results from moderator analyses showed no significant effect of IQ on the results in the present meta-analysis. Nonetheless, ToM deficits in adults with ASD are suggested to be manifest and lifespan persistent.

Similarly, schizophrenia is often divided into first-episode patients (FES), patients with longer lasting illness (LLS), and remitted patients. The prognosis and course of schizophrenia varies greatly as some schizophrenia patients recover from the disorder, while other schizophrenia patients have a more chronic cause of illness. Results from two distinct meta-analyses revealed that LLS patients tend to have more severe ToM deficits compared to FES patients (Bliksted et al. 2016; Bora and Pantelis 2013b). This emphasizes the influence of ToM deficits on functional outcome in schizophrenia (Fett et al. 2011). Furthermore, remitted patients with schizophrenia had less severe ToM deficits compared to non-remitted schizophrenia patients (Bora et al. 2008).

In the present meta-analysis, duration of illness is stated in five of the 10 included studies ranging from approximately three years to almost 20 years (see Table 1). The schizophrenia patients in the included studies were either inpatients or recruited from psychiatric outpatient clinics, which indicates a poor prognosis due to hospitalization and attendance in

psychiatric treatment even several years after diagnosing. Duration of illness is not stated for the ASD sample in any of the included studies, presumably due to the fact that ASD exists from birth and persists throughout life, whereas schizophrenia primarily appears in young adulthood. For this reason, it makes no sense to compare the two patient groups regarding duration of illness. Instead, we looked at the samples' age, and our results revealed that the schizophrenia sample were significantly older than the ASD sample. This could also contribute to the assumption that the schizophrenia group should be considered a LLS group rather than a FES group. However, moderator analyses showed no significant effect of age on the results.

Patients with schizophrenia constitute a very heterogeneous group, why interest in associations between social cognition and different symptoms groups has increased in recent years (Green et al. 2008; Penn et al. 2008). It has been argued that different symptom subgroups should be considered separately when assessing social cognition in schizophrenia (Ventura et al. 2013). Recent findings indicate that ToM deficits in schizophrenia should be considered trait related because the ToM deficits have proven to be stable throughout course of illness, with no changes at 12 months follow-up (Bora et al. 2008; Green et al. 2012; Horan et al. 2012). Recent research in schizophrenia symptom subgroups revealed that difference in social cognition may exist between schizophrenia patients with high versus low levels of negative symptoms (Bell et al. 2013; Bliksted et al. 2017). In accordance to this, results from a study by Ozguven and colleagues indicate that schizophrenia patients with prominent negative symptoms have more severe social cognitive deficits than those without prominent negative symptoms (Ozguven et al. 2010). Furthermore, their results revealed that the ToM deficits in the negative symptoms subgroup are comparable to the ToM deficits in ASD. Results from the study by Couture and colleagues likewise revealed that the ToM deficits in ASD are more similar to the negative symptom subgroup than to a paranoia subgroup of schizophrenia patients. Schizophrenia patients may be characterized by either hypo-mentalizing or hyper-mentalizing (Abu-Akel and Bailey 2000; Frith 2004). Given that hypo-mentalizing is thought to be highly correlated to negative symptoms, this distinction of hypo-mentalizing and hyper-mentalizing seems to emphasize the fact that the ToM deficits in schizophrenia patients with prominent negative symptoms may be most similar to the ToM deficits in ASD, which is also a condition characterized by hypo-mentalizing rather than hyper-mentalizing (Crespi and Badcock 2008). Thereby, ASD and the negative symptom subgroup of schizophrenia may be difficult to distinguish in clinical conditions. On the other hand, the ToM deficits seen in the schizophrenia subgroup with pronounced paranoia may be more distinct from those seen in ASD (Crespi and Badcock 2008). Closer examination of the schizophrenia samples

included in the present meta-analysis reveals that the schizophrenia samples in the studies by Craig and colleagues as well as Radeloff and colleagues were all paranoid or delusional patients (Craig et al. 2004; Radeloff et al. 2014). On the other hand, Couture and colleagues as well as Martinez and colleagues both included schizophrenia patients with prominent negative symptoms as well as patients with pronounced paranoia (Couture et al. 2010; Martinez et al. 2019). The study by Krawczyk et al. had patients with paranoid schizophrenia, schizoaffective disorder, and undifferentiated schizophrenia (Krawczyk et al. 2014). The remaining studies have not delineated the schizophrenia samples in detail but presumably, they cover varying symptom groups. This indicates that the results from the present meta-analysis should be interpreted cautiously given that the included studies encompass different schizophrenia symptom subgroups, presumably with an overrepresentation of schizophrenia patients with pronounced positive (paranoid) symptoms. It may be deficient that no distinction of the schizophrenia symptom subgroups was made in the present meta-analysis, but due to missing information about symptoms in some of the included studies, this was not possible.

Clinical Implications

The results from this meta-analysis state important clinical issues. Subgroups in both disorders may require different social cognitive remediation programs, and so treatment should to a greater extent be individualized or tailor-made for specific symptom subgroups. It can be questioned whether the ASD patients as well as the schizophrenia patients included in the present meta-analysis constitute representative samples of the two mental disorders. This is an important limitation, and future research in this area should aim at including and distinguishing between the different subgroups in both disorders. Until now, studies comparing ToM in ASD and schizophrenia have not taken these issues into account sufficiently. As such, it appears that previous research primarily has been comparing high-functioning ASD patients to chronic schizophrenia patients with pronounced paranoid symptoms, which causes important biases. Another important limitation of the present meta-analysis is the limited number of included studies. Nonetheless, no more studies directly comparing ToM in ASD and schizophrenia were available at the time of the literature search, as most existing research in this area relies on studies focusing on ToM deficits in either ASD or schizophrenia, respectively. However, the limited number of included studies emphasizes the need for further comparisons of ToM in ASD and schizophrenia with an awareness of possible subgroups in both disorders.

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Author Contribution Both authors contributed to the study conception and design. The literature search was performed by the first author and repeated by a research assistant in order to decrease the risk of selection bias. The first draft was written by the first author, and the last author commented and guided the process of finishing the paper. The last author was responsible for data analysis. Both authors have read and approved the final manuscript.

Data Availability Research data are not shared.

Declarations

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