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Research Article

A Meta-Analysis Taxonomizing Empathy in Schizophrenia

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Abstract

Background

Trait empathy is integral to relationship development and maintenance. Therefore, impairment in this ability can have an adverse effect on many domains of life including social, sexual, and marital. Previous reviews show in schizophrenia, this ability to be impaired but with a high amount of heterogeneity that is yet to be explored more thoroughly.

Aim and method

Considering this, we aim to synthesise the extent literature using a meta-analytic approach and examine the source of the heterogeneity observed in previous reviews and develop taxonomy of empathy deficits in schizophrenia. Hedges' *g* was calculated for cognitive and affective empathy using random effects models. Meta-regression models of key cognitive, clinical and demographic risk and protective factors were run. These included: Impact year of publication, age, gender, ethnicity, education, general IQ, verbal/pre-morbid IQ, global neuro-cognition, positive, negative and general symptoms of schizophrenia, age at schizophrenia diagnosis, duration of illness and medication has on cognitive and affective empathy.

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Results

A literature search revealed 39 independent studies examining empathy in schizophrenia. Healthy controls scored higher than people with a diagnosis of schizophrenia, with a small effect size for affective empathy (Hedges' *g* = 0.29) and a medium effect size for cognitive empathy (Hedges' *g* = 0.53). Both components were heterogeneous. Analyses using meta-regression models found age at diagnosis and the duration of illness moderated the difference in effect size for cognitive empathy, such that those with an earlier diagnosis or a more chronic course exhibit greater difficulty in cognitive empathy compared to healthy controls.

Conclusion

We find a longer duration of illness and younger age at clinical diagnosis enhances impairments in cognitive empathy in severe and enduring schizophrenia. For affective empathy, we conclude, compared to healthy controls, some patients report having a deficit [i.e. experience lower affective empathy], others report comparable levels, and the remaining report to be experiencing higher emotional arousal. As an earlier diagnosis, prolonged illness course and dysfunctional emotional reactions are significant risk factors of poorer empathic interactions, it will be important to address the underlying mechanisms of this deficit in future work.

Keywords: Affective empathy; Cognitive empathy; Meta-Analysis; Schizophrenia

Introduction

Empathy is a critical interpersonal social skill that is necessary for everyday social communication. It helps us participate in groups, socialise, develop and maintain close relationships [1] and is a potential determinant of pro-social behaviours [2,3] including altruism [4]. Therefore, an impairment in this ability can have a significant impact on an individual's mental health and well-being, and as such, understanding its structure, purpose and mechanism is of clinical and public health relevance [5]. Psychopathy [6] and related clinical disorders (e.g., antisocial personality disorder, conduct disorder, acquired sociopathy [7] and disorders of the autistic spectrum [6,8]), have often been characterised by low or absent empathy for others. Prior work has also suggested a potential connection between the clinical characteristics of autism and schizophrenia (e.g., see Bleuler's [9] four A's of schizophrenia) and as such, a body of literature has now accrued investigating empathy in people with a diagnosis of schizophrenia [10-12].

Measuring and defining empathy in schizophrenia disorders

Historically, references to empathic deficits in schizophrenia dates back to Bleuler [13] and Kraepelin [14], but only over the last 11 years have researchers carried out studies comparing people with a diagnosis of schizophrenia and related disorders to controls without mental health difficulties (recruited from the general population), on measures purported to assess empathy. Commonly, studies have used the Interpersonal Reactivity Index (IRI) [15], a self-report questionnaire using four sub-scales: Fantasy, perspective-taking, personal

distress and empathic concern. Scholars do not universally accept this four-component empathic conceptualisation [4,5,16-18], instead, suggesting empathy is better represented and measured as two independent domains: Cognitive and affective [5]. The cognitive domain involves understanding and measuring the internal states of others, such as thoughts, intentions, and emotions [19] and the affective domain involves being "sensitive to and vicariously experiencing the feelings of others" (p. 85 [5]).

What is known in relation to empathy and schizophrenia

Several meta-analyses have been beneficial in quantifying empathy deficits in people with schizophrenia [10-12]. Of these reviews, Bonfils and colleagues [11,12] demonstrated the importance of using self-report and performance-based empathy measures during analysis and the need to explore additional clinical characteristics (such as symptom severity, age at illness onset and medication) to further this field of research. As such, in this study, we discuss and examine for the first time, the moderating effect of these, and demographic (age, gender, education, and year of publication) and neuro-cognitive variables (i.e. global neuro-cognition, verbal/pre-morbid and general IQ), with the aim of assessing the sources of heterogeneity (i.e. variability) observed in previous reviews [11,12]. In doing this, we seek to develop an evidence-based taxonomy of empathy deficits in schizophrenia.

Empathy and Clinical Characteristics of Schizophrenia

Clinical symptoms and empathy

Due to clinical heterogeneity, symptoms of schizophrenia have historically been understood in a variety of ways (for a review see Harrington, et al., [20]). However, reflecting the amendments made to the latest diagnostic manual, the DSM-5 (APA, [21]), which did away with sub-type specifiers (i.e. paranoid, disorganised, catatonic and undifferentiated) for the schizophrenia diagnosis, symptom severity is now examined. Although a variety of symptom assessment tools are available, the Scales for the Assessment of Negative/Positive Symptoms (SANS/SAPS) [20,21] and the Positive and Negative Syndrome Scale (PANSS) [22] have been commonly used to assess positive symptoms (e.g., symptoms of delusions, hallucinations and disorganisation), negative symptoms (e.g., anhedonia, avolition, apathy, asocialty, flattened affect and alogia) and general symptoms (e.g., anxiety, depression, and psychomotor symptoms) in schizophrenia.

In studies of empathy, the primary focus of some studies was not on examining symptom severity in schizophrenia [23-33]. For other studies, however, examining symptom severity in schizophrenia patients was included as part of secondary analyses, with mixed findings reported across individual studies. For example, Montag and colleagues [34] found in patients, the IRI Empathic Concern related negatively to PANSS negative and general symptoms, Thirioux, et al., [35] found, using the same sub-scales, only negative symptoms associated negatively with the IRI Perspective-Taking sub-scale. Lam, et al., [36] found a negative relationship between PANSS general symptoms and overall empathy score, and Shamay-Tsoory and colleagues [37] reported the degree of impaired empathy (total IRI score) depended on how severe negative symptoms were. However, several studies reported no significant relationship between PANSS and IRI sub-scales [38-43] and performance-based measures of cognitive and affective empathy [44,45]. These discrepancies further extend to the

SANS and SAPS symptom measurements [46-48]. Critically, these in consistencies have prevented the field from gaining a more nuanced understanding of how core symptoms of schizophrenia (i.e. positive, negative and general) relate to self-reported empathy. By examining this relationship in a meta-analytic framework, we can further our understanding of the mechanisms underlying empathy deficits in schizophrenia and develop, in a systematic manner, relevant clinical profiles.

Medication

In the UK, for people diagnosed with a schizophrenia disorder, medication is recommended as the first line of treatment (National institute for health and social care [49]). The rationale behind this is, if prescribed at the correct dosage, medication can help manage acute symptoms, prevent relapse, and optimise level of functioning. However, whether medication also benefits interpersonal skills such as empathy remains unclear. Like symptom severity, the association between medication dosage and empathy (Chlorpromazine equivalent, mg/day) has either not been examined [26,28,34,35,38,41,50,51] or has shown not to correlate with components of empathy [29,32,44,47]. These variations may have contributed to the heterogeneity observed for empathy deficits in previous reviews [11,12]. Therefore, it is important that this moderator is included and examined for its effect on empathy further.

Individual Differences in Empathy

Demographic variables and empathy in schizophrenia and related disorders

Empathy can vary as a function of inherent psychological similarities and differences between individuals, referred to in the Psychology literature as individual differences [15]. In schizophrenia, several protective factors have been reported to be of benefit when re-adjusting socially post-illness. These include shorter illness duration, later age at illness onset and female gender. Schizophrenia females have shown to have a better prognosis [52] and pre-morbid adjustments in domains of life which are integral to empathy. These include: Social, sexual and marital domains. Thus, females are thought to have better outcomes and social re-integration post-illness onset than their male counterpart [53-57]. As most studies in the literature have included predominantly male schizophrenia samples [10,24,27-33,37,39,46-48,51,58,59], included wide age ranges [10,38,61-64] with patients often reporting fewer years in education compared to healthy control groups [23,27,41,46,50,51,58,60,65-69] and studies making a note of key variables such as ethnicity in patients but not necessarily examining its effect on empathy [25,27,32,36,43,44,50,51,58,66,70]. The current findings make it unclear as to whether demographic risk factors exacerbate deficits in empathy and consequently, in part, explain some of the heterogeneity observed in previous reviews [11,12].

Empathy and neuro-cognition in schizophrenia and related disorders

Neuro-cognition is central to empathy, as empathy involves making inferences in which observation, memory, reasoning and cognitive flexibility/inhibitory control are all important [28,36,37,47]. Broadly, neuro-cognition refers to the mental operations or processes used to acquire knowledge, meaning and understanding [71] of a

specific task or context. Experts in this field formed the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)-as commissioned by the national institute of mental health. This group identified six neuro-cognitive domains: Attention, working memory (verbal and non-verbal), speed of processing, reasoning and problem solving, visual learning and verbal learning as important areas for further research in schizophrenia that are to be assessed using the MATRICS Consensus Cognitive Battery (MCCB) [72,73].

In the current literature, we found only two studies to have used the MATRICS developed Consensus Cognitive Battery (MCCB) to assess all six neuro-cognitive domains [23,38]. More specifically, amongst the identified studies, authors have commonly produced a global/composite neuro-cognitive score, and examined its relation with empathy, with several studies finding no relationship between global cognition (i.e. the sixneuro-cognitive abilities) and self-reported empathy in schizophrenia [23,27,38]. Other studies however, reported a positive correlation between affective empathy and globalneuro-cognitive scores [67]. Two studies also reported having assessed neuro-cognitive domains proposed by the MATRICS panel (i.e. working memory (verbal and non-verbal) and attention) using measures closely aligning to the MCCB battery [31,74]. However, as neuro-cognition was not the focus of these studies, this ability was not examined in relation to empathy. Since very few studies have examined all six of the neuro-cognitive domains proposed, examining each domain separately may not be possible. However, we can gather studies which have assessed anyone, or more of the neuro cognitive domains identified by the MATRICS panel into a global neuro-cognitive score and assess its impact on cognitive and affective empathy. In this way, we would have sufficient studies to make provisional inferences relating to heterogeneity and taxonomize the role of neuro-cognition on empathy in schizophrenia.

As well as neuro cognition, findings relating to Intelligent Quotient (IQ) and empathy are also unclear. Two types of IQ's have been measured in studies of empathy in schizophrenia: Verbal or pre-morbid IQ, and general IQ. Some studies have reported subtle impairments in pre-morbid/verbal IQ [29,30,50,66,74], while others have reported a more pronounced impairment in general IQ [36,59,67,68, 75]. Since previous studies have found significant negative relationships between measures of IQ and empathetic responding in schizophrenia [23,68], it will be important to include this variable for the purposes of heterogeneity assessment and taxonomy development.

The goal of current research

Inconsistent findings have been reported for clinical, demographic and cognitive variables across studies, thereby making the understanding of the observed heterogeneity for empathy in previous reviews unclear [11,12]. As such, a synthesis of the current evidence is timely and necessary. We, therefore, aimed to undertake a meta-analysis of the available evidence to address the heterogeneity detailed above. In doing this, we went beyond the basic associations detailed in the literature and developed an evidence-based taxonomy of empathy deficits in schizophrenia.

A meta-analytic framework was chosen as it enabled us to gather data systematically and provide us with a large schizophrenia sample, which to some extent helped us in overcoming some of the problems associated with small sample sizes (a common issue in this area of research). This meta-analysis aimed to: (1) Synthesise the extant literature on self-reported cognitive and affective empathy in schizophrenia using a meta-analytic approach. (2) Examine in detail the heterogeneity observed in previous reviews by examining for the first time, the moderating effect of several important variables to create taxonomy. These included: Severity of positive, negative, and general symptoms, duration of illness, age at diagnosis, medication dosages, age, gender, ethnicity, education, global neuro-cognition, verbal/pre-morbid IQ, general IQ and year of publication on the difference in performance on self-reported empathy between schizophrenia patients and healthy controls. Consistent with Bonfils and colleagues reviews [11,12] we hypothesised that healthy controls would report higher levels of cognitive and affective empathy than people with a diagnosis of schizophrenia. Due to mixed findings in the literature for clinical, demographic and cognitive variables, these moderators were examined in an exploratory manner.

Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [76] checklist and literature flow chart was used to carry out and report findings for this study.

Database search

The following databases were searched electronically: Psych Info, Psych Article, Embase, Web of Science Core Collection and PubMed using the keywords (with an English language filter applied, when possible): Empathy, empathising, empathising, empath* appearing with either schizophrenia, schizoaffective, or schizo* were searched up until the 1st week of February 2018. References of relevant meta-analyses [10-12] were also searched. In cases where a study reported to have assessed empathy and met the eligibility criteria, but no data was provided, the corresponding author of the study wascontacted (via email) for additional data.

Study selection criteria

The following study inclusion criteria were used to include/exclude studies: (1) Studies were required to compare people with a diagnosis of schizophrenia or a related disorder with a healthy (control) group on measures purported to assess empathy. (2) Participants had to be adults aged between 16 and 65 years. (3) Studies must have been written in the English language. (4) Studies must have measured each component of empathy (cognitive and affective) separately. (5) Studies had to provide sufficient data to calculate effect sizes and univariate relationships. If the necessary data could not be obtained through available records or contact with the author, the study was excluded.

Data extraction

First, year of publication, publication type, country (including the place where the study was conducted) and the sample size was extracted followed by mean age, education level (in years), gender and ethnicity (both in percent) for schizophrenia patients and healthy controls. For the schizophrenia samples, medication dosage mg/day (chlorpromazine equivalents) [77], duration of illness (in years) and diagnosis (schizophrenia, schizo-affective disorder or a schizophrenia-related disorder) in percent were coded. Mean severity of symptom score was also coded according to categories most frequently reported in studies: Positive, negative and general. Mean scores for

general IQ, verbal/pre-morbid IQ and individual neuro cognitive data based on the six neuro-cognitive domains (attention, speed of processing, working memory (verbal and non-verbal), visual learning, verbal learning, reasoning and problem-solving) as identified by the MATRICS consensus panel [72,73] was coded for both, schizophrenia patients and healthy controls. Also, we identified a few studies including measures assessing cognitive flexibility/inhibitory control. The measures used to assess this ability were entirely different from the neuro-cognitive measures measuring the six domains. However, considering the importance of cognitive flexibility/inhibitory control in empathy (see for example, [3,78]) we included this as an additional neuro-cognitive domain and extracted data for schizophrenia and healthy controls, before calculating a mean global neuro-cognitive score for each group.

Effect sizes

The effect size was computed using Hedges'*g* [78,79]. The mean, standard deviation and sample size for cognitive and affective empathy for each group (schizophrenia and healthy control) were extracted. In cases where this data was unavailable, but other values (e.g. independent sample *t*-value or Cohen's *d*) were, then those were used instead. Where studies reported data for cognitive and affective empathy using more than one measure, then an average study effect was calculated for each component to avoid multiple effect sizes per study, which would violate the assumption of independent observations for each study in a meta-analytic framework [80]. In cases where a study reported to have used two self-report measures of empathy, but data were available only for one, then the scale for which data was reported/available was included. A positive value of *g* signified that healthy controls scored higher than people with schizophrenia and a negative value of *g* signified that people with schizophrenia scored higher than healthy controls.

Analyses

Preliminary analyses

Before conducting the main analyses, descriptive statistics were derived using SPSS version 23.0. Then, one-study remove sensitivity analysis was conducted to assess if anyone study effect size unduly affected the overall effect size for cognitive and affective empathy [81]. Forest plots were produced for each domain to assess for outliers. Visually, any effect size which looked as though it might be an outlier, but when examined statistically (via sensitivity analysis), did not differ was retained. Publication bias was examined first via funnel plots, then using Duval and Tweedie's [82] Trim and Fill random effects model. Funnel plots were created and inspected visually for asymmetry. The Trim and Fill approach were checked for biases or extreme values. If the model showed there to be no statistically significant difference (i.e. *p* >.05) between the included effect sizes, then we can have greater confidence that publication bias does not effectcurrent results [81,83]. However, in cases where the Trim and Fill approach showed to be statistically significant, the Fail-Safe *N* was then examined to ascertain the number of non-significant studies necessary to make current findings nil.

Main analyses

Standardised mean differences were calculated for each component of empathy (cognitive and affective) using a Hedges' *g* random effects model. This model was used as it accounted for both, within

and between study variability [84]. As Hedges' *g* is like Cohen's *d*, the magnitude of the computed effect sizes was interpreted according to the guidelines provided by Cohen [85] such that: ≤0.20 were considered small, 0.50 were considered medium, and ≥0.80 were considered large effect sizes. The inverse variance was also computed to estimate the standard error for each effect size [84].

Heterogeneity and moderator analyses

Heterogeneity was assessed using Q-statistics and degree of heterogeneity using I^2index [83]. When Q-statistics was significant (i.e. *p*< .05), and the I^2index above 25% heterogeneity could be said to be present and therefore, an assessment of moderator analysis proper [85]. Moderators were examined using a random effects meta-regression model. A moderator was of significance if there was significant beta-weight (*p* < .05) and a decrease in the I^2index.

Barring descriptive statistics, all other meta-analytic analyses were conducted on Comprehensive Meta-Analysis Version 2 (CMA) [86].

Results

In total, 39 studies assessing affective empathy and 36 assessing cognitive empathy were identified as meeting the inclusion criteria of this meta-analysis (See Figure 1 for the flowchart of the literature search).
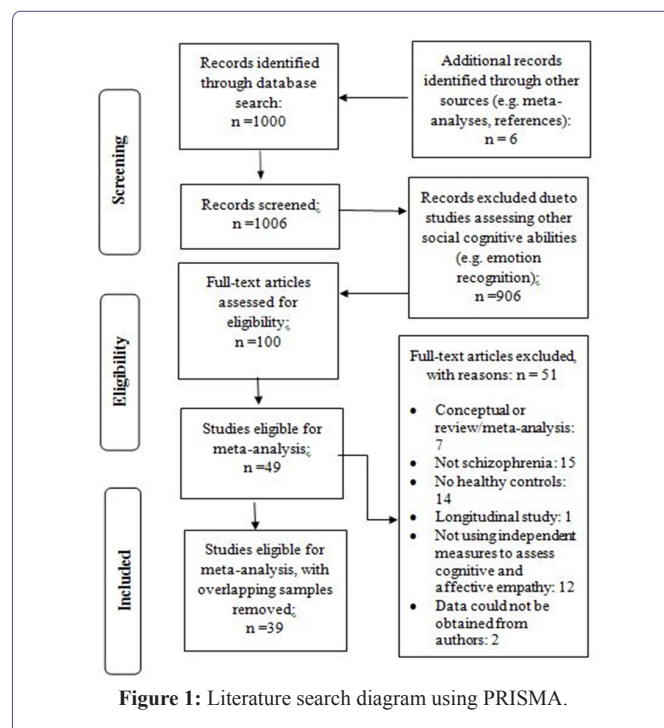

Figure 1: Literature search diagram using PRISMA.

Study characteristics

The meta-analysis included 1,479 participants with a schizophrenia disorder and 1,293 healthy controls. See Tables 1-3 for detailed study characteristics at the individual study level and Tables 4-7 for aggregate study, clinical, cognitive and demographic data (Tables 1-7).

Citation: Varachhia S, Ferguson E, Doody GA (2018) A Meta-Analysis Taxonomizing Empathy in Schizophrenia. J Psychiatry Depress Anxiety 4: 016.

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Citation (K = 39)	Country (City)	SSD N	HC N	% Patients in study with a Schizophrenia Diagnosis	M Age SSD	M Age HC	% Male SSD	% Male HC	M Years in Education SSD	M Years in Education HC	% Ethnicity SSD	% Ethnicity HC
Achim, et al., [10]	Canada (Québec)	31	31	74.2	24.9	25.2	83.9	83.8				
Andrews, et al., [87]	Australia (Victoria)	18	18	61.1	44.1	38.4	61.1	44.4	13.3	15.6		
Berrada-Baby, et al., [88]	France (Versailles)	20	20	100	46.3	41.5	54.0	54.0	12.2	12.5		
Brown, et al., [24]	USA (Baltimore)	17	17	100	41.7	38.2	52.9	52.9				
Chiang, et al., [68]	Taiwan (Hualien County)	70	35	100	44.5	46.0	47.1	48.0	10.9	13.0		
Corbera, et al., [58]	USA (New Haven)	30	24	66.7	46.5	39.7	46.7	62.5	13.1	16.2	43.3-Caucasian 56.5 - Non-Caucasian	54.2-Caucasian 45.8-Non- Caucasian
Corbera, et al., [50]	USA (New Haven)	21	26	100	32.2	30.1	61.9	57.7	14.9	14.9	45.0 -Caucasian 55.0- Non-Caucasian	42.3-Caucasian 57.7 - Non- Caucasian
Derntl, et al., (2012a) ᵗ[44]	Germany (Aachen)	15	15	100	34.2	30.4	66.7	66.7			100-Caucasian	100-Caucasian
Derntl, et al., [70]	Germany (Aachen)	24	24	100	40.1	39.9	50	50.0			100-Caucasian	100-Caucasian
Didehnani, et al., [75]	USA (Dallas)	19	21	63.2	32.4	27.1	88.5		12.6	14.6		
Fischer-Shofty, et al., [25]	Israel (Haifa)	35	48	100		30.0		69.9	12.2	15.0	100-Non-Caucasian	100-Non -Caucasian
Fujino, et al., [39]	Japan (Kyoto)	69	69	100	36.6	24.2	57.9	57.9	13.9	14.5		
Fujiwara, et al [40]	Japan (Kyoto)	24	20	100	37	34.6	50	50.0	13.7	14.3		
Gizewski, et al., [26]	Germany (Essen)	12	12	100	37.8	36.6	100	100	9.3	9.8		
Haker, et al., [65]	Switzerland (Zurich)	43	45	100	34	35.0	39.5	73.0	13	14.0		
Hooker, et al., [23]	USA (Berkeley/San Francisco)	21	17	52	44.3	43.7	80.9	76.4	13.0	15.0		
Horon, et al., [51]	USA (Los Angeles)	32	26	100	47.9	44.4	81.3	73.1	12.9	14.9	56.3 -Caucasian 43.7- Non-Caucasian	76.0 -Caucasian 24.0- Non-Caucasian
Horon, et al., [27]	USA (Los Angeles and Chapel Hill)	145	45	100	40.9	43.3	75	71.0	12.5	14.2	48.3-Caucasian 51.7-Non-Caucasian	31.0 -Caucasian 69.0- Non-Caucasian
Kucharska-Pietura, et al., [61]	Poland (Lublin)	100	50	100	31.3	29.6			12.8	13.7		
Lam, et al., [36]	China (Hong Kong)	58	61	100	40.1	41.3	50	50.8	10.4	11.3	100-Non- Caucasian	100-Non-Caucasian
Lee, et al., [28]	South Korea (Seoul)	15	18	100	26.0	25.8	46.6	50.0	15.1	15.4		
Lee, et al., [69]	USA (Los Angeles)	30	22	100	46.1	44.3	83.3	77.2	12.8	14.7		
Lehmann, et al., [29]	Germany (Berlin)	55	55	100	39.8	38.9	58.1	54.5	14.0	15.0		
Matsumoto, et al., [30]	Japan (Kyoto)	17	18	100	40.0	35.0	35.0	66.6				
McCormick, et al., [48]	USA (Iowa City)	16	16	88	37.0	36.6	88	87.5	13.9	15.4		
McGuire, et al., [31]	Australia (Sydney)	24	20	83	46.6	38.6						
McGuire, et al., [74]	Australia (Sydney)	45	27		43.7	40.7	82.2	62.9				

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Montag, et al., [42]	Germany (Berlin)	45	45	100	37.5	38.8	77.7	77.7	12.6	15.0		
Montag, et al., [58]	Germany (Berlin)	145	145	97	36.9	37.2	62.7	54.4	13.0	15.1	100-Caucasian	100-Caucasian
Pijnenborg, et al., [60]	The Netherlands (Groningen)	46	53	100	27.4	31.1	73.0	46.0				
Ramos-Loyo, et al., [62]	Mexico (Guadalajara)	38	38	100	36.1	34.2	47.3	47.3	13.1	13.8		
Regenbogen, et al., [43]	Germany (Aachen)	20	24	100	37.3	35.2	54.1	65.0	11.5	12.3		
Smith, et al., [47]	USA (Chicago)	45	60	100	35.3	33.0	63.3	53.3			43.3-Caucasian 56.7-Non-Caucasian	48.9-Caucasian 51.1-Non-Caucasian
Singh, et al., [32]	India (New Delhi)	14	14	100	31.5	27.2	78.5	71.4	9.6	11.3	100-Non-Caucasian	100-Non-Caucasian
Shamay-Tsoory, et al., [37]	Israel (Haifa)	26	31	100		26.6	69.2	51.6				
Sparks, et al., [46]	Australia (Sydney)	28	25	89	45.9	35.7	57.1	40.0	13.2	16.7		
Thirioux, et al., [35]	France (Paris)	10	10	100	33.3	32.5	100	100	11.8			
Vistoli, et al., [59]	Canada (Québec)	27	21	67	29.7	29.2	85.1	80.9				
Wojakiewicz, et al., [33]	France (Paris)	29	27	100	36.5	31.0	68.9	74.0	10.3	10.5		

Table 1: Individual demographic characteristics of the studies included in the meta-analysis.

Note: SSD = Schizophrenia-Spectrum Disorder Sample; HC = Healthy Control Sample; M = Mean. ⁺Supplemental information was provided by authors to assist in the coding of these studies.

Citation (*K* = 39)	Country (City)	M Age at Diagnosis	M Duration of Illness	M Medication Dosage (Chlorpromazine equivalents) – mg/day	M Positive Symptom Severity Score	M Negative Symptom Severity Score	M General Symptom Severity Score
Achim, et al., [10]	Canada (Québec)	-	1.7	-	15.1	16.0	32.0
Andrews, et al., ⁺[87]	Australia (Victoria)	21.4	21.1	-	-	-	-
Berrada-Baby, et al., [88]	France (Versailles)	-	-	406.0	-	-	-
Brown, et al., [24]	USA (Baltimore)	30.5	9.3	-	19.1	24.9	45.4
Corbera, et al., [58]	USA (New Haven)	24.3	22.2	654.0	18.9	N-17.0	30.2
Corbera, et al., [50]	USA (New Haven)	-	-	181.3	15.2	15.2	29.2
Derntl, et al., [44]	Germany (Aachen)	26.8	7.3	329.9	12.3	14.6	24.5
Derntl, et al., [70]	Germany (Aachen)	28.9	11.5	601.4	14.0	14.2	28.9
Didehnani, et al., [75]	USA (Dallas)	-	-	-	18.9	16.5	37.1
Fischer-Shofty, et al., [25]	Israel (Haifa)	-	11.8	-	15.4	19.3	34.5
Fujino, et al., [39]	Japan (Kyoto)	24.2	13.1	-	14.2	15.9	31.4
Fujiwara, et al., [40]	Japan (Kyoto)	26.9	10.4	-	14.3	13.9	32.7
Gizewski, et al., [26]	Germany (Essen)	21.0	16.8	672.3	14.6	20.5	31.9
Haker, et al., [65]	Switzerland (Zurich)	24.0	11.0	297.0	12.2	14.6	26.3
Hooker, et al., [23]	USA (Berkeley/San Francisco)	-	24.5	-	11.7	16.5	-
Horon, et al., [51]	USA (Los Angeles)	20.8	26.8	282.5	1.5	1.7	-
Horon, et al., [27]	USA (Los Angeles and Chapel Hill)	21.0	20.0	-	2.5	2.1	-
Kucharska-Pietura, et al., [68]	Poland (Lublin)	-	8.6	408.1	39.4	59.8	-

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Lam, et al., [36]	China (Hong Kong)	25.9	13.4	-	9.7	13.3	20.6
Lee, et al., [28]	South Korea (Seoul)	21.7	4.6	422.1	13.1	15.4	30.6
Lee, et al., [68]	USA (Los Angeles)	-	-	-	5.9	5.3	-
Lehmann, et al., [29]	Germany (Berlin)	29.8	10.0	407.8	13.2	15.9	-
Matsumoto, et al., [30]	Japan (Kyoto)	-	15.2	-	16.1	6.6	10.6
McCormick, et al., [48]	USA (Iowa City)	20.7	15.8	-	4.6	9.2	-
McGuire, et al., [31]	Australia (Sydney)	22.5	22.7	-	1.3	2.1	-
McGuire, et al., [73]	Australia (Sydney)	21.6	21.80	-	1.7	2.1	-
Montag, et al., [42]	Germany (Berlin)	25.8	11.6	-	19.7	19.7	-
Montag, et al., [58]	Germany (Berlin)	26.5	10.4	453.8	17.0	19.4	35.6
Pijnenborg, et al., [60]	The Netherlands (Groningen)	24.2	7.0	-	12.8	15.3	29.2
Ramos-Loyo, et al., [62]	Mexico (Guadalajara)	-	23.4	200.0	16.9	17.8	28.9
Regenbogen, et al., [43]	Germany (Aachen)	27.8	9.5	-	14.2	23.1	-
Smith, et al., [47]	USA (Chicago)	-	14.4	360.9	0.6	0.6	-
Singh, et al., [32]	India (New Delhi)	23.7	9.3	389.3	8.6	12.6	-
Shamay-Tsoory, et al., [37]	Israel (Haifa)	-	-	-	16.5	21.0	-
Sparks, et al., [46]	Australia (Sydney)	-	-	300.9	38.8	39.3	--
Thirioux, et al., [35]	France (Paris)	-	11.8	664.4	21.6	32.2	-
Vistoli, et al., [59]	Canada (Québec)	-	7.6	547.7	16.0	9.6	-
Wojakiewicz, et al., [33]	France (Paris)	-	8.0	-	14.2	19.2	-

Table 2: Clinical data coded for patients with schizophrenia spectrum disorders from individual studies included in the meta-analysis.

Note: M = Mean; CPZ-equivalent-mg/day = Chlorpromazine Equivalent in milligram per day. ᵗSupplemental data was provided by authors. M = Mean. In this table, only that study for which data was available is included.

	M General IQ Score in SSD	M General IQ Score in HC	M Pre-morbid/ Verbal IQ Score in SSD	M Pre-morbid/Verbal IQ Score in HC	M Global Neuro-cogni-tion Score in SSD	M Global Neu-ro-cognition Score in HC
Achim, et al., [10]	100.4	101.8	-	-	-	-
Berrada-Baby, et al., [87]	-	-	26.5	28.9	-	-
Chiang, et al., [68]	83.9	100.4	-	-	-	-
Corbera, et al., [58]	-	-	-	-	39.6	52.0
Corbera, et al., [50]	89.5	-	-	-	32.1	32.0
Derntl, et al., ᵗ[44]	-	114.2	30.2	32.0	-	-
Derntl, et al., [70]	-	-	107.7	111.3	-	-
Didehnani, et al., [75]	102.2	112.1	-	-	-	-
Fujino, et al., [39]	-	-	103.1	105.3	-	-
Fujiwara, et al., [40]	104.0	109.0	104.0	107.0	-	-
Gizewski, et al., [26]	-	-	102.2	109.8	-	-
Haker, et al., [65]	-	-	24.4	33.1	16.8	22.5
Hooker, et al., [23]	101.1	-	-	-	-0.32	0.4
Kucharska-Pietura, et al., [61]	-	-	-	-	24.4	37.4
Lam, et al., [36]	34.9	49.8	-	-	16.6	20.4
Lee, et al., [28]	-	-	11.4	12.7	14.5	10.4
Lehmann, et al., [29]	-	-	108.5	118.8	25.0	21.9
Matsumoto, et al., [30]	-	-	101.7	107.9	-	-
McGuire, et al., [31]	-	-	105.6	107.7	35.1	37.5
McGuire, et al., [74]	-	-	103.0	109.5	27.9	33.5
Montag, et al., [42]	-	-	25.8	29.6	-	-
Montag, et al., [58]	-	-	103.9	108.9	-	-
Pijnenborg, et al., [60]	90.2	103.4	41.9	52.1	36.3	31.3

Regenbogen, et al., [43]	-		71.4	82.1	22.3	17.7
Smith, et al., [47]	-	-	-	-	0.32	0.4
Sparks. et al., [46]	-	-	104.9	110.0	-	-
Thirioux, et al., [35]	-	-	-	-	-	-
Vistoli, et al., [59]	99.9	109.3	-	-	-	-
Wojakiewicz, et al., [33]	90.3	93.6	-	-	--	-

Table 3: Mean general IQ, pre-morbid/verbal IQ and global neuro cognitive scores for schizophrenia spectrum disorders and healthy controls coded from individual studies included in the meta-analysis.

Note: M = Mean; CPZ-equivalent-mg/day = Chlorpromazine Equivalent in milligram per day. ʲSupplemental data was provided by authors. M = Mean. In this table, only that study for which data was available is included.

	Mean (SD)/Mean Percent (SD)	Range	K
Sample Type			
Published Article	94.9	-	37
Poster (data from authors)	5.1	-	2
Year	2012	2007-2017	39
SPD Sample Size	37.9 (31.4)	10-145	39
HC Sample Size	33.2 (23.9)	10-145	39
Location			
Europe	33.3	-	13
United States	33.3	-	13
Asia	23.2	-	9
Oceania	10.3	-	4

Table 4: Study characteristics of included studies in the meta-analysis.

Note: Standard Deviation; *K* = Number of studies included; SPD = Schizophrenia Spectrum Disorders; HC = Healthy Control.

	Mean (SD)/Mean Percent (SD)	Range	K
General IQ, Healthy Controls	99.29 (19.6)	49.8-14.2	9
General IQ, Schizophrenia Spectrum Disorder	89.6 (20.4)	34.9-04.0	10
Verbal/Pre-morbid IQ, Healthy Controls	79.9 (40.7)	12.7-18.8	15
Verbal/Pre-morbid IQ, Schizophrenia Spectrum Disorder	74.9 (39.7)	11.4-08.5	15
Global Neuro-cognition, Healthy Controls	24.4 (15.03)	0.43-52.1	13
Global Neuro-cognition, Schizophrenia Spectrum Disorder	22.3 (12.6)	-0.32-39.5	13

Table 6: Cognitive characteristics of samples included in the meta-analysis.

Note: SD = Standards Deviation *K* = Number of studies included.

	Mean (SD)/Mean Percent (SD)	Range	K
Diagnosis			
Schizophrenia	93.2 (13.6)	52.4-100	38
Shizo-affective	4.65 (15.6)	2.7-42.9	10
Other Psychoses	1.86 (9.2)	6.3-19.3	2
Age at Diagnosis	24.6 (3.1)	20.7-30.5	22
Duration of Schizophrenia	13.5 (6.3)	1.7-26.8	32
Symptom Severity			
Positive Symptoms	13.9 (8.4)	0.61-39.40	36
Negative Symptoms	16.6 (10.9)	0.66-59.80	36
General Symptoms	31.0 (5.3)	20.6-45.4	18
Medication Dosage (Chlorpromazine equivalents) – mg/day	414.3 (38.02)	162.1-642.3	18

Table 5: Clinical characteristics of samples included in the meta-analysis.

Note: SD = Standard Deviation; *K* = Number of studies included

Demographic variables	Mean (SD)/Mean Percent (SD)	Range	K
Age, Healthy Controls	35.2 (5.9)	24-46	39
Age, Schizophrenia Spectrum Disorders	37.8 (6.1)	25-48	38
Education, Healthy Controls	14.0 (1.7)	9.8-16.7	27
Education, Schizophrenia Spectrum Disorders	12.5 (1.3)	9.3-15.1	28
Male, Healthy Controls	63.9 (15.2)	40-100	36
Male, Schizophrenia Spectrum Disorder	67.5 (15.6)	47-100	36
Ethnicity, Healthy Controls	Caucasian-69.1 (28.6) Non-Caucasian- 31.3 (28.1)	31-100 / 24-100	8 / 7
Ethnicity, Schizophrenia Spectrum Disorder	Caucasian-67.0 (27.6) Non-Caucasian-33.0 (24.8)	43.3-100 / 43.7-100	8 / 8

Table 7: Demographic characteristic of samples included in the meta-analysis.

Note: SD = Standard Deviation; K = Number of studies.

Empathy measures

The Interpersonal Reactivity Index (IRI) [19] was used in 87.2% ($k = 34$) of included studies. Besides this, five studies [37,60,61,63,75] used The Empathy Quotient [89], Balanced Emotional Empathy Scale [89], Questionnaire Measure of Emotional Empathy [90] and Social Context Emotional Recognition Task [62] respectively (Supplementary Table S1 for a description of the empathy measures included).

Symptom assessment

Symptoms of schizophrenia was assessed in 92.3% ($k = 36$) of included studies. Assessment tools included the PANSS [22]; SAPS [91]; SANS [92] and the Brief Psychiatric Rating Scale (BPRS) [93] (Supplementary Table S2).

Assessment of neuro-cognition

Broadly, data for neuro-cognition was available for $k = 13$ studies. We identified several studies assessing neuro-cognition [37,44,51,70] for which we could not gather the required data within our data collection timeframe.

One study [58] measured all six neuro-cognitive domains (i.e. attention, speed of processing, working memory (verbal and non-verbal), visual learning, verbal learning, reasoning and problem solving) using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) [94]). Barring the attention domain, Hooker, et al., [23] also measured the above-mentioned domains using the MCCB. Although Smith and colleagues [47] reported not to have used the MCCB battery, nonetheless assessed the six neuro-cognitive domains using approximate measures representing the MCCB assessment battery [94]. Across the remaining ten studies [29,31,36,43,51,60,61,65,69,74] few, but not all six neuro-cognitive domains were assessed using tests that differed from but comparable to the MCCB. For example, Lam, et al., [36] assessed the reasoning and problem solving, and visual learning domain, whereasother studies (see for example, [61]), assessed the attention and working memory (non-verbal) domain. We also found few studies [31,51,65,88] to have examined cognitive flexibility, which we additionally included within the global neuro-cognitive moderator (Supplementary Table S3 for a description of the neuro-cognitive measures used in individual studies and the corresponding neurocognitive domain examined).

In total, 15 studies measured pre-morbid/verbal IQ. Pre-morbid/verbal IQ was measured in 13 of these studies using either the Multiple-choice vocabulary test (German version) (MCVT; [95]) or National Adult Reading Test (NART; [96]). MCVT was included by seven studies [26,29,42-44,58,70] and NART by six studies [30,31,39,46,73,74,88]. The remaining two studies [28,40] used the verbal sub-set from the Wechsler's Adult Intelligence Scale - III [97] (Supplementary Table S4 for a short description of each of the verbal task used by the included studies).

Data for general IQ was available for ten of the included studies. Eight of these studies [10,23,33,40,50,59,68,75] used several versions of the Wechsler's Adult Intelligence Scales (e.g. [97]). The remaining two studies [36,60] used the Raven's Progressive Matrices

Test (120) and Groninger Intelligence Test [98] respectively (Supplementary Table S5 for a description of the general IQ measures used by the included studies).

Sensitivity analysis

One study removed sensitivity analysis, and visual assessment of forest plots (available on request from the author) was carried out for the effect sizes for cognitive and affective empathy separately. We found, when the point effect size for each study was removed the overall mean effect sizes for each component of empathy did not differ significantly. Thus, all studies were retained for the main meta-analysis.

Meta-analyses

For cognitive empathy, a medium effect size ($k = 36$, Hedges' $g = 0.53$, 95% CI [0.43, 0.64], $p<0.001$) was found, such that the healthy control group reported to have better perspective-taking ability then the schizophrenia group (Figure 2). The Q-statistics was significant (Q-statistics = 52.88, df = 35, $p = .02$) with an I^2 index of 33.82%.
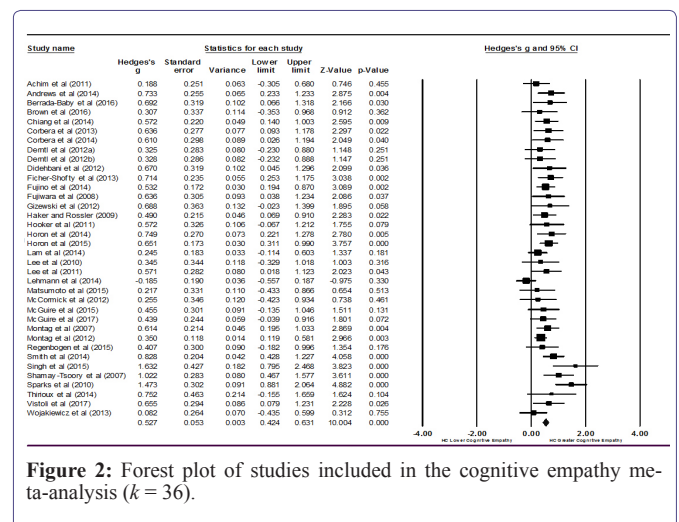

Figure 2: Forest plot of studies included in the cognitive empathy meta-analysis ($k = 36$).

For affective empathy, a small effect size was found ($k = 39$, Hedges' $g = 0.29$, 95% CI [0.16, 0.42], $p<0.001$) (Figure 3). This indicated the healthy control group had better affective empathic ability than the schizophrenia group. The Q-statistic was significant (Q-statistic = 98.21, df = 38, $p<0.001$) with an I^2 index of 61.31%.

Meta-analyses examining impact of co-morbid psychiatric condition on empathy

We ran additional meta-analyses, excluding studies including schizo-affective patients. For cognitive empathy, the effect size remained medium ($k = 26$, Hedges' $g = 0.51$, 95% CI [0.39,0.63], $p<0.05$) and for affective empathy, it remained small ($k = 29$, Hedges' $g = 0.24$, 95% CI [0.12,0.30], $p<0.05$). Thus, all samples were retained for subsequent analyses.
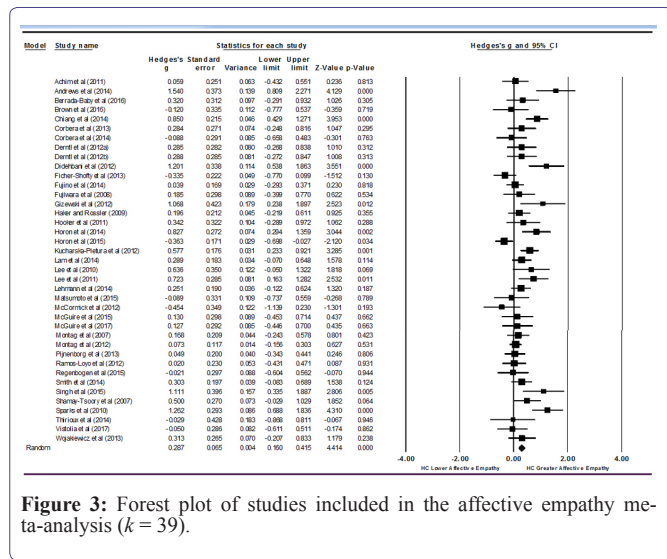
Citation: Varachhia S, Ferguson E, Doody GA (2018) A Meta-Analysis Taxonomizing Empathy in Schizophrenia. J Psychiatry Depress Anxiety 4: 016.

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Figure 3: Forest plot of studies included in the affective empathy meta-analysis ($k = 39$).

Moderator analyses

The clinical characteristics: Duration of illness (in years), age at diagnosis (in years) mean symptom severity score (positive, negative and general), and medication dosage (mg/day) (chlorpromazine equivalents). Neuro-cognition: Mean general, verbal/pre-morbid and global neuro-cognition score, and demographic variables: Mean age of schizophrenia patients (in years), gender (higher percent of schizophrenia male samples), education (lower educational attainment in schizophrenia) (in years), ethnicity (higher percent of non-Caucasian compared to Caucasian schizophrenia patient) and year of study publication were examined as continuous moderators for each domain of empathy.

Cognitive empathy

Meta-regression found the duration of illness significantly moderated the difference between samples (i.e., schizophrenia vs healthy controls) on measures of cognitive empathy. Such that for every one-year increase in duration of illness, the standardised mean difference in performance between schizophrenia and healthy controls increased by 0.012. This significant finding was accompanied by a decrease in the I^2index to 3.27%. Thus, the duration of illness explained 30.55% of the initially observed I^2index. Age at diagnosis was also found to negatively moderate the difference in performance between patients and controls, such that as the age of symptom onset decreased, differences in performance between the two groups increased by -0.06 points. This effect was accompanied by a decrease in the I^2 index by 5.12%, thus explaining 28.70% of the initially observed I^2index (Table 8). Besides this, none of the other moderators reached statistical significance (Table S6-S8).

	k	B	SE	95% CI	Z	P	Reduction in I^2
Age at Diagnosis	20	-0.06	0.018	[-0.09, -0.02]	-3.35	0.0008	28.7
Duration of Illness	29	0.01	0.008	[0.001,0.03]	2.11	0.03	30.6

Table 8: Significant moderator variables for cognitive empathy.

Affective empathy

Meta-regression analyses found none of the clinical, cognitive and demographic moderators reached statistical significance (Table S9-S11).

Publication bias

For affective empathy, the Trim and Fill approach [81] identified four missing studies, with the effect size increasing to Hedges' $g = 0.37$ ($p<0.05$). However, the classic fail-safe N identified that we would need 409 missing studies to bring the p-value of the current observed effect size to non-significance. For cognitive empathy, nine studies were identified as missing, with the effect size reducing to Hedges' $g = 0.41$ ($p < 0.05$). Here the fail-safe N identified 1,367 non-significant studies necessary to bring the current effect size to nil (see Figures 4 and 5 for the funnel plots with imputed studies).
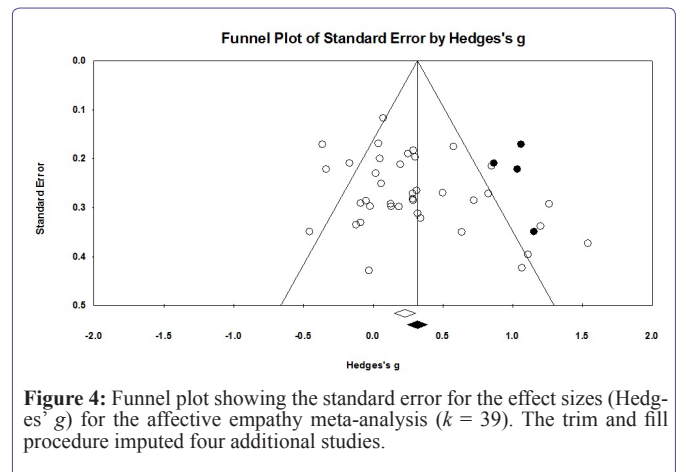

Figure 4: Funnel plot showing the standard error for the effect sizes (Hedges' g) for the affective empathy meta-analysis ($k = 39$). The trim and fill procedure imputed four additional studies.
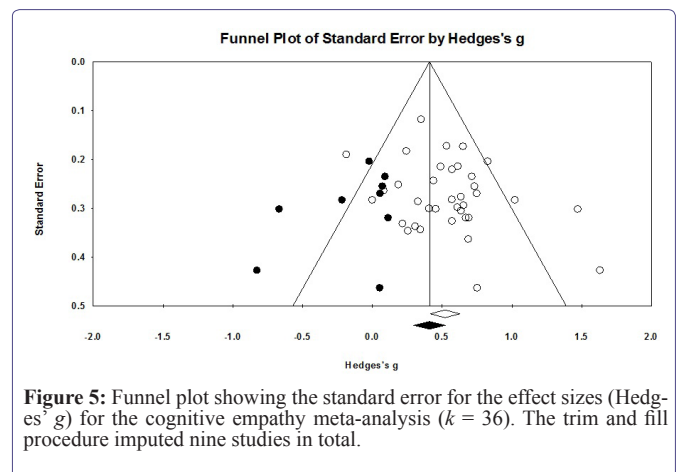

Figure 5: Funnel plot showing the standard error for the effect sizes (Hedges' g) for the cognitive empathy meta-analysis ($k = 36$). The trim and fill procedure imputed nine studies in total.

Discussion

As well as synthesising the extant literature on empathy in schizophrenia, this study considerably expanded past work by examining the moderating effect of clinical (positive, negative, general, medication effect, age at diagnosis and duration of illness), demographic (age, gender, education, ethnicity and year of publication) and

cognitive (verbal/pre-morbid IQ, general IQ and global neuro-cognition) variables on cognitive and affective empathy. In doing this, we went beyond examining basic associations observed in the literature and developed an evidence-based taxonomy of empathy in schizophrenia. Consistent with our hypotheses, we found, healthy controls reported higher levels of affective empathy than schizophrenia patients (a small effect size). For cognitive empathy, the difference in reporting between the two groups was of a medium effect, with healthy controls reporting higher perspective-taking ability then the patient group. Amongst the variables studied, duration of illness and age at illness onset significantly moderated the difference in performance between patients and controls on measures of cognitive empathy. Besides these, none of the other moderators reached statistical significance. The effect sizes reported in this study are in line with previous reviews on this topic [11,12].

Moderating Effect of Clinical variables on Empathy

Duration of illness and empathy

For the moderating effect of duration of illness, we found, for every one-year increase in illness duration, the difference in perspective-taking ability between patients and healthy controls increased by 0.012 points. This observation is consistent with a previous meta-analysis on this topic [12]. Adding further, we found this effect to be independent of any age-related decline in schizophrenia. Cross-sectional studies are the norm rather than the exception in this field of research. However, as the current evidence points to a progressive decline in self-reported cognitive empathy, our findings can be said to provide indirect, longitudinal evidence of deterioration over time. This can be explained by several reasons. For example, the distress caused by psychotic thinking, perhaps due to poorer clinical insight can make people with a diagnosis of schizophrenia mistrustful of others, which in turn could lead to social withdrawal [99] or a restriction in their social network [100]. Over time, this can lead to patients having fewer opportunities to socialise and hone their empathic skills, thus increasing the probability of empathic atrophy over time. Besides this, long-term residual symptom experiences, medication side-effects, sensitivity to stress, and substance misuse may also affect key cortical regions associated with empathy [23,32,39]. High level of stigma associated with schizophrenia [101], as well as a loss of morale and self-esteem over time can also lead to a loss of hope, confidence and motivation in people with schizophrenia [102], all of which can negatively impede a patient's ability to engage confidently or communicate effectively in an empathetic manner.

Age at clinical diagnosis also had a moderating effect on cognitive empathy. As the age at diagnosis decreased, the difference in performance between patients and controls on self-reported cognitive empathy increased. This means that those with an earlier diagnosis reported having greater difficulties in perspective-taking then those whose symptom onset was at a later age. Duration of illness and age at diagnosis are related. Both are reliable indicators of severity of illness in schizophrenia (i.e. the earlier the onset, the worse it is regarding functional outcome, and the longer it persists without remission, the less likely you are to improve) [103]. Therefore, it will be important to address the underlying mechanisms of this deficit in future work.

Clinical symptoms and empathy

We found none of the schizophrenia symptoms (i.e., positive, negative and general symptoms) moderated the effect sizes for cognitive or affective empathy. Amongst the included studies ($k = 39$), only a few studies reported a significant association between severity of clinical symptoms and empathy [37,46,47,51,58,61,62], with several studies not finding any statistically significant relationship between either one of the core schizophrenia symptoms and self-reported empathy [10,23,29,32,36,39,40,47,42,43,58,65,70,88]. A closer inspection of the clinical profile of the schizophrenia group we were analysing indicated that this group was on a stable dosage of antipsychotics at the time of testing and were, therefore, only really experiencing symptoms residually (Table 5). Therefore, a restricted range in the symptom severity score or the fact that most patients were not experiencing symptoms acutely could explain the lack of relationship with empathy.

We found no moderating effect of chlorpromazine equivalents (mg/day) on self-reported cognitive and affective empathy. These findings are consistent with studies that directly compared the effects of chlorpromazine equivalent on self-reported empathy [29,32,44,46,47]. These findings also extend to haloperidol equivalents [32,39,40]. Singh, et al., [32] also reported having found no effect of duration of antipsychotic drug taken on any of the IRI scores in an enduring schizophrenia sample. Also, in one of the largest sample study comparing patients treated on conventional versus atypical antipsychotic drugs on social cognitive abilities, Kucharska-Pietura and colleagues [61] found no clear advantage of atypical antipsychotics over typical antipsychotics on emotional functioning in patients with schizophrenia. Results from several longitudinal studies [104] have also indicated no significant effect of antipsychotic drug treatment on several other related social-cognitive domains (e.g. facial affect perception). Thus, it appears that while antipsychotic drugs are useful in treating core symptoms of schizophrenia, deficits in empathy may perhaps be resistant to pharmacological intervention.

Demographic variables and empathy

This study included many studies which provided us with a large sample to examine several demographic variables more thoroughly. These included; the impact of age-related decline, a higher proportion of male patients (compared to female patients), ethnicity (higher proportion of non-Caucasian schizophrenia patients compared to Caucasian patients), and lower educational attainment in the schizophrenia group (compared to the healthy group), on self-reported cognitive and affective empathy. None of these demographic variables directly moderated the difference in performance between patients and controls on self-reported measures of empathy, which is consistent with several independent studies in the literature. In relation to age, several studies included this variable as a covariate and consistent with the current findings, found schizophrenia patients and controls continued to differ on empathic abilities [46,75]. Similarly, a direct examination of gender-related effects in schizophrenia patients, on measures of cognitive and affective empathy, also revealed no significant interaction [39,40,58,105] or any impact of lower education attainment on empathy [36,46,61,68]. Collectively, these findings suggest other risk factors not observed here may have superseded current demographic risk factors in patients with schizophrenia.

Neuro-cognition and empathy

Several neuro-cognitive variables were examined in relation to empathy. These included: Verbal/pre-morbid IQ, general IQ and global

neuro-cognition. Regarding general and pre-morbid/verbal IQ, neither variable moderated the differences in performance between patients and controls. This finding is consistent with several studies in which differences on measures of empathy remained between groups of interest after controlling for these initial differences [40,42,75]. Together these findings indicate, that while impairments in general and verbal/pre-morbid IQ remain apparent in patients with more severe and enduring schizophrenia [29,30,36,38,58,59,60,68,74,75] they do not adequately account for the heterogeneity observed in empathy in this or previous reviews [12].

In this study, instead of examining individual neuro-cognitive domains, we examined what we termed 'global neuro-cognitive abilities' by including studies that assessed all, few or one of the six neuro-cognitive domains defined and recommended by the MATRICS panel [72,73] as well as an additional, cognitive flexibility/inhibitory control domain. Overall, we did not find any impact of this variable on cognitive or affective empathy which is consistent with several of the published studies in the field [23,27,58]. However, as it is well established that like IQ, neuro-cognitive deficits do exist in patients with more severe and enduring schizophrenia [106] and is an essential component of empathy [31,36,47,51,74]. Therefore, the lack of association is somewhat surprising. It may be that this moderator was somewhat underpowered, or there was a lack of dispersion in the neuro cognitive scores. Alternatively, it may have been that for neuro-cognitive abilities to relate to empathy; tasks need tapping into specific cognitive abilities. In other words, specific executive function tasks (e.g. emotion-regulation) relating to empathy [78,101] is perhaps necessary to find a significant effect.

Affective empathy and heterogeneity

For affective empathy, we found, healthy controls reported higher affective empathy then schizophrenia patients, with a small effect size (Hedges' $g = 0.29$) with significant heterogeneity ($I^2 = 61.31\%$), both findings are consistent with previous reviews in the field [11,12]. However, none of the moderators we examined explained the observed heterogeneity. This may be due to variability in the affective responses by the included patients. Across individual studies, we found, three affective responses: (1) Some patients reported to have deficits in affective empathy (i.e. lower levels than healthy controls) [26-29,31-33,36,37,47,51,58,68,69,74]. (2) Other studies reported comparable levels of affective empathy in schizophrenia patients and healthy controls [10,24,39,59,60,62] and (3) the remaining, reported higher levels of affective empathy in patients than in controls [27,29,30,35,43,50,88]. Thus, under the rubric of schizophrenia, several affective responses may have been present, which could explain both, the small effect size and lack of moderator influence found in this study.

Limitations

Publication bias

We found an interesting effect of publication bias on current findings. For affective empathy, we found that the missing studies increased the overall effect size from the observed Hedges' $g = 0.29$ to Hedges' $g = 0.37$. In the studies we included, we found, patients were medically stable at the time of testing (symptom severity score; Table 5). The nature of some symptoms, especially negative symptoms means social withdrawal and anhedonia are common, and as such, patients with these experiences are unlikely to participate in research studies. Therefore, for affective empathy, the publication bias is perhaps reflective of missing studies of patients with predominantly negative symptoms where deficits in affective empathy are likely to be more pronounced.

For cognitive empathy the opposite held. In total, nine studies were identified as missing (Figure 5) and including them would have reduced the effect size from Hedges' $g = 0.53$ to Hedges' $g = 0.41$. This observation is consistent with a previous meta-analysis in the field [12] and together highlight two important issues: (1) The need to also publish nil findings and (2) where possible, include schizophrenia samples at different stages of the illness course, particularly at the earlier phase, where deficits in perspective-taking are likely to be less pronounced then in the more severe and enduring phase.

Measures of empathy: Self-report

Our findings for empathy are reported from self-report measures. Thus, they must be interpreted as showing how patients perceive their abilities as opposed to their actual abilities, which may differ [11]. We did not include performance-based measures since few studies have been published and a lack of psychometric properties was available for those measures [33]. Moreover, self-reported measures are more acceptable to patients, and since they tap into a wide range of situations, they are more apt in providing broader estimates of empathy levels than other measures (e.g. performance-based) which evaluate responses to specific circumstances.

Impact of additional variables

The impact substance misuse (drugs and alcohol), co-morbid medical illness, and family history of psychiatric illness has on self-reported empathy was not be examined as no or insufficient data was available for these variables. Nonetheless, these are important variables commonly found to affect patients with a diagnosis of schizophrenia [23,26,32,39] and may have therefore conflated current findings. Thus, it is important that readers take this into account when interpreting current results and report on these additional variables in future work.

Generalisability of current findings

We did not find any impact of year of publication on reported effect sizes. This means, over the years, there have been no significant changes in the methodology and samples recruited. We found schizophrenia samples in this, and previous reviews [10-12], can be classified as 'stereotypical schizophrenia samples'. This includes a predominantly chronic, male sample, on medication, with core schizophrenia symptoms stable, with minimum (if any) negative symptoms. Since schizophrenia is a heterogenous syndromic disorder, care must be taken in term of the extent to which we generalise current findings to other phases or schizophrenia samples.

Also, over 90 percent of the studies included were conducted in developed countries (Table 1). Better outcomes have been found in many developing compared to developed countries [101]. Thus, findings from this study may not be fully general is able to those recovering in developing countries.

Citation: Varachhia S, Ferguson E, Doody GA (2018) A Meta-Analysis Taxonomizing Empathy in Schizophrenia. J Psychiatry Depress Anxiety 4: 016.

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Conclusion

In conclusion, we found a prolonged illness course or earlier diagnosis taxonomized deficits in cognitive empathy in patients with enduring schizophrenia. For affective empathy, we conclude, some patients report a deficit; others report comparable levels to healthy controls, and the remaining report experiencing higher emotional arousal then healthy controls. As an earlier diagnosis, prolonged illness course and dysfunctional emotional reactions are significant risk factors of poorer empathic interactions; it will be important to address the underlying mechanisms of these deficits in future work.

Supplementary Material

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Supplementary

Measures of Empathy	Original Article	Studies in Meta-Analysis	Description of Tasks and Scores Produced
Interpersonal Reactivity Index (IRI)	[1]	[2-35]	A 28-item self-report scale including four sub-scales: Empathic Concern, Perspective-Taking, Personal Distress and Fantasy. The Empathic Concern sub-scale taps into 'other-orientated' feelings of sympathy and concern for unfortunate other. The Perspective-Taking sub-scale assesses the ability to see things from the others perspective or how the other person thinks. The Personal Distress sub-scale measures levels of anxiety, sorrow or emotional distress in emergency situations. The Fantasy sub-scale measures the ability to relate to fictional characters (e.g. books or movies). Items on these sub-scales are measured on a 5-point Likert-scale, with responses ranging between does not describe me well, to describes me very well
Empathy Quotient (EQ)	[36]	[37]	A 60-item self-report scale. 40 items measure empathy on the cognitive and affective dimension and the remaining are included as control items. Each response is measured on a 4-point Likert scale, with responses ranging between strongly agree-to-strongly disagree
Questionnaire for Cognitive and Affective Empathy (QCAE)	[38]	[17,39]	A 31-item self-report scale consisting of five sub-scales: Perspective-Taking and Online Stimulation, measuring cognitive empathy. Emotion Contagion, Proximal Responsivity and Peripheral Responsivity measuring affective empathy The Perspective-Taking sub-scale measures a respondent's ability to understand the perspective of others. The Online Stimulation sub-scale measures how well a respondent can mentally represent another's emotional state. The Emotion Contagion taps into assessing the extent to which self-orientated emotions match the affective state of others. The Proximal Responsivity sub-scale examines a respondent's emotional response to the moods of significant others (e.g. friends) and the Peripheral Responsivity sub-scale measures affective responsiveness to detached, or fictional social context (e.g. characters in movies, plays, books etc). Items on these subscales are measured on 4-point Likert scale, with responses ranging between describes me very well to does not describe me well
Balanced Emotional Empathy Scale (BEES)	[40]	[41]	A 30-item self-report scale measuring spontaneous, or vicarious emotional reactions in response to another's emotional distress (i.e. affective/emotional empathy). Each item is rated on a 9-point extent to which you agree-disagree spectrum
Questionnaire Measure of Emotional Empathy (QMEE) (also referred to as the emotional empathic tendency scale)	[42]	[43]	A 33-item self-report scale assessing affective role-taking empathy. In other words, this scale measures the extent to which the respondent agrees with the self-orientated emotional responses someone would typically experience in response to another's emotional distress. Items on this scale are measured on a 4-point Likert scale, ranging between strongly agree to strongly disagree
Social context emotional recognition task	[44]	[44]	In this task, participants watched short films representing a happy, sad, angry and fearful context. Participants rated their emotional reaction (affective empathy) to each film and the intensity of the emotion they felt using a rating scale. The rating scale consisted of a continuous 10 cm line on which participants had to make a mark: Scores to the extreme left corresponded to the lowest intensity (0 cm) and scores to the extreme right corresponded to the highest intensity

Table S1: List of empathy measures used by studies included in the meta-analysis.

Symptom Assessment Measure	Studies in meta-analysis	Description of Measure
Positive and Negative Syndrome Scale (PANSS) [45]	[2-44]	A 30-item semi-structured measure completed by clinicians in an interview or observation format. 7 items measure positive symptoms of schizophrenia, 7 items measure negative symptoms and 16 items measures general psychopathology
Schedule for the ASSESSMENT of Positive Symptoms(SAPS) [46]	[23-25,29,30,32,41]	A 34-item clinician rated scale which is used to measure the following positive symptoms: Bizarre behaviour, formal thought disorder, hallucinations and delusions
Schedule for the Assessment of Negative Symptoms (SANS) [47]	[17,23-25,29,30,32,41]	The originally published scale consisted of 25 items. Currently, SANS comprises of 19-items, representing 5 scales: Blunted/flattened affect, alogia, avolition-apathy, anhedonia/associability and inattention. Items on this scale are rated by clinicians
Brief Psychiatric Rating Scale (BPRS)-positive symptom sub-scale [48]	[16,17,20]	A 24-item scale assessing positive symptoms of schizophrenia via self-report and clinical observations. Each item on this scale is measured on a 2 (very mild) to 7 (extremely severe) anchor points
BPRS-Negative symptom subscale [48]	[16,20]	This sub-scale consists of items assessing negative symptoms of schizophrenia and is measured in the same way as the BPRS-positive symptom sub-scale

Table S2: List of symptom assessments used by studies included in the meta-analysis.

Citation: Varachhia S, Ferguson E, Doody GA (2018) A Meta-Analysis Taxonomizing Empathy in Schizophrenia. J Psychiatry Depress Anxiety 4: 016.

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Neurocognitive Domain	Neurocognitive Measures	Description of Measure	Studies in Meta-Analysis
Attention/ Vigilance (reported by three studies)	The test of everyday attention [49]	This test included three tasks: 1. Visual selective attention task. This task involved searching a map for 2 minutes. 2. Auditory selective attention task. In this task participants must count the number of times they hear a tone while ignoring a distracting tone of a higher intensity. 3. Sustained visual attention task-The Visual elevator task. In this task participants are presented with an elevator which they are told represents floors. Participants are instructed to count the number of elevator doors they pass	[41]
	Continuous performance task-identical pairs [50]	A computerised test assessing sustained attention. A button must be pressed each time the participant sees two numbers matching onscreen	[6,29]
2. Verbal learning (reported by six studies)	Hopkins verbal learning test-revised [51]	The task administrator presents 12 words from three categories (e.g. animal, colours and numbers). Participant is assessed on how many words they can recall after each of three learning trials	[6,7,15]
	Rey auditory verbal learning test (English version) [52]	Participants are presented with 15 words over five trials. Participants must say the words immediately. An interference trial is then presented which involved presenting new words. Participants are asked to recall words from the initial list presented	[26,43]
	California verbal learning test-second edition [53]	Participants are presented with a list of 16 words which they recall immediately over five trials. This is followed by an interference list, in which 16 words are presented in a single trial which must be recalled immediately. 20 minutes later a recognition trial is administered. Recall can be free or category-cued	[29]
3a. Working Memory (verbal) (Reported by Five Studies)	Wechsler memory scale-third edition (WMS-III): Letter-number span [54]	Participants are instructed to mentally re-order strings of numbers and letters and repeat them orally to the test administrator	[6,15,24,29]
	WAIS Digit Span Forward/Backwards Subtest [55]	Participants are instructed to repeat the numbers presented to them either in the same or reverse order. Over the course of the task, the number sequence increases	[29]
	Repeatable battery for the assessment of neuropsychological status-story memory sub-test [56]	A 12-item short story is presented visually in three separate parts over two trials. Each story is read aloud with a low reading speed. Participants recall as much of the story as they can after each presentation. A verbatim criterionis used to score participant response	[25]
3b. Working memory (non-verbal) (reported by five studies)	WAIS-Revised (R)-working memory subtest [57]	This test uses an arithmetic and digit span test. For the digit span test, participant recalls a series of number in a specific order (i.e., ascending, backward or same order). For the arithmetic test, participants work within a specified time limit to mentally resolve a series of mental arithmetic problems	[28]
	WMS-III: Spatial span [54]	Participants are presented with 12 blocks on which a sequence is tapped by the administrator. Participants must tap the blocks in the order requested by the administer (either reverse or same order)	[7,15,29]
	Short recognition memory test for faces [58]	Participants are presented with 25 grey scale faces of male actors at a rate of 1 face every 3 seconds. Participants decide (using a forced choice option) whether the image presented is pleasant or unpleasant immediately post stimulus onset. Each stimulus item is paired with a distractor item	[41]
4. Speed of processing (reported by eight studies)	Trail Making Test A (TMT A) [59]	In this test, numbers a placed irregularly on a sheet of paper, which participants are instructed to join correctly? This is a timed pencil and paper test	[6,15,28,29,43]
	Trail Making Test B (TMT B) [59]	In part B, participants are presented with numbers and letters in random order, which they connect in alternating order	[28,43]
	Brief Assessment of Cognition in Schizophrenia (BACS): Symbol coding [60]	This is a timed test in which participants are required to write down the digit corresponding to nonsense symbols within 90 seconds	[6,15]
	WAIS-III Digit symbol substitution sub-test [55]	Participants are presented with a series of numbers and symbols in a grid. Participants reproduce symbols corresponding to the numbers in the grid within a 120 second time limit	[29]
	Category fluency-animal subtest [61]	In this test, participants are instructed to generate exemplars of animals within 60 seconds. The total number of true animal exemplars within the time frame is measured	[6,15,29]
	Five-point test [62]	There are two parts to this test: Verbal and non-verbal. In the verbal test participants must make words that begin with a specific letter (e.g., "A") within three minutes. Participants are instructed not to produce nouns or repeat words. In the non-verbal test participants are presented with 40 squares on a sheet of paper. Each square consists of 5 symmetrical dots. Within a 2-minute timeframe, participants must create as many designs as they can by joining the dots in each square with one or more straight lines	[14]
	Repeatable battery for the assessment of neuropsychological status-coding sub-set [63]	A page filled with symbols is presented to participants. Each symbol corresponds to a number on top of the page. Participant must match the symbol to its corresponding number within 90 seconds	[25]
5. Cognitive flexibility (reported by Three studies)	Stroop test [64]	There are three sub-tests to this task: The colour word sub-test in which participants must read the colour of the word presented in black ink. The colour name sub-test, in which participants must name the colour of the triangle, and in the interference sub-test, participants ignore the word they see and say the colour of the word (e.g. if the word black is written in the colour red, then the correct answer would be red)	[14,16]
	Delis-kaplan executive function scale-colour word interference sub-test [65]	In this test, a participant must inhibit a dominant and automatic verbal response of a word presented, and instead, name the colour of the ink for the word presented	[24]

6. Reasoning and problem solving (reported by six studies)	Tower of London Test [66]	Participants are presented with coloured beads arranged vertically on pegs of different heights. How they must be arranged,andthe number of moves allowed is determined by the experimenter, which they (the participant) must follow in order to achieve a specific arrangement	[21]
	Neuropsychological assessment battery: Mazes sub-test [67]	Participants are presented with seven mazes, each increasing in difficulty. Participants complete each maze within a 300-second time limit	[6,15]
	WAIS-III-Matrix reasoning sub-test [55]	Participants are presented with different figures. Each figure must be analysed in order to determine which figure best fits the order of the sequence presented	[29]
	Wisconsin card sorting test [68]	Participants sort a series of cards by a specific rule (e.g. by colour, shape or number of shapes). Feedback on performance is provided. After ten correct sorts, the rules for sorting are changed to a new rule without warning	[18,19]
7. Visual learning (reported by three studies)	Brief visuospatial memory test-revised [69]	The instructor presents six geometric figures which participants reproduce from memory	[6,15]
	The Judgement of Line Orientation test [70]	Participants are presented with two angle lines. They are instructed to match the set to a set of 11 lines by re-arranging them so that all the lines are 18 degrees apart and form a semi-circle	[21]

Table S3: List of studies included in meta-analysis measuring neurocognition in schizophrenia and healthy controls

Noncognitive Domain	Neuro-cognitive Measures	Description of Task	Studies in Meta-Analysis
Pre-morbid verbal IQ (reported by 13 studies)	Multiple-choice vocabulary test (german version) [71]	This measure presents 37 rows of five words. From each row participants pick the actual word and rule out the pseudo-words. The number of correctly identified words provides the test result	[8,9,13,18,26-28]
	National adult reading test [72]	This test comprises of 50 words with irregular spellings (e.g. aisle). Participants are assessed on their vocabulary comprehension rather than their ability to apply regular pronunciation rules	[11,22,24,25,32,39]
Verbal IQ (reported by two studies)	WAIS-III- verbal subset [55]	In this test, participants name the object in the picture or define the words presented to them	[12,19]

Table S4: List of the studies in the meta-analysis measuring verbal comprehension in schizophrenia and healthy controls

Neuro-cognitive Domain	Neurocognitive Measures	Studies in Meta-Analysis	Description of General IQ Tests
General IQ (reported by 10 studies)	Wechsler abbreviated adult intelligence scale [73]	[12,15,37]	The many versions of the Wechsler's Adult Intelligence Scales measure a person's ability to act purposefully, reason and deal effectively with his/her surrounding/environment [74]. This aim is fulfilled using several verbal ability and cognitive reasoning/style sub-tests (for a detailed description of each sub-test refer to Wechsler's administration manual and scales [54,55,57,73,75]
	Wechsler Adult Intelligence Scale III [55]	[2,5,7,35]	
	Wechsler adult intelligence scale-IV [75]	[34]	
	Raven's progressive matrices test [76]	[21]	This is a non-verbal group test designed to measure abstract reasoning
	Groninger Intelligence Test [77]	[43]	This test is used in the Netherlands as a reliable alternative to the Wechsler Adult Intelligence Tests. As such, this test includes examining the same cognitive and verbal abilities as the WAIS sub-tests [55]

Table S5: List of studies in the meta-analysis that examined general IQ

Cognitive Empathy	k	B	SE	95% CI	Z	P	I^2
Age at Diagnosis	20	-0.06	0.018	[-0.09, -0.02]	-3.35	0.0008	28.70
Duration of Illness	29	0.012	0.008	[0.001,0.03]	2.11	0.03	30.55
Positive symptoms	33	0.008	0.008	[-0.007,0.024]	1.004	0.31	30.73
Negative Symptom severity	33	0.004	0.007	[-0.009,0.01]	0.67	0.50	30.04
General Symptom Severity	15	0.01	0.01	[-0.01,0.03]	1.06	0.28	5.04
CPZ-Equivalent -mg/day	16	-0.0005	0.0006	[-0.001,0.0008]	-0.77	0.43	13.50

Table S6: Moderating effect of clinical characteristics on the difference in performance between schizophrenia patients and healthy controls on cognitive empathy.

Note: *K* = Number of studies. *B* = regression coefficient. *SE* = standard error. 95% CI = 95% confidence interval. *Z* = indicates the extent of uncertainty in the regression coefficient. *P* = statistical significance, 2-tailed. *I^2* indicates the amount of between-study heterogeneity. CPZ-equivalent-mg/day = Chlorpromazine Equivalent, milligram per day.

Affective Empathy	k	B	SE	95% CI	Z	P	I^2
General IQ, Schizophrenia Spectrum Disorders	9	0.003	0.003	[-0.002,0.010]	1.12	0.25	4.98
Verbal IQ, Schizophrenia Spectrum Disorders	15	0.0001	0.002	[-0.005,0.005]	0.04	0.96	12.51
Global Neuro-cognition, Schizophrenia Spectrum Disorder	11	-0.004	0.008	[-0.020,0.012]	-0.52	0.60	6.54

Table S7: Moderating effect ofneuro-cognitive abilities on the difference in performance between schizophrenia patients and healthy controls on cognitive empathy

Note: K = Number of studies. B = regression coefficient. SE = standard error. 95% CI = 95% confidence interval. Z = indicates the extent of uncertainty in the regression coefficient. P = statistical significance, 2-tailed. I^2 indicates the amount of between-study heterogeneity. CPZ-equivalent-mg/day = Chlorpromazine Equivalent in milligram per day

Affective Empathy	K	B	SE	95% CI	Z	P	I^2
Age, Schizophrenia spectrum	35	0.007	0.009	[-0.01,0.02]	0.79	0.42	32.38
Lower Education in Schizophrenia compared to Healthy Controls	21	-0.04	0.05	[-0.15,0.06]	-0.75	0.45	18.47
Higher Proportion of Male Schizophreniathen Female Schizophrenia	28	0.003	0.005	[-0.006, 0.01]	0.71	0.47	26.14
Higher Proportion of Non-Caucasian Schizophrenia then Caucasian Schizophrenia	7	-0.0004	0.006	[-0.01,0.01]	0-0.06	0.94	5.05
Year of Study Publication	36	-0.02	0.02	[-0.06,0.02]	-1.009	0.31	33.49

Table S8: Moderating effect of demographic variables on the difference in performance between schizophrenia patients and healthy controls on cognitive empathy

Note: K = Number of studies. B = regression coefficient. SE = standard error. 95% CI = 95% confidence interval. Z = indicates the extent of uncertainty in the regression coefficient. P = statistical significance, 2-tailed. I^2 indicates the amount of between-study heterogeneity. CPZ-equivalent-mg/day = Chlorpromazine Equivalent in milligram per day

Affective Empathy	K	B	SE	95% CI	Z	P	I^2
Age at Diagnosis	21	-0.02	0.02	[-0.08, 0.02]	-1.01	0.31	23.26
Duration of Illness	32	0.007	0.01	[-0.01,0.02]	0.68	0.49	33.15
Severity of Positive Symptom	36	0.012	0.007	[-0.001,0.02]	1.68	0.09	39.85
Severity of Negative Symptoms	36	0.007	0.005	[-0.002,0.01]	1.52	0.12	39.60
Severity of General symptom	17	-0.004	0.01	[-0.03,0.02]	-0.30	0.76	16.32
CPZ-Equivalent Mg/Day	18	-0.00015	0.0006	[-0.001,0.001]	-0.24	0.80	4.97

Table S9: Moderating effect of clinical characteristics on the difference in performance between schizophrenia patients and healthy controls on affective empathy

Note: K = Number of studies. B = regression coefficient. SE = standard error. 95% CI = 95% confidence interval. Z = indicates the extent of uncertainty in the regression coefficient. P = statistical significance, 2-tailed. I^2 indicates the amount of between-study heterogeneity. CPZ-equivalent-mg/day = Chlorpromazine Equivalent in milligram per day

Affective Empathy	K	B	SE	95% CI	Z	P	I^2
General IQ, Schizophrenia	10	-0.0005	0.003	[-0.007,0.005]	-0.17	0.85	54.02
Pre-morbid/Verbal IQ, Schizophrenia	15	-0.00009	0.002	[-0.005,0.005]	-0.03	0.97	14.22
Global Neuro-cognition, Schizophrenia	13	-0.005	0.005	[-0.016,0.005]	-1.03	0.29	7.01

Table S10: Moderating effect of cognition on the difference in performance between schizophrenia patients and healthy controls on affective empathy

Note: K = Number of studies. B = regression coefficient. SE = standard error. 95% CI = 95% confidence interval. Z = indicates the extent of uncertainty in the regression coefficient. P = statistical significance, 2-tailed. I^2 indicates the amount of between-study heterogeneity. CPZ-equivalent-mg/day = Chlorpromazine Equivalent in milligram per day

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Affective Empathy	K	B	SE	95% CI	Z	P	I²
Age, Schizophrenia	36	0.01	0.01	[-0.005,0.03]	1.43	0.15	39.60
Fewer Years in Education in Schizophrenia compared to Healthy Controls	23	-0.04	0.07	[-0.19,0.10]	-0.55	0.57	25.46
Higher Proportion of Male Schizophrenia then Female Schizophrenia	29	-0.001	0.006	[-0.01,0.01]	-0.30	0.76	31.43
Higher Proportion of Non-Caucasian Schizophrenia compared to Caucasian Patients	7	0.005	0.007	[-0.009,0.021]	0.74	0.45	5.28
Year of Study Publication	39	-0.04	0.02	[-0.09,0.008]	-1.65	0.09	41.16

Table S11: Moderating effect of demographic variables on the difference in performance between schizophrenia patientsand healthy controls on affective empathy

Note: K = Number of studies. B = regression coefficient. SE = standard error. 95% CI = 95% confidence interval. Z= indicates the extent of uncertainty in the regression coefficient. P = statistical significance, 2-tailed. I^2 indicates the amount of between-study heterogeneity. CPZ-equivalent-mg/day =Chlorpromazine Equivalent in milligram per day

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