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The association between polygenic risk scores for mental disorders and social cognition: A scoping review

Laura Fusar-Poli [a,b,*], Alessandro Rodolico [b], Miriam Martinez [b], Clarissa Fichera [b], Bochao D. Lin [c], Ilaria Basadonne [a], Carmen Concerto [b], Eugenio Aguglia [b], Sinan Guloksuz [c,d], Maria Salvina Signorelli [b]

[a] Department of Brain and Behavioral Sciences, University of Pavia, Italy
[b] Department of Clinical and Experimental Medicine, Psychiatry Unit, University of Catania, Italy
[c] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, the Netherlands
[d] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, United States

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ABSTRACT

People with mental disorders, such as psychosis or autism spectrum disorder (ASD), often present impairments in social cognition (SC), which may cause significant difficulties in real-world functioning. SC deficits are seen also in unaffected relatives, indicating a genetic substratum. The present review evaluated the evidence on the association between SC and the polygenic risk score (PRS), a single metric of the molecular genetic risk to develop a specific disorder. In July 2022, we conducted systematic searches in Scopus and PubMed following the PRISMA-ScR guidelines. We selected original articles written in English reporting results on the association between PRSs for any mental disorder and domains of SC either in people with mental disorders or controls. The search yielded 244 papers, of which 13 were selected for inclusion. Studies tested mainly PRSs for schizophrenia, ASD, and attention-deficit hyperactivity disorder. Emotion recognition was the most investigated domain of SC. Overall, evidence revealed that currently available PRSs for mental disorders do not explain variation in SC performances. To enhance the understanding of mechanisms underlying SC in mental disorders, future research should focus on the development of transdiagnostic PRSs, study their interaction with environmental risk factors, and standardize outcome measurement.

1. Introduction

Social cognition (SC) refers to a multifaceted and complex set of cognitive processes that underlie social interaction, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others (Colman, 2015). Literature has identified five main domains of SC: 1) emotional processing, that is the ability to effectively identify emotions in others and to manage one's own emotions; 2) social perception, representing the ability to identify social roles, rules, and context from non-verbal cues including body language, prosody, and social schema knowledge; 3) social knowledge, that refers to the awareness of roles, rules, and goals that characterize social situations and guide social interactions; 4) attribution style, that is how individuals explain the causes and make sense of social events or interactions; 5) theory of mind, also called mental state attribution or mentalizing, that is the ability to represent the mental states of others and make inferences about their intentions and beliefs (Barrett and Salovey, 2002; Green et al., 2005; Penn et al., 2008).

Research has shown that impairments in SC are present in several psychopathological conditions (Cotter et al., 2018), including autism spectrum disorder (ASD) (Velikonja et al., 2019), psychosis spectrum disorders (Savla et al., 2013), bipolar disorder (BD) (Samamé et al., 2012), major depressive disorder (MDD) (Weightman et al., 2014), and borderline personality disorder (BPD) (Roepke et al., 2013). SC dysfunctions are relevant for disease outcomes as they may cause impairments across a wide range of functional outcome areas, such as psychosocial functioning and daily living skills (Couture et al., 2006; Fett et al., 2011; Galderisi et al., 2014; Knight and Baune, 2019).

Of note, SC appears impaired not only in people with mental disorders but also in their unaffected relatives, although with minor severity.

* Corresponding author. Department of Brain and Behavioral Sciences, University of Pavia, Via Bassi 21, 27100, Pavia, Italy.
E-mail address: laura.fusarpoli@unipv.it (L. Fusar-Poli).

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This has been shown in psychosis (Fusar-Poli et al., 2022a; Lavoie et al., 2013), BD (Bora and Özerdem, 2017), ASD (Dorris et al., 2004), and anorexia nervosa (Tapajóz et al., 2019). Thus, it has been hypothesized that SC deficits might be heritable genetically determined and heritable (Adolphs, 2001; Skuse, 2006).

Nevertheless, the genetic substratum of SC has yet to be clarified. Different methodologies have been used to investigate putative genetic mechanisms. Research has mostly focused on candidate genes, such as single nucleotide polymorphisms (SNPs) within the oxytocin and vasopressin receptors (Barlati et al., 2020; Wilczyński et al., 2019). Other studies have reported associations between genetics and SC in subjects with the 22q11.2 deletion syndrome that has a robust representation of genetic proneness to psychosis (Frascarelli et al., 2020). Some authors have argued that neural pathways underlying SC might be modulated by one or more X-linked genes and that the emotional responsiveness of the amygdala might be influenced by functional polymorphisms in the promoter of the serotonin transporter gene (Skuse, 2006). Recently, a genome-wide association study (GWAS) meta-analysis of data from two independent cohorts of patients with schizophrenia found a significant association between the Transmembrane Protein 74 (TMEM74) gene – a gene that plays an essential role in autophagy - and a domain of SC (Gennarelli et al., 2022).

One increasingly utilized tool in psychiatric genetics is the Polygenic Risk Score (PRS). A PRS is calculated by summing the log odds ratios of individual SNPs multiplied by the number of risk alleles present at the corresponding loci (Wray et al., 2021). The calculation of a PRS requires two datasets: (1) a discovery dataset - that is the genome wide association study (GWAS), consisting of summary statistics of SNPs, and (2) a target dataset - consisting of genotypes, and usually also phenotypes, in individuals from an independent sample. Both datasets must undergo a rigorous quality control. PRSs is calculated from the discovery dataset using different approaches, including the construction of multiple PRSs based on different threshold values for SNP association with the trait of interest, the shrinkage of effect sizes, and adjustment for linkage disequilibrium using techniques such as pruning and clumping. Once PRS is calculated, the association between the PRS and a trait in the target sample is calculated, with covariates included as appropriate (Choi et al., 2020).

PRSs estimate the "risk" based on common genetic variants only and explains only a small proportion of variance compared to twin or family studies. However, PRSs present some advantages: for instance, it is possible to measure PRSs through a single blood or saliva sample at a relatively low cost. Moreover, PRSs may ideally have different applications in research settings, such as risk stratification, diagnostic decision-making, and treatment choice (Lewis and Vassos, 2020), although their factual utility in clinical practice has yet to be proven (Fusar-Poli et al., 2022b). Therefore, PRSs may represent a promising approach to studying the molecular genetic risk of developing a certain disorder or phenotype (e.g., a mental disorder or SC).

In the present paper, we aimed to review the original literature examining the association between PRSs for mental disorders and SC. Considering the expected heterogeneity of published studies in terms of conditions investigated and methodology adopted, we primarily aimed to map the literature evidence on the topic. As deficits in SC are common across a wide range of mental disorders, examining the relationship between SC and PRSs might shed further light on the genetic basis of SC and highlight potential literature gaps which will be worth being addressed in future research.

2. Methods

2.1. Search strategy

In performing this scoping review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines (Tricco et al., 2018). A preliminary search for existing scoping reviews on the topic was conducted. On July 5, 2022, we conducted systematic searches in Scopus and PubMed. The search strings used are reported in the Supplementary Materials. The electronic search was supplemented by hand-searching of reference lists of all included systematic reviews and meta-analyses to identify additional relevant articles.

2.2. Selection procedure

All records were extracted to Rayyan, an online tool specifically designed for the management of references while conducting systematic reviews (https://www.rayyan.ai/). Duplicates were detected and deleted. Two independent reviewers (MM and CF) initially screened the titles and abstracts, and then selected the studies to be included after checking the full text. In case of disagreement, the final decision was made with the help of a third reviewer (LF-P).

The eligibility criteria were as follows: (1) original studies evaluating the association between PRS for any mental disorder and SC domains; (2) studies including either individuals from the general population or people with a psychiatric diagnosis; (3) studies written in English. We excluded (1) genome-wide association studies (GWAS) or studies focusing on SNPs or individual genetic variants only, without a calculation of PRS; (2) studies including neuroimaging outcomes only; (3) conference abstracts.

2.3. Data extraction and synthesis

Relevant data were extracted in a predefined form. The following characteristics were collected: author, year, target sample, characteristics of participants, characteristics of PRSs tested, tools for SC, main findings, and covariates. We provided a narrative synthesis of the findings focused on participants, outcomes, and main results of the included studies.

3. Results

3.1. Search results

The PRISMA flow diagram of the study selection process is reported in Fig. 1. Our literature search identified a total of 244 publications. After removing duplicates, 183 titles and abstracts were screened. The full texts of 18 articles were then fully read for a more detailed evaluation. Finally, 13 papers were included in the scoping review. Characteristics of the included studies are presented in Table 1. Characteristics of the PRSs are presented in Table 2.

3.2. Participants

Seven studies (Coleman et al., 2017; Hubbard et al., 2016; Martin et al., 2014, 2015; Reed et al., 2021; St Pourcain et al., 2018; Warrier and Baron-Cohen, 2018) included participants from the Avon Longitudinal Study of Parents and Children (ALSPAC; Golding, 1990), a multi-generational prospective birth cohort study that followed up and charted the health of children born in the Avon county (England) between 1991 and 1992 and their families. Of note, the study by Hubbard et al. (Hubbard et al., 2016) used the CLOZUK as a replication dataset. The CLOZUK included individuals with schizophrenia who were prescribed clozapine and received a clinician diagnosis of treatment-resistant schizophrenia (Schizophrenia Working Group of the Pscyhiatric Genomics Consortium, 2014).

Two studies (Fusar-Poli et al., 2022a; Tripoli et al., 2022) utilized datasets from the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI; van Os et al., 2014), which aimed to identify the interactive genetic, clinical, and environmental determinants involved in the development, severity, and outcome of schizophrenia through a family-based, multidisciplinary

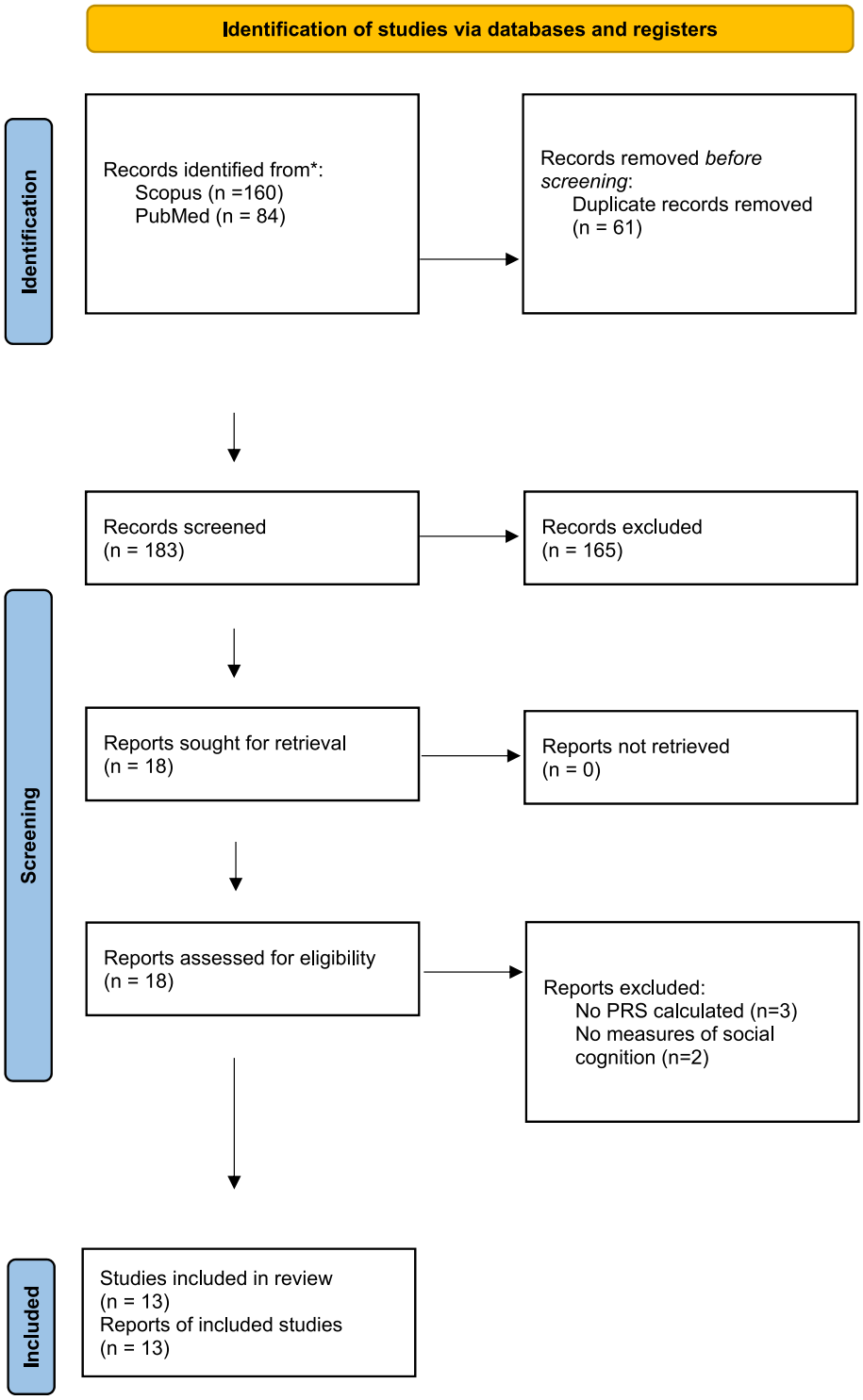

Fig. 1. PRISMA flow diagram of the study selection process.

research paradigm. Specifically, Fusar-Poli et al. (Fusar-Poli et al., 2022a) leveraged data from the EU-GEI Work Package (WP) 6, including a sample of patients with schizophrenia, their siblings, and ethnicity-matched healthy controls. The dataset was merged with data from the Genetic Risk and Outcome of Psychosis (GROUP), a multi-site longitudinal cohort study conducted in the Netherlands that focused on gene-environment interaction (Korver et al., 2012). Tripoli ad colleagues (Tripoli et al., 2022) used data from the WP2, involving two groups of participants: patients with FEP and healthy controls.

Germine et al. (2016) included participants from the Philadelphia Neurodevelopmental Cohort (PNC), a large-scale cohort that investigated how brain maturation mediates cognitive development and vulnerability to mental illness and the role of genetics in this process (Calkins et al., 2015). A sample from the Harvard/Massachusetts General Hospital (MGH) Brain Genomics Superstruct Project (GSP) was then used for replication.

Waddington et al. (2021) included participants from the NeuroIMAGE study and Biological Origins of Autism (BOA) cohorts. The NeuroIMAGE was a Dutch multi-site prospective cohort study designed to investigate the course of ADHD, its genetic and environmental

Table 1
Characteristics of the included studies.

First author	Year	Country	Target sample	Participants	Ancestry	PRS tested	Tools for social cognition	Findings	Covariates
Coleman	2017	England	ALSPAC	4097 participants from a population-based birth cohort, 49.6% males, mean age 8.65 years old, age range: 7–10.	Western European	SCZ, BD, MDD, ASD, ANOR, ANX	DANVA, proportion index calculated for the total number of correct responses, unbiased hit rate calculated for individual emotions (happiness, sadness, anger, fear)	PRS-ASD predicted fear recognition ($p = 7.32 \times 10^{-4}$), PRS-ANX as a case-control phenotype predicted recognition of happy faces ($p = 6.72 \times 10^{-4}$) and PRS-ANX as a factor score predicted angry faces ($p = 6.62 \times 10^{-4}$). However, none remained significant when taking into account the testing of multiple phenotypes-	Gender, age at assessment (in weeks), IQ at assessment, and whether the activities session was the first, second, third, or fourth performed. DAEBA and FAI not used as uncorrelated with the DANVA. Correction with SCDC not reported since results yielded were very similar to those withouth correction.
Fusar-Poli	2022	Serbia, Spain, the Netherlands, Turkey	EUGEI WP6 and GROUP combined	1428 patients with SCZ (70.31% males, mean age 31.26 years), 1619 siblings (46.08% males, mean age 31.61 years), 1505 healthy controls (49.44% males, mean age 33.45 years)	European	SCZ	DFAR, number of correct responses for total and individual emotions (neutral, happy, angry, fearful)	No significant associations detected.in SCZ, siblings, or heatlthy controls	Gender, age, country, clustering within the same family, 10 PCs
Germine	2016	United States	PNC (main); Harvard/MGH Brain GSP (replication)	Main sample: 4303 participants, 50% female, age range: 8–21, mean age 13.8 years. Replication sample: 695 participants, 53% female, age range 18–35 years, mean age 21.5 years.	White non-Hispanic	SCZ	Penn emotion identification test, Penn emotion differentiation test, Penn age discrimination test (accuracy and speed for each test)	Higher PRS-SCZ was associated with reduced speed of emotion identification, confirmed in the replication sample.	General intelligence (as estimated by matrix reasoning performance) and a measure of psychomotor response speed.
Hubbard	2016	England	(1) and (2) ALSPAC, (3) CLOZUK SCZ	ALSPAC: 5109 participants from a population-based birth cohort, ~8 years old. CLOZUK SCZ: 5554 individuals with treatment-resistant SCZ taking clozapine and 6299 controls	European	SCZ	DANVA, total number of errors (incorrect assignment of emotions) across four emotional domains (neutral, happy, angry, fearful)	No significant associations.	None
Martin	2014	England	ALSPAC	5653 children from a birth cohort (including children with ASD or ADHD), 51.2% males, ~7 years, 7 months old,	European	ADHD	SCDC	No significant associations.	Gender, 10 EIGENSTRAT PCs
Martin	2015	England	ALSPAC	4213 participants, 51.2% males, ~8.5 years old	European	ADHD	DANVA, including four emotions (happy, sad, angry or fearful) shown at high	No significant associations.	Gender, 10 EIGENSTRAT PCs

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Table 1 (*continued*)

First author	Year	Country	Target sample	Participants	Ancestry	PRS tested	Tools for social cognition	Findings	Covariates
							(easy condition) and low (hard condition) intensities. The total number of errors made on the 12 low emotional intensity was used for analysis SCDC		
Qin	2020	China	Sample recruited from the inpatient and outpatient services at Shenyang Mental Health Center and Department of Psychiatry, First Affiliated Hospital of China Medical University, Shenyang, China.	116 patients with SCZ (mean age 24.24, 36 males), 212 healthy controls (mean age 34.71, 83 males)	Asian	ASD	Chinese Facial Affective Picture System, grey scale images for six basic emotions (anger, disgust, fear, sadness, surprise, happiness) and neutral. Three conditions recorded: positive, negative, or neutral. Total score was the sum of the correct responses for each of the three gorups.	Negative correlation between PRS-ASD and negative emotions (strongest association at P threshold = 0.2 (r = −0.2288, P uncorrected = 0.000149, Pcorrected = 0.0006). Negative correlation between PRS-ASD and total emotion (at P threshold = 0.09, r = −0.1789, P uncorrected = 0.00318, P corrected = 0.013). No significant interaction between PRS-ASD and illness status.	Age, sex, education, disease status, first four components for population stratification.
Reed	2021	England	ALSPAC	N = 5306 for SCDC at age 8 (mean age 7.66, 51% male), N = 2555 for ERT at age 24 (mean age 24.46, 37% male), N = 4901 for DANVA at age 8 (mean age 8.65, 50% male)	European	ASD	SCDC DANVA proportion index ERT total score	PRS-ASD associated with SCDC for SNP atp≥0.01 (b = 0.05, p = 0.01), associated with ERT with the strongest association at p = 0.001 (b = 0.40, p = 0.01). Non significant after correcting for multiple testing. No associations with ERT.	Sex, first 10 PCs
St Pourcain	2018	England	ALSPAC	N = 5553 (8 years), N = 5462 (11 years), N = 5060 (14 years), N = 4175 (17 years)	White European	ASD, SCZ	SCDC	PRS-ASD associated with variation in SCDC scores at 8 years (adjusted R^2 max = 0.13%, Pmin = 0.0042). PRS-SCZ explained predominantly variation in SCDC at 17 years, based on risk alleles in both PGC-SCZ subsamples	Fixed: sex, age at assessment plus random intercepts.

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Table 1 (*continued*)

First author	Year	Country	Target sample	Participants	Ancestry	PRS tested	Tools for social cognition	Findings	Covariates
								(PGC-SCZ1: adjusted R^2 max = 0.26%, Pmin = 0.00058; PGC-SCZ2i: adjusted R^2 max = 0.19%, Pmin = 0.0028) and the combined PGCSCZ2 sample (adjusted R^2 max = 0.43%, Pmin = 0.000012).	
Tripoli	2022	England, France, the Netherlands, Italy, Spain, and Brazil.	EUGEI WP2	524 first episode psychosis patients (mean age 36.2, male 47.4%), 899 population controls (mean age 30.9, male 61.8)	Majority of European ancestry, African ancestry excluded	BD, MDD, SCZ	DFAR	PRS-SCZ was negatively associated with DFAR anger in the overall sample (B = −3.5, P = 0.04). Statistical significance maintained in controls only (B = −5.7, P = 0.009) No significant associations between DFAR and PRS-MDD or PS-BD.	Case/control status, age, sex, BFRT, IQ, 20 PCs
Waddington	2021	The Netherlands	NeuroIMAGE and Biological Origins of Autism (BOA) cohorts	552 participants: 74 with ADHD, 85 with ASD, 60 with ASD + ADHD, 177 unaffected siblings of ADHD or ASD probands, and 156 controls 51.4% male (NeuroIMAGE); 59.7% male (BOA) Mean age 12.5; age range: 7–18 years.	European	ADHD, ASD	Facial Expressions Identification and Affective Prosody Tasks from the ANT, speed and accuracy. Four emotion recognition factors were identified: speed of visual emotion recognition; accuracy of visual emotion recognition; speed of auditory emotion recognition; accuracy of auditory emotion recognition). According to performance, participants were divided into 4 classes: class 1: average visual, impulsive auditory (N = 173); class 2: average strong visual and auditory (N = 303); class 3: Impulsive/ imprecise visual, average auditory (N = 50); class 4: weak visual and	Higher PRS-ASD associated with faster visual emotion recognition factor at p = 0.05 threshold. PRS-ASD associated with emotion recognition classes at p = 1 threshold: class 3 had significantly reduced PRS-ASD compared to class 1, class 2, and class 4. No significant associations between PRS-ADHD and either factors or classes.	Age, sex, IQ, cohort, diagnosis, population stratification, family structure, modality counterpart

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Table 1 (*continued*)

First author	Year	Country	Target sample	Participants	Ancestry	PRS tested	Tools for social cognition	Findings	Covariates
							auditory(N = 149)		
Warrier	2018	United Kingdom	ALSPAC	4577 participants (n = 2217 females, and n = 2360 males) 13 years	European	ASD, ANOR, ADHD, BD, MDD, SCZ, cognitive aptitude, self-reported empathy (EQ), cognitive empathy (eyes test).	ETT, a measure of theory of mind. Four mental states were tested: happiness, sadness, anger and fear.	No significant associations between PRSs for mental disorders and ETT. PRSs for cognitive attitude (at P = 0.01, 0.05, 0.1, 0.15, 0.2, 0.5, 0.8, and 1 thresholds) and cognitive empathy (at P = 0.1 and 0.15 thresholds) positively associated with ETT.	Sex, first two ancestry PCs
Xavier	2018	United States	CATIE-Schizophrenia trials	730 patients with SCZ, 73.8% males, mean age: 40.6 years, age range: 18–65.	White, Black/ African American, American Indian or Alaska native, Asian, Native Hawaiian or Pacific Islander, or Other	SCZ	Facial Emotion Recognition Task, total score	No significant associations	Age, sex, ancestry usign four multidimensional scaling components

Legend: ADHD: attention deficit hyperactivity disorder; ALSPAC: Avon Longitudinal Study of Parents and Children; ANOR: anorexia; ANS: Amsterdam Neuropsychological Test; ANX: anxiety; ASD: autism spectrum disorder; BD: bipolar disorder; BFRT: Benton Facial Recognition test; CATIE: Clinical Antipsychotics Trials of Intervention Effectiveness; DANVA: Diagnostic Analysis of Nonverbal Accuracy; DFAR: Degraded Facial Affect Recognition task; EQ: Empathy Quotient; ERT: Emotion Recognition Task; ETT: Emotional Triangle Task; MDD: major depressive disorder; PC: principal component; SCDC: Social and Communication Disorders Checklist; SCZ: schizophrenia.

determinants, its cognitive and neurobiological underpinnings, and its consequences in adolescence and adulthood (von Rhein et al., 2015). The BOA was a family genetic study aimed at examining the genetic, biochemical, and cognitive origins of ASD and studying the overlap between ASD and ADHD (van Steijn et al., 2012).

Finally, Xavier and colleagues (Xavier et al., 2018) included a sample from the Clinical Antipsychotics Trials of Intervention Effectiveness (CATIE)-schizophrenia trial. The CATIE was a United States-based multisite trial designed to assess differences in antipsychotic efficacy (Sullivan et al., 2007).

3.3. Outcome measures

Most of the included studies evaluated the domain of emotion recognition (ER) and particularly facial ER. Four papers (Coleman et al., 2017; Hubbard et al., 2016; Martin et al., 2015; Reed et al., 2021) used the Diagnostic Analysis of Nonverbal Accuracy (DANVA), a tool that measures the ability to extract emotional information from the vocal tone or the face (Nowicki and Duke, 1994). However, all the studies employed uniquely the face task. One study (Coleman et al., 2017) calculated the proportion index for the total number of correct responses and the unbiased hit rate for four individual emotions (happy, sad, angry, fearful). One study (Hubbard et al., 2016) calculated the total number of errors. In Martin et al. (2015), faces were shown at high and low intensities, and the total number of errors made on the low emotional intensity was adopted for analysis. Reed et al. (2021) calculated the proportion index for the total score.

Two studies (Fusar-Poli et al., 2022a; Tripoli et al., 2022) evaluated facial ER using the Degraded Facial Emotion Recognition (DFAR) task (van 't Wout et al., 2007), in which 16 sequences of 4 faces showing different emotions (neutral, happy, angry, fearful) were shown to participants. Both the total score (i.e., number of correct responses) and the scores for subscales were examined. Germine and colleagues (Germine et al., 2016) used different trials of the Penn emotion test, specifically those for emotion identification, emotion differentiation, and age discrimination. Both accuracy and speed were evaluated. Qin et al. (2020) employed the Chinese Facial Affective Picture System, in which grayscale images for six basic emotions and a neutral face were presented. The total number of correct responses was divided based on three conditions (positive, negative, neutral) and a total score was then computed. In the paper by Reed et al. (2021), during the Emotion Recognition Task (ERT; Penton-Voak et al., 2012); participants were asked to assign one out of six emotions (i.e. happy, sad, angry, disgusted, surprised and fearful) to facial images. There were eight levels of intensity for each emotion, and each was presented twice, resulting in a total of 96 trials. One study (Xavier et al., 2018) used the Facial Emotion Recognition Task (Kerr and Neale, 1993), in which subjects were asked to discriminate if two faces presented had the same emotional expression.

Four studies (Martin et al., 2014, 2015; Reed et al., 2021; St Pourcain et al., 2018) employed the Social and Communication Disorders Checklist (SCDC; Skuse, 2006) as outcome tool. The SCDC is a 12-item screening questionnaire for autistic traits rated by participants' parents; it has been previously employed to measure the heritability of SC

Table 2
Characteristics of the polygenic risk scores.

First author	Year	PRS generation tool	P-values thresholds	GWASs to calculate the PRS (base data)[a]
Coleman	2017	PRSice	Variants were included if their associated p-value from the external GWAS fell beneath this threshold (p = 0.00005 to p = 0.5 in steps of 0.00005)	Schizophrenia (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014) Bipolar disorder (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011) Depression (Ripke et al., 2013) Anxiety (Otowa et al., 2016) ASD (Autism Spectrum Disorders Working Group of the Psychiatric Genomics Consortium, 2017) Anorexia (Bulik et al., 2017)
Fusar-Poli	2022	PLINK	p = 0.05	Schizophrenia (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014) removing GROUP cohort
Germine	2016	PLINK	p = 0.05	Schizophrenia (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014)
Hubbard	2016	PLINK	p = 0.0001, p = 0.01, p = 0.1, p = 0.3	Schizophrenia (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014) removing CLOZUK cohort CLOZUK (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014)
Martin	2014	PLINK	p = 0.05	British and Irish children with and without ADHD (Stergiakouli et al., 2012)
Martin	2015	PLINK	p = 0.05	British and Irish children with and without ADHD (Stergiakouli et al., 2012)
Qin	2020	PRSice	103 thresholds (ranging from 0 to 0.5 with increments of 0.005, plus 10^{-5}, 10^{-4}, and 10^{-3})	ASD (Grove et al., 2019) Schizophrenia (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018)
Reed	2021	PLINK	p = 0.5, p = 0.4, p = 0.3, p = 0.2, p = 0.1, p = 0.05, p = 0.01, p = $1x10^{-3}$, p = $1x10^{-4}$, p = $1x10^{-5}$, p = $1x10^{-6}$, p = $1x10^{-7}$, p = $5x10^{-8}$	ASD (Grove et al., 2019)
St Pourcain	2018	PLINK	p = 1, p = 0.9, p = 0.7, p = 0.5, p = 0.3, p = 0.1, p = 0.05, p = 0.01, p = 0.001	ASD (Autism Spectrum Disorders Working Group of the Psychiatric Genomics Consortium, 2017) Schizophrenia (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014)
Tripoli	2022	PRSice	p = 0.05	Schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) Bipolar disorder (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Stahl et al., 2019) Major depressive disorder (Howard et al., 2019; Roepke et al., 2013)
Waddington	2021	PRSice	p = 5×10^{-8} (GWAS significance), p = 10^{-6} (GWAS suggestive significance), p = 0.05, p = 1	ADHD (Demontis et al., 2019) ASD (Grove et al., 2019)
Warrier	2018	PRSice	p = 0.01, p = 0.05, p = 0.1, p = 0.15, p = 0.20, p = 0.5, p = 0.8, p = 1	ADHD (Demontis et al., 2019) Anorexia (Duncan et al., 2017) Autism (Autism Spectrum Disorders Working Group of the Psychiatric Genomics Consortium, 2017) Bipolar disorder (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011) Major depressive disorder (Roepke et al., 2013) Schizophrenia (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014)
Xavier	2018	PRSice	p = 5^{e-08}, 1^{e-07}, 1^{e-06}, 1^{e-05}, 1^{e-04}, 1^{e-03}, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5	Schizophrenia (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014)

Legend: ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; GWAS: genome-wide association study.

[a] Target sample information are shown in Table 1.

skills in children and adolescents (Scourfield et al., 1999).

Only one study (Warrier and Baron-Cohen, 2018) evaluated the domain of the theory of mind using a modified version of the Emotional Triangles Task (Boraston et al., 2007). During the task, participants were required to attribute mental states to animated triangles based on their motion-cues, choosing from a forced choice format.

3.4. Association between PRSs for mental disorders and social cognition

3.4.1. PRS for schizophrenia

Eight studies (Coleman et al., 2017; Fusar-Poli et al., 2022a; Germine et al., 2016; Hubbard et al., 2016; St Pourcain et al., 2018; Tripoli et al., 2022; Warrier and Baron-Cohen, 2018; Xavier et al., 2018) tested the association between PRS for schizophrenia (PRS-SCZ) and SC.

Germine et al. (Germine et al., 2016) found that emotion identification speed was negatively associated with PRS-SCZ in a group of children and young adults (aged 8–21 years) from the general population, even after controlling for emotion identification accuracy. PRS-SCZ accounted for approximately 0.3–0.5% of the variation in SC. The finding was replicated in an independent sample of adult participants aged 18–35 years, surviving control for general intelligence and a measure of psychomotor response speed. These results may indicate that a higher genetic load for schizophrenia is associated with slower emotion identification.

Tripoli et al. (Tripoli et al., 2022) found that PRS-SCZ was negatively associated with DFAR anger in a sample including both FEP patients and controls ($B = -3.5$, $P = 0.04$). However, after group stratification, statistical significance was maintained in controls only ($B = -5.7$, $P = 0.009$). This finding may indicate that a higher genetic load for schizophrenia may cause impairments in the identification of angry faces in healthy controls.

No significant associations were reported by the other studies.

3.4.2. PRS for autism spectrum disorder

Six studies (Coleman et al., 2017; Qin et al., 2020; Reed et al., 2021; St Pourcain et al., 2018; Waddington et al., 2021; Warrier and Baron-Cohen, 2018) investigated the association between PRS for autism spectrum disorder (PRS-ASD) and SC.

Qin et al. (2020) found a negative correlation between PRS-ASD and total emotions as well as a negative correlation between PRS-ASD and negative emotions, without significant interaction between PRS-ASD and illness status (schizophrenia vs healthy controls). These findings might indicate that a higher genetic load for ASD is associated with a poorer recognition of total and negative emotions.

St. Pourcain et al. (St Pourcain et al., 2018) reported that PRS-ASD was significantly associated with variation in SCDC scores at 8 years. A similar result was found by Reed et al. (2021). Results would not change after excluding children with a clinical diagnosis of ASD or correcting for PRS-SCZ. The authors argued that this result may provide evidence for genetic overlap between ASD and social communication difficulties during middle childhood.

Waddington et al. (2021) found that higher PRS-ASD was associated with faster visual ER at $p = 0.05$. Moreover, PRS-ASD was significantly reduced in participants classified as having impulsive/imprecise visual ER and average auditory ER.

No significant associations were found in the other studies.

3.4.3. Association between PRS for ADHD and social cognition

Four studies (Martin et al., 2014, 2015; Waddington et al., 2021; Warrier and Baron-Cohen, 2018) investigated the association between PRS for attention deficit-hyperactivity disorder (PRS-ADHD) and SC.

No significant associations were found wither in children from a birth cohort study (Martin et al., 2014, 2015; Warrier and Baron-Cohen, 2018) or in a mixed sample of children with ASD, ADHD, or both, their siblings, and controls (Waddington et al., 2021).

3.4.4. Association between PRS for other mental disorders and social cognition

Two studies investigated the association between PRSs for BD (PRS-BD), MDD (PRD-MDD), and anorexia (PRS-ANOR) and facial ER (Coleman et al., 2017) or theory of mind (Warrier and Baron-Cohen, 2018). Both reported no significant associations. PRS-BD and PRS-MDD were investigated also by Tripoli and colleagues that did not find any significant association with a task for facial ER (Tripoli et al., 2022).

Coleman et al. (2017) investigated the association between PRS for anxiety (PRS-ANX) and SC, reporting that PRS-ANX significantly predicted the recognition of happy faces as a case-control phenotype ($P = 6.72x10^{-4}$) and in predicting angry faces as factor score ($P = 6.62x10^{-4}$). However, these results lost significance after taking into account the testing of multiple phenotypes.

4. Discussion

The present review included studies exploring the association between PRSs for mental disorders and domains of SC. Our literature search yielded 13 papers providing insufficient evidence to link PRSs for mental disorders and domains of SC.

According to the results of our search, PRS-ASD and PRS-SCZ have been the most investigated PRSs by researchers in the field of SC. Although findings have been substantially inconclusive so far, there is some preliminary evidence that higher genetic loading for ASD or schizophrenia may cause impairments in some domains of SC, such as ER in the case of both conditions, and social communication difficulties in the case of ASD. This is not surprising as deficits in SC are prominent both in ASD and psychosis (Barlati et al., 2020; Boada et al., 2020; Fusar-Poli et al., 2021; Oliver et al., 2021). Unfortunately, the heterogeneity of study designs, samples, and outcome measurements does not allow drawing any specific conclusion and warrants caution in the interpretation of findings.

The present review highlighted that the tools used to measure SC are sparse. Even in the case of studies focusing on the same domain (e.g., ER), the instruments used and even the interpretation of results substantially differ. In some cases (e.g., Waddington et al., 2021), ad-hoc analyses with non-standardized utilization of measures were implemented. Also, the heterogeneity of methodologies adopted in PRS calculation across the included studies may represent another major confounder. In fact, software used, p-value thresholds, number of variants included in the PRSs, methods for clumping, and quality control differ among the studies, thus hampering a comprehensive interpretation of the results. Additionally, as argued by Ioannidis, "flexibility in designs, definitions, outcomes, and analytical modes increases the potential for transforming what would be 'negative' results into 'positive' results" (Ioannidis, 2005). Thus, researchers in the field of mental health should work toward the development and implementation of standardized and reliable instruments to measure the different domains of SC across mental disorders.

One reason that may explain the overall lack of associations between psychiatric PRSs and SC is that PRS is estimated based on common variants only. However, rare variants confer risk for highly complex mental disorder phenotypes and play an important role in mental disorders, such as schizophrenia (Singh et al., 2022) and ASD (Wang et al., 2022). More specifically, rare variants and rare structural changes might be particularly relevant for trans-diagnostically expressed SC impairments. SC difficulties have a close connection with ASD, which includes the presence of "persistent deficits in social communication and social interaction" among core symptoms (American Psychiatric Association, 2013). It has been observed that ASD is much more strongly associated with rare *de novo* mutations than with common variants (Wang et al.,

2022). Moreover, copy number variants (CNVs) conferring risk for ASD or schizophrenia seem to affect cognition in controls (Stefansson et al., 2014) and rare CNVs have been associated with poorer cognition in schizophrenia (Hubbard et al., 2021). Therefore, approaches going beyond SNPs, such as the whole-exome sequencing (WES) or the whole-genome sequencing (WGS), might be more useful in disentangling the genetic basis of SC.

Although PRS represents a valid measure of genetic susceptibility to a disorder, it might not capture the specific association between SC and mental disorders. Indeed, the genetic mechanisms underlying variation in SC within mental disorders may be at least partly independent from those that predispose an individual to the diagnosis of the disorder itself. Up to date, GWAS have principally focused on genetic vulnerability for individual diagnostic entities rather than trans-diagnostic phenotypes (Glahn and McIntosh, 2017). However, the ideal approach would be to construct specific PRS that capture genetic vulnerability for the putative transdiagnostic outcome, which is SC in this case.

Another important limitation of PRSs is related to the trans-ancestry portability of PRSs. Population stratification is a major confounder in genetic research and currently available PRSs perform poorly in ancestries different from those of the GWAS training dataset, which are typically European. Therefore, the generalizability of findings based on genomic-based prediction models to non-European populations is still very limited (Burkhard et al., 2021) and may explain some of the non-significant findings of the selected studies.It is interesting to mention that one of the studies included in the present review (Warrier and Baron-Cohen, 2018) evaluated not only the association between SC and PRSs for mental disorders but also developed and tested PRSs for cognitive empathy. Cognitive empathy basically corresponds to theory of mind, which is one of the main domains of SC. Specifically, cognitive empathy is measured using the "Reading the Mind in the Eyes" test, which consists of the visual recognition of another's mental state, including their emotion (Baron-Cohen and Wheelwright, 2004). In adults, cognitive empathy identified a significant twin heritability of approximately 28%, and a smaller additive SNP heritability of approximately 6% (Warrier et al., 2018). Hopefully, these efforts of researchers on the harmonization of phenotypical data that go beyond diagnosis would result in more precise capturing of the genetic architecture of putative transdiagnostic mechanisms and may provide better alternatives than PRS for specific psychiatric diagnoses.

Even though genetic vulnerability for SC deficits has been proven, environmental risk and protective factors may also represent critical elements influencing not only mental disorders but also transdiagnostic phenotypes such as SC. For instance, childhood trauma may negatively influence SC in people with mental disorders (Dauvermann and Donohoe, 2019), while cannabis has been reported to be positively associated with facial ER (Fusar-Poli et al., 2022a). Additionally, it has been recently shown that the exposome score for schizophrenia (ES-SCZ), a cumulative measure of environmental liability for schizophrenia (Pries et al., 2021), was associated with SC in non-psychotic samples (Fusar--Poli et al., 2023). Of note, both cognition and social processes are listed among the six major domains of the Research Domain Criteria (RDoC) framework, which aims to investigate mental disorders cutting across established diagnostic categories. Recently, the RDoC Unit at the NIMH has acknowledged the importance of better delineating and integrating the environment within the framework. Therefore, it is desirable to evaluate the role of environmental factors and integrate them into models linking genetics to SC.

To our knowledge, this is the first review to systematically summarize the evidence on PRSs for mental disorders and SC. Nevertheless, some limitations should be mentioned. A major limitation is that the review was conducted without a pre-registered study-protocol. Second, although we conducted a comprehensive literature search in compliance with the AMSTAR-2 criteria, we did not consult the grey literature and excluded conference abstracts and studies written in languages other than English. Third, the scope of our review was limited to SC, while neurocognition was not examined. However, we acknowledge the importance of investigating the relationship between PRSs for mental disorders and neurocognitive domains in future reviews. Finally, we did not investigate non-psychometric outcomes, such as neuroimaging, which could provide additional relevant information on the topic in the future.

To conclude, although research on the topic is still in the preliminary phase, our review highlighted that PRSs for mental disorders do not currently explain SC variations in people with mental disorders. Studies adopting standardized outcome measures, PRSs for transdiagnostic phenotypes, and the integration of genetic risk with environmental factors may help clarify the association between mental disorders and SC and the shared genetic roots.

Declaration of competing interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2023.06.029.

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