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Reviews in psychiatry schizophrenia 2023

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Reviews in psychiatry 2023: Schizophrenia

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Editorial: Reviews in psychiatry 2023: schizophrenia

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Editorial on the Research Topic
Reviews in psychiatry 2023: schizophrenia

Schizophrenia is a severe psychiatric disorder that imposes a considerable burden on patients, their families, and society as a whole (1). The fact that the burden of schizophrenia is compounded by the insufficient efficacy of available treatment options has motivated a wide range of clinical and pre-clinical research endeavors. The contributions to this Research Topic represent this diversity of research and thereby mirror the complexity of the disorder itself. Schizophrenia is a nosological entity with a very heterogeneous spectrum of deficits. These are categorically identified as positive, negative, and cognitive symptoms (2). Moreover, recent discoveries regarding inherent biomarkers (3) and neurodevelopmental disease progression (4) increasingly suggest possible overlap with other psychiatric disorders, such as bipolar disorder (5–7). This overlap ranges from genetic (5) and environmental (6, 7) risk factors to pathophysiological mechanisms and symptoms (8, 9). Recognition of symptomatologic patterns and familiarities between disorders may provide a more precise diagnostic framing and better management of clinical aspects. It is important to identify factors that can support the differential diagnosis and allow the most appropriate treatment for Schizophrenia patients who represent nosographic clusters of considerable complexity (10). Thus, an overview of both quantitative and qualitative data on clinical characteristics and treatment outcomes may elucidate the patterns and mechanisms of Schizophrenia pathogenesis and its modifiability (11, 12). In this regard, the reviews included in this Research Topic allow for an in-depth reflection on several aspects of mental pathology in general and highlight possible future directions of scientific advancement (13).

Several reviews have examined the effectiveness of non-pharmacological treatment options for Schizophrenia. For example, in parallel with standard psychosocial and pharmacological treatment, the use of virtual reality offers new solutions that can lead to appreciable results in various functional and symptomatic domains. The review by Holopainen et al. on the efficacy of immersive extended reality (XR) interventions on different symptom domains of Schizophrenia spectrum disorders showed that treatment gamification allows for greater patient engagement in therapy, harnessing the motivation of novelty represented by this virtuous technology. Furthermore, unlike drug treatment which is often associated with many side effects and stigma, this therapeutic approach is believed to be devoid of such drawbacks and likely to provide a favorable end-user experience and

greater overall adherence to the treatment. Similarly, Cao and Zhou described the effects of computerized cognitive remediation therapy (CCRT) on mental time travel in patients with Schizophrenia. Their review highlighted how this treatment may prove to be a relatively simple, inexpensive and effective way to improve symptoms.

In contrast, Tyssedalu et al. highlighted how interventions with dogs for adults diagnosed with Schizophrenia can improve their quality of life, well-being, and several positive and negative symptoms, including features associated with the severity of psychosis. However, the results of some of the reviewed studies should be interpreted with caution.

In a systematic review conducted on the treatment effects of adjunctive group music therapy in inpatients with chronic Schizophrenia, Lam et al. found that, as an add-on to standard treatment, this intervention can produce an additional improvement. Several of the 13 randomized controlled trials included in the review found beneficial effects at the level of positive symptoms - particularly auditory hallucinations -, cognitive function – especially attention - and/or negative symptoms. For the latter, improvements in avolition, social withdrawal, anhedonia, and self-care were particularly evident. At the level of subjective perception, patients also reported improvements in energy, mood, anxiety, relaxation, and quality of life.

Exploring the possibility of alternative pharmacological treatments, Bortoletto et al. reviewed the evidence for the role of the endogenous lipid palmitoylethanolamide (PEA) in psychosis. Although it does not activate the cannabinoid receptors CB1 and CB2 directly, it shares several other targets with classical endocannabinoids and enhances the availability of the latter (*entourage effect*). As it has been suggested that disruption of the endocannabinoid (eCB) system may be implicated in the etiopathogenesis of psychosis, PEA may represent a better-tolerated antipsychotic agent acting through the eCB system. In addition to its well-known analgesic properties, PEA also exerts neuroprotective and anti-inflammatory effects that may ameliorate the pathological development of Schizophrenia. Evidence suggests that PEA may specifically improve manic and negative symptoms, including apathy. Importantly, no serious adverse effects were reported in any of the human studies reviewed, suggesting a very beneficial safety profile for PEA.

Several other reviews have investigated the symptomatology of schizophrenia and related disorders. Motut et al. conducted a meta-analysis that revealed a significant correlation between social cognition and metacognition in subjects with Schizophrenia Spectrum Disorder. They were able to identify this association in various cognitive and social domains particularly those related to theory of mind, attribution and emotion processing, while no correlations emerged with indicators of cognitive intuition, self-reflexivity, or understanding others' minds. Beyond symptomatology, the authors also noted that metacognitive training and insight therapy represent non-pharmacological interventions that may benefit social cognition and possibly other cognitive functions in individuals with Schizophrenia Spectrum Disorders.

In addition, Di Luzio et al. reviewed the clinical features and comorbidities of *very early onset Schizophrenia* (VEOS) and reported that it appears to be very similar to *early-onset* (EOS) and *adult-onset* forms of Schizophrenia (AOS). However, VEOS has some peculiar characteristics, especially a greater presence of visual hallucinations and more common resistance to conventional treatment in female patients. Moreover, men and women are equally likely to develop VEOS, which differs from the usual 1.5 times higher prevalence of general Schizophrenia in men. Guiral et al., in turn, emphasized the critical role of neuropsychological dimensions related to alterations in verbal self-monitoring of language production in Schizophrenia patients. A general consensus emerged from the review that language processing and associated mechanisms of verbal self-monitoring are not deemed secondary, but rather fundamental to the disorder. A particularly clear link with emotional and cognitive dimensions, such as perception, is reported, and accompanying neurophysiological measurements have revealed the involvement of frontotemporal networks and regions such as the insula, amygdala, putamen and cingulate cortex. Based on these findings the authors suggested the development of neuropsychological techniques and tests for a better diagnosis and treatment of Schizophrenia.

Similarly, Calciu et al. investigated the psychotic phenomenon of dissociation and its relationship to recovery from psychosis. The authors reported that dissociative psychotic experiences are a very complex phenomenon that involves multiple mechanisms and influences recovery, whereas this field appears to be clearly understudied.

Finally, Hui et al. reviewed studies comparing Delusional Disorder (DD) and Schizophrenia and reported that, overall, no differences emerge between age-matched and non-age-matched features. However, compared to Schizophrenia, DD is associated with generally better outcomes in terms of psychopathology and functioning.

In summary, the reviews included in this Research Topic highlight a number of aspects and draw synoptic conclusions that are not easily identifiable in individual research articles given the considerable methodological and conceptual diversity in Schizophrenia research. For example, more confidence could be gained regarding the effectiveness of alternative or adjunct treatment approaches, such as VR- or animal-based therapy, computerized cognitive remediation therapy, or music therapy. Furthermore, the summaries of current evidence provided for rather understudied conditions in the Schizophrenia-related spectrum such as VEOS, dissociation, verbal self-monitoring, metacognition, and Delusional Disorder point to future research needs and directions. Overall, the reviews underscore that an approach to complex mental pathologies like Schizophrenia or the psychotic spectrum (14) based solely on isolated symptomatic aspects appears to be suboptimal. Therapies using multiple technologies and integrated approaches promise that treatment can be more comprehensive and humanely respectful. It is also

evident that the integration of multiple aspects can stimulate the scientific community to develop new strands of clinical, basic and technological research with a view to achieving an increasingly optimal outcome in terms of satisfactory symptom management and improved quality of life.

Author contributions

MT: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. DK: Writing – review & editing. TS-G: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Dog-assisted interventions for adults diagnosed with schizophrenia and related disorders: a systematic review

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Background: Many individuals diagnosed with schizophrenia and related disorders experience insufficient symptom relief from currently available treatment options. Researching additional venues should be prioritized. This systematic review, designed in accordance with PRISMA, examined the effect of targeted and structured dog-assisted interventions as a supplementary treatment.

Methods: Randomized as well as non-randomized studies were included. Systematic searches were conducted in APA PsycInfo, AMED, CENTRAL, Cinahl, Embase, Medline, Web of Science, and in several sources covering "gray" (unpublished) literature. In addition, forward and backward citation searches were performed. A narrative synthesis was conducted. Quality of evidence and risk of bias were assessed in accordance with GRADE and RoB2/ROBINS-I criteria.

Results: 12 publications from 11 different studies met eligibility criteria. Overall, studies showed diverging results. General psychopathology, positive and negative symptoms of psychosis, anxiety, stress, self-esteem, self-determination, lower body strength, social function, and quality of life were among the outcome measures with significant improvement. Most documentation for significant improvement was found for positive symptoms. One study indicated significant deterioration of non-personal social behavior. The risk of bias was high or serious for most of the outcome measures. Three outcome measures were associated with some concerns regarding risk of bias, and three with low risk of bias. Quality of evidence was graded low or very low for all outcome measures.

Conclusions: The included studies indicate potential effects of dog-assisted interventions for adults diagnosed with schizophrenia and related disorders, mostly beneficial. Nevertheless, low number of participants, heterogeneity, and risk of bias complicate the interpretation of results. Carefully designed randomized controlled trials are needed to determine causality between interventions and treatment effects.

KEYWORDS

animal-assisted interventions, therapy dog, PANSS, psychosocial outcomes, psychosis, severe mental illness

1. Introduction

Schizophrenia and related psychotic disorders are characterized by positive symptoms, negative symptoms, and cognitive difficulties. Hallucinations, delusions, and disorganized speech are examples of positive symptoms, while amotivation, anhedonia, and affective flattening are examples of negative symptoms. Genetic predisposition, substance use, trauma, and acute stress are among the risk factors for development of severe psychotic disorders. In addition, neurobiological factors, such as dopamine dysfunction, are associated with presence of positive symptoms and negative symptoms, as well as cognitive difficulties (1, 2). Overall lifetime prevalence for schizophrenia and related disorders is stated as 7.49 per 1,000 (3). The prognosis varies among individuals and extends between recovery and a chronic, lifelong course (4). Life expectancy is reduced by several years, with somatic comorbidity as one of the major causes (5). Overall, severe psychotic disorders are associated with a high burden of disease (6).

Treatment recommendations consist of a combination of pharmacological and non-pharmacological interventions (7). Current antipsychotic medications are shown to be more effective for positive symptoms than for negative and cognitive symptoms (1), and the latter two symptom groups are important determinants of disability (8). Numerous non-pharmacological interventions are considered in the guidelines by the *Norwegian Directorate of Health* (7), in accordance with international standards. Psychoeducation, family interventions, cognitive therapy, physical activity, and music therapy are among the included options. However, a substantial group of individuals diagnosed with schizophrenia and related disorders do not experience sufficient symptom relief (9). The heterogenous pathophysiology and phenotypes of severe psychotic disorders underpin the need for varied treatment options (10). Direct interpersonal engagement can be too demanding in some individuals. Interaction with therapeutic animals might theoretically be a less stressful alternative.

Animals have been included in the treatment for several disorders through centuries (11). Currently, there has been a development where anecdotal evidence to a larger extent is replaced by scientific research (12). The *International Association of Human-Animal Interaction Organizations* (IAHAIO) (13) has published specific guidelines for animal-assisted interventions (AAI). These guidelines are stating that AAI must be targeted and structured, with therapeutic benefits as purpose. Animal-assisted therapy (AAT) and animal-assisted activity (AAA) are two examples of AAI relevant to health care. While AAT must be planned, measurable, and documented, AAA signifies informal interaction. The guidelines are further stating that AAT is targeted toward physical, cognitive, behavioral, and/or socio-emotional functioning, while AAA is targeted toward motivation, education, and/or recreation. Knowledge related to health and behavior of included animals is required for providers of both AAT and AAA. Professional expertise, for example within health care, is in addition required for providers of AAT.

Studies have suggested treatment effects related to AAI for a range of health conditions and diseases (14). Biophilia, stress buffering, and distraction are elements in some theories and hypotheses that may explain potential effects (15). The biophilia hypothesis describes the affinity of humans to other living species (16). Effects related to the biophilia hypothesis may involve feelings of safety and facilitation of interpersonal interactions where animals may serve as social catalysators (17). In addition, decreased levels of cortisol and increased levels of oxytocin, β-endorphin, prolactin, phenyl acetic acid, and dopamine have been detected after interaction with dogs (18). These changes may be associated with physiological and psychosocial benefits, such as stress relief and improvement of social bonding and learning (18–21). Summarized, AAI are aimed at a wide range of symptoms and features, including those presented in severe psychotic disorders. Increased motivation for therapeutic activities due to interaction with animals has been described, for example in a study including individuals with acquired brain injury (22). Treatment effects of AAI will be highly relevant to investigate further for individuals with severe psychotic disorders. This is particularly justified by the fact that lack of motivation, which affects adherence to treatment, is a core feature among the negative symptoms (23).

A systematic review (SR) from 2018 on equine-assisted interventions indicated potential effects for individuals diagnosed with schizophrenia and related disorders. Significant improvement was shown for several outcome measures, such as negative symptoms, social functioning, pharmacological compliance, and risk of violence. The authors stated that further research is needed (24). A SR from 2019, including randomized controlled trials (RCTs) on AAI with several animal species, found inconclusive results regarding treatment effects for individuals diagnosed

Abbreviations: 5MWT, 5-Meter Walk Test; AAA, Animal-assisted activity; AAI, Animal-assisted interventions; AAT, Animal-assisted therapy; ACIS, Assessment of Communication and Interaction Skills; BGRS, Budapest Gesture Rating Scale; C, Control group; CHI, Chinese Happiness Inventory; CST, Chair Stand Test; DAI, Dog-assisted interventions; DANS, Data Archiving and Networked Services; DASS-21, Depression Anxiety Stress Scales Assessment; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders-IV-text revision; EQ-5D, EuroQoL-5 Dimensions questionnaire; F, Females; GRADE, Grading of Recommendations Assessment, Development and Evaluation; I, Intervention group; IAHAIO, The International Association of Human-Animal Interaction Organizations; ICD, International Classification of Diseases; ILSS, Independent Living Scale Survey; IPT, Integrated psychological treatment; LSP, Living Skills Profile; M, Males; MHSFS, Mental health-social functioning scale; MoCA, Montreal Cognitive Assessment; N/A, Not applicable; NIPH, Norwegian Institute of Public Health; NORA, Norwegian Open Research Archives; NRS, Non-randomized studies; NS, Not significant; PANSS, Positive and Negative Syndrome Scale; PICO, Population, intervention, comparison, outcome; PRESS, Peer Review Of Electronic Search Strategies; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QLESQ, Quality of Life Enjoyment and Satisfaction Questionnaire; RCT, Randomized controlled trial; RoB2, Risk of Bias 2; ROBINS-I, Risk Of Bias In Non-randomized Studies - of Interventions; SAFS, Social adaptive function scale; SANS, Schedule for the Assessment of Negative Symptoms; SD, Standard deviation; SE, Standard error; SHAPS, Snaith-Hamilton Pleasure Scale; SQLS, Subjective Quality of Life Scale; SR, Systematic review; SRD, Success rate difference; STAI, State-Trait Anxiety Inventory; TUG, Timed Up-and-Go; V.s, Versus; WHOQOL-BREF, The World Health Organization Quality of Life Brief Version.

with schizophrenia and related disorders. However, potential benefits were found for some outcome measures, such as positive symptoms, negative symptoms, emotional symptoms, and self-view (25).

As different animal species have different properties, we sought to investigate effects of dog-assisted interventions (DAI) specifically to increase directness and complement previous SRs. An investigation of therapeutic effects of DAI is also relevant due to findings in a survey among individuals diagnosed with schizophrenia, indicating that the dog was a preferred animal (26). A meta-analysis found that dogs were the most commonly involved animal in AAT (27). Beneficial therapeutic effects may be related to the cognitive and emotional capacities in dogs, in addition to an evolutionary connection with humans (28). Feasibility is also an important issue as dogs can thrive in same environments as humans. We sought to evaluate effects of targeted and structured interventions with therapeutic benefits as purpose. Therefore, both AAT and AAA were included.

Due to an existing knowledge gap, in addition to an extension of the field by four articles published during 2021–2023 (29–32), we found it relevant to perform a modified and updated SR on the topic. Summarized, modifications consisted of broader inclusion regarding study designs, and a narrower approach regarding the objective. The aim of the SR was to investigate effect of DAI for adults diagnosed with shizophrenia and related disorders. To our knowledge, this isolated topic has not been specifically covered by previous SRs.

2. Methods

The SR was designed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (33). In addition, a document with examples from the guidelines was used (34). Two handbooks, by Cochrane (35) and by the Norwegian Institute of Public Health (NIPH) (36), were also used as references.

2.1. Eligibility criteria

Eligibility criteria are presented in Table 1.

2.2. Search strategies, information sources and study selection

A detailed description of the search strategies can be found in Supplementary Tables 2–13. Briefly, the search strategy was developed in accordance with chapter 4 in Cochrane's method book (38) and chapter 4 in the method book by NIPH (36). Furthermore, two SRs (24, 25) on related topics, in addition to IAHAIOs definition of animal-assisted interventions (13), were used as references. Relevant articles detected through initial, non-systematic searches in Google Scholar and PubMed were reviewed for additional search terms and used for validation of the search strategy (29, 39–45).

The main searches were conducted 21.05.22 in APA PsycInfo (Ovid), AMED (Ovid), CENTRAL (Cochrane), Cinahl (Ebsco), Embase (Ovid), Medline (Ovid) and Web of Science. Automatic alerts regarding new publications until submission were set up. Duplicates from the main search were initially removed by automatic duplicate detection in EndNote version 20. Remaining duplicates were removed manually. Title and abstracts of all the remaining articles were screened by two reviewers working independently (by AB and EJ from A to K, and by MT and SS from L to AA, sorted by authors last name). Articles were initially excluded if the title or abstract did not include DAI or AAI not further specified, and schizophrenia, other psychotic disorders or mental disorders not specified.

The assessments of which articles to read in full text version and which to include in the SR, were also made independently by two reviewers for each study. The supplementary searches were conducted in the period from 30.04.22 to 28.05.23. For supplementary sources, please refer to the detailed description found in the Supplementary material. These searches consisted of both forward and backward reference searching, in addition to searches in databases, registers, and in websites of organizations. Backward citation searches in relevant reviews were conducted by EJ from A to K, and by MT from L to AA, sorted by authors last name. Beyond this, the supplementary searches were conducted by one reviewer (MT).

2.3. Data collection and synthesis of results

Study properties were collected in accordance with the PICO (population, intervention, comparison, outcome) model (46). Report properties were also collected, in addition to information regarding study design. Measurements regarding overall change, final values and/or follow-up for all outcomes related to effects were sought for extraction. Some of the elements were not documented in all articles. The data elements presented in Tables 2–4 were collected by one reviewer (MT) and controlled by one reviewer (EJ). Supplementary Table 15 provides an overview over data elements sought for extraction.

The results were presented as significant or non-significant. Significant results were presented with p-values and associated statistics, most commonly averages and standard deviations. As statistical methods varied among the studies and confidence intervals were not stated, it was not possible to select a common effect measure across studies. Substantial heterogeneity regarding interventions and outcomes prohibited meta-analysis. Studies were grouped for narrative synthesis based on outcome measures. Effect sizes were presented in the synthesis for the outcomes where effect size was calculated.

Effect sizes measured by Cohen's *d* were categorized as small for values from 0.2 to 0.49, as medium for values from 0.50 to 0.79, and as large for values above 0.79 (49). Effect sizes measured by SRD were categorized as small for values from 0.11 to 0.27, as medium for values from 0.28 to 0.43, and as large for values above 0.43 (50). The categorization corresponded to the presentation of effect sizes in one of the studies (29). In another study, effect sizes were described by percentage and not presented as small, medium,

TABLE 1 Eligibility criteria.

	Inclusion criteria	Exclusion criteria
Population	Participants aged 18 years or older diagnosed with schizophrenia or related disorders (37)[a] Ongoing treatment in a psychiatric ward, outpatient clinic or residential institution	Lack of distinguishing between measurements from participants with other diagnoses than schizophrenia and related disorders
Intervention	Dog-assisted interventions with aim of therapeutic benefits	Lack of distinguishing between measurements from interventions with different animal species
Outcome	Outcomes measured with validated instruments on at least two time points throughout the study	N/A
Study design	Quantitative studies of all designs	N/A
Report properties	Both published articles and gray literature No restrictions regarding year of publication	Articles written in other languages than English or Scandinavian
Risk of bias	N/A	Critical risk of bias

N/A, Not applicable.
[a]Schizophrenia and related disorders: Schizophrenia, schizotypal and delusional disorders (F20-F29) in International Classification of Diseases, ICD-10, and corresponding diagnoses in Diagnostic Statistical Manual, DSM-IV and DSM-V, assessed using a tool from New Zealand Health Information Service. Nevertheless, studies were not excluded due to missing diagnosis codes.

or large (44). In this SR, the descriptive presentations of effect sizes from the abovementioned study (44) were therefore based on recommendations by Cohen (49).

2.4. Risk of bias and quality of evidence

Risk of bias was assessed independently by two reviewers (MT and SS) for each outcome using RoB2 (Risk of Bias 2) tool (51) for RCTs, a specialized version of RoB2 for cluster-randomized trials (52), and ROBINS-I (Risk Of Bias In Non-randomized Studies—of Interventions) (53) for the remaining studies. In addition to assessments related to reporting bias covered under RoB2 and ROBINS-I (bias due to missing data), correlation between trial registers (ClinicalTrials.gov) and published studies were considered with regard to publication bias.

The quality of evidence was assessed independently by two reviewers (EJ and MT) based on guidelines from GRADE (Grading of Recommendations Assessment, Development and Evaluation) handbook (54) and an article regarding imprecision (55). In addition, an article with guidelines regarding quality of evidence in SRs without meta-analyses was used (56). In accordance with GRADE (54), the evidence across studies was graded as high, moderate, low, or very low for each outcome. Risk of bias, publication bias, inconsistency, indirectness, and imprecision were assessed for potential downgrading of the certainty of evidence. While serious limitations may lead to downgrading by one level, very serious limitations may lead to downgrading by two levels. On the other hand, large magnitude of effect may lead to upgrading by one or two levels, while large dose-response gradient and effect-reducing confounders may lead to upgrading by one level.

3. Results

3.1. Selection of studies

The main searches retrieved a total of 2,296 records. The total number of identified records was 2,329 after supplementary searches in additional databases. Searches in Google Scholar, in websites of organizations, and citation searches additionally expanded the number of records to 5,587. Details are presented in Figure 1. Nine of the articles from the main database searches met eligibility criteria. Three additional articles published during 2022 and 2023 were included after updated searches in Google Scholar. These articles were also detected through automatic database alerts. No additional articles were included after searches for unpublished literature or through citation searches. At the time of the most updated search, performed 28.05.23 in Google Scholar, no new publications were discovered. This was consistent with simultaneous assessments of the automatic database alerts from the main searches. Summarized, 12 articles, based on 11 studies, met eligibility criteria. An overview of studies excluded after review in full text version, or due to lack of access to full text version, is presented in Supplementary Table 14.

3.2. Study characteristics

References and details regarding study characteristics are presented in Table 2. In the 11 eligible studies, a total of 196 participants were included in intervention groups and 179 were included in control groups. The phase of disorder was described as chronic in six of the studies, as acute in two, and not specified in the remaining. All studies included both females and males. The participants were recruited from inpatient settings in eight of the studies, from a residential treatment center in one, from a day-care unit in one, and from both a psychiatric rehabilitation ward and a day-care ward in one. Baseline treatment, which was not stated in all studies, consisted of antipsychotic medications and different psychosocial treatments. In some of the studies, it was stated that all participants received stable antipsychotic treatment (29, 30, 43, 44). Where analyzed, no significant differences were found between the intervention group and the control group regarding antipsychotics (31).

The interventions were described as therapy in nine of the studies, as activity in one, and as interview in one. Four studies were designed as RCTs, one as a controlled pilot study, two as crossover studies, two as pilot/exploratory studies, one

TABLE 2 Study characteristics.

	Population	Intervention	Comparison	Outcome measure	Study design
Barker and Dawson, 1998 (47)	Schizophrenia, schizoaffective disorder and other psychotic disorders, acute Inpatients Sex[a]: F 174, M 139 Age[b]: Mean 37 years, SD 12	*n* = 34 participants (26 included in analyses) Dog-assisted *therapy* 30 min x1	*n* = 45 participants (39 included in analyses) Therapeutic recreation group session (music and art activities, education about leisure time and resources) x1 (duration not specified)	STAI (anxiety)	Crossover design
Calvo et al., 2016 (39)	Schizophrenia, chronic (DSM-IV-TR) Inpatients Sex: F 7, M 17 Age: Mean 47.8 years, SD 6.7 Age at diagnosis: Mean 20.5 years, SD 5.0	*n* = 16 participants (14 included in analyses) Dog-assisted *therapy* in addition to psychosocial rehabilitation program 6 months, 60 min x2 per week	*n* = 8 participants (8 included in analyses) One activity from the functional program (art therapy, group sports, dynamic psycho-stimulation or gymnastics) in addition to other programs of the psychosocial rehabilitation program 6 months, 60 min x2 per week	Primary outcomes: PANSS (positive, negative, general symptoms) EQ-5D (quality of life) Secondary outcomes: Adherence (patient experience) Salivary cortisol, alpha-amylase (stress relief)	RCT (non-blinded)
Chen et al., 2021 (29)	Schizophrenia, chronic (DSM-5) Inpatients and day care patients Sex: F 22, M 18 Age ≥ 40 years (mean 54.7)	*n* = 20 participants (20 included in analyses) Dog-assisted *therapy* in addition to usual treatment programs 12 weeks, 60–65 min x1 per week	*n* = 20 participants (20 included in analyses) Addition of nursing intervention and occupational therapy from the usual treatment program 12 weeks, 60 min x1 per week	Primary outcomes: PANSS (negative and general symptoms) DASS-21 (depression, anxiety, stress) Secondary outcomes: PANSS (positive symptoms) CHI (well-being)	RCT (non-blinded)
Chen et al., 2022 (30)	Same population as Chen et al., 2021 (29)	Same intervention as Chen et al., 2021 (29)	Same comparison as Chen et al., 2021 (29)	MoCa (global cognitive function) CST (lower body strength) TUG (agility) 5MWT (mobility) ACIS (communication and interaction skills)	Same design as Chen et al., 2021 (29)
Chu et al., 2009 (45)	Schizophrenia Inpatients Sex:? (authors state no significant difference between groups) Age < 60 years Duration of illness >10 years	*n* = 15 participants (12 included in analyses) Dog-assisted *activity* 8 weeks, 50 min x 1 per week	*n* = 15 participants (15 included in analyses) Treatment as usual	Questionnaire: Self-esteem Self-determination Extent of social support Adverse psychiatric symptoms (positive, negative and emotional)	RCT (assessment blinded)
Kovacs et al., 2004 (40)	Schizophrenia, chronic (DSM-IV) Inpatients Sex: F 4, M 3 Age 29–58 years (mean 43.6) Duration of illness >10 years	*n* = 7 participants (7 included in analyses) Dog-assisted *therapy* 9 months, 50 min x 1 per week	N/A	ILSS (living skills)	Pilot study (pre-post)
Kovacs et al., 2006 (41)	Schizophrenia, chronic (DSM-IV) Day-care Sex: F 3, M 2 Age: 32–71 years	*n* = 5 participants (3 included in the analyses) Dog-assisted *therapy* 6 months, 50 min x1 per week	N/A	BGRS (non-verbal communication)	Exploratory study (pre-post)

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TABLE 2 (Continued)

	Population	Intervention	Comparison	Outcome measure	Study design
Lang et al., 2010 (42)	Schizophrenia, acute (DSM-IV) Inpatients? Sex: F 7, M 7 Age: Mean 37.3 years, SD 13.8 Duration of illness: Mean 6 years, SD 9	*n* = 14 participants (14 included in analyses) Dog-assisted *interview* 30 min x 1	*n* = 14 participants (14 included in analyses) Interview without dog 30 min x1	STAI (anxiety)	Crossover design
Monfort et al., 2022 (31)	Schizophrenia-spectrum disorders and substance-use disorders (dual pathology) Residential treatment Age: Mean 40.3 years, SD 6.1 Sex: F: 13.9%, M: 86.1%	*n* = 18 participants (13 included in analyses)[c] Dog-assisted *therapy* in addition to standard treatment Maximum of 12 weeks (10 sessions), 45 min per week	*n* = 13 participants (10 included in analyses)[d] Standard treatment (antipsychotics, psychotherapy, psychoeducation, cognitive therapy)	LSP-20 (life skills) PANSS (positive, negative, and general symptoms) (Lack of baseline recordings[e])	Quasi-experimental prospective study
Nathans Barel et al., 2005 (43)	Schizophrenia, chronic (DSM-IV) Inpatients Sex: F 8, M 12 Age: Mean 39.9 years, SD 11.67 Duration of illness: Mean 18.1 years, SD 11.2	*n* = 10 participants (lost to follow-up not specified) Dog-assisted *therapy* in addition to psychosocial treatment 10 weeks x 60 min per week	*n* = 10 participants (lost to follow-up not specified) Learning about caring for animals, going for walks and participating in discussions in addition to psychosocial treatment 10 weeks x 60 min per week	Primary outcome SHAPS (anhedonia) Secondary outcomes SANS (negative symptoms) PANSS (total) PANSS (positive symptoms) SQLS (quality of life in relation to treatment) QLESQ (quality of life)	Controlled pilot study
Shih et al., 2023 (32)	Schizophrenia, chronic (DSM-5) Inpatients Sex: F 45, M 45 Age: Mean 50.2, SD 9.6 Age of morbidity: Mean 30.6, SD 11.0	*n* = 45 participants (45 included in analyses) Dog-assisted *therapy* 12 weeks, 60 min x1 per week	*n* = 45 participants (45 included in analyses) Discussion groups, including films about animals 12 weeks, 60 min x1 per week	MHSFS (Social competence and abilities in daily life) SAFS (day-to-day living abilities, social functioning, occupational abilities) WHOQOL-BREF (quality of life)	Longitudinal, single-blind experimental study
Villalta-Gil et al., 2009 (44)	Schizophrenia, (DSM-IV) Inpatients, long term Sex: F 3, M:18 Age in intervention group: Mean 49.1 years, SD 9.4 Age in control group: Mean 48.9, SD 8.6 Duration of illness: >10 years (mean 28.79)	*n* = 12 participants (11 included in the analyses) Modified IPT with dog-assisted *therapy* 12.5 weeks, 45 min x2 per week	*n* = 9 participants (7 included in the analyses) IPT 12.5 weeks, 45 min, x2 per week	LSP (social competence) PANSS (positive, negative and general symptoms) WHOQOL-BREF (quality of life)	RCT (assessment blinded)

5MWT, 5-Meter Walk Test; ACIS, Assessment of Communication and Interaction Skills; BGRS, Budapest Gesture Rating Scale; CHI, Chinese Happiness Inventory; CST, Chair Stand Test; DASS-21, Depression Anxiety Stress Scales Assessment; EQ-5D, EuroQoL-5 Dimensions questionnaire; ILSS, Independent Living Scale Survey; LSP, Living Skills Profile; MHSFS, Mental health-social functioning scale; MoCA, Montreal Cognitive Assessment; PANSS, Positive and Negative Syndrome Scale; QLESQ, Quality of Life Enjoyment and Satisfaction Questionnaire; SAFS, Social adaptive function scale; SANS, Schedule for the Assessment of Negative Symptoms; SHAPS, Snaith-Hamilton Pleasure Scale; SQLS, Subjective Quality of Life Scale; STAI, State-Trait Anxiety Inventory; TUG, Timed Up-and-Go; WHOQOL-BREF, Brief World Health Organization Quality of Life Assessment.

DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders-IV-text revision; F, Females; IPT, Integrated psychological treatment; M, Males; N/A, Not applicable; RCT, Randomized controlled trial; SD, Standard deviation.

[a,b]Subgroup data not available. The numbers refer to the whole group, including mood disorders, psychotic disorders, substance use disorders and other disorders.

[c]Reviewer's interpretation based on the following information: 21 took part in the intervention group, 5 dropped out and 3 did not meet eligibility criteria. Nevertheless, Tables 1, 2 in the article are showing n = 21 in the intervention group.

[d]Reviewer's interpretation based on the following information: 15 took part in the control group, 3 dropped out and 2 did not meet eligibility criteria. Nevertheless, Tables 1, 2 in the article are showing n = 15 in the control group.

[e]Measured after session 3, 6 and 10.

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TABLE 3 Intervention details, modified version of TIDieR (template for intervention description and replication) (48).

Study	Description of the intervention	Aim	Description of the dogs	Key elements of intervention	Intervention provider	Modes of delivery	Location	Duration
Barker and Dawson, 1998 (47)	Animal-assisted therapy	Investigate effect on anxiety levels	Two therapy dogs meeting hospital policy for AAT (including vaccination, controllability and temperament)	Handler talked generally about dog and encouraged discussion about pets; dog moved freely around interacting/carrying out basic obedience commands.	Dog handlers	Group session	Hospital setting, USA	30 min x1 (one single session)
Calvo et al., 2016 (39)	Animal-assisted therapy	Analyze impact of AAT on symptomatology and quality of life; Evaluate the patient's experience of AAT sessions; Assess stress relief during AAT sessions.	Five therapy dogs experienced in AAT. Physical and behavioral examination by specialists in veterinary behavioral medicine	Establish emotional bond between participant and dogs; walk the dogs; train and play with the dogs Participants worked in pairs at the start of each session	Researcher (unspecified education)	Group session with eight participants in each group, four of the five dogs present	Outdoors, hospital setting, Spain	6 months, 1 h x2 per week
Chen et al., 2021 (29)	Animal-assisted therapy	Evaluate effect of AAT for middle-aged and older patients with schizophrenia, on psychotic symptoms, negative emotions, and well-being.	Four therapy dogs certified by the Professional Animal-Assisted Therapy Association of Taiwan	Warm-up (establishing contact); therapeutic activities (activity for positive emotions, social activity, cognitive activity, physical activity); grooming and feeding; feedback	Certified animal-assisted therapist Occupational therapist (specialized in psychiatric rehabilitation) Certified dog handler	Group sessions with 10 participants in each group	Spacious and quiet classroom, rehabilitation ward/day care ward, Taiwan	12 weeks, 60–65 min x1 per week
Chen et al., 2022 (30)	Same intervention as Chen et al., 2021 (29)	Evaluate the efficacy of AAT for middle-aged patients with schizophrenia on cognition, physical and social functions	Same dogs as Chen et al., 2021 (29)	Same intervention as Chen et al., 2021 (29)	Same intervention providers as Chen et al., 2021 (29)	Same modes of delivery as Chen et al., 2021 (29)	Same location as Chen et al., 2021 (29)	Same duration as Chen et al., 2021 (29)
Chu et al., 2009 (45)	Animal-assisted activity	Examine a program for pet-assisted activity to determine whether such interactions can positively influence the physiological and psychological aspects of patients with schizophrenia	Two dogs, unspecified training	Dogs led in circle around the participants; participants encouraged to interact with dogs and other participants; physical activity	Researchers (unspecified education)	Group sessions with 15 participants	Garden and activity hall, hospital setting, Taiwan	8 weeks, 50 min x1 per week

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TABLE 3 (Continued)

Study	Description of the intervention	Aim	Description of the dogs	Key elements of intervention	Intervention provider	Modes of delivery	Location	Duration
Kovacs et al., 2004 (40)	Animal-assisted therapy	Evaluate effects of AAT in institutionalized middle-aged patients with schizophrenia with regards to adaptive functioning.	One dog (no further descriptions)	Establish contact as dog went around participants; simple or complex exercises including interaction with other participants; physical activity; grooming and feeding	Psychiatrist Social worker Dog handler	Group sessions with seven participants	Garden and occupational room, social institute, Hungary	9 months, 50 min x1 per week
Kovacs et al., 2006 (41)	Animal-assisted therapy	Examine effects of AAT in chronic schizophrenia to increase non-verbal communication	Two dogs (one participated in the majority of sessions), well-trained, examined by a veterinarian	Warm-up (establishing contact); goal oriented phase with grooming and feeding the dog; specific exercises and interaction with therapy staff and other participants	Psychiatrist, experienced with group therapy and AAT for patients with schizophrenia Co-therapist (psychology student) Dog handler (psychology student)	Group sessions with five participants	Day-care-unit, Hungary	6 months, 50 min x1 per week
Lang et al., 2010 (42)	Dog-assisted interviews	Evaluate effect of dog assisted interviews on state anxiety in patients with schizophrenia	Two therapy dogs that had been working at the unit several months	Level of interaction with dog determined by participants, but physical interaction not allowed	Research assistant (unspecified education)	Group session with seven participants in each group	Quiet room, hospital setting, Germany	30 min x1
Monfort et al., 2022 (31)	Dog-assisted therapy	Evaluate the AAT-efficacy for patients with dual diagnosis (schizophrenia-spectrum disorders and substance-use disorders) in residential treatment with regard to positive symptoms, negative symptoms, general psychopathology and functionality	A therapy dog	Presentation and greeting, interaction with the dogs and other participants, grooming, information regarding canine behavior, sharing experiences	Psychologist Social educator AAT technician Dog trainer	Groups of maximum 10 participants in each	Residential setting, Spain	Maximum of 12 weeks (10 sessions), 45 min per week
Nathans-Barel et al., 2005 (43)	Animal-assisted therapy	Examine beneficial effects of animal-assisted therapy on anhedonia in chronic schizophrenia	One dog approved by a veterinarian	Participants could choose from different activities with the dog including talking, making contact, petting, feeding, cleaning, teaching, taking the dog for a walk	Psychology student qualified as animal trainer and experienced with animal assisted interventions	Group sessions with 10 participants	Hospital setting, Israel	10 weeks, 60 min x1 per week

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TABLE 3 (Continued)

Study	Description of the intervention	Aim	Description of the dogs	Key elements of intervention	Intervention provider	Modes of delivery	Location	Duration
Shih et al., 2023 (32)	Animal-assisted therapy	Evaluate effectiveness of AAT on social interactions and quality of life for patients with schizophrenia during COVID-19	Two service dogs, minimum 3 months of training	Building relationships with dogs and other participants; brief interaction (including simple instructions, walking and feeding); deeper interaction (including grooming and group activities)	Researchers Social workers Two professional AAT-therapists (minimum 6 months of training/courses)	Group sessions	The reception hall, hospital setting, Taiwan	12 weeks, 1 h x1 per week
Villalta-Gil et al., 2009 (44)	Dog-assisted therapy	Assess effectiveness of trained therapy dog in institutionalized patients with chronic schizophrenia	One certified therapy dog	Cognitive activities; interaction with the dogs and other participants	Psychologist Dog handler	Group sessions with four participants in each group	Hospital setting, Spain	12.5 weeks, 45 min x2 per week

AAT, Animal-assisted therapy.

as longitudinal, single-blind experimental study, and one as quasi-experimental prospective study. Outcome measures were overall positive and negative symptoms, anhedonia, general psychopathology including isolated measurements of depression, emotional symptoms and anxiety, living skills, social function, social adaptive function, stress, extent of social support, self-determination, self-esteem, global cognitive function, lower body strength, agility, mobility, communication and interaction skills including isolated measurements of non-verbal communication, quality of life, well-being, and patient experience (adherence).

3.2.1. Intervention details

References and further details regarding the interventions are presented in Table 3. The extent of interventions ranged from a single session consisting of 30 minutes to sessions of 50 minutes per week for nine months. Although there was no standardized program across the studies, elements such as physical activity, cognitive activities, and interaction with other participants were common across several of the studies. Specific information regarding certification of therapy dogs was provided in two studies, and information regarding veterinary examinations was provided in three. It was stated that the intervention providers were both educated in psychiatry and had experience or training within AAI in four of the studies. In two of the studies, the intervention was led by a psychiatrist and a social worker, and by a psychologist without further information given. In one of the studies, the intervention was led by researchers, social workers and professional AAT therapists. In four of the studies, it was stated that the intervention providers were researchers and/or handlers without further information given.

3.3. Results of individual studies

Significant results were defined as $p \leq 0.05$ or $p < 0.05$ by the included studies. The results from each study are presented in Table 4.

3.4. Synthesis

3.4.1. Positive and negative symptoms

Three studies showed significant improvement for the intervention group compared with the control group for positive symptoms (29, 31, 45). The effect size in one of the studies was small (29). Two studies showed significant improvement both within the intervention group and within the control group, and no significant differences were found between the groups (39, 44). The effect sizes within both groups in one of the studies were large (44). One study found no significant difference between the groups, and significance within the groups was not stated (43).

With regard to negative symptoms in general, one study showed significant improvement, with large effect size for the intervention group compared with the control group (29). One study showed significant improvement for the intervention group compared with the control group for anhedonia (43). Two studies showed

TABLE 4 Results of individual studies.

	Between groups	Within intervention groups	Within control groups
Barker and Dawson, 1998 (47)	**STAI** (change) Anxiety: I = C	*Stated as mean (SD)* **STAI** (change) Anxiety: 5.77 (13.72), $p < 0.006$	**STAI** Anxiety: NS
Calvo et al., 2016 (39)	*Stated as mean (SD)* **PANSS** (change/posttreatment) Positive: I = C Negative: I = C General: I = C **EQ-5D** (change/posttreatment) Total score: I = C Health today 12m: I = C Mobility: I = C Pain/discomfort: I = C Health state today: I = C Anxiety/depression: I = C Daily activities: I = C Personal care: I = C **Adherence** Overall: I > C: 92.9% (4.7) vs. 61.2% (24.8), $p = 0.001$ Specific functional rehabilitation interventions: AAT vs. art therapy: I > C, $p = 0.01$ AAT vs. gymnastics: I > C, $p = 0.01$ AAT vs. psychodynamic therapy: N/A AAT vs. group sport: N/A	*Stated as mean (SD)* **PANSS** (change) Positive: 5.28 (4.78), $p = 0.001$ Negative: 5.64 (8.19), $p = 0.022$ General: 10.00 (8.70), $p = 0.001$ **EQ-5D** Total score: NS Health today 12m[a]: NS Mobility: NS Pain/discomfort: NS Health state today: NS Anxiety/depression: NS Daily activities: NS Personal care: NS **Stress relief** Salivary cortisol[b]: Decrease, $p < 0.05$ Salivary alpha-amylase[a]: Change, NS	*Stated as mean (SD)* **PANSS** (change) Positive: 7.87 (4.29), $p = 0.001$ Negative: NS General: 12.63 (13.57), $p = 0.033$ **EQ-5D** Total score: NS Health today 12m: NS Mobility: NS Pain/discomfort: NS Health state today: NS Anxiety/depression: NS Daily activities: NS Personal care: NS
Chen et al., 2021 (29)	*Stated as median* **PANSS** Total (change): I > C: −1.0 vs. 0, $p = 0.001$, SRD 0.15 Total (posttreatment): I = C Positive (change): I > C: −3 vs. 0, $p < 0.001$ Positive (posttreatment): I = C Negative (change): I > C: −3 vs. 0, $p < 0.001$, SRD 0.50 Negative (posttreatment): I = C General (change): I > C: −7 vs. 0, $p < 0.001$, SRD 0.20 General (posttreatment): I = C **DASS-21** Total (change/posttreatment): I = C Stress (change): I > C, −1.0 vs. 1.5, $p = 0.012$, SRD 0.15 Stress (posttreatment): I = C Anxiety (change/posttreatment): I = C Depression (change/posttreatment): I = C **CHI** Well-being (change/posttreatment): I = C	N/A	N/A
Chen et al., 2022 (30)	*Stated as median* **MoCa** Global cognitive function (change): I = C Global cognitive function (posttreatment): I = C **CST** Lower body strength (change) I > C, 0.50 vs. −1.00, $p = 0.007$ Lower body strength (posttreatment): I = C	N/A	N/A

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TABLE 4 (Continued)

	Between groups	Within intervention groups	Within control groups
	TUG Agility (change): I = C Agility (posttreatment): I = C **5MWT** Mobility (change): I = C Mobility (posttreatment): I = C **ACIS** Communication and interaction skills (change): I > C, 5.00 vs. 0.50, $p < 0.001$ Communication and interaction skills (posttreatment): I > C, 71.50 vs. 65.00, $p = 0.003$		
Chu et al., 2009 (45)	*Stated as mean* **Questionnaire** (change) Self-esteem: I > C 6.03 vs. −0.19, $p = 0.025$ Self-determination: I > C: 5.87 vs. −0.21, $p = 0.020$ Social support: I = C Positive symptoms: I > C: −6.42 vs. 0.69, $p = 0.005$ Negative symptoms: I = C Emotional symptoms: I > C: −5.62 vs. 0.13, $p = 0.048$	N/A	N/A
Kovacs et al., 2004 (40)	N/A	*Stated as mean (SD)* **ILSS, degree of behavioral problems** Domestic activities: 0.97 (0.93) to 0.37 (0.58), $p = 0.01$ Health: 0.90 (0.77) to 0.33 (0.66), $p = 0.02$ Leisure: NS Money management: NS Transportation: NS Eating: NS Grooming: NS **ILSS, frequency of occurrence of behaviors** Domestic activities: 2.06 (1.18) to 3.26 (0.74), $p = 0.01$ Health: 2.71 (0.48) to 3.40 (0.24), $p = 0.01$ Leisure: NS Money management: NS Transportation: NS Eating: NS Grooming: NS	N/A
Kovacs et al., 2006 (41)	N/A	**BGRS** Nonverbal communication: Significance was not investigated	N/A
Lang et al., 2010 (42)	*Stated as mean (SD)* **STAI** (change) Anxiety: I > C: 45.9 (11.8) to 35.6 (11.0) vs. 42.4 (11.1) to 40.1 (10.5), $p < 0.0001$	N/A	N/A
Monfort et al., 2022 (31)	*Stated as mean* **PANSS** (posttreatment) Positive: I > C, 27.81, $p = 0.002$ Negative: I = C General: I = C **LSP-20** (posttreatment) Life skills (total): I > C, 20.44, $p = 0.001$	N/A	N/A

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TABLE 4 (Continued)

	Between groups	Within intervention groups	Within control groups
Nathans-Barel et al., 2005 (43)	*Stated as mean (SD)* **SHAPS** (posttreatment) Hedonic tone: I > C, 3.44 (0.40) vs. 3.12 (0.34), $p = 0.02$ **QLESQ** (posttreatment) Leisure time activities: I > C: 3.75 (0.91) vs. 3.47 (0.71), $p = 0.01$ Physical health: I = C Subjective feelings: I = C Social relationships: I = C General activities: I = C Work: I = C Household duties: I = C Medication satisfaction: I = C School/course work: I = C Life satisfaction and enjoyment: I = C **SQLS** (posttreatment) Psychological: I = C Motivation: I = C Side effects: I = C **PANSS** (posttreatment) Total: I = C Positive: I = C **SANS** (posttreatment) Negative symptoms: I = C	N/A	N/A
Shih et al., 2023 (32)	*Stated as B (SE) group x time (reference control group x baseline)* **MHSFS** Social function (T2): I > C, B (SE) = 1.16, $p = 0.043$ Social function (T3): I < C, B (SE) = −5.37, $p = 0.037$ **SAFS** Social adaptive function (T2): I = C Social adaptive function (T3): I = C **WHOQOL** Quality of life (T2): I > C, B (SE) = 4.44, $p = 0.044$ Quality of life (T3): I > C, B (SE) = 11.06, $p = 0.007$	*Stated as mean (SD)* **MHSFS** Social function (change t^1): 50.56 (11.89) to 52.80 (11.93), $p < 0.01$ Social function (change, t^2): NS **SAFS** Social adaptive function (change t^1): 11.56 (7.66) to 9.87 (7.69), $p < 0.01$ Social adaptive function (change, t^2): NS **WHOQOL** Quality of life (change t^1): 79.33 (13.40) to 86.42 (17.98), $p < 0.01$ Quality of life (change, t^2): 79.33 (13.40) to 86.64 (15.92), $p < 0.01$	*Stated as mean (SD)* **MHSFS** Social function (change, t^1): 54.09 (13.80) to 55.18 (14.34), $p < 0.05$ Social function (change, t^2): NS **SAFS** Social adaptive function (change t^1): 11.87 (7.67) to 10.51 (8.21), $p < 0.05$ Social adaptive function (change, t^2): 11.87 (7.67) to 10.16 (7.46), $p < 0.05$ **WHOQOL** Quality of life (change t^1): NS Quality of life (change, t^2): NS

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TABLE 4 (Continued)

	Between groups	Within intervention groups	Within control groups
Villalta-Gil et al., 2009 (44)	**LSP** (posttreatment) Self-care: I = C Social behavior: I = C Social contact: I = C Non-personal social behavior: I = C Autonomous life: I = C **PANSS** (posttreatment) Total: I = C Positive: I = C Negative: I = C General: I = C **WHOQOL-BREF** (posttreatment) Physical health: I = C Psychological: I = C Social relationships: I = C Environment: I = C	*Stated as mean (SD)* **LSP** Self-care: NS Social behavior: NS Social contact: 13.67 (2.67) to 18.00 (4.40), $p < 0.05$, Cohen's d -1.19 Non-personal social behavior: 22.50 (1.38) to 20.55 (2.94), $p < 0.05$, Cohen's d 0.85 Autonomous life: NS **PANSS** Total: 88.25 (12.17) to 73.64 (18.69), $p < 0.05$ Positive: 20.83 (5.46) to 15.64 (4.03), $p < 0.01$, Cohen's d 1.08 Negative: 28.92 (5.25) to 19.36 (6.34), $p < 0.01$, Cohen's d 1.64 General: NS **WHOQOL-BREF** Physical health: NS Psychological: NS Social relationships: 2.08 (0.79) to 2.85 (0.56), $p < 0.05$, Cohen's d −1.12 Environment: NS	*Stated as mean (SD)* **LSP** Self-care: NS Social behavior: NS Social contact: NS Non-personal social behavior: NS Autonomous life: NS **PANSS** Total: 86.22 (10.03) to 61.83 (12.69), $p < 0.05$ Positive: 22.67 (7.71) to 17.00 (6.07), $p < 0.05$, Cohen's d 0.82 Negative: NS General: 38.11 (5.82) to 28.50 (5.58), $p < 0.05$, Cohen's d 1.69 **WHOQOL-BREF** Physical health: NS Psychological: NS Social relationships: NS Environment: NS

5MWT, 5-Meter Walk Test; ACIS, Assessment of Communication and Interaction Skills; BGRS, Budapest Gesture Rating Scale; CHI, Chinese Happiness Inventory; CST, Chair Stand Test; DASS-21, Depression Anxiety Stress Scales Assessment; EQ-5D, EuroQoL-5 Dimensions questionnaire; ILSS, Independent Living Scale Survey; LSP, Living Skills Profile; MHSFS, Mental health-social functioning scale; MoCA, Montreal Cognitive Assessment; PANSS, Positive and Negative Syndrome Scale; QLESQ, Quality of Life Enjoyment and Satisfaction Questionnaire; SAFS, Social adaptive function scale; SANS, Schedule for the Assessment of Negative Symptoms; SHAPS, Snaith-Hamilton Pleasure Scale; SQLS, Subjective Quality of Life Scale; STAI, State-Trait Anxiety Inventory; TUG, Timed Up-and-Go; WHOQOL-BREF, Brief World Health Organization Quality of Life Assessment.

AAT, Animal assisted therapy; C, Control group; I, Intervention group; N/A, Not applicable; NS, Not significant; SD, standard deviation; SE, standard Error; SRD, Success rate difference; t^1, Change from baseline to posttreatment; t^2, Change from baseline to follow-up 3 months after intervention; T2, Posttreatment; T3, 5 months follow-up; v.s., Vs.

[a]Significant before Bonferroni correction, non-significant after Bonferroni correction.

[b]Only measured within the intervention group.

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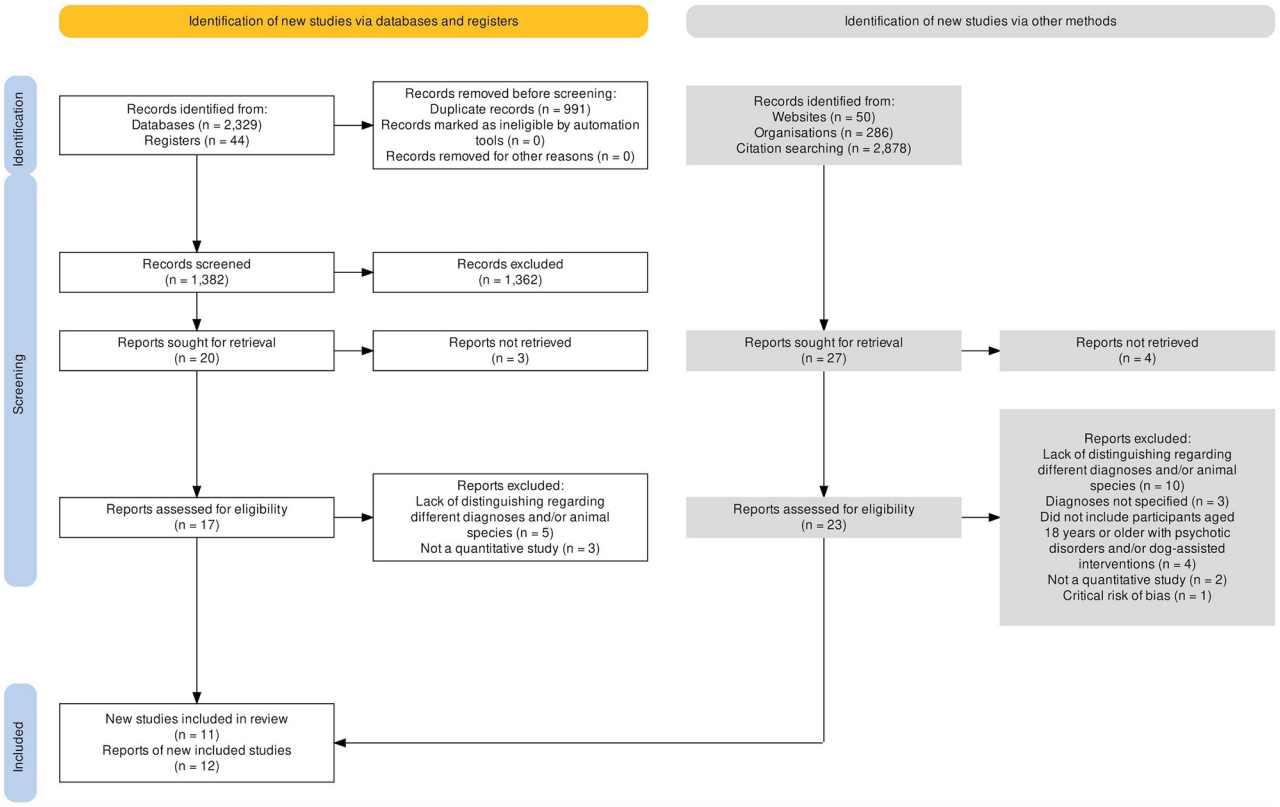

FIGURE 1
PRISMA flow diagram. Overview of the selection process. The flow diagram was created via a tool in accordance with the PRISMA statement (57).

significant improvement within the intervention groups, and not within the control groups, for negative symptoms in general (39, 44). The effect size was large in one of the studies (44). The differences between the groups were not significant. Two studies found no significant differences between the groups. Significance within the groups were not stated (43, 45). In one of the studies, the groups were described as "not comparable" due to significant pre-intervention differences. There were no significant differences at the end of the intervention (31).

3.4.2. General psychopathology including isolated assessments of emotional symptoms, anxiety and depressive symptoms

With regard to general psychopathology, one study showed significant improvement, with small effect size, for the intervention group compared with the control group (29). One study showed significant improvement both within the intervention group and within the control group. No significant difference was found between the groups (39). One study showed significant improvement, with large effect size, within the control group, and no significant change within the intervention group. The difference between the groups was not significant (44). One study showed no significant differences between the intervention group and the control group. Significance within the groups was not stated (31).

One study showed significant improvement for the intervention group compared with the control group for emotional symptoms (45). With regard to anxiety, one study showed significant improvement for the intervention group compared with the control group (42). Furthermore, one study showed significant improvement within the intervention group, and not within the control group. There was no significant difference between the groups (47). One study found no significant improvement for anxiety and depressive symptoms. Significance within the groups was not stated (29).

3.4.3. Living skills, stress, self-esteem, self-determination, social contact and cognition

One study showed significant improvement for living skills for the intervention group compared with the control group (31). One study, not including a control group, showed significant improvement within the intervention group for independent living skills related to domestic activities and health. There were no significant changes for several other aspects of living skills in the same study (40). Another study showed significant improvement within the intervention group, with large effect size, for living skills related to social contact. No significant improvement was observed within the control group. The difference between the groups was not significant. Furthermore, the study showed a significant deterioration, with large effect size, for non-personal social behavior within the intervention group. There was no significant change in non-personal social behavior within the control group. The difference between the groups was not significant. The same study found no significant change for other domains of living skills (44).

One study showed significant improvement, with small effect size, for the intervention group compared with the control group for stress (29). Another study showed significant improvement within the intervention group for change in cortisol levels. No significance was found for change in alpha-amylase. These markers were not investigated within the control group (39). With regard to self-esteem and self-determination, one study showed significant improvement for the intervention group compared with the control group. The same study found no significant difference between the groups for extent of social support. Significance within the groups was not stated (45). One study showed significant improvement for the intervention group compared with the control group for social function measured at the end of the intervention period. However, at 3 months follow-up, results were opposite, with significant improvement for the control group compared with the intervention group. Regarding social adaptive function, the same study showed no significant change between the groups. There were significant improvements both within the intervention group and within the control group at post-intervention. Nevertheless, only the control group had significant improvement at 3 months follow-up

One study showed significant improvement for the intervention group compared with the control group for communication and interaction skills (30). One study, without a control group, indicated improvement within the intervention group for use of space during communication and partial improvement for anatomy of movement, dynamics of movements and regulating movements. Calculation of significance was not performed (41). One study found no significant difference between the intervention group and the control group in global cognitive function (30).

3.4.4. Physical performance

One study showed significant improvement for the intervention group compared with the control group for lower body strength. No significant changes between the groups were found for agility and mobility measured by the same study. Significance within the groups was not stated (30).

3.4.5. Quality of life and wellbeing

One study showed significant improvement for the intervention group compared with the control group for quality of life in general, both with regard to post-treatment and 3 months follow-up compared with baseline (32). One study showed significant improvement for the intervention group compared with the control group for quality of life related to utilization of leisure time. There was no significant difference between the groups for a range of other factors of quality of life. Significance within the groups was not stated (43). Another study showed significant improvement, with large effect size, within the intervention group for quality of life related to social relationships. There was no significant findings within the control group. The difference between the groups was not significant. Further, there were no significant findings in this study for quality of life related to other factors (44). One study showed significant improvement before Bonferroni correction within the intervention group, and not within the control group, for quality of life related to general health. The difference between the groups was not significant. There were no significant findings for other domains of quality of life in this study (39). With regard to well-being, one study found no significant difference between the intervention group and the control group. Significance within the groups were not stated (29).

3.4.6. Adherence

One study showed significantly higher adherence, 93% compared with 61%, for the intervention group compared with the control group (39). The reasons for non-adherence within the intervention group were mostly related to family or health issues.

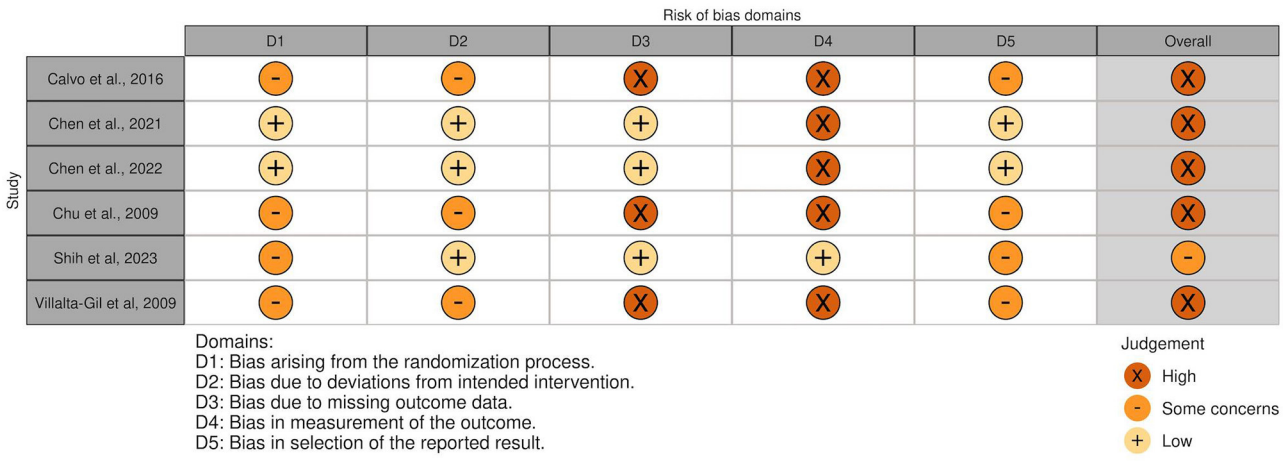

FIGURE 2
Risk of bias in RCTs and cluster-randomized trials. The highest overall risk for each study is presented as most of the outcomes within each study were associated with the same risk. An exception applied to domain 4. For this domain, alpha-amylase, cortisol and adherence measured by Calvo et al. (39) were associated with low risk. The same applied to agility, lower body strength, and mobility measured by Chen et al., (30), which resulted in overall low risk of bias for these three outcomes. Social competence measued by Villalta-Gil et al. (44) was associated with some concerns for the abovementioned domain. The figure was created via "Risk-of-bias VISualization"-tool (58).

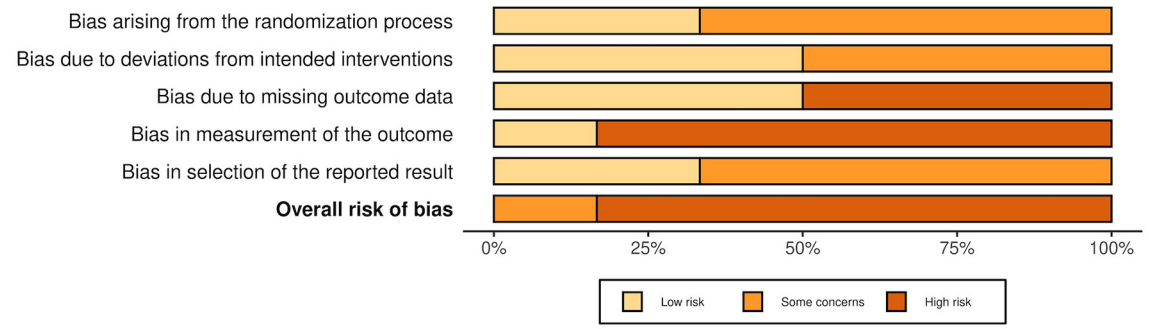

FIGURE 3
Summarized risk of bias in RCTs and cluster-randomized trials. Summarized risk of bias across studies. The figure was created via "Risk-of-bias VISualization"-tool (58).

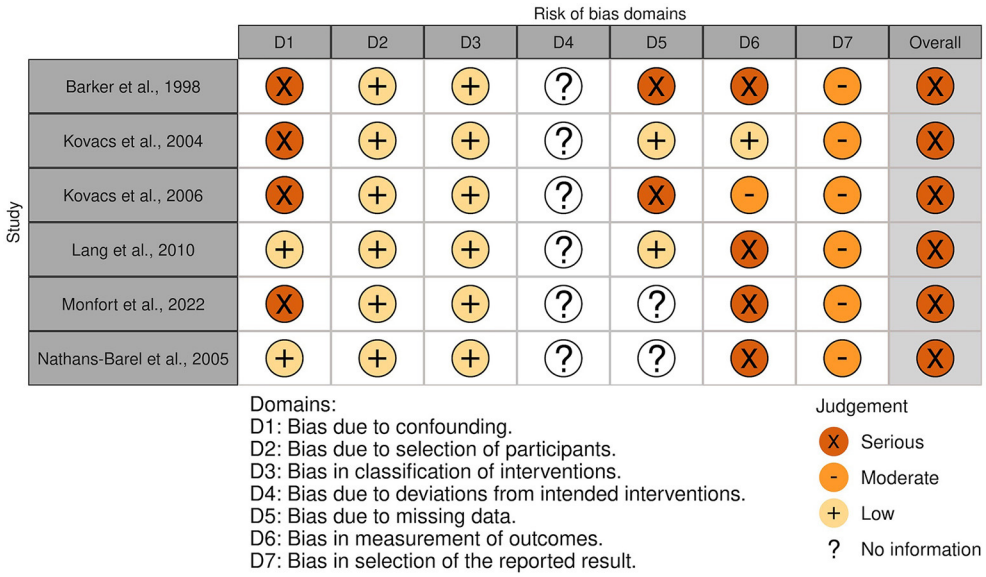

FIGURE 4
Risk of bias in NRSs. The highest overall risk for each study is presented as most of the outcomes within each study were associated with the same risk. An exception applied to domain 6. For this domain, life skills measured by Monfort et al. (31) were associated with low risk. The figure was created via "Risk-of-bias VISualization"-tool (58).

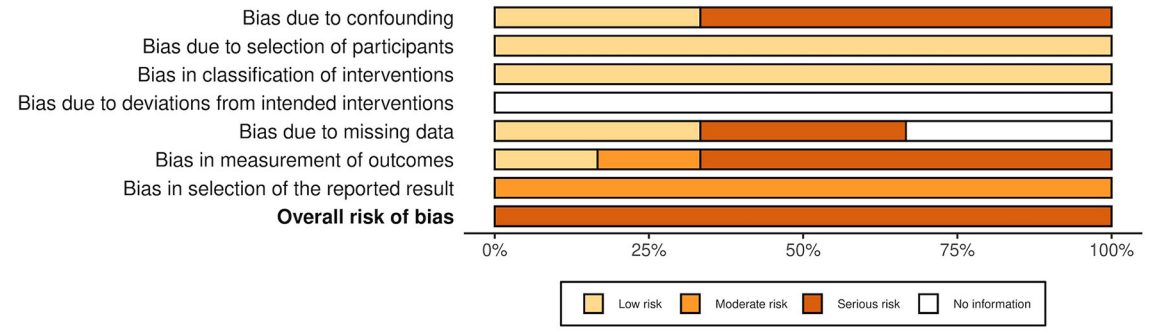

FIGURE 5
Summarized risk of bias in NRSs. Summarized risk of bias across studies. The figure was created via "Risk-of-bias VISualization"-tool (58).

Adherence, measured as proportion of attended sessions, was not stated as an outcome measure in the other studies. However, lost to follow-up was documented in most of the studies (presented in Table 2).

3.5. Risk of bias

The overall risk of bias was associated with some concerns for all outcomes in the cluster-randomized trial (32) and with high risk for most of the outcomes in the RCTs (29, 30, 39, 44, 45). Agility, lower body strength, and mobility measured by Chen et al. (30) were outcome measures with low risk of bias. For the non-randomized studies (NRS) (31, 40–43, 47), the overall risk of bias was categorized as serious for all outcomes. An overview is presented in Figures 2–5. One NRS was excluded due to critical risk of bias (59). The material included both studies with significant and non-significant results. No findings were made of studies reported in trial registers not published. Consequently, the risk of publication bias on the field was considered low. Nevertheless, most of the included studies lacked protocols.

3.6. Certainty of evidence

Inconsistency, indirectness, imprecision, and risk of bias were factors that led to downgrading of the quality. It was not possible to upgrade the quality due to serious and very serious limitations. The quality of evidence was considered low for agility, lower body strength, and mobility. For the rest of the outcomes, the quality of evidence was considered very low. Details concerning the assessments are presented in Supplementary Tables 16–38.

4. Discussion

In this SR, exclusively including studies with isolated results for adults diagnosed with schizophrenia and related disorders, numerous outcomes of DAI were examined. Both significant improvement and non-significant findings for the intervention groups compared with the control groups were reported for general symptoms, positive symptoms, negative symptoms, anxiety, living skills and quality of life. Significant improvement in the intervention groups compared with the control groups was also described for emotional symptoms, stress, self-esteem, self-determination, social function, communication and interaction skills, lower body strength, and adherence, but each of these outcome measures was only examined in single studies.

Within intervention groups, significant improvement was in addition described for salivary cortisol and social adaptive function, also examined in single studies. One study indicated significant deterioration of non-personal social behavior within the intervention group. Specific investigation of wellbeing, depression, agility, mobility, global cognitive function, alpha-amylase, and extent of social support was performed in single studies, and these outcome measures had no significant changes. Significance for non-verbal communication was not stated.

Heterogeneity in study design and lack of statistical calculations complicated the assessment of study outcomes. Therefore, we considered the findings in relation to factors that may have influenced results. Positive symptom score was the outcome measure with the most convincing findings. Significant improvement was demonstrated in several studies, but it should be noted that this was the outcome measure investigated by most studies. Findings concerning negative symptoms, the second most investigated outcome measure, were more divergent. Overall, inconsistent results were reported for the majority of outcome measures examined by more than one study. In the following sections, we highlight some potential explanations.

Importantly, a substantial difference across the studies was related to the content of the control groups. As an example, the studies by Villalta-Gil et al. (44) and Calvo et al. (39) included specific treatment programs focusing on psychosocial aspects with and without DAT. On the other hand, Chu et al. (45) compared AAA with treatment as usual. While significant improvement for several outcomes occurred within the groups in the first two studies, results from the latter contrasted the two abovementioned studies with a substantially larger degree of significant effects of active treatment. Active intervention also occurred in control groups in other studies—e.g. therapeutic recreation (music, art and education) as comparator in the study by Barker et al. (47). No significant changes for anxiety were seen between the groups in this study. The findings were contrasted by results in the study by Lang et al. (42) where the presence of a dog seemed to be the only difference between the groups (42). The findings suggest that the content in the control group may contribute largely to the heterogeneity of results across studies. As there are many uncertainties related to the effects of components only presented in DAI, a specific recommendation for future research is to conduct component studies. This suggestion is in accordance with a SR regarding factors of AAI (60) and a study on the role of common factors in psychotherapy (61).

A second issue contributing to lack of significant results may be related to other aspects of study design: low numbers of participants or short duration of interventions. As an example, the study by Shih et al. (32) showed significant improvement for quality of life between the groups. Increased overall quality of life was not shown in the other studies, neither between the groups or within the groups. The study by Shih et al. (32) stood out with a higher number of participants. Similarly, in one study showing significant improvement for the intervention group compared with the control group for both positive and negative symptoms, the population consisted of 40 participants (29). For the four studies with non-significant changes for negative symptoms, the samples were smaller with 18 to 23 participants included in analyses (31, 39, 43, 44).

Finally, study participant heterogeneity is likely to influence results on many levels. It is conceivable that treatment effects of different psychosocial interventions will vary based on individual characteristics such as symptom burden and preferences. Conditions reflecting symptom burden and level of functioning are reflected in the included trials: participants in the studies with significant changes between the groups for positive symptoms measured by PANSS, were recruited from a

psychiatric rehabilitation ward (29), from a day care center (29) and from a residential center (31), whereas participants in the studies with non-significant changes were hospitalized (39, 43, 44). Nevertheless, analyses of 27 hospitalized participants showed significant changes between the groups for positive symptoms, and not for negative symptoms, measured by a questionnaire (45). Recommendations for further research include dividing participants into subpopulations as well as investigating whether the effectiveness of AAI varies based on severity of symptoms, demanding a relatively high number of participants.

Diverging results have also been documented in previous SRs on related topics. As an example, a SR on dog presence and therapeutic alliance stated that half of the studies showed effect. Heterogeneity in study characteristics was described as an important limitation (62). Some of the results in our SR, however, contrasted earlier findings. In the SR by Hawkins et al. (25) including RCTs on AAI in general for individuals diagnosed with schizophrenia and related disorders, no improvement regarding quality of life was reported. One of the studies included in our SR indicated the opposite (32). This underpins that the field is under continuous development.

One of the purposes of this SR was to examine somatic effects, which were directly assessed in some of the studies through examination of physical skills and measurements of biochemical markers (30, 39). However, heart rate, blood pressure, HbA1c and lipid levels have not yet been investigated for adults diagnosed with schizophrenia and related disorders participating in DAI. This will be of importance as the population is at high risk of metabolic syndrome (63). Beneficial effects on cardiovascular risk factors have been associated with dog companionship or therapy for varied populations, but it is stated that further research is needed (64).

Another outcome measure especially relevant for further investigation is motivation. No significant changes were found for motivation related to treatment as a measure of quality of life, but this was only investigated in one study (43). Adherence can also function as an indicator of motivation. The adherence was significantly higher in the intervention group compared with the control group in one study (39). However, the results remain inconclusive. In addition to stating of reasons for non-adherence and lost to follow-up, validated instruments such as IMI-SR (65) may provide valuable information in further studies.

Significant worsening of non-personal social behavior within the intervention group was reported in one study (44). According to the authors, the intervention was not directed at these aspects and a similar trend was seen within the control group. Overall, prevention of negative consequences should have high priority. Examination by specialists in veterinary behavioral medicine was one of the preventive interventions described in one of the studies (39). Another example was inclusion of another dog in the later stages to reduce anxiety and grief due to removal of the dog at the end of the study (41). In a SR specifically addressing the benefits and risks associated with AAI, allergies, infections and accidents were described as the major risk factors. It was stated that these factors were outweighed by benefits (14). Animal welfare was only mentioned specifically by one of the included studies in our SR (39). Methods for overall safety, prevention of negative consequences and welfare for both participants and animals are of importance to describe in further articles. Development of interventions must be performed in accordance with guidelines for safety and welfare, for example from IAHAIO (13). A specific recommendation for further research is to describe evaluations regarding signs of stress in the participating dogs. In addition, a predetermined plan of action in case of negative consequences is of importance to include.

In addition to abovementioned limitations regarding consistency, a low number of participants led to imprecision. Furthermore, three outcome measures were associated with indirectness due to surrogate measures or use of inappropriate measurement methods. Risk of bias was categorized as high or serious for most of the included studies. Some factors that entailed the risk were missing outcome data, deficient blinding of personnel who assessed the measurements and risk of confounding. However, some of the factors causing risk of bias could not be avoided due to the nature of the interventions.

Exclusion of articles written in other languages than English and Scandinavian led to risk of selection bias in the review process. Lack of access to potentially relevant studies may also have caused bias. Due to lack of variables, such as confidence intervals, findings were reported as significant or non-significant. Such reporting is against the principles of Cochrane, and it must be emphasized that lack of evidence is not the same as lack of effect (66). Therefore, both significant and non-significant findings must be interpreted with caution.

Although inclusion of other designs than RCTs led to lower quality of evidence, these studies proved valuable in this SR through presentation of outcome measures not synthesized in a previous SR (25). Furthermore, inclusion of recent published studies led to novel insight on the topic. Isolated assessments of anhedonia, social function (including social adaptive function), communication and interaction skills (including non-verbal communication), lower body strength, mobility, agility and cognitive function, were among the outcome measures that expanded the knowledge. Specific examination of dog-assisted interventions increased the directness and complemented more general reviews on related topics.

Summarized, the findings suggest that DAI may have an effect on a range of symptoms and features associated with severe psychotic disorders. However, the findings must be interpreted with caution. Due to several knowledge gaps, it is challenging to state specific implications for policy and practice. The trade-off regarding potential benefits and potential harms are important. Based on available data, we consider the potential benefits of DAI to outweigh risk of harmful effects, given that all required precautions are taken. A potential negative consequence was described by only one of the included studies, and the causality of the finding remained uncertain (44). A specific implication for practice, which must be emphasized, is the necessity of development and implementation of interventions in accordance with guidelines for safety and welfare. The lack of data regarding animal welfare assessments is considerable, and the area is overall described as under-researched (67). In addition to the specific recommendations for further research presented in the paragraphs above and in Supplementary Table 39, reduction of bias and increase of quality will be essential. Accordingly, there is a specific need for carefully designed RCTs. This is particularly justified by the risk of confounding associated with NRS.

5. Conclusion

The included studies indicate potential effects of dog-assisted interventions for adults diagnosed with schizophrenia and related disorders, mostly beneficial. However, the results must be interpreted with caution due to methodological limitations such as low number of participants, heterogeneity among study design and included participants, and risk of bias. Findings of both significant and non-significant results are in accordance with reviews on animal-assisted interventions in general. Importantly, inclusion of several study designs and novel trials enabled synthesizing of outcome measures not covered by previous reviews. Some of the results, such as significant improvement for quality of life, contrast earlier findings. This underpins that the field is under continuous development, and further examination of causality is warranted. Recommendations for future research include factors such as calculation of effect sizes, development of more standardized programs, and investigation of effects related to motivation and somatic effects.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MT designed this systematic review with contributions from all co-authors, wrote the original draft, and all authors participated in revision. EJ and MT extracted data and graded the quality. MT and SS assessed risk of bias. All authors participated in screening and selection of articles and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1192075/full#supplementary-material

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Questioning the role of palmitoylethanolamide in psychosis: a systematic review of clinical and preclinical evidence

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Introduction: The endocannabinoid (eCB) system disruption has been suggested to underpin the development of psychosis, fueling the search for novel, better-tolerated antipsychotic agents that target the eCB system. Among these, palmitoylethanolamide (PEA), an N-acylethanolamine (AE) with neuroprotective, anti-inflammatory, and analgesic properties, has drawn attention for its antipsychotic potential.

Methods: This Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020-compliant systematic review aimed at reappraising all clinical and preclinical studies investigating the biobehavioral role of PEA in psychosis.

Results: Overall, 13 studies were eligible for data extraction (11 human, 2 animal). Observational studies investigating PEA tone in psychosis patients converged on the evidence for increased PEA plasma (6 human) and central nervous system (CNS; 1 human) levels, as a potential early compensatory response to illness and its severity, that seems to be lost in the longer-term (CNS; 1 human), opening to the possibility of exogenously supplementing it to sustain control of the disorder. Consistently, PEA oral supplementation reduced negative psychotic and manic symptoms among psychosis patients, with no serious adverse events (3 human). No PEA changes emerged in either preclinical psychosis model (2 animal) studied.

Discussion: Evidence supports PEA signaling as a potential psychosis biomarker, also indicating a therapeutic role of its supplementation in the disorder.

Systematic review registration: https://doi.org/10.17605/OSF.IO/AFMTK.

KEYWORDS

Schizophrenia, bipolar disorder, major depressive disorder, antipsychotics, cannabidiol, nutraceuticals

1. Introduction

Psychotic disorders—non-affective (e.g., schizophrenia (SCZ), schizophreniform disorder) and affective psychoses (e.g., bipolar disorder (BPAD), major depressive disorder with psychotic symptoms)—are a heterogeneous group of disabling mental health disturbances (1), sharing common phenomenological, neurobiological, and genetic characteristics (2–5). These conditions generally emerge between late adolescence and early adulthood (6), with a lifetime prevalence exceeding 3% (7–9), and severely affect the patients' and their families' quality of life. The dopaminergic and glutamatergic hypotheses still play a pivotal role in the attempt to describe the neurobiological mechanisms underlying psychosis (10–13), with potential for an integrated model explaining both positive (e.g., delusions, hallucinations) and

negative (e.g., restricted emotional expression, avolition) psychotic symptoms (12).

To date, antipsychotic (AP) medications represent the cornerstone treatment for these conditions, although not always devoid of suboptimal clinical response and unpleasant side-effects (14, 15). Therefore, the exploration of other perturbed systems potentially underpinning psychotic disorders has aimed at identifying novel therapeutic targets. The endocannabinoid (eCB) system has been recognized as a mediator of the dopaminergic and glutamatergic systems via the cannabinoid receptor 1 (CB1) in the central nervous system (CNS), and found to be altered in the early phases of the disorder (16–19). Consistently, accumulating evidence has highlighted the therapeutic potential of the eCB system modulation. Particularly, cannabidiol (CBD) has shown promising results for both psychosis and clinical high-risk (CHR) for psychosis state (20–23). Further, reduced diversity of gut microbiota and gut-brain axis metabolic alterations associated have been indicated as having a putative role in the patho-etiological cascade toward psychosis (24). To this end, reduced microbiota diversity has been observed to contribute to common SCZ negative symptoms such as anhedonia and amotivation via eCB-like compound palmitoylethanolamide (PEA) fecal levels, warranting the possibility to target the gut microbiota-eCB axis (25). Finally, growing evidence emphasizes the importance of inflammation and oxidative stress in the stages preceding psychosis onset and throughout illness progression (26, 27).

PEA is an N-acylethanolamine (AE), produced "on demand" by different cell types as a response to actual or potential damage (28, 29). Importantly, PEA has been proven to down-regulate central and peripheral activity of mast cells and non-neuronal cells (e.g., astrocytes, microglia) (30–32) and to exert protective functions against glutamate neuro-toxicity, accounting for its naturally-occurring anti-inflammatory, analgesic, and anticonvulsant properties (33). It directly activates the Peroxisome Proliferator Activated Receptor-α (PPAR-α) and the GPR55, allosterically modulates the Transient Receptor Potential Vanilloid 1 (TRPV1), and indirectly interacts with CB1 and cannabinoid receptor 2 (CB2) (32, 34, 35). Due to the shared pharmacodynamic properties, PEA is considered as the endogenous equivalent of CBD (36, 37). A growing body of literature has confirmed the role of PEA in most neurobiological mechanisms underpinning several neuropsychiatric conditions both in clinical and preclinical settings (38–40).

1.1. Objectives

The effect of PEA over neuroinflammation and glutamate signaling may represent a promising biobehavioral mechanism underlying its clinical utility in psychosis. This systematic review aimed to collect and discuss all available clinical and preclinical data generated by studies investigating the role of PEA in non-affective and affective psychoses. We reviewed all interventional and observational studies, employing either retrospective or prospective methodological approaches with any PEA neuro-biological correlates investigated in psychosis.

2. Materials and methods

2.1. Inclusion and exclusion criteria

All clinical and preclinical evidence about the topic was gathered and systematically reviewed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (41). Inclusion criteria were defined as follows: 1. analytic, observational, and interventional studies; 2. studies assessing (i) acute or long-term effects of palmitoylethanolamide (PEA) administration over psychosis-related biological underpinnings (e.g., neuroimmune disruption, hypothalamus-pituitary-adrenal axis dysregulation); and behavioral features (e.g., negative psychotic symptoms, manic symptoms); or (ii) PEA and PEA signaling-related molecular marker (e.g., other endocannabinoids/acylethanolamines, PEA-related enzymes) modulation in peripheral tissues (e.g., plasma, serum), or in the central nervous system (e.g. cerebrospinal fluid, brain tissue) in psychosis and related conditions. Exclusion criteria were defined as outlined: 1. studies in which (i) PEA was not the intervention or outcome of interest (e.g., studies evaluating only exogenous cannabinoid administration or assessing endogenous cannabinoid levels); and (ii) PEA bio-behavioral correlates were not investigated with reference to psychosis; and (iii) PEA bio-behavioral correlates were not directly reported on; 2. reviews; 3. systematic reviews; 4. meta-analyses.

2.2. Search strategy and data extraction

A literature search was performed using electronic databases (PubMed, Scopus, and Web of Science) for any published original study written in English, on 16 January 2023. In order to be as much inclusive as possible, a combination of broad-meaning terms describing and/or concerning PEA ("palmitoylethanolamide," "palmitylethanolamide," "N-2-hydroxyethyl-hexadecanamide," "N-2-hydroxyethyl-palmitate," "N-palmitoylethanolamine," "PEA," and "palmitoyl-ethanolamine") and psychosis ("schizophreni*," 'psychosis," "psychoses," "psychotic," "bipolar," "mania," "manic") was adopted. Reference lists of all selected studies were scrutinized to identify any adjunctive eligible evidence. Data screening and extraction were conducted according to a two-step selection process (conventional double-screening), performed by two researchers (RB and MC) independently from each other. In the instances of conflicting opinions regarding papers' inclusion, a consensus was sought through discussion with a third senior reviewer (MB).

2.3. Risk of bias assessment

In light of the methodological heterogeneity of collected evidence, quality of studies assessment was conducted in accordance to an adapted and suitably flexible set of criteria suggested by the Agency for Healthcare Research and Quality (AHRQ) guidance (42), in line with previous research in the field (38–40). Risk of systematic bias across human studies was ruled

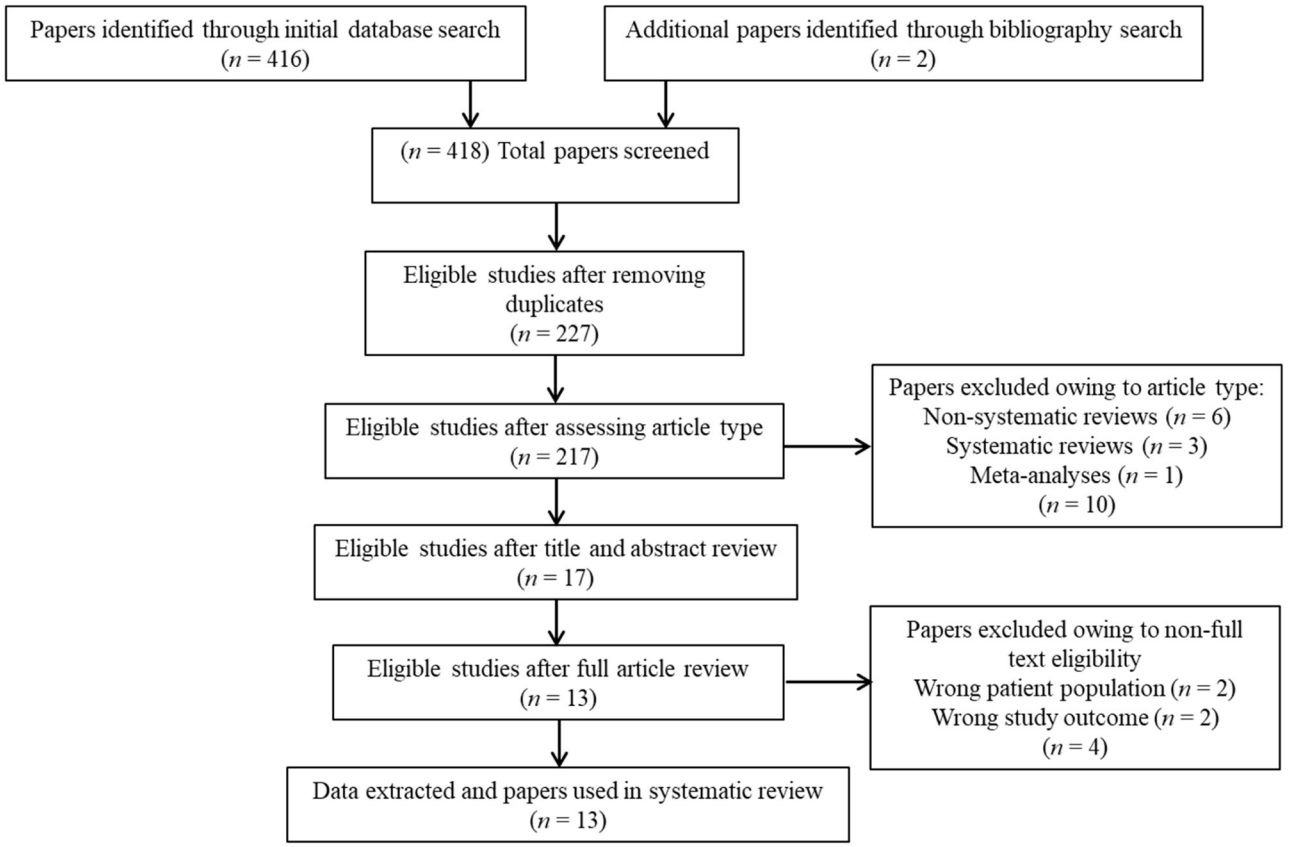

FIGURE 1
PRISMA flowchart of search strategy for systematic review.

out by screening all papers for potential confounding factors (e.g., gender, age, smoking status, level of education). Furthermore, factors possibly accounting for similarities and differences between all studies were assessed, extracting information about study characteristics, including study design (e.g., observational, interventional), defined study population (for human studies: e.g., schizophrenia (SCZ) patients, clinical high-risk (CHR) subjects; for animal studies: e.g., mouse or rat model), age or developmental stage, gender, adequate psychosis model (for animal studies only: e.g., maternal deprivation, methylazoxymethanol acetate (MAM) prenatal exposure), PEA measure (e.g., PEA dosage and administration route, PEA assessment in tissues), adequate PEA evaluation (e.g., time of exposure, single or multiple assessments), defined control group, comparability of subjects (for human studies only), exclusion criteria/adjusting factors (for human studies only), statistical analyses, and declaration of fundings/sponsorship. The full study protocol is available at https://doi.org/10.17605/OSF.IO/AFMTK.

3. Results

3.1. Study selection

Overall, 418 studies were retrieved through the initial data search. After removing duplicates as well as excluding articles owing to article type (e.g., non-systematic reviews, systematic reviews, meta-analyses), titles, abstracts, or full texts of all records were examined against the inclusion and exclusion criteria following a three-step screening process (Figure 1). A final list of thirteen studies was used for systematic analysis in this review, including 11 studies conducted only in human populations and two studies performed in animal models, exploring various aspects of palmitoylethanolamide (PEA) signaling pathway (Table 1). These include (i) *in vivo* PEA add-on treatment exposure in humans with different types of psychoses (e.g., non-affective psychosis, affective psychosis) or psychotic symptoms (e.g., hallucinations) (3 studies; Table 1); (ii) PEA quantitative blood assessment in humans with psychosis clinical high-risk (CHR) state (1 study; Table 1); (iii) PEA quantitative blood assessment in humans with different types of psychoses (e.g., non-affective psychosis, affective psychosis) at different stages of illness (5 studies; Table 1); (iv) PEA quantitative central nervous system (CNS; e.g., brain tissue, cerebrospinal fluid) assessment in humans with schizophrenia (SCZ; 2 studies; Table 1); (v) PEA quantitative brain tissue assessment in animal models of SCZ (2 studies; Table 1). Additional data on methodological quality of studies conducted in humans and animals are reported in Tables 2, 3. A brief synthesis of the main results is presented below and summarized in Table 1.

TABLE 1 Summary of clinical and preclinical studies investigating palmitoylethanolamide and its correlations to psychotic disorders.

Study (year)	Country	Aim of study	Type of PEA study	Population	Total sample size	Outcome measure (test name or description)	Summary results
Leweke et al. (43)	Germany	To assess PEA and other eCBs/AEs levels in SCZ patients	Quantitative assessment in humans	1. SCZ (n=10); 2. HC (n=11)	21	eCBs/AEs CSF levels (HPLC, GC/MS)	1. **PEA levels: SCZ > HC;** 2. **AEA levels: SCZ > HC**; 3. OEA levels: SCZ vs. HC, NS
Leweke et al. (44)	Germany	To assess PEA, other eCBs/AEs, and related enzymes levels in CBD-treated SCZ patients	Quantitative assessment in humans	1. CBD (n=20); 2. AMI (n=19)	39	eCBs/AEs and related enzymes serum levels (LC/MS, FAAH assay)	CBD group > AMI group: 1. **PEA levels: Day 14, Day 28 > Baseline;** 2. **AEA levels: Day 14, Day 28 > Baseline**; 3. **OEA levels: Day 14 > Baseline;** Day 28 vs. Baseline, NS
Muguruza et al. (45)	Spain	To assess postmortem PEA and other eCBs/AEs levels in SCZ patients	Quantitative assessment in humans	1. AP-F (n=11); 2. AP-T (n=8); 3. CTRL (n=19)	38	eCBs/AEs brain tissue levels (LC/MS)	1. Effect on eCBs/AEs levels: (a) **2-AG levels: SCZ, ↑**; **brain region**; SCZ x brain region interaction, NS; (b) **AEA levels: SCZ, ↓**; brain region, NS; SCZ x brain region interaction, NS; (c) **DHEA levels: SCZ, ↓**; **brain region**; **SCZ x brain region interaction**; (d) **PEA**, (e) **LEA levels: SCZ, ↓**; **brain region**; SCZ x brain region interaction, NS; (f) **OEA levels**: SCZ, NS; **brain region**; SCZ x brain region interaction, NS; 2. **PEA brain tissue levels**: (a) **CB: SCZ < CTRL**; **AP-F < CTRL**; AP-T vs. CTRL, NS; AP-T vs. AP-F, NS; (b) HIP, (c) PFC: all comparisons, NS; 3. **LEA brain tissue levels**: (a) **CB: SCZ < CTRL**; other comparisons, NS; (b) HIP: all comparisons, NS; (c) **PFC: AP-T < CTRL**; other comparisons, NS; 4. **DHEA brain tissue levels:** (a) **CB: SCZ < CTRL**; **AP-F, AP-T < CTRL**; AP-F vs. AP-T, NS; (b) **HIP: SCZ < CTRL**; **AP-F < CTRL**; other comparisons, NS; (c) PFC: all comparisons, NS; 5. **AEA brain tissue levels**: (a) **CB: SCZ < CTRL**; **AP-F < CTRL**; other comparisons, NS; (b) **HIP: SCZ < CTRL**; **AP-F, AP-T < CTRL**; AP-F vs. AP-T, NS; (c) **PFC: AP-T < CTRL**; other comparisons, NS; 6. **2-AG brain tissue levels**: (a) CB: all comparisons, NS; (b) **HIP: SCZ > CTRL**; **AP-F > CTRL**; other comparisons, NS; (c) **PFC: SCZ > CTRL**; **AP-F > CTRL**; other comparisons, NS; 7. OEA brain tissue levels: all comparisons, NS; 8. **2-AG/PEA ratio**: (a) **CB**, (b) **PFC: SCZ > CTRL**; (c) HIP: SCZ vs. CTRL, NS; 9. **2-AG/other AEs ratio: SCZ > CTRL (all brain regions; all comparisons)**
Koethe et al. (46)	United States	To assess PEA and other eCBs/AEs levels in SCZ and BPAD discordant twin patients	Quantitative assessment in humans	1. SCZ discordant twin pairs: (a) SCZ (n=25); (b) noSCZ (n=25); 2. BPAD discordant twin pairs: (a) BPAD (n=7); (b) noBPAD (n=7); 3. HC twins (n=16)	80	eCBs/AEs plasma levels (LC/MS)	1. **PEA plasma levels: SCZ, noSCZ > HC**; SCZ vs. noSCZ, NS; **BPAD, noBPAD > HC** (NS after Bonferroni's correction); BPAD vs. noBPAD, NS; SCZ-transit vs. SCZ-non transit, NS; **SCZ discordant > BPAD discordant**; 2. **AEA plasma levels: SCZ, noSCZ > HC**; SCZ vs. noSCZ, NS; **BPAD, noBPAD > HC**; BPAD vs. noBPAD, NS; **SCZ-transit < SCZ-non transit**; 3. 2-AG plasma levels: SCZ vs. noSCZ vs. HC, NS; BPAD vs. noBPAD vs. HC, NS; **SCZ-transit < SCZ-non transit**; 4. OEA plasma levels: SCZ vs. noSCZ vs. HC, NS; BPAD vs. noBPAD vs. HC, NS; SCZ-transit vs. SCZ-non transit, NS

(Continued)

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TABLE 1 (Continued)

Study (year)	Country	Aim of study	Type of PEA study	Population	Total sample size	Outcome measure (test name or description)	Summary results
Appiah-Kusi et al. (47)	United Kingdom	To assess PEA and other eCBs/AEs levels in CT-exposed CHR patients	Quantitative assessment in humans	1. HC (*n*=58); 2. CHR (*n*=33)	91	eCBs/AEs plasma levels (LC/MS)	1. Group differences on AEs/eCBs **plasma levels**: (a) PEA: CHR > HC (trend effect); (b) **OEA**, (c) **AEA**, (d) **2-AG: CHR > HC**; 2. (a) **CT effect: ↑ PEA, AEA, 2-AG levels**; (b) **CHR effect: ↑ AEA, 2-AG levels**; (c) **CHR x CT interaction: ↑ PEA levels**; ↑ AEA levels (trend effect); 3. **Effects of 2 vs. 1 RF on AEs/eCBs plasma levels**: (a) **PEA**, (b) **AEA**, (c) **OEA**, (d) **2-AG: 2RF > 1RF**; 4. **Effects of RF number on AEs/eCBs plasma levels**: (a) **PEA**, (b) **AEA**, (c) **OEA**, (d) **2-AG: noRF < 1RF < 2RF**; 5. **↑ PEA levels: ↑ total CAARMS score**; **↑ total CTQ score**; 6. ↑ AEA levels: ↑ total CAARMS score (trend effect)
Ibarra-Lecue et al. (48)	Spain	To assess PEA and other eCBs/AEs levels in DUAL patients	Quantitative assessment in humans	1. CUD (*n*=26); 2. HC1 (n=24); 3. SCZ (*n*=22); 4. HC2 (n=19); 5. DUAL (*n*=13); 6. HC3 (*n*=10)	114	1. eCBs/AEs plasma levels (HPLC/MS); 2. CB1R protein expression in PLTs (Western blot); 3. Inflammatory response measurements (ELISA)	1. CB1R protein expression: (a) **CUD main effect**; (b) **SCZ main effect**; (c) **CUD x SCZ interaction**; (d) **% from control: CUD, SCZ, DUAL < HC**; 2. eCBs/AEs plasma levels: (a) **SCZ main effect: PEA, OEA**; (b) **CUD main effect: PEA, AEA, DEA, LEA, NADA**; (c) **SCZ x CUD interaction: PEA, AEA, DEA, OEA**; (d) **PEA plasma levels (ng/ml): SCZ > DUAL; SCZ > HC > CUD**; other comparisons, NS; (e) **AEA plasma levels (ng/ml): SCZ > DUAL, CUD, HC**; other comparisons, NS; (f) **DEA plasma levels (ng/ml): SCZ > DUAL, CUD**; other comparisons, NS; (g) **OEA plasma levels (ng/ml): SCZ, CUD, HC > DUAL**; other comparisons, NS; (h) **NADA plasma levels (ng/ml): DUAL > HC**; other comparisons, NS; (i) 2-AG, (l) 1-AG, (m) LEA plasma levels (ng/ml): all comparisons, NS; 3. **IL-6 plasma levels (pg/ml): SCZ > DUAL, CUD, HC**; other comparisons, NS
Parksepp et al. (49)	Estonia	To assess PEA and other eCBs/AEs levels in FEP patients	Quantitative assessment in humans	1. FEP (*n*=54); 2. HC (*n*=58)	112	eCBs/AEs serum levels (HPLC/MS, flow injection analysis tandem MS)	1. eCBs/AEs serum levels: (a) PEA, (b) AEA, (c) LEA, (d) OEA: FEPb > HC (trend effect); FEP(0.6-year) vs. HC, NS; FEP(5.1-year) vs. HC, NS; (e) **2-AG**: FEPb < HC (trend effect); FEP(0.6-year) vs. HC, NS; **FEP(5.1-year) > HC**; 2. (eCBs/AEs)/2-AG ratio levels: (a) **PEA/2-AG: FEPb > HC**; FEP(0.6-year) vs. HC, NS; FEP(5.1-year) < HC (trend effect); (b) **AEA/2-AG**, (c) **OEA/2-AG: FEPb > HC**; FEP(0.6-year) vs. HC, NS; FEP(5.1-year) vs. HC, NS; (d) **LEA/2-AG: FEPb > HC**; FEP(0.6-year) vs. HC, NS; **FEP(5.1-year) < HC**; 3. (eCBs/AEs)/AEA ratio levels: (a) PEA/AEA, (b) OEA/AEA: FEPb vs. HC, NS; FEP(0.6-year) vs. HC, NS; FEP(5.1-year) vs. HC, NS; (c) **LEA/AEA**: FEPb vs. HC, NS; FEP(0.6-year) vs. HC, NS; **FEP(5.1-year) < HC**

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TABLE 1 (Continued)

Study (year)	Country	Aim of study	Type of PEA study	Population	Total sample size	Outcome measure (test name or description)	Summary results
Topuz et al. (50)	Turkey	To assess PEA and other eCBs/AEs levels in BPAD patients	Quantitative assessment in humans	1. Past depressive episode: (a) NoPastDEP (*n*=37); (b) PastDEP (*n*=42); 2. First episode type: (a) Manic/hypomanic (*n*=52); (b) Depressive (*n*=27)	79	eCBs/AEs serum levels (LC/MS)	1. eCBs/AEs serum levels: (a) AEA: NoPastDEP vs. PastDEP, NS; Manic/hypomanic vs. Depressive, NS; (b) **PEA: NoPastDEP < PastDEP**; **Manic/hypomanic < Depressive**; (c) **OEA: NoPastDEP < PastDEP**; Manic/hypomanic vs. Depressive, NS; (d) AEA: NoPastDEP vs. PastDEP, NS; Manic/hypomanic vs. Depressive, NS; 2. Correlations between illness course and eCBs/AEs serum levels: (a) **PEA: ↑ number of depressive episodes, ↑**; **↑ number of hypomanic episodes, ↓**; **↑ number of hospitalizations, ↓**; **↑ duration of VPA usage, ↓**; other correlations, NS; (b) **AEA: ↑ duration of VPA usage, ↑**; other correlations, NS; (c) **OEA: ↑ age of onset, ↑; ↑ number of depressive episodes, ↑**; other correlations, NS; (d) **2-AG: ↑ number of depressive episodes, ↑**; other correlations, NS; 3. Relation of symptoms and eCBs/AEs serum levels: (a) **PEA: presence of depressive mood, ↑**; **presence of increased sexual desire, ↓**; **presence of anxiety, ↑**; **presence of flight of ideas, ↓**; **presence of delusion, ↓**; **presence of grandiosity, ↓**; presence of other symptoms, NS; (b) **AEA: presence of flight of ideas, ↓**; **presence of increased motor activity, ↓**; **presence of Schneiderian symptoms, ↑**; presence of other symptoms, NS; (c) **OEA: presence of depressive mood, ↑**; **presence of anxiety, ↑**; presence of other symptoms, NS; (d) **2-AG: presence of euphoria, ↑**; presence of other symptoms, NS; 4. Relation of medical history and eCBs/AEs serum levels: (a) **PEA: presence of another disease, ↓**; any other medical history, NS; (b) AEA: all medical history, NS; (c) OEA: all medical history, NS; (d) **2-AG: presence of diabetes mellitus, ↓**; **presence of another disease, ↓**; any other medical history, NS
Brotini et al. (51)	Italy	To assess PEA add-on effects on psychotic symptoms in PD patients	*In vivo* treatment in humans	PD patients	30	nM-EDL assessment (MDS-UPDRS)	Effect on hallucinations and psychosis (nM-EDL scores): post-PEA vs. pre-PEA, NS
Salehi et al. (52)	Iran	To assess PEA add-on effects on negative symptoms in SCZ patients	*In vivo* treatment in humans	1. PEA (*n*=25); 2. PLB (*n*=25)	50	1. Symptoms assessment (PANSS, HDRS); 2. Adverse events assessment (ESRS, open-ended questions, comprehensive side effect checklist)	1. **Effect on PANSS negative: time, ↓; time x treatment interaction, ↓**; 2. **Effect on PANSS positive: time, ↓**; time x treatment interaction, NS; 3. **Effect on PANSS general: time, ↓; time x treatment interaction, ↓**; 4. **Effect on PANSS total: time, ↓; time x treatment interaction, ↓**; 5. Effect on HDRS: time x treatment interaction, NS; 6. Effect on ESRS global score: time, NS; time x treatment interaction, NS; 7. Frequency of adverse events (drowsiness, dizziness, tremor, increased appetite, nervousness, restlessness, skin rash, blurred vision, fatigue, diarrhea, dry mouth, sore throat, tachycardia): PEA vs. PLB, NS

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TABLE 1 (Continued)

Study (year)	Country	Aim of study	Type of PEA study	Population	Total sample size	Outcome measure (test name or description)	Summary results
Abedini et al. (53)	Iran	To assess PEA add-on effects on acute mania in BPAD patients	*In vivo* treatment in humans	1. PEA (*n*=32); 2. PLB (*n*=31)	63	1. Symptoms assessment (YMRS, HDRS); 2. Adverse events assessment (ESRS, open-ended questions, comprehensive side effect checklist)	1. Effect on psychometric measures: (a) **YMRS: time x treatment interaction**; (b) ESRS: time x treatment interaction, NS; 2. **YMRS global score**: (a) Baseline, (b) Week 2, (c) Week 4: PEA vs. PLB, NS; (d) **Week 6: PEA < PLB**; 3. **YMRS score changes**: (a) From Baseline to Week 2: PEA vs. PLB, NS; (b) **From Baseline to Week 4**, (c) **From Baseline to Week 6: PEA > PLB**; 4. **HDRS global score**: (a) Baseline: PEA vs. PLB, NS; (b) **Week 6: PEA > PLB**; 5. HDRS score changes: From Baseline to Week 6: PEA vs. PLB, NS; 6. ESRS global score: (a) Baseline, (b) Week 1, (c) Week 2, (d) Week 4, (e) Week 6: PEA vs. PLB, NS; 7. ESRS score changes: all comparisons, NS; 8. Frequency of adverse events (drowsiness, dizziness, increased appetite, skin rash, diarrhea, dry mouth, sore throat, tachycardia): PEA vs. PLB, NS
Stark et al. (54)	Czech Republic/Italy	To assess PEA and other eCBs/AEs brain levels following CBD, CB1R antagonist/inverse agonist, and HAL in MAM rats	Quantitative assessment in animals	1. CTRL+VHI; 2. CTRL+CBD10; 3. CTRL+CBD30; 4. CTRL+AM251; 5. CTRL+HAL; 6. MAM+VHI; 7. MAM+CBD10; 8. MAM+CBD30; 9. MAM+AM251; 10. MAM+HAL	12-15 per group	eCBs/AEs brain levels (LC-APCI/MS)	1. Effects of peripubertal treatment (PND 19-39) on social interactions (SI test) from PND 100: (a) **effect on time: MAM; treatment; MAM x treatment interaction**; (b) **time: MAM+VHI < CTRL+VHI; MAM+CBD30 > MAM+VHI; CTRL+AM251 < CTRL+VHI; MAM+AM251 > MAM+VHI; CTRL+VHI > CTRL+HAL**; other comparisons, NS; (c) effect on number of social interactions: MAM, NS; treatment, NS; MAM x treatment interaction, NS; (d) number of interactions: all comparisons, NS; 2. Effects of peripubertal treatment (PND 19-39) on exploratory activity (NORT, OFT) from PND 100: (a) **effect on DI: MAM**; treatment, NS; **MAM x treatment interaction**; (b) **DI: MAM+VHI < CTRL+VHI; MAM+CBD30 > MAM+VHI**; other comparisons, NS; (c) effect on total exploration time: MAM, NS; treatment, NS; MAM x treatment interaction, NS; (d) total exploration time: all comparisons, NS; (e) effect on number of crossings: MAM, NS; treatment, NS; MAM x treatment interaction, NS; (f) number of crossings: all comparisons, NS; (g) effect on number of rearings: MAM, NS; treatment, NS; MAM x treatment interaction, NS; (h) number of crossings: all comparisons, NS; 3. Effects of peripubertal treatment (PND 19-39) on PFC CB1R expression from PND 100: (a) **effect on mRNA expression**: MAM, NS; treatment, NS; **MAM x treatment interaction**; (b) **% mRNA methylation: MAM+VHI < CTRL+VHI; MAM+CBD30 > MAM+VHI; CTRL+AM251 > CTRL+VHI; CTRL+HAL > CTRL+VHI; MAM+HAL > MAM+VHI**; other comparisons, NS; (c) **mRNA fold change: MAM+VHI > CTRL+VHI; MAM+CBD30 < MAM+VHI; MAM+AM251 < MAM+VHI**; other comparisons, NS; (d) **protein expression level: MAM+VHI > CTRL+VHI**; **CTRL+CBD30 < CTRL+VHI; MAM+CBD30 < MAM+VHI; MAM+AM251 > CTRL+VHI; MAM+HAL > CTRL+VHI**; other comparisons, NS; 4. Effects of peripubertal treatment (PND 19-39) on PFC eCBs/AEs expression from PND 100: (a) effect on PEA levels: MAM, NS; treatment, NS; MAM x treatment interaction, NS; (b) PEA levels: all comparisons, NS; (c) **effect on 2-AG levels: MAM; treatment; MAM x treatment interaction**; (d) **2-AG levels: MAM+CBD30 < MAM+VHI; CTRL+AM251 > CTRL+VHI**; **MAM+AM251 < MAM+VHI; CTRL+HAL > CTRL+VHI**; other comparisons, NS; (e) effect on AEA levels: MAM; treatment, NS; MAM x treatment interaction; (f) **AEA levels: CTRL+CBD30 > CTRL+VHI**; other comparisons, NS; (g) effect on OEA levels: MAM, NS; treatment, NS; MAM x treatment interaction, NS; (b) OEA levels: all comparisons, NS

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TABLE 1 (Continued)

Study (year)	Country	Aim of study	Type of PEA study	Population	Total sample size	Outcome measure (test name or description)	Summary results
Di Bartolomeo et al. (55)	Czech Republic/Italy	To assess PEA and other eCBs/AEs brain levels following CBD in pTHC rats	Quantitative assessment in animals	1. CTRL+VHI; 2. CTRL+CBD; 3. pTHC+VHI; 4. pTHC+CBD	3-20 per group	eCBs/AEs brain levels (LC/MS)	1. Effects of pTHC on neonatal behavior: (a) **righting (PND 1-2)**, (b) **cliff aversion (PND 2-8)**, (c) **forelimb placing (PND 3-9)**, (d) **forelimb grasping (PND 2-4)**, (e) **bar holding (PND 5)**, (f) **negative geotaxis (PND 3-4)**, (g) **nest time**: **pTHC+VHI < CTRL+VHI**; (h) nest exploration: pTHC+VHI vs. CTRL+VHI, NS 2. Effects of pTHC on PFC eCBs/AEs expression at PND 10: (a) PEA, (b) AEA, (c) OEA levels: pTHC+VHI vs. CTRL+VHI, NS; (d) **2-AG levels: pTHC+VHI < CTRL+VHI**; (e) **Magl**, (f) **Faah mRNA expression: pTHC+VHI > CTRL+VHI**; (g) Cnr1, (h) Trpv1, (i) other eCBs/AEs enzymes mRNA expression: pTHC+VHI vs. CTRL+VHI, NS; 3. Effects of pTHC on PFC Drd2 gene expression at PND 10: pTHC+VHI > CTRL+VHI (trend effect); 4. Effects of peripubertal CBD (PND 19-39) on adult behavior: (a) number of crossings, (b) number of rearings (OFT): all comparisons, NS; (c) **SI time: pTHC+VHI < CTRL+VHI**; **pTHC+CBD < pTHC+VHI**; (d) SI number of interactions: all comparisons, NS; (e) **discrimination index (NORT): pTHC+VHI < CTRL+VHI**; **pTHC+CBD > pTHC+VHI**; (f) time (NORT): all comparisons, NS; 5. Effects of peripubertal CBD (PND 19-39) on PFC genes expression from PND 100: (a) %DNA methylation Cnr1 gene: all comparisons, NS; (b) **%DNA methylation Drd2 gene: pTHC+VHI < CTRL+VHI**; **CTRL+CBD < CTRL+VHI**; **pTHC+CBD > pTHC+VHI**; other comparisons, NS; (c) **Cnr1 relative gene expression: pTHC+VHI > CTRL+VHI**; other comparisons, NS; (d) **Drd2 relative gene expression: pTHC+VHI > CTRL+VHI; pTHC+CBD > CTRL+CBD**; (e) Cnr1 protein expression level: all comparisons, NS; (f) **Drd2 protein expression level: pTHC+VHI > CTRL+VHI**; other comparisons, NS; 6. Effects of peripubertal CBD (PND 19-39) on PFC eCBs/AEs expression from PND 100: (a) PEA levels: CTRL+VHI vs. pTHC+VHI vs. pTHC+CBD, NS; (b) **2-AG levels: pTHC+VHI < CTRL+VHI**; **pTHC+CBD < CTRL+VHI**; pTHC+CBD vs. pTHC+VHI, NS; (c) **AEA levels: pTHC+VHI > CTRL+VHI**; pTHC+VHI vs. pTHC+CBD, NS; pTHC+CBD vs. CTRL+VHI, NS; (d) OEA levels: all comparisons, NS

<, Lower/less than; >, Greater/more than; ↑, Increase; ↓, Decrease; 2-AG, 2-Arachidonoylglycerol; AEA, Anandamide; AEs, Acylethanolamines; AM251, CB1 antagonist/inverse agonist; AMI, Amisulpride; AP-F, Antipsychotic-free patients; AP-T, Antipsychotic-treated patients; BPAD, Bipolar Affective Disorder; CAARMS, Comprehensive Assessment of At-Risk Mental State; CB, Cerebellum; CB1R, Cannabinoid receptor type 1; CBD, Cannabidiol; CBD10, Cannabidiol (10 mg/kg/day); CBD30, Cannabidiol (30 mg/kg/day); CHR, Clinical High-Risk; Cnr1, Cannabinoid CB1 receptor gene; CSF, Cerebrospinal fluid; CT, Childhood trauma; CTQ, Childhood Trauma Questionnaire; CTRL, Control group; CUD, Cannabis Use Disorder; DEA, Docosatetraenylethanolamide; DHEA, N-docosahexaenoylethanolamine; DI, Discrimination index; DNA, Deoxyribonucleic acid; Drd2, Dopamine D2 receptor gene; DUAL, Dual diagnosis; eCBs, Endocannabinoids; ELISA, Enzyme linked immunosorbent assay; ESRS, Extrapyramidal Symptom Rating Scale; FAAH/Faah, Fatty Acid Amide Hydrolase; FEP, First-episode psychosis; FEPb, First-episode psychosis (baseline); GC/MS, Gas Chromatography-Mass Spectrometry; HAL, Haloperidol; HC, Healthy controls; HDRS, Hamilton Depression Rating Scale; HIP, Hippocampus; HPLC, High Pressure Liquid Chromatography; HPLC/MS, High Pressure Liquid Chromatography-Mass Spectrometry; IL-6, Interleukin 6; LC/MS, Liquid Chromatography-Mass Spectrometry; LC-APCI/MS, Liquid Chromatography-Atmospheric Pressure Chemical Ionization-Mass Spectrometry; LEA, Dihomo-linolenoylethanolamine; Magl, Monoacylglycerol lipase; MAM, Methylazoxymethanol acetate; MDS-UPDRS, MDS-Unified Parkinson's Disease Rating Scale; mRNA, Messenger ribonucleic acid; n, Sub-sample size; NADA, N-Arachidonoyldopamine; ng/ml, Nanograms per milliliter; nM-EDL, Non-Motor Aspects of Experiences of Daily Living; NoPastDEP, No prior depressive episodes; NORT, Novel object recognition test; noBPAD, healthy twins of BPAD patients; noSCZ, healthy twins of SCZ patients; NS, Not significant; OEA, Oleoylethanolamide; OFT, Open-field test; PANSS, Positive and Negative Syndrome Scale; PastDEP, At least one prior depressive episode; PD, Parkinson's Disease; PEA, Palmitoylethanolamide; PFC, Prefrontal cortex; PLB, Placebo; PLTs, Platelets; PND, Postnatal day; pTHC, Perinatal THC; RF, Risk factor; SCZ, Schizophrenia; SI, Social interaction; THC, Delta-9-tetrahydrocannabinol; Trpv1, Transient receptor potential vanilloid 1 gene; VHI, Vehicle; VPA, Valproic Acid; vs., Compared to; YMRS, Young Mania Rating Scale. Bold font emphasizes statistically significant results.

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TABLE 2 Methodological quality of clinical studies investigating palmitoylethanolamide and its correlations to psychotic disorders.

Study (year)	Study design	Defined study population	Age (years, mean ± SD)	Male gender count (%)	PEA measure	Adequate PEA Evaluation	Control	Comparability of Subjects	Excluded/adjusted for confounding factors	Statistical analyses	Funding or sponsorship
Leweke et al. (43)	√ Analytic, observational	√ SCZ or schizophreniform disorder patients: DSM-IV; BPRS	√/X SCZ: 27.7 ± 9.6	√/X SCZ: 7 (70%)	√ CSF levels	√ Single assessment	√ HC	√ Matched for age	X	√ *t*-test	√
Leweke et al. (44)	√ Analytic, observational	√ SCZ or schizophreniform disorder patients: DSM-IV; 18-50 years; BPRS ≥ 36; BPRS THOT factor ≥ 12	√ CBD: 29.7 ± 8.3; AMI: 30.6 ± 9.4	√ CBD: 15 (75%); AMI: 17 (89%)	√ Serum levels	√ Multiple assessment (baseline, day 14, day 28)	√ AMI	√/X Matched for age, weight, pulse, blood pressure, gender, PANSS, BPRS, SAS, EPS; not matched for CGI severity, Lorazepam mg/day	√ Excluded if positive UDS, history of SUDs, previous depot antipsychotic treatment (< 3 months before the study), history of treatment resistance, present relevant/unstable condition, pregnancy, or breastfeeding	√ Mixed effects repeated measures model (unstructured covariance matrix), Fisher's exact test	√
Muguruza et al. (45)	√ Analytic, observational	√ Postmortem SCZ patients' brain samples: DSM-IV	√ AP-F: 45 ± 4; AP-T: 49 ± 5; CTRL: 45 ± 3	√ AP-F: 9 (81.8%); AP-T: 6 (75%); CTRL: 15 (78.9%)	√ Brain tissue levels	√ Single assessment	√ CTRL	√ Matched for age, gender, PMI, pH, RIN, storage (months)	√ Excluded if positive toxicological test for cannabis; HC excluded if history of neuropsychiatric disorder, history of drug abuse	√ Two-way ANOVA, Fisher LSD test, Pearson's coefficient, *t*-test, one-way ANOVA, Dunnett's multiple comparison *post-hoc* test	√
Koethe et al. (46)	√ Analytic, observational	√ SCZ or BPAD discordant twin patients: DSM-III-R; stable clinical condition; SANS; clinical records review; GAF scale	√ SCZ discordant: 30; BPAD discordant: 33; HC twins: 31	√ SCZ discordant: 14 (56%); BPAD discordant: 1 (14.29%); HC twins: 3 (27.27%)	√ Plasma levels	√ Single assessment	√ noSCZ; noBPAD; HC	X	√ Excluded if positive UDS	√ Wilcoxon rank sum test, exact Wilcoxon signed rank test, Bonferroni's correction	√

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TABLE 2 (Continued)

Study (year)	Study design	Defined study population	Age (years, mean ± SD)	Male gender count (%)	PEA measure	Adequate PEA Evaluation	Control	Comparability of Subjects	Excluded/adjusted for confounding factors	Statistical analyses	Funding or sponsorship
Appiah-Kusi et al. (47)	√ Analytic, observational	√ CHR individuals: CAARMS criteria	√ HC: 25.05 ± 4.90; CHR: 23.82 ± 5.28	√ 1. HC: 53.00%; 2. CHR: 51.00%	√ Plasma levels	√ Single assessment	√ HC	√ Matched for age, gender, current CU	√ Excluded if history of psychotic or manic episode, past or current CNS disorder, current substance dependence (DSM-IV), IQ < 70, any contraindications to CBD treatment or MRI, drug use during the entire study	√ ANCOVA, *t*-test, chi-square, correlation analysis	√
Ibarra-Lecue et al. (48)	√ Analytic, observational	√ SCZ, CUD, or DUAL patients: SCID (DSM-IV, DSM-IV-TR); ICD	√ CUD: 32.5 ± 1.9; HC1: 32.8 ± 2.0; SCZ: 48.9 ± 1.8; HC2: 49 ± 2.1; DUAL: 38.0 ± 2.9; HC3: 37.3 ± 3.4;	√ CUD: 21 (80.77%); HC1: 19 (79.17%); SCZ: 13 (59.09%); HC2: 10 (52.63%); DUAL: 12 (92.31%); HC3: 10 (100%)	√ Plasma levels	√ Single assessment	√ HC1; HC2; HC3	√ Matched for age, gender	√ HC excluded if any neuropsychiatric disease, any past 2 years CU	√ Two-way ANOVA, Tukey's test	√
Parksepp et al. (49)	√ Analytic, observational	√ FEP patients: ICD-10; DUP < 3 years; no AP use before the study; 18–45 years	√ FEPb: 26.6 ± 6.1; FEP(0.6-year): 27.3 ± 6.4; FEP(5.1-year): 31.8 ± 5.9; HC: 24.7 ± 4.5	√ FEPb: 31 (57%); FEP(0.6-year): 27 (51%); FEP(5.1-year): 23 (43%); HC: 24 (44%)	√ Serum levels	√ Multiple assessment (baseline, 0.59 ± 0.06 years after baseline, 5.15 ± 1.25 years after baseline)	√ HC	√/X FEP and HC matched for age, gender, smoking status, BMI; FEP and HC not matched for length of education; FEP groups matched for AP dose; FEP groups not matched for BMI, BPRS score	√ Excluded if current organic or drug-induced psychosis, current psychotic disorders due to other medical conditions; Adjusted for gender, age at first visit, smoking status, Δt between the visits	√ Shapiro-Wilk test, *t*-test, repeated measure ANOVA, Scheffé *post-hoc* test, chi-square test, LME models, maximum likelihood method, likelihood ratio test, FDR procedure	√

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TABLE 2 (Continued)

Study (year)	Study design	Defined study population	Age (years, mean ± SD)	Male gender count (%)	PEA measure	Adequate PEA Evaluation	Control	Comparability of Subjects	Excluded/adjusted for confounding factors	Statistical analyses	Funding or sponsorship
Topuz et al. (50)	√ Analytic, observational	√ BPAD patients: DSM-5; euthymic period; 18–65 years	√ 42.40 ± 1.10	√ 35 (44.30%)	√ Serum levels	√ Single assessment	X	NA	X	√ Shapiro-Wilk test, *t*-test, Mann-Whitney U test, Spearman correlation analysis	√
Brotini et al. (51)	√ Analytic, observational, interventional	√ levodopa treated PD patients (PDSBB criteria): (a) HY scale > 0; (b) MMSE ≥26/30; (c) age>18 years; (d) levodopa therapy (eventually other PD medication) without modification over four consecutive weeks	√ 73 ± 8	√ 14 (46.67%)	√ um-PEA 600 mg	√ Twice per day administration (12 weeks), then daily administration (36 weeks)	X	NA	√ Excluded if other forms of parkinsonism, other forms of dementia, unreliable patients, non-compliant patients	√ GLMM, Wilcoxon signed-rank test, Bonferroni's correction, Tukey-Kramer adjusted test	√
Salehi et al. (52)	√ Analytic, observational, interventional	√ SCZ patients: 18–60 years; SCID (DSM-5); illness duration ≥ 2 years; PANSS negative ≥15; HDRS < 14; clinical stability on stable risperidone (PANSS total change ≤ 20% on 2 subsequent assessments within 2 weeks)	√ PEA: 33.76 ± 6.93; PLB: 36.80 ± 9.60	√ 1. PEA: 23 (92%); 2. PLB: 21 (84%)	√ PEA 600 mg (oral administration)	√ Twice per day administration (8 weeks)	√ PLB	√ Matched for age, gender, literacy, smoking status, marital status, overall SCZ duration, baseline HDRS, baseline PANSS, baseline ESRS	√ Excluded if IQ < 70, history of head trauma, prior 3 months history of ECT, prior 6 months substance or alcohol dependence, breastfeeding, pregnancy, suicidal ideation, history of neurosurgery, current acute or chronic medical disease, history of allergy to risperidone or PEA	√ Shapiro-Wilk test, Q-Q probability graphics, *t*-test, Levene's test, Fisher's exact test, ANOVA, Greenhouse-Geisser test	√

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TABLE 2 (Continued)

Study (year)	Study design	Defined study population	Age (years, mean ± SD)	Male gender count (%)	PEA measure	Adequate PEA Evaluation	Control	Comparability of Subjects	Excluded/adjusted for confounding factors	Statistical analyses	Funding or sponsorship
Abedini et al. (53)	√ Analytic, observational, interventional	√ BPAD patients: SCID (DSM-5); MINI; moderate to severe manic episode assessed (YMRS)	√ PEA: 30.78 ± 9.80; PLB: 32.74 ± 9.04	√ 1. PEA: 21 (71.9%); 2. PLB: 20 (64.5%)	√ PEA 600 mg (oral administration)	√ Twice per day administration (6 weeks)	√ PLB	√ Matched for age, gender, education, smoking status, marital status, overall BPAD duration, baseline HDRS, baseline YMRS, baseline ESRS	√ Excluded if IQ < 70, history of allergy to lithium, risperidone, or PEA, substance dependence (except nicotine and caffeine), receiving manic-inducing medications, metabolic disorders such as hypothyroidism or hyperthyroidism, current severe hepatic disease	√ *t*-test, chi-square, Fisher's exact test, general linear model repeated-measures analysis, Mauchly test, Greenhouse-Geisser test	√

<, Lower/less than; >, Greater/more than; ≤, Less than or equal to; ≥, More than or equal to; AMI, Amisulpride; ANCOVA, Analysis of Covariance; ANOVA, Analysis of Variance; AP, Antipsychotic; AP-F, Antipsychotic-free patients; AP-T, Antipsychotic-treated patients; BMI, Body Mass Index; BPAD, Bipolar Affective Disorder; BPRS, Brief Psychiatric Rating Scale; CAARMS, Comprehensive Assessment of At-Risk Mental State; CBD, Cannabidiol; CGI, Clinical Global Impression; CHR, Clinical High-Risk; CNS, Central nervous system; CSF, Cerebrospinal fluid; CTRL, Control group; CU, Cannabis use; CUD, Cannabis Use Disorder; DSM-5, Diagnostic and Statistical Manual of mental disorders, Fifth Edition; DSM-III-R, Diagnostic and Statistical Manual of mental disorders, Third Edition Revised; DSM-IV, Diagnostic and Statistical Manual of mental disorders, Fourth Edition; DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders, Fourth Edition-Text Revision; DUAL, Dual diagnosis; DUP, Duration of untreated psychosis; ECT, Electroconvulsive therapy; EPS, Extrapyramidal Symptoms; ESRS, Extrapyramidal Symptom Rating Scale; FDR, False discovery rate; FEP, First-episode psychosis; FEPb, First-episode psychosis (baseline); GAF, Global Assessment of Functioning; GLMM, Generalized Linear Mixed Model; HC, Healthy controls; HDRS, Hamilton Depression Rating Scale; HY, Hoehn and Yahr; ICD, International Classification of Diseases; ICD-10, International Classification of Diseases, Tenth Edition; IQ, Intelligence Quotient; LME, Linear mixed-effects; LSD, Least Significant Difference; mg, Milligrams; mg/day, Milligrams per day; MINI, Mini-International Neuropsychiatric Interview; MMSE, Mini Mental State Examination; MRI, Magnetic Resonance imaging; NA, Not applicable; noBPAD, healthy twins of BPAD patients; noSCZ, healthy twins of SCZ patients; PANSS, Positive and Negative Syndrome Scale; PD, Parkinson's Disease; PDSBB, PD Society Brain Bank; PEA, Palmitoylethanolamide; PLB, Placebo; PMI, Postmortem interval; RIN, RNA intergrity number; SANS, Scale for the Assessment of Negative Symptoms; SAS, Social Anxiety Scale; SCID, Structured Clinical Interview for DSM; SCZ, Schizophrenia; SD, Standard Deviation; SUDs, Substance Use Disorders; THOT, Thought Disorder; UDS, Urine drugs screening; um-PEA, Ultramicronized-PEA; YMRS, Young Mania Rating Scale; Δt, Time period.

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3.2. *In vivo* palmitoylethanolamide (PEA) add-on treatment exposure in humans with different types of psychoses or psychotic symptoms

Three human studies have addressed this area (Table 1) using similar but not overlapping methodologies in terms of study population [chronic schizophrenia (SCZ) patients (52), bipolar disorder (BPAD) patients with manic symptoms (53), Parkinson's disease (PD) patients (51)], PEA formulation [oral native PEA (52, 53), oral Ultramicronized (um)-PEA (51)], PEA dosage [600 milligrams (mg) daily (51), 600 mg twice/daily (51–53)], and PEA period of exposure [6 weeks (53), 8 weeks (52), 12 months (51)]. Apart from a single study lacking a controlled condition (51), all studies adopted a randomized, double-blind, placebo-controlled design (52, 53). Overall, results indicated a beneficial effect of PEA adjunctive therapy on residual negative and general psychopathological symptoms, but not positive symptoms, of risperidone-treated SCZ patients (52), as well as on manic symptoms of lithium- plus risperidone-treated BPAD patients (53). Coherent data emerged regarding depressive symptomatology, which did not appear to be improved in both SCZ and BPAD patients treated with PEA add-on as compared to placebo (52, 53). A single study addressing the effect of PEA over non-motor symptoms among levodopa-treated PD patients, showed no reduction in the number of subjects presenting with hallucinations and psychosis (51). Noteworthy, PEA was well-tolerated, in the absence of extrapyramidal symptoms or any other relevant side effect across the three studies, and for the entire duration of the compound administration.

3.3. Palmitoylethanolamide quantitative blood assessment in humans with psychosis clinical high-risk state

This systematic reappraisal identified a single human study specifically assessing peripheral blood PEA levels in individuals suffering from CHR state, as compared to healthy controls (HC) (47) (Table 1). PEA levels tended to be elevated in CHR patients, even though just approaching statistical significance. Intriguingly, PEA levels appeared to be significantly higher in those who were both CHR and had been exposed to childhood trauma (CT), compared to individuals having none of the above-mentioned risk factors or one risk factor alone. Furthermore, a significant positive correlation between PEA levels and the severity of CHR state and CT was observed (47).

3.4. Palmitoylethanolamide quantitative blood assessment in humans with different types of psychoses at different stages of illness

Most of the studies retrieved investigated peripheral blood PEA levels in patients with non-affective [e.g., schizophrenia (SCZ)

TABLE 3 Methodological quality of preclinical studies investigating palmitoylethanolamide and its correlations to psychotic disorders.

Study (year)	Study design	Defined study population	Adequate psychosis model	Developmental stage	Gender	PEA Measure	Adequate PEA evaluation	Control	Statistical analyses	Funding or sponsorship
Stark et al. (54)	√ Analytic, observational	√ Offsprings of MAM-exposed Sprague-Dawley rats	√ MAM 22 mg/Kg ip administration on GD 17	√ from PND 100	√ Male	√ Brain tissue levels	√ Single assessment	√ CTRL+VHI; CTRL+CBD10; CTRL+CBD30; CTRL+AM251; CTRL+HAL	√ Shapiro-Wilk test, two-way ANOVA, Fisher's LSD, *t*-test	√
Di Bartolomeo et al. (55)	√ Analytic, observational	√ Offsprings of THC-exposed Sprague-Dawley rats	√ THC 5 mg/Kg oral administration from GD 15 to PND 9	√ PND 10; from PND 100	√ Male	√ Brain tissue levels	√ Double assessment	√ CTRL+VHI; CTRL+CBD	√ two-way ANOVA, Bonferroni's correction, Mann-Whitney U test, *t*-test, Shapiro-Wilk test	√

AM251, CB1 antagonist/inverse agonist; ANOVA, Analysis of Variance; CBD, Cannabidiol; CBD10, Cannabidiol (10 mg/kg/day); CBD30, Cannabidiol (30 mg/kg/day); CTRL, Control group; GD, Gestational day; HAL, Haloperidol; ip, intra-peritoneal; LSD, Least Significant Difference; MAM, Methylazoxymethanol acetate; mg/Kg, Milligrams per kilogram; PEA, Palmitoylethanolamide; PND, Postnatal day; THC, Delta-9-tetrahydrocannabinol; VHI, Vehicle.

(44, 46, 48, 49) and schizophreniform psychosis (44)] or affective [e.g., bipolar disorder (BPAD) (46, 50)] psychoses at different stages of illness (Table 1). Two studies converged on the evidence of higher PEA levels in SCZ patients than in healthy controls (HC) (46, 48), one of which further suggesting significantly higher PEA plasma concentration in SCZ patients compared to patients meeting criteria for cannabis use disorder (CUD) or dual diagnosis of CUD and SCZ (48). Interestingly, compared to HC, unaffected twin siblings of SCZ patients also showed increased PEA levels, that did not differ from those of patients (46). Remarkably, antipsychotic (AP)-naïve first-episode psychosis (FEP) patients compared to HC showed a tendency to elevated PEA plasma levels and a significantly higher PEA/2-arachidonoylglycerol (2-AG) ratio, with both that subsided an average of 0.6 and 5.1 years after the initiation of AP treatment (49). The modulating effect of AP treatment over acylethanolamines (AEs) levels was also investigated through a double-blind, randomized, parallel-group, controlled clinical trial, showing elevated serum PEA concentration in cannabidiol (CBD)-treated SCZ patients, compared with those treated with the antipsychotic amisulpride (44). Studies measuring PEA levels among BPAD patients showed a less pronounced increase in affected and unaffected siblings of illness-discordant twin couples, when compared to HC (46). Further, a higher PEA plasma concentration was found in BPAD patients having first episode as depression than in those who had their first episode as mania (50) as well as in those who had at least one depressive episode than in patients who had no prior depressive episodes (50). Finally, PEA levels were increased according to the number of depressive episodes and the presence of depressive mood and anxiety, while inversely correlating with the number of hypomanic episodes, the number of hospitalizations, the duration of valproate (VPA) treatment, sexual desire, presence of flight of ideas, delusion, and grandiosity (50).

3.5. Palmitoylethanolamide quantitative central nervous system assessment in humans with schizophrenia

Two studies analyzed PEA levels in the CNS of patients with psychosis (43, 45) (Table 1). In particular, PEA levels were reported to be elevated in the cerebrospinal fluid (CSF) of SCZ and schizophreniform psychosis patients compared with healthy controls (HC) (43). Conversely, a study on postmortem brain samples from subjects diagnosed with SCZ compared to controls indicated lower PEA levels in the cerebellum of antipsychotic (AP)-free patients only (45). No significant differences in PEA brain quantification were detected among all study groups in the other brain areas investigated (45).

3.6. Palmitoylethanolamide quantitative brain tissue assessment in animal models of schizophrenia

In total, two studies evaluated PEA levels in the prefrontal cortex (PFC) (54, 55), hippocampus (HIP) (54), and nucleus accumbens (NAc) (54) of rats exposed to either prenatal methylazoxymethanol acetate (MAM) (54) or perinatal delta-9-tetrahydrocannabinol (THC) (55), which present with many SCZ-relevant biobehavioral deficits at neonatal age (55) and adulthood (54, 55) (Table 1). While modulating endocannabinoids [eCBs; e.g., anandamide (AEA) and 2-acylglycerol (2-AG) (54, 55)] and other acylethanolamines [AEs; e.g., oleoylethanolamide (OEA) (54)], both MAM and THC exposure did not significantly affect PEA levels in all investigated brain areas, as neither did the peripubertal exposure to cannabidiol (CBD) (54, 55), Cannabinoid receptor type 1 (CB1)-antagonist/agonist AM251 (54), and first-generation antipsychotic haloperidol (HAL) (54), compared to control conditions.

4. Discussion

This is the first systematic review of all evidence exploring the biobehavioral correlates of palmitoylethanolamide (PEA) in psychosis across human and animal studies. Unlike previous research in this field (38–40), the greatest majority of records included consisted of human studies. Existing reviews focusing on the role of the major phytocannabinoid cannabidiol (CBD) as a potential treatment for schizophrenia (SCZ) patients (20, 56, 57) gathered still preliminary evidence supporting its antipsychotic (AP) efficacy, while highlighting its advantageous side effect profile and good tolerability. Targeting similar pathways, PEA may be considered as a viable alternative to CBD with implications for many therapeutic areas, due to its established safety and the development of formulations maximizing its bioavailability (33, 37).

Overall, the present review demonstrated that PEA may be involved in different psychotic phenotypes. Also, it found initial evidence that PEA levels may reflect the severity of the disorder as well as the stage of illness. Evidence was obtained from both interventional studies addressing the AP potential of PEA supplementation, and observational studies of PEA tone in peripheral blood and in the central nervous system (CNS) in the context of clinical high-risk (CHR) for psychosis and psychotic disorders at different stages of illness.

Some important findings from this systematic review deserve to be highlighted. First, despite its promise, evidence regarding the therapeutic potential of PEA supplementation for psychosis is still limited (51–53) and provides findings about selective efficacy on specific symptoms. In particular, PEA add-on to conventional psychotropic medications did not significantly reduce positive psychotic symptoms (51–53), while ameliorating negative psychotic (52) and acute manic (53) symptoms. Importantly, while not being the focus of this review, results presented here are inconclusive about a potential role of PEA in ameliorating depressive symptoms among psychosis patients (53). Also, in only one study participants were clearly asked to avoid forms of cognitive behavioral therapies during the trial period (52), thus requiring future interventional studies to clearly

rule out a potential masking effect of add-on psychotherapy over symptoms.

Second, a line of research investigating endocannabinoids (eCBs) tone in blood among subjects with genetic vulnerability to psychosis (i.e., unaffected twins of SCZ patients) (46), CHR individuals (47), untreated first-episode psychosis (FEP) patients (49), and longer-course SCZ patients (46, 48), converged on the evidence of increased PEA plasma levels as compared to healthy subjects. Also, among CHR patients, the more severe the clinical picture (i.e., greater symptom severity) and the risk profile (i.e., more severe childhood trauma), the higher were the PEA levels (47). Based on PEA-related neurobiological mechanisms, the finding of augmented PEA release across different populations may reflect an endogenous attempt to restore homodynamic balance under disease conditions (28, 29). However, follow-up studies revealed that PEA plasma levels are no longer heightened in AP-treated SCZ patients after 0.6 years of treatment, and further decreased at 5.1 years from baseline (49), potentially suggesting that such biological self-regulation of PEA levels is lost as the diseases progresses. Interestingly, a 2- to 4-week CBD treatment among SCZ patients was associated with higher PEA levels (44) when compared with a 2- to 4-week AP treatment (44), possibly indicating a CBD-specific property in sustaining PEA tone.

Further, differently from SCZ spectrum disorders, PEA plasma level increase was less pronounced in bipolar disorder (BPAD) patients and unaffected twins of BPAD patients, when compared to healthy subjects (46), perhaps accounting for existing phenotypical discrepancies within the affective psychosis group. In fact, PEA plasma levels were greater among BPAD patients having first episode as depression and increased consistently as a function of the lifetime number of depressive episodes (50). Instead, the occurrence of positive psychotic symptoms, manic symptoms, and hypomanic episodes, was correlated with reduced PEA tone (50). Based on evidence that BPAD patients with manic onset have an older age at diagnosis and a longer duration of untreated illness than those with depressive onset (58), and that polarity of episodes over time often reflects polarity at onset (59), such different findings among BPAD patients may suggest a changing pattern in PEA levels over time. In other words, PEA plasma levels would be higher in the first phases of the disorder, while declining because of disease progression, in line with what observed for non-affective psychosis, and thus strengthening the rationale for its supplementation.

Third, CNS PEA levels were found to be augmented in the cerebrospinal fluid (CSF) of young adults with SCZ and schizophreniform disorder (43), whereas reduced in postmortem cerebellar samples of AP-free middle-aged SCZ patients (45), as compared to healthy controls. Similarly, brain PEA levels did not differ between AP-treated middle-aged SCZ patients and healthy controls (45). Again, it can be assumed that PEA levels are elevated in the early stages of psychosis, potentially reflecting an innate compensatory mechanism, before dropping concomitantly to disease progression. With reference to AP treatment, while on one hand it did not appear to increase PEA levels, on the other it is not clear if it prevented a more pronounced longer-term decrease (45).

Only two studies assessed PEA levels in the prefrontal cortex (PFC) of preclinical models of psychosis. They did not show any significant differences as compared to the control condition (54, 55). Further animal studies will need to yield a more robust understanding of the neurobiological mechanisms involving PEA in psychosis.

The findings of this review should be seen considering some strengths and limitations. Despite supporting PEA tone alterations in psychosis and effectiveness of PEA supplementation as a therapeutic strategy, research in this field needs to be expanded, especially to fully comprehend the potential of PEA supplementation as add-on therapy for psychosis across all its symptoms dimensions. Indeed, evidence points toward a beneficial effect of PEA over negative psychotic symptoms and acute manic symptoms, reasonably due to the protective role of the compound against altered neuroinflammation and related mechanisms (28, 29), while PEA effect over positive psychotic symptoms remains to be clarified. Further, future follow-up studies will have to investigate whether PEA effect is sustained in the longer-term. Besides, to date, evidence of PEA effect as monotherapy in the clinical stages preceding full-blown psychosis onset to prevent the risk of progression is totally lacking and is worth of exploration. Finally, PEA levels appear to be altered in psychosis. However, further clarification is needed as to whether PEA tone is altered to a different extent depending on the stage of illness and whether this can be considered a biomarker of psychosis. In line with this, whether any AP treatment may be beneficial through PEA tone modulation requires additional investigation. Biobehavioral comparisons between CBD and PEA are also worth of consideration, especially whether CBD antipsychotic effects are mediated by PEA signaling and similar effects can be obtained directly supplementing PEA. The latter would be inevitably more advantageous, due to its safer profile and shorter biological distance from the therapeutic target.

5. Conclusions

This systematic review provided a first overview of all observational and experimental studies of PEA and its biobehavioral correlates in psychosis. Although in its infancy and still limited, research in this field is primarily carried out on humans and provides evidence for both alterations in PEA signaling, implications for psychosis-related behavioral features, and benefits from PEA supplementation. In particular, PEA may be useful to improve negative psychotic symptoms and manic symptoms. Noteworthy, no serious adverse events were reported across all human studies investigating its administration, further supporting PEA potential effectiveness and elevated safety as a therapeutic intervention in psychosis.

Author contributions

Conceptualization, methodology, validation, resources, writing—review and editing, and visualization: RB, FP, AC, SB, MB, and MC. Software, data curation, writing—original draft preparation, supervision, and project administration: RB and MC.

Investigation: RB, MB, and MC. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

MC has been a consultant/advisor to GW Pharma Limited, F. Hoffmann-La Roche Limited, and GW Pharma Italy SRL, outside of this work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy of immersive extended reality (XR) interventions on different symptom domains of schizophrenia spectrum disorders. A systematic review

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Introduction: Extended reality (XR) is an umbrella term for virtual reality (VR) and augmented reality (AR), both novel vectors for therapeutic intervention modalities. In VR, head-mounted devices (HMD) allow interaction with three-dimensional virtual environments and simulated avatars, while AR overlaps virtual, simulated objects to observe physical reality. Treatment through immersive VR has been studied in psychiatry, including patients suffering from schizophrenia spectrum disorders, while there has not been much attention to AR technologies in psychiatry. Our systematic review aimed to examine the currently available literature regarding the treatment efficacy of immersive VR or AR technologies on different symptom domains of schizophrenia spectrum disorders, screen for potential adverse effects, and gather data on the technological and human resource requirements of such interventions to help guide future research.

Methods: We conducted a systematic literature review with database searches carried out between 9/2021 and 8/2022 through PubMed, Scopus, EBSCOhost Academic Search Premier, and Web of Science.

Results: We identified 2,157 records, 214 were assessed further for eligibility and 12 met inclusion criteria. All included articles studied immersive VR and none used AR technology. Included studies were heterogenous in nature, including AVATAR therapy (3) and CBT-based (5) VR interventions, as well as cognitive (2), social (1), and relaxation (1) training through VR. The comparison groups were either passive controls (waitlist and treatment as usual), therapeutic interventions (CBT and Integrated psychological treatment), passive VR environments, or traditional, comparable, non-virtual treatment modalities (social roleplay and progressive muscle relaxation training). Pooled together, the included studies on VR show positive treatment effects in all major symptom domains of schizophrenia spectrum disorders with hardly any adverse effects related to the intervention modalities.

Conclusions: In this review, we have showcased how different symptom domains can be targeted through VR interventions, highlighting VR as a potential new vector for a diverse range of psychosocial therapeutic modalities that allow for completely new possibilities in the treatment of schizophrenia spectrum disorders. VR technology still requires more research and validation. Our review also shows that there are currently no studies examining AR technology in the treatment of schizophrenia spectrum disorders, indicating a distinctive research gap.

KEYWORDS

schizophrenia, psychotic disorder, extended reality, virtual reality, augmented reality, treatment, rehabilitation, review

1. Introduction

Schizophrenia is a syndrome characterized by an assortment of heterogenous and diverse symptoms, with the core features usually divided into positive, negative, and cognitive categories (1). Positive (or psychotic) symptoms manifest as a loss of contact with reality, disorganization of thought, delusions, and hallucinations. The negative symptoms include impaired motivation, anhedonia, affective flattening, reduction of spontaneous speech, and social withdrawal while the cognitive symptoms manifest as a wide array of cognitive impairments. The positive symptoms tend to relapse and remit, while the negative and cognitive symptomology often causes severe and chronic, long-term functional impairment (1, 2).

Schizophrenia and its treatment impact the global economy widely, with estimations of the total economic burden of the patient population reaching an estimated range of 0.02 to 1.65% of the gross domestic product at national levels according to a systematic review (3). Most of the total costs (50 to 85%) were associated with indirect costs, which could indicate that the treatments and services as of now are insufficient to treat the full facet of the problems faced by the patient population (3). With refractory symptomology and associated comorbidity, treatment resistance, and reduced quality of life and life expectancy, as well as high disability levels in the patient group (1–4), the psychiatric field desperately requires new effective and easily deliverable treatment modalities for patients with schizophrenia to augment those already available.

Extended reality (XR) is an umbrella term, including technological solutions such as virtual reality (VR), augmented reality (AR), and mixed reality (MR), a technology utilizing aspects of both through environments in which the real world together with virtual objects and stimuli are presented together within a single percept (5–7). Multiple definitions for this continuum of virtuality and reality exist within the field (5–7). These modern tools are used to virtually generate environments or objects and allow for the creation of virtual scenarios that would be impossible or impractical to recreate in physical reality. The effortlessness of visualization and immersion into the virtually generated world can be utilized in a variety of ways to administer or augment therapeutic approaches while simultaneously allowing for the real-time observation, easy repetition, and scoring of such situations and protocols and their efficacy (5–7).

Fully or partially virtual worlds can be constructed in different ways. At present, four basic "reality" categories exist in the field: (1) physical reality or the real world; (2) augmented reality, where computer-based imagery is superimposed on the real-world image; (3) augmented virtuality, where real-life data are superimposed on the computer-generated world; and (4) VR, where the world is entirely computer-generated (6). Mixed reality, as priorly explained, mixes multiple categories (5).

Studies support the potential of VR technologies in their usability to treat psychiatric disorders ranging from, e.g., neurodevelopmental issues to psychoses to depressive and anxiety disorders (8), as well as an objective measurement tool in psychiatric diagnostics (9). The lucrative possibilities that real-time observation of the patient's psychological coping mechanisms in ecologically valid situations offer for the psychiatric research field have also been noted (10). VR technology can even be self-guided and ambulatory, possibly allowing for self-treatment at home (11). As a new tool, the evidence on VR technology is still somewhat preliminary and requires further validation.

In medical literature, there is a lot of ambiguity about the term "virtual reality," which is often confused or used interchangeably with computerized approaches utilizing screens and gamified treatment modalities such as serious or exergaming (12), the former meaning the use of games in treatment and the latter exercising via game-like systems. Some prior reviews (13, 14) have differentiated immersive VR from such approaches. Immersive VR uses Head-Mounted Devices (HMD) to visually transport the patient to a different, virtually simulated three-dimensional environment, isolating them visually from physical reality, meaningfully improving immersion. Usually, the patient can interact with the virtual environment through a controller and movement.

AR can be used through a larger variety of media; through smartphone and tablet cameras or specifically created headwear that enhances the physical reality with superimposed imagery (15). There is scarce research on AR in the treatment of psychiatric disorders with some explorative studies on neuropsychiatric disorders and phobias (16). AR has mostly been studied in surgical fields or medical education (6).

Prior reviews have examined the effects of immersive and non-immersive VR interventions and examined the validity of VR technology as an assessment and treatment tool for neuropsychiatric, psychotic, and schizophrenia spectrum disorders or with paranoia and cognition as targets for intervention or evaluation (13, 14, 17, 18).

To expand and update on these prior reviews, we carried out a systematic review to study the available evidence on the treatment efficacy of immersive VR and AR technologies in the treatment of different symptom domains of schizophrenia spectrum disorders.

To complement prior reviews and to better clarify the effects of the interventions in the studied population, we chose to include only articles studying the treatment effects of immersive XR technologies (both VR and AR, as a clear distinction between the two might not always be evident), focusing only on patients suffering from schizophrenia spectrum disorders. For these goals, we chose to exclude studies utilizing non-immersive screen-based technologies for treatment and XR-based methods for the assessment of symptoms. We also excluded studies of healthy populations (e.g., trait paranoia or those in ultra-high risk for psychoses) and studies including populations with etiologically clearly different causes for psychoses (such as mood disorder-based psychoses). We aimed to examine the reported effects for all major symptom categories of schizophrenia spectrum disorders (namely positive, negative, and cognitive symptoms), including social and comorbid symptomology as categories as well.

To control the quality of the studies, only peer-reviewed studies with clear comparison groups were chosen to be included and a risk-of-bias assessment was carried out. Furthermore, to better inform future research and clinical work for individualized treatment and study protocols, we also screened the studies for possible adverse events and gathered available data on the technological and human resources requirements of included studies.

2. Methods

We performed a systematic literature search using PubMed, EBSCOhost Academic Search Premier, SCOPUS, and Web of Science databases on 28 September 2021.

The search words were chosen so we could identify all relevant studies targeting the population, interventions, and intervention targets of interest. Words near in meaning were also used to make sure no important studies would be missed. The following search words and their permutations were used with Boolean logic operators as each database utilized a slightly different search engine:

(Schizophrenia, "schizophrenia spectrum disorder," "psychotic disorder," psychosis) AND ("Virtual Reality," VR, "Virtual Reality Exposure Therapy," "Virtual Reality Therapy," "Augmented Reality," AR, "Extended reality," XR, "Mixed reality," MR, "Augmented Virtuality," "Avatar therapy") AND (rehabilitation, training, application, game, intervention, therapy, treatment) AND (negative, cognitive, "negative symptom," "cognitive symptom," social, refractory, motivation, function, impairment, affect, anhedonia, withdrawal).

Depending on the possibilities of each database, searches were restricted to clinical trials and randomized controlled trials, and articles in peer-reviewed medical journals written in English language. All databases were searched using search fields for keyword, title, and abstract information. For PubMed, appropriate MeSH terms were also used.

After the literature search, article lists from each database were imported into Mendeley reference management software (Ver 1.19.8., Mendeley Ltd). In Mendeley, we ran a check for duplicates, which were then excluded. Then, we screened the articles based on article title and abstract until only relevant articles were left for further review.

To update the search results, a complementary database search was conducted with the same search parameters on 22 August 2022.

The relevant articles were manually read to decide whether they were to be included in the review. In case of uncertainty, the article was discussed between R.H. and M.L. (Roope Holopainen and Markku Lähteenvuo, respectively) until a decision to include or not to include the article in the review was reached.

Articles were included based on the PICO (Patient, Intervention, Comparison, Outcome) protocol (19).

The inclusion criteria were as follows:

Original clinical trials and randomized controlled trials reported in English.

1. Studies targeting patients suffering from schizophrenia spectrum disorders.
2. Studies using immersive virtual reality, augmented reality, or similar immersive technology for intervention. Defined as the use of a head-mounted device for immersion.
3. Studies including a comparison/control group.
4. Studies including outcome measures targeting refractory positive, negative, cognitive, or social domain symptoms or comorbid psychiatric symptomology.

To assess the risk of bias in the studies included, we used the Cochrane risk-of-bias tool ROB 2, meant to assess randomized trials (20), and the ROBINS-I tool, meant for assessing non-randomized studies of interventions (21). The risk assessments were carried out on primary outcomes measuring targeted symptoms.

3. Results

The systematic literature search yielded 2,247 results. After removing duplicates, 1,848 results remained. After exclusion based on title and abstract, 176 articles were selected for further review.

After conducting a complementary search, 384 articles were identified, and after the removal of duplicates, 309 remained; 38 articles were selected for further review after exclusion based on name and abstract.

In total, 214 articles were analyzed, and 202 articles were excluded. The reasons for exclusion were as follows: article not in English ($n = 10$), review, theoretical paper, brief or a conference paper ($n = 36$), case study ($n = 5$), study protocol paper ($n = 13$), the article did not study an intervention with an effect on the studied outcome measures ($n = 85$), used methods were not immersive VR or AR technology ($n = 32$), did not study patients with a schizophrenia spectrum disorder ($n = 8$), the article did not have a comparison group ($n = 3$), and not the original study population or a sub-cohort ($n = 10$).

Three of the exclusions were discussed between RH and ML and were excluded (1) because the immersivity of VR could not be found out in the article and (2) because of mixed patient populations.

After careful evaluation of each article, 12 articles were included in the review. For the full flowchart of the systematic search, see the PRISMA flowchart (22) in Figure 1.

4. Intervention types

4.1. Augmented reality interventions

We could not identify any study utilizing immersive AR technology in the treatment of patients with schizophrenia.

4.2. Virtual reality interventions

We could broadly differentiate five intervention types utilizing immersive VR in this review: social training, cognitive training, cognitive behavioral therapy-based interventions, avatar therapy-based interventions, and relaxation training. The characteristics of different intervention modalities and research studies are listed in Tables 1, 2, respectively. The risk-of-bias assessments are presented in Figures 2, 3.

One study utilized VR social training (23), two VR cognitive training (24, 31), five VR-CBT-based intervention methods (11, 25, 26, 30, 32), three avatar therapy (27, 29, 33), and one relaxation training (28).

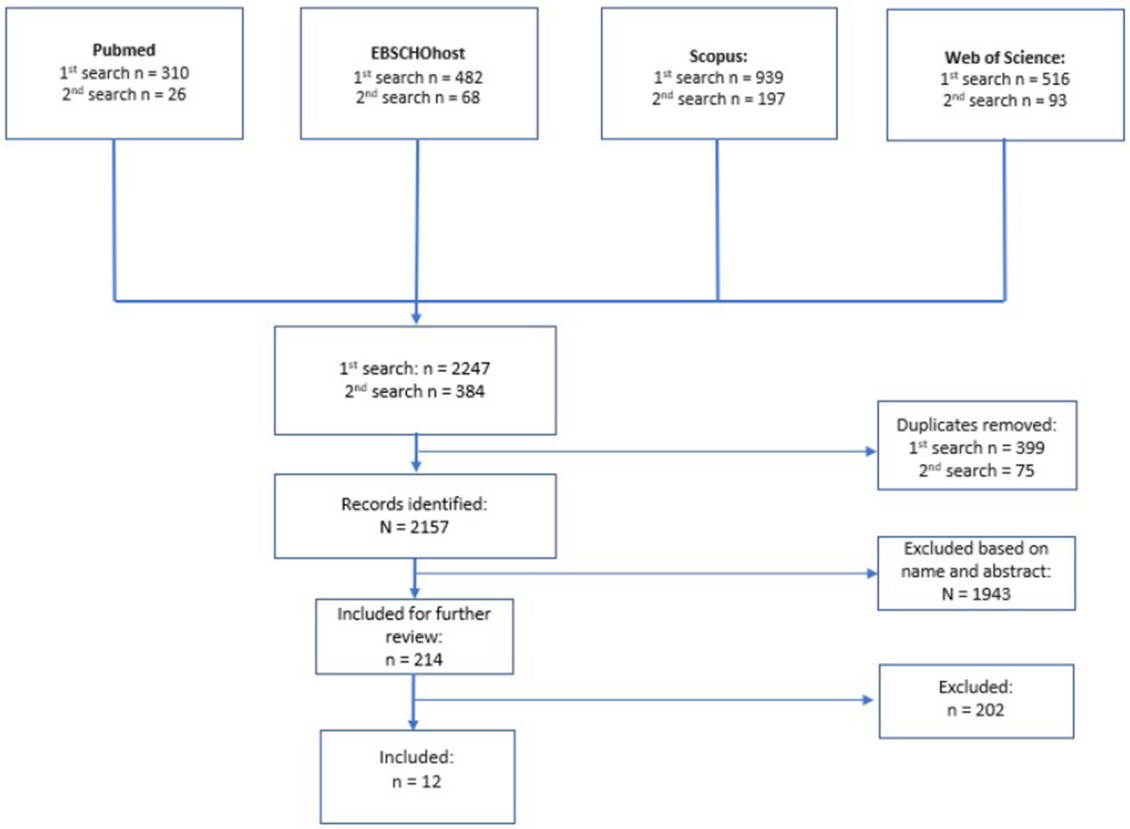

FIGURE 1
Modified PRISMA flowchart of the systematic literature search.

TABLE 1 Intervention characteristics.

Intervention modality	Description
VR Social training	Immersive virtual environments, scenarios, game avatars, and dialogue are used to help train the patient to be more socially fluent.
VR Cognitive training	Diverse virtual reality tasks are used to help patients rehabilitate certain aspects of their (neuro)cognition.
VR CBT-based intervention	Immersive virtual environments are used to augment cognitive and behavioral therapeutic methods, often with the goal of social exposure.
Avatar therapy-based intervention	Avatar therapy is a therapeutic method, which uses a virtual, audiovisual construction of the patient's audiovisual hallucination through therapist-guided roleplay to practice different responses. VRT and AVATAR therapy are differentiated by the use of HMD as the vector of intervention. CATS adds real-time full-body and facial motion capture to VRT to help the therapist animate the avatar.
VR Relaxation training	Virtual environment is used in the augmentation or creation of a relaxing effect.

VRT, Virtual reality-assisted therapy; CATS, virtual reality-based computer AT system.

5. Rehabilitation of symptom domains

5.1. Refractory positive symptoms

5.1.1. Avatar therapy interventions

Du Sert et al. (27) carried out a pilot study for a randomized, partial cross-over clinical trial for avatar therapy-based VR-assisted therapy in comparison to treatment-as-usual (TAU). The patients suffered from treatment-resistant schizophrenia (defined as not responding to at least two antipsychotic medications), with half of the final sample unresponsive even to clozapine. Also, 19 patients (with 15 finishing the treatment and follow-up) were randomly assigned in a 1:1 manner to either 7 weeks of VR-assisted (avatar) therapy (VRT) or control condition (TAU) without blinding. After the first treatment period, the TAU group received the VRT as well. Follow-up was scheduled 3 months after the last VRT therapy session.

The outcome measures for the study were changes in psychotic symptoms (Psychotic Symptoms Rating Scale, PSYRATS) and beliefs related to audiovisual hallucinations (AVH) (Beliefs About Voices Questionnaire-Revised, BAVQ-R), positive and negative symptoms (PANSS), depression symptomology (BDI-II), and quality of life were also assessed (Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form). The presence of

TABLE 2 Study characteristics.

Study	Year	Study design	Country	Diagnosis	Total sample size	Intervention type	Control condition	Primary Outcome measure	Secondary Outcome measures	Main finding
Park et al. (23)	2011	RCT	South Korea	Schizophrenia	64/91	VR Social Training	Traditional social roleplay	Social skills: voice quality, nonverbal skills, conversational properties. Social competence: unstructured roleplay test (10 roleplay tests, SBS)	RAS, RCS, SPSI-R, Interest-in-Participation Questionnaire, and Right-or-wrong questions regarding the session.	Social skills training (SST) through virtual reality roleplay improved conversational skills and assertiveness more than SST through traditional roleplay, but nonverbal skills less.
La Paglia et al. (24)	2016	Clinical trial	Italy	Schizophrenia	15	VR Cognitive training	Integrated Psychological Treatment	MMSE, FAB, TMT (A, B, B-A), ToL, WCST	-	VR cognitive training improved neurocognition (general cognitive functioning, planning skills, and sustained attention) in comparison to integrated therapy.
Freeman et al. (25)	2016	RCT	UK	Schizophrenia, schizoaffective disorder, delusional disorder, or psychosis NAS	30	VR CBT-based intervention.	VR environment exposure	Conviction of paranoid beliefs, distress related to the beliefs, real-life social behavior test (VAS-scale).	-	A brief immersive VR cognitive therapy (dropping of safety behaviors) led to a significant reduction in paranoid beliefs and distress in comparison to simple VR exposure.
Pot-Kolder et al. (26)	2018	RCT	Netherlands	Psychotic disorder	116	VR CBT-based intervention	Wait-list	ESM	SBQ, GPTS, BDI, SOFAS, MANSA, BCCS, BARS, IPQ, SSQ	Immersive VR CBT -therapy reduced paranoid ideation, momentary anxiety, and safety behaviors in real-life social situations, but did not significantly increase social participation. The results remained significant at follow-up.

(Continued)

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TABLE 2 (Continued)

Study	Year	Study design	Country	Diagnosis	Total sample size	Intervention type	Control condition	Primary Outcome measure	Secondary Outcome measures	Main finding
Du Sert et al. (27)	2018	RCT	Canada	Schizophrenia or schizoaffective disorder.	19	Avatar therapy-based intervention	TAU	PSYRATS	BAVQ-R, Q-LES-Q-SF, BDI-II, PANSS	Avatar therapy in immersive virtual reality (VRT) showed a large therapeutic effect in treatment-resistant schizophrenics compared to TAU. The effects remained significant at 3-month follow-up.
Fusco et al. (28)	2018	RCT	Italy	Schizophrenia spectrum disorder or other psychotic disorder	22	VR relaxation training	PMR	BAI, STAI-Y	-	Progressive Muscle Relaxation (PMR) in immersive VR was more effective in reducing anxiety than traditional PMR.
Dellazizzo et al. (29)	2021	RCT	Canada	Schizophrenia or schizoaffective disorder.	74	Avatar therapy-based intervention	CBT	PSYRATS	BAVQ-R, Q-LES-Q-SF, BDI-II, PANSS	Avatar therapy in immersive virtual reality (VRT) found similar and even superior effects compared to CBT in treatment-resistant schizophrenics, with effects lasting at 12-month follow-up.
Vass et al. (30)	2021	RCT	Hungary	Schizophrenia	17/21	VR CBT-based intervention	Passive VR environment	PANSS, neurocognitive deficits (RBANS, WCST), BCMET, faux pas test, cartoon stories, Hungarian metaphor and irony test, LQoLP, SSQ, patient's subjective opinion of intervention, subjective evaluation of perceived changes by a relative of a patient.	-	A Theory of mind intervention through immersive virtual reality led to diverse effects in comparison to passive VR environment exposure in patients suffering from schizophrenia.

(Continued)

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TABLE 2 (Continued)

Study	Year	Study design	Country	Diagnosis	Total sample size	Intervention type	Control condition	Primary Outcome measure	Secondary Outcome measures	Main finding
Wang et al. (31)	2022	RCT	China	Schizophrenia	64	Cognitive training	TAU	B-CATS (Including DSST, TMTA, and B, AF	-	Intensive, immersive, and active VR serious games in addition to standard psychiatric care can improve working memory and executive function in patients with schizophrenia.
Freeman et al. (11)	2022	RCT	UK	Schizophrenia Spectrum Disorder or an affective disorder with psychotic symptoms	346	VR CBT-Based intervention	TAU	O-AS	MIA, CSSR, RGPTS, PWQ, PHQ, O-BAT, EQ-5D, ReQoL, QPR. Activity levels are measured using actigraphy (over 7 days), and a time budget assessing meaningful activity (that considers the complexity of activities and effort required).	TAU augmented by automated immersive VR therapy led to significant reductions in anxious avoidance of, and distress in, everyday situations compared to usual care alone in psychosis patients. Especially in severe agoraphobia.
Cella et al. (32)	2022	RCT	UK	A documented episode of psychosis or a schizophrenia diagnosis.	30	VR CBT-Based intervention	TAU	GAS	CAINS, SNS, WSAS, EEfrT, WCST, semi-structured subjective feedback on the intervention.	TAU augmented by CBT delivered through immersive virtual reality was useful in supporting patients' recovery goals in comparison to TAU alone in a pilot RCT feasibility study.

(Continued)

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TABLE 2 (Continued)

Study	Year	Study design	Country	Diagnosis	Total sample size	Intervention type	Control condition	Primary Outcome measure	Secondary Outcome measures	Main finding
Liang et al. (33)	2022	RCT	China	Schizophrenia	65	Avatar therapy-based intervention	CBT	PSYRATS	P300 recording, BAVQ-R, PANSS, HAMD, HAMA, SES, Q-LES-Q-SF.	Avatar Therapy-based intervention through immersive VR (CATS) was similar in treatment effect of AVH in comparison to CBT in patients with treatment-resistant schizophrenia. The changes in PSYRATS and BAVQ-R scores correlated with changes in P300 amplitudes.

Abbreviations for outcome measures: SBS, Trower's Social Behavior Scales; RAS, Rathus Assertiveness Schedule; RCS, Relationship Change Scale; SPSI-R, Social Problem Solving Inventory -Revised; MMSE, Mini-Mental State Examination; FAB, Frontal Assesment Battery; TMT A; B; B-A, Trail Making test (forms A,B and B-A; respectively); ToL, Tower of London; WCST, Wisconsin Card Sorting Test; VAS, Visual Analoq Scale; ESM, Experience Sampling Method; SBQ, Safety Behavior Questionnaire; GPTS, Green Paranoid thoughts Scale; SIAS, Social Interaction Anxiety Scale; BDI, Beck Depression Inventory; SOFAS, Social and Occupational Functioning Assessment Scale; MANSA, Manchester Short Assessment of Quality of Life; ISMI, Internalized Stigma of Mental Illness questionnaire; BCCS, Brief Core Schema Scale; DACOBS, the self-reported Davos Assessment of Cognitive Biases Scale; BARS, Brief Adherence Rating Scale; IPQ, Igroup Presence Questionnaire; SSQ, Simulator Sickness Questionnaire; PSYRATS, Psychotic Symptoms Rating Scale; BAVQ-R, Beliefs About Voices Questionnaire-Revised; Q-LES-QF, Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; BDI-II, Beck Depression Inventory-II; PANSS, Positive and Negative Symptoms Scale; BAI, Beck Anxiety Inventory; STAI-Y, State Trait Anxiety inventory form Y; RBANS, Repeated Battery for the Assessment of Neuropsychological Status; BCMET, Baron-Cohen Mind in the Eyes Test; LQoLP, Lancashire Quality of Life Profile; B-CATS, Brief Cognitive Assessment Tool for Schizophrenia; DSST, Digital Symbol Substitution Test; AF, Animal Fluency; O-AS, Oxford Agoraphobic Avoidance Scale; MIA, Agoraphobia Mobility Inventory-Avoidance scale; CSSR, Columbia Suicide Severity Rating Scale; RGPTS, Revised Green et al. Paranoid Thoughts Scale; PWQ, Paranoia Worries Questionnaire; PHQ9, Patient Health Questionnaire; O-BAT: Oxford-Behavioral Assessment Task; EQ-5d, Quality of life - five-level EQ-5D; ReQoL, Recovering Quality of Life questionnaire; QPR, Questionnaire about the Process of Recovery; GAS, The Goal Attainment Scaling; CAINS, The Clinical Assessment Interview for Negative Symptoms; SNS, The Self-evaluation of Negative Symptoms; WSAS, The work and social adjustment scale; EEfrT, Effort Expenditure for Reward Task; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; SES, Rosenberg self-esteem scale. Abbreviations for treatments: VR, Virtual Reality; PMR, Progressive muscle relaxation; CBT, Cognitive Behavioral Therapy; TAU, Treatment As Usual; VRT, Virtual Reality Assisted Therapy; CATS, virtual reality–based Computer Avatar Therapy System . Other abbreviations: AVH, Audiovisual hallucination; ESM, Experience Sampling Method; SBQ, Safety Behavior Questionnaire; GPTS, Green Paranoid.

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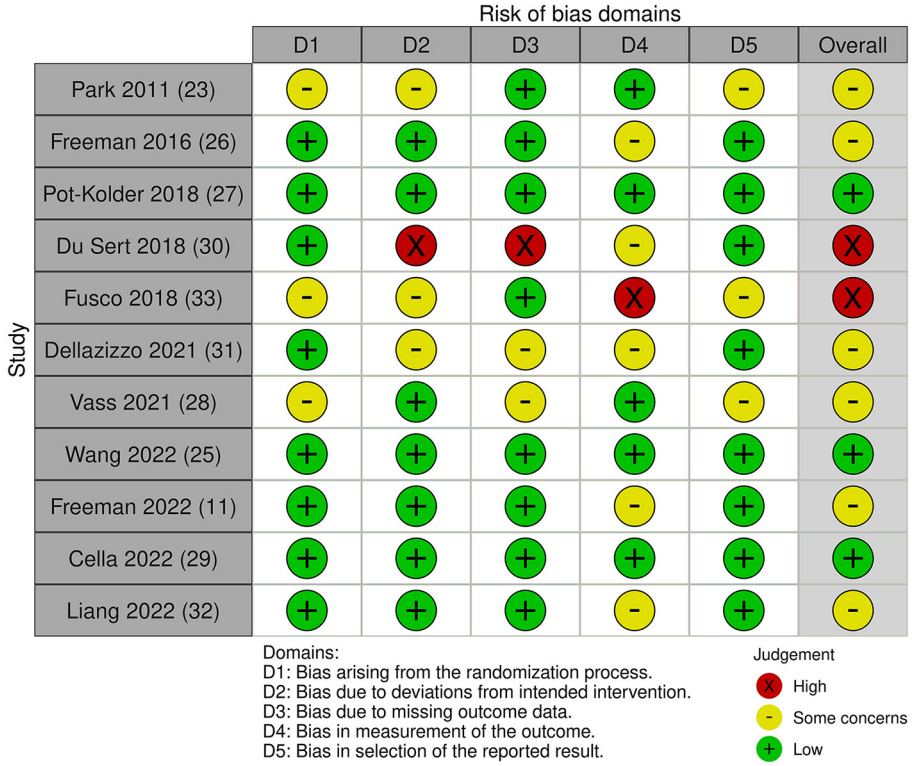

FIGURE 2
Risk-of-bias assessment for included studies (randomized controlled trials).

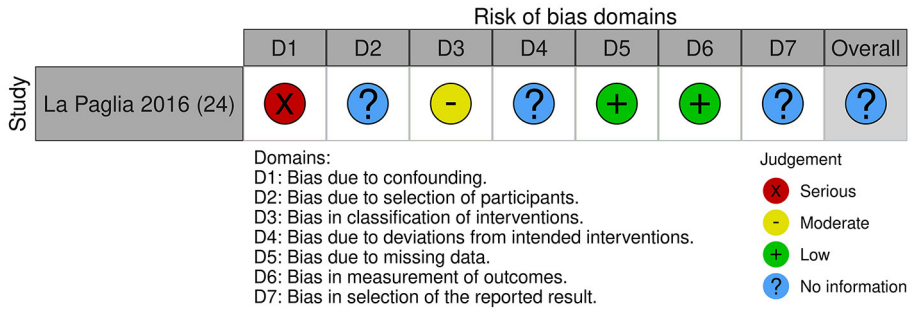

FIGURE 3
Risk-of-bias assessment for included studies (clinical trials).

persecutory AVH, fear, and anxiety after each session were also measured on a 0–10 numerical scale.

Patients in the experimental group received weekly six 45-min sessions of avatar therapy and before this, one meeting was used to create a personified, virtual avatar of their persecutory AVH (most distressing or dominant in case of multiple AVHs) which would be controlled by the therapist in subsequent sessions. The sessions included confronting the avatar to improve emotional regulation and assertiveness and gain self-esteem, as well as consolidation sessions to apply previously learned skills in the scenario. Throughout VRT, the avatar's interactions grew less abusive and more supportive. Three patients received 1 to 4 additional consolidation sessions.

The psychiatric symptoms remained unchanged throughout the TAU period while there was a significant reduction in AVH symptoms seen ($p < 0.01$), especially regarding distress ($p < 0.001$), omnipotence, and malevolence related to the AVH ($p < 0.05$) during VRT. General psychiatric symptoms measured by PANSS and BDI were also reduced significantly ($p < 0.05$) and an improvement in quality of life was seen ($p < 0.05$). Improvements remained significant at the 3-month follow-up. There was no significant correlation between the number of therapy sessions and clinical outcomes. Patients also reported significant subjective decreases in anxiety and fear beginning at week 4 as the first 2 weeks of the intervention were seen as most anxiogenic and led to dropouts after the first sessions.

Dellazizzo et al. (29) expanded on the du Sert study with a 1-year-long RCT comparing VR-assisted therapy in adjunction to TAU ($n = 37$) to cognitive behavioral therapy in adjunction to TAU ($n = 37$) in patients with treatment-resistant schizophrenia. The intervention comprised 7–9 sessions administered weekly.

The study found a significant reduction in AVH symptoms between baseline and 3-month follow-up in both groups assessed by PSYRATS-AH with large effect sizes for VRT and small-moderate for CBT ($p < 0.001$, $d = 1.080$ for VRT; $p = 0.001$, $d = 0.555$ for CBT), most prominently on the frequency of and distress related to AVH ($d = 0.701$ and $d = 0.998$, respectively). VRT also showed significant improvement regarding persecutory beliefs, whereas the CBT findings were on trend level and not statistically significant. Both interventions showed moderate effects on persecutory beliefs about voices. Depressive symptoms diminished in both treatment groups and overall psychiatric general symptoms as measured with the PANSS significantly diminished with VRT ($p = 0.008$), while not significantly in the CBT arm. Most effects were observed on the excited/hostility and anxio-depressive subscales ($p < 0.001$). The effect of VRT was of moderate range for overall symptomatology and was found to be larger for affective symptoms. In addition, VRT significantly ameliorated quality of life with an effect of moderate magnitude.

Results for VRT were maintained long term up to the 1-year follow-up with no statistically significant differences from the 3-month follow-up for most outcomes, except for the engagement subscales of the BAVQ-R for VRT, which was found to diminish significantly ($p = 0.002$) from 3- to 12-month follow-up and returned to baseline. CBT showed no statistically significant differences in any of the outcomes.

Liang et al. (33) carried out a pilot RCT where they compared a 7–9-session VR-based computerized avatar therapy system (CATS) treatment to CBT in patients with treatment-resistant schizophrenia. Both groups continued to receive their normal psychopharmacologic treatment during the study, with no changes to dosage. The study recruited 65/85 eligible patients with 30/32 in the experimental group and 28/33 in the control group finishing the treatment and final assessments.

The intervention included 1 avatar creation session and six 60-min therapeutic sessions divided into three parts: (1) predialogue (review, discussion of objectives, and agree to focus on patient–avatar dialogue); (2) trialogue of 10–15 min among therapist (in a separate room), patient, and avatar of the AVH; and (3) postdialogue focusing on the feedback following the trialogue. The dialogue with the avatar was provided to the patient in MP3 format for continued use at home. The study measured hallucinations (PSYRATS), beliefs regarding hallucinations (BAVQ-R), psychiatric symptomology (PANSS, Hamilton Depression and Anxiety Scales, HAMD HAMA), self-esteem (Rosenberg self-esteem scale, SES), and quality of life before and after interventions and at 12-week follow-up. The study also measured electroencephalographic (EEG) data for visual P300 recording at baseline and post-interventions. The visual P300 component is an attention-dependent event-related potential (ERP), a neurological marker considered to reflect complex cognitive functions, such as selective attention and working memory.

From baseline to 12-week follow-up, the severity of AVH as measured by PSYRATS decreased significantly over time for both treatment groups ($p < 0.001$ for CATS and $p = 0.012$ for CBT) showing a reduction in distress related to ($p < 0.001$ for CATS and $p = 0.020$ for CBT) and frequency of AVH ($p = 0.002$ for CATS and $p = 0.032$ for CBT), with a large effect size for CATS and moderate for CBT (effect on AVH symptoms for VRT $d = 1.230$ and CBT $d = 0.713$). The CATS also significantly reduced beliefs of omnipotence regarding the AVH, while the effect for CBT was trend-level and not statistically significant. Improvement in positive symptoms for PANSS, self-esteem, and quality of life was only seen for the CATS group. For affective symptoms, the study did not find an interaction effect, but a significant time effect with the CATS group showing improvement in HAMA scores ($p = 0.022$). The study found significantly higher P300 amplitudes in the CATS group in comparison to the CBT group in post-intervention measures. The P300 amplitude change correlated with changes in PSYRATS total scores and BAVQR-O in the CATS group. No correlations were found for the CBT group.

5.1.2. CBT-based interventions

Freeman et al. studied the effects of cognitive therapy tools in brief immersive VR therapy sessions in comparison to a simple VR exposure (in the same environment) in a small non-blinded RCT (25). The included 30 patients suffering from persecutory delusions with a diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, or psychosis NAS were randomized either to the threat belief testing group ($n = 15$) or VR exposure group ($n = 15$).

For intervention, there were two VR environments that patients could move in: an underground train and a lift. The number of game avatars present varied depending on difficulty from 0 to 22 in the train and from 2 to 6 in the lift. Both groups used the same virtual environment but were given slightly different instructions at the start of immersion in the virtual environment. The first part of the instructions for both groups was the same, with a short explanation and encouragement for virtual exposure as a treatment tool. The last part of the instructions differed between the two groups; the exposure group was encouraged to use their safety behaviors while the therapy group was encouraged to drop them and test their threat beliefs in a VR environment. The whole intervention and testing took ~60–90 min with 30 min spent inside the VR environment.

Before the intervention, the patient's conviction in the delusions was rated, after which they completed a 5-min behavior testing in a real-life social environment of their choice and which they wanted help with. The tests were done either at a patient's home or at a hospital ward. The patients were then brought to a VR laboratory for the intervention, which included seven short VR periods and delusion conviction ratings before and after VR immersion. The key variables, the conviction of persecutory beliefs and distress, were assessed with visual analog scales at the end and beginning of the testing day, and before and after VR immersion. After the VR intervention, the behavior test and delusion ratings were repeated at home. The study also measured PANSS (positive subscale), PSYRATS (delusions), the

Safety Behaviors Questionnaire (persecutory beliefs), BAI, and BDI before the testing.

The study found that the threat testing group was significantly more likely to move inside a social VR environment in comparison to the control group (additional 10.5 m, $p < 0.001$). There was no difference in the movement between the groups in a VR environment empty of people (virtual game avatars). For conviction in paranoid beliefs, a gradual and significant reduction for the threat testing group was seen throughout the VR scenarios while the scores remained stable in the control group. The conviction ratings by the final scenario were significantly more reduced in the threat belief testing group in measures of scores (additional 20.9% reduction, $p < 0.001$) taken before VR and in post-VR scores (additional 12.9% reduction, $p = 0.039$), with a mixed model of both variables showing additional reduction by 17.9% ($p < 0.001$). After the first scenario, there was no within-session (pre- to post-score) change in allocation to level, indicating that both variables are changing in parallel as the intervention went on. The same pattern of gradual reduction in the testing group was seen in distress related to paranoia, while the scores were stable in the exposure group. With the means of pre- and post-scores measured over the intervention, by the last scenario, there was a significantly higher reduction in the threat testing group in comparison to the control group (additional reduction of 17.6 points, $p = 0.001$). Overall, there was a significantly higher reduction (22%, $p = 0.024$, $d = 1.3$.) in the level of conviction to the paranoid beliefs in the testing group between the start and end of testing (79.8 to 46.5%) compared to the exposure group (78.5 to 67.6%).

For the repeated real-life social situation behavior test, the threat belief testing group found the task less distressing than the exposure group. After controlling for the level of distress caused by the real-world situation at the first time of entering, the brief VR cognitive therapy significantly reduced distress in the real-world situation in comparison to the exposure group (additional 19.6% reduction, $p = 0.020$, $d = 0.8$).

Pot-Kolder et al. (26) studied the effects of immersive virtual reality-based cognitive behavioral therapy in comparison to wait-list control on paranoid ideation and social participation in outpatients with psychotic disorder in a single-blinded RCT.

In total, 116 patients suffering from schizophrenia, schizoaffective disorder, delusional disorder or not-otherwise specified psychotic disorder, and simultaneous avoidant behavior and paranoid ideation were recruited from seven mental health centers. The participants were randomized in a 1:1 manner into a group receiving either VR-CBT treatment in addition to TAU ($n = 58$) or to wait-list control group (TAU, $n = 58$), who were then subsequently offered VR-CBT after a follow-up period. The physicians treating patients were asked to not change patient medication during the study period.

The intervention was CBT in an immersive VR environment (four locations: street, bus, cafe, and supermarket). Stimuli were controlled by the therapist and thus the experiences were personalized for each patient. The goal of the VR exercises was to guide exposure to cues in social environments that caused fear, paranoid ideation, and safety behaviors. The therapist communicated with the patients and guided them to explore and challenge thoughts and behaviors and to test harm expectancies in the VR environment. There was no homework or tasks given to patients between sessions. The VR-CBT was delivered in 16 sessions over 8 to 12 weeks, with each session lasting 60 min. The session included 40 min of social VR exercises and 20 min of planning and reflecting on exercises. Patients in both groups received treatment as usual, such as antipsychotic pharmacologic treatment. The control group had regular contact with psychiatrists and psychiatric nurses.

As the primary outcome, the study measured social participation; objectively (amount of time spent with others) and subjectively (momentary paranoia, perceived social threat, and momentary anxiety in company) through an Experience Sampling Method (ESM), a structured diary through a carried electronic device called PsyMate. It beeped at quasi-random time intervals 10 times per day for 6 days and asked patients to report the momentary thoughts, feelings, symptoms, social contexts, and appraisals of the contexts (7-point Likert scales). The patients had 15 min to answer, and for the measures to be included, at least one-third of the beeps had to be included (minimum 20 measurements). Time spent with others was measured by the proportion of beeps that participants reported to be in the company of others (excluding mental health professionals). Secondary outcomes for symptom measures were the Safety Behavior Questionnaire-Persecutory Delusions, Paranoid Thoughts Scale, Social Interaction Anxiety Scale, and Beck Depression Inventory, and for functional outcomes the Social and Occupational Functioning Assessment Scale and Manchester Short Assessment of Quality of Life. Stigma was assessed with the Internalized Stigma of Mental Illness questionnaire. To examine the putative working mechanisms of the therapy, cognitive constructs were assessed with the Brief Core Schema Scales and the self-reported Davos Assessment of Cognitive Biases Scale. Medication adherence was measured with the Brief Adherence Rating Scale. After the fourth and eighth sessions, presence in VR was assessed with the Igroup Presence Questionnaire and Cybersickness symptoms through the Simulator Sickness Questionnaire. The assessments were done at baseline, after the treatment period (3 months from baseline), and at follow-up (6 months after baseline). The analysis was intention-to-treat, and patients who dropped out were included.

In total, 11 patients in the VR-CBT group dropped out, 17 changes in psychiatric medication were reported, 96 participants completed the post-treatment assessment sufficiently, and 87 participants completed the follow-up. Both groups were similar at baseline, except for the use of safety behaviors, which was significantly lower in the control group.

The VR-CBT in comparison to TAU reduced momentary paranoid ideation ($p < 0.0001$, effect size $= -1.49$) and momentary anxiety ($p = 0.0002$, effect size $= -0.75$), with effect sizes remaining significant at follow-up. VR-CBT did not significantly improve social participation. Time spent with others decreased by 2.4% in the control group between baseline and the follow-up assessment, whereas the amount of time marginally increased by 0.3% in the VR-CBT group. No significant interaction effects were noted for perceived social threat at the post-treatment or follow-up assessments.

Compared with the control group, the use of safety behaviors decreased significantly in the VR-CBT group at both the post-treatment and follow-up assessment and at post-treatment (score of 28.8 in SBQ at baseline to 21.1 at post-treatment and 20.2 at follow-up). The largest reduction at the post-treatment visit was for the *in situ* safety behaviors subscale. Treatment effects of VR-CBT on paranoid ideation were significant in comparison to the control group: at the post-treatment and follow-up assessments regarding levels of ideas of persecution and social reference (Reduction in paranoid thoughts scale scores of 41.2 at baseline to 33.4 at post-treatment and 31.4 at follow-up for persecutory ideation and similarly from 43.6 to 35.4 and 34.0 for social reference). No significant change between groups was found for depression and anxiety or quality of life. The VR-CBT group had improvements in self-stigmatization and social functioning at follow-up, whereas the control group did not.

Part of the treatment effect for paranoid ideation at the follow-up was mediated by a change in safety behaviors and a change in social cognitive problems. Those who received VR-CBT used fewer safety behaviors and reported fewer social cognition problems than those in the control group, subsequently experiencing less paranoid ideation. The direct effect of the treatment on paranoid ideation was no longer significant after the inclusion of the mediators in the model. No significant mediators of VR-CBT were found for momentary paranoia. The total effect (independent of mediators) and direct effect (including the mediators) of treatment were both significant for momentary paranoia. Regarding the feeling of presence in the VR environments, participants reported sufficient presence.

5.2. Negative symptoms

Cella et al. (32) studied the effects of augmentation of normal psychiatric treatment (TAU, treatment as usual) of schizophrenia with immersive VR in comparison to TAU only for goal attainment, negative symptomology, and functioning.

In a single-blind, randomized, and controlled feasibility study, 29 out of 30 eligible patients with a documented episode of psychosis and/or schizophrenia diagnosis were randomized into either a treatment or control group (Experimental group, $n = 14$, TAU, $n = 15$).

The intervention studied was a 12-session virtual reality-negative symptom therapy (V-NeST) based on CBT and cognitive remediation techniques supported by virtual environments, where patients are encouraged to approach motivational and unique challenges ranging in motivational requirement (such as lounge for passive activities; music or watching tv, or a factory, game room, or a social space, where patients were asked to perform tasks or interact with avatars). The minimum number of intervention sessions to attend was six. The experiences were guided, supported, and discussed with a graduate-level psychotherapist with clinical experience with the target population. The therapist received tailored training and weekly supervision.

As the primary outcome, the study measured Goal attainment scaling (GAS), a scale reflecting the achievements of patients' pre-selected treatment goals. For secondary outcomes, Clinical assessment interview for negative symptoms (CAINS), self-evaluation of negative symptoms (SNS), Work and social adjustment scale (WSAS), and Effort expenditure for reward task (EEFrT) were used. The patients also completed semi-structured subjective feedback on the intervention. The study followed an intention-to-treat principle.

Although there was a higher level of adverse effects in the experimental group in comparison to TAU during the study (7 vs. 4), none of these were considered to be associated with the study participation. Therefore, 9 out of 15 patients in the experimental group were interviewed and only 6 out of 15 completed EEfRT and WCST tasks. The study observed a significantly large effect size in the primary outcome GAS in comparison to the TAU group ($p = 0.001$, $d = 1.48$) but the treatment effects observed for secondary outcomes (clinically and self-assessed negative symptomology) were considered by the authors to be too small and varied to draw any conclusion. The intervention was well received by the patients.

5.3. Social symptoms

Park et al. (23) compared social skills training through immersive VR to conventional roleplay methods in 91 in patients with schizophrenia. The patients were randomized into either virtual reality social skills training (VR-SST, $n = 45$) or social skills training through traditional roleplay (SST-TR, $n = 46$).

Both groups went through 10 semiweekly therapeutic sessions for 5 weeks, each lasting for 90 min. The manualized program included five sessions of conversational skill training, three sessions of assertiveness training, two sessions of emotional expression skills training, and included revision and homework. Each session included three roleplays with different scenes, first modeled by the therapist, then followed by the participant, after which feedback was given, and the scene was then repeated. The group delivering the interventions included a main therapist and co-therapists (social workers). The only difference between the two groups was in the materials used for the delivery of the intervention with the VR-SST group utilizing an immersive VR system and the SST-TR group verbal, writing, picture, and video material, as well as therapists as actors.

The primary outcomes studied were social skills and competence through unstructured roleplay tests, which were recorded and rated by a blinded evaluator using the SBS scale (SBS, Trower's Social BehaviorScale), e.g., voice, non-verbal, and conversational skills. Secondary outcomes were self-reports for assertiveness (RAS, Rathus Assertiveness Schedule), interpersonal relationship skills (RCS, Relationship Change Scale), and cognitive, affective, and behavioral responses to real-life problems (SPSI-R, Social Problem-Solving Inventory-Revised). The study also examined proxy methods for motivation (Interest-In-Participation Questionnaire) and generalization of skills (right-or-wrong questions related to the topics of corresponding sessions). Possible confounders that were controlled for were session duration, age, time spent for instructions, orientation, contact with the main therapist and therapist recommendations, group size of the intervention group (4 to 5), and protocols for encouraging attendance.

Both SSTs improved social skills overall, but there were differences between the interventions. VR-SST group showed better improvement on the SBS scale in conversational skill than SST-TR ($F_{1,62} = 17.261$, $p < 0.001$, partial $\eta^2 = 0.218$), but inferior improvement in non-verbal skills ($F_{1,62} = 6.201$, $p = 0.015$, partial $\eta^2 = 0.091$). The VR-SST intervention also showed greater improvement in assertiveness on the RAS ($F_{1,62} = 4.957$, $p = 0.030$, partial $\eta^2 = 0.074$). VR-SST group also scored higher in attendance than SST-TR (attendance rate 95.3 ± 6.8% and 91.0 ± 7.3%, respectively; $t_{62} = 2.411$, $p = 0.0199$), as well as on generalization of the learned skills.

Freeman et al. (11) studied the effects of an automated, immersive VR intervention in a multicenter, parallel-group single-blind RCT on patients suffering from schizophrenia spectrum disorder or an affective disorder with psychotic symptoms. In total, 174 patients were assigned to the intervention group and 172 to the control condition (TAU).

The intervention was an immersive, automated VR application "Gamechange," which aimed to relearn safety by testing fear expectations through repeated behavioral self-experiment. Inside the VR environment, a programmed virtual coach helped to guide the therapy, modify and test behavior, and gave feedback. Participants selected one of six VR social scenarios (café, general practice waiting room, pub, bus, opening the front door of the home onto the street, and small local shop). Each scenario comprised five levels of difficulty (based on the number and proximity of people in the social situation and the degree of social interaction) and participants worked their way through each level. There were differences in the level of interaction with the avatars and the level of attention given to the participant by the avatars depending on difficulty. After finishing a scenario, the participant could choose a different scenario in each session or repeat a previous scenario and/or level. Each session lasted 30 min once per week. The program was carried out over 6 weeks, with a protocol minimum of at least 3 sessions. A mental health worker (either peer support worker, assistant psychologist, or clinical psychologist) was in the room when the therapy was provided. The staff had a wide range of clinical experience and were given half a day of training for VR therapy and weekly supervision. Their job was to help set up the system and provide guidance, but they did not actively participate in the program. The VR sessions were conducted in the participant's home or a clinic room. The usual care included antipsychotic medication, mental health worker visits, and psychiatrist appointments.

The main outcome was the Oxford Agoraphobic Avoidance Scale (OAS), measuring avoidance and distress in everyday situations. The secondary outcomes measured were agoraphobia (Agoraphobia Mobility Inventory-Avoidance scale), suicidal ideation (Columbia Suicide Severity Rating Scale), paranoia (Revised Green et al. Paranoid Thoughts Scale) and paranoia worries (Paranoia Worries Questionnaire), depression (Patient Health Questionnaire), and activity levels (measured using actigraphy over 7 days and a time budget assessing meaningful activity considering the complexity of activities and effort). Agoraphobic avoidance was also assessed using a behavioral assessment task (O-BAT) where the personalized hierarchy of five real-world situations was created and participants were asked to enter them in order of difficulty, stopping when unable to progress (O-BAT was originally the primary outcome, but changes to the study protocol were made due to COVID-19 pandemic). Ratings of distress were also obtained for each step completed. The study also measured quality of life (five-level EQ-5D, Recovering Quality of Life questionnaire, and Questionnaire about the Process of Recovery). Assessment of threat cognitions and use of within-situation defense behaviors as mediators were measured using the Oxford Cognitions and Defenses Questionnaire (O-CDQ) and strength of safety beliefs. Moderators were assessed at baseline with a short assessment of negative hallucinations when outside and through the Beck Hopelessness Scale, the Body Esteem Scale for Adolescents and Adults, and the O-CDQ. Medical notes were also checked after the trial for serious and not serious adverse effects.

The level of agoraphobic avoidance varied at baseline in the VR group (average in 17%, moderate in 32%, high in 29%, and severe in 22%, with data missing in 1%) and in the TAU group (average in 19%, moderate in 23%, high in 30%, and severe in 28%).

Compared to the TAU-only group, the VR-intervention group had a significant reduction in agoraphobic avoidance ($p = 0.026$, $d = -0.18$) and distress ($p = 0{\cdot}014$, $d = -0.26$) at 6 weeks, as measured by the O-AS and large size reductions in O-BAT for agoraphobic avoidance and distress (in those who provided the data, $p = 0.0004$, $d = 0.068$ and $p = 0.0.52$, $d = 0.43$, respectively). The differences between the groups in O-AS scores were not statistically significant at 26 weeks.

The study found no significant differences in secondary outcomes between the two groups, except for improvement in the VR group in comparison to the control group in recovery assessed by a questionnaire about the process of recovery at 6 weeks and O-BAT avoidance at 6 and 26 weeks.

For avoidance and distress, the study found that threat cognitions and within-situation-defense behaviors (but not safety beliefs) significantly mediated treatment outcomes at 6 weeks, although at 26 weeks failed to reach statistical significance. Each of these mechanisms was found to separately explain approximately one-third of the treatment effect of the VR intervention.

Greater severity of threat cognitions (assessed by the O-CDQ) at baseline resulted in greater treatment benefits with the VR therapy at 6 weeks, indicating moderation by the severity of agoraphobia. The *post hoc* analysis of the primary outcome showed that the benefits of the VR intervention were only seen in patients with severe and high levels of agoraphobia, with the benefits maintained at 26 weeks.

Neither occurrence of negative verbal hallucinations, hopelessness, appearance concerns, age, or gender showed moderation effects.

5.4. Cognitive symptoms

A small study by La Paglia et al. (24) examined the effects of VR training in comparison to pharmacotherapy and integrated therapy in outpatients suffering from schizophrenia. In total, 15 patients were assigned to either VR training or control group without randomization (VR training, $n = 9$, control, $n = 6$). Both groups received normal psychopharmacologic treatment as well.

The VR cognitive training focusing on attention was delivered through the head-mounted device in three virtual environments with different, interactive tasks: a park, a valley, or a beach. The park environment trained sustained attention through catching balls shot at irregular intervals, the valley selective attention through identifying correct targets, and the beach both selective and divided attention, through identifying correct targets with interruptions. There was hierarchical sequencing for different tasks. The immersive VR cognitive rehabilitation intervention was implemented once a week over 10 individual sessions lasting ∼90 min per session. The control group received 10 group sessions of IPT (integrated psychological therapy) once per week.

Before and after training, the study subjects were tested with neuropsychological assessments to overview general and executive cognitive functioning, sustained and divided attention, planning, brief and long-term memory, and cognitive flexibility through MMSE (Mini-Mental State Examination), FAB (Frontal Assessment Battery), TMT (Trail Making test forms A, B and B-A), ToL (Tower of London Test), Memory Battery, and WCST (Wisconsin Card Sorting Test) tests. The study also measured the following items at the first and last sessions of the VR intervention: task execution time and total errors made, requests for assistance and therapist's interventions, sustained and divided attention, maintained sequencing of the task, self-correction, absence of perseveration, and maintained task objective to completion.

In the study, both groups improved in performance on the divided attention task (TMT-B), with the VR training group showing better improvement in sustained attention (TMT-A, $p = 0.033$), general functioning (MMSE, $p = 0.026$), and planning (ToL, $p = 0.042$) when the improvement from baseline to the end of the intervention was measured, separately in each group. Over the VR training, the patients improved their execution times ($p = 0.008$) and had reduced need for assistance (lesser requests, $p = 0.018$ and therapist interventions, $p = 0.008$). They also reduced their errors ($p = 0.042$) and showed improvement in sustained attention ($p = 0.046$) in the tasks.

A study by Wang et al. (31) explored the potential benefits of adding cognitive training through immersive VR serious gaming to standard psychiatric care.

In total, 64 inpatients were randomized to either the experimental VR training group ($n = 31$) or the control group ($n = 33$). While the control group received only standard psychiatric care, the experimental group also played a VR game twice daily for 10 days.

The VR intervention component was "Fruit Pioneer," an active, serious VR game played from a first-person perspective, where the player (patient) tries to score points by cutting moving fruits and avoiding penalty-inducing iron balls. As the fruits could fly from any direction, the players had to stay vigilant of their surroundings in the virtual environment. As the game progressed, it became increasingly more demanding. Each game level was 2 min and there was a 10-second pause between each level. Each session lasted 20–30 min, twice daily. Each participant finished at least 20 sessions. A psychiatric nurse explained the game rules, recorded the sessions, and accompanied the patient in case of adverse effects. A diameter of 2 m was required as a safe space for the intervention. The control group received standard inpatient psychiatric care, such as medication and group psychiatric rehabilitation including psychoeducation about symptom and medication management, learning or occupational goal setting and plan making, and social skills training. The patients in the intervention group could also participate in these activities if they wanted to. The psychiatric treatment was based on medical needs.

The primary outcomes assessed were working memory, executive function, and verbal fluency associated with social cognition. These were tested through the Brief Cognitive Assessment tool for Schizophrenia (B-CATS), including the Digital Symbol Substitution Test (DSST), Trail Making Test parts A and B (TMTA and B), and Animal Fluency (AF) test.

No participant dropped out or failed to complete the training sessions. There was no difference in AF scores, but significantly higher scores for DSST ($p = 0.001$, $d = 0.87$) and faster completion times in TMTA ($p = 0.023$ d =0.59) and TMTB ($p = 0.018$ d =0.62) in the intervention group in comparison to the control group, indicating a therapeutic effect on executive functioning and working memory.

Vass et al. (30) explored the effects of an immersive Virtual Reality Theory of Mind-intervention (VR-ToMIS) in a population of 21 stable outpatients with schizophrenia in comparison to passive VR exposure in a pilot randomized controlled study. Three patients dropped out before the first VR session and one patient was excluded due to an adverse effect not related to the intervention, leaving ultimately 17 patients, who were randomized to either the VR intervention group ($n = 9$) or passive VR exposure control group ($n = 8$).

The structured intervention was based on cognitive and behavioral therapy principles and targeted the Theory of Mind (ToM); broadly defined as the ability to deduce the mental states of another person, which is impaired in patients suffering from schizophrenia. The intervention was carried out once a week over 9 weeks, with each session lasting 50 min. The program included one preliminary session and eight active sessions. Active sessions included 3 consecutive steps preceded by a short warm-up and reviewing of the activity between sessions (homework and self-monitoring for the intervention group) and key procedures for change (e.g., how to keep up conversations). The three steps were as follows: 1. Simulated social interaction with game avatars in immersive VR environments with structured and pre-recorded dialogue elements designed to induce ToM impairment through social cues (such as double-meaning sentences, overstatements, and irony) for later interventions; 2. After each simulation, the patient had to visualize the inferred emotions of the avatar by use of the Temporal Disc Controller (TDC) task, helping to differentiate inconsistencies between verbalized and visualized mental states for observation; 3. Finally, the experience of the simulation was reviewed with a psychotherapist, who used cognitive and metacognitive techniques to guide the patient to develop more adequate behavioral strategies. The learned strategies were then tested by repeating the prior simulation. The control group could freely explore virtual environments but could not interact with avatars and did not receive any intervention.

Patients completed baseline and post-treatment assessments for psychopathology (PANSS), neurocognitive skills (Repeated Battery for the Assessment of Neuropsychological Status, RBANS and

Wisconsin Card Sorting Test, WCST-64), ToM (BCMET, faux pas test, and cartoon stories task were administered to test the ability of mental state attribution), pragmatic language skills (non-literal language processing through Hungarian metaphor and irony test, consisting of four subtests: metaphor, irony, implicatures, and semantic subtests), and quality of life (Lancashire Quality of Life Profile (LQoLP). After each VR session, the participants were assessed for symptoms of simulator sickness using the Simulator Sickness Questionnaire and after the last session, all participants in the VR-ToMIS group were asked for their subjective opinion on the intervention (5-point Likert Scale). One relative of each patient evaluated the perceived changes (5-point Likert Scale).

The study found significant improvements in the VR-intervention group on negative symptoms on PANSS scores in comparison to the control group [effect size was large, Cramer's phi (ϕ) = 0.58, $p = 0.01$], and statistically non-significant but small effect sizes for positive and affective symptoms and non-significant but medium effect sizes for cognitive symptoms and activity scores.

Regarding neurocognition tests, the only statistically significant improvements in the VR group in comparison to the control condition were seen in reduction of errors [WCST-64, number of correct responses, $p = 0.05$, effect size was large, Cohen's partial eta squared () = 0.24] and on visuospatial and attention subtests of RBANS with medium effect sizes (visuospatial $p = 0.01$, $\eta_p^2 = 0.34$, attention $p = 0.02$, $\eta_p^2 = 0.32$). On WCST-64 and RBANS, non-significant improvements with large effect sizes were also seen for rate-of non-perseverative errors and immediate memory subtests.

The study found significant between-groups differences favoring VR intervention in several other tests in comparison to the passive VR exposure, seen both for lower and higher order ToM, for cognitive and affective subcomponents, and underactive ToM-tests in cartoon test first- and third-order tasks ($p = 0.04$, $\eta_p^2 = 0.24$, $p = 0.02$, $\phi = 0.55$, respectively), faux pas-test overall scores ($p = 0.003$, $\eta_p^2 = 0.46$), and faux pas empathy and detection scores ($p = 0.01$, $\eta_p^2 = 0.37$, $p = 0.02$, $\eta_p^2 = 0.032$ respectively), as well as in metaphor-irony subscore ($p = 0.005$, $\phi = 0.67$).

VR intervention was also associated with significant changes regarding the understanding of inappropriateness in the faux pas test ($p = 0.03$, $\phi = 0.52$) and faux pas detection ($p = 0.007$, $\eta_p^2 = 0.40$). Positive, but non-significant changes were seen for BCMET scores, second-order Tom (Cartoon stories), faux pas-overall, and empathy scores.

Regarding pragmatic language skills, a significant change between groups was seen only in the interpretation of metaphors ($p = 0.03$, $\phi = 0.50$, large effect size).

No significant differences were found in quality of life. Patients found the intervention interesting, engaging, easy, and safe to use. Relatives ($n = 7$) who observed patients reported a reduction in distrust patients exhibited toward others and a positive change in being involved with and more willingness to initiate conversations.

5.5. Comorbid symptomology

In a small study, Fusco et al. (28) compared the effects of progressive muscle relaxation (PMR) training with or without augmentation through VR on learning the technique as a coping mechanism for stress and anxiety and the intervention's effects on anxiety (STAI-y, BAI) in a population of psychotic patients at medium intensity level psychiatric facility.

In total, 22 patients suffering from schizophrenia, or another psychotic disorder, were randomized into experimental and control groups ($n = 11$ in both groups). The intervention was divided into two phases. In phase one, both groups received two 45-min sessions on learning to recognize psycho-physical tension of situations perceived as threatening. In phase two, both groups received 2 months of progressive muscle relaxation training (PMR) with descending levels of intensity; First twice weekly for 2 weeks, then once weekly for 2 weeks, and then once every 2 weeks for a month. The experimental group ($n = 11$) learned the technique through an immersive VR scenario involving a beach overlooking an ocean, with guided voice and background music while the control group used a more conventional setting ($n = 11$). The relaxation technique was 10 min in duration in both groups. The measurements were carried out in Phase 1 and at the end of training (although the abstract mentions a follow-up at 6 months after the intervention, this was not in the results).

Both groups reported positively on subjective feelings of relaxation with the experimental group having less difficulty in stretching muscles. Reduction in anxiety symptomology was seen in both groups between baseline and end of training with VR-augmented PMR more effective in comparison (BAI, $p < 0.006$; STAI-Y, $p < 0.005$).

6. Adverse effects

In total, 8 out of 12 included studies reported measuring for adverse events during the study with 1 studying VR social training, 3 VR CBT-based interventions, and 3 VR avatar therapy-based interventions.

Park et al. (23) reported checking patients for subjective feelings of simulator sickness after each immersion with HMD in their study of VR social training. They reported no health problems related to the use of HMD, but their study-progress flowchart reports two dropouts in the VR group and one in the control group due to symptom aggravation.

Regarding the use of CBT-based VR therapies, Pot-Kolder et al. (26) reported no adverse events related to the VR-CBT but found discomfort, cybersickness, or fear related to the equipment use or therapy modality ($n = 4$). In total, 11 out of 58 (19%) patients in the intervention were dropped from the study; either never starting the intervention ($n = 4$) or discontinuing due to logistics ($n = 2$), equipment-related discomfort (nausea, $n = 1$, HMD too uncomfortable $n = 2$), being afraid to continue ($n = 1$), or not being able to comply alcohol sobriety ($n = 1$). Vass et al. (30) report that no patient dropped out during VR intervention (ToMIS). One patient was excluded due to an adverse event, which was not related to the intervention and 3 patients did not start the intervention. Although the study reports assessing symptoms of simulator sickness with SSQ after each VR use, it does not report results. Cella et al. (24) report 2 serious adverse events and four adverse events in the control group and seven adverse events in the VR intervention group during the study period. None of the events were considered to be associated with study participation. Freeman

et al. (11) studying automated VR-CBT reported 25 adverse events from 21 different patients (12 were serious in nine patients) in the intervention group. In the TAU group, there were 29 adverse events from 19 different patients (eight in seven patients were considered serious). In addition, 10 out of 12 serious adverse events in the VR group were considered to be "definitely not related" to the intervention and 2 out of 12 were "probably not related."

All the studies utilizing VR-based avatar therapy; either VRT or CATS, mentioned measuring for adverse events. In the study by du Sert et al. (27), 4 out of 19 patients dropped out due to anxiety or lack of engagement in intervention after the first VRT session. The study reports the first 2 weeks as most anxiogenic, with significant reductions in anxiety and fear seen at week 4. No rehospitalizations occurred during the study, but one patient entered a counseling and support center temporarily at week 1 of VRT. Dellazizzo et al. (29) report in their 1-year follow-up trial studying VRT in comparison to CBT, that 12/74 withdrew from the study intervention groups (9 from VRT and 3 from CBT), with differing reasons (lack of motivation, not wanting to reduce voices, and moving away). The study reports no rehospitalizations during the totality of the trial. Moreover, 37.5% of the patients in the VRT group found the therapy stressful in the beginning, but after that, found it interesting and enjoyable. Liang et al. (29) report that there were no adverse events related to either CATS or the CBT-control condition but does not specify how the adverse events were screened for.

7. Requirements for VR interventions

7.1. Technical requirements

We have gathered the technological information available from the study documents in Table 3 below.

7.2. Human resource requirements

We have gathered the human resources requirements information available from study documents in Table 4 below.

8. Discussion

In our review, we found 12 studies using immersive VR and no studies using AR in the treatment of patients suffering from schizophrenia spectrum disorders.

There are several possible reasons why the general academic interest is focused more on VR solutions. First, and most important, the studied therapeutic modalities utilize the unique possibilities provided by immersive VR; such as the use of virtual environments and intersocial interactions with precoded game characters (avatars) for safe, easily repeatable, and otherwise demanding treatment modalities (e.g., exposure-based methods). AR solutions either lack the immersivity (depending on the chosen media) offered through VR-HMD or the capability to meaningfully alter virtual surroundings. The second important factor is the level of commercial availability; head-mounted devices for immersive VR have become more affordable and thus commercially available while there are less easy-to-use immersive AR solutions fitting for psychiatric interventions. It is possible that commercially available non-immersive AR technology still lacks the aforementioned qualities needed to augment therapy modalities. It could be argued that modalities that focus on communication with a single avatar and do not focus otherwise on surroundings (such as avatar therapy-based modalities) could utilize AR-based methods. For example, one study targeting stigma toward schizophrenia patients already demonstrated the possible use of augmenting physical reality with pseudohallucinations (34). There is no available evidence as of yet to argue whether such methods would or would not augment avatar therapy. Overall, there is a research gap regarding the use of AR in the treatment of schizophrenia.

The studied VR-based intervention modalities were diverse in nature, with most studies using VR to augment CBT-based techniques ($n = 5$). Other modalities are either augmented avatar therapy ($n = 3$), otherwise utilized virtual environment ($n = 2$), or gamified treatment ($n = 2$). These modalities had most likely been chosen either as they were based on previously proven psychological treatments (social roleplay, CBT, and avatar therapy) or due to the ease of creating a study setting (relaxation and serious gaming for neurocognitive training). While receiving VR interventions, the patients also received their standard psychiatric treatment.

VR seems a useful tool to utilize in CBT because it allows for a safe method to study the behavior in-virtuo; a gradual, less intense way than real life to habituate the patient into real-life situations, while also allowing the therapist to observe, support, and correct the patient's behaviors in real time, as well as allowing for easy replication of prior situations so they can be gone over multiple times for reinforced learning. The range of CBT-based modalities was diverse with different targets such as lowering safety behaviors to reduce paranoid ideation, social distress, and agoraphobia, improving social functioning, and ameliorating negative or ToM deficits as well as motivational deficiencies. In the included studies, VR-CBT was used to augment treatment as usual in comparison to either TAU-alone or simple VR exposure and found positive effects on all priorly mentioned targets. Freeman et al. (21) found a single session of VR-CBT used to reduce safety behaviors in the virtual environment to reduce paranoid ideation and distress related to paranoia in VR settings and subsequently to reduce real-life social distress in comparison to VR exposure without the CBT component. Pot-Kolder et al. (25) also reported that 16-session VR-based CBT in comparison to wait-list control (TAU), reduced momentary paranoid ideation, momentary anxiety regarding social situations, and use of safety behaviors, with the effects maintained at 6-month follow-up. The treatment on the other hand did not increase social participation. Cella et al. (32) found positive changes in goal attainment of preselected goals through their 12-session VR-CBT modality (V-Nest) and Vass et al. (30) showed that a 9-session VR-CBT targeting ToM deficits improved negative symptomology (PANSS score), ToM deficits, and neurocognition in comparison to simple VR exposure. Freeman et al. (11) also exhibited that a self-guided, ambulatory VR-CBT modality (GameChange) in comparison to wait-list control (TAU) over 6 weeks and with a minimum of 3 sessions reduced agoraphobic avoidance and distress at post-treatment, although at follow-up at 26 weeks

TABLE 3 Technological requirements for VR intervention.

Study	HMD	Other technology required	Software used
Park et al. (23)	Eye Trek 250W, Olympus	Joystick, Computer (rendering and virtual environment), 120-inch screen where others in the group can follow what happens inside an immersive environment., Position tracker (InterTrax2, InterSense) for following head direction.	Not mentioned
La Paglia et al. (24)	Non-specified HMD	Non-specified trackers and a joypad, computer for accessing VR-environment	Neuro-VR 2.0 software for accessing VR environment.
Freeman et al. (25)	nVisor SX111	12 Interse Sonistrip ceiling and Intersense IS-900 SimTracker system to specify for viewer's position and orientation. Computer for running VR application (custom build; core i7 processor, NVIDIA GeForce GTX 780 ti graphics card with 3072 mb of memory. 16GB of RAM. Asus Maximus VII Ranger motherboard. Computer for tracking (Dell T5500 workstation with a core i7 processor and 4 GB RAM. Audio rendering with Realtek audio controller.	Train environment rendering: XVR application platform. Lift environment rendering: Unity3D application platform.
Pot-Kolder et al. (26)	Sony HMZ-T1/T2/T3	Logitech F310 Gamepad for movement in VR environment. 3DOF tracker for head rotation.	Vizard Software
Du Sert et al. (27)	Samsung GearVR	Samsung Galaxy S6 smartphone for running software.	AVATAR creation: Idiosyncratic avatars: Unity 3D game engine and Morph3D Character System. The avatar's voice simulation with Roland AIRA VT-3 voice transformer, lip synchronization prosody of intonation and language through SALSA via RandomEyes Unity 3D extension
Fusco et al. (28)	Non-Specified HMD	Headphones for relaxation instructions	Not mentioned
Dellazizzo et al. (29)	Samsung GearVR or Oculus Rift	Not mentioned.	AVATAR creation: Idiosyncratic avatars: Unity 3D game engine and Morph3D Character System. The avatar's voice simulation with Roland AIRA VT-3 voice transformer, lip synchronization prosody of intonation and language through SALSA via RandomEyes Unity 3D extension
Vass et al. (30)	Samsung Gear VR	A Samsung S7 smartphone for running the software and a Samsung simple controller for interaction in the VR environment.	VR environment by vTIme
Wang et al. (31)	HTC Vive	Computer for running software: HP PC, Intel Core i5-9400F processor, 16 GB DDR4 3000 MHz memory, GTX 1660 6GB graphics card, 256 GB solid-state drive, and 1 TB hard disk drive. Handle-held devices were used for interaction. HMD-linked headphones were used for audio.	Software developed using Unity3D
Freeman et al. (11)	HTC Vive Pro	Computer: Dell G5 15 5590.	Software programmed by Oxford VR.
Cella et al. (32)	Oculus Rift-S	VR-ready laptop to run the software, ear-covering headphones for sound.	VR environments were designed by Virtualware (Unity).
Liang et al. (33)	HTC Vive	MP3-player	Intervention: CATS software. AVATAR creation: 2D creation of avatar and generation to 3D with headshot plug-in in Character Creator (Reallusion, part of CATS software) and then creation of idiosyncratic character through Unity 3D Game engine and Blendshape. Voice simulation through voice conversion technology (Faceware Live Server) and facial and full-body motion capture (Perception Neuron PRO).

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TABLE 4 Human resources requirements for VR interventions.

Study	Human resources required for intervention	Manualized	Individual or group sessions	Length of session (minutes)	Intensity of treatment	Number of sessions	Body position of patient during intervention
Park et al. (23)	Main therapist (education level not specified) and co-therapists (social workers).	Yes	Group (size 4-5)	90	semiweekly	10	Not mentioned
La Paglia et al. (24)	Not mentioned	Yes	Individual	90	Weekly	10	Not mentioned
Freeman et al. (25)	A clinical psychologist explained experimental conditions and a research worker conducted assessments.	Not mentioned	Individual	60-90 (30 min in VR)	Once	1	Standing
Pot-Kolder et al. (26)	VR CBT therapists (Psychologists with at least basic CBT training) received two days of training in VR-CBT.	Yes	Individual	60 (40 min VR)	16 sessions over 8-12 weeks	16	
Du Sert et al. (27)	Therapy was delivered by a psychiatrist with 5 years of experience, with clinical experience of the sample population. The therapist animated the avatar's dialogue.	Yes	Individual	45	Weekly	1 avatar creation session and 6 therapy sessions	Not mentioned
Fusco et al. (28)	Not mentioned	Not mentioned	Not mentioned	Psychoeducation session: 45 min, VR: relaxation: 10 min	Phase I: 2 psychoeducation sessions (Non-VR), Phase II: VR sessions semiweekly for 2 weeks, then weekly for 2 weeks, then every 2 weeks for a month.	Phase I: 2 Phase II: 8	Not mentioned
Dellazizzo et al. (29)	Therapy was delivered by an experienced psychiatrist with 7 years of experience, with clinical experience of the sample population. Patients sat in an adjacent separate room from the therapist who animated the voice of the avatar or spoke as themselves, keeping up a trialogue.	Yes	Individual	60 (Obtained from study pre-registration)	Weekly	1 avatar creation session and 6 to 8 therapy sessions	Not mentioned
Vass et al. (30)	A trained psychotherapist delivered the intervention.	Yes	Individual	50	Weekly	9	Not mentioned
Wang et al. (31)	A psychiatric nurse explained the game rules and accompanied the patient in case of adverse events.	No	Individual	20–30	Twice a day	Min. 20	Standing
Freeman et al. (11)	1 mental health worker (Peer support workers, assistant psychologists, or clinical psychologists with a wide range of clinical experience and half a day of training for VR modality) was in the room to help set up and explain the procedure. The therapy was guided by an in-game virtual coach.	Yes	Individual	30	Weekly	6	Not mentioned
Cella et al. (32)	Therapist (Therapists were graduate-level psychologists with clinical experience with the target population)	Yes	Individual	Not mentioned	Not mentioned	12	Sitting
Liang et al. (33)	CATS team (psychiatrists and therapists with ~5 years of experience.). Therapist in an adjacent room alternating as a therapist or animating and voicing the AVH in a trialogue.	Yes	Individual	60	Weekly	1 avatar creation session and 6–8 therapy sessions	Not mentioned

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failed to reach statistical significance, except for those rated highly or severely agoraphobic. Overall, the studies show preliminary evidence supporting the use of VR-based CBT interventions but require larger studies to validate their findings. VR-CBT also needs to be compared with other, priorly validated treatment modalities (such as regular CBT) to see whether augmentation of treatment using VR has further clinical significance.

VR social training, by using precoded avatars in the virtual environment to help patients train their social skills, is closely related to CBT techniques of exposure and holds the same benefits offered by the virtual environment. Park et al. (23) in their 10-session study showed that such a method in comparison to traditional social roleplay (through verbal, picture, video material, and acting) had an advantage when it came to learning conversational skills, but a disadvantage in learning non-verbal skills. This is understandable, since as of 2011 (and possibly as of now as well), when the study was published, VR graphics were not up to a point, that could properly and realistically enough animate non-verbal cues.

Avatar therapy has priorly been studied through computerized methods and its effect on patients with schizophrenia is still uncertain (35). In the studies included, avatar therapy using immersive VR had an ameliorating effect on persecutory hallucinations in patients with treatment-resistant schizophrenia. The studies show that augmenting trialogue among patient, virtualized avatar of the AVH, and therapist by adding 3-dimensionality and life-likeness through VR and lip-sync, voice transformation (27, 29), and even body motion capture technology (33) for movement to add a higher level of immersivity and realism to the therapeutic experience could be of clinical significance, although we still require more research on the subject; especially comparing screen-based and VR-augmented methods.

For VR training, two studies showed that gamification of treatment through neurocognition-enhancing tasks (24, 31) in VR could be used to improve neurocognition. The first study by La Paglia et al. (24) compared 10-session VR training in different settings with different tasks to integrated psychological treatment. It found that both groups improved scores on divided attention and VR training on general functioning and planning. The patients in the VR group also improved their scores on the training tasks that they were doing. Wang et al. (31) compared the 20-session VR training to treatment as usual. An active VR serious game "Fruit pioneer" improved scores on executive functioning and working memory in comparison to treatment as usual.

One study by Fusco et al. (28) showed that including a relaxing VR environment for progressive muscle relaxation could help patients learn the technique better for stress relief and thus reduce anxiety.

The included studies found close to no adverse effects related to the VR intervention modalities; indicating a safe profile for VR use. Even intense treatment such as immersive avatar therapy led to no adverse effects in the study settings in the long run, with the introductory and starting period of the treatment being the most anxiogenic, in line with general effects related to exposure treatments (27, 29). Most of the found adverse effects mediated by the treatment were mild and related to the use of HMD, such as simulator sickness. This adverse effect is likely to lessen in future as technological solutions evolve. It is important to note that patients suffering from schizophrenia seem to rely more on sight than other mechanisms for balance and postural stability and whether the inability to rely on sight during the VR intervention could lead to more falls in the patient group (36). Thus, far we have also yet to find whether there are any clear contraindications for the use of VR other than physical incapability to use the equipment. Although the exclusion criteria of the studies might give some guidance regarding this, more research is required to find out which patient characteristics increase potential adverse effects. The ethical questions related to the use of emerging technology also require further research (37).

Regarding the use of VR in general, the HMDs and adjacent technology are getting cheaper with more commercial availability. Most of the attached costs of the treatments are likely to come from research and development costs of virtual treatment modalities, as well as future licensing prices for treatments and from the human resources required to conduct the treatment. In most cases, the augmentation of CBT and avatar therapy through VR still requires a highly trained professional to deliver the intervention and guide it. Freeman et al. (11) have offered an interesting solution to have a pre-programmed in-game guide to deliver the intervention modality. This could allow for mass production of such interventions, freeing mental health professionals from other duties, and possibly giving patients more responsibility and freedom in their treatment.

The included studies were diverse in the quality of their reporting as well as regarding their risks for bias (see Figures 2, 3). The studies were mostly of good quality, with the bias exhibited mostly unavoidable in the study setting, except for two studies by La Paglia et al. (24) and Fusco et al. (28) with scarce reporting and lack of informing data. Due to a lack of information, the study by La Paglia et al. (24) could not be properly assessed. The study by Fusco was flagged for high risk for bias. Caution should be exercised when attempting to replicate the results. The study by du Sert et al. (27) although well-reported also carries a high risk for bias because of the intervention leading to a significant amount of drop-out due to anxiety and non-inclusion of dropouts in the analyses and the cross-over design. It is important to note that multiple studies were exploratory in nature (feasibility and pilot trials). Regarding the assessed potential risks for bias in general, when delivering an intervention through a psychosocial method and a distinct device such as HMD, the patient, and assessor cannot understandably be fully blinded to the intervention received. Some of the studies tried to answer this challenge by comparing the active VR intervention to a passive VR environment or another active psychosocial intervention (such as CBT). The use of patient-reported outcomes of symptoms, especially without blinding the participants to the intervention, can introduce bias in such situations. Also, in some of the VR studies, the patients either really enjoyed the intervention or felt the intervention anxiety inducing; although this is a potential part of the treatment effect, it might lead to a difference in adherence rate, and if not accounted for, could lead to bias in the study.

Multiple studies which were excluded were either non-interventional studies of assessment and evaluation, feasibility studies not studying intervention effects, without a comparison

group or included participants with mood disorder-based psychosis or healthy population, and included non-immersive methods or did not target pre-specified target symptoms (e.g., studies of public stigma reduction). These studies could be of interest to clinicians and researchers but were out of the scope of this review.

In conclusion, VR solutions allow for a completely new way of treatment in comparison to standard psychopharmacologic and psychosocial treatments to affect patient behavior and ameliorate multiple domains of their symptoms with so far, few identifiable problems related to the treatment. The gamification of treatment has the potential to inspire the patients to better engage in their own treatment, although this might lessen if the novelty felt toward the technology wears off in the future. With especially pharmacologic treatment carrying with it significant side-effect burden, new treatment modalities to augment the regular treatment are most likely to be welcomed by the patients and their close ones to motivate and help them better adhere to their treatment regimen. This line of thinking advocates for further research into VR as a treatment vector for interventions targeting patients suffering from schizophrenia spectrum disorders. Regarding AR, there is no research on immersive treatment interventions available targeting this patient group, indicating a clear research gap.

Author contributions

ML and RH planned the study protocol. RH conducted the literature review, analysis of studies, and wrote the initial draft of the manuscript. The risk-of-bias assessment was done by RH and ML. ML had a supervising role in the study. ML and JT revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Publisher's note

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Age-matched versus non-age-matched comparison of clinical and functional differences between delusional disorder and schizophrenia: a systematic review

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Background: It has been widely suggested that delusional disorder (DD) differs from schizophrenia (SZ). However, whether the two disorders are truly distinct from each other is inconclusive as an older age of onset is closely linked to a better prognosis in psychotic disorders. In order to delineate the potential influence of age on outcomes, we undertook a systematic review on the clinical and functional differences between DD and SZ in age-matched and non-age-matched cohorts.

Methods: Electronic databases were retrieved up to May 2022. Included studies were analyzed with reference to statements about clinical, cognitive and functional differences between DD and SZ.

Results: Data synthesized from 8 studies showed (1) extensive effects of age on positive, general psychopathological symptoms and functioning, but (2) consistent differences between the two disorders in terms of negative symptoms and hospitalizations regardless of age matching.

Conclusion: There is currently insufficient evidence to conclude whether DD is completely distinct from SZ, but our review showed support for the confounding effect of age in comparisons of psychotic disorders with different ages of onset. Future studies shall take note of other possible confounding variables, methods of age-matching and the importance of longitudinal information in deducing whether the two disorders differ from each other in course and outcome.

KEYWORDS

psychopathology, psychotic disorders, symptoms, cognition, functioning, outcomes, systematic review

1. Background

Kraepelin (1) first described "paranoia" as a chronic illness characterized by well-organized delusions in the absence of hallucinations while applying "paraphrenia" to schizophrenia (SZ) patients who experienced hallucinations in addition to delusions. Subsequently, Winokur (2) defined delusional disorder (DD) as non-bizarre delusions without accompanying hallucinations. Currently, DSM-V defines DD as per the presence of one or more delusions lasting for at least 1 month in the absence of prominent affective symptoms. Any hallucinations present must not be prominent, nor should patients appear odd or report functional impairments beyond the behavioral ramifications of their delusions.

The nosology of DD from other psychotic disorders such as SZ has always been of major interest in DD literature. A classic review of 17 studies (3) suggested that compared to paranoid psychosis, DD was characterized by an older age of onset, a shorter hospitalization, a greater number of females, married, non-foreign-born patients and slightly greater social disadvantages. Later studies reported similar findings in addition to better social functioning in DD (4). Until only recently, however, few studies have examined whether DD and SZ are separate entities (5, 6). This is potentially due to DD only making up around 0.03–0.18% of the general population and 0.4–4% of the hospital population (7). Features of the disorder such as high functioning and lack of insight may further limit the recruitment of an optimal sample size (8).

In the three decades since Kendler's review (3), there has only been one longitudinal study comparing 43 patients with DD to 42 patients with paranoid SZ – although only 26 pure DD and 38 SZ patients remained after 12.9 years (5). In addition to confirming their many dissimilarities in symptoms, course and outcomes, including better social and functional outcomes in DD patients, DD was also found to be influenced more by environmental factors than genetics compared to SZ. Therefore, evidence has generally been in favor of differentiating between SZ and DD amongst the few existing studies in the area.

However, whether DD is truly distinct from SZ remains even more inconclusive because of existing biases in study samples. Notably, studies by Marneros et al. (5) and Jager et al. (4) included only inpatients in their cohort, which may pose issues such as sample representation. More importantly, neither study matched for age despite that DD is associated with an older age of onset. Psychotic symptoms during adolescence may have a more far-reaching detrimental effect on social and work functioning than if presented in later life considering that older patients are more likely to have better established careers and social networks (9). Indeed, an older age of onset has been closely linked to not only a better prognosis, but also compensates for symptoms prior to treatment (10, 11).

We previously attempted to provide empirical data on the issue of whether SZ encompasses a broad spectrum of or represents a separate disorder from other non-affective psychoses in an age-matched cohort (6). The cross-sectional comparison between 71 pairs of outpatients with adult-onset DD and SZ found that DD patients were more likely to be married and had less premorbid schizoid and schizotypal traits than SZ. Interestingly, no significant differences were found between the age-matched DD and SZ groups in terms of symptoms severity, functioning and neurocognitive performance. Therefore, it is crucial to pinpoint the potential confounding effect of age in order to address whether DD is truly distinct from SZ.

No reviews to date have examined the differences between comparing age and non-age-matched DD and SZ cohorts. To address this literature gap, this paper aimed to systematically review clinical, cognitive and functional differences between DD and SZ in age-matched as well as non-age-matched samples. We hypothesize that there may be differential outcomes when the moderating effects of age is taken into account.

2. Methods

2.1. Search strategy

Electronic searches were performed using the online databases of PsycINFO, Embase and PubMed from inception to 5th May 2022. Search terms are detailed in Table 1. Reference lists of relevant publications were manually checked to identify potential studies related to DD and SZ.

This yielded 5,900 records. Subsequent to the removal of duplicates, studies were screened for eligibility by titles and abstracts, and then by full texts (Figure 1). The search strategy was performed by three independent authors (LC, PH and CH). Any disagreement among the authors was resolved through discussions.

2.2. Inclusion and exclusion criteria

Articles were included if they met the following criteria: (1) included comparative data in the clinical, cognitive or functioning outcome of DD and SZ; (2) consisted of patients with DD and SZ according to ICD or DSM criteria; and (3) published in an English, peer-reviewed journal.

Articles were excluded if they were: (1) case reports, systematic reviews, protocols, conference abstracts, commentary or meta-analyses; (2) not comparing between DD and SZ; or (3) included patients without a clear description of the diagnostic criteria for DD and SZ according to the ICD or DSM.

2.3. Data collection and analysis

Titles and abstracts of retrieved publications were reviewed by three independent authors (LC, PH and CH) to determine relevance. Where titles and abstracts failed to provide sufficient indication of relevance, full articles were examined for eligibility with regards to the abovementioned inclusion and exclusion criteria. Studies included in

TABLE 1 Search terms applied in literature search.

PubMed and Embase shared the same set of search terms: (delusional disorder) AND ((schizophrenia) OR (psychosis) OR (psychotic disorders)) AND ((clinical) OR (cognitive) OR (cognition) OR (functioning)) while the following search strategy was used for PsycINFO: NOFT(delusional disorder) AND (NOFT(schizophrenia) OR NOFT(psychosis) OR NOFT(psychotic disorders)) AND (NOFT(clinical) OR NOFT(cognitive) OR NOFT(cognition) OR NOFT(functioning)

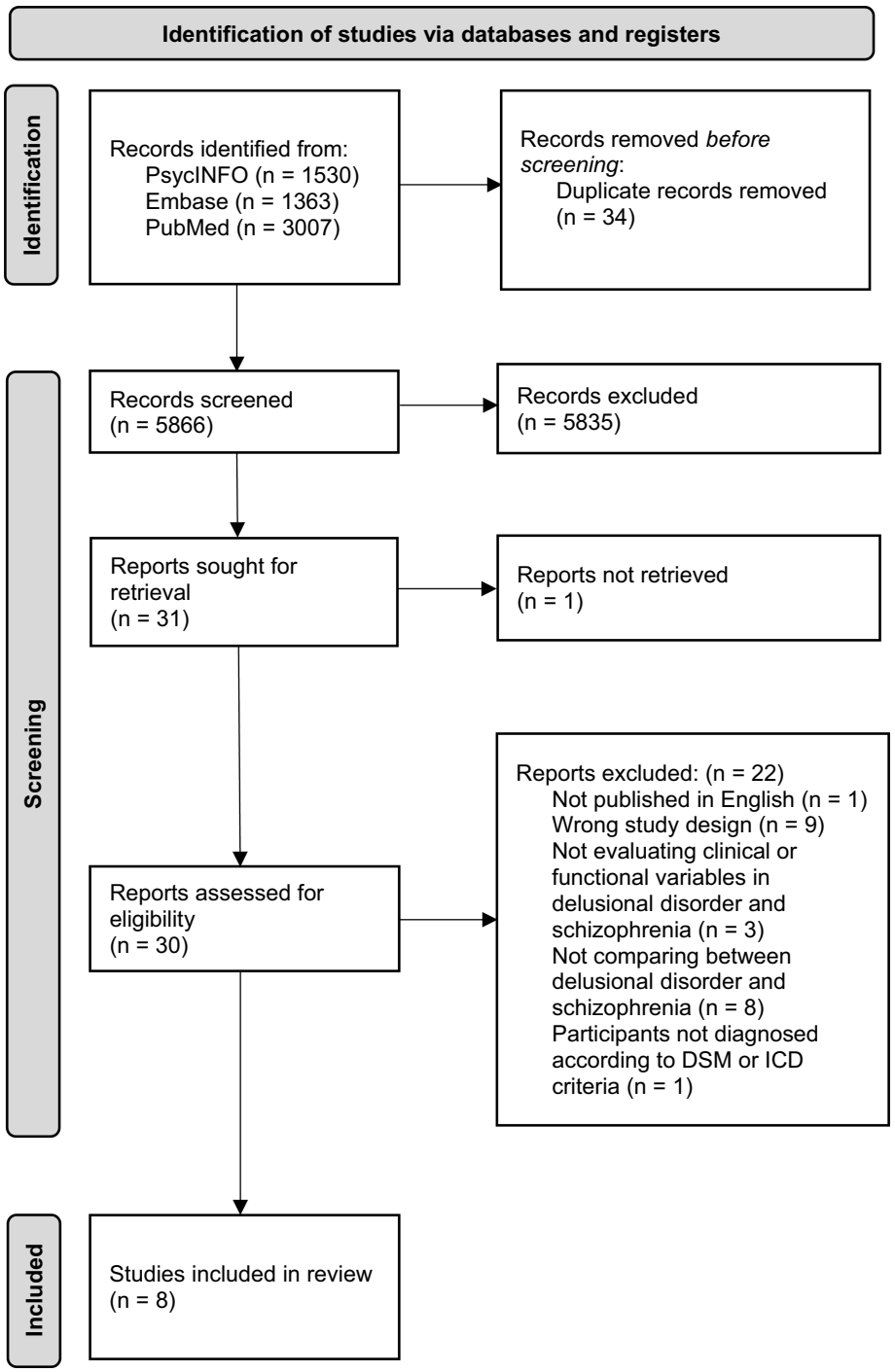

FIGURE 1
PRISMA flow diagram of included studies.

the systematic review were then analyzed with reference to statements about clinical, cognitive or functional differences between DD and SZ.

2.4. Recorded variables and data synthesis

For each included study, the following variables were recorded: authors and year of publication, title, objectives, study design, study setting, location of study, participants' age, onset age, diagnosis and its change over time and the outcome measures used. Main findings on the clinical, cognitive or functional outcomes between DD and SZ were presented separately for non-age-matched and age-matched samples, if available.

2.5. Risk of bias and quality assessment

For cross-sectional studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical cross-sectional studies was used (12). One out of eight items were removed because of its

irrelevance to the studies included (Table 2). The appraisal tool assessed the methodological quality of a study and addressed the possibility of bias in its design, conduct and analysis based on sample inclusion criteria, study setting, condition measurement, confounding factors, outcome measurement and statistical analysis. Each item was addressed with "Yes," "No" or "Unclear."

For longitudinal studies, the JBI Critical Appraisal Checklist for cohort studies was adopted (15). Four out of 11 items were removed since the questions were not relevant to the studies included (Table 2). The checklist assessed the methodological quality of a study and addressed the possibility of bias in its design, conduct and analysis based on confounding factors, outcome measurement, statistical analysis and follow up strategies. Each item was addressed with "Yes," "No" or "Unclear." For both types of studies, the risk of bias was ranked as high when "yes" scores were ≤ 49%, moderate when "yes" scores were between 50 and 69% and low when "yes" scores were above 70%.

3. Results

3.1. Study selection

Of the 5,900 articles initially retrieved, 1,530 were identified in PsycINFO, 1,363 in Embase and 3,007 in PubMed. Following title and abstract screening, 31 articles remained for full-text retrieval, one of which was excluded for lacking documentation of a full article. Of the remaining 30 articles, 22 were excluded: one was not published in English, nine were excluded due to study design, three did not evaluate clinical or functional variables in DD and SZ, eight did not compare between DD and SZ, and one included participants without a clear description of the diagnostic criteria for DD and SZ according to the ICD or DSM. In total, eight studies fulfilled our inclusion/exclusion criteria and were therefore included in the systematic review (Figure 1). Two of those studies shared the same sample pool (16, 17). Characteristics of the included studies were summarized and discussed in Table 3.

3.2. Study design and setting

Of the eight included studies, six were cross-sectional studies and two were longitudinal with a follow-up period of 13 years (5) and 7 years (18). Four studies were compiled and published in Spain, one in Canada, one in the United States, one in Germany and one in Hong Kong. Four out of eight studies recruited patients from outpatient clinics, three recruited from inpatient facilities and one recruited from a university medical center as well as the community.

3.3. Patients and diagnoses

Three of the eight studies compared between DD and SZ (6, 17, 19). Two studies compared between DD, SZ and schizoaffective disorder (16, 17). One study compared between DD, paranoid SZ and non-paranoid SZ (20), one study compared patients with late-onset SZ, DD with hallucination and DD without hallucination (18), and one study compared between DD and paranoid SZ (5). DD and paranoid SZ patients in the last study were diagnosed according to ICD and DSM criteria, while the diagnosis in all other studies was made according to DSM criteria. This comprised of a total of 585 DD patients, 1,124 SZ patients and 63 schizoaffective disorder patients.

3.4. Age-matched cohorts

Four studies conducted age-matched comparisons. Evans et al. (14) selected only patients with illness onset after aged 40 to produce an age-matched cohort. The mean onset age was 60.4 years for DD patients and 54 years for SZ patients.

Hui et al. (6) identified an age-matched cohort by propensity score matching, including DD patients with a mean age of 39.4 and SZ patients with a mean age of 39.1 at first episodes.

Two other studies (19, 20) performed age-matched comparisons between DD and SZ patients by statistical age-adjustment. In one study, the mean onset age was 38.8 for DD patients, 30.5 for paranoid SZ patients and 23.9 for non-paranoid SZ patients (20). The age of onset was not documented by Muñoz-Negro et al. (19).

Three of the four aforementioned studies conducted non-age-matched comparisons as well.

The remaining four studies (5, 16–18) performed only non-age-matched comparisons between non-matched DD and SZ cohorts.

3.5. Group differences in age-matched cohorts

3.5.1. Group differences in clinical aspects

Out of the three studies that examined differences in positive symptoms between DD and SZ, Hui et al. (6) reported fewer hallucinations but insignificantly more delusions in DD. Peralta and Cuesta (20) reported less but more severe delusions in DD when compared to paranoid SZ and non-paranoid SZ, while Evans et al. (14) observed an insignificant trend of DD displaying more positive symptoms than SZ.

Two studies compared negative symptoms between DD and SZ, where both found an insignificant trend for DD to demonstrate less severe negative symptoms (6, 14).

Of the four studies that performed age-matched comparisons, three examined differences in general psychopathology between DD and SZ. Whilst two out of three studies reported DD having higher psychopathology ratings (6, 14), this trend was not significant in Hui et al.'s study (6). On the contrary, the third study reported DD with less severe psychopathology compared to SZ (19).

All three studies (6, 14, 20) that examined hospitalization in DD and SZ reported fewer hospitalizations in DD.

3.5.2. Group differences in functioning and cognitive functioning

Results on social and occupational functioning between DD and SZ varied across studies. While one study did not see any difference on functioning between the two groups (6), Muñoz-Negro et al. (19) found that DD patients have better global functioning. Further, at one-year follow-up, Peralta and Cuesta (20) found that DD patients had *better* personal care, social functioning and having a higher number of paid work, but *poorer* occupational functioning.

TABLE 2 Quality assessment for cross-sectional studies (JBI Critical Appraisal Checklist for analytical cross-sectional studies) and longitudinal studies (JBI Critical Appraisal Checklist for cohort studies).

Authors and year of publication	Sample inclusion criteria clearly defined?	Study subjects and the setting described?	Objective, standard criteria used for measurement of the condition?	Confounding factors identified?	Strategies to deal with confounding factors stated?	Outcomes measured in a valid and reliable way?	Appropriate statistical analysis used?	Follow up time reported and long enough for outcomes to occur?	Follow up complete or were reasons to loss to follow up described?	Strategies to address incomplete follow up utilized?	% yes	Risk
Cross-sectional studies												
Evans et al., 1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes	/	/	/	100%	Low
Hui et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	/	/	/	100%	Low
Muñoz-Negro et al., 2015	Yes	Yes	Yes	No	No	Yes	Yes	/	/	/	71%	Low
Muñoz-Negro et al., 2017	Yes	Yes	Yes	No	No	Yes	Yes	/	/	/	71%	Low
Muñoz-Negro et al., 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	/	/	/	100%	Low
Peralta and Cuesta, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	/	/	/	100%	Low
Longitudinal studies												
Marneros et al., 2012	/	/	/	Yes	No	Yes	Yes	Yes	No	Yes	71%	Low
Yassa and Suranyi-Cadotte, 1993	/	/	/	No	No	Unclear	Yes	Yes	No	No	29%	High

For cross-sectional studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical cross-sectional studies was used (13). One out of 8 items was removed because the question was not relevant to the studies included. The appraisal tool assessed the methodological quality of a study and addressed the possibility of bias in its design, conduct and analysis based on sample inclusion criteria, study setting, condition measurement, confounding factors, outcome measurement and statistical analysis. Each item was addressed with "Yes," "No" or "Unclear." For longitudinal studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cohort studies was adopted (14). Four out of 11 items were removed since the questions were not relevant to the studies included. The checklist assessed the methodological quality of a study and addressed the possibility of bias in its design, conduct and analysis based on confounding factors, outcome measurement, statistical analysis and follow up strategies. Each item was addressed with "Yes," "No" or "Unclear." For both types of studies, the risk of bias was ranked as high when "yes" scores were $\leq$ 49%, moderate when "yes" scores were between 50 and 69%, and low when "yes" scores were above 70%.

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Two studies that explored cognitive functioning between SZ and DD yielded insignificant findings. Although Evans et al. (14) found that neuropsychological impairment was generally lower in DD, this was not significant. Neither was the trend observed by Hui et al. (6), as the two groups performed similarly across a broad range of neurocognitive assessments.

3.5.3. Group differences in demographics

Two studies compared gender differences, years of education and premorbid functioning between DD and SZ. Neither study found significant differences between the two groups (6, 14).

Results on marital status between DD and SZ, however, varied. While Evans et al. (14) reported DD patients as being less likely to be married, Hui et al. (6) found opposite results.

3.6. Group differences in non-age-matched cohorts

3.6.1. Group differences in clinical aspects

Out of the six studies that examined differences in positive symptoms between DD and SZ, one did not find any group difference (17) while five reported positive symptoms to be less frequent in DD (5, 16, 18–20). Specifically, two studies found that first-rank symptoms did not occur in DD (5, 18). As for hallucinations, two studies reported DD as having fewer hallucinations when compared to SZ (5, 19).

With regard to delusions, two studies revealed no significant differences (5, 19) and one study reported DD as having less but more severe delusions (20). One study found SZ to be characterized by bizarre delusions and DD by non-bizarre delusions (18).

Findings on negative symptoms between DD and SZ were consistent across five studies. All studies reported less frequent negative symptoms in DD when compared to SZ (5, 16–19).

Of the seven studies that performed non-age-matched comparisons, three studies analyzed general psychopathology between DD and SZ. Two out of 3 studies (5, 19) reported DD with less severe psychopathology although Marneros et al. (5) indicated the trend to be insignificant. Meanwhile, Muñoz-Negro et al. (17) found no significant differences between DD and SZ.

Three studies examined hospitalization in DD and SZ. Marneros et al. (5) revealed DD as having less frequent hospitalizations and a shorter duration of their hospitalizations compared to paranoid SZ. Yassa and Suranyi-Cadotte (18) reported similar findings, but the results not reach statistical significance. When compared to both paranoid SZ and non-paranoid SZ, Peralta and Cuesta (20) also found DD to have fewer hospitalizations.

3.6.2. Group differences in functioning and cognitive functioning

Results of the five studies comparing social and occupational functioning between DD and SZ were in agreement with each other, with all reporting DD to have better functioning. Specifically, two studies reported better global functioning (16, 19) and one study reported more full-time employment in DD (6). Another study reported DD patients as being more likely to be employed and less likely to retire early as well as having lower scores in the Disability Assessment Scale when compared to paranoid SZ patients (5). The final study reported DD to be associated with better personal care and social functioning and a higher number of paid work, but poorer occupational functioning than paranoid and non-paranoid SZ at one-year follow up (20).

Of the seven studies that performed non-age-matched comparisons, only one study explored cognitive functioning in SZ and DD (6). In line with the age-matched comparison within the study, Hui et al. (6) revealed that neurocognitive performance was not significantly different between non-matched DD and SZ cohorts.

3.6.3. Group differences in demographics

Of the seven studies that conducted non-age-matched comparisons, three studies compared onset age differences between DD and SZ with all reporting DD as having an older age of onset (5, 18, 20).

Six studies compared gender differences between DD and SZ. Despite that three studies found no gender differences between DD and SZ (6, 17, 20), three other studies reported a higher prevalence of women among DD patients (17–19).

Of the six studies that explored education differences, four studies reported insignificant differences between DD and SZ (5, 17–19), one study noted that incomplete primary studies were more frequent among DD patients whilst complete higher studies were more frequent among SZ patients (16) and one study reported DD as having less years of education than paranoid and non-paranoid SZ patients (20).

Furthermore, three studies examined marital status among DD and SZ patients. Two demonstrated a higher frequency of marriage in DD (19, 20) while one (18) found no difference in marital status between the two disorders.

3.7. Diagnostic change over time

Two out of eight studies documented diagnostic change over time. Over the follow-up period of up to 8 years, none of the DD or SZ patients had a change in their primary clinical diagnosis (14). Meanwhile, another study recorded 21.2% of the DD patients shifting into SZ or schizoaffective disorder during a period of 10.8 years (5). The remaining 78.8% of DD patients had no syndrome shift.

4. Discussion

This is the first systematic review to compare DD and SZ in age-matched and non-age-matched cohorts. Eight studies were included to evaluate the clinical, cognitive and functional differences between DD and SZ. DD was found to have *less* severe positive and general psychopathology symptoms in studies that did not control for age. But consistently across age-matched and non-age-matched cohorts, DD had fewer negative symptoms, better functioning and fewer hospitalizations. Though no differences in cognitive functioning, gender, education and premorbid functioning were observed, DD was more likely to be married in both age-matched and non-age-matched comparisons. While it remains questionable whether DD and SZ are separate entities, our systematic review reveals consistent findings across age-matched and non-age-matched analyses on a number of

TABLE 3 Characteristics of included studies.

Study	Study design	Study setting	Participants - diagnoses	Participants - age	Participants - onset age	Outcomes	Key results - age-matched	Key results - non-age-matched
Evans et al., 1996 (14)	Cross-sectional	California United States; From the University of California Medical Center and the Community	Out of 14 DD + 253 SZ (DSM-III), aged-matched cohort of 14 DD + 50 SZ were used for comparison (the cohort is aged-matched by selecting only patients with illness onset after age 40)	Age-matched samples: DD: 66.9 (13.6) years SZ: 63.5 (8.9) years	Age-matched samples: DD: 60.4 (13.9) years SZ: 54 (9.7) years	• Clinical: BPRS, SAPS, SANS, HAMD, G-K (on premorbidity), AIMS •Neuropsychological: Attention, Verbal, Motor, Psychomotor, Learning, Memory, Abstraction, Sensory	Age-matched patients (onset after the age of 40): • DD: greater psychopathology (on BPRS); insignificant trend of fewer negative symptoms, fewer hospitalizations, lower daily neuroleptic doses • DD: lower neuropsychological impairment but not significantly • DD: less likely to be married; no significant difference in gender, years of education, premorbid adjustment (on G-K)	/
Hui et al., 2015 (6)	Cross-sectional	Hong Kong; From outpatient psychiatric units at an early intervention clinic (the Jockey Club Early Psychosis (JCEP) Project)	Out of 72 first episode DD + 157 first episode SZ (DSM-IV), aged-matched cohort of 71 DD + 71 SZ were used for comparison (propensity score matching)	Age-matched samples: DD: 41.8 (8.3) years SZ: 40.8 (8.7) years	Age-matched samples: DD: 39.4 (8.7) years SZ: 39.1 (9.3) years	• Premorbid and help-seeking characteristics: PAS, PSST • Clinical: hospitalization, comorbidities, medical illness, PANSS, SAPS, SANS, antipsychotic medication • Functioning: SOFAS, RFS • Cognitive: information, arithmetic, digit symbol, VPT, digit span, logical memory, verbal fluency	Age-matched patients: • DD: fewer hallucination (on SAPS), insignificantly more delusions (on SAPS), fewer hospitalizations, more psychiatric comorbidities (affective disorder); no difference in psychopathology (on PANSS) • No significant differences in social and occupational functioning and neurocognitive performance • DD: less premorbid schizoid and schizotypal traits (thought content), more likely to be married; no significant difference in gender, education, premorbid adjustment (on PAS)	• Cognitive functioning and gender were not significantly different • DD: more full-time employment
Marneros et al., 2012 (5)	Prospective, longitudinal follow-up of an average of 13 years following onset	Germany; From inpatient at the Department of Psychiatry, Psychotherapy and Psychosomatics at the Martin Luther University	43 DD (DSM-IV and ICD-10) + 42 PSZ (DSM-IV)	Age at index admission: DD: 51.8 (12.6) years PSZ: 41.1 (12.4) years	DD: 46.9 (13.2) years PSZ: 35.3 (13.9) years	• Clinical: PANSS • Functioning: SOFAS, GAF, DAS	/	• DD: less severe psychopathology but not significant; no first-rank symptoms, primary hallucinations, or relevant negative symptoms; no difference in delusion; less frequent and shorter hospitalization • DD: better employment, fewer early retirement due to the disorder, fewer on psychopharmacological medication; more often autarkic (living independently); lower scores in the DAS • DD: an older age of onset, broken home background; no significant difference in education.

(Continued)

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TABLE 3 (Continued)

Study	Study design	Study setting	Participants - diagnoses	Participants - age	Participants - onset age	Outcomes	Key results - age-matched	Key results - non-age-matched
Muñoz-Negro et al., 2015 (16)	Observational; the study combined data from 5 independent studies using compatible and similar assessment methods	Spain; From psychiatric outpatient clinics	550 psychotic disorders (373 SZ + 137 DD + 40 SA) (DSM-IV)	DD: 49.8 (14.7) years SZ: 35.9 (13.1) years SA: 46.7 (14.4) years	/	• 5 dimensions (manic, negative, depression, positive, cognitive) derived from PANSS and GAF measures	/	• DD had less positive and negative psychotic symptoms lower negative, cognitive dimensions; lower positive dimension (intermediate in SZ, higher in SA); depressive and manic dimensions higher among SA • DD had higher global functioning (lower in SZ, intermediate in SA); no gender differences but more males within SZ; more frequent incomplete primary studies, whilst complete higher studies were more frequent among SZ patients
Muñoz-Negro et al., 2017 (17)	Observational	Spain; From outpatient department at different hospitals and community mental health settings	112 psychotic disorders (67 SZ + 22 DD + 23 SA) (DSM-IV)	DD: 49.6 (12.6) years SZ: 40.4 (11.5) years SA: 44.4 (13.4) years	/	PANSS, Premorbid IQ, educational level	/	• No difference in general psychopathology, positive symptoms; SA had more severe positive symptoms than DD and SZ; SA and SZ had more severe negative symptoms than DD • No gender difference between DD and SZ; premorbid IQ and years of education were not significantly different between DD, SZ and SA
Muñoz-Negro et al., 2018 (19)	Cross-sectional comparisons, the study combined data from 3 independent studies, including both Muñoz-Negro et al. (16, 17)	Andalusia and Catalonia, Spain; From psychiatric outpatient clinics (public or private mental health services integrated or commissioned by the Spanish National Health Service)	275 patients (132 DD + 143 SZ) (DSM-IV)	DD: 50.3 (14.6) years SZ: 36.6 (11.1) years	/	•Sociodemographics (marital status, premorbid IQ, employment status, educational level) • Clinical: PANSS • Functioning: GAF	Age-adjusted patients: • DD: less severe psychopathology (on PANSS), better global functioning	On crude analysis: • DD: less severe psychopathology (on PANSS), fewer positive, negative symptoms, hallucination; no significant difference in delusion • DD: better global functioning, less work-related disability • DD: older, more frequently married; had higher estimated premorbid IQ; no gender difference in DD but more males in SZ

(Continued)

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TABLE 3 (Continued)

Study	Study design	Study setting	Participants - diagnoses	Participants - age	Participants - onset age	Outcomes	Key results - age-matched	Key results - non-age-matched
Peralta and Cuesta, 2016 (20)	Cross-sectional study with 1 year fup	Spain; From inpatient at the Virgen del Camino Hospital	146 DD + 114 PSZ + 244 NPSZ (DSM-IV)	DD: 49.4 (15.0) years PSZ: 40.0 (15.7) years NPSZ: 34.5 (13.1) years (DD > PSZ > NPSZ)	DD: 38.8 (14.3) years PSZ: 30.5 (13.4) years NPSZ: 23.9 (8.54) years (DD > PSZ > NPSZ)	• CASH (premorbid, SAPS, mood disorders) • 1-year fup functioning: personal care, occupation, household, social context, paid work, GAF	Age-adjusted patients: • DD: less but more severe delusions especially on jealousy, higher conviction and lower disorganization of delusional experiences, higher likelihood of major depression, chronic illness course, lack of insight, less hospitalizations • At 1-year fup, DD: better personal care and social functioning, higher numbers of paid work, poorer occupational functioning • DD: older onset age	• Of 52 variables, 40 differentiated DD from PSZ and/or NPSZ; 29 differentiated DD from both SZ, 9 differentiated DD from NPSZ, 2 differentiated DD from PSZ • PSZ was similar to NPSZ on 17 variables but similar to DD on only 7 • DD associated with the following clinical features: less but more severe delusions, especially on jealousy/somatic, higher conviction and lower disorganization of delusional experience, less hospitalization; more likelihood of major depression, higher index episode ratings of depressed mood, dysphoria, anxiety, chronic illness course, lack of insight, poorer responses to antipsychotic drugs • DD associated with the following psychosocial functioning features (at 1-year fup): better personal care and social functioning, higher numbers of paid work, poorer occupational functioning • DD associated with the following demographics: less years of education, more likely married, older, older onset age; no significant gender difference

(Continued)

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TABLE 3 (Continued)

Study	Study design	Study setting	Participants - diagnoses	Participants - age	Participants - onset age	Outcomes	Key results - age-matched	Key results - non-age-matched
Yassa and Suranyi-Cadotte, 1993 (18)	Longitudinal, 7-year observation period	Canada; From inpatient at the acute psychogeriatric unit	20 LOS + 7 DD with hallucinations +13 DD without hallucinations (DSM-III)	DD: 77.3 (7.2) years DD + H: 74.1 (3.8) years SZ: 78.7 (8.0) years	Age of first admission: DD: 71.3 (9.0) years DD + H: 58.9 (9.3) years SZ: 62.1 (10.7) years	• Clinical variables • Concomitant physical disorders	/	Clinical features: • LOS characterized by: bizarre delusions, AH, first-rank and negative symptoms, premorbid paranoid/schizoid personality • DD associated with: non-occurrence of negative symptoms, non-bizarre delusions, late onset of symptoms, relatively intact premorbid personality, underlying physical stratum, fewer hospitalizations and shorter duration of hospitalization but difference was insignificant • DD + H associated with: non-bizarre delusions, AH, earlier onset of symptoms, premorbid paranoid/schizoid personality Demographics: • DD: older age of onset, higher prevalence of women; no significant differences in education level and marital status

"/", not applicable; Fup, follow-up; DD, delusional disorder; SZ, schizophrenia; SA, schizoaffective disorder; PSZ, paranoid schizophrenia; NPSZ, non-paranoid schizophrenia; LOS, late-onset schizophrenia; H, hallucinations; AH, auditory hallucination; BPRS, Brief Psychiatric Rating Scale; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; HAMD, Hamilton Depression Rating Scale; G-K, Gittelman-Klein Premorbid Social Adjustment Scale; AIMS, Abnormal Involuntary Movement Scale; PAS, Premorbid Adjustment Scale; PSST, Assessment of Premorbid Schizoid and Schizotypal Traits; PANSS, Positive and Negative Syndrome Scale; SOFAS, Social Occupational Functioning Scale; RFS, Role Functioning Scale; VPT, Visual Patterns Test; GAF, Global Assessment of Functioning; DAS, Disability Assessment Scale; CASH, Comprehensive Assessment of Symptoms and History.

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variables. It is also pertinent to note the effect of age on outcomes such as clinical variables and occupational functioning.

4.1. Age effect on positive and general psychopathology symptoms

The effect of age was apparent on positive and general psychopathology symptoms, but absent for negative symptoms, functioning and hospitalizations. Regarding positive symptoms and general psychopathology, DD patients were found to have more severe symptoms in age-matched cohorts but less severe symptoms in non-age-matched cohorts when compared to SZ patients. With existing research suggesting younger age to be associated with a poorer prognosis in SZ (10, 11), one may reasonably expect DD patients who are generally older (3, 4) to have less severe positive and general psychopathology symptoms than SZ patients in non-age-matched comparisons.

However, the effect of age on negative symptoms and hospitalization remains ambiguous. In accordance with other studies indicating DD patients to be characterized by less pronounced negative symptoms like flat affect and alogia (4), we found the DD displayed less severe negative symptoms irrespective of age-matching. This may be because studies that included only outpatients were biased towards clinically less severe samples, particularly in DD patients, leading to more notable differences between DD and SZ. Though unable to conclude DD and SZ as completely separate entities, our results reiterated dissimilarities between the two groups and suggested the possibility of a psychopathological gradient regarding negative symptoms among psychotic disorders.

Similarly, we found DD patients to have fewer hospitalizations regardless of age-matching. Existing studies that reported non-age-matched DD cohorts as having fewer hospitalizations may reflect the observation of a better prognosis for DD patients who tend to be older (5, 13). Our consistent findings across age-matched and non-age-matched studies, however, challenged this explanation considering the minimal effect of age on hospitalizations. The fact that most DD patients were hospitalized due to social reasons (5) may imply that they were less disturbed by clinical symptoms in the first place, accounting for fewer hospitalizations in general. It should also be noted that most of the existing studies did not explore reasons of hospital admissions. It would therefore be worthy to compare reasons of admissions such as relapse, suicide, or comorbid health conditions. Moreover, very few studies looked at voluntary and involuntary admissions. Further investigation on the types of hospital admission and its relationship with help-seeking behaviors or insight would be meaningful. Despite the absence of age effect on negative symptoms and hospitalizations, the inconsistent findings regarding positive and general psychopathology symptoms reveal how the effect of age on clinical characteristics remains pivotal.

4.2. Age effect on functioning

Given that an older age of onset was closely linked with better prognosis in psychotic disorders (10, 11), it is reasonable to expect aged- and non-age-matched differences in functioning outcomes between DD and SZ.

In non-age-matched samples, our results consistently pointed towards better global, social and occupational functioning in DD patients. This observation was in line with our expectation that in comparison to their SZ counterparts, DD patients would be more likely to manifest better functioning due to their older age.

However, further investigation into studies that compared both aged-matched and non-aged-matched cohorts may provide more important clues as to the impact of age on these outcomes. For instance, Hui et al. (6) found better occupational outcome in DD in non-aged-matched analyses, but the same study did not observe such a difference when patients were matched by age, implying the substantial impact age has on functioning outcomes. Meanwhile, Peralta and Cuesta (20) found age-matched and non-age-matched DD patients to consistently demonstrate better functioning, potentially due to the age adjustment method adopted.

As for cognitive functioning, both age-matched and non-age-matched studies consistently found no difference between DD and SZ. However, it should be noted that only two studies looked at neurocognitive functioning, rendering insufficient data in concluding with certainty that DD and SZ do not differ from each other in terms of cognitive functioning.

4.3. Age effect on gender, education and premorbid functioning

While age influences gender, education and premorbid functioning between the two groups, it has little to no effect on marital status. In line with previous studies that reported DD patients with less deterioration of social, intimate and established relationship before onset (3, 4, 21), we found that more DD patients were married regardless of age-matching. Additionally, the mean age of onset for DD patients in our included studies was above 40. Since the illness occurred during middle-to-late adult life, it is more likely for DD patients to have been married by the time they fell ill. The consistent findings across age-matched and non-age-matched studies thus diminished the effect of age on marital status.

Nevertheless, we observed inconsistent results for other demographic variables. While DD patients were found to be less educated and were predominated by women in non-age-matched cohorts, no differences in gender, education and premorbid functioning were recorded in age-matched cohorts. In view of the discrete results, it is plausible to speculate an effect of age regarding the aforementioned variables.

4.4. Limitations

While the consistency of findings was generally good across studies, it was difficult to conclude the relative impairment between DD and SZ in several of the outcomes. For instance, ratings of general psychopathology between age-matched cohorts tended to be higher for DD in two studies (6, 14), but the opposite was observed in another (19). This may be related to the large discrepancies between the studies reviewed, as not all had matched for age. Further, some of the non-age-matched studies recruited only inpatients (5, 18, 20), some combined samples from five independent studies (16, 19) and one recruited DD and SZ patients at slightly different periods (20). That the majority of

the samples were not truly representative makes age-matching of paramount importance. Additionally, longitudinal studies are crucial in identifying the distinctions between DD and SZ in the long term, but the two included were both non-age-matched and recruited only inpatients. They only provided enough information to conclude DD and SZ inpatients to be distinct from each other when not matched for age.

Furthermore, methods of age-matching varied across studies. One study conducted propensity score matching (6) while another selected only patients with illness onset after age 40 (14), which may have led to fewer SZ cases in the sample. Some performed statistical age adjustments (19, 20) which may not have yielded accurate measures of actual differences. Given the above discrepancies, a truly representative sample accurately matched by age may be needed for comparison between DD and SZ.

The directness of evidence is also limited by the discrepancies in patient groups across studies. For instance, some studies only involved patients with DD and PSZ (4) while others also included SA groups in their comparisons (16, 17). As previously mentioned, some of the studies also only recruited inpatients while others only outpatients. Recruiting DD inpatients may create a bias towards admission due to functional reasons instead of sheer clinical symptoms (5), with a greater severity of symptoms across all inpatients. Therefore, outpatients should also be included to secure a more representative sample of DD, especially given the questionable accuracy of hospital admission data regarding the true occurrence of DD in the population (3).

Further detracting from directness is the discrepancies in outcomes measures between studies. While most of the studies assessed clinical characteristics using the Positive and Negative Syndrome Scale, one study (20) adopted the Comprehensive Assessment of Symptoms and History. Another study (18) did not indicate the clinical scales used in their assessment. Assessment materials for functioning also varied across studies, with some adopting Social and Occupational Functioning Assessment Scale, some using Global Assessment of Functioning and some Disability Assessment Scale.

Similarly, diagnostic classification systems varied across studies. While the majority of the studies made diagnosis according to DSM criteria, one study had patients diagnosed according to ICD and DSM criteria. Additionally, while most of the studies that adopted DSM criteria diagnosed according to DSM-IV, two opted for DSM-III which may now be considered outdated. Using uniform and updated diagnostic classification systems shall thus be useful to ensure diagnostic categorizations are met.

Multiple comparisons were not always controlled for in the included studies. Some studies (6, 17) took the problem of multiple testing into account, but some (17, 20) did not. This might inflate the possibility of Type I errors which may cause an overestimation of existing differences between DD and SZ.

With the primary focus being on English literature, not all available data pertaining to the topic may have been identified. Conclusions about the differential outcomes of DD and SZ may consequently be underestimated especially when applied to non-Western countries. Further selection bias may have been introduced by including three studies that were conducted by the same authors (16, 17, 19), in which one (19) partially derived their data from the other two independent studies (16, 17). Conclusions about the quality of the studies reviewed may also be limited as the relevant authors were not contacted for clarifications, despite one study neglecting to state the materials they used to measure clinical outcomes (18).

4.5. Clinical and research implications

Neurobiological research into the cellular and molecular mechanisms underlying psychotic disorders may provide additional insight about the nosologies of DD and SZ. Previously, gray matter reductions in the superior temporal gyrus and cerebellum were indicated as neuroanatomical markers of psychosis (22). Future research may be guided by the Research Domain Criteria project to identify genes, cells, and other units of analysis associated with the superordinate functional constructs of psychotic disorders, such as negative and positive affect, cognition, and social processes (23). In this way, neurobiological advances may help to further refine diagnostic classification beyond observable characteristics, and better account for the outcomes of DD and SZ.

As of now, current evidence suggests that DD and SZ demonstrate similar levels of cognitive impairments regardless of age. Cognitive treatments that have recently been recommended for SZ (24) may thus also be applicable to improving the cognitive performance of patients with DD. Of particular relevance is cognitive remediation therapy, which offers benefits across different cognitive domains including memory, planning, problem solving and social cognition, independently of age (25).

4.6. Current and future directions

There is currently insufficient evidence to conclude whether DD is completely distinct from SZ. Our systematic review has found extensive effect of age on positive and general psychopathological symptoms as well as functioning, but consistent differences between DD and SZ in terms of negative symptoms and hospitalizations regardless of age matching. From these we can only infer that DD and SZ exhibit dissimilarities regarding negative symptoms and hospitalizations at the time of data collection. Moreover, since too few studies explored cognitive functioning, there is insufficient empirical data to determine whether SZ and DD patients differ from each other in terms of cognition. Another reason for the evasive conclusion would be due to difficulty in ascertaining enough DD sample. Given DD accounting for less than 1% of hospital admissions (3), studies that recruited inpatients only might end up with a small DD sample size. Also, many studies did not control for multiple comparisons, therefore existing differences between DD and SZ might be overestimated.

Our systematic review supports that age is an important prognostic factor in SZ, future studies should thus bear in mind the confounding effect of age when comparing different psychotic disorders with different ages of onset. As mentioned above, whether statistical age adjustments are accurate measures of actual differences remains questionable and that the selection of patients with older onset age would bias towards fewer SZ cases. When DD and SZ patients of all age groups are recruited during a particular period for comparison, the problem of neglecting adolescent-onset cases would be minimized. Alternatively, future studies should at least include

outpatients to ascertain a more representative DD sample, while making sure to collect longitudinal information which is crucial to determine whether DD is distinct from SZ in terms of course and outcome in the long term. Future studies should take into account other confounding variables such as cultural differences. For instance, there is lower cannabis use in Asia (<0.5%) than in the Western countries (>10%) (26), thereby influencing risk factors such as substance abuse before onset. Also, the fact that Chinese population who suffers from serious mental illness tend to demonstrate more self-blame (27), might give rise to reduced openness domestically and less prevalent professional help seeking behaviors.

5. Conclusion

Despite insufficient evidence to conclude whether DD is completely distinct from SZ, our review showed support for the confounding effect of age in the comparisons of psychotic disorders with different ages of onset. This review also better informs the differential clinical categorization of DD and SZ by taking age into account. Overall, DD was generally associated with better psychopathological and functioning outcomes regardless of age. However, neglecting age from considerations may lead to misinterpretations as positive and general psychopathology were only less severe for DD patients when the current cohorts were age-matched.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

CH: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. TC: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. EvC: Writing – review & editing. PH: Writing – review & editing. TT: Writing – review & editing. YS: Writing – review & editing. SC: Writing – review & editing. WC: Writing – review & editing. EL: Writing – review & editing. ErC: Writing – review & editing.

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Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

AIMS	Abnormal Involuntary Movement Scale
AH	Auditory hallucination
BPRS	Brief Psychiatric Rating Scale
CASH	Comprehensive Assessment of Symptoms and History
DAS	Disability Assessment Scale
DD	Delusional disorder
DSM	Diagnostic and Statistical Manual of Mental Disorders
Fup	Follow-up
GAF	Global Assessment of Functioning
G-K	Gittelman-Klein Premorbid Social Adjustment Scale
H	Hallucinations
HAMD	Hamilton Depression Rating Scale
ICD	International Classification of Diseases
JBI	Joanna Briggs Institute
JCEP	Jockey Club Early Psychosis
LOS	Late-onset schizophrenia
NPSZ	Non-paranoid schizophrenia
PANSS	Positive and Negative Syndrome Scale
PAS	Premorbid Adjustment Scale
PSST	Assessment of Premorbid Schizoid and Schizotypal Traits
PSZ	Paranoid schizophrenia
RFS	Role Functioning Scale
SA	Schizoaffective disorder
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SOFAS	Social Occupational Functioning Scale
SZ	Schizophrenia
VPT	Visual Patterns Test

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Clinical features and comorbidity in very early-onset schizophrenia: a systematic review

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Background: Very early-onset schizophrenia (VEOS) is a form of schizophrenia that manifests before the age of 13 years and is characterized by the presence of positive, negative, and disorganized symptoms. The condition is exceptionally rare and, to date, limited studies have been conducted, resulting in incomplete information about its clinical features.

Methods: The present study involves a systematic review of the existing literature regarding the clinical features and comorbidities of VEOS.

Results: The first search retrieved 384 studies. Of these, 366 were removed following the application of exclusion criteria, resulting in 18 studies for the final set.

Conclusion: The results highlight that VEOS shares similarities with early-onset and adult-onset schizophrenia but also exhibits distinct and recognizable characteristics, including a more severe clinical profile (particularly in females), increased visual hallucinations, and high comorbidities with neurodevelopmental disorders. These findings may support clinicians in formulating early diagnoses and developing effective treatment strategies for pediatric and adolescent patients with psychosis.

KEYWORDS

very early-onset schizophrenia (VEOS), adult-onset schizophrenia, clinical features, comorbidities, psychotic symptoms

1 Introduction

Schizophrenia is a major psychiatric disorder that is characterized in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* by the presence of positive (i.e., delusions, hallucinations), negative (i.e., blunted affect, social withdrawal, anhedonia), and disorganized (i.e., disorganized speech and behavior) symptoms (1). Very early-onset schizophrenia (VEOS) is a specific form of schizophrenia that manifests very early in life, typically before the age of 13 years (2, 3). The disorder shares diagnostic criteria with both adult-onset schizophrenia (AOS), which manifests after the age of 18 years, and early-onset schizophrenia (EOS), which is characterized by symptom onset between the ages of 13 and 18 years (2–6). Of note, some

authors refer to VEOS as childhood-onset schizophrenia (COS). The National Institute of Mental Health (NIMH) in the United States defines that COS is present when the diagnostic criteria for schizophrenia are met prior to the age of 13 years, alongside a premorbid IQ higher than 70 and a lack of any other neurological disorder (7, 8). In this text, we will use the term VEOS interchangeably with COS and consider adolescent-onset schizophrenia (AdOS) equivalent to EOS.

Several clinical studies have emphasized the connection between VEOS, EOS, and AOS (3, 9, 10). In particular, some studies have underlined that the genetic risk factors are similar across the three disorders (11). In support of this claim, neuroimaging studies have revealed comparable gray matter alterations in VEOS, EOS, and AOS patients, although the alterations in VEOS patients manifest as more severe. Evidence from these studies reveals a complex and extensive pattern of both gray and white matter changes, particularly in patients whose alterations began during childhood. This suggests a form of altered neurodevelopment rather than regression resulting from the onset of psychiatric pathology (12). Furthermore, genetic studies have also highlighted the possibility that psychiatric disorders, including schizophrenia and bipolar disorder, may belong to the same psychopathological continuum as neurodevelopmental disorders (13). Within this framework, VEOS can be considered one of the possible "missing links" in the psychopathological continuum between neurodevelopmental disorders and adult schizophrenia.

VEOS is an exceptionally rare disorder, and there is a lack of comprehensive epidemiological data due to the limited research conducted to date. However, a study by the NIMH indicated a VEOS prevalence rate of 1 in 40,000 (7). Another study examining the entire English population revealed an incidence rate of hospitalization for VEOS of 0.03 per 100,000 among males and 0.01 per 100,000 among females, with no significant difference between sexes (14). Moreover, the diagnosis of VEOS can be challenging for several reasons. First, as reviewed by Giannitelli et al. (15), organic causes that can lead to psychotic symptoms in childhood must be excluded, as these may have specific treatments and solutions. Second, positive psychotic symptoms (e.g., hallucinations, unusual/bizarre thought contents) can be relatively common in pre-adolescents, before showing spontaneous remission. Thus, such symptoms may not progress into a full-blown psychotic disorder or another psychiatric condition, particularly if they occur as isolated symptoms in individuals younger than 12 years (16, 17). Indeed, the prevalence of such symptoms in the general child population is significantly higher than the relatively low prevalence of VEOS. Specifically, a review and meta-analysis by Kelleher et al. (17) revealed an average prevalence of psychotic symptoms in children aged 9–12 years and adolescents aged 13–18 years of 17 and 7.5%, respectively. Third, VEOS is often accompanied by high rates of co-occurring neurodevelopmental disorders, either as full syndromes or sub-threshold conditions. Driver et al. (7) observed that, among the NIMH study cohort, 72% of the VEOS patients exhibited socio-relational difficulties, 55% demonstrated academic difficulties, 50% reflected language difficulties, 44% displayed motor difficulties, and up to 20% had a comorbid diagnosis of autism spectrum disorder (ASD) (7). Finally, the characteristics of VEOS, compared to AOS, are not well-defined and have not yet been extensively studied. There is a scarcity of research on this topic, and the limited number of studies that have been conducted have generally involved small sample sizes, due to the rarity of VEOS and challenges associated with differential diagnosis (i.e., distinguishing VEOS from mood disorders, multidimensional impairment, and childhood anxiety disorders) (18). Furthermore, it can be particularly challenging to discriminate between schizophrenia and schizophrenia spectrum disorders. In this context, it is possible that studies may exhibit heterogeneity in the inclusion of patients within the VEOS diagnosis. In fact, they may also include patients with the broad dimension of schizophrenia spectrum disorder (brief psychotic disorder, schizotypal disorder, delusional disorder, schizophrenia, schizophreniform disorder, and schizoaffective disorder) (1), treating them collectively as VEOS. However, it is important to acknowledge the potential heterogeneity within this group and the need for further research to distinguish specific subtypes and their unique characteristics.

For the present review, we hypothesized that VEOS would share clinical features with EOS and AOS, while also displaying distinct and identifiable characteristics. Accordingly, a comprehensive review was conducted to consolidate the scientific literature regarding the clinical characteristics and comorbidities of VEOS. The aim was to summarize the major findings to date, providing clinicians with more tools to support their diagnostic process and development of tailored treatment plans, and enhance the overall understanding of VEOS.

2 Methods

2.1 Search strategy

This study is based on a PubMed/MEDLINE exploration for studies published from the beginning of the database until February 28, 2023, employing the following search terms: "Very early-onset schizophrenia" OR "Childhood-onset schizophrenia." The entire research team reached a consensus on the search approach and collectively contributed to the examination of the literature. The chosen articles fulfilled the subsequent eligibility criteria: (1) they constituted original research studies; (2) they included subjects with a diagnosis of VEOS (< 13 years), as assessed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders third/fourth/fifth edition (DSM-III/IV/5) or the International Classification of Diseases ninth/tenth edition (ICD-9/10); (3) they separated data for VEOS; and (4) they utilized questionnaires or interviews to assess anamnestic data, clinical features such as signs and symptoms, and comorbidities.

2.2 Eligibility and study selection

The following studies were not considered: (1) reviews and meta-analyses (nevertheless, the reference lists of these studies were scrutinized to identify potentially eligible studies that might have been missed during the initial database search) (i.e., "Review"); (2) case reports or case series (i.e., "Case"); (3) studies that did not assess individuals with schizophrenia onset before 13 years (i.e., "No VEOS"); (4) studies that did not focus the assessment on clinical features (i.e., "No Clinical"); (5) qualitative studies not supported by statistical analysis (i.e., "No Data"); (6) research that did not offer distinct data for VEOS subjects in comparison to EOS, AOS, healthy controls, or individuals with different psychiatric diagnoses (i.e.,

"Lumping); (7) studies unrelated to the pertinent topic (i.e., "Unrelated"); (8) editorials, letters to the editor, opinion articles not supported by data (i.e., "Letters"); (9) protocols and ongoing studies; (10) corrections to existing article; and (11) studies for which no English translation was available (i.e., "No English"). The criteria for including and excluding studies, established through two rounds of the Delphi method, gained unanimous acceptance from all authors. The research adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (19). The online Supplementary material comprises the PRISMA checklist and flowchart, along with comprehensive results and data regarding included/excluded studies (refer to Supplementary Figures S1, S2 and Supplementary Table S1).

2.3 Data extraction and synthesis

Information extracted from the chosen articles was systematically recorded in a standardized spreadsheet. Precisely, the subsequent variables were recorded: primary author, publication year, sample size, participant age, sex ratio (male/female), study design (incorporating interviews, tests, or questionnaires employed), and outcomes pertaining to key clinical characteristics among individuals diagnosed with VEOS. A summary of the included studies is included in Table 1.

2.4 Risk of bias assessment

In order to evaluate the reliability of the review and its quality, and to rigorously analyze the outcomes of the chosen studies, a risk of bias analysis was performed. This analysis adhered to the indications and criteria put forth by the Agency for Health Care Research and Quality (37). The online Supplementary material delineate the criteria utilized for assessing the risk of bias. Each study underwent bias assessment in accordance with the stipulated criteria, encompassing selection bias, performance bias, detection bias, attrition bias, and reporting bias. Subsequently, a bias level, categorized as low, medium, or high, was assigned to each study based on the assessment. The included studies were independently evaluated by the authors, and any disparities in the assessments were resolved through discussions. The evaluation of the risk of bias is detailed in the online Supplementary material, specifically in Supplementary Table S2.

3 Results

3.1 Search results

The aforementioned search yielded an initial collection of 384 articles, spanning publication dates from February 1984 to January 2023. Through the application of inclusion and exclusion criteria, a total of 366 articles were excluded, culminating in a final selection of 18 articles (refer to Table 1). Detailed explanations for the rejection of each study can be found in the Supplementary material, specifically Supplementary Table S1. The complete search results, along with reasons for exclusion when applicable, are depicted in the PRISMA flowchart, accessible in the Supplementary material (Supplementary Figure S1).

3.2 Overview of the included studies

The studies exhibit overlapping results across different issues, making it challenging to categorize them distinctly. Nevertheless, we have attempted to identify the primary focus of each study based on the argument that received the most attention. Six of the included studies focused on the risk factors, in particular, sex differences and premorbid neurodevelopment comorbidities before developing psychotic symptoms. Another six studies investigated the main clinical features of VEOS. The remaining six studies underlined the evidence of specific neuropsychological deficits in these patients. Each of these groups of studies is discussed in the following paragraphs.

3.2.1 Risk factors and premorbid neurodevelopmental comorbidities

In Ordóñez et al. (24), a longitudinal study conducted in 2016 on the NIMH cohort, the authors assessed 133 inpatients with COS. The aim of the study was to expand on sex differences in the COS population. The mean age at psychosis onset was 10.29 years for females and 9.51 years for males. This study was conducted on the NIMH cohort, so it shares some characteristics with other NIMH studies. The NIMH study was conducted from 1990 to 2017, and individuals were longitudinally assessed in a period of inpatient hospitalization and observation of up to 3 months. Patient diagnosis of VEOS was re-evaluated after a period of medication wash-out of up to 3 weeks. Similarly to other studies on NIMH cohorts, individuals underwent several tests and interviews, including clinical and anamnestic assessment (CA); Scale for the Assessment Positive (SAPS), and Negative Symptoms (SANS), which are scales used to assess positive and negative symptoms in schizophrenia; Brief Psychiatric Rating Scale (BPRS), a rating scale that is useful for rapidly assessing psychiatric symptoms in patients; Children's Global Assessment Scale (CGAS), which evaluates the influence of psychiatric symptoms on the subject's functioning; Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS), a semi-structured interview based on DSM-5 criteria that investigates the occurrence of psychiatric symptoms in adolescent or child subjects; Autism Screening Questionnaire (ASQ), used to assess the presence of Pervasive Developmental Disorder (PDD); different editions of the Wechsler Intelligence Scale for Adults (WAIS), an IQ test designed to measure intelligence and cognitive ability in adults, and the revised version for children (WISC-R), an individually administered intelligence test for children between the ages of 6 and 16, (due to the longitudinal design of the NIMH studies, intelligence tests included adult and children's versions and included different editions); Simpson-Angus Extrapyramidal Side Effect (SIM), used to evaluate adverse effects from antipsychotic medication; and Abnormal Involuntary Movement Scale (AIMS), used to measure involuntary movements known as tardive dyskinesia. Females had lower verbal IQs than males. Moreover, males displayed younger ages of onset and higher rates of comorbidity with PDD and Attention Deficit Hyperactivity Disorder (ADHD) than females with COS. However, no differences were found between groups in most clinical measures and in premorbid abnormalities across academic, language, and motor domains.

TABLE 1 Summary of included studies.

Study	Population	Design	Results	Observations
Cheng et al. (20)	216 ids with COS (F 126; M 90; x̄ at onset =10.66 ± 1.79). 366 ids with AdOS (F 221; M 145; x̄ at onset =14.17 ± 1.07).	RS. CA, PANSS.	No difference in sex, days of hospitalization, psychiatric family history, comorbidity, DUP, and PANSS total score at admission for AdOS and COS. COS had a ↑ illness course, ↓ PANSS positive score upon admission and PANSS reduction rate, and a ↑ PANSS negative score upon admission and PANSS total score on discharge than AdOS ($p < 0.05$). COS had ↑ insidious onset ($p < 0.01$), bizarre behaviors, impulsive behaviors, visual hallucinations, and formal thought disorder and ↓ delusions than AdOS ($p < 0.05$). No significant differences in the incidence of hallucinations, negative symptoms or early non-specific symptoms between the two groups. COS showed ↓ treatment efficacy than AdOS ($p < 0.05$).	Results about clinical manifestations and severity of illness in COS with respect to SCZ in older ids are in line with previous studies. Instead, the absence of differences in DUP and in premorbid neurodevelopment alterations appear to be in contrast with the literature. This study presents data on a large group of COS.
Galitzer et al. (21)	20 ids with COSS (F 13; M 7; x̄ at admission = 11 ± 1.83). 191 ids non-COSS (F 82; M 109; x̄ at admission =10.78 ± 1.65)	RS. CA, CGAS.	COSS had ↓ CGAS scores at admission compared to non-COSS ($p = 0.006$), while scores at discharge were not statistically different between the groups. COSS were more likely compared to non-COSS to be on medication at discharge ($p = 0.009$) and on medication with antipsychotics at any point ($p = 0.001$) and at discharge ($p = 0.001$). These results were more pronounced in F and in older (> 11.16 y) COSS. Older COSS were in 90.1% F. In addition, F were not in education at admission ($p = 0.025$) and had ↑ duration of admissions ($p = 0.016$) and ↓ CGAS at discharge. No differences in comorbidity between groups.	This study was poorly informative about clinical features. Highlighted worse functioning in COSS, in particular at admission. Interestingly, F showed worse functioning and an older age compared to M. The sample of COSS was small.
Coulon et al. (22)	22 ids with VEOS (F 8; M 14; x̄ at onset = 9.55 ± 2.5); 154 ids with EOS (F 38; M 116; x̄ at onset = 15.9 ± 1.2); 551 ids with AOS (F142; M 409; x̄ at onset = 23.7 ± 5.9)	RS. CA, PANSS, CDRS, EHI, GAF, WAIS III/IV, NART.	VEOS had a fourfold ↑ DUP than the EOS ($p < 0.0001$) and an eightfold ↑ DUP than the AOS ($p < 0.0001$). VEOS had ↑ PANSS scores for the psychopathology general score ($p = 0.021$) and total score ($p = 0.041$) than EOS and AOS. VEOS had ↓ educational levels than EOS and AOS ($p < 0.0001$). No significant differences in neuropsychological scores among the three groups, and no difference in the premorbid IQ scores between the three groups. VEOS exhibited ↑ history of learning disabilities than AOS ($p = 0.020$) and ↓ right-handedness quotient than AOS ($p = 0.048$).	In the present study, a ↑ DUP and a ↑ illness severity are confirmed for VEOS with respect to EOS and AOS. These results were in line with previous literature. However, no differences were noted for positive or negative symptoms between the groups as in other studies.
Craddock et al. (23)	125 ids with COS (F 60; M 65; x̄ at onset = 9.90 ± 2.03)	LS. CA, SAPS, SANS, BPRS, CGAS, KSADS, ASQ, WIS.	A two-factor solution containing positive and negative dimensions was found from CFA and 3-cluster solution using K-means cluster analysis. The three groups had low scores on both dimensions (LM), high negative scores with low positive scores (HN), and high scores on both dimensions (HM). LM had ↑ full-scale IQ than HN and HM ($p = 1.50E-03$). LM had ↑ CGAS scores than HM ($p = 2.13E-09$), while HN showed intermediate scores. A trend was observed for age of onset, with HN being older at onset than LM and HM. LM showed a trend in comorbidity with behavioral disorders (ADHD, ODD, CD) than HN and HM.	This study shows the importance of negative symptoms in COS. Moreover, it highlights the relationship between psychotic symptom severity, worse functioning, and lower IQ. Results are similar to those found on EOS and AOS. A possible secondary role for disorganized symptoms was noted.

(Continued)

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TABLE 1 (Continued)

Study	Population	Design	Results	Observations
Ordonez et al. (24)	133 ids with COS; F 61, $\bar{x}$ at onset = 10.29 ± 1.63; M 72, $\bar{x}$ at onset = 9.51 ± 2.28.	LS. CA, SAPS, SANS, BPRS, CGAS, KSADS, ASQ, WIS, SIM, AIMS	F had ↓ verbal IQ than M ($p = 0.03$). M had a lower age of onset than F ($p = 0.03$). M showed ↑ rates of comorbidity with PDD and ADHD the F. No differences between groups in most clinical measures or in premorbid abnormalities across academic, language, or motor domains.	These results point out some sex differences in COS. In particular, F showed ↓ IQ and this, in light of the literature, might suggest worse functioning and most severe psychotic symptoms in F with COS.
Greenstein et al. (8)	85 ids with COS (F 38; M 47; $\bar{x}$ at onset =9.92 ± 2.06), 53 ids with AD (F 18; M 35; $\bar{x}$ at onset =8.33 ± 2.35).	LS. CA, SAPS, SANS, BPRS, CGAS, KSADS, WIS, NIMHGS	COS had ↑ scores for positive and negative symptoms in SANS ($p < 0.0001$), SAPS ($p < 0.0001$), BPRS ($p = 0.0002$), and NIMHGS PsyS ($p < 0.0001$) and ↓ scores in IQ ($p = 0.0004$), CGAS ($p < 0.0001$) and NIMH DepS ($p <$. 0001)/AnxS ($p = 0.015$) than AD. COS were older at age of onset than AD ($p < 0.0001$). Results of multiple logistic regression, two predictor models including only NIMHGS PsyS and DepS, showed: PPV = 91.34%, NPV = 55.20%, sensitivity = 78.71%, specificity = 77.56%, overall accuracy = 78.42%, AUC = 87.12%. These results indicated that ↑ psychosis ratings and ↓ depression ratings combine to increase the probability that a patient has COS.	The authors purpose a worksheet to be used in clinical settings to determine the likelihood that a child or adolescent has COS. These results highlight the difference between depressive symptoms and negative psychotic symptoms. The severity, not just the presence, of psychotic symptoms differentiates COS children from AD children.
David et al. (25)	117 ids with COS (F 50; M 67; 24 NVH with $\bar{x}$ at onset =10.7 ± 1.59; 94 VH with $\bar{x}$ at onset =9.7 ± 2.1)	LS. CA, SAPS, SANS, CGAS, WIS.	COS had: 95% auditory Ha, 80.3% visual Ha, 60.7% somatic/tactile Ha, and 30% olfactory Ha. There was a considerable overlap between all the Ha modalities: all ids with visual Ha had auditory Ha (not vice versa) and all ids with somatic/tactile and olfactory Ha had visual and auditory Ha. VH compared to NVH had an earlier age of psychosis onset ($p < 0.05$), younger age at assessment ($p < 0.01$), ↓ full-scale IQ ($p < 0.01$), ↓ CGAS, and ↓ duration of illness from age of 1st symptom onset ($p < 0.01$).	Auditory Ha also appears to be a fundamental psychotic symptom in COS. However, visual Ha is highly represented and could be considered an index of COS severity.
White et al. (26)	26 ids with COSS (F 9 M 17; age $\bar{x}$ = 14.8 ± 2.9) 37 HC (M 22 F 15, age $\bar{x}$ = 14.5 ± 3.2)	LS. SIRP	COS patients performed worse than HC within all three age groups in both verbal ($p < 0.0001$) and visuospatial modalities ($p < 0.001$). The trajectory of the verbal SIRP showed a disproportionately lower performance in the VEOS group compared with the older two age groups ($p < 0.002$).	According to adults' data, verbal and visuospatial modalities are deficient in patients with COS. This study highlighted that the early onset SCZ, at a time when verbal short-term memory is rapidly maturing, could impair cognitive performance and, in particular, verbal performance.
Mattai et al. (27)	61 ids with COS divided into two groups: "good sleepers" (> 6 h, $n = 30$, M 10 F 20, $\bar{x}$ = 10.93 ± 2.18) and "poor sleepers" (< 6 h, $n = 31$, M 16 F 15 $\bar{x}$=10.50 ± 3.32).	LS. CGAS, CGI, BPRS, SAPS SANS, Psyc-BH, Mania-BH, Ansx-BH, Dep-BH.	"Good sleepers" showed better functioning in BPRS ($p = 0.008$), SAPS ($p = 0.018$), and SANS ($p = 0.020$) upon admission. "Poor sleepers" showed ↑ BH-Anxiety scores ($p = 0.042$) upon admission. "Poor sleepers" without medications had a significantly ↑ score in SAPS ($p = 0.017$) SANS ($p = 0.0125$), BH-Anxiety ($p = 0.014$), CGAS ($p = 0.08$), and BPRS ($p = 0.07$). "Poor sleepers" had ↑ scores in SAPS and SANS at admission (Pearson's $p < 0.001$ and Spearman's ($p = 0.003$) respectively) and during the medication wash-out period (Pearson's $p = 0.01$ and Pearson's $p = 0.002$).	COS patients suffer from significant sleep disturbances and sleep disturbance is closely related to symptom severity. This supports the idea that subjects suffering from more severe symptoms upon hospital admission could be supposed to have significant sleep disturbance, which would continue with discontinuation of the medication

(Continued)

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TABLE 1 (Continued)

Study	Population	Design	Results	Observations
Biswas et al. (28)	15 ids with COS (F 8; M 7; $\bar{x}$ at onset = 12.25 ± 1.16), 20 AdOS (10 M,10F; $\bar{x}$ at onset = 21.81 ± 2.31) and 20 with AOS (M10, F10; $\bar{x}$ at onset = 31.45 ± 8.35)	LS MISIC, PGI, BVMG, NBT, PANSS	The COS group had significantly ↑ PANSS Positive scores ($p < 0.01$) and ↑ PANSS Negative scores ($p < 0.001$) and PANSS General Psychopathology scores ($p < 0.001$) than AdOS and AOS. The COS group performed ↓ on all the subtests of memory PGI ($p < 0.001$) except for recent memory and had ↑ error scores ($p = 0.001$) and ↑ dysfunction rating scores ($p < 0.05$) on BVMG and NBT.	This study supports the hypothesis that the earlier the onset and greater the severity of illness and neuropsychological deficits, in particular, verbal learning, visual learning, overall memory, and visuospatial and visuomotor organization deficit.
Abu-Akel et al. (29)	32 ids with COS (M 27, F 5; age $\bar{x}$ 10.34 ± 1.56) medicated ($n = 15$),unmedicated ($n = 17$) and 34 HC (M27 F7; age $\bar{x}$ 9.28 ± 2.07)	RS K-FTDS, WISC-R	COS ids, treated and untreated, had a significant inappropriate response to the Yes/No ($p < 0.001$) and Wh ($p < 0.02$) questions, compared to HC. In terms of increased use of speech functions, the medicated group showed ↑ no responses to both Yes/No ($p < 0.003$) and Wh- questions ($p < 0.02$), and inappropriate responses to both Yes/No ($p < 0.002$) and Wh- questions ($p < 0.01$), compared to HC. Conversely, the unmedicated group gave significantly ↑ inadequate responses to Yes/No questions ($p < 0.03$) than HC. However, regarding the decrease in the use of speech functions, the drug-treated group gave ↓ direct responses (Yes/No, $p < 0.06$; Wh-questions, $p < 0.001$) and ↓ additional responses (Yes/No, $p < 0.002$; Wh-questions, $p < 0.005$) compared to HC. The unmedicated group differed only in the use of fewer direct responses to Wh- questions ($p < 0.01$) than HC. The medicated group differed from the unmedicated group only by a higher use of supplementary answers to Yes/No questions ($p < 0.05$) No correlations of Full-Scale, Verbal, or Performance IQ with any of the speech function variables. However, SCZ ids presented a significant correlation between the WISC-R Distractibility factor score with no responses ($p < 0.04$), direct responses ($p < 0.05$), implied responses ($p < 0.005$), and inappropriate responses to Yes/No questions ($p < 0.07$).	This study showed that the SCZ group differed significantly from the HC group in the use of speech functions. The medicated patients seem to have a wider range of abnormal uses of speech functions than the unmedicated patients: less responsive and less likely to generate speech after their initial response to questions (i.e., supplementary responses) compared with the unmedicated patients. In addition, speech functions appear to be associated with specific (WISC-R Distractibility) rather than with global cognitive deficits.
Frazier et al. (30)	28 ids with VEOS (F 14; M 14; $\bar{x}$ at onset of psychosis = 10.2 ± 1.7); 20 HC (F 11; M 9; in pubertal age)	RS FSIQ, Mean Tanner Stage	A significant correlation was found between the age of onset of secondary sexual characteristics and the age of onset of psychosis in F ($p = 0.002$) but not in M. Additionally, the onset of menarche did not show any relationship with the onset of psychosis ($p = 0.41$.). The study also found that the ages of onset of pubertal changes were similar in M and F siblings of the study participants, and there were no significant differences between the ages of onset of menarche in F VEOS and their sisters ($p = 0.22$).	This study found an absence of a clear relationship between onset of psychosis and indices of sexual development for VEOS.

(Continued)

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TABLE 1 (Continued)

Study	Population	Design	Results	Observations
Caplan et al. (31)	32 ids (F 5; 27 M; $\bar{x}$ 10.3 ± 1.56) with VEOS (18 medicated; F4; M 14; age between 7.4 and 12.3 y; 14 unmedicated; F 1; M 13; age between 8.5 and 12.2 y); 47 HC (F 12; M 35; $\bar{x}$ 9.3 ± 2.03).	LS Interview for Childhood Disorders and Schizophrenia, Story Game, K-FTDS, WISC-R	HC used significantly ↑ referential revision ($p < 0.0005$), word choice revision ($p < 0.05$), false starts ($p < 0.003$), and fillers ($p < 0.003$) than the medicated VEOS. The medicated VEOS used ↓ referential cohesion, conjunctions, and words per clause than the HC and ↓ referential revision ($p < 0.05$), postponement ($p < 0.01$), and fillers ($p = 0.006$) than the unmedicated patients. VEOS had ↑ illogical thinking scores than HC ($p < 0.002$). VEOS with loose associations used ↑ false starts ($p < 0.01$) and fillers ($p < 0.01$) than those without loose associations. Within the VEOS group, there was a significant correlation of the WISC-R Distractibility factor score with false start ($p < 0.006$), repetition ($p < 0.004$), and loose associations ($p < 0.006$). There was a diagnostic effect for the following cohesive variables: referential cohesion ($p < 0.001$), conjunction ($p < 0.0001$), unclear/ambiguous reference ($p < 0.02$), and verbal productivity (words per clause) ($p < 0.001$)	This study represents the first attempt to investigate self-initiated repair measures in VEOS, along with the correlation with clinical indicators of formal thought disorder, linguistic cohesion metrics, and cognitive distractibility score. The study's findings suggest that, alongside formal thought disorder, diminished employment of repair strategies, lower employment of cohesive elements, and decreased verbal output for expressing thoughts could potentially signify adverse manifestations in VEOS.
Alaghband-Rad et al. (32)	23 ids with VEOS (15 M and 8 F; $\bar{x}$ at onset of psychosis < or = 12).	RS K-SADS-E, DICA-P, DICA-C, PAS, ADI-R, FSIQ	There were more delays for crawling in M ($p = 0.04$). Delays were most striking for language development; the mean age of first sentence was 26.5 months (±7.4), which is significantly delayed compared which is significantly delayed compared with the adult cases ($p < 0.0001$). Ids showed low-normal IQ and inconsistent cognitive decline ($p = 0.48$.). In general, the sample showed quantitative and qualitative abnormalities, similarly to previous reports on VEOS: 36% with at least some features of PDD (autism and transient motor features) and 30% with ADHD.	The findings indicate greater premorbid abnormalities in VEOS. This, together with the chronicity and severity of childhood cases, indicates that VEOS may be a more severe form of the disorder.
Hollis et al. (33)	18 ids with VEOS (F 5; M 13; age between 7 and 13 y) and 43 ids with EOS (F 22; M 21; age between 14 and 17 y); 61 HC coupled for age and sex with.	RS CA	The VEOS and EOS showed no significant differences in the occurrence of psychotic symptoms. The disorder of language production is significantly ↑ in VEOS ($p = 0.012$), and the difference in disordered language comprehension with EOS is not statistically significant. Among disturbances in motor development, only "restlessness and fidgetiness" were significantly ↑ in the EOS ($p < 0.02$). VEOS had ↑ insidious start, but this was not statistically significant ($p = 0.07$).	This study found that language impairments were more common in VEOS than in EOS and were independent of sex. A limitation of the study is that the comparison with HC is made with all schizophrenic patients without distinguishing between VEOS and EOS.
Caplan et al. (34)	29 ids with VEOS (F 6; M 23; $\bar{x}$=10.2 ± 1.6); 10 schizotypal (F 3; M 7; $\bar{x}$=9.3 ± 1.4); 54 HC (F 12; M 42; age between 5 and 12.5 y)	LS CA, K-FTDS, WISC-R	VEOS ($p < 0.0002$) and schizotypal ids ($p < 0.0001$) both had significantly ↑ illogical thinking and total FTD scores than HC. In total, 70% of VEOS ($p < 0.0001$) and 64% of the schizotypal children ($p < 0.003$) had loose associations scores above zero. The data among VEOS, schizotypal children, and HC demonstrated that IQ did not affect the diagnostic differences in the K-FTDS scores of patients and HC.	The K-FTDS could be used to detect FTD in children at risk of schizophrenia. Also of note is the correlation found between IQ and FTD in VEOS.

(Continued)

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TABLE 1 (Continued)

Study	Population	Design	Results	Observations
Caplan et al. (35)	31 ids with VEOS (F 6; M 25; $\bar{x}$ 10.2 ± 1.5)	LS CA, K-SADS, K-FTDS, WISC-R, Span of apprehension task	Illogical thinking and loose associations were not significantly correlated ($p < 0.5$). Loose associations were negatively and significantly correlated with FSIQ ($p < 0.01$) and the WISC-R distractibility factor ($p < 0.02$) but not with the verbal IQ ($p < 0.2$) and performance IQ sub-scores ($p < 0.05$). After partializing out the variance from the distractibility factor scores, loose associations were not significantly correlated with FSIQ ($p < 0.2$) and performance IQ ($p < 0.6$). Illogical thinking was not significantly associated with FSIQ ($p < 0.4$) verbal IQ ($p < 0.7$), performance IQ ($p < 0.3$), or distractibility factor scores ($p < 0.3$). VEOS with partial report span of apprehension scores had ↑ illogical thinking scores ($p < 0.05$).	This study found that illogical thinking and loose associations reflect different aspects of attention/information processing in VEOS. There were significant associations between illogical thinking and the span of apprehension and between loose associations and distractibility. Neuropsychological impairments could have a role in clinical manifestations and in the severity of the disorder.
Watkins et al. (36)	18 ids with VEOS (F 5; M 13; age at onset of psychosis <10 y): 7 with a history of autism (SA group) and 11 with a history of COPDD (S group).	RS CA, K-SADS, CBCL, CPRS-D, WISC-R	The SA group had a significantly earlier onset of SCZ than the S group ($p < 0.05$). In total, 7 of the 15 DSM-III symptoms of autism and COPDD were present in the SA group at significantly ↑ levels ($p < 0.05$) than in the S group between 31 months and 6 years.	This article investigates the comorbidities between early schizophrenia and other psychopathological disorders of childhood and their evolution over time. In particular, it highlights the association between VEOS and neurodevelopmental disorders.

AD, alternate diagnosis; ADI-R, Autism Diagnostic Interview; ADHD, attention deficit hyperactivity disorder; AdOS, Adolescent-Onset Schizophrenia; AFH, age of first hospitalization; AFS, age of first non-specific psychiatric symptoms; AIMS, Abnormal Involuntary Movement Scale; AnxS, Anxiety Score; AOS, Adult-Onset Schizophrenia; ASQ, Autism Screening Questionnaire; AUC, area under the curve; BH-Bunny Hamburg; BPRS, Brief Psychiatric Rating Scale; BVMG, Bender Visuo-motor Gestalt test, CA, clinical and anamnestic assessment; CBCL, Achenbach Child Behavior Checklist; CD, conduct disorder; CDRS, Calgary Depression Rating Scale for Schizophrenia; CFA, confirmatory factor analysis; CGAS, Children's Global Assessment Scale; CGI, Clinical Global Impression; COPDD, childhood onset pervasive developmental disorder; COS, Childhood-Onset Schizophrenia; COSS, Childhood-Onset Schizophrenia Spectrum disorders; CS, comparative study; DAS, Psychiatric Disability Assessment Schedule; DepS, Depression Score; DICA-C, Diagnostic Interview for Children and Adolescents- Child Version; DICA-P, Diagnostic Interview for Children and Adolescents-Parent Version; DIGS, Diagnostic Interview for Genetic Studies; DUP, duration of untreated psychosis; EHI, Edinburgh Handedness Inventory; EOS, Early-Onset Schizophrenia; F, female; ids, individuals; FSIQ, full scale intelligence quotient; GAF, Global Functional Assessment Scale; Ha, hallucinations; HC, healthy controls; HM, high mixed; HN, high negative; IQ, Intelligence quotient; LM, low mixed; LS, longitudinal study; K-FTDS, Kiddie Formal Thought Disorder Rating Scale; KSADS, Kiddie Schedule for Affective Disorders and Schizophrenia; K-SADS-E, Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version; M, male; MDD, major depressive disorder; MDI, Multidimensionally Impaired Children; MISIC, Malin's Intelligence scale for Indian children; M-PAS, Modified Premorbid Adjustment Scale; NART, National Adult Reading Test; NBT, Nahor Benson test; NIMHGS, National Institute of Mental Health Global Scale; non-COSS, children with other severe non-psychotic psychiatric conditions; NPV, negative predictive value; NVH, No Visual hallucinations group; ODD, oppositional defiant disorder; PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale; PDD, pervasive developmental disorder; PPV, positive predictive value; PsyS, Psychosis Score; pts, patients; RS, retrospective study; SANS, Scale for the Assessment Negative Symptoms; SAPS, Scale for the Assessment Positive Symptoms; SCZ, schizophrenia; SIM, Simpson-Angus Extrapyramidal Side Effect Scale; SIRP, Sternberg Item Recognition Paradigm; VEOS, very early onset schizophrenia; VH, visual hallucinations group; WAIS, Wechsler Adult Intelligence Scale; Wh- = what, who, when, why, where; WIS, Wechsler Intelligence Scale; WISC-R, Wechsler Intelligence Scale for Children-Revised; $\bar{x}$, mean age in years; y, years; ↑, longer/higher/more; ↓, shorter/lower/worse/fewer/less.

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Frazier et al. (30) conducted a retrospective study on a sample of 28 outpatients with VEOS compared to their siblings during puberty. The mean age at psychosis onset was 10.2 years. The sample was assessed by a WISC and Mean Tanner Stage, a scale for measuring physical development as children transition into adolescence and then adulthood. The results showed a significant correlation between the age of onset of secondary sexual characteristics and the age of onset of psychosis, but this correlation was observed only in females. However, the onset of menarche was not related to the onset of psychosis. The study also found that the age of onset of pubertal changes was similar in siblings of the study participants, and there were no significant differences between the age of onset of menarche in females with VEOS and their sisters.

Galitzer et al. (21), aimed to compare clinical characteristics and treatment outcomes of inpatients with Childhood-Onset Schizophrenia Spectrum Disorder (COSS) and those of others with a severe non-psychotic condition (non-COSS). The sample consisted of 20 individuals with a mean age at admission of 11 years, while there were 191 non-COSS patients, with a mean age at admission of 10.7. CGAS and CA were used to assess individuals. COSS showed statistically lower CGAS scores at admission but not on discharge in comparison to non-COSS. Furthermore, COSS were more likely to be on medication with antipsychotics than non-COSS. Females with COSS and older COSS (>11.16 years old) showed a worse profile in terms of CGAS scores, longer duration of admission, and a major presence of medication treatments.

Watkins et al. (36) proposed a retrospective study to describe symptom development from birth to 12 years of age in 18 prepubertal patients (13 inpatients and 5 outpatients), who met DSM-III criteria for VEOS. Data were collected over a 3-year period through the submission of interview protocols: CA, K-SADS, CBCL, WISC-R, and the Children's Psychiatric Rating Scale (CPRS-D), a clinical tool for obtaining parental reports of childhood behavior problems. The results showed the presence of a history of autism (SA group) in 7 patients and a history of childhood-onset pervasive developmental disorder (COPDD) in 11 patients (S group). The SA group had a significantly earlier onset of schizophrenia than the S group. Girls appeared to have better premorbid histories than boys and a later onset of schizophrenia.

Alaghband-Rad et al. (32) conducted a retrospective study in a sample of 23 outpatients with VEOS. The mean age of onset of psychosis was 12 years or younger. Several tests, questionnaires, and interviews were conducted: Schedule for Affective Disorders and Schizophrenia for School-Age Children in the Epidemiologic Version (K-SADS-E); selected portions of the Diagnostic Interview for Children and Adolescents, Parent Version (DICA-P) and Child Version (DICA-C), for disruptive behavior disorders, substance abuse, and child psychosis; Premorbid Adjustment Scale (PAS), a rating scale that assesses the extent to which developmental goals were met at different times in a person's life before the onset of schizophrenia; Autism Diagnostic Interview-Revised (ADI-R), a standardized and structured interview for the assessment of children and adolescents suspected of being on the ASD; an unspecified cognitive test or scale developed by Kydd and Werry based on school performance. The results examined quantitative and qualitative abnormalities in the patients that were similar to those in previous reports of very early-onset schizophrenia: 36% of the patients with at least one feature of pervasive developmental disorder, such as autism or transient motor features; 30% with ADHD. The subjects showed low normal IQs, with no consistent cognitive decline, and the most pronounced delays were in language development; furthermore, in males, there were more delays in crawling.

Hollis et al. (33) proposed a retrospective study in a sample of 18 children with VEOS aged between 7 and 13 years and 43 children with EOS aged between 14 and 17 years were compared with 61 healthy controls (HC) matched for age and sex. The sample was recruited from both inpatients and outpatients. The results showed that there were no significant differences in the occurrence of psychotic symptoms. In the VEOS group, the disorder of language production is more common, and onset of symptoms was found to be more insidious. In the EOS group, among the disturbances in motor development, "restlessness and fidgetiness" were more significant.

3.2.2 Clinical features of VEOS

In 2014, Greenstein et al. (8) studied the differences in clinical manifestations between COS and child patients who received a psychiatric alternative diagnosis during the COS differential diagnosis process (AD). The aim was to develop an algorithm through the clinical evaluation of symptoms to better distinguish patients with COS. This study was conducted within the NIMH cohort and shares recruitment and patient assessment characteristics with other NIMH studies. A total of 85 individuals with COS and a mean age at psychosis onset of 9.92 years were compared with 53 individuals with AD and a mean age at psychiatric onset of 8.33 years. Several tests and questionnaires or interviews were conducted: CA, SAPS, SANS, BPRS, CGAS, KSADS, WAIS, WISC, and the National Institute of Mental Health Global Scale (NIMHGS). The latter is a modified Bunney–Hamburg scale (BH) (38) and includes four different scores: psychosis score (PsyS), mania score (ManS), anxiety score (AnxS), and depression score (DepS). Results showed that, in comparison to AD, COS had augmented scores on positive and negative symptoms in SANS, SAPS, BPRS, and NIMHGS PsyS and diminished scores in IQ, CGAS, and NIMHGS DepS and AnxS. Moreover, it emerged that COS had a later age of onset compared to AD. In the multiple logistic regression, the two predictor models including only NIMHGS PsyS and DepS showed a positive predictive value (PPV) of 91.34%, a negative predictive value (NPV) of 55.20%, sensitivity of 78.71%, specificity of 77.56%, and an overall accuracy of 78.42%, with Area Under the Curve (AUC) showing 87.12%. These results indicate that higher psychosis ratings and lower depression ratings combine to increase the probability that a patient has COS respect to another diagnosis.

VEOS individuals show a duration of untreated psychosis (DUP) fourfold longer than EOS and eightfold longer than AOS. These results emerged from a study conducted by Coulon et al. (22) on outpatients with Schizophrenia: 22 with VEOS, 154 with EOS, and 551 with AOS. The mean ages at psychosis onset for the groups were 9.55, 15.9, and 23.7 years, respectively. VEOS were assessed using various tools: CA; the positive and negative syndrome scale (PANSS), a scale used by clinicians for measuring negative and positive symptom severity of patients with schizophrenia, in particular in response to treatments; Calgary Depression Rating Scale for Schizophrenia (CDRS), a measure used to assess the level of depression in people with schizophrenia; Edinburgh Handedness Inventory (EHI), to objectively ascertain the handedness of a subject in activities of daily living; Global Functional Assessment Scale (GAF), which is used to rate the

severity of a mental illness; WAIS and National Adult Reading Test (NART), tests that estimate premorbid intelligence. In addition to results related to DUP, authors highlighted that VEOS had higher psychopathological general and total scores on PANSS. Furthermore, VEOS had a lower educational level than EOS and AOS and was associated with a higher presence of learning disabilities compared to AOS. Premorbid IQ did not appear to be altered in VEOS compared to the other groups.

In one longitudinal NIMH study conducted in 2011, David et al. (25) explored the role of hallucinations in COS patients. In particular, 117 inpatients diagnosed with COS were divided into two groups, one with visual hallucinations (VH) (mean age at psychosis onset of 9.7 years) and one with no visual hallucinations (NVH) (mean age at psychosis onset of 10.7 years). The assessment included SAPS, SANS, CGAS, WAIS, and WISC. The results showed a higher prevalence of auditory hallucinations (95%) compared to visual (80.3%), somatic/tactile (60.7%), and olfactory (30%) hallucinations. Furthermore, this study highlights the overlap of hallucination modalities: all individuals with visual hallucinations also experienced auditory hallucinations (but not vice versa) and all individuals with somatic/tactile and olfactory hallucinations also had visual and auditory hallucinations. Finally, VH, in comparison to NVH, had an earlier age of psychosis onset, a younger age at assessment, a lower full-scale IQ, lower CGAS scores, and a shorter duration of illness from the age of first symptom onset. These results report the importance of auditory hallucinations in COS as in AOS but indicate the role of visual hallucinations in the level of illness severity and in association with lower patient IQ.

Cheng et al. (20) conducted a retrospective comparation of 216 individuals affected by COS with 366 individuals with AdOS. Inpatients with COS and AdOS were assessed upon admission to the hospital and at discharge throughout CA and PANSS. COS had a mean age at psychosis onset of 10.6 years, whereas the mean onset age of AdOS was 14.1 years. No differences were found between COS and AdOS in terms of sex, days of hospitalization, psychiatric family history, comorbidity, DUP, and PANSS total score at admission. COS had a lower PANSS positive score at admission and PANSS reduction rate and a higher PANSS negative score at admission and PANSS total score at discharge compared to AdOS. COS more frequently had an insidious onset and a longer illness course. As to clinical features, COS individuals showed more bizarre and impulsive behaviors, visual hallucinations, and formal thought disorder with diminished delusions than AdOS. However, no significant differences were found in the incidence of overall hallucinations, negative symptoms, and early non-specific symptoms between the two groups. Moreover, COS showed less treatment efficacy than AdOS.

In a longitudinal NIMH study, Mattai et al. (27) aimed to examine the relationship between sleep disturbance, clinical severity, and comorbid diagnoses (e.g., anxiety) in a population diagnosed with COS. As a NIMH study, it shares some characteristics in recruitment with other NIMH studies, as previously described. The sample consisted of 61 inpatients with COS, divided into two groups: "good sleepers" (> 6 h, $n = 30$) and "poor sleepers" (< 6 h, $n = 31$) based on the average total hours of sleep per night. The sleep pattern data were collected by measuring safety records and daily nursing notes and examining them in relation to clinical, biological, and genetic markers of COS. Clinical symptoms were assessed using the SAPS; SANS; BPRS; CGAS; Clinical Global Impression (CGI), a measure of symptom severity, treatment response, and treatment efficacy; and BH for depression, mania, psychosis, and anxiety. These assessments were conducted upon admission and weekly during the medication-free period while hospitalized. The results highlighted that "good sleepers" showed better functioning in BPRS, SAPS, and SANS upon admission, and "poor sleepers" showed higher BH-Anxiety scores upon admission. Moreover, "poor sleepers" without any medications had significantly higher scores for SAPS, SANS, and BH-Anxiety and lower scores for CGAS and BPRS. The results supported the correlations between average sleep scores and clinical ratings measured by SAPS and SANS: "poor sleepers" had higher scores in SAPS and SANS upon admission.

In a longitudinal NIMH study, Craddock et al. (23) analyzed the clinical features of 125 inpatients with COS, with a median age of psychosis onset of 9.90 years. The assessment was conducted similarly to other NIMH studies using a CA, along with the following tests: SAPS, SANS, BPRS, CGAS, KSADS, ASQ, WAIS, and WISC. The authors employed confirmatory factor analysis (CFA) and cluster analysis on SAPS and SANS scores. A two-factor solution, including positive and negative symptoms, was found to best fit the COS population. Furthermore, the authors favored a 3-cluster solution after performing K-means cluster analysis using the positive and negative dimensions from the CFA. The three emerging groups were described as follows: low scores on both dimensions (LM), high negative with low positive scores (HN), and high scores on both dimensions (HM). The LM group showed a higher full-scale IQ than HN and HM. The LM group had higher CGAS scores than HM, while HN showed intermediate scores. A trend was observed in the age of onset, with HN being older at onset than LM and HM groups. The LM group showed a stronger trend in comorbidity with behavioral disorders (ADHD, oppositional-defiant disorder, conduct disorder) compared to the HN and HM groups.

3.2.3 Neuropsychological deficits

In a longitudinal study, White et al. (26) attempted to analyze the trajectory of verbal and visuospatial Working Memory (WkM) deficits in COS patients. The sample consisted of 26 inpatients with a diagnosis of COS, and 37 HC, divided into three age groups: 8–11 years, 12–15 years, and 16 years and older. The verbal and visuospatial WkM tasks were evaluated using a modified version of the verbal and visuospatial Sternberg Item Recognition Paradigm (SIRP). The results showed that COS patients performed worse than HC within all three age groups in both verbal and visuospatial modalities. In addition, the trajectory of the verbal SIRP showed a disproportionately lower performance in the COS group (8–12) compared to the older two age groups.

Abu-Akel et al. (29) aimed to characterize the communicative deficits associated with COS. Speech function variables, formal thought disorder, and cohesion were coded in 32 COS inpatients and outpatients, under treatment (15) and not (17), in comparison with 34 HC, aged from 5.6 to 12.4 years. The assessment of speech function was conducted by a videotaped Story Game in which the children answered open-ended standardized questions on each story, and the raters coded the speech function categories from the transcripts of the children's responses (Yes/No or Wh-questions (what, who, when, why, where)). Formal thought disorder was evaluated from videotapes of the Story Game using the Kiddie Formal Thought Disorder Rating Scale (K-FTDS) and cognitive testing (WISC-R). The analysis of FSIQ revealed inappropriate responses in SCZ subjects, and a correlation of

the WISC-R Distractibility factor score with no responses, direct responses, implied responses, and inadequate responses to Yes/No questions in these patients. Regarding the increased use of speech functions, the medicated group had significantly higher scores of no responses and inappropriate responses than the HC. On the contrary, the unmedicated group had significantly more inadequate responses to Yes/No questions compared to the control group. Analyzing the use of speech functions, the medicated group used fewer direct and supplementary responses than the HC, while the unmedicated group used fewer direct responses to Wh-questions. Lastly, when comparing the two groups, the drug-treated group differed from the untreated group only in the higher number of supplementary responses.

Caplan et al. (34) aimed to analyze the thought disorder in a sample of inpatients and outpatients diagnosed with schizophrenia ($n = 29$) and schizotypal ($n = 10$) disorder and 54 healthy children aged 5–12.5 years. Videotapes of 20–25 min story games were independently rated with the K-FTDS by two trained raters who had no previous knowledge of the individual child's diagnosis. The subject's total formal thought disorder (FTD) score was the sum of the scores for illogical thinking, loose associations, and poverty of content of speech. The results showed that VEOS and schizotypal subjects had significantly higher scores for illogical thinking and total FTD compared to the control group. A total of 70% of VEOS and 64% of the schizotypal children had loose associations scores above zero. The data among VEOS, schizotypal children, and HC demonstrated that IQ did not affect the diagnostic differences in K-FTDS scores between patients and HC.

In a subsequent study, Caplan et al. (31) conducted research that delved into self-initiated repair in a sample of 32 inpatients and outpatients with VEOS (18 medicated and 14 unmedicated) and in 47 HC, along with the correlation with cohesion of language, distractibility, and clinical measures of FTD. The mean age of patients with VEOS was 10.3 years. Several tests and questionnaires or interviews were conducted: Interview for Childhood Disorders and Schizophrenia, a diagnostic interview for schizophrenia; Story Game, a test in which the child listens to two recorded stories, then retells them and answers standardized open-ended questions about the stories, the child also has to invent a tale selected from various suggested topics; K-FTDS; and WISC-R. The results showed a diagnostic effect for the following cohesive variables: referential cohesion, conjunctions, unclear/ambiguous reference, and verbal productivity (words per clause). Within the VEOS group, the WISC-R Distractibility factor score was found to be significantly related to false starts, repetitions, and loose associations, and higher scores for illogical thinking were reported. The medicated VEOS used less referential cohesion, referential revision, and word choice revision and fewer conjunctions, words per clause, false starts, and fillers than the controls and less referential revision and postponement and fewer fillers than the patients without medication. VEOS with loose associations used more false starts and fillers than those without loose associations.

The goal of Caplan et al. study in 1990 (35) was to examine whether loose associations represent a clinical manifestation of impaired attention/information processing and global cognitive deficits in children with schizophrenia. The authors conducted a longitudinal study with a sample of 31 inpatients (70%) and outpatients with VEOS, with an average age of 10.2 years. They assessed patients using K-FTDS, WISC-R, and the Span of Apprehension, which provides an index of the rate of visual information processing. The results showed no significant correlation between illogical thinking and loose associations. Loose associations were negatively and significantly correlated with FSIQ and the WISC-R distractibility factor but not with the verbal IQ and performance IQ subscores. After partializing out the variance from the distractibility factor scores, loose associations were not significantly correlated with FSIQ and performance IQ illogical thinking was not significantly associated with FSIQ verbal IQ, performance IQ, or the distractibility factor scores. VEOS individuals with a partial span of apprehension scores had higher illogical thinking scores.

Biswas et al. (28) aimed to test the hypothesis that the earlier the onset, the greater the severity of illness and neuropsychological deficits. The authors conducted a comparison of the neuropsychological profiles of 15 outpatients affected by COS, with 20 individuals with AdOS and 20 AOS patients. An assessment of neuropsychological profile was carried out using the Malin's Intelligence Scale for Indian Children (MISIC), which is an Indian adaptation of the Wechsler Intelligence Scale for Children; Memory scale (PGI) was used to assess memory functioning; perceptuomotor skills were assessed using the Nahor Benson Test (NBT) and the Bender Visual Motor Gestalt Test (BVMG); and clinical symptoms were assessed with PANSS. The results showed that the COS group had significantly higher PANSS Positive and Negative scores and PANSS General Psychopathology scores than AdOS and AOS. The COS group performed poorly on all the subtests of memory PGI, except for recent memory. The authors had higher error scores and dysfunction rating scores in BVMG and NBT.

4 Discussion

VEOS has characteristics that are distinct from other psychiatric disorders and other forms of schizophrenia (i.e., EOS, AOS). To draw out these distinctions, in this section, we will compare the results of our review with the literature on EOS and AOS.

The first notable difference between these conditions is that, while EOS and AOS tend to exhibit varying frequency rates among sexes, no sex differences have been found with respect to the frequency of VEOS. A study conducted over a 15-year period on the entire English population by Seminog et al. (14) revealed that sex differences in schizophrenia only emerge at around 14 years of age, revealing a progressively higher incidence in males compared to females. In contrast, in adulthood, schizophrenia is more frequent in males, although the prevalence of the disorder has shown minor differences, leading to some controversies in the field (14, 39–43). An intriguing finding that emerged from our review is that, in females, VEOS onset appears to be associated with the emergence of secondary sexual characteristics, and no significant timing differences have been observed concerning menarche between VEOS and healthy subjects (30).

Sex differences in schizophrenia may also refer to clinical features. In this respect, Abel et al. (40) suggested that females tend to exhibit a milder form of AOS. Additionally, other studies have found that females are more likely to demonstrate a later onset of psychosis, a better response to drug therapy, and fewer negative symptoms (44, 45). However, these observations only partially align

with evidence collected from VEOS samples. Males with VEOS consistently displayed an earlier onset of symptoms, while females tended to have poorer functional outcomes (as indicated by CGAS scores), longer periods of hospitalization, and greater use of medication (21). However, Ordonez et al. reported no differences in clinical characteristics between sexes (24). Therefore, susceptibility to VEOS appears to be influenced by the onset of puberty and sexual differentiation during adolescence, with female hormones—particularly estrogens—possibly serving as protective factors (46). As a result, females with AOS might exhibit a more favorable clinical profile because, after puberty, estrogen may contribute to symptom improvement. Indeed, in the case of VEOS, females tend to exhibit more severe symptoms, which contrasts with the findings for AOS. Conversely, males with any of the three schizophrenia subtypes (i.e., AOS, EOS, and VEOS) tend to experience earlier symptom onset and increased comorbidities with neurodevelopmental disorders. Among VEOS patients, males tend to show greater comorbidities with PDD and ADHD (47). Similar comorbidities have also been observed among males in the EOS population (43). This aligns with findings that VEOS patients with a history of autism may experience earlier symptom onset (36). However, no sex differences have been found in premorbid levels of academic, motor, and language performance (24).

Regardless of sex differences, VEOS is often associated with high comorbidity rates of approximately 30%, for both PDD and ADHD. Individuals with VEOS also tend to experience neurodevelopmental difficulties, primarily in language and school skills (22, 32, 33). This aligns with results pointing out that VEOS patients exhibited more impulsive and bizarre behaviors compared to patients with AOS (20). A study focusing on childhood and early adolescent patients with VEOS and schizoaffective disorder confirmed the high comorbidity with ADHD (48). Additionally, the NIMH cohort study revealed a high percentage of ASD (approximately 20%) and non-specific neurodevelopmental impairments (e.g., in motor, language, and social skills) in individuals with VEOS (7, 47). In the adult population, there appears to be a correlation between ASD and schizophrenia, in terms of both shared clinical characteristics (e.g., social communication deficits and reduced emotional expression) (49) and high comorbidity (50, 51). Genetic studies have provided further support for the correlation between schizophrenia and neurodevelopmental disorders, demonstrating a link between autism and schizophrenia (11, 52), as well as between autism, schizophrenia, and ADHD (13, 53). However, it is important to note that imaging studies have indicated distinct brain changes in autism and schizophrenia, suggesting that the correlation between these two disorders may not be straightforward (47). Regarding intelligence, a study found no evidence of impaired premorbid IQ in VEOS patients, compared to those with EOS and AOS (22). However, this finding may have been influenced by the NIMH criteria, which set a minimum cut-off of 70 for premorbid IQ in VEOS patients. This criterion is controversial, given observations that AOS patients show a lower lifelong IQ, and any IQ reduction tends to occur mostly in the months preceding psychotic onset, before stabilizing for the remainder of the illness (54).

Compared to AOS and EOS, VEOS exhibits some distinct characteristics in illness onset. Notably, VEOS typically presents with a more insidious onset and follows a longer course compared to EOS (20). Additionally, studies have highlighted a low percentage of acute onset of psychosis in VEOS (55, 56). Moreover, the DUP in VEOS is generally longer than that of both EOS and AOS (22). However, one study found similarity in the DUP of VEOS and EOS (20). Generally, patients with schizophrenia who experience an earlier onset tend to have longer DUP (57, 58). According to Coulon et al. (22), the DUP of VEOS is four times longer (approximately 8 years) than that of EOS (1.8 years) and eight times longer than that of AOS (1 year). These findings align with the study of Stentebjerg-Olesen et al. (51), which identified that the DUP of EOS is 3.5 times longer than that of AOS. This insidious onset and prolonged DUP in VEOS may contribute to delayed recognition of the disorder and, consequently, a worse prognosis, given that prolonged DUP is associated with poorer outcomes (59). VEOS appears to be more clinically severe than EOS and AOS. In more detail, VEOS patients score higher overall on the PANSS compared to EOS and AOS patients (22). Furthermore, among VEOS patients (compared to EOS and AOS patients), higher PANSS scores have been shown to be associated with greater impairment in neuropsychological aspects such as memory and visuomotor abilities (28). However, a study by Cheng et al. (20) found no significant differences in PANSS scores at ward admission between diagnostic groups, with the exception of higher scores for negative symptoms among VEOS patients and higher PANSS scores among VEOS patients at discharge, suggesting a lower treatment response of VEOS patients (20). Additionally, the greater severity of VEOS is evident in the early brain alterations observed in neuroimaging studies, which align with the alterations observed in AOS but exhibit increased severity. Specifically, in VEOS, gray matter alterations show increased volume loss, progressing from posterior to anterior regions (i.e., parieto-fronto-temporal) and persisting throughout adolescence, with normalization occurring at around the age of 20 years (7, 12). These early alterations are associated with slower white matter growth and decreased cerebellum and insula volume (7, 12), indicating greater disrupted neurodevelopment in VEOS and suggesting a neurodevelopmental etiology for AOS, as well (12). Furthermore, studies have observed a tendency for VEOS patients to demonstrate greater resistance to pharmacological treatment (6) and a higher familial presence of schizophrenia, compared to AOS patients (11). Moreover, it is widely accepted that treatment for VEOS tends to be initiated later and is less effective (6).

From a clinical perspective, VEOS appears to exhibit distinct features in negative and positive psychotic symptoms. An interesting correlation has been found between the presence of these symptoms and IQ, with more psychotic symptoms associated with lower IQs and worse global functioning (23). Concerning negative symptoms, Craddock et al. (23) concluded that, among VEOS patients, negative symptoms may play a crucial role and exhibit a strong association with poor clinical manifestations, as, in their study, the group with only higher negative symptoms (HN group) exhibited intermediate scores relative to the other groups. This suggested a more relevant role of negative symptoms compared to positive symptoms. The centrality of negative symptoms in schizophrenia and the correlation between negative symptoms and disorder severity has also been recognized in AOS (60–62). However, the combination of both positive and negative symptoms appears to be a typical feature of VEOS and is therefore useful for distinguishing VEOS from other psychiatric diagnoses in childhood (8). Of note, depressive symptoms have been found to

be more associated with non-VEOS diagnoses, further underscoring the distinction between negative and depressive symptoms in this disorder. Pontillo et al. (59) emphasized that the clinical presentations of VEOS and EOS may vary depending on the presence or absence of comorbid neurodevelopmental disorders. In this vein, one study found associations between neurodevelopmental disorders and more positive and disorganized symptoms, as well as between a lack of neurodevelopmental disorders and more negative symptoms (63). While different clinical profiles may emerge depending on comorbidities with neurodevelopmental disorders, negative symptoms appear pivotal for defining schizophrenic symptomatology. Nonetheless, a better characterization of the negative dimension of VEOS is needed, as knowledge of the precise manifestation of different negative symptoms (e.g., blunted affect, social withdrawal, and anhedonia) is currently lacking.

Regarding positive symptoms, VEOS is strongly correlated with the presence of auditory hallucinations—similar to what has been observed in AOS samples (64). Such hallucinations seem to play a central role in the disorder (25), and they have been found to be associated with increased risk of psychotic onset (65, 66). Compared to patients with AOS and EOS, VEOS patients demonstrate a higher frequency of visual hallucinations (20, 25). However, auditory hallucinations remain fundamental to the disorder. Indeed, in VEOS, different types of hallucination can overlap, but auditory hallucinations are consistently reported, and visual and olfactory/somatic hallucinations are experienced only in association with auditory hallucinations. Nevertheless, visual hallucinations, in particular, appear to be an indicator of severity associated with lower IQ (23), poorer functioning, and earlier symptom onset (25). In schizophrenia, hallucinations take on greater significance when they are accompanied by other symptoms, such as thought disorders (67, 68). This is particularly relevant to VEOS, as the disorder is characterized by a poverty of language content, illogicality, and loss of association (31, 35). This partly corresponds to the observation that VEOS exhibits both more formal thought alterations and more hallucinations (20, 25). Thought disorders, which alter the perception of one's internal dialog, appear to be associated with the development of auditory hallucinations (69, 70) and may relate to the neuropsychological changes observed in schizophrenia patients. Similarly, greater hallucination in AOS patients has been shown to correlate with lower cognitive performance (71). Impaired executive functioning relating to working memory and attention has also been shown to be a consistent feature of schizophrenia (54), as evidenced by functional neuroimaging studies (72, 73). More specifically, both AOS and VEOS patients tend to show impairments in linguistic and visuospatial working memory (26). Mixed evidence has emerged regarding the association of greater impairment of working memory and auditory hallucinations (74, 75).

Further research is needed to investigate the frequency and characteristics of delusions in VEOS. To date, only a few studies have explored this topic, observing the frequency of symptom presentation in a clinical group without conducting a statistical analysis or establishing a direct correlation with AOS. Nevertheless, the findings of these studies suggest that delusions may be prevalent in the majority of patients with VEOS (55, 56, 76). Notably, Russell (55) observed a lower complexity in delusions, with a greater presence of infantile themes and a possible lower frequency overall, in VEOS patients compared to AOS patients. Only one study included found a lower frequency of delusions in VEOS patients relative to EOS patients (20). No comparisons of delusions between VEOS and AOS patients were drawn in the included studies.

Furthermore, brain imaging studies have demonstrated differences between VEOS patients and children with similar symptoms but a non-schizophrenia diagnosis (7, 12). From a clinical perspective, VEOS appears to be distinct from other disorders with similar presentations by virtue of the higher prevalence of both positive and negative psychotic symptoms, compared to depressive symptoms (8). VEOS also exhibits a later onset compared to other psychiatric conditions in childhood (20). These findings help to distinguish VEOS from psychiatric conditions with similar symptoms, such as mood disorders and multidimensional impairment (77). Therefore, VEOS stands apart from not only other forms of schizophrenia but also from other childhood psychiatric disorders.

The findings of this review, when compared to the existing scientific literature on EOS and AOS, shed light on VEOS while leaving numerous questions unanswered. Schizophrenia typically arises following significant alterations of central nervous system (CNS) maturation, such as during early neurodevelopment (e.g., synaptogenesis) and adolescence (e.g., synaptic pruning) (78–80). In particular, synaptic pruning is associated with dysregulation of the CNS excitation and inhibition systems and dysregulation of the dopaminergic and glutamatergic networks, which may contribute to schizophrenic symptoms (78). VEOS onset precedes adolescent neurodevelopment, suggesting the presence of pathogenetic differences compared to AOS. However, many clinical features and fundamental brain changes exhibit a high degree of continuity between VEOS and AOS. It may be that schizophrenia, as a multifactorial disorder, involves various etiological and pathogenetic elements (e.g., genetic susceptibility, traumatic life events, altered synaptogenesis, altered synaptic pruning, and neurotransmitter network dysregulation), of which only a subset applies to VEOS. Notably, VEOS suggests that earlier factors (e.g., genetic components and early brain development) may play a greater role, as supported by the comorbidities with neurodevelopmental disorders. While the impact of traumatic life events in VEOS may appear less evident, such events may still occur very early on, even during gestation and birth (81).

Furthermore, since synaptic pruning occurs at a later age, the brain alterations observed in VEOS must be linked to either premature synaptic pruning or other early changes in brain processes, leading to a structural and functional similarity with AOS. However, this theory must be subjected to further research investigating the structural and functional brain diversity in VEOS with respect to AOS. The variations in pathogenesis observed in VEOS may account for the epidemiological and clinical specificity. As discussed, onset at prepuberal age also appears to affect the course of the disorder, especially among female subjects, who cannot yet benefit from the possible protective role played by estrogens. The lower response to drug therapies and higher frequency of visual hallucinations in VEOS may account for the distinct neurotransmission alterations, compared to AOS, possibly involving dysregulation in the dopamine network. On the other hand, VEOS and AOS have some common clinical elements (e.g., negative symptomatology and the importance of

auditory hallucinations), suggesting shared pathogenetic processes. The presence of a prodromal phase in VEOS is yet to be clarified. While the long DUP and insidious onset associated with VEOS suggest its presence, this topic remains underexplored.

5 Limitations and strengths

The present review has both limitations and strengths, which should be underlined. First, the number of available studies was relatively limited, and the investigated studies applied a variety of population selection criteria. Additionally, some topics were more extensively researched than others. For example, a lack of research on delusions in VEOS and the qualitative characteristics of positive and negative symptoms in this population was evident. Moreover, some studies (e.g., the NIMH studies) employed more rigorous selection methods. VEOS is an extremely rare and challenging condition to recognize, and this may have led to recruitment errors in the absence of a strict and well-structured selection process. Another potential weakness is the heterogeneity in sample sizes and evaluation methods across the studies, including variations in inpatient and outpatient assessments. Similarly, variation in the drug therapies among the study populations may represent a confounding factor. For example, the NIMH studies evaluated patients after a pharmacological wash-out period, while other studies assessed patients with a regular medication regimen. Finally, the present review only consulted a single database (PubMed/MEDLINE) to retrieve relevant studies. This can potentially affect the quality of a systematic review, as emphasized by other authors (82).

On the other hand, the present study represents one of the few attempts to systematically review and summarize the literature on the clinical and neuropsychological features of VEOS. Thus, this review contributes to the existing knowledge by providing a comprehensive overview of current research.

6 Conclusion

In conclusion, VEOS appears to be continuous with EOS and AOS while also exhibiting distinct and recognizable characteristics. An absence of sex differences in frequency, the worse clinical profile demonstrated by females, increased severity and treatment resistance, higher presence of visual hallucinations, and comorbidities with neurodevelopmental disorders appear to be specific to VEOS. At the same time, VEOS seems to share with AOS and EOS the importance of auditory hallucinations and negative symptoms as clinical features, specific brain alterations, genetic risk factors, and some comorbidities with neurodevelopmental disorders (e.g., autism spectrum disorder).

While interest in VEOS has been growing in recent years, the literature examining the clinical characteristics of this disorder remains limited. Further research is needed to establish a definitive VEOS profile. The present study aimed to raise awareness of this rare condition, providing support for clinicians' efforts to establish an early diagnosis and develop effective treatment plans for children with psychosis.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

ML: Writing – original draft, Writing – review & editing. MP: Writing – review & editing. MV: Writing – original draft. AA: Writing – original draft. DB: Writing – original draft. CV: Writing – original draft. SV: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1270799/full#supplementary-material

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Treatment effects of adjunct group music therapy in inpatients with chronic schizophrenia: a systematic review

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Introduction: Pharmacological treatment may be effective for treating positive symptoms of schizophrenia; no evidence of clinically significant effects on negative and cognitive symptoms, social and behavioral functioning. This review investigated treatment outcomes of multiple (at least four sessions in 4 weeks) group music therapy sessions adjunct to standard care in inpatients with chronic schizophrenia.

Methods: A systematic review search of five electronic medical and psychological databases conducted using keywords "music therapy" and "schizophrenia" up to December 2021. Screening was performed for published articles on any adjunct multiple group music therapy (four sessions in 4 weeks minimum) adjunct to "treatment as usual" for inpatients with "chronic" schizophrenia. All study outcomes were all included. Risk of bias of all studies was assessed.

Results: 1160 articles were screened, and 13 randomized controlled trials (RCTs) with a total of 1,114 inpatients were included. Ten RCTs reported open group sessions with active structured music making (ASMM) combining passive music listening (PML) and/or active singing, playing instruments, and improvisations while three other studies applied PML only. Four studies reported significant outcomes for both positive and negative symptoms. Ten of the thirteen studies recorded significant improvements in negative symptoms, behavioral and social functioning. Lasting significant effects were found in a longitudinal RCT with 272 samples evaluated unguided pre-recorded PML as a coping method lasting up to six months and similar results found in another two longitudinal RCTs. Secondary outcomes measured cognition, mood, social interest and function, self-care ability, interpersonal relationships, and QoL all showed significant outcomes. The significance level for pre-post intervention and between-group measures ranged from $p < 0.001$ to $p < 0.05$. No negative effects were reported in any studies.

Conclusion: Evidence from this review suggests rehabilitation with adjunctive regular PML or combined ASMM in group settings may provide therapeutic engagement, contributing to improvements in social interest and participation. PML is low-cost and non-invasive therapy. Enhancing overall QoL as one type of psychosocial therapy. More rigorous longitudinal studies with larger sample sizes are needed to investigate whether regular long-term individual PML and active group music therapy have the same significant treatment effects as coping and rehabilitation strategies.

KEYWORDS

adjunctive therapy, chronic schizophrenia, group music therapy, music-based intervention, psychiatric rehabilitation, psychosocial rehabilitation, coping and rehabilitation

1 Introduction

The Global Burden of Disease Study reported that mental disorders affected 125.3 million people in 2019 worldwide, a 56% increase from a previous report in 1990 (1). Although depressive and anxiety disorders have the highest prevalence among mental disorders, schizophrenia is estimated to have doubled from 1 to 2% (2). According to available data, one in seven individuals diagnosed with schizophrenia can experience functional recovery, suggesting that a major treatment objective should not only be symptomatic clinical remission but also improved social and cognitive functions (3). For these reasons, alternative and adjunctive non-pharmacological treatment approaches maybe required to optimize long-term outcomes.

1.1 Description of schizophrenia and standard treatment

Schizophrenia is a pathological and neurodevelopmental mental illness in which a person's ideas and perceptions are typically detached from reality, significantly affecting their mood and behavior. It is characterized by a unique combination of symptoms and experiences. In clinical practice, positive symptoms include hallucinations, delusions, and disorganized speech and/or behavior, whereas negative symptoms include blunted affect, alogia, avolition, asociality, and anhedonia. The main treatments for patients with schizophrenia have traditionally been pharmacological, including first-generation antipsychotics (FGA), also known as neuroleptics, which were introduced in the 1950s, followed by second-generation antipsychotics (SGA) in the 1980s. FGA and SGA are effective for treating positive symptoms in some patients with schizophrenia. A meta-analysis of 168 randomized placebo-controlled trials investigating existing treatments for the management of negative and cognitive symptoms found that most treatments had non-statistically significant effects and no clinically significant improvement (4). An updated clinical review reported that antipsychotics might worsen negative and cognitive symptoms if taken over time and that side effects range from weight gain, sedation, acute movement disorders, decreased blood pressure with dizziness, and Parkinsonism (5). Long-term neurodevelopmental illness courses that coincide with progressive brain structural changes are well documented. These include enlarged ventricles as a result of loss of gray matter that are related to positive symptoms, whereas loss of the fusiform gyrus and white matter is related to impaired face recognition, negative symptoms, and reduced cortical thickness and neural connectivity. This affects motor control, motor and sensory integration, and spatial attention, which result in gesture deficits, attention impairments, and reduced verbal fluency in addition to a range of cognitive tasks related to short- and long-term memory, decision-making, and emotion processing across phases of the disorder (6), which in turn may affect normal cognitive and behavioral function. Further, discernment of drug-induced side effects of "secondary" negative symptoms from "primary" negative symptoms can be challenging (7).

Patients with chronic schizophrenia are more resistant to drug treatment than those with acute schizophrenia (8), and pharmacological treatment options for negative and cognitive symptoms are limited (4, 9, 10). Long-term antipsychotic treatment-induced structural brain volume reduction, dopamine receptor sensitization, and reduced cognitive function are also associated with relapse and disease progression (11). Clinical study findings have indicated that negative symptoms and cognitive impairment may be important predictors of poor social and occupational performance (12).

Studies have demonstrated both the potential and limitations of FGA and SGA. Antipsychotics have therapeutic effects mainly on positive symptoms, agitation, aggression, and, to some extent, suicidality, as well as relapse prevention treatment (5). The amelioration of negative and cognitive symptoms remains a largely unmet medical need. Owing to strong associations between negative and cognitive symptoms and poor functional outcomes, as demonstrated in a longitudinal first-episode study with a 7-year follow-up (13), a meta-analysis found that negative symptoms were significantly correlated with functional outcome (14) and psychosocial function (15), while another statistical study demonstrated that cognitive function, both positive and negative symptoms, affected over 56% of the variance in quality of life (QoL) of patients with schizophrenia (16). Improvements in QoL and overall functional "recovery" constitute "real-world" therapeutic aims in which both negative and cognitive symptoms are more relevant, as indicated in a clinical review (5). Another recent review informed urgently needed effective interventions for these domains (9, 17).

1.2 Description of illness course

The illness course of schizophrenia is progressive and is usually classified into three phases (prodrome, acute, and chronic) (9). The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) defined the "acute" phase as the sudden onset of at least one psychotic symptom (s) for a duration of less than 1 month from onset and classified as a "reactive type" with transient psychotic symptoms. This is distinct from the "chronic" phase of schizophrenia with a symptom duration of greater than 2 years since illness onset (18). In clinical practice, the distinction between the "chronic" and "acute" phases of schizophrenia is key in that better prognosis is found for the acute phase compared to chronic schizophrenia (19). In diagnostic manuals for acute schizophrenia, International Classification of Diseases, 10th Revision (ICD-10) are being named and coded brief psychotic disorder (BPD) (code F23) and is same as in the DSM-V

(BPD, code 298.8) in which this disorder may or may not be recurrent (20).

1.3 Music as an intervention for schizophrenia

Roederer cited music as a co-product of the development of human language and an essential environmental sensory stimulus for perception, information processing, analysis, storage, and retrieval operations (21). These are essential for voice sound detection, identification, and speech comprehension in brain development. Music has also been recognized as being socially prominent in gatherings of all cultural and religious backgrounds, with activities such as singing, dancing, and generating music extending beyond personal enjoyment to encourage the social good (22). A recent meta-analysis of 18 randomized controlled trials (RCTs) aimed to evaluate the efficacy of adjunct music therapy in patients with schizophrenia demonstrated improved total and negative symptoms, depressive symptoms, and QoL in people with schizophrenia compared with the control group (23).

Music is a complex, polygenic trait. Genome-wide association studies have shown that genes implicated in musicality (musical ability) are associated with psychiatric disorders and neurodegenerative diseases. Music is more than a sociocultural concept, as several genes related to social and cognitive traits have been identified in children with musical abilities (24).

With the advancement of neuroimaging techniques over the past 30 years, researchers have found evidence of how environmental stimuli such as music impact brain activity. The dynamics of brain activity in numerous cortical and subcortical areas have been identified in association with attention, memory, motor functions, semantics, and music syntactic processing, in addition to areas linking emotions, such as the limbic and paralimbic regions, which are still being studied (25–27). Recent discoveries on neural mechanisms specific to music perception and neural population in the human auditory cortex and its pathways suggest that they respond selectively to music, but not to speech or environmental sounds (28). There are further findings in the neural population selective for music with singing (29), including enhanced brain plasticity by selective music listening (30).

Music therapy is a form of psychosocial rehabilitation because of its unique contribution to facilitating self-expression, communication, socialization, social cohesiveness, and psychological and physiological well-being (31). A comprehensive systematic analysis of all RCTs found that music therapy for schizophrenia and schizophrenia-like diseases improves overall health, mental health (particularly negative symptoms), social function, and QoL when compared with conventional care or no treatment (32). Another expert panel study reported a strong consensus (92.3%) that psychosocial interventions are necessary for the functional recovery of people with schizophrenia (33).

A decade-old systematic review of music-based interventions for hospitalized individuals with acute schizophrenia concluded that at least four sessions of structured active musical participation had significant positive effects (34). A more recent systematic review on the influence of music on symptom management and the rehabilitation of patients with schizophrenia concluded that dosage had a greater impact on the effects of music therapy than type and format (35).

Despite encouraging evidence of the positive effects of music therapy for acute schizophrenia, no systematic review has been conducted on the effects of group music therapy with a duration of greater than 4 weeks for individuals with chronic schizophrenia. This systematic review aimed to address the following question:

"What are the treatment effects of regular group music therapy sessions adjunctive to treatment as usual (TAU) in patients hospitalized with chronic schizophrenia?"

2 Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews, 2020 (36). A single researcher (LL) performed all steps.

2.1 Eligibility criteria

2.1.1 Search framework

2.1.1.1 Population

Adult inpatients with chronic schizophrenia; aged ≥18 years; diagnosed with schizophrenia using the DSM-III diagnostic criteria (37), DSM-IV (38), DSM-V (39), ICD-10 (40), or CCMD-2,3 (41) with greater than 2 years of ongoing symptoms' duration even with medication or therapy. The chronic phase was defined as illness duration of greater than 2 years from initial onset (18).

2.1.1.2 Intervention

Adjunct multiple-guided (minimum four sessions in four weeks) group music therapy.

2.1.1.3 Comparator

TAU.

2.1.1.4 Outcome

Any reported (for instance, both positive and negative symptoms, mood, social interests, function, and QoL).

2.1.2 Inclusion criteria

Any RCT or non-RCT, as appropriate, reporting outcomes of guided music therapy or music-based intervention (active, receptive, or combination) applied to patients with chronic schizophrenia receiving standard care in hospital settings. Music therapy must be delivered in groups guided by professional music therapists; doctors, including psychiatrists, or nurses; psychotherapists; trained research assistants; or researchers. Articles written in English and Chinese were included. Data were obtained from the inception of databases to December 2021.

2.1.3 Exclusion criteria

Articles in non-English or non-Chinese languages or those with music therapy or music intervention mixed with other activities, such as dancing; trials providing individual or single sessions of music therapy; case reports; or series trials were excluded.

2.2 Sources of information and search strategies

PubMed, the Cochrane Library, MEDLINE, EMBASE, and PsychoINFO databases were searched from inception to December 31, 2021. The search terms were "(music therapy)" and "(schizophrenia)."

2.3 Study selection and data extraction

The abstracts and titles of articles were assessed, and potentially relevant studies were screened for the full text. A bespoke MS Excel spreadsheet was constructed to record the extracted information on the study title, authors, study period, study aims, country, study duration, intervention frequency, guided sessions offered and attended, music therapy methodologies and techniques, protocol designs, unique setting characteristics, patient diagnoses, informed consent, sample size, randomization, and allocation procedures.

2.4 Data items

Music therapy characteristics were recorded in terms of frequency, duration, and intervention protocols/formats. Reported outcomes at baseline and after intervention, measurement timepoints, potential confounders, type of analysis, and treatment effects were also recorded.

2.5 Synthesis methods

The method of synthesis was descriptive analysis of reported interventions and outcomes.

3 Results

3.1 Study selection

Figure 1 shows the flow diagram of methods used to screen and search the literature. Initially, 1,160 articles were included, of which 967 were excluded because of irrelevant titles and abstracts after the initial screening. On further screening, 111 articles were excluded because they did not meet the inclusion criteria. Diagnosis of acute schizophrenia was excluded because there is no specific definition of the acute phase of schizophrenia spectrum disorder in the ICD-10 diagnostic manual. It was considered whether to include acute schizophrenia as a subgroup. A recent 3-year longitudinal study reported that only 37% of BPD transitioned to schizophrenia; psychotic symptoms were mainly psychosis or positive symptoms and sometimes neurological dysfunction and biological lesions related to substance abuse were reported (42). Furthermore, with the risk of self-harm or suicidal ideation, higher non-adherence, and discontinuation of antipsychotic treatments in patients with acute schizophrenia, the individual might not be sufficiently stabilized in these vulnerable populations and may not be ready for group therapies (43). To reduce the risk of bias, we excluded acute schizophrenia because its treatment strategy is different from that of chronic schizophrenia, which are acute care and usually hospitalization in an emergency psychiatric ward or daycare center for a duration of less than 1 month (44–48); therefore, our primary inclusion criterion of minimum 4 weeks of music intervention period was not met.

One of our main inclusion criteria was the effect of multiple adjunct music therapy of a minimum of four sessions in 4 weeks. We set this minimum dosage (frequency) criterion based on an indication from a recent systematic review on music therapy effects in inpatients with acute schizophrenia, which showed a significant positive effect with more than four sessions of structured active musical participation (34). Another systematic review concluded that dosage had a greater impact on the effect of music therapy compared with music type and format for symptom management and rehabilitation (35). After a clearly defined population, the minimum dosage was determined to be four music therapy sessions in 4 weeks, based on the findings from the above two systematic reviews. Another inclusion criterion was inclusion of RCT and non-RCTs, as appropriate. After exclusion of studies that did not meet our eligibility criteria, the remaining studies were all clinical RCTs.

Four of the included studies had English titles and abstracts, but the main content was in Chinese (49–53) and Korean (54). A free online translation tool for Health Science (55) was used to translate the Korean study. Chinese is the author's first language. All included studies reported that informed consent was obtained from all participants. Only one trial (52) reported the randomization procedures.

3.2 Risk of bias assessment and reporting

Figure 2 shows the Cochrane risk-of-bias tool (56) was used for bias assessment and reporting. This tool includes seven items: (i) sequence generation, (ii) allocation concealment, (iii) blinding of participants and personnel, (iv) blinding of outcome assessment, (v) blinding of outcome assessment, (vi) incomplete outcome data, (vii) selective outcome reporting, and (vii) other biases.

3.3 Summary of socio-demographic and clinical profiles of study participants

The studies were heterogeneous in sociodemographic profiles, comorbidities, symptom type and severity, illness duration, frequency and length of hospitalization, and medical and family histories.

Table 1 is the summary of sociodemographic and clinical characteristics of participants from the included studies. Thirteen trials including 1,114 inpatients were examined. All included studies reported that informed consent was obtained from all participants. The publishing years span from 1990 through 2020. Included studies were conducted in China (49–53, 60, 61), Korea (54, 57), Taiwan (63), Iran (58), India (62), and Turkey (59). The largest sample size was 272 inpatients (62), and the smallest sample size was 28 inpatients (59).

Only eight studies recorded TAU in terms of medication and daily dosage. The mean age in six trials was the mid-30s; three trials, the mid-40s; two trials, the 50s; and two trials, <55 years. The maximum age range was 18–60 years. Two trials (53, 62) did not report the sex ratio, whereas only four trials had 50 ± 10% female participants. The highest sex ratio reported was 78.6% (59) and the lowest was 19.7% (60). Included studies were those with inpatients with chronic schizophrenia with over 2 years since

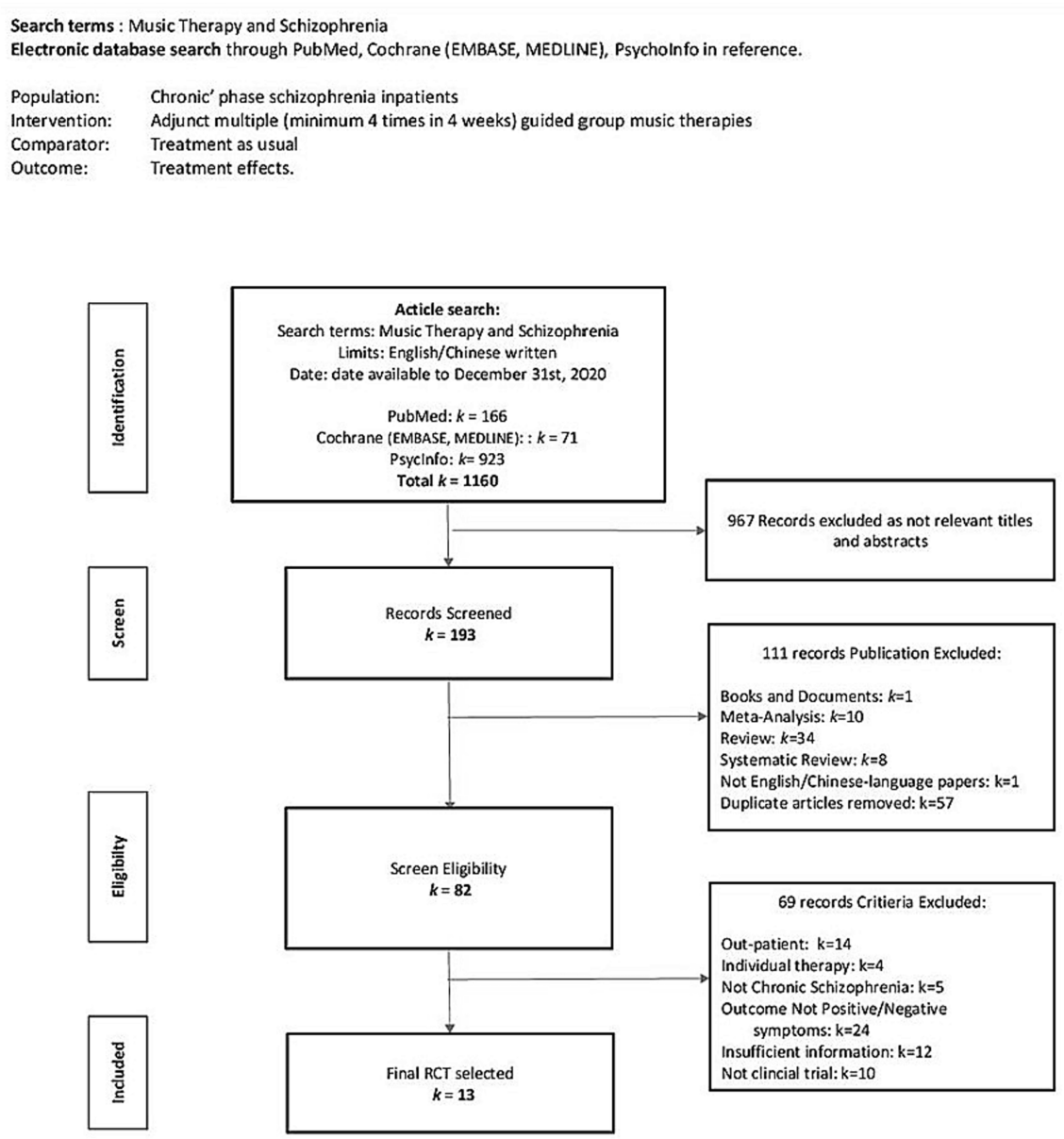

FIGURE 1
PRISMA flow chart of search and screening process.

disease diagnosis; however, the disease duration ranged from 1 year to 1–34.78 years, with only seven studies reporting a mean duration of 10–24.84 years (52–54, 57, 59, 61, 63). Six trials (49, 50, 52, 53, 60, 63) reported the medication type, specifically the FGA chloropromazine or equivalent, daily mean dose of >300 mg (SD 80 mg). Two trials (59, 62) reported the use of the SGA olanzapine and risperidone.

3.4 Description of interventions

All trials had specific protocols and reported programs as listed in Table 2; one trial used questions in their music discussion sessions (53) and four trials provided specific activity/content details (53, 54, 57, 58). Three trials (49, 52, 59) used regular passive music listening (PML), whereas one trial (60) added singing to PML. In one trial (58), participants were randomly assigned to one of the three groups: active structured music making (ASMM), PML, or no music therapy as an adjunct to TAU.

The interventions were heterogeneous in structure, session duration and frequency, music type, active improvision methods, and PML. The sessions lasted from 30 to 120 min. The shortest intervention was four sessions in 4 weeks (58), and the longest was 45-min sessions twice daily and 5 days a week for 24 weeks (51). All trials were guided by professional music therapists, psychiatrists, research assistants, or nurses.

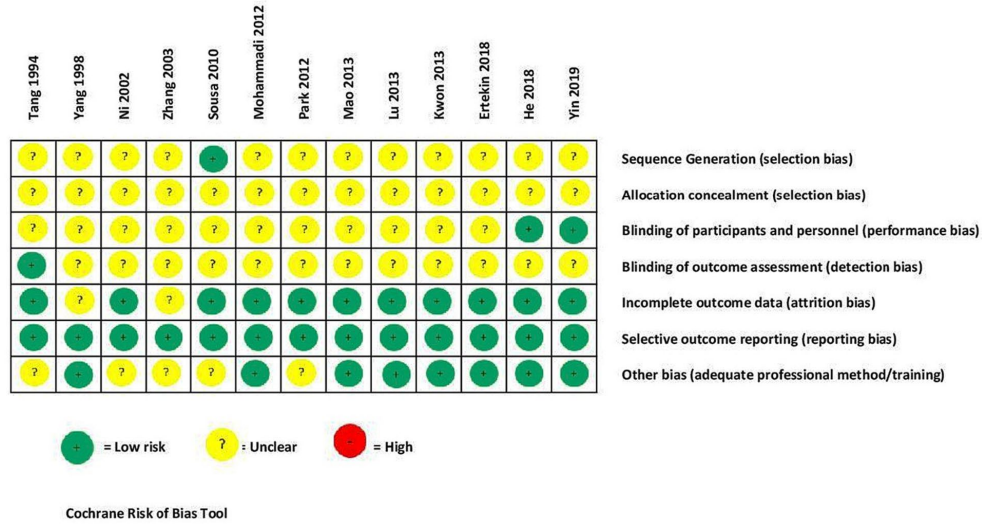

FIGURE 2
Assessing methodological risk of bias in studies.

In one study (59), music therapy was the only intervention with no specific structure. This allowed participants to engage in PML with their pre-arranged recorded music in MP3 format whenever they had auditory hallucinations as a symptom-coping method. Music types ranged from Western, Chinese, Indian, Turkish, and Korean classical music without lyrics to Taiwanese and Persian pop songs with lyrics for PML. Ten trials included singing in their music therapies (50, 51, 53, 54, 57, 58, 60–63). Four trials provided instruments for participants to play (51, 54, 57, 63), with added improvisation performance (61); two trials added movement (57, 58); and three added songwriting (50, 54, 57).

Four trials added music appreciation through discussions on lyrics, composition, and knowledge (54, 57, 58, 63). Three trials added music games, such as improvised playing concert musical instruments, for inducement of interpersonal relationship; lyrics discussion for positive self-expression (54); singing along with discussion; songwriting; personal and group dancing; and movement improvisations (57). Another form of music appreciation included recitation and adaptation of song lyrics such as "I Believe," "Invisible Wings," and, "Starting Again," and conducting a small chorus to group division and selection of response strategies of different scenarios, etc. (53). Most of these Asian music interventions are structured specifically from song selections, music instruments, rewriting song lyrics, and discussion with specific intentions with varied types, durations, and intents in each session.

3.5 Description of outcome measures

Primary and secondary outcomes were heterogenous; instruments listed in Table 3A.

Primary outcomes included scores of the Positive and Negative Symptoms Scale (PANSS) (64), Scale for the Assessment of Negative Symptoms (SANS) (65), Scale for the Assessment of Positive Symptoms (SAPS) (66), and Brief Psychiatric Rating Scale (BPRS) (67).

Secondary outcomes measured mental state and social and behavioral changes using the Calgary Depression Scale (68), Nurses' Observation Scale for Inpatient Evaluation (NOSIE) (69), WHO's Quality of Life-Brief Scale (WHOQoL-BREF) (70), Depression Anxiety and Stress Scale (DAS) (71), Physical Self-Efficacy Scale (PSE) (72), Social Disability Schedule for Inpatient (SDSI) (61), Social Disability Screening Schedule (SDSS) (73), Activity of Daily Living (74), Mini-Mental State Examination (MMSE) (75), Auditory Hallucination Questionnaire (AHQ) (76), Independent Living Skill Survey (ILSS) (77), and Coping Questionnaire for Schizophrenia Patients (CQSP) (53).

Objective brainwave electroencephalogram (EEG) (78) and functional magnetic resonance imaging (fMRI) (79) measures were also used to record functional brain changes.

3.6 Dropout rate summary

Five studies did not report dropout rates (49–51, 58, 59). In one trial ($n = 288$), 16 participants (5%) dropped out because of hospital discharge during intervention (62). Yin et al. (53) reported a 12% dropout rate ($n = 125$) due to hospital discharge, refusal, and other health issues. Lu et al. (63) reported that three participants out of 63 (4.7%) dropped out but provided no reason. One trial ($n = 80$) reported an 8% dropout rate due to relocation to acute wards and loss to follow-up at post-test and 3 months. Two longitudinal studies with objective measures with EEG and fMRI had higher dropout rates: Kwon et al. (57) reported that 13 participants (19%) dropped out at 7 weeks after intervention, while He et al. (52) reported a 20% dropout rate at 1 month and 31% at 6 months, first due to discharge from hospital, and second due to some patients declining to undergo another fMRI.

TABLE 1 Summary of socio-demographic and clinical profiles of subjects.

Author/ year/ country	Diagnostic criteria	Diagnosis	In-patient	Comparison	Study design	Sample size (E/C)		Gender (female %)	Mean age (years) (age range)	Illness duration (years)	Drug and dosage (mg/ day)
Tang et al. (1994) (60) China	DSM-III-R	Residual type schizophrenia	In-patient	Group music therapy vs. control	RCT	38	38	19.7	33.5 (17–52)	8.7 (SD 6.5, range 1–25)	CPZ 530 (SD 225, range 100–990) GMT: CPZ 582 (SD 228) Control: CPZ 480 (SD 213)
Yang et al. (1998) (61) China	CCMD	Chronic schizophrenia	In-patient	Individual + group music therapy vs. control	RCT	40	30	44.4	38.67 (21–55)	12.92 (SD 7.36, range 5.56–20.28)	
Ni and Liu, (2002) (49) China	CCMD-2-R	Chronic Schizophrenia	In-patient	Group Music Therapy vs. Control	RCT	32	32	34.38	<55	>5	CPZ 330.92 (±86.7)
Zhang (2003) (50) China	CCMD-2-R	Chronic schizophrenia	In-patient	Group music therapy vs. control	RCT	36	36	37.5	GMT: 37.5 (SD 10.2) Control: 38.7 (SD 11.6)	GMT: 6.7 (SD 2.7) Control: 7.1 (SD 4.1)	GMT: CPZ 310.2 (±98.2) Control: CPZ 330.92 (±86.76)
Sousa and Sousa, (2010) (62) India	DSM-IV	Chronic schizophrenia	In-patient	Group music therapy vs. control	RCT	136	136		(18–60)	>3	Olanzapine 10–20 or Risperidone 2–6
Mohammadi et al. (2012) (58) Iran	DSM-IV	Schizophrenia paranoid + residual + undifferentiated + disorganized + catatonic	In-patient	Group 1 active music therapy vs. group 2 passive music therapy vs. group 3 control	RCT	62	34	37.5	34.6 (20–50)		
Park and Kwon, (2012) (54) Korea	DSM-IV	Chronic schizophrenia	In-patient	Group music therapy vs. control	RCT	30	30	53.33	43.1 (35.4–50.7)	GMT: 19.7 (SD 10.9)	
Mao et al. (2013) (51) China	CCMD-III	Chronic schizophrenia	In-patient	Group music therapy vs. control	RCT	45	45	51.1	34.6 (26–50)	GMT: 1.65 ± 1.34 Control: 1.65 ± 1.51	
Lu et al. (2013) (63) Taiwan	DSM-IV	Chronic schizophrenia	In-patient	Group music therapy vs. control	RCT	38	42	26.3	52.02 (35–65)	Diagnosis: 24.96 (SD 9.82) Mean length of stay: 8.01 (SD 7.52)	GMT: CPZ 548.4 (±156.5) Control: CPZ 513.8 (±134.5)

(Continued)

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TABLE 1 (Continued)

Author/ year/ country	Diagnostic criteria	Diagnosis	In-patient	Comparison	Study design	Sample size (E/C)		Gender (female %)	Mean age (years) (age range)	Illness duration (years)	Drug and dosage (mg/ day)
Kwon et al. (2013) (57) Korea	DSM-IV-TR	Chronic schizophrenia	In-patient	Group music therapy vs. control	RCT	28	27	45.5	48.3 (44.88–51.72)	over 10 (81.8%) 5–10 (10.9%) less than 5 (7.3%)	
Ertekin Pinar and Tel, (2018) (59) Turkey	DSM-IV	Schizophrenia	In-patient	Group music therapy vs. control	RCT	14	14	78.6	37 (22–58)	GMT: 0–5 (42.8%) Control: 11+ (42.8%)	GMT: SGA (71.4%) Control: SGA (85.7%)
He et al. (2018) (52) China	DSM-IV	Chronic schizophrenia	In-patient	Group music therapy (22) vs. no music (23) vs. healthy control (19)	RCT	22	23	38.46	MT: 45.72 (9.69) UMT: 45.72 (7.63)	MT: 19.66 (SD 11.11) UMTSZ: 18.00 (SD 8.18)	MT: CPZ 339.23 ± 94.15 UMT: CPZ 320.53 ± 142.5
Yin et al. (2019) (53) China	DSM-IV	Chronic schizophrenia	In-patient	Group music therapy vs. control	RCT	89	36		50.64 (18–60)	Length: 24.9 ± 9.5 From onset: 25.7 ± 8.5	CPZ 406 ± 155

3.7 Summary of data analysis results from all studies

Table 3A reports the baseline and post-intervention total scores of both primary and secondary measures in the experimental group. Table 3B reports data analysis of post-intervention outcome total scores between groups after intervention. Trials used heterogenous statistical methods including *t*-test, chi-square test, analysis of variance, and analysis of covariance to describe pre- and post-intervention outcomes and difference between the groups. Data analysis for sub-domains of measures were reported using SANS (49, 50, 60, 61), SAPS, WHOQoL-BREF (59), PANSS (52, 53), EEG (57), and fMRI (52).

3.7.1 Primary outcomes

The most common clinical rating scales used for positive symptoms were the PANSS, SAPS, SANS and BPRS. Only one trial measured EEG as their primary outcome (57, 59) used the AHQ to measure cognitive function and coping with auditory hallucinations. Measurements were taken at baseline, pre-, and post-intervention. All studies reported a significant decrease in total symptom severity (clinical improvement), with p values ranging from <0.001 to 0.05 (see Tables 2, 3A, 3B). One study reported a substantial decrease in verbal and pseudo types of hallucinations in positive symptoms (61), whereas two studies reported a significant decrease in anxiety and lack of energy (49, 61). Two studies (52, 59) applied passive pre-recorded music for PML with little guidance and showed significant results in both primary and sub-domain measures.

For negative symptoms, the common clinical rating scales used were PANSS, SANS, and BPRS in all but three trials (51, 57, 59), while one of these trials did not measure any negative symptoms (59). One study reported a significant improvement in attention deficit after 1 month (60). Significant speech and initiative improvement were recorded in one trial (61). Two studies (49, 50) reported significant improvements in blunted affect, avolition, and interest in external events.

3.7.2 Secondary outcomes

Secondary outcomes measured were behavioral and social function, mental state, and self-care ability. Four studies (51, 57, 60, 61) used DAS, SDSS, SDSI, and NOSIE measures. The SDSS was used in one trial (51). Problem solving and cognitive adjustment domains were reported using the CQSP in one study after 12 weeks, and the ILSS was used by another trial (54).

One study showed alpha brainwave activity in test participants at eight sites more than in controls, where the experimental group had significant increases in cognitive function and decrease in negative behavior (57). It also measured participants' mental state using the MMSE and observations by nurses on inpatients' social interest and competence, personal neatness, and mood states using the NOSIE. Another study found that even 6 months after baseline, improvement was observed in neural connectivity function in the dorsal anterior insula and posterior insular networks in the insular cortex, resulting in psychiatric symptom improvement by normalizing the salience and sensorimotor networks. For more details, see Tables 2, 3A, 3B.

TABLE 2 Summary of group music intervention formation, duration, and outcome.

Author/year/country	Implementer	Intervention	Intervention duration		Outcome measure	Outcome
Tang et al. (1994) (60) China	Doctor and nurses with prior interest in music	Music listening + singing (popular song)	4 weeks/19 sessions	1 h × 5 times	SANS, DAS	* Negative symptoms improved (esp. flattened affect) * Sig. drop in mean dosage Chlorpromazine after 1 month treatment * Improved Conversational ability * Reduced Social withdrawal, isolation * SANS total score and Attention Deficit $p < 0.01$
Yang et al. (1998) (61) China	Professional music therapist	Music listening, singing and music knowledge lessons, provided instruments and improvisation performance	12 weeks/72 sessions	6 sessions × 2 h/week	SANS, BPRS, PSE, SDSI	* Over 72.5% (40 patients ↑ 3 months) * Sig. improved Negative symptoms (sig. in sluggishness, blunted affect and poverty of thoughts) * Decreased social disability/function improved * Verbal and pseudo hallucination ↓ 55 and 77.8%
Ni and Liu, (2002) (49) China	Researcher	Music listening (Western - Mozart, and Chinese classical music)	8 weeks/40 sessions	30 min/day; 5 times/week	SANS, BPRS	* Sig. improved Negative symptoms in SANS total scores (sig. in Anxiety and Depression, Withdrawal Retardation, Emotional withdrawal, Avolition, Anhedonia) * BPRS total scores sig. Improved in Anxiety/Lack of energy
Zhang (2003) (50) China	Psychiatrist	Music listening (Western - Mozart and Beethove, and Chinese classical music), singing songs, songwriting, improvisation	8 weeks/80 sessions	Active: 45–60 min per day × 5 times weekly Passive: 45–60 min per day × 5 times weekly	SANS, BPRS	* Sig. improved Negative symptoms in SANS total scores (sig. in Anxiety and Depression, Withdrawal retardation, Emotional withdrawal, Avolition, Anhedonia)
Sousa and Sousa, (2010) (62) India	Psychiatrists	Music listening, singing, music listening of Indian classic songs via CDs - explained instruments used in songs	4 weeks/±30 sessions	30 min/daily	PANSS	* Sig. reduced Positive and Negative symptoms * Sig. difference in Anergia, Activation and depression subscales of PANSS
Mohammadi et al. (2012) (58) Iran	Professional music therapist	Group 1- Individual and group playing, improvisation, singing and movement (Persian popular songs) Group 2 - Passive music listening Group 3 - Control	4 weeks/4 sessions		SANS, SAPS	* Sig. reduction for Negative symptoms (anhedonia, asociality in SANS total scores) * both active + passive music therapies - more pervasive and deeper effects for Female * Reduction for Positive symptoms and Negative symptoms (esp. Anhedonia – asociality) * Better motivation expression and communication

(Continued)

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TABLE 2 (Continued)

Author/year/ country	Implementer	Intervention	Intervention duration		Outcome measure	Outcome
Park and Kwon, (2012) (54) Korea	Professional music therapist	Music listening, singing songs, playing instruments music game, music appreciation (classical music), discussions, writing lyrics	4 weeks/8 sessions	60 min × 2 times/week	PANSS, ILSS	* Sig. improve for Negative symptoms * Interpersonal relationships $p < 0.001$
Mao et al. (2013) (51) China	Music teacher, psychotherapist	Music listening, singing songs, playing instruments	24 weeks/240 sessions	45 min each AM and PM, 5 times/weeks	PANSS, ADL, SDSS	* Sig. improve for Negative symptoms * SDSS - sig. Increase in ability selfcare/energy, decrease in social disability # Sig. improvement at follow-up 3rd and 6th month after intervention
Lu et al. (2013) (63) Taiwan	Research assistant	Music listening, singing, playing percussion instruments, watching music videos, and discussions popular Taiwanese songs	5 weeks/10 sessions	60 min × 2 times/week	PANSS, CDSS	* Sig. difference in Positive and Negative symptoms, Depression status, and total symptoms
Kwon et al. (2013) (57) Korea	Professional music therapist and study researchers	Music listening, singing, songwriting, improvisation, movement, discussion	7 weeks/13 sessions	50 min × 2 times/week	MMSE, NOSIE, Brainwave - EEG	* Sig. difference in *Cognitive function*; especially Attention, Language * No diff. - Orientation, Memory and Learning * Improved - *Behavior* - *Positive behavior* (Social competence, Social interest and Personal neatness) *Negative behavior* (Irritability, Manifest psychosis, Psychotic depression) * Activated *alpha Brainwave* - Improved emotional relaxation (joyful emotions)
Ertekin Pinar and Tel, (2018) (59) Turkey	2 faculty members of University, Faculty of Fine Arts, Music Department and a member of the Group for the Research and Promotion of Turkish Music.	Music listening Turkish music Rast tonality	24 weeks	whenever experience Auditory Hallucinations (AH), MP3 player through the headset for 15 min. during hospital stays and after discharge	SAPS, WHOQOL- BREF Auditory Hallucination questionnaire	* AH - helps manage AH, reduced duration and severity 6 months after discharge * SAPS - lower scores * QOL – Improved # sig. Effect after 3rd, 6th months after hospital discharges

(Continued)

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TABLE 2 (Continued)

Author/year/country	Implementer	Intervention	Intervention duration		Outcome measure	Outcome
He et al. (2018) (52) China	Professional music therapist	Music listening (Mozart's sonata K.448)	4 weeks/30 sessions	30 min./day	PANSS, fMRI	* Sig. improved in Positive, Negative symptoms, and total symptoms * No sig. Diff. in Cognition function * Increased neural insular cortex connectivity thus improved psychiatric symptoms thus normalizing salience and sensorimotor networks (improvements vanished after 6 months) # sig. Effect at 1st and 6th months after music intervention
Yin et al. (2019) (53) China	Professional music therapist	Music listening, singing songs, playing game	12 weeks/ 36–60 sessions	1 h/session 3–5 sessions/ week	PANSS, CQSP	* Sig. improved in Negative symptoms (sig. in Social withdrawal, Emotional withdrawal, Avolition, Anhedonia) * SQSP - problem solving and cognitive impairment improved $p < 0.05$

3.7.3 Longitudinal effects in patients after multiple group music therapy

Three trials (51, 52, 59) reported follow-up measures at 1, 3, and 6 months after completion of intervention. One of these trials reported significant findings 6 months after hospital discharge in physical, mental, environmental, QoL, and national domains.

Furthermore, the studies primarily measured positive symptoms only and followed up using the AHQ to assess coping effects; the participants only listened to pre-recorded music (PML) whenever they had auditory disturbances within the total experiment duration of 24 weeks. After hospital discharge, nearly 80% of patients in the experimental group still had occasional auditory hallucinations and continued to listen to music; symptoms reduced to almost half from the first month up to the sixth month (59). One trial had music therapy sessions (PML with singing) of 45-min duration for 5 days a week in the morning and evening for 6 months, with a total of 240 sessions. Baseline, 3-month, and 6-month measures were recorded for symptoms, ADL, and social disability screening; significant findings were found in the total scores of all three scales at $p < 0.05$ (51). Another trial studied neural connectivity and clinical symptoms in schizophrenia and found significant findings in predicting symptom remission in response to daily 30 min ($p < 0.01$). With PML to Mozart after 1 month; non-significant findings were observed at 1-month after intervention, which vanished after 6 months (52).

3.7.4 Overall outcomes

Overall, there were no significant negative findings in any of the trials, and only one study reported no significant differences in DAS measures (60). Seven trials provided data measuring between pre-post intervention in both groups (Table 3A), but only performed statistical calculations and reported findings between groups (Table 3B). Reports of some subscale results might indicate no difference in the pre-post group music therapy. The implications inform engagement in promoting therapeutic relationships. Active involvement in group music therapy, whether PML or ASMM, fosters motivation and volition, management, and alleviation of negative emotions (anxiety, depressed mood, or arousal) in addition to improving both non-verbal and verbal self-expression. In turn, these non-verbal contact with others might elevate social interests and build and improve teamwork, interpersonal relationships, and socialization.

3.8 Assessment of methodological quality

Figure 2 reports the risk-of-bias assessment results. In most studies, there was unclear reporting in sequence generation, allocation concealment, participant and personnel blinding, and outcome assessment. All trials provided detailed descriptions of the outcome data assessment, reporting of outcomes, and data analysis. One included study by Sousa and Sousa indicated four tables with data (sociodemographic, diagnosis of schizophrenia types, PANSS measure scores), but did not respond to our request for these data. Only one trial (62) reported a sealed-envelope method for allocation.

TABLE 3A Effect measures of pre-post intervention total scores of both primary and secondary outcomes in experimental group.

Researchers	Tang et al. (60)	Yang et al. (61)	Ni and Liu (49)	Zhang (50)	Sousa and Sousa (62)	Mohammadi et al. (58)	Park and Kwon (54)	Mao et al. (51)	Lu et al. (63)	Kwon et al. (57)	Ertekin and Tel (59)	He et al. (52)	Yin et al. (53)
Music intervention measures	ASMM	ASMM	PML	ASMM	ASMM	ASMM	ASMM	# PML and singing - follow-up at 3rd/6th month	ASMM	ASMM	# PML - follow-up at 3rd/6th month	# PML - follow-up at 6th month	ASMM
Primary outcome (positive and negative symptoms)													
PANSS					No info.		No info.		√			√	√ Neg. Sym.
BPRS		**	***	*									
SAPS						√					**	√	
SANS	*	**	***	*		√							
Brain activity										√ EEG		√ fMRI	
Secondary outcome (behavior/social functioning)													
MMSE										√			
SDSS								√					
SDSI		**											
NOSIE										√			
Others	X DAS	** PSE						√ ADL	√ CDSS		*** QoL		√ CQSP
							√ ILSS				** AHQ		

***$p < 0.001$, **$p < 0.005$, *$p < 0.01$–0.05, X, No sig. Diff, √, Only data avail.

The Positive And Negative Symptoms Scales (PANSS), the Scale for the Assessment of Negative Symptoms (SANS), Assessment of Positive Symptoms (SAPs), Brief Psychiatric Rating Scales (BPRS). Secondary outcome medical scale included Disability Assessment Scale (DAS), Social disability screening schedule (SDSS), Mini Mental State Examination (MMSE), Nurses' Observation Scale for Inpatient Evaluation (NOSIE), Physical Self-Efficacy Scale (PSE), Social Disability Schedule for In-patient (SDSI), Activity of Daily Living (ADL), The Calgary Depression Scale for Schizophrenia (CDSS), Electroencephalogram (EEG), WHO's Quality of Life –Brief Scale (WHOQOL-BREF), Auditory Hallucination Questionnaire (AHQ), The Independent Living Skill Survey (ILSS), functional Magnetic Resonance Imaging (fMRI), Coping Questionnaire for Schizophrenia Patients (CQSP). Statistical Package for the Social Sciences (SPSS), Intra-class correlation coefficient (ICC), Analysis of variance (ANOVA), Analysis of covariance (ANCOVA).

ASMM, Active Structured Music Making; PML, Passive music listening only.

PML - Passive music listening only, longitudinal design; follow-up measure at 1st, 3rd, and 6th month after intervention or after hospital discharge.

Sousa and Sousa (62) informed there is table with data, tied to retrieve but no reply.

√ Only datas avail., but no statistical reporting in Pre-Post Intervention measures, only reported between groups statistical findings in Table 3B.

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TABLE 3B Effect measures of total scores post intervention of both primary and secondary outcomes BETWEEN groups.

Researchers	Tang et al. (60)	Yang et al. (61)	Ni and Liu (49)	Zhang (50)	Sousa and Sousa (62)	Mohammadi et al. (58)	Park and Kwon (54)	Mao et al. (51)	Lu et al. (63)	Kwon et al. (57)	Ertekin and Tel (59)	He et al. (52)	Yin et al. (53)
Music intervention measures	ASMM	ASMM	PML	ASMM	ASMM	ASMM	ASMM	# PML and singing - follow-up at 3rd/6th month	ASMM	ASMM	# PML - follow-up at 3rd/6th month	# PML - follow-up at 6th month	ASMM
Primary outcome (positive and negative symptoms)													
PANSS					*** Neg. Sym.		*** Pos. and Neg.	** Pos. and Neg.	*** Pos. and Neg.			** Pos. and Neg.	** Neg. Sym.
BPRS		**	***	*									
SAPS						** Pos vs. Neg.					**		
SANS	**	**	*	*		**							
Brain Activity										* EEG		* fMRI	
Secondary outcome (behavior/social functioning)													
MMSE										***			
SDSS								**					
SDSI		**											
NOSIE										** negative behaviors			
Others	X DAS	** PSE					*** ILSS	** ADL	* CDSS		* QoL		* CQSP
											* AHQ		

***$p < 0.001$, **$p < 0.005$, *$p < 0.01$–0.05, X, No sig. Diff, √, Only data avail.

The Positive and Negative Symptoms Scales (PANSS), the Scale for the Assessment of Negative Symptoms (SANS), Assessment of Positive Symptoms (SAPs), Brief Psychiatric Rating Scales (BPRS). Secondary outcome medical scale included Disability Assessment Scale (DAS), Social disability screening schedule (SDSS), Mini Mental State Examination (MMSE), Nurses' Observation Scale for Inpatient Evaluation (NOSIE), Physical Self-Efficacy Scale (PSE), Social Disability Schedule for In-patient (SDSI), Activity of Daily Living (ADL), The Calgary Depression Scale for Schizophrenia (CDSS), Electroencephalogram (EEG), WHO's Quality of Life –Brief Scale (WHOQOL-BREF), Auditory Hallucination Questionnaire (AHQ), The Independent Living Skill Survey (ILSS), functional Magnetic Resonance Imaging (fMRI), Coping Questionnaire for Schizophrenia Patients (CQSP). Statistical Package for the Social Sciences (SPSS), Intra-class correlation coefficient (ICC), Analysis of variance (ANOVA), Analysis of covariance (ANCOVA).

ASMM, Active Structured Music Making; PML, Passive music listening only.

PML - Passive music listening only, longitudinal design; follow-up measure at 1st, 3rd, and 6th month after intervention or after hospital discharge.

** He et al. (52) and Yin et al. (53) compared difference in music time interaction; effects of time and music intervention factor and PANSS scores through repeated measure ANOVA between groups.

Pos vs. Neg ** Mohammadi et al. (58) compared difference between SAP and SAN total scores between groups.

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4 Discussion

Although there are several systematic reviews on music therapies for patients with schizophrenia (32, 80, 81), there are none on multiple sessions of group music therapy for inpatients with chronic schizophrenia. This review found promising evidence for multiple sessions of group music therapy as an effective adjunct treatment to TAU, resulting in greater improvements in both positive and negative symptoms and behavioral and social function, which may contribute to improved QoL and functional recovery.

4.1 Summary of main findings

Music therapy as an adjunct to standard treatment may produce significantly enhanced treatment effects in patients with chronic schizophrenia compared with TAU for both positive and negative symptoms. On the negative symptoms' subscale, significant improvements have been reported in blunted affect, attention, avolition, asociality, and anhedonia (50, 51, 53, 54, 58, 60, 61, 63). For behavioral and social function, increased social interest, better conversational ability related to motivation to communicate, and social engagement, and increased energy related to better self-care ability translated to improved QoL, even though only one study measured QoL improvement (51, 57, 59, 60, 61). Mental state measures, including mood, such as depression and anxiety, have also shown significant improvements (49, 50, 57, 63). Two trials employed objective measures of brain activities that correlated improved emotional relaxation with increased joyful emotion (57) as well as cognitive function improvement in attention and language with group music therapy (52). There have been reports that these positive effects might last for 1 month after intervention, but these are not conclusive. PML demonstrated positive treatment effects as a coping method to auditory hallucinations. Longitudinal treatment effects and general symptom management and improvements contribute to better social function and enhanced interpersonal relationships (54, 57, 58, 60, 61).

4.1.1 Strengths

This review is comprehensive, having searched relevant library databases for over 30 years of publications, and included all relevant trials. Despite the heterogeneous symptom severity, confounding factors, delivery of interventions, and measurement of outcomes, the consistently reported significant positive effects on the symptom management of mental and social domains are encouraging. Whether active or passive, music therapy stimulates brain activity, producing significant positive adjunctive treatment effects for all symptoms.

4.1.2 Limitations

The data set was screened, extracted, analyzed, and drafted the manuscript by a single author (LL), which may have contributed to the risk of selection and interpretation bias. Included patients and settings were hospital inpatients, which limited the opportunities for independent raters. Individual studies showed significant positive primary outcomes in positive and or negative symptoms. However, heterogeneity of music interventions (active ASSM and or passive PML), intervention duration and variable sample profiles and sizes, measures constrained to generate combined results. The dropout rates reflect high refusal rates in longitudinal studies. Many trials did not provide training details of therapists or practice experience.

No study reported any psychotherapy or counseling intervention provided for subjects which might also help prevent or alleviate symptoms at onset. No study reported the number of relapses. Compared with antipsychotic medication, adherence to music therapy may be important for ongoing symptom management. Poor adherence can be caused by multiple environmental, psychosocial, and economic factors, which result in higher relapse risk, poorer prognosis, longer remission time, higher suicide rates, higher hospitalization rates for individuals (82), and higher costs to the public healthcare system (74). In our systematic review, the participants presumably adhered to the full medication regimen, and the low dropout rates in most studies were potentially due to hospital settings. Further studies are required to test whether participants voluntarily adhere to both pharmacological and music therapies and maintain therapeutic results after hospital discharge.

Ten of the included studies (76.9%) were conducted in developing countries, and all the RCTs were conducted in Asian countries. Therefore, this review may not represent the general population of patients with chronic schizophrenia.

5 Conclusion

This review identified effective objective and subjective measures for symptom reduction and improved psychosocial function. Group music therapy (irrespective of delivery) showed encouraging adjunctive effects compared with TAU in patients with chronic schizophrenia. Music therapy is low-cost, non-invasive, and has no apparent side effects; thus, wider applications for people suffering from schizophrenia are recommended. Rigorous longitudinal study designs with larger sample sizes are suggested to investigate whether regular long-term PML or ASMM and group music therapies have the same significant treatment effects on chronic schizophrenia after hospital discharge.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer JL declared a past co-authorship with the author WC to the handling editor.

Publisher's note

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Link between metacognition and social cognition in schizophrenia: a systematic review and meta-analysis

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Introduction: Metacognition is the ability to reflect on one's own cognitive processes, monitor and regulate them to enhance mental performance. Social cognition involves the capacity to perceive and respond to social cues from others. The study of metacognition and social cognition is an expanding research field in psychiatry. Both domains are related to neurocognition, symptoms and psychosocial functioning in schizophrenia. Understanding the relationship between social cognition and metacognition may be pivotal for enhancing the treatment of cognitive symptoms in schizophrenia.

Methods: We conducted a PRISMA systematic review and meta-analysis on quantitative studies comparing metacognition to social cognitive outcomes in adult outpatients with a schizophrenia spectrum disorder. Reports were retrieved from the Medline, ScienceDirect and PsycINFO databases up to July 13th, 2023. Risk of bias was assessed with the Cochrane tool.

Results: Our review included 1,036 participants across 17 reports, with 12 reports included in the meta-analysis. We found a significant positive correlation ($r = 0.28$, 95% CI: [0.14, 0.41]) between social cognition and metacognition. Subgroup analyses indicated that metacognition was specifically associated with theory of mind, attribution, and emotion processing. Different patterns of correlations were observed according to the assessment of metacognition and its subdimensions.

Conclusion: Despite discrepancies among the included studies, no publication bias was detected. The results suggest that metacognition and social cognition are distinct but related constructs. Those processes should be assessed and treated together, along with neurocognition, in schizophrenia.

KEYWORDS

metacognition, social cognition, schizophrenia, cognition, mental health

Introduction

During the last 30 years, metacognition has become one of the main areas of cognitive research. Originally, metacognition was defined by Flavell as knowledge of one's own cognitive processes, their products, and everything related to them (1). This concept is used to describe not only reflection upon specific mental experiences (i.e., thoughts or

sensations) but also a more synthetic process of integrating thoughts, intentions, emotions and relationships over events to form a dynamic representation of the self and others (2).

This definition was expanded to include three distinct functional components. First, metacognitive knowledge refers to acquired knowledge about cognitive processes (e.g., knowing that one is more attentive in a quiet place than in a noisy place). Second, metacognitive monitoring corresponds to the assessment of cognitive functioning (e.g., evaluating one's understanding of a read text). Finally, metacognitive regulation or metacognitive control refer to the reorientation of cognitive activity toward cognitive performance (e.g., using a new strategy to memorize a complex text). Monitoring and regulation thus operate between two separate levels: a cognitive "object-level" and a "meta-level" (3). These components are conceptualized as metacognitive awareness. Overall, metacognition is a useful concept for cognitive activities as it increases the effectiveness and efficiency of cognitive functions (4, 5).

Social cognition is generally defined as the set of mental operations underlying social interactions. These mental operations make it possible to infer intentions and produce behaviors (6). It is composed of theory of mind, emotion processing, attributional style, social perception, and social knowledge (6). Theory of mind is the ability to identify the thoughts and mental states of others. It includes three orders (i.e., level of representation) and two processes: cognitive (i.e., understanding others' thoughts regardless of emotions) and emotional (i.e., inferring others' emotional mental states) (7). Emotion processing is the ability to perceive and use emotions. Attribution style is the way in which individuals explain the causes of events. Social perception represents how individuals perceive social cues and social knowledge refers to the awareness of the functioning of society and social interactions (6). These social cognitive functions support the roles, rules and goals of social interactions (8).

Metacognition is a rapidly expanding field of study in psychiatric disorders (i.e., schizophrenia, mood disorders, substance-related disorders, anxiety) because metacognitive deficits seem to be a common feature of psychiatric disorders, particularly psychosis (9, 10). The most impaired metacognitive process in schizophrenia may be mastery (11–13), which is the ability to work with one's mental representations and states, in order to implement effective action strategies for performing cognitive tasks or coping with problematic mental states (2). Poor metacognitive skills and poor social functioning have been demonstrated in patients with schizophrenia (14, 15). Impaired metacognitive skills are correlated with occupational impairment, low self-esteem and social anxiety (11, 16, 17). Metacognitive skills could therefore be key in translating cognitive performance into life skills. Schizophrenia presents the greatest metacognitive challenges among psychiatric illnesses (18–22). According to some studies, metacognitive difficulties do not significantly differ between patients with schizophrenia and people without psychiatric problems (23, 24). Other studies have observed greater deficits in metacognition among patients with schizophrenia compared to healthy subjects, particularly in forming complex ideas about themselves and others (20, 25, 26).

Alterations in social cognition have been widely demonstrated in schizophrenia (25, 26). These deficits are thought to be the most frequent and earliest impairments and may be the root of clinical symptom formation (27). Many studies have consistently documented significant impairments in several social cognitive domains in schizophrenia, such as theory of mind and emotion perception and processing, social perception and social knowledge (26, 28–30). These impairments may be as severe as or more severe than neuropsychological deficits (31, 32). Indeed, neurocognition was conceptualized as a necessary basis for social cognitive abilities (33). Thus, social cognition deficits may be present without neurocognitive impairments, whereas the opposite is rare (32). Among them, theory of mind is the most impaired function and the most strongly related to functional deficits (26, 34, 35).

The broadest definitions of metacognition appear to have considerable overlap with neurocognition or aspects of social cognition. Indeed, some authors argue that the ability to infer the emotional states and cognitions of others falls within the scope of metacognition (2), while other authors incorporate these processes into the definition of theory of mind (36). Although the extent of this overlap is still debated (36), several authors have argued that these are separate constructs (37, 38). Conceptually, metacognition includes the processing of internal information associated with social cues to enable synthesis. On the other hand, social cognition is a measure of performance because it assesses the accuracy of judgments of social cues (23). Beyond those conceptual differences, discrepancies in brain activation have been reported. Both self-referential thought processes and thinking about other people with similar thoughts lead to similar activation of the ventromedial prefrontal cortex. In contrast, thinking about the thoughts of people perceived as different from oneself activates a more dorsal region of the ventromedial prefrontal cortex, which is not involved in self-reflection processes (39).

Furthermore, clinical and cognitive symptoms in schizophrenia differ in their relationship to social cognition and metacognition. Negative symptoms have been correlated with metacognition and social cognition, whereas positive symptoms have been associated with only social cognition (14, 35). Neurocognition encompasses mental processes like thinking, problem-solving, memory, attention, and executive functions (40). Social cognition, especially theory of mind, may be more generally linked to neurocognition (41), whereas metacognition has been primarily associated with verbal memory (42, 43) and cognitive flexibility (44, 45).

In contrast, some studies have suggested that metacognitive skills are necessary to address social cognition abilities. During a social cognition task in an fMRI study, brain activations related to metacognitive skills preceded brain activations related to social cognition. These results suggest that metacognition is a lower-order process used for understanding others' mental state (46). Reciprocally, social cognition abilities may serve as a basis for metacognitive activity. In particular, emotion processing may be required for metacognitive regulation and for integrating the representation of others (2). Mirror neurons are implicated in the conceptualization of others' goals, meanings and intentions through simulation processes (47).

Since there are similarities and discrepancies between social cognition and metacognition on the conceptual, clinical and neurological levels in schizophrenia, elucidating the correlation between them seems essential. To the best of our knowledge, no systematic review has examined the correlation between social cognition and metacognitive outcomes in schizophrenia. To examine this correlation, we reviewed quantitative studies that compared metacognitive assessments to social cognition evaluations (theory of mind, emotion processing, attributional style, or social perception

and knowledge) in adult outpatients with a schizophrenia spectrum disorder.

Methods

In line with the PRISMA guidelines, a systematic search was performed of clinical trials published in English or French in the Medline, ScienceDirect, and PsycINFO databases from inception and extraction to April 30th, 2020 and updated to include articles published up to July 13th, 2023 following the same protocol. We searched the Medline, ScienceDirect, and PsycINFO databases with the same search strategy (see Appendix 1) using the following search terms to describe our population ("schizophrenia," "psychosis," "schizoaffective"), metacognitive outcome ("metacognition," "metacognitive") and social cognitive outcome ("social cognition," "social cognitive," "social intelligence," "theory of mind," "ToM," "mentalizing," "emotion processing," "emotion perception," "face perception," "faces perception," "social perception," "attribution"). The aims, inclusion criteria, data collection and analysis of this review were specified in advance in the PROSPERO database (CRD42020160259).

For this review, we selected clinical trials assessing the correlation between social cognition and metacognitive outcomes in adult patients living with a schizophrenia spectrum disorder. First, we excluded reports that did not involve a study (e.g., reviews, letters to the editor), involved studies without results (e.g., presentations of a study design) and case studies. Moreover, we restricted our selection to peer-reviewed written communications such as articles and doctoral theses, excluding poster presentations, verbal communications, and chapters of books. No restrictions were applied regarding publication date. We considered all publications in English or French. We included studies with or without a control group, but we did not include control in the statistical analyses. Finally, studies needed to include at least one social cognitive measure and one metacognitive measure derived from a cognitive assessment, a rater-administered scale or a questionnaire. To assess whether a score was a social cognition or metacognitive measure, we searched the original article on the corresponding assessment or scale. All statistical analyses comparing those two scores were accepted.

Reports that were identified in the databases were compared on the basis of their author, title and Digital Object Identifier to eliminate duplicates. Reports were screened for eligibility on the basis of their title and abstract independently by the first two authors. Reports that clearly did not meet the inclusion criteria were excluded, and the remaining reports were then assessed independently by the same two authors on the basis of their full text. Multiple publications were combined when the same patient sample was used in two or more reports. Disagreements were resolved through discussion between the two authors. Finally, a manual search was conducted to identify potential additional reports.

Using a data extraction form, we collected relevant information from the selected studies, including sample characteristics, patient assessments, outcomes and study design. The first author extracted the data from the reports, and the second author confirmed the collected data. As needed, the authors of selected reports were contacted by email with the request to provide missing or complementary information.

Reports that compared a metacognitive measure with a social cognitive measure were included in the review. All reports using a correlation coefficient to examine the relationship between these measures were included in the meta-analysis as well. When a report did not specify the correlation value, we asked the authors to provide it; if the value was not provided, the report was excluded from the meta-analysis. Using the Meta-Essential Package for correlation coefficients in Microsoft Excel (48), we used a Fisher Z transformation of the correlation coefficients and weighted each report according to the number of statistical analyses performed. We computed a weighted summary two-tailed correlation coefficient, an I-squared statistic and a Q statistic for all included studies. Furthermore, we performed analyses for four different social cognitive domains (i.e., emotion processing, theory of mind, attribution, other social cognitive functions), retaining only reports with assessments related to these domains. For each analysis, a forest plot was generated. When I-squared and Q statistics suggested heterogeneity, subgroup and sensitivity analyses were performed to identify the potential source of discrepancy. Finally, publication bias was assessed with Egger regression and Begg and Mazumdar test, and a fail-safe number was computed.

Risks of bias were assessed with the Cochrane risk of bias tool, and a risk of bias form with nine variables was completed by the first two authors. Disagreements between the two authors were resolved through discussion. Risks of bias were assessed using a classification table (see Supplementary Table S1). The risk of bias for medication was considered low when the participants' treatment was stable for at least 15 days and homogeneous in the population (i.e., same class of medication). The risk was considered medium when the medication was either stable or homogeneous and was considered high if none of these criteria was met or if no information on medication was provided by the authors. The risk of bias in the blinding of the metacognition rating was considered low if the investigator performing the metacognitive assessment was blind to the participants' social cognitive performance. This risk was considered high if metacognition and social cognition assessments were administered or rated by the same person or by two investigators without blinding. Concerning the validation of the assessments, the risk of bias was rated as follows: (a) low when metacognition and social cognition assessments were validated in the language of the participant in a previous study; (b) medium if the assessments were only translated, without a validation study; and (c) high if at least one study was neither validated nor translated. The risk of bias for ethical committee approval was considered low if the study was approved by any local or national ethical committee. Finally, the risk of bias for the outcome was considered: (a) low when the correlation between social cognition and metacognition was the primary outcome of the study; (b) medium when this correlation was a secondary outcome; and (c) high when the correlation was the subject of an ancillary study and not a part of the outcomes of the main study.

Results

Study selection

The selection process is described in Figure 1. The search of the Medline, ScienceDirect and PsycINFO databases provided a total of 609 studies. No additional reports were found through a manual

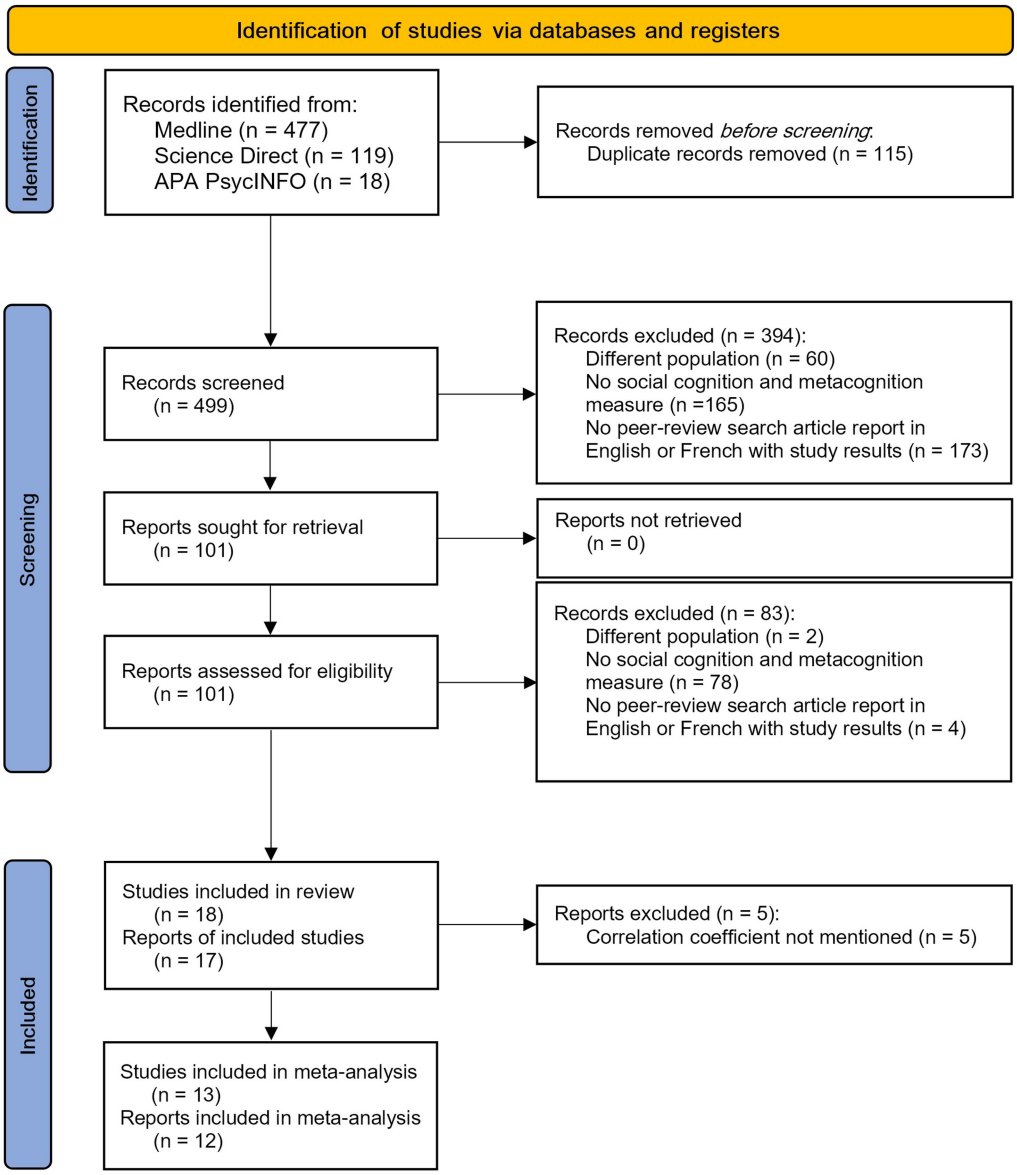


FIGURE 1
Report selection process.

search. After removing duplicates, 494 publications remained. After reviewing the title and the abstract, 394 reports were discarded because it appeared that these studies did not meet the inclusion criteria (different population, no social cognition or metacognitive measure, not peer reviewed, missing study results).

In total, 83 reports were excluded because the full text did not meet the inclusion criteria. Among them, one report was initially included in the review because it used the Interpersonal Reactivity Index, which appeared to assess social cognition, particularly theory of mind (49). We finally excluded this report because the "perspective taking" measure assesses the tendency to take another person's perspective (i.e., cognitive empathy) rather than the cognitive ability to do so. Another report was excluded from the review because the authors used an experimental social cognition task with a metacognitive measure; as such, the metacognitive and social cognitive measures were not independent (50). Finally, a report was excluded from the review because the metacognitive and social cognitive measures were extracted from the same experimental task (51).

One report included two distinct populations with schizophrenia spectrum disorders (52), and thus was considered two studies. Consequently, our analysis comprises a total of 18 studies and 17 reports included in the systematic review (see Appendix 2). Five reports were excluded from the meta-analysis because they did not report a correlation coefficient or did not provide results for all metacognition subscales. We contacted five authors because we were missing correlation coefficients. One author provided further information, and we were able to include their study in the meta-analysis (53). The other authors did not answer, and we only included their reports in the review (17, 54–56).

Study characteristics

The characteristics of the included studies are presented in Supplementary Table S2. The reports selected for the meta-analysis were published in English between 2008 and 2021. The 18 studies included a total of 1,036 patients. Included participants had first-episode psychosis (FEP) in two studies, schizophrenia in four studies and schizophrenia spectrum disorder in 12 studies. Seven reports had a control group, with a total of 147 healthy volunteers, 30 patients with major depression, 30 patients with autism spectrum disorder and 58 patients with substance use disorder. We included two prospective studies, and the remaining eight studies were cross-sectional.

The included studies used 14 social cognition assessments and two metacognition questionnaires (see Table 1). Twelve studies used emotion processing assessments: the Bell Lysaker Emotion Recognition Task (BLERT), the Derntl task, the Face Emotion Identification Task (FEIT), the Eckman 60 Faces Test or the Tool for Recognition of Emotions in Neuropsychiatric DisorderS (TRENDS). The BLERT uses videos depicting professional interpersonal situations where the participant must recognize the emotion of the main character (57). The Derntl (58), FEIT (59), Eckman 60 Faces Test (60) and TRENDS (61) are four performance tasks in which the participant identifies facial emotions.

Nine studies used theory of mind assessments: the Hinting Test, the Reading the Mind in the Eyes Test (RMET), the Picture Sequencing Task, the Movie for the Assessment of Social Cognition (MASC) and the Yoni task. In the Hinting test, the participant indicates the implied intention of characters in stories (62). In the RMET, the participant infers the state of mind or thoughts of a person while seeing only their eyes (63). The Picture Sequencing Task uses cartoon strips where characters collaborate or betray one another; the participant sorts the strips to create a story (64). The Yoni task assesses affective and cognitive, first-order and second-order theory of mind using a cartoon character called Yoni; the participant guesses what Yoni thinks or likes using Yoni's facial expressions (65). The MASC assesses theory of mind using a 15-min film depicting four individuals, with participants answering questions about the mental state of these individuals (66).

Three studies used attribution assessments: the Social Attribution Task – Multiple Choice (SAT-MC) and the Social Cognition and Object Relations Scale – Understanding Social Causality subscale (SCORS-USC). In the SAT-MC, the participant guesses the purpose of a geometric shape mimicking social interactions with other shapes (67). The SCORS-USC assesses the accuracy of the attribution of intention in a participant's Thematic Apperception Test narratives (68).

Four studies used other social cognitive assessments: the Social Cognition subscale of the MATRICS Consensus Cognitive Battery (MCCB-SC) or the Faux-Pas Task. The MCCB-SC is an emotional intelligence test that assesses the ability to manage emotions (69). The Faux-Pas Task assesses the ability to identify social missteps and the consequences for others' mental states throughout ten stories (70).

The 18 studies provided 84 correlations in total (see Supplementary Table S2). Fifteen studies used the Metacognitive Assessment Scale – Abbreviated (MAS-A), including ten that correlated the total score with social cognitive measures. The MAS-A consists of four scales that assess four metacognitive processes: Self-Reflectivity (MAS-SR), the ability to understand Other's mind (MAS-O), Decentration (MAS-D) and Mastery (MAS-M). Self-reflectivity refers to the ability to generate representations of one's self, decentration is the ability to understand the environment from different perspectives, and mastery is the ability to implement effective strategies to accomplish cognitive tasks and regulate one's behavior (2).

(a) In the eight studies that examined the correlation of the MAS-A total score with emotion processing assessments, the MAS-A was significantly correlated with emotion processing. The correlation was positive in seven studies and negative in one study (52). One study examined the correlation of MAS-A subscale scores with the FEIT and observed similar results (71). However, in the three other studies that used MAS-A subscales, the results were heterogeneous: one study

TABLE 1 Social cognitive and metacognitive assessments.

Cognitive functions	Assessment	Author
Theory of mind	Hinting Test	Corcoran et al., 1995
	Picture Sequencing Task	Brüne, 2003
	Reading the Mind in the Eyes Test (RMET)	Baron-Cohen, 2001
	Yoni Task	Shamay-Tsoory et al., 2007
	Movie for the Assessment of Social Cognition (MASC)	Dubreucq et al., 2022
Emotion processing	Face Emotion Identification Task (FEIT)	Kerr et al., 1993
	Derntl Task	Derntl, 2009
	Bell Lysaker Emotion Recognition Task (BLERT)	Bell et al., 1997
	Ekman 60 Faces Test	Young et al., 2002
	Tool for Recognition of Emotions in Neuropsychiatric DisorderS (TRENDS)	Behere et al., 2008
Attribution	Social Attribution Task - Multiple Choice (SAT-MC)	Klin, 2000
	Social Cognition and Object Relations Scale (SCORS)	Westen et al., 1990
Social cognition	Matrics Consensus Cognitive Battery - Social Cognition (MCCB-SC)	Nuechterlein et al., 2008
	Faux-Pas Task	Stone et al., 1998
Metacognition	Metacognitive Assessment Scale - Abbreviated (MAS-A)	Semerari et al., 2003
	Beck Cognitive Insight Scale (BCIS)	Beck et al., 2004

observed significant correlations between the BLERT and MAS-A subscale scores except for the MAS-D (53); one study found significant correlations between the Derntl task and MAS-SR scores but heterogeneous results for the other subscales depending on the emotion assessed (72); and one study observed no significant correlation between the TRENDS and MAS-SR or MAS-O scores (54). Finally, one report used MAS-A total scores and repeated exploratory partial correlation analyses with MAS-A subscale scores; the authors observed significant correlations between the Ekman 60 Faces Test scores and MAS-SR, MAS-O and MAS-D scores (52).

(b) The results of the studies were heterogeneous for theory of mind and attribution. Three studies assessed the correlation between scores on the MAS-A and the Hinting Task, one of which reported a significant positive correlation (19). Interestingly, the study that found a significant correlation included patients with a higher mean level of education (16.64 years) than the two other studies (12.66 and 12.88 years). In addition, one study used MAS-A subscale scores and observed a significant correlation only for the MAS-SR score (53). Three studies used other assessments and found positive correlations between the MAS-A score and theory of mind. One study reported a significant correlation between scores on the MAS-A and the RMET (19). The two other studies described significant correlations of scores on the MAS-SR and MAS-O with the RMET (73) or the Picture Sequencing Task (53). One study reported a significant correlation between the MAS-A score and attribution (74), and one study found nonsignificant results (75). Furthermore, the study that used MAS-A subscale scores reported a significant correlation only for MAS-D scores.

(c) Two studies used the MCCB-SC score and described significant correlations with MAS-A scores (75) and with the MAS-SR and MAS-M scores but not the MAS-O and MAS-D scores (53). Finally, the only study that used the Faux-Pas Task found significant correlations of this score with only the MAS-SR and MAS-O scores (71).

Four studies reported nonsignificant correlations between the Beck Cognitive Insight Scale (BCIS) score and social cognitive measures. The BCIS is a self-rated questionnaire with two subscales: (a) Self-Reflectiveness (BCIS-SR), which assesses the ability to observe one's own mental production and consider different explanations; and (b) Self-Certainty (BCIS-SC), which assesses overconfidence in the validity of one's own beliefs (76). Two studies reported both subscales, one used only the BCIS-SR, and one study generated a composite score using the two subscales (24). One additional study used the BCIS but did not report any correlations (55).

Finally, six studies provided complementary results. The description of regression analyses, additional correlations and group comparisons in the included studies can be found in Supplementary material S1.

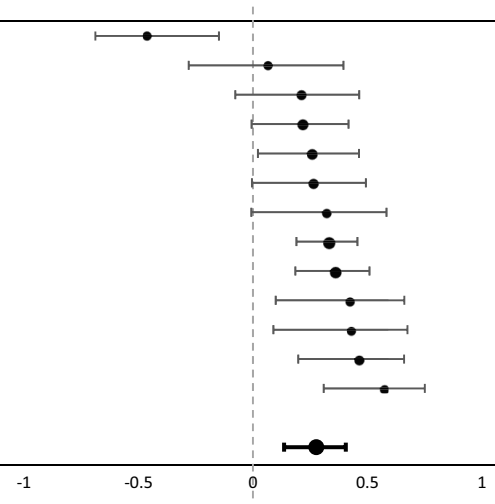
Meta-analysis

Random effect analysis of the 13 studies showed a significant weighted summary correlation coefficient ($r = 0.28$, 95% CI: [0.14, 0.41], $z = 4.18$, $p < 0.001$), as shown in Table 2. I^2 and Q values ($I^2 = 60.80\%$; Q (11) = 33.16, $p = 0.002$) suggested heterogeneity. A statistically significant effect was observed when comparing the 11 studies that used the MAS-A and the two studies that used the BCIS in a fixed-effect subgroup analysis (Q (12) = 33.30, $p = 0.001$), with a significant correlation coefficient for MAS-A studies ($r = 0.31$, 95% CI: [0.23, 0.38], $p = 0.001$) and a non-significant correlation coefficient for BCIS studies ($r = 0.15$, 95% CI: [−0.85, 0.92], $p = 0.513$). Due to the discrepancy in social cognition assessments, we performed four secondary analyses to assess the correlations among theory of mind, emotion processing, attribution and other social cognitive components.

There was a significant weighted summary correlation coefficient ($r = 0.23$, 95% CI: [0.11, 0.34], $z = 5.22$, $p < 0.001$) for the five studies that used theory of mind assessments. I^2 and Q values ($I^2 = 0.00\%$; Q (4) = 2.61, $p = 0.625$) suggested no heterogeneity (see Table 3). Random effect analysis of the three studies that used attribution assessments revealed a significant weighted summary correlation coefficient ($r = 0.25$, 95% CI: [−0.03, 0.49], $z = 3.90$, $p < 0.001$). I^2 and

TABLE 2 Funnel plot representing the weighted correlation of each study included in the meta-analysis, with respective weight ($n = 12$).

Authors	N	Weight (%)	Correlation (random) 95% CI
Lysaker et al., 2021 (1)	37	6.47	-.46 [-.69 ; -.15]
Lysaker, Dimaggio, et al., 2011	36	6.38	.07 [-.28 ; .40]
Lepage et al., 2008	51	7.56	.21 [-.08 ; .46]
Hasson-Ohayon et al., 2018	81	8.96	.22 [-.01 ; .42]
James et al., 2018	72	8.62	.26 [.02 ; .46]
Bonfils, Haas, et al., 2020	57	7.91	.26 [.00 ; .49]
Hasson-Ohayon et al., 2015	39	6.66	.32 [-.01 ; .58]
Luther et al., 2016	175	10.69	.33 [.19 ; .46]
Lysaker et al., 2014	115	9.84	.36 [.19 ; .51]
Lysaker et al., 2010	37	6.47	.42 [.10 ; .66]
Aydin et al., 2018	34	6.18	.43 [.09 ; .68]
Hamm et al., 2012	49	7.43	.46 [.20 ; .66]
Lysaker et al., 2021 (2)	41	6.83	.57 [.31 ; .75]
Total	**824**	**100**	**.28 [.14 ; .41]**



(1) Early schizophrenia spectrum disorders population; (2) Prolonged schizophrenia population.

TABLE 3 Funnel plot representing the weighted correlation of each study included in the meta-analysis and using theory of mind assessment, with respective weight ($n = 5$).

Authors	N	Weight (%)	Correlation (random) 95% CI
Lysaker, Dimaggio, et al., 2011	36	10.22	.08 [-.27 ; .41]
James et al., 2018	72	21.36	.19 [-.05 ; .41]
Hasson-Ohayon et al., 2018	81	24.15	.20 [-.02 ; .41]
Lysaker et al., 2014	115	34.67	.26 [.08 ; .42]
Aydın et al., 2018	34	9.60	.43 [.09 ; .68]
Total	**338**	**100**	**.23 [.11 ; .34]**

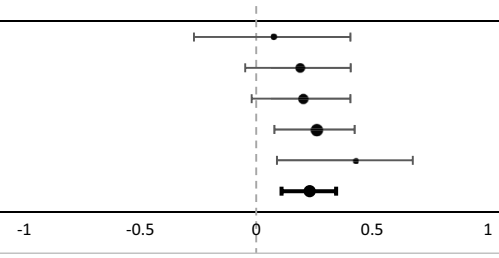


TABLE 4 Funnel plot representing the weighted correlation of each study included in the meta-analysis and using attribution assessment, with respective weight (n = 3).

Authors	N	Weight (%)	Correlation (random) 95% CI
Hasson-Ohayon et al., 2018	81	43.09	.20 [-.02 ; .40]
James et al., 2018	72	38.12	.22 [-.02 ; .43]
Lysaker et al., 2010	37	18.78	.42 [.10 ; .66]
Total	**190**	**100**	**.25 [-.03 ; .49]**

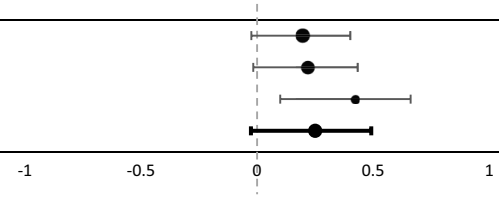
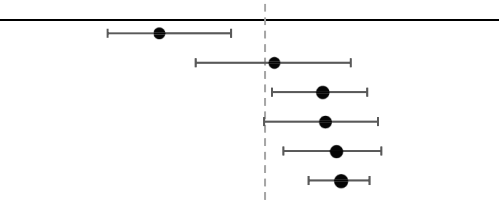


TABLE 5 Funnel plot representing the weighted correlation of each study included in the meta-analysis and using emotion processing assessment, with respective weight ($n = 9$).

Authors	N	Weight (%)	Correlation (random) 95% CI
Lysaker et al., 2021 (1)	37	8.68	-.46 [-.69 ; -.15]
Lysaker, Dimaggio, et al., 2011	36	8.59	.04 [-.30 ; .37]
Hasson-Ohayon et al., 2018	81	10.88	.25 [.03 ; .45]
Bonfils, Haas, et al., 2020	57	10.01	.26 [.00 ; .49]
James et al., 2018	72	10.61	.31 [.08 ; .51]
Luther et al., 2016	175	12.19	.33 [.19 ; .46]
Hasson-Ohayon et al., 2015	39	8.86	.33 [.01 ; .59]
Hamm et al., 2012	49	9.58	.46 [.20 ; .66]
Lysaker et al., 2014	115	11.57	.53 [.38 ; .65]
Lysaker et al., 2021 (2)	41	9.02	.57 [.31 ; .75]
Total	**702**	**100**	**.29 [.07 ; .48]**



(1) Early schizophrenia spectrum disorders population; (2) Prolonged schizophrenia population.

Q values ($I^2 = 0.00\%$; Q (2) = 1.56, $p = 0.458$) suggested no heterogeneity (see Table 4). Ten studies assessed the correlation between emotion processing and metacognition. Random effect analysis revealed a significant weighted summary correlation coefficient ($r = 0.29$, 95% CI: [0.07, 0.48], $z = 3.02$, $p = 0.002$), as shown in Table 5. I^2 and Q values ($I^2 = 77.16\%$; Q (9) = 39.40, $p < 0.001$) suggested heterogeneity. No statistically significant effect was observed when comparing the six studies that used the BLERT and the four studies that used another emotion processing assessment in a fixed-effect subgroup analysis (Q (9) = 9.25, $p = 0.42$, see Supplementary Table S3). A sensitivity analysis excluding the study with atypical populations (52) revealed a significant weighted summary correlation coefficient ($r = 0.34$, 95% CI: [0.22, 0.45], $z = 6.42$, $p < 0.001$) with lower heterogeneity ($I^2 = 39.88\%$, Q (8) = 11.64, $p = 0.113$). Random effect analysis of the four studies that used other social cognition assessments showed a significant weighted summary correlation coefficient ($r = 0.26$, 95% CI: [0.18, 0.33], $z = 10.33$, $p < 0.001$). I^2 and Q values ($I^2 = 0.00\%$; Q (3) = 0.45, $p = 0.93$) suggested no heterogeneity (see Table 6).

The description of risk of bias analysis in the included studies can be found in Supplementary material S2 and presented in Supplementary Table S4. The funnel plot for the 13 studies included in the meta-analysis is shown in Figure 2. Egger regression ($t = -0.50$, $p = 0.63$) and Begg and Mazumdar test for rank correlation ($z = 0.06$, $p = 0.95$) indicated no evidence of publication bias. Additionally, the fail-safe number was 85, which is considered large (77). The results of Egger regression and Begg and Mazumdar test for each social cognitive function are shown in Supplementary Table S5. Possible publication bias was identified for the correlation between attribution and metacognition (Egger regression: $t = 26.78$, $p = 0.02$).

TABLE 6 Funnel plot representing the weighted correlation of each study included in the meta-analysis and using other social cognitive assessment, with respective weight ($n = 4$).

Authors	N	Weight (%)	Correlation (random) 95% CI
Lepage et al., 2008	51	20.78	.21 [-.08 ; .46]
Hasson-Ohayon et al., 2018	81	33.77	.23 [.00 ; .43]
James et al., 2018	72	29.87	.30 [.07 ; .50]
Hasson-Ohayon et al., 2015	39	15.58	.31 [-.02 ; .57]
Total	**243**	**100**	**.26 [.18 ; .33]**

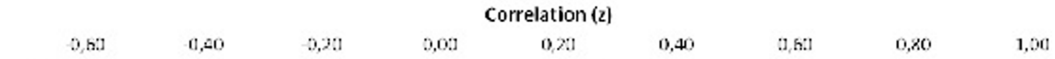


FIGURE 2
Funnel plot of the meta-analysis of published studies.

Discussion

To our knowledge, the present meta-analysis is the first to examine the correlation between metacognition and social cognition in schizophrenia. This systematic review included 1,036 participants in 17 reports published between 2008 and 2023. Twelve reports were included in the meta-analysis, with a total of 824 participants. There was a significant positive weighted summary correlation between social cognition and metacognition assessments in individuals with a schizophrenia spectrum disorder. The correlation coefficient was 0.28, which indicates a small to medium effect size (78). There was no evidence of publication bias, but we found some heterogeneity among studies.

Are metacognition and social cognition correlated in schizophrenia?

Seven reports described only significant correlations between social cognition and metacognition, six of which were included in the meta-analysis. No individual risk of bias seemed to differentiate those reports from the ones with nonsignificant results. However, the reports with significant results were among those with overall lower risks of bias. Two of them were the only reports with a low risk of bias for medication. Moreover, all of them had independent and blinded metacognition and social cognition assessments. Furthermore, one of those reports was an ancillary study. These data strengthen the robustness of the main result. On the other hand, one report included in the meta-analysis and three additional reports included in the review found only nonsignificant correlations. Of note, two of those reports had a high risk of bias for medication, three of them had a high risk of bias for blindness of assessments and two had a high risk of bias for the validation of the assessment.

The small-to-medium correlation between social cognition and metacognition in participants with a schizophrenia spectrum disorder is consistent with theories that postulate that these factors represent two semi-independent domains of cognition (9). As previously stated, social cognition and metacognition are related to distinct activations of the same brain regions in healthy volunteers (39). Tamir and

Mitchel (46) proposed a hierarchical relationship between social cognition and metacognition, suggesting that inferring the judgment on another person requires reflection on one's own judgment followed by a series of adjustments. On the contrary, Kukla and Lysaker (79) have posited that social cognition is a lower-order process needed for metacognition. Another explanation for this range of correlation coefficients is that those two domains are interrelated with neurocognition. A longitudinal study found that improvements in metacognition were associated with improvements in neurocognition and social cognition, indicating parallel trajectories for these three domains (79). In schizophrenia, the correlation between social cognition and metacognition could be mediated by neurocognition and symptoms (80).

The discrepancy in the main analysis could be explained by the metacognition assessments that were used. Indeed, included studies only used two metacognitive assessments, the BCIS and the MAS-A. The correlation coefficients with social cognition were statistically different for these two assessments, with a positive correlation for MAS-A and no correlation for BCIS. It is possible that cognitive insight (assessed by the BCIS) is distinct from metacognition (assessed by the MAS-A). Four studies in the review examined the correlation of BCIS scores with social cognition. Regardless of use of the BCIS-SR score, BCIS-SC score or a composite score, no correlation was identified with social cognition. The BCIS was designed within the framework of cognitive theory and derived "cognitive insight" from the concept of "insight," defined as the awareness of one's own mental illness (76). As such, the BCIS defines cognitive insight as the ability of people living with schizophrenia to appraise and correct misinterpretations or distorted beliefs that can occur. In contrast, the MAS-A total score assesses metacognition which is understood as the ability to monitor one's mental state and regulate behavior, regardless of the occurrence of delusional beliefs and thoughts (2). The MAS-A also considers metacognition the capacity to form and integrate complex representations of the self and others. These variables could represent two ends of a spectrum, ranging from discrete metacognitive activities, assessed primarily by the BCIS, to synthetic metacognition, assessed by the MAS-A (81). Our results suggest that social cognition would then be correlated with general mentalizing abilities in schizophrenia and not with a more specific reflection upon distorted or delusional experiences. The fact that the BCIS is a self-rated questionnaire, in contrast to the MAS-A, can also explain the lack of correlation between the BCIS score and social cognitive measures. Indeed, it is possible that patients with the same level of cognitive insight scored differently on the BCIS because of a different subjective judgment or understanding of the sentences of the scale.

The results also emphasize that social cognition may exhibit different correlations according to the metacognitive dimension assessed. Indeed, the MAS-SR score was more frequently correlated with social cognitive measures than other MAS subscale scores. This result is in line with our main result because the ability to recognize and define one's own emotions and cognitive processes seems to be the closest to metacognition as defined by Flavell (1). In contrast, the MAS-M score exhibited the weakest correlations with social cognitive measures in the review. Mastery (i.e., implementation of cognitive strategies and behavioral regulation) was the most impaired metacognitive function in previous work (11). Our results may be due to a floor effect for mastery scores in the included studies, which reduced the range of the data. Conversely, this lack of significant correlations may originate from an indirect relationship between social cognition and mastery that is mediated by quality of life. Indeed, improvements in social cognition and quality of life over time can significantly predict improvements in self-reflectivity and mastery (79). Surprisingly, the relationship between the ability to understand the mental states of others and social cognition has been inconsistent in the literature. Some authors suggest that this inconsistency is tied to the development of the MAS-A (72). The MAS-SR and MAS-O subscales are rated by assessing first the cognitive component and then the emotional component of each subdimension. Furthermore, the MAS-O assesses the tendency to address others' thoughts or emotions in reasoning activities rather than the ability to do so effectively. In contrast, social cognitive assessments provide performance-based measures. People living with schizophrenia could continue to address the thoughts and emotions of others despite impairments in the ability to do so.

Overall, these results are consistent with the hypothesis of metacognition as a modular skill composed of related but functionally independent subfunctions (2). This is also consistent with findings that metacognitive subdimensions are associated with different neurocognitive functions or exhibit different correlations with quality of life in schizophrenia (43, 71).

Is metacognition correlated with emotion processing?

The most studied social cognitive component in the meta-analysis was emotion processing. The results suggest a significant small-to-medium correlation between metacognition and emotion processing in schizophrenia. Metacognition and emotion processing are conceptually associated because emotion processing is thought to be a key component in metacognitive mastery and understanding of others' minds (2). Furthermore, a previous study on the metacognition of emotion recognition in neurodegenerative diseases suggested that emotion processing and metacognitive impairments share cerebral substrates (i.e., amygdala, insula, frontal and temporal regions) (82).

There was a discrepancy among studies that was not attributable to the emotion recognition assessment used but rather partly due to inclusion of an atypical population in one study. Lysaker et al. included one group of 37 patients with early psychosis (i.e., 5 years of illness and three episodes or less) and one group of 41 patients meeting the criteria for schizophrenia for a minimum of 6 years (52). The correlation between the MAS-A score and the emotion processing assessment was significant in both groups; however, this correlation was positive for the schizophrenia group and negative for the early psychosis group. Surprisingly, this was the only study in the meta-analysis that reported a significant negative correlation between social cognition and metacognition, even though two other studies in the review included patients with first-episode psychosis. Although the emotion processing assessment does not seem to explain the discrepancy in the results, it is noteworthy that these assessments greatly differed from one another. Some of these assessments used pictures of faces displaying emotions, while others used video sequences, which provide more visual and verbal cues. The participants may have to name the emotion among two or six propositions, or they may have to guess the emotional face of someone in a social situation. Some tests use the six basic emotions (i.e., happiness, fear, surprise, anger, disgust, sadness), while others use shame instead of

disgust. The emotions used in the assessments could be crucial because different emotions may not need the same level of metacognition. Indeed, in the study by Bonfils et al. (72), disgust was correlated with all MAS dimensions, while anger was only correlated with self-reflectivity.

Is metacognition correlated with theory of mind and attribution?

There was a significant positive weighted summary correlation of metacognition with theory of mind and attribution. The effect sizes of the correlation coefficients were small to medium with no evidence of heterogeneity in the meta-analysis. Theory of mind and attribution share conceptual similarities and have been associated in previous work (83); consistent with these findings, they share similar correlations with metacognition. Nevertheless, the review identified differences among studies. Three studies assessed the correlation between scores on the MAS-A and the Hinting Task, and only one of them reported a significant positive correlation (19). In contrast, the two studies that assessed the correlation between scores on the MAS-A and the RMET, as well as the study that used the Picture Sequencing Task, found significant results. The Hinting Task assesses verbal theory of mind, while the RMET and the Picture Sequencing Task use nonverbal material. This result is perplexing, no difference has been identified between verbal and nonverbal theory of mind performance in schizophrenia in previous studies (29). The distinction between verbal and nonverbal theory of mind requires further investigation for definitive conclusions.

Limits and future direction

Our meta-analysis has three main limitations. First, we observed selective reporting of quantitative data in several studies included in the review. This suggests that the correlations included in the meta-analysis do not encompass the entirety of scientific data on the subject. However, our results indicate no risk of publication bias across the whole meta-analysis and only a possible risk of publication bias for attribution studies. Furthermore, we performed subgroup analyses to better understand the correlation between metacognition and each social cognitive function. Subgroup analyses in meta-analyses lack statistical power, and their results should be interpreted with caution (84), especially in meta-analyses that include only a few studies. Finally, we found that studies used a wide variety of tests to assess social cognition, either as a whole or in specific components. We observed different results when the test assessed "hot" (i.e., emotional) or "cold" (i.e., cognitive) social cognition. For instance, in the same population, James et al. (75) found that emotional social cognition assessments (emotion recognition and emotion management) were correlated with metacognition, while more cognitive assessments of social cognition (cognitive theory of mind and attribution) were not correlated with metacognition. Other studies support the distinction between cognitive and affective processes when thinking about others (85). Emotional and cognitive social cognition may be understood as separate processes (86). Future studies on the association between metacognition and social cognition may differentiate between social cognition processes rather than social cognitive functions. It would be particularly interesting to compare the correlation between metacognition and cognitive or affective theory of mind. Comparing the correlation between metacognition and verbal or nonverbal social cognition assessments may also contribute to a better understanding of the relationship between those constructs. Furthermore, our results emphasize the importance of addressing metacognitive impairments, as it is well-established that interventions targeting metacognition have a positive impact on social cognitive difficulties. However, the extent of their transfer to daily life remains to be demonstrated (87).

Further research is needed on the correlation between attribution and metacognition, as there were a limited number of studies on the subject. Future studies may also use other metacognition assessments to better understand the different patterns of correlations between scores on the MAS-A and the BCIS observed in this review. In this regard, the metacognition questionnaire may be an interesting assessment because it is a self-rated questionnaire (such as the BCIS) but considers metacognition as a thinking style regarding one's own thought processes, which is closer to the MAS-A definition of metacognition (81). Other scales used in the field of educational psychology to assess metacognitive monitoring and regulation during problem solving (88), such as the metacognitive assessment inventory, could also be adapted in psychiatric populations and compared to social cognition measures. Alternatively, systematic reviews in the future could refine their inclusion criteria to target schizophrenia or FEP. Emphasis could also be placed on a social cognition component such as theory of mind.

Conclusion

Our systematic review and meta-analysis that adhered to PRISMA guidelines indicated a significant correlation between social cognition and metacognition in individuals with a schizophrenia spectrum disorder. This result was replicated with three social cognitive domains: theory of mind, attribution and emotion processing. In contrast, we observed different patterns of correlation for different metacognitive concepts or components (i.e., cognitive insight, self-reflectivity, understanding others' minds, decentration, mastery). These results are in line with the theory that social cognition and metacognition are two distinct but interrelated constructs.

The association between metacognition and social cognition, as well as neurocognition, needs to further study to better identify and treat the cognitive symptomatology of schizophrenia. This meta-analysis included studies reporting correlations rather than causal relationships between metacognition and social cognition. Nonetheless, our results are in line with previous work that stressed the need to treat metacognitive impairments to improve other spheres of cognition and psychosocial functioning in patients with schizophrenia (81). Metacognitive training (89) or metacognitive reflection and insight therapy (90) are two nonpharmaceutical interventions that target discrete or synthetic metacognition. Oxytocin may also be a promising treatment to improve metacognition and social cognition (91). Improvements in social cognition over time are positively correlated with improvements in metacognition (79). Thus, enhancing social cognition with cognitive remediation programs could potentially be beneficial for the broad

network of cognition. Finally, individuals living with a schizophrenia spectrum disorder may benefit from an integrated cognitive remediation approach that addresses neurocognition, social cognition and metacognition in its discrete and synthetic aspects.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AM: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. CI: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing, Software. M-CC: Writing – review & editing. DJ: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1285993/full#supplementary-material

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Neuropsychological dimensions related to alterations of verbal self-monitoring neural networks in schizophrenic language: systematic review

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Although schizophrenia has traditionally been interpreted as a disorder of thought, contemporary perspectives suggest that it may be more appropriate to conceptualize it as a disorder of language connectivity. The linguistic anomalies present in schizophrenia possess distinctive characteristics that, despite certain connections, are not comparable to aphasic disorders. It is proposed that these anomalies are the result of dysfunctions in verbal self-monitoring mechanisms, which may influence other neuropsychological dimensions. This study set out to examine the neuropsychological dimensions associated with alterations in the neural networks of verbal self-monitoring in schizophrenic language, based on the scientific evidence published to date. Exhaustive searches were conducted in PubMed, Web of Science, and Scopus to identify magnetic resonance studies that evaluated verbal self-monitoring mechanisms in schizophrenia. Of a total of 133 articles identified, 22 were selected for qualitative analysis. The general findings indicated alterations in frontotemporoparietal networks and in systems such as the insula, amygdala, anterior cingulate cortex, putamen, and hippocampus. Despite the heterogeneity of the data, it is concluded that language plays a fundamental role in schizophrenia and that its alterations are linked with other neuropsychological dimensions, particularly emotional and perceptual ones.

KEYWORDS

language, verbal-self-monitoring, schizophrenic, inner speech, neural networks

1 Introduction

Schizophrenia is considered a disorder of neuronal connectivity and is closely linked to language impairments. According to the DSM-5, delusions, hallucinations, and disorganized speech are the three primary symptoms of schizophrenia, and at least one of these symptoms must be present for a minimum duration of one month for an accurate

diagnosis (1). While schizophrenia has traditionally been understood as a thought disorder, particularly due to the presence of these so-called positive symptoms, this categorization has become merely descriptive in contemporary discourse, as it refers to a variety of phenomena manifested in some form of verbal communication impairment (2, 3). This suggests that both delusions and hallucinations, as well as disorganized speech, have their functional correlate in various language impairments (3–5), and consequently, their neuroanatomical correlate in the neural networks that facilitate their functioning.

Language in schizophrenia, commonly known as disorganized speech or Positive Thought Disorder (PTD) (6), possesses distinct characteristics that differentiate it from other language disorders. Due to the similarities between the two, schizophrenic language has traditionally been associated with and explained through aphasic language (7), particularly due to the presence of neo logistic jargon with alliterations and assonances in both cases (8), as well as semantic aphasia, given the presence of agrammatism in both cases (9). The limitations of studying schizophrenic language from an aphasiological perspective have been highlighted by Barr et al. (10), who, from a frontal lobe dysfunction perspective, suggest that schizophrenic language is characterized by the presence of Field-Dependent Responses (FDR) and Verbal Perseverations (VP) as a result of alterations in verbal monitoring mechanisms, especially at the semantic and phonological levels. Verbal self-monitoring mechanisms, closely related to the acquisition of inner speech and consequently the regulation of behavior through speech (11, 12), provide a promising avenue for the differential study of schizophrenic language.

Verbal self-monitoring is defined as the ability to assess what is being said in relation to what was intended to be said and occurs at least on three levels: at the level of the speech command, in the realm of inner speech, and at the sensory level (13). This means that verbal self-monitoring is involved in the entire generative process of language, which encompasses sense construction, internal language, and meaning elaboration (14). It has been suggested that in schizophrenia, these mechanisms of verbal self-monitoring are impaired (15, 16). Given their relationship with the generative process of language as a whole and considering schizophrenia as a disorder of connectivity, particularly in language networks, the alteration of verbal self-monitoring mechanisms could be associated with the core symptoms of schizophrenia. In addition to these symptoms, and due to the fundamental role of language in neuropsychological development in general (11), it has been found that language impairments in schizophrenia not only affect linguistic aspects but also other cognitive, emotional, behavioral, and social domains (6).

The networks involved in cognitive self-monitoring in general have been associated with a network that includes the prefrontal and cingulate cortex, the parahippocampal region, the septal nuclei, motor regions, and the hippocampus as a hub (17, 18). According to Frith's classic model (19) based on Positron Emission Tomography (PET) data, the verbal self-monitoring network includes the Anterior Cingulate Cortex as the main source for vocalization control, through the Broca and Wernicke areas, thereby modifying speech perception, which in turn is influenced by the thalamus. In a magnetic resonance imaging study involving various tasks related to the process of verbal self-monitoring, such as self-distorted feedback, alienated non-distorted feedback, imagining another person speaking, and monitoring externally generated speech, a significant involvement of the bilateral temporal cortex (middle and superior), auditory cortex, thalamus, cerebellum, and hippocampus was found (20).

Recent studies have investigated the relationship between language impairments in schizophrenia from various perspectives. Cavelti et al. (21) conducted a systematic review aiming to examine the neural correlates of Formal Thought Disorder (FTD) in schizophrenia and its relationship with alterations in the language network. They concluded that their hypothesis was only partially supported. Firstly, there were studies that did not find any relationship between FTD and alterations in the language network. Secondly, studies using a "whole-brain" approach revealed altered neural regions in FTD that are not part of the language network. Lastly, the high degree of heterogeneity among the studies was attributed to the multidimensionality of FTD, methodological differences, and the limited research conducted to date. On the other hand, Barber et al. (22) conducted a meta-analysis on the functional and structural neural correlates of inner speech in relation to Auditory Verbal Hallucinations (AVH) in schizophrenia. They concluded that the insula plays a fundamental role in AVH and the attribution of inner speech errors.

Despite the abundance of literature regarding the relationship between language and schizophrenia, there is no consensus on the specific nature of this relationship. The lack of consensus is partly due to the vast amount of disjointed information available. Exploring how language relates to the core symptoms of schizophrenia, the specific alterations that can occur at the level of networks and language errors, and how these alterations may impact other neuropsychological dimensions that are associated with other symptomatic manifestations of schizophrenia, are topics that have not been extensively studied. However, they can contribute to the discussion on how language is specifically involved in schizophrenia. This, in turn, can help determine whether schizophrenic language is an isolated characteristic separate from other symptoms and alterations in schizophrenia or if it forms the foundation of the disorder. Such understanding can further contribute to the neuropsychological approach to schizophrenia. Therefore, the objective of this research was to analyze the existing scientific evidence on the neuropsychological dimensions related to alterations in the neural networks of verbal self-monitoring in schizophrenic language. The aim was to test the hypothesis that alterations in the neural networks of verbal self-monitoring in schizophrenic language are associated with multiple neuropsychological dimensions.

2 Methods

2.1 Search strategy

The PRISMA guidelines were followed to conduct a systematic review, with predetermined inclusion and exclusion criteria. The selected articles were reviewed by the author and a collaborator

before reaching a consensus for inclusion. Data extraction was performed by the author and reviewed by the collaborator. The Newcastle-Ottawa Scale for case-control studies was used to assess the risk of bias in the included studies.

An extensive search was conducted in the PubMed, Web of Science, and Scopus databases to identify studies on structural and functional neuroimaging using Magnetic Resonance Imaging (MRI) and its various techniques, investigating the alteration of neural correlates of verbal self-monitoring in schizophrenia and their neuropsychological effects. The literature search was conducted using the following combination of keywords: ("verbal self-monitoring" OR "speech monitoring" OR "speech self-monitoring" OR "inner speech" OR "speech error detection" OR "auditory verbal imagery") AND ("schizophrenia" OR "schizophrenic speech" OR "schizophrenic language" OR "psychosis" OR "psychotic speech" OR "psychotic language" OR "formal thought disorder" OR "thought disorder" OR "positive thought disorder" OR "disorganized speech") AND ("Magnetic Resonance Imaging" OR "MRI" OR "Functional Magnetic Resonance Imaging" OR "fMRI" OR "Diffusion Tensor Imaging" OR "DTI" OR "Diffusion Spectrum Imaging" OR "DSI").

2.2 Selection and exclusion criteria

The selected studies met the following eligibility criteria: 1) adult patients aged between 17 and 50 years diagnosed with schizophrenia, 2) application of neuroimaging using MRI, and 3) articles written in English. All types of studies were considered, except for systematic reviews and meta-analyses. Both resting-state and task-based studies were included. There was no specific publication year criterion as all available scientific evidence up until 2023 was reviewed. Cases with comorbidities of other neuropsychiatric disorders, psychoactive substance use, or neurodegenerative diseases were excluded from the study.

2.3 Data extraction

The variables of interest extracted from the studies were as follows: study design, number of participants, sex, age, diagnosis, MRI category (structural/functional/effective), acquisition sequence (Spin-Echo/Inversion-Recovery/Gradient-Echo), MRI technique (spectroscopy/Diffusion Tensor Imaging/Diffusion Spectrum Imaging/Functional Magnetic Resonance Imaging), imaging scope (ROI/Whole Brain), modality (resting-state/task-based), imaging outcome measure, reported neural networks, and neuropsychological dimensions (behavioral/emotional/cognitive). Data extraction was independently performed by the author and the pair. The results were compared, and disagreements were resolved through discussion.

2.4 Data analysis

Meta-analysis was not conducted due to heterogeneity in definition and measurement of outcomes.

3 Results

With the employed search strategy, 133 articles were identified (see Figure 1). After excluding 55 duplicates, 78 articles were examined for eligibility. Fifty-five articles were excluded for the following reasons: articles in languages other than English (n = 9), systematic reviews (n = 4), literature reviews (n = 2), meta-analyses (n = 2), not involving patients with schizophrenia (n = 19), no use of MRI (n = 13), no reference to verbal self-monitoring or inner speech (n = 6), and incomplete information (n = 1). Finally, 22 articles met the eligibility criteria for the systematic review, which were grouped according to the type of MRI technique into structural studies (n = 4), functional studies (n = 14), and effective studies (n = 4). The analyzed studies included a total of 771 patients with schizophrenia and 630 controls. The qualitative synthesis involved extracting information on the reported neural correlates of verbal self-monitoring or inner speech and their relationship with schizophrenia, and subsequently determining the associated neuropsychological functions.

3.1 Structural MRI studies

3.1.1 Volumetric studies

The volumetric study (Table 1), which utilized Local Gyrification Index (LGI) as the outcome measure, revealed lower LGI in the Broca's Area (BA), lower LGI in the right BA and the Superior Medial Frontal Cortex (SMFC), and increased LGI in the precuneus and the Superior Parietal Cortex (SPC). Abnormalities were found in areas of the Anterior Cingulate Cortex (ACC) and the Superior Frontal Cingulate Cortex (SFCC). This study suggests that the bilateral hypogyrification of BA, ACC, and SFCC, areas closely related to language and inner speech, which in turn are associated with verbal self-monitoring, may serve as a marker for the subsequent development of Auditory Verbal Hallucinations (AVH) (24).

3.1.2 DTI studies

White Matter (WM) connectivity studies using DTI, with Fractional Anisotropy (FA) as the outcome measure (23, 25, 26), as well as measurements of the Magnetic Transfer Ratio (MTR) (25), revealed hyperconnectivity (increased FA) in the long segment of the left perisylvian network, encompassing the BA, Wernicke's Area (WA), and the Arcuate Fasciculus (AF) (23). Furthermore, hypoconnectivity (decreased FA) was observed in the AF, Uncinate Fasciculus (UF), and Corticospinal Tract (CST), while hyperconnectivity (increased FA) was found in the Cingulate Cortex (CC).

Furthermore, hypoconnectivity (decreased FA) and degraded axons or glial cells (increased MTR) were found in the bilateral AF, which is related to the severity of positive symptoms as it hinders effective corollary discharge from the inferior frontal regions of speech to temporoparietal regions (from production to perception), leading to inadequate recognition of thoughts (25). Finally, an imbalanced directionality was found in the arcuate fasciculus, with increased directionality (increased FA) in the lateral part and

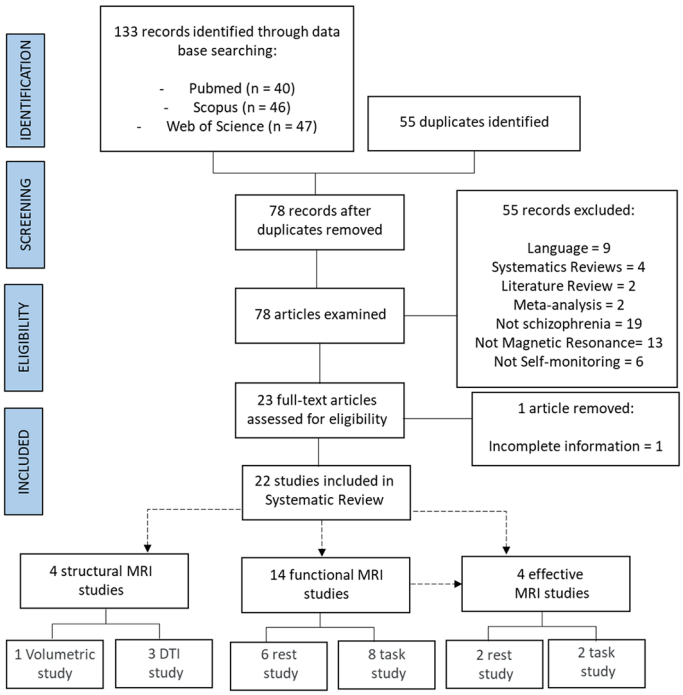

FIGURE 1
Flowchart.

decreased directionality (decreased FA) of white matter fibers in the medial part, suggesting that during inner speech, these alterations lead to abnormal coactivation in these areas related to the acoustic processing of external stimuli (26).

In conclusion, structural MRI studies suggest structural and microstructural difficulties in frontal, parietal, temporal areas, and their respective WM connections (especially in the AF), with a particular involvement of the Cingulate Cortex (CC). All of these areas and tracts are related to inner speech, but there was no reference to other related neuropsychological functions.

3.2 Functional MRI studies

3.2.1 Resting-state studies

Alterations in Global Functional Connectivity Density (GFC) (Table 2) were reported in patients with AVH, showing hyperactivity in the hippocampus, bilateral insula, and most components of the default mode network (DMN), and hypoactivity in the left Temporoparietal Junction (TPJ) and components of the Frontoparietal Network (FPN) (27). Increased functional connectivity was observed between the Anterior Cingulate Cortex (ACC), insula,

TABLE 1 Structural MRI studies.

Authors	Sample	Age (M/SD)	Gender (M/F)	Image Scope	Modality	Self-Monitoring Networks
Xie, S. et al. (23)	478 (AVH=113 NAVH=96 HC=269)	(26.77/5.86) (26.95/5.43) (27.04/5.82)	(56/57) (54/42) (136/133)	ROI: AF	DTI	BA, WA, AF
Kubera, K. et al. (24)	34 (AVH=10 NAVH=10 HC=14)	(36.5/9.0) (32.1/6.2) (33.7/8.6)	(6/4) (8/2) (7/7)	ROI: BA	Volumetric	BA, SPC, ACC, SFCC
de Weijer, A.D. et al. (25)	86 (AVH=44 HC=42)	(36.9/12.0) (38.4/12.6)	(25/19) (23/19)	ROI: PFC, TPJ	DTI	PFC, TPJ, BAF, CST, CC, UF
Hubl, D. et al. (26)	39 (AVH=13 NAVH=13 HC=13)	(33.3/8.5) (31.0/9.3) (32.0/8.4)	(8/5) (8/5) (8/5)	ROI: MBAF, LBAF	DTI	FTP, MBAF, LBAF, UF, SLF

AVH, Auditory Verbal Hallucinations; NAVH, No Auditory Verbal Hallucinations; HC, Healthy Controls; M/SD, mean/standard deviation; M/F, male/female; ROI, Region of Interest; DTI, Diffusion Tensor Imaging; BA, Broca's Area; WA, Wernicke's Area; AF, Arcuate Fasciculus; SPC, Superior Parietal Cortex; ACC, Anterior Cingulate Cortex; SFCC, Superior Frontal Cingulate Cortex; PFC, Prefrontal Cortex; TPJ, Temporoparietal Junction; BAF, Bilateral Arcuate Fasciculus; CST, Corticospinal Tract; CC, Cingulate Cortex; UF, Uncinate Fasciculus; FTP, Frontotemporal Areas; MBAF, Medial Bilateral Arcuate Fasciculus; LBAF, Lateral Bilateral Arcuate Fasciculus; UF, Uncinate Fasciculus; SLF, Superior Longitudinal Fasciculus.

TABLE 2 Resting state functional MR studies.

Authors	Sample	Age (M/SD)	Gender (M/F)	Image Scope	Modality	Self-Monitoring Networks
Zhuo, C. et al. (27)	55 (AVH=20 NVAH=15 HC=20)	(25.5/2.9) (23.5/2.5) (22.0/1.6)	(7/13) (5/10) (10/10)	Whole Brain	Resting state	Hippocampus, PPC, TPJ, STG, PFC.
Chang, X. et al. (28)	54 (AVH=18 NAVH=18 HC=18)	(22.56/6.73) (22.67/3.80) (24.44/3.73)	(10/8) (9/9) (10/8)	ROI: MTG, STG, IPL, IFG, ACC, PCC, ínsula	Resting state	MTG, STG, IPL, IFG, ACC, PCC, insula.
Cui, L. et al. (29)	75 (AVH=25 NAVH=25 HC=25)	(24/7) (24/5) (26/5)	(14/11) (13/12) (12/13)	Whole Brain	Resting state	DLPFC, SMA
Clos, M. et al. (30)	98 (AVH=49 HC=49)	(37.3/11.9) (39.5/14.8)	(22/27) (19/30)	ROI: MTG, thalamus, AG, IFG	Resting State	BA, DLPFC-L, VLPFC, IFG
Vercammen, A. et al. (31)	54 (AVH=27 HC=27)	(36.67/13.13) (32.48/10.90)	(13/14) (13/14)	ROI: TPJ, IFG, ACC, amygdala, insula.	Resting state	TPJ, IFG, ACC, amygdala, insula.
Shergill, S. et al. (32)	2 (AVH=2)	(47) (26)	(2)	Whole Brain	Resting state	IFG-L, RMTG

AVH, Auditory Verbal Hallucinations; NAVH, No Auditory Verbal Hallucinations; HC, Healthy Controls; M/SD, mean/standard deviation; M/F, male/female; ROI, Region of Interest; PPC, Posterior Parietal Cortex; TPJ, Temporoparietal Junction; STG, Left Superior Temporal Gyrus; PFC, Prefrontal Cortex; MTG, Middle Temporal Gyrus; STG, Superior Temporal Gyrus; IPL, Inferior Parietal Lobule; IFG, Inferior Frontal Gyrus; ACC, Anterior Cingulate Cortex; PCC, Postcentral Gyrus; DLPFC, Dorsolateral Prefrontal Cortex; SMA, Supplementary Motor Area; AG, Angular Gyrus; BA, Broca's Area; DLPFC-L, Left Dorsolateral Prefrontal Cortex; VLPFC, Ventrolateral Prefrontal Cortex; IPL, Inferior Parietal Lobule; IFG, Inferior Frontal Gyrus; IFG-L, Left Inferior Frontal Gyrus; RMTG, Right Middle Temporal Gyrus.

and language-related regions (28). Alterations in Cerebral Blood Flow (CBF) were also found in areas such as the bilateral Dorsolateral Prefrontal Cortex (DLPFC) (internal speech monitoring), Postcentral Gyri (speech production), and the right Supplementary Motor Area (SMA) (speech imagery) (29).

Altered coupling was reported in connections between Broca's Area (BA), insula, SMA, and DLPFC, Ventrolateral Prefrontal Cortex (VLPFC), and Inferior Parietal Cortex (IPC) (30). Reduced connectivity was also reported between the Right Inferior Frontal Area and temporal speech perception areas. Particularly, activity in the left TPJ, a critical node in the speech perception/AVH network, appears to be disconnected from brain activity in areas involved in agency attribution, self-referential processing, and attention control (31).

According to Shergill (32), who also reported alterations in frontotemporal connections, insula activation occurred particularly when patients became aware of their hallucination and involved the Left Inferior Insula (LII), bilateral Superior Temporal Gyri (STG), bilateral Middle Temporal Gyri (MTG), Middle Frontal Gyrus (MFG), and Sensorimotor Cortex (SMC). Insula activation persisted after hallucinations and extended to the Orbitofrontal Cortex (OFC).

Frontal and temporal activations were reported in all resting-state functional MRI studies, with the involvement of additional systems such as ACC, insula, hippocampus, and TPJ. Connections between frontal and temporoparietal areas predominantly showed hypoactivity and were related to the FPN in relation to hyperactivity in systems such as the insula, hippocampus, and most components of the DMN, resulting in a "false attribution of inner speech" (27). This false attribution of inner speech, suggested as an explanation for AVH (29), is closely linked to dysfunction between language processing networks (BA, insula, SMA) and self-monitoring systems (DLPFC, VLPFC, IPC) (30). The alterations, however, were not only observed between frontotemporal connections and the mentioned adjacent systems but also at the interhemispheric level, between the left TPJ, anterior cingulate, and right BA. Furthermore, the importance of the emotional component of language was reported, both in its right hemisphere processing and in the decreased synchronization between TPJ activity and the amygdala, which may indicate reduced appreciation of verbal relevance during internal speech processing (31).

In conclusion, resting-state functional MRI studies suggest alterations between language processing networks that are closely linked to self-monitoring systems and involve important neural systems or networks such as ACC, insula, hippocampus, and amygdala. The disconnection, decoupling, and alterations in blood flow in these networks might not only affect language networks and systems, but also emotional processing systems that provide a broader perspective on AVH.

3.2.2 Task-based studies

Task-based studies focusing on self-monitoring (33, 36) (Table 3) have shown that insight processes, divided into "self" and "other," and self-monitoring are disrupted in patients with AVH due to alterations in networks involving bilateral thalamus, left lentiform nucleus (in the "self" condition), and alterations in the Posterior Cingulate Cortex (PCC), Inferior Parietal Lobule (IPL), insula, bilateral superior temporal cortices (STC), putamen, and right thalamus (in the "other" condition) (33). Furthermore, these studies revealed alterations in a network comprising bilateral Medial Geniculate Nucleus (MGN) of the thalamus, middle and superior temporal lobes (MTL and STL), inferior frontal cortex (IFC), insula, putamen, and Posterior Cingulate (PC). The increased response in MGN, along with MTL and IFC, coupled with reduced response in the Default

TABLE 3 Task functional MR studies.

Authors	Sample	Age (M/SD)	Gender (M/F)	Image Scope	Modality	Self-Monitoring Networks
Sapara, A. et al. (33)	42 (PRIG=13 POIG= 13 HC = 16)	(31.15/9.77) (37.85/ 7.43) (31.81/9.36)	(11/2) (9/4) (13/3)	ROI: ACC, DLPFC, IFG, TL, PCC, IPL, STG, Putamen.	Birchwood insight scale (BIS)	ACC, DLPFC, IFG, TL, PCC, IPL, STG, Putamen.
Matsumoto, K. et al. (34)	12 (AVH=6 HC=6)	(34.3/11.5) (34.0/7.9)	Not reported	Whole Brain	Story about Rosch's ink stains	LSTG, LI
Vercammen, A. et al. (35)	22 (AVH = 22)	(36.18/12.31)	(11/11)	ROI: IFGop, IFGtri, insula, SMA, STS ACC, MTS, AG, SMG	Acentuación métrica	IFGop, IFGtri, insula, SMA, STS, ACC, CITM, AG, SMG
Kumari, V. et al. (36)	83 (AVH=63 HC=20)	(37.95/9.63) (33.95/10.37)	(74.6%/25.4%) HC (70%/30%)	Whole Brain	Verbal self-monitoring task	Thalamus (MGN), TL, IFG, MFG, PCC, STS
Simons, C. et al. (37)	27 (AVH=15 HC=12)	(34.7/8.7) (34.4/7.9)	Not reported	Whole Brain	Listening vs inner speech	LSTG, CG, IFG, ACC
Shergill, S. et al. (38)	16 (AVH=8 HC=8)	(31/9) (29/5)	Not reported	Whole Brain	Fast covert articulation vs slow covert articulation	BTC, PHC, RLC
Bentaleb, L. et al. (39)	2 (AVH=1 HC=1)	(36) (36)	(0/1) (0/1)	Whole Brain	External speech	LSTG, STS, PAC
Shergill, S. et al. (40)	14 (AVH=8 HC=6)	(32/10) (34/4)	Not reported	Whole Brain	verbal auditory imagery	PCC, BLN, RT, TCM, TCS, LNA

PRIG, Preserved Insight Group; POIG, Poor Insight Group; AVH, Auditory Verbal Hallucinations; NAVH, No Auditory Verbal Hallucinations; HC, Healthy Controls; M/SD, mean/standard deviation; M/F, male/female; ROI, Region of Interest; ACC, Anterior Cingulate Cortex; DLPFC, Dorsolateral Prefrontal Cortex; IFG, Inferior Frontal Gyrus; TL, Temporal Lobe; PCC, Posterior Cingulate Cortex; IPL, Inferior Parietal Lobe; STG, Superior Temporal Gyrus; LSTG, Left Superior Temporal Gyrus; LI, Left Insula IFGop, Inferior Frontal Gyrus Opercularis; IFGtri, Inferior Frontal Gyrus Triangularis; SMA, Supplementary Motor Area; STS, Superior Temporal Sulcus; MTS, Medial Temporal Sulcus; AG, Angular Gyrus; SMG, Supramarginal Gyrus; MGN, Medial Geniculate Nucleus; IFG, Inferior Frontal Gyrus; MFG, Medial Frontal Gyrus; TCS, Temporal Cortical Sulcus; CG, Cingulate Gyrus; BTC, Bilateral Temporal Cortex; PHC, Parahippocampal Cortex; PAC, Primary Auditory Cortex; RLC, Right Lateral Cerebellum; PCC, Posterior Cerebellar Cortex; BLN, Bilateral Lenticular Nucleus; RT= Right Thalamus; TCM, Temporal Cortical Medial; TCS, Temporal Cortical Superior; LNA, Left Nucleus Accumbens.

Mode Network (DMN), primarily involving PC and Inferior Frontal Cortex (IFC), indicated faulty monitoring of internal speech processes in patients with AVH, with greater modulation in those presenting symptoms of blunted affect, emotional withdrawal, poor rapport, and passive social avoidance (36).

On the other hand, task-based studies involving some form of external speech processing (Table 3), such as listening vs. covert speech, slow covert articulation vs. fast covert articulation, and external speech, demonstrated that internal speech was associated with increased activation in the Inferior Frontal Cortex (IFC) and Anterior Cingulate Cortex (ACC) (37), and attenuated activation in the Bilateral Temporal Cortex (BTC), Right Parahippocampal Cortex (RPHC), and Right Lateral Cerebellum (RLC) (38). In contrast, the listening task was associated with activation in bilateral temporoparietal and occipital areas (37). In the absence of external speech, AVH patients exhibited activation in the Superior Temporal Gyrus (STG), Superior Temporal Pole (STP), and Primary Auditory Cortex (PAC) (39).

Finally, studies employing tasks involving internal processing and production (Table 3), such as the Rorschach inkblot task, metric accentuation, and verbal auditory imagery, reported the following: 1) reduced activation in STG and Left Insula (LI) during the generation of pauses and filled pauses between phrases in the inkblot task in AVH patients (34); 2) negative correlations between loudness and activation in bilateral ACC, bilateral Inferior Parietal Cortex (IPC), Inferior Triangular Frontal Cortex (ITFC), Inferior Opercular Frontal Cortex (IOFC), MTG, and LI, all involved in internal speech processing (35); and 3) association of internal speech with activation in IFC and insula, as well as attenuated activation in the Superior Temporal Cortex (STC), and verbal self-monitoring with temporal activation, which is relevant to AVH. Additional attenuated activations were observed in bilateral hippocampal complex, right thalamus, and left nucleus accumbens during verbal auditory imagery processes, which are also implicated in AVH (40).

In summary, task-based functional MRI studies focusing on internal speech processing have revealed alterations, particularly in temporoparietal areas, with frequent involvement of parahippocampal, cerebellar, thalamic, Posterior Cingulate, and Primary Auditory Cortex regions. These areas and networks, when disrupted, are associated with AVH.

3.3 Effective connectivity studies

3.3.1 Resting-state studies

It has been reported that the Auditory Cortex (PAC), Left Dorsolateral Prefrontal Cortex (LDPFC), and Broca's Area (BA) form a bidirectionally connected network in patients with AVH.

This network exhibits reciprocal connectivity between the AC and the hippocampus, between the AC and the thalamus, between the AC and BA, and between the LDPFC and BA. Additionally, there is unilateral connectivity from the hippocampus to the LDPFC. This results in cortico-thalamo-auditory hyperconnectivity and cortico-hippocampal-auditory hypoconnectivity. The thalamo-AC hyperconnectivity leads to increased sensitivity of the AC to thalamic inputs in patients with AVH, which is associated with elevated AC activity in these patients. Disruption of this network, which is involved in language production (BA) and verbal self-monitoring (LDPFC), is associated with the default mode network (DMN), insula networks, striatal networks, and is implicated in AVH (42) (Table 4).

Furthermore, decreased effective connectivity between the Left Inferior Frontal Gyrus (LIFG) and the Left Middle Temporal Gyrus (LMTG) has been reported, suggesting irregular patterns of causal interactions within the language network. There was also a decrease in effective connectivity from the Left Inferior Parietal Lobule (IPL) to the LMTG and from the LIFG to the LMTG, indicating a lack of effective inhibition from the Frontal Lobe (FL) on the internal verbal signal generated by the Temporal Lobe (TL), which in turn leads to an inability to integrate information related to internal speech. These deficits are associated with impaired self-monitoring and thus with AVH (41).

In conclusion, these studies generally report decreased effective connectivity in language networks, including subcortical and auditory areas.

3.3.2 Task-based studies

According to the study performed by Mechelli et al. (44) (Table 5), participants were asked to indicate whether each word, manipulated in terms of their source and acoustic quality, was spoken in their own voice or in another person's voice. Four conditions were measured: undistorted self-voice, distorted self-voice, undistorted other-voice, and distorted other-voice. The study found an intrinsic connection (the impact that one region exerts on another) between the Left Superior Temporal Cortex (LSTC) and the Anterior Cingulate Cortex (ACC). This connection, especially in the self-generated and other-generated speech conditions, was modulated by the source of speech. According to the study, this supports the hypothesis that dysfunction in the temporal-cingulate network could lead to false perceptions in schizophrenia.

In a task involving metric accentuation, which aimed to measure internal speech processing, reduced connectivity was found between bilateral Auditory Wordform Area (AW) and Broca's Area (BA), as well as from the left BA to the right BA. The reduction of information flow from AW to BA may lead to a loss of feedback (self-monitoring) and an increase in top-down efforts that are less constrained by perceptual information from BA. This has been theorized as a possible cause of AVH. The reduction of information flow from the left BA to the right BA appears to be associated with the emotional content of hallucinations, as the Right Inferior Frontal Gyrus (RIFG) has been implicated in emotional aspects of speech and monitoring processes (43).

In conclusion, task-based effective connectivity studies, in line with resting-state studies, suggest altered information flow in both the frontotemporal network and networks involving the interaction of these regions with the ACC. These alterations not only have effects on self-monitoring and internal speech processes but also on the emotional aspects conveyed by language.

TABLE 4 Rest effective MRI studies.

Authors	Sample	Age (M/SD)	Gender (M/F)	Image Scope	Modality	Self-Monitoring Networks
Zhang, L. et al. (41)	73 (AVH=18 NAVH=18 HC=37)	(22.56/6.7) (22.67/3.85) (22.48/5.84)	(10/8) (9/9) (19/18)	ROI: LIFG, LMTG, LIPL	Resting state	LIFG, LMTG, LIPL
Li, B. et al. (42)	51 (AVH=17 NAVH=15 HC=19)	Not reported	Not reported	ROI: LDPFC, PAC, Hippocampus, Thalamus, BA	Resting state	LDPFC, PAC, Hippocampus, Thalamus, BA

AVH, Auditory Verbal Hallucinations; NAVH, No Auditory Verbal Hallucinations; HC, Healthy Controls M/SD, mean/standard deviation; M/F, male/female; ROI, Region of Interest; LIFG, Left Inferior Frontal Gyrus; LMTG, Left Middle Temporal Gyrus; LIPL, Left Inferior Parietal Lobe; LDPFC, Left Dorsolateral Prefrontal Cortex; PAC, Primary Auditory Cortex; BA, Broca's Area.

TABLE 5 Task effective MRI studies.

Authors	Sample	Age (M/SD)	Gender (M/F)	Image Scope	Modality	Self-Monitoring Networks
Curcic, B. et al. (43)	53 (AVH=21 NAVH=14 HC=18)	(34/13) (30/5) (31/10)	(11/10) (13/1) (11/7)	ROI: LBA, RBA LWA, RWA	Metric accentuation	LBA, RBA LWA, RWA
Mechelli, A. et al. (44)	31 (AVH=11 NAVH=10 HC=10)	(35.33/6.63) (34.78/11.4) (28.50/4.37)	Not reported	ROI= LSTC, RSTC, LIFG, RFG, ACC	Manipulated Word Series	LSTC, RSTC, LIFG, RFG, ACC

AVH, Auditory Verbal Hallucinations; NAVH, No Auditory Verbal Hallucinations; HC, Healthy Controls; M/SD, mean/standard deviation; M/F, male/female; ROI, Region of Interest; LBA, Left Broca's Area; RBA, Right Broca's Area; LWA, Left Wernicke's Area; RWA, Right Wernicke's Area; LSTC, Left Superior Temporal Cortex; RSTC, Right Superior Temporal Cortex; LIFG, Left Inferior Frontal Gyrus; RIFG, Right Inferior Frontal Gyrus; ACC, Anterior Cingulate Cortex.

4 Discussion

This research systematically reviewed the published studies to date on fMRI that examined the neuropsychological dimensions related to verbal self-monitoring impairments in schizophrenic language. The significant methodological heterogeneity among the articles precluded a statistical analysis. Despite this limitation, several important conclusions can be drawn from this review, even though only a few articles directly addressed neuropsychological dimensions other than language.

Without exception, all studies indicated some form of language network alteration in patients with schizophrenia, supporting the hypothesis that language and its impairments are fundamental elements of the disorder (3, 4, 18, 2). As noted in some studies (12, 45), inner speech is a crucial component of verbal self-monitoring processes, and its disturbances, which can lead to misattribution or externalization, appear to provide a consistent explanation for auditory verbal hallucinations (AVHs), as demonstrated particularly by functional MRI studies. As mentioned in the introduction, verbal self-monitoring is involved in the generative process of language, which encompasses the transition from sense to meaning and determines language processing (encoding-decoding). Disruptions in this process due to brain lesions result in various forms of aphasia (14). However, when impairments are due to aberrations in connectivity, as in schizophrenia, symptomatic manifestations are expected to acquire a distinct character.

While it was found that verbal self-monitoring processes are closely related to frontal areas (29, 30), their complexity suggests that, rather than frontal lobe dysfunctions (10), altered verbal self-monitoring in schizophrenia involves frontotemporal parietal networks, with significant involvement of systems such as the putamen (33, 36), hippocampus (27, 38, 42), thalamus (36, 42), amygdala (31), and notably, the Cingulate Cortex (24, 28, 31, 33, 37, 44, 35), insula (27, 28, 32–36), the default mode network (DMN), and the frontoparietal network (FPN) (27). Therefore, the specificity of language impairments in schizophrenia appears to be a consequence of the multiplicity of affected areas and networks, both at the structural, functional, and effective levels, resulting in general language processing impairments and other neuropsychological dimensions. This is in contrast to aphasia, where more specific neural areas and networks are affected, allowing for the dissociation of its symptoms from other neuropsychological functions (46). Thus, these findings are somewhat consistent with Frith's (19) classic model of verbal self-monitoring, thereby expanding the perspective on frontal dysfunctions in the neuropsychology of schizophrenic language.

Based on these findings, it is suggestive to propose understanding schizophrenia as an impairment that affects various levels of the language generative process, with the presence of verbal self-monitoring within these levels. These alterations are related to abnormal constructions of meaning during comprehension, perception, action, and production of language, giving rise to delusions (comprehension), hallucinations (perception), disorganized behavior (action), and disorganized speech or thought disorder (production) (47). Verbal self-monitoring also influences other neuropsychological dimensions, particularly perception (33, 39) - which integrates the theory of auditory perception and inner speech of AVHs - and emotion (31, 43). This suggests the need for studies that place language as a fundamental focus in schizophrenia and, with a solid theory of language processing, determine its specific relationship with schizophrenia.

In the relationship between language, other neuropsychological dimensions, and schizophrenia, studies on effective connectivity are of particular interest. These studies allow for the estimation and inference of the influence that one neuronal system or network exerts on another, either directly or indirectly, through Dynamic Causal Models (DCM) (48). In other words, structural connectivity enables spatial correlations, functional connectivity enables temporal correlations, and effective connectivity enables dynamic correlations between functional systems or networks. Consequently, the influence of language networks on other neuropsychological functions, both in healthy populations and in populations with neuropsychiatric disorders such as schizophrenia, could be better estimated using these types of measures. In relation to the findings, it is not only important to know that there are alterations in frontotemporal networks and other mentioned neuronal groups, but it is also relevant to understand, for example, how the information flow from the anterior to the posterior language regions is altered. This knowledge can help establish stimulation processes that emphasize tasks aimed at compensating for these informational alterations. Therefore, the knowledge or findings of effective connectivity can be a promising avenue for the study of neuropsychological rehabilitation in schizophrenia.

According to Andreasen (49), the neuropsychological approach to schizophrenic language should propose three fundamental objectives: clinical description of the phenomena, functional or cognitive mapping of the presented deficits, and neuroanatomical mapping based on functional deficits. The findings allow for direct neuroanatomical mapping based on the networks and their (hypo-hyper) structural, functional, and effective connectivity alterations. They also enable functional or cognitive mapping based on the affected neuropsychological dimensions beyond language. However, the clinical description, to the extent that it depends on neuroanatomical and functional networks and the processes that could compensate for their alterations, is a posteriori construction that should provide practical elements for neuropsychological intervention (52, 53). Currently, these constructions can take at least two clinical-practical paths: the development of innovative neuroimaging techniques and representations that use these data as measures for the diagnosis and treatment of schizophrenia, such as the SpeechGraphs project of the "Instituto do Cérebro" in Brazil, which uses Graph Theory and develops speech graphs software for diagnostic processes and suggestions for neurolinguistic interventions in schizophrenia (50, 51); and the development of neuropsychological tests for schizophrenia that emphasize language tasks, particularly tasks involving the activation (hypo-hyper, as the case may be) of inner speech - due to its relationship with the positive symptomatology of schizophrenia - such as verbal auditory imagery.

One final point of discussion and limitation is the absence of theoretical justification regarding the selection of age in the sampled articles. Although some of them studied the early appearances of

AVHs, which could explain the inclusion of patients aged between 18 and 25 years, this was not explicitly stated in all articles. Age in schizophrenia can be relevant, especially when studied in relation to language, as symptomatology can vary depending on the patient's developmental stage and the progression of the disease. Another limitation, as mentioned before, was the heterogeneity of the data, which did not allow for quantitative analysis of the results.

5 Conclusion

Despite the high methodological heterogeneity and the variability in reported networks among the reviewed articles, there is a general consensus suggesting that language and its verbal self-monitoring mechanisms are not secondary in schizophrenia but rather fundamental to the disorder. These mechanisms are also related to alterations in other neuropsychological dimensions, particularly emotional and cognitive dimensions such as perception. The networks that showed the most commonalities form a complex system involving frontotemporal networks and regions such as the insula, amygdala, putamen, and cingulate cortex, which are associated with the default mode network (DMN) and frontotemporal networks (FTN). These findings provide valuable insights for the development of techniques and tests that enable the diagnosis and treatment of schizophrenia from a neuropsychological perspective. Language tasks involving the processing of inner speech, such as verbal auditory imagery tasks, may be particularly relevant in this regard.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

JG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Dissociation and recovery in psychosis – an overview of the literature

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Background: The relationship between dissociation and recovery from psychosis is a new topic, which could attract the interest of the researchers in the field of dissociation due to its relevance to their daily clinical practice. This review brings together a diversity of international research and theoretical views on the phenomenology of dissociation, psychosis and recovery and provides a synthesis by narrative and tabulation of the existing knowledge related to these concepts.

Aims: The objective was to make a synthesis by narrative and tabulation about what is known on the topic.

Methods: The systematic search was conducted according to the PRISMA-statement in the databases Medline, PsycInfo, PubMed and Google Scholar. 2110 articles were selected according to the inclusion and exclusion criteria detailed in the methods, and 19 records were included in the review.

Outcomes: None of the included publications put together, in the same conceptualisation or hypothesis, dissociation and the recovery from an episode of psychosis, therefore this matter remains unstudied at this time.

Conclusion: The process of reviewing the existing scientific literature in the field of dissociation and recovery from psychosis has been very useful for charting the direction that future research will take.

KEYWORDS

dissociation, recovery, rehabilitation, psychosis, schizophrenia

1 Introduction

The NHS is going through a transformation process as it is moving to a more inclusive, flexible model of care, in which patients get properly joined-up care at the right time in the optimal care setting. The focus will be on prevention, inequalities reduction, and on responsiveness to all those who use and fund the health service. As part of the new model, there is a strong drive to invest in the transformation of dedicated community mental health rehabilitation functions (1). The concept of recovery is at the core of this transformation plan, associated with that of severe mental illness. This means that the model will need to be more differentiated in its support offer to individuals. Improving access to psychological therapies for those with severe mental health problems is a top priority on the transformation agenda (2).

The transformation process and the reshaping of the rehabilitation community services has to be founded on robust and up to date evidence-based data and research. This is the right time for new psychological interventions, more person tailored and more innovative, focusing on different concepts such as 'trauma', 'dissociation' and 'recovery', to be created.

For about a century, dissociative disorders and dissociative symptoms have been associated with trauma and traumatic experiences. There is a vast body of literature demonstrating the relationship between trauma and dissociative experiences, in longitudinal and prospective studies (3, 4). The meaning of dissociation has been a topic for scientific debate for a very long time and although there continue to be differences in opinion among clinicians and researchers, one aspect has been unanimously agreed upon; namely the fact that dissociation involves the loss of the ability of the mind to integrate some of its superior functions (4).

Whereas there is extensive scientific literature on the relationship between dissociation and psychosis (5–7) there is little if any on the topic of dissociative mechanisms and the process of recovery from psychotic episodes. Research in the field of recovery is difficult to undertake, but has included publications in the form of outcome studies, theoretical publications, meta-analyses, book chapters and conference presentations. The authors believed that the process of reviewing the existing scientific literature in the field of dissociation and recovery from psychosis may be useful to understand the current state of knowledge and for charting the direction of future research.

2 Concepts

2.1 Dissociation

Dissociation is "*the fragmentation of the usual continuity of subjective experience*";[8] "*disruption of and/or discontinuity in the normal integration of conscience, memory, identity, emotion, perception, body representation, motor control and behaviour*" (8) "*partial or total loss of the normal integration between the memory of the past, identity awareness and body movements control*" (9). This idea derived from the concept of "disintegration" of the integrative function, introduced by Pierre Janet (1859-1947). This would result in a process of fragmentation at different mental levels, from consciousness to the personality unity itself (10). As opposed to Freud's theory which defined dissociation as a defensive mechanism, Janet associated it with the loss of the connexion between normally integrated and overlapped mental functions, due to a "structural collapse" caused by traumatic experiences (10).

2.2 Psychosis

"The term "psychosis" lies at the heart of modern psychiatry" (11). DSM (8) and ICD-10 (9) describe specific diagnostic criteria for different psychotic conditions. Sadock and colleagues define the concept of psychosis as a group of mental illnesses where the loss of reality testing and the boundaries of the self are the main characteristics (12). Schizophrenia is often referred to in the specialist literature as representative for the psychosis group. It is a serious mental illness where the misinterpretation of stimuli from the external environment influences the information processing. As a result, a series of abnormal phenomena will occur in the form of positive symptoms (delusions and hallucinations), negative symptoms (apathy, anhedonia, dull affect, and loss of social cohesion), and cognitive ones.

Although distinctive symptoms for schizophrenia and dissociative disorders are listed by both ICD-10 and DSM-5, studies have shown an overlap between psychotic symptoms (for example, auditory hallucinations) and dissociation manifestations (13, 14). The causal relationship between dissociation and psychosis remains unexplored (3). Cernis and colleagues are of the view that this may be due to a possible lack of clarity about the role of dissociation in mental health (15).

2.3 Recovery

There are different points view of recovery but in this paper, the definition we used is the one coined by Anthony (16), who defined recovery as "*a deeply personal, unique process of changing one's attitudes, values, feelings, goals, skills and roles. It is a way of living a satisfying, hopeful, and contributing life even with limitations caused by the illness. Recovery involves the development of new meaning and purpose in one's life as one grows beyond the catastrophic effects of mental illness*". For this review, we aimed to identify articles that defined personal recovery.

3 Aim of the literature review

The aim of this review is to conduct an evaluation of the literature on recovery from psychosis and dissociation, using broader inclusion criteria thereby providing a synthesis by narrative and tabulation about what is known on the topic.

4 Methods

4.1 Search strategy

We limited the search to papers in the English language as we did not have access to volunteer or paid interpreters. We restricted the search to papers referring to population of any age within the interval 18-65. Medline, PsycInfo, PubMed databases were systematically searched using strings for dissociation, psychosis and recovery concepts: (dissociat* OR compartmentali* OR detach* OR absorption OR depersonalisation OR derealisation OR amnesia* OR "coping mechanism*" OR fragment*) AND (psychosis OR psychotic OR hallucinat* OR delusion* OR "positive symptom*" OR "negative symptom*" OR schizophreni* OR "thought disorder*" OR schizoaffective) AND (recover* OR outcome* OR recuperat* OR rehabilitat* OR improve* OR hope*). Google Scholar database was also searched using the following search strategy: Articles with any of these words in the article (Dissociate/compartmentali/psychosis/schizophrenia/psychot/hallucinate/recover/rehabilitat/outcome) or with these words in the title (psychosis/dissociation/therapeutic). 14 studies were identified using this method.

Beside the database search, a hand-search of references and citations from eligible articles was also performed in order to identify additional studies. Five studies were included using this method.

Articles were assessed for eligibility based on screening of titles, abstracts and full texts and only retained for review with consensus agreement from four reviewers. The search and screening procedure are presented in Figure 1.

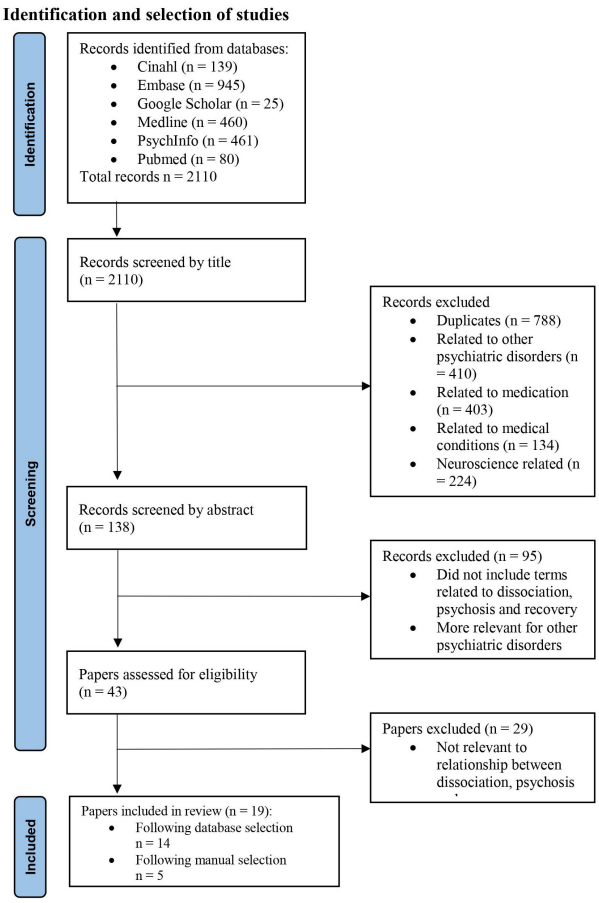

FIGURE 1
Study selection.

4.2 Inclusion and exclusion criteria

Inclusion criteria:

1. Publications on dissociation and psychosis and recovery, including terms (utilised in the search strategy) such as:

- Dissociation – compartmentalisation, detachment, absorption, depersonalisation, derealisation, amnesia, copying mechanism, fragmentation.
- Psychosis - hallucinations, delusions, positive symptoms, negative symptoms, schizophrenia, thought disorder, schizoaffective, psychotic, delusional.
- Recovery – outcome, recuperation, rehabilitation, improvement, hopefulness.

2. Articles published in English;
3. No date or age limits;
4. Studies on clinical and/or non-clinical population.

Exclusion criteria:

1. Articles about dissociation and psychiatric conditions other than psychosis;
2. Articles about dissociation and medical conditions;
3. Studies from the neuroscience domain.

4.3 Identification and selection of studies

Following the selection process, 19 articles were included in this review. They are described in Table 1.

4.4 Quality assessment

Studies were reviewed by four authors individually. Disagreements related to the eligibility of the studies were resolved by finding additional information and through discussions between the authors. Due to the diverse designs of the studies and articles included, a narrative synthesis approach was employed in order to obtain a summary of the information and data encompassed by the selected literature.

4.5 Data extraction

Data extraction was conducted by three authors and systematically checked for accuracy by the main author. Information extracted from the primary studies was recorded on a standardised form including general characteristics (authors,

TABLE 1 Description of articles.

Nr	Article - full citation	Country	Study design	Aim	Population	N	Age	Recruitment method
1	Longden, E.; Branitsky, A.; Moskowitz, A.; Berry, K.; Bucci, S.;Varese, F. The Relationship between dissociation and symptoms of psychosis: A Meta-analysis, Schizophrenia Bulletin.2020 doi:10.1093/schbul/sbaa037		Meta-analysis	To quantify the magnitude of association between dissociative experiences and all symptoms in psychosis.	Clinical and non-clinical population	20436	Mean age 27.07	
2	Farrelly, S.; Peters, E.; Azis, M.; David, A.; Hunter, E.C. A brief CBT intervention for depersonalisation/derealisation in psychosis: study protocol for a feasibility randomised controlled trial, Pilot and Feasibility Studies. 2016 2:47.	UK	Single-blinded RCT	To determine the feasibility and acceptability of a brief CBT intervention for clinically significant depersonalisation in people with psychotic symptoms	clinical population	30	18-70	Secondary mental health trust – community mental health teams, psychological therapies services and research registers.
3	Hwu, H.G.; Chen, C.C.; Tsuang, M.T.; Tseng, W.S. Derealization syndrome and the outcome of schizophrenia: A report from the international pilot study of schizophrenia, British Journal of Psychiatry. 1981, 139,313-318.		Two-year follow-up from the International Pilot Study of Schizophrenia (IPPS, WHO, 1973)-transcultural psychiatric investigation	Prognostic implication of the clinical manifestations of derealisation at initial evaluation in relation to outcome at two-year-follow-up from the Pilot Study of Schizophrenia (IPPS) (WHO, 1973)	clinical population	133 in follow up study (137 original study)	15 +	
4	Perona-Garcelan, S.; Cuevas-Yust, C.; Garcıa-Montes, J.M.; Perez-Alvarez, M.; Ductor-Recuerda, M.; Salas-Azcona, R.; Gomez-Gomez, M.T.; Rodrıguez-Martın, M.&B. Relationship Between Self-Focused Attention and Dissociation in Patients With and Without Auditory Hallucinations, The Journal of Nervous and Mental Disease. 2008;196: 190–197.	Spain	Cross-sectional	To study the relationship between self-focussed attention and dissociative experiences.	clinical population and non-clinical control group	68	20 - 62 (Mean age 38.65, SD 9.04)	Patients with auditory verbal hallucinations, with ICD 10 diagnosis. Attending the mental health units of the Virgen del Rocío Hospital (Seville, Spain), the Sierrallana Hospital (Santander, Spain) and the San Carlos Clinical Hospital (Madrid, Spain). Control grup - staff and trainees from the Virgen del Rocío Hospital (Seville, Spain).
5	Perona-Garcelán, S.; García-Montes, J. M.; Ductor-Recuerda, M. J.; Vallina-Fernández, O.; Cuevas-Yust, C.; Pérez-Álvarez, M.; Salas-Azcona, R.;	Spain	Cross-sectional	To study the relationship of metacognition, absorption, and depersonalisation in hallucinating patients.	clinical population and non-clinical control group	124	16-65 (Mean age 37.9; SD 9.92)	"Patients diagnosed with psychosis, selected from those receiving attention at the Virgen del Roc´ıo Hospital in Seville (southern Spain) or the Sierrallana Hospital in

(Continued)

TABLE 1 Continued

Nr	Article - full citation	Country	Study design	Aim	Population	N	Age	Recruitment method
	Gómez-Gómez, M. T. Relationship of metacognition, absorption, and depersonalisation in patients with auditory hallucinations, British Journal of Clinical Psychology. 2012, 51, 100-118.							Torrelavega (northern Spain), and treated with neuroleptic medication. The patients in the clinical control group were receiving attention at the outpatient health services or from private psychologists.
6	Wright, A.; Fowlerb, D.; Greenwood, K. Influences on functional outcome and subjective recovery in individuals with and without First Episode Psychosis: A metacognitive model, Psychiatry Research. 2020, 284, 112643.	UK	Cross-sectional	Association of metacognition and subjective recovery in first episode of psychosis	clinical population and non-clinical control group	135	Clinical group18-43 (mean age 26.24, SD 5.66) Control (mean age 26.3, SD 6.6)	Individuals with psychosis were recruited through a convenience sample from Early Intervention in Psychosis services in Sussex Partnership NHS Foundation Trust, with a minority of these from a previous first episode psychosis (FEP) sample. Healthy control participants were recruited through advertisement within the local community, for example, in libraries and cafes, and online, for example, through social media and Gumtree.
7	Rosen, C.; Jones, N.; Chase, K.A.; Melbourne, J.K.; Grossman, L.S.; Sharma, R.P. Immersion in altered experience: An investigation of the relationship between absorption and psychopathology, Consciousness and Cognition. 2017, 49, 215–226.	USA	Cross-sectional	To explore the phenomenological construct of absorption and psychotic experiences in clinical and non-clinical participants.	clinical population and non-clinical control group.	115 (76 African American, 10 Asian, 19 Caucasian, 10 Hispanic)	21-60	Population randomly selected from a large urban university medical centre but included referrals from community treatment facilities. Non-clinical participants were recruited from neighbouring communities.
8	Úbeda-Gómeza, J.; León-Palaciosa, M.G.; Escudero-Péreza, S.; Barros-Albarrána, M.D.; López-Jiménezb, A.M.; Perona-Garcelána, S. Relationship between self-focussed attention, mindfulness and distress in individuals with auditory verbal hallucinations, Cognitive Neuropsychiatry. 2015, 20: 6, 482–488.	Spain	Cross-sectional	To investigate the relationships among self-focussed attention, mindfulness and distress caused by the voices in psychiatric patients.	Clinical population	51	18-65 (mean 38, DS 10.24)	The participants were inpatients in the mental health units of the Virgen del Rocío Hospital (Seville, Spain), the Sierrallana Hospital (Santander, Spain) and the San Carlos Clinical Hospital (Madrid, Spain).

(Continued)

TABLE 1 Continued

Nr	Article - full citation	Country	Study design	Aim	Population	N	Age	Recruitment method
9	"Humpston, C.S.; Walsh, E.; Oakley, D.A.; Mehta, M.A.; Bell, V.; Deeley, Q. The relationship between different types of dissociation and psychosis-like experiences in a non-clinical sample, Consciousness and Cognition. 2016, 4, 83–92. "	UK	Cross-sectional	To investigate whether detachment, compartmentalisation or absorption were most strongly associated with psychosis-like experiences in the general population.	Non-clinical population	215	18-67 (Mean age 27.16; SD9.28)	General population sample recruited through adverts placed on the gumtree.com website in London and from an email circular that was distributed to all staff and students at three central London universities.
10	Lynch, S.; Holttum, S.; Huet, V, The experience of art therapy for individuals following a first diagnosis of a psychotic disorder: a grounded theory study, International Journal of Art Therapy. 2018, 24:1, 1-11.	UK	Qualitative research	To explore how service users experienced art therapy following their first diagnosis of a psychotic disorder, and the processes through which art therapy might be helpful for such individuals.	Clinical population	8	24-52 (Mean age 34.75)	Participants were recruited through art therapists in 4 NHS mental health trusts in southern UK. Interviews took place either face-to-face or by telephone and were audio-recorded.
11	Bacon, T. & Kennedy, A. Clinical perspectives on the relationship between psychosis and dissociation: utility of structural dissociation and implications for practice, Psychosis. 2014, 7:1, 81-91.	Patients from England, Scotland, Sweden, Germany, USA	Qualitative research	To present a qualitative research project that explored practice-based perspectives on the relationship between psychosis and dissociation. To conceptualise the model of Structural Dissociation of the Personality		10		8 - The International Society for the Psychological and Social Treatments of Psychosis 2- The European Society for the Study of Trauma and Dissociation
12	Ross, C.A.; Keyes, B.B., Clinical features of dissociative schizophrenia in China, Psychosis. 2009,1:1, 51-60.	China	Mixed - Qualitative study and case reports	To describe some clinical examples of dissociative schizophrenia from China. To describe the dissociative subtype, and to demonstrate that it occurs outside North America, where most of the research supporting the existence of the subtype has been conducted.	Clinical population	50	19 - 70 (Mean age 43.3; SD 12.4)	All were inpatients at Shanghai Mental Health Center and had clinical diagnoses of schizophrenia made by their attending psychiatrists using Chinese diagnostic criteria.
13	Lysaker, P.H.; Minor, K.S.; Lysaker, J.T.; Hasson-Ohayon, I.; Bonfils, K.; Hochheiser, J.; Vohs, J.L.Metacognitive function and fragmentation in schizophrenia: Relationship to		Literature overview/ summary of research on quantifying metacognition	To review research seeking to measure some of the aspects of fragmentation related to the experience of the self and others				

(Continued)

TABLE 1 Continued

Nr	Article - full citation	Country	Study design	Aim	Population	N	Age	Recruitment method
	cognition, self-experience and developing treatments, Schizophrenia Research: Cognition. 2020,19 100142.							
14	Lysaker, P.H.; Hamm, J.A.; Vohs, J.; Kukla, M.; Pattison, M.L.; Leonhardt, B.L.; Lysaker, J.T. Understanding the course of self-disorders and aterations in self-experience in schizophrenia: implications from research on metacognition, Current Psychiatry Reviews. 2018, 14, 160-170.		Literature review/ theoretical models	To review research on the integrated model of metacognition in schizophrenia and explore five descriptions of alterations in subjective experience, which are sometimes called self-disorders.				
15	Kumar, D.; Venkatasubramanian, G. Metacognition and mindfulness integrated therapy reduces severity of hallucination in a patient not taking antipsychotic medication, Journal of Cognitive Psychotherapy. 2018, 32: 3,192-202.	India	Case report	Efficacy of metacognition & mindfulness integrated therapy in reduction of hallucination of patients not taking antipsychotic medication.	Clinical population	1	55	
16	Perivoliotis, D.; Grant, P.M.; Beck, A.T. Advances in Cognitive therapy for schizophrenia: Empowerment and recovery in the absence of insight, Clinical Case Studies. 2009, 8(6) 424-437.	USA	Case report	To describe a cognitive therapy approach innovated to circumvent limited insight in a patient with severe paranoia and auditory hallucinations	Clinical population	1	24	Not specified, although parents encouraged her to enrol
17	Pec, O.; Lysaker, P.H.; Probstova, V.; Leonhardt, B.L.; Hamm, J.A.; Bob, B. The psychotherapeutic treatment of schizophrenia: Psychoanalytical explorations of the metacognitive movement, Journal of Contemporary Psychotherapy. 2020, 50, 205–212.		Theoretical (psychoanalytical conceptualisation)	To explore how psychoanalytic theory can explain how the effects of MERIT upon metacognition and self-experience in schizophrenia may reflect its effects on repairing the collapse of the boundary/ connection between self and the world, mental fragmentation and the lack of symbolisation.				

(Continued)

TABLE 1 Continued

Nr	Article - full citation	Country	Study design	Aim	Population	N	Age	Recruitment method
18	Bob, P. & Mashour, G.A. Schizophrenia, dissociation and consciousness, Consciousness and Cognition. 2011, 20, 1042-1049.		Theoretical	A review of findings on dissociation, conscious disintegration and schizophrenia				
19	Ross, C. A. (2006). Dissociation and psychosis: The need for integration of theory and practice. In J. O. Johannessen, B. V. Martindale, & J. Cullberg (Eds.), Evolving psychosis (pp. 238–254). Routledge/Taylor & Francis Group.		Theoretical-Book chapter	To point out logical and scientific errors in the dominant conceptual system of psychosis and dissociation.				

publication title, country, publication year), design, sample characteristics (age, clinical/non-clinical, recruitment method), measures used to assess dissociation, psychosis and other dimensions, who applied the instruments and the limitations of the studies.

5 Results

5.1 Study design

The design and the type of included studies and articles were diverse, including: a randomised controlled trial (17), a meta-analysis (7), a longitudinal study (18), seven cross-sectional studies (6, 19–24), two qualitative studies (5, 25), one mixed methods design (26), two literature reviews (27, 28), a case report (29), two articles summarising theoretical views (30, 31), and a book chapter (32).

The included studies and articles are described in Table 1, which has inevitably some incomplete sections as the information that would have populated the respective sections, was not reported in the publications included.

5.2 Definitions used in the included publications

There are different conceptualisations of the notions on which we focussed our review. We did not analyse them as they were not always reported in the included articles, therefore we thought appropriate to presented them as used in the studies that reported them.

We looked at how the papers defined the keywords included in the database search (dissociation, psychosis and recovery) and the associated terms (compartmentalisation, detachment, absorption, depersonalisation, derealisation, amnesia, copying mechanism, fragmentation, hallucinations, delusions, positive symptoms, negative symptoms, schizophrenia, thought disorder, schizoaffective, psychotic, delusional, outcome, recuperation, rehabilitation, improvement, hopefulness). Most commonly defined terms were schizophrenia, psychosis, dissociation, compartmentalisation, and absorption.

The term psychosis as a broader concept is used in three papers (5, 17, 25). Most of them use the notion of schizophrenia as representative for psychosis (18, 22, 24, 27, 28, 31, 32). None of the papers include definitions for terms related to recovery or rehabilitation. Five publications do not include any definitions of the concepts relevant to this paper (20, 21, 23, 30, 32).

The concept of dissociation was defined either as a general concept or by referring to specific dissociative mechanisms. Longden and colleagues refer to the DSM-5 definition of dissociation as ‘‘*a disruption of and/or discontinuity in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control and behaviour*” (7, 8). Humpston and colleagues look at which type of dissociation is most associated with psychosis-like experiences (6). They refer to the notions of “*compartmentalisation-type dissociation which stems from the work of Pierre Janet […] who originated the modern concept of dissociation as the compartmentalisation of normally integrated mental functions leading to the loss of conscious control or awareness of specific mental, physical or sensory processes*” (33) and absorption “which relates to the ability to become immersed in thoughts and experiences” (6, 34).

Farelly and colleagues define psychosis as “a general term covering a range of psychiatric diagnoses such as schizophrenia, schizoaffective disorder and delusional disorder” (17) and dissociation “*as a disruption of and/or discontinuity in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control and behaviour*” (17), as per DSM-5 (8). Further, they offer definitions for detachment: “(it)

concerns a person's sense of separation from experience, including from their sense of self […] or from the external world" and for compartmentalisation: "*a disruption in normally integrated functions that is not accessible to conscious control and includes dissociation*" (17).

Rosen and colleagues talk about the "*ipseity of schizophrenia* (the term refers to the nature of self in schizophrenia), *involving two core components of disturbed basic sense of self: hyperreflexivity and diminished self-affection* (22). Hyperreflexivity refers to the process by which events, sensations and cognitions that would normally be experienced as tacit […] become explicit" and "diminished self-affection described the loss of attenuation of a normal sense of the self-existing as the subject […] of consciousness" (22). They also define the concept of absorption, which "describes a state of immersion in (or capture by) mental imagery or perceptual stimuli and correlates vivid imagination or fantasy" (22).

Bacon and Kennedy differentiate between "psychosis-as-PTSD" and "psychosis-as-dissociation" (5). Focusing on the term relevant to this paper (dissociation), they further explain that in the case of ''psychosis-as-dissociation'' is ''where psychotic symptoms represent interplay between deeply fragmented and incohesive ego-states, and the deterioration of the ego" (5).

Bob and Mashour refer to Eugen Bleuler's definitions of schizophrenia: "in 1911 Eugen Bleuler introduced the term schizophrenia as a description of this mental illness […], which replaced Kraepelin's term dementia praecox" (31). For the term dissociation they mention several definitions, from Pierre Janet and Bleuler's definition: "Janet used the term dissociation to denote a splitting of the psyche and analogously Bleuler […] used the term dissociation as a synonym for splitting" to a more recent definition: "the recent definition of dissociation as a special form of consciousness in which events that would ordinarily be connected are divided from one another, leading to a disturbance or alteration in the normally integrative functions of identity, memory, consciousness" (31).

Lysaker and colleagues discuss the concept of schizophrenia from different perspectives: as defined by Kraepelin, Bleuler, Rosenbaum ("disconnection of images, affects and ideas and causes a breach in the unity of the self and threatens the many symbolic link characterising its integrating capacities and its reality testing"), from a psychoanalytic point of view, from an existential perspective with Laing's focus on subjective experience of schizophrenia ("fundamental kind of alienation or a rent in his relation with his world […] and a disruption of his relation with himself"), the phenomenological and ipseity model of self-experience in schizophrenia, the rehabilitation and recovery based models of disturbance in self-experience in schizophrenia, and the dialogical models of schizophrenia (27, 28).

Two articles refer to the definitions and diagnostic criteria from DSM-IV-TR and the American Psychiatric Association for a dissociative subtype of schizophrenia (32, 35). Perivoliotis and colleagues define schizophrenia as a "chronic disorder associated with significant disability and poor quality of life" (24). Hwu and colleagues refer to Eugen Bleuler's definition of schizophrenia "as a constellation of fundamental symptoms" (18). Lynch and colleagues mention that "there are different ways of conceptualising 'psychosis' or 'psychotic experiences' (25) which include hearing voices and having unusual beliefs" (36).

Perona-Garcelan and colleagues use terms such as dissociation, hallucinations, schizophrenia, absorption, depersonalisation, however they do not define them (20).

Detachment and absorption are two dissociative phenomena explored by some of the studies included in this review. Detachment refers to a mental process also sometimes termed depersonalisation/derealisation. These phenomena encompass the experience of detachment from self and environment where the self and the environment are experienced as unfamiliar or altered (37). DSM-5 describes depersonalisation/derealisation as a dissociative disorder per se and also as a symptom characterising other psychiatric conditions (8).

Other authors describe a more "normal" aspect of dissociation. Buttler introduces the idea of "normal" dissociation and describes absorption as representative for this type of dissociation (38). Absorption is very often referred to as "normal" or non-pathological dissociation (39). It represents the involuntary tendency to attention narrowing to the extension of ignoring the environment and implies a temporary suspension of the reflective consciousness (38).

5.3 Participants

14 studies of the 19 publications selected for this review, included population samples of different sizes (see Table 1), the total number of participants being 21.377. The study by Logden was substantially the largest (7). They were recruited from the adult population aged between 18 and 70, with two studies recruiting younger participants (18, 20). The majority of the studies recruited participants from the clinical population. Seven studies were developed on clinical popuations only (17, 18, 23–26, 29). One cross-sectional study included only a non-clinical population (6). Five studies selected their control groups from a non-clinical population (7, 19–22). One study does not report which population the participants were recruited from (5).

5.4 Assessment tools

The 19 studies included in our review encompass a wide variety of tools. Out of them, one appears in a third of the studies, namely the Positive and Negative Syndrome Scale (PANSS) (40). A total of 33 measuring instruments including clinical interviews were used (see Table 2), which we grouped into the following categories:

- Scales for the measurement of psychosis (see Table 3).
- Scales for the measurement of dissociative experiences (see Table 4).
- Other scales (see Table 5).

There is a huge variation in the degree of detail in which they were described by the authors of the articles included in this literature review, and also with regards to reporting aspects related to the reliability and validity of the instruments used.

TABLE 2 Classification of instruments.

Nr	Article – author/year	Instruments			Who applied
		Psychosis/other psychopathology	Dissociation	Other	
1	Longden et al. (2020)"	PANSS (Kay, Fiszbein & Opler, 1988); not all mentioned	DES-II (Bernstein & Putnam, 1986); not all mentioned	not mentioned	
2	Farrelly et al. (2016)	PSYRATS (Haddock et al., 1999)	CDS (Sierra & Berrios, 2000)	BDI (Beck, Steer & Brown, 1996); BAI (Beck & Steer, 1990), PDS (Foa et al., 1997), SCID-D (Steinberg, 1994)	Researcher
3	Hwu et al. (1981)				
4	Perona-Garcelan et al. (2008)	PANSS (Kay, Fiszbein & Opler, 1988)	DES-II (Bernstein & Putnam, 1986)	SCS-R (Scheier & Carver, 1985)	Clinical psychologist
5	Perona-Garcelan et al. (2012)	PANSS (Kay, Fiszbein & Opler, 1988)	TAS (Tellegen & Atkinson, 1974); CDS (Sierra & Berrios, 2000)	MCQ-30 (Wells & Cartwright-Hatton, 2004)	Self-report (TAS) Self-administered (CDS) Administered by the clinical psychologist who was responsible for the patient's care (PANSS)
6	Wright et al. (2020)	PANSS (Kay, Fiszbein & Opler, 1987)		Computer based visual and auditory detection tasks; The cognitive insight scale (Beck et al., 2004), The Metacognitive Assessment Interview (Semerari et al., 2012), Time Use Survey (Short, 2006), The UCSD Performance-Based Skills Assessment (Patterson et al., 2001), The Questionnaire of Process of Recovery (Neil et al., 2009), The Wechsler Abbreviated Scale of Intelligence (Wechsler 1999)	
7	Rosen et al. (2017)	SCID (First et al., 2002) PANSS ((Kay, Fiszbein & Opler, 1988)	TAS (Tellegen & Atkinson, 1974);		
8	Úbeda-Gómez et al. (2015)	PSYRATS (Haddock et al., 1999)	SAS (Mckenzie & Hoyle, 2008)	MAAS (Brown & Ryan, 2003)	
9	Humpston et al. (2016)	PDI (Peters et al., 2004); CAPS (Bell, Halligan &Ellis, 2006)	DES (Bernstein &Putnam, 1986); TAS (Tellegen & Atkinson, 1974)	HGSHS: A (Shor &Orne, 1962)	HGSHS: A was administered at group level, then each participant was given a questionnaire pack containing the HGSHS: A, the PDI-21, the CAPS, the TAS and the DES
10	Lynch et al. (2018)			Semi-structured interview developed in discussion with the other two authors, with open and non-leading questions, and adapted as the research progressed, in line with grounded theory methodology.	First author (Clinical psychologist)
11	Bacon & Kenedy (2014)			Interpretative Phenomenological Analysis (IPA; Smith, Flowers, & Larkin, 2009) of semi-structured telephone interviews - detailed scrutiny of interview transcripts, development of conceptual themes, and repeating this with each set of	

(Continued)

TABLE 2 Continued

Nr	Article – author/year	Instruments			Who applied
		Psychosis/other psychopathology	Dissociation	Other	
				interview data before superordinate and subordinate themes accommodating all experiences were produced.	
12	Ross & Keyes (2009)			Clinical interview	The authors (The histories were taken with a psychiatry resident acting as translator)
13	Lysaker et al. (2020)			MAS-A (Lysaker et al., 2005)	
14	Lysaker et al. (2018)				
15	Kumar et al. (2018)	PSYRATS (Haddock et al., 1999)			clinician
16	Perivolioitis et al. (2009)	PSYRATS (Haddock et al., 1999), SANS (Andreasen, 1984), BAVQ-R (Chadwick et al., 2000)		BDI -II (Beck, Steer & Brown, 1996); BAI (Beck & Steer, 1990); Strauss-Carpenter Levels of Function Scale (Strauss & Carpenter, 1974); QoL Inventory (Frisch, 1994); BCIS (Beck et al., 2004)	Assessors blind to treatment condition; Self-report; Administered by therapist during therapy
17	Pec et al. (2020)				
18	Bob & Mashour (2011)				
19	Ross (2206)				

TABLE 3 Instruments used to measure psychosis.

Nr	Instrument, Author	Items/ Time/Formats	Domains assessed	Reliability	Validity
1	PANNS *(Kay, Fiszbein & Opler, 1988)* 5 studies: Perona-Garcelan et al., 2008, 2012; Wright et al., 2020; Rosen et al., 2017; Longden et al., 2020	30 items Positive scale items (7) Negative scale items (7) General psychopathology scale items (16) observations from interview/verbal report/ information from care givers Time: 1 hour Response: PANNS rating anchors 1-7 (absent to extreme)	*Psychotic symptoms:* *positive symptoms* (delusions, grandiosity suspiciousness/ persecution, unusual thought content) *negative symptoms* (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation, active social avoidance	Reported: *Rosen et al.,2017* Internal consistency α = 0.77 – 0.89 Test-retest reliability r=0.80 Inter-rater reliability – Kappa = 0.85 Not reported: *Perona-Garcelan et al., 2008, 2012; Wright et al., 2020; Longden et al., 2020*	Not reported by any of the 5 studies
2	PSYRATS (*Haddock et al., 1999*) 4 studies: Kumar et al., 2018; Ubeda-Gomez et al., 2015;	Interviewer -scored 2 subscales: hallucinations subscale (11 items); delusions subscale (6 items) Response: 5-point Likert-	Measures various dimensions (presence, typology, beliefs/ conviction, distress and disruption associated) of delusions and auditory hallucinations	Reported: *Ubeda-Gomez et al., 2015* Inter-rater reliability 0.80	Not reported by any of the 4 studies

(Continued)

TABLE 3 Continued

Nr	Instrument, Author	Items/ Time/Formats	Domains assessed	Reliability	Validity
	Perivoliotis et al., 2009; Farrelly et al., 2016	type scale (0 'not present' -4'present continuously')		Not reported: Kumar et al., 2018; Perivoliotis et al., 2009; Farrelly et al., 2016	
3	SCID (*First et al., 2002*) 1 study: Rosen et al., 2017	Structured clinical interview for the DSM Response: 3 point scale (1- absent; 2- subthreshold; 3 – threshold or true present)	Psychopathological assessments of types of hallucinations and forms of delusions	Inter-rater reliability Kappa 0.83	Not reported
4	SANS (*Andreasen, 1984)* 1 study: Perivoliotis et al., 2009	25 items Interviewer-scored scale	Negative symptoms of schizophrenia	Not reported	Not reported
5	BAVQ-R (*Chadwick et al., 2000)* 1 study: Perivoliotis et al., 2009	Not described	Auditory hallucinations	Not reported	Not reported
6	PDI (Peters et al., 2004) 1 study: Humpston et al., 2016	21 item- scale	Delusional ideation	Cronbach's alpha 0.77	Not reported
7	CAPS (bell, Halligan & Ellis, 2006) 1 study: Humpston et al., 2016	32 items- scale Subscales: Distress, intrusiveness, frequency	Anomalous perceptual experiences psychosis-like	Cronbach's alpha 0.87	Good construct validity

6 Discussion

Studies that looked at the relationship between trauma and dissociation in people with psychosis demonstrate that patients with psychosis who have had traumatic experiences in childhood score higher on the Dissociative Experiences Scale (DES) than those who have not experienced traumas (26).

Classically but not always, dissociative experiences occur in response to psychological trauma. Watkins and Watkins referred to dissociation as an organising principle which allows people to adapt, thus moving the focus from a pathological perspective to a constructive potential and adaptive function of dissociation (41). Bowins expressed his view that dissociative manifestations can buffer disturbing emotional states, facilitating adaptive coping; they are employed by individuals to protect themselves against stress, therefore aiding recovery (42, 43). This shift in the way dissociation is now seen, and our clinical observations that people who are recovering from an episode of psychosis, are at the core of our initiative to carry out this overview of the existent literature looking at the usage of dissociation in the process of recovery from psychosis.

The review brings together a diversity of international research and theoretical views on the phenomenology of dissociation, psychosis and recovery. Due to the diverse designs of the studies and articles included, a narrative synthesis approach was more appropriate in order to try and understand the views on these three concepts and how they may be linked to each other. While none of them includes studies or views on the relationship between dissociation and recovery from psychosis, they do provide some perspectives and findings that could guide the discussion on this pioneering topic and inform and stimulate specific research on the matter.

The findings of this review (see Table 6) indicate that the prevalence of the derealisation syndrome is not different between the groups of participants diagnosed with schizophrenia and those without this diagnosis (18). An important finding showed that patients recovered from hallucinations had a significantly higher mean DES-II score than the nonclinical control group (t=11·130, p=0·009) and that the participants with psychotic disorder who had never had hallucinations, had a significantly higher score on the DES-II scale than the participants in the non-clinical control group (t=5·668, p=0·007) (19). Other findings were that compartmentalisation-type dissociation did not predict psychosis-like experiences and a *post hoc* cluster analysis indicated that detachment-type dissociation and absorption are largely distinct from psychosis-like experiences and do not reflect similar constructs (6).

These findings are consistent with the views that dissociation phenomena can spread on a continuum of distress and disability (7), ranging from nonpathological experiences to chronic and extremely disabling conditions (44).

TABLE 4 Instruments measuring dissociation.

Nr	Instrument, Author	Items/Time/format	Domains assessed	Reliability	Validity
1	DES-II *(Bernstein & Putnam, 1986)* 3 studies: Perona-Garcelan et al., 2008; Humpston et al., 2016; Longden et al., 2020	28 questions Self-test Response: 11-point percentage scale (0% "never" to 100% "always") 3 subscales: amnesia, absorption and detachment	Dissociation – frequency of experiences: Amnesia, Absorption/ imaginative involvement, Depersonalisation/ derealisation	Reported: *Perona-Garcelan et al., 2008* Internal consistency α = 0.91 *Humpston et al., 2016* Internal consistency α = 0.95 Not reported: *Longden et al., 2020*	Reported: *Humpston et al., 2016* "good construct validity" Not reported: *Perona-Garcelan et al., 2008 Longden et al., 2020*
2	TAS *(Tellegen & Atkinson, 1974)* 3 studies: Perona-Garcelan et al., 2012; Rosen et al., 2017; Humpston et al., 2016	34-item 5 subscales: synaesthesia, altered state of consciousness, aesthetic involvement, imaginative involvement and extrasensory perception Self-report Response: 5-point Likert scale (0 'never' to 4 'always')	Levels of mental involvement with the object of experience	Reported: *Perona-Garcelan et al., 2012* Internal consistency α = 0.93 *Rosen et al., 2017* Internal reliability r=0.88 Test-retest reliability r=0.91 *Humpston et al., 2016* Internal consistency α =0.93	Not reported by any of the 3 studies
3	CDS *(Sierra & Berrios, 2000)* 2 studies: Perona-Garcelan et al., 2012; Farrelly et al. (2016)	29 items Self report Response: 2 Likert-type scales: 1.frequency of the experience, from 0 (never) to 4 (always) 2.Duration of the depersonalisation experience from 0 (a few seconds) to 6 (over a week)	descriptive evaluation of depersonalisation experiences	Reported: *Perona-Garcelan et al., 2012* Cronbach's alpha of.947 for the total scale score,.937 for the frequency scale and.943 for the duration scale. Not reported: *Farrelly et al. (2016)*	Not reported by either of the 2 studies
4	SAS (*Mckenzie & Hoyle, 2008)* 1 study: Ubeda-Gomez et al., 2015	17 items scale 2 subscales: Private self-absorption (8 items); Public self-absorption (9 items) Response: 5-point Likert scale (0 'never' to 4 'always')	The level of self-absorption	Internal consistency α =0.85 (private) and 0.91 (public)	Not reported

TABLE 5 Other instruments.

Nr	Instrument, Author	Items/Time/format	Domains assessed	Reliability	Validity
1	Semi-structured interview 1 study: Lynch et al., 2018	Face-to-face or telephone & audio recorded Time: 20 – 51 minutes Response: Grounded theory	Experience of art therapy following first diagnosis of psychiatric disorder Processes through which art therapy might help *Psychosis*	Qualitative	Qualitative
2	Clinical interview 1 study: Ross & Keyes, 2009	Clinical interviews	*Dissociation* *Dissociation subtype*	Qualitative	Qualitative
3	SCS-R *(Scheier & Carver, 1985)* 1 study: Perona-Garcelan et al., 2008	22 items 3 subscales: Self-focussed attention items (9) Public self-consciousness items (7) Social anxiety items (6) Response: 4-choice answer (completely agree to completely disagree)	Self-consciousness (self-focussed attention) as a trait or disposition	Internal consistency α= 0.92, 0.75, and 0.81 for each of the subscales, respectively	Not reported

(Continued)

TABLE 5 Continued

Nr	Instrument, Author	Items/Time/format	Domains assessed	Reliability	Validity
4	MCQ-30 *(Wells & Cartwright-Hatton, 2004)* 1 study: Perona-Garcelan et al., 2012	30 items questionnaire Five factors: 'Loss of cognitive confidence' 'Positive beliefs about worry' 'Cognitive self-consciousness' 'Negative beliefs about uncontrollability and danger' 'Need to control thoughts' Response: a scale of 1 (do not agree) to 4 (completely agree)	A range of metacognitive domains which are important in conceptualising psychopathological processes	Reliability for each of the 5 factors: 'Cognitive confidence' α = 0.85 'Positive beliefs' α = 0.84 'Cognitive self-consciousness' α = 0.75 'Uncontrollability and danger' α = 0.79 'Need to control thoughts' α = 0.78	"The construct and convergent validity are supported by empirical studies"
5	MAS-A (*Lysaker et al., 2005)* 1 study: Lysaker et al., 2020	A rating scale -not described in the paper	Metacognition as it is apparent within personal narratives *Metacognitive acts* *Metacognitive knowledge*	Not reported	Not reported
6	Computer based visual and auditory tasks 1 study: Wright et al., 2020	Task: to make 2 forced-choice binary judgements of 1.a) whether a stimulus was present or not within a noisy picture or presentation of white noise; 2.b) whether confidence in this decision was high or low; 2) to discriminate between correct and incorrect judgements	Metacognition efficiency Metacognitive sensitivity Metacognitive experience		
7	CIS (*Beck et al., 2004*) 1 study: Wright et al., 2020	9 items Self-reflective subscale of the cognitive insight scale	Metacognitive monitoring	Internal consistency α =0.68; test-retest reliability r= 0.90	Convergent validity r = -0.67
8	MAI (*Semerari et al., 2012*) 1 study: Wright et al., 2020	Requires the participant to reflect on a recent difficult interpersonal experience and answer a series of questions	Metacognitive ability	Internal consistency α =0.90; reliability r= 0.62 to 0.90	Good factorial validity
9	TUS (*Short, 2006*) 1 study: Wright et al., 2020	Structured interview Questions re the number of hours spent engaged in specific structured activities for the preceding month	Functional outcome	Inter-rater reliability 0.99	Good validity as TUS is comparable to studies using functioning measures
10	The UCSD Performance-based Skills Assessment (*Patterson et al., 2001*) 1 study: Wright et al., 2020	Total score for real-life performance skill based on role-play tasks. 0-20 scale 5 Sections: *Finance* *Communication* *Planning* *Transport* *Household*	Functional capacity	Internal consistency α =0.88; test-retest reliability r= 0.91	Validity r= 0.86
11	QPR (Neil et al., 2009) 1 study: Wright et al., 2020	22 items Self -reported questionnaire 2 subscales: Interpersonal subscale; Intrapersonal subscale	Individual's subjective recovery; hope, empowerment; confidence, connectedness with others, reliance	Internal consistency α =0.94 (intrapersonal subscale) and 0.77 (interpersonal	Construct validity Intra, r= -0.83; inter, r= 0.52

(Continued)

TABLE 5 Continued

Nr	Instrument, Author	Items/Time/format	Domains assessed	Reliability	Validity
		Response: a scale from 0 (strongly disagree) to 4 (strongly agree)		subscale); Reliability Intra, r= 0.87; Inter, r= 0.77	
12	WASI (*Wechsler, 1999*) 1 study: Wright et al., 2020	2 IQ tasks (verbal IQ and performance IQ) were used from the WASI	IQ (measure of neurocognition)	Not reported	Not reported
13	MAAS (*Brown & Ryan, 2003*) 1 study: Ubeda-Gomez et al., 2015	15 items Self-reported scale Response: Likert scale of 1-6	The dispositional capacity of awareness or attention to the experience of the present moment in daily life	Cronbach's alpha = 0.89	Not reported
14	BDI-II (*Beck, Steer & Brown, 1996*) 2 studies: Perivoliotis et al., 2009; Farrelly et al., 2016	21 item- scale Self-report Response: 4-point Likert scale (0- symptom not present, to 3- present with significant distress)	Symptoms of depression	Not reported	Validated in patients with schizophrenia
15	BAI (*Beck & Steer, 1974*) 2 studies: Perivoliotis et al., 2009; Farrelly et al., 2016	21 item- scale Self-report Response: 4-point Likert scale (0- symptom not present, to 3- present with significant distress)	Symptoms of anxiety	Not reported	Validated in patients with schizophrenia
16	SCLF (*Strauss & Carpenter, 1974*) 1 study: Perivoliotis et al., 2009	9 item- questionnaire Interviewer-scored Not described	Levels of social and occupational functioning	Not reported	One of the most commonly used validated questionnaires of functioning
17	QoL Inventory (*Frisch, 1994*) 1 study: Perivoliotis et al., 2009	32-item Self-report Measures subjective functioning on 16 life domains	Satisfaction with life	Not reported	Not reported
18	BCIS (*Beck et al., 2004*) 1 study: Perivoliotis et al., 2009	15 items Self-report 2 dimensions of cognitive insight: Self-reflectiveness and self-certainty	Cognitive insight- the ability to question one's beliefs, consider alternative explanations for one's experiences and accept that beliefs are fallible.	Not reported	Validated
19	PDS (*Foa et al., 1997*) 1 study: Farrelly et al., 2016	49 items Total score ranging from 0 to 51 Response scale not described	A checklist of potentially traumatising events and an indication of the distress, intrusive thoughts, avoidance and hyperarousal in the last month	Not reported	Not reported
20	SCID-D (*Steinberg, 1994*) 1 study: Farrelly et al., 2016	Structured clinical interview for DSM-IV dissociative disorders 9 items	Depersonalisation symptoms	Not reported	Not reported

(Continued)

TABLE 5 Continued

Nr	Instrument, Author	Items/Time/format	Domains assessed	Reliability	Validity
21	IPA (*Smith, Flowers, & Larkin, 2009*) 1 study: Bacon & Kenedy, 2014	Telephone interviews	Interpretative Phenomenological Analysis of semi-structured telephone interviews - detailed scrutiny of interview transcripts, development of conceptual themes, and repeating this with each set of interview data before superordinate and subordinate themes accommodating all experiences were produced.	Qualitative	Qualitative
22	HGSHS: A (*Shor & Orne, 1962*) 1 study: Humpston et al., 2016	Short hypnotic induction session followed by a series of 12 suggestions and a de-induction procedure 3 psychometric factors: ideomotor; challenge, cognitive	Compartmentalisation- type dissociative experiences through suggestion	Cronbach's alpha 0.79	Well-validated

7 Limitations

Table 6 summarises the limitations of the studies as reported by the authors.

One of the major limitations is the small number of publications included in the review and their very diverse nature. Because research in this field is difficult to undertake due to the difficulty to conceptualise dissociation and the overlapping of the phenomenological manifestations of dissociation and psychosis (35), we identified a very small number of publications that could be included in our review, despite the initial identification of a large number of publications in the world literature. None of them put together, in the same conceptualisation or hypothesis, dissociation and the recovery from an episode of psychosis, therefore this matter remains unstudied at this time. For the purpose of this review of the literature, we did not differentiate between the psychotic conditions because they are a large group of nosological entities. Although characterised by similar types of symptoms, psychotic conditions can differ in their manifestations, severity, response to treatment, prognosis and duration (45). This is an aspect that may be helpful to consider in a future research project.

We acknowledge the fact that our review of the literature only focussed on the relationship between dissociation and recovery from psychosis, and did not evaluate the factors that can influence the complex interaction between dissociation and psychosis, such as treatment, psychotherapy and history of trauma. The role of psychotherapeutic interventions in the recovery from psychosis is essential (46–48) but this was not evaluated during our survey. Another important factor is the treatment and response to treatment. There are instances where recovery can be difficult to achieve due to resistance to treatment. Resistance to drug therapy is reported in approximately 30–50% of patients with schizophrenia (49, 50). Panov (2022) (51) conducted a study that looked at the relationship between the degree of dissociation and resistance to therapy. The findings showed a high degree of dissociation in patients with resistant schizophrenia compared with those in remission. It has been demonstrated that those with a high degree of dissociation have a more severe course of illness (52). Consideration needs to be given also to the mechanism of action of antipsychotics as pharmacotherapy is crucial in the process of recovery from psychosis. An interesting hypothesis about the mechanism of action of atypical antipsychotics is proposed by Kapur and Seeman (2001) (53) explaining the "atypical" antipsychotic effect of the second generation antipsychotics. According to that, the fast dissociation from the D2 receptor makes an antipsychotic more accommodating of physiological dopamine transmission, permitting an antipsychotic effect without major side effects. This will improve compliance with treatment and subsequently facilitate the alleviation of symptoms and the process of recovery (54). Trauma is another factor that mediates the relationship between dissociation and psychosis (55, 56) and would need to be addressed in order to facilitate recovery. An interesting finding was reported by Van der Linde et al. (2023) who conducted a study that investigated the role of dissociation related beliefs about memory in trauma-focussed treatment. The results showed that dissociation-related beliefs do not influence the outcome of trauma-focussed treatment (57), The authors of some of the included studies report limitations to their projects. These, we believe, are important sources of learning and they could inform further research and stimulate curiosity to explore whether dissociative mechanisms are used by people with psychosis when they recover from an episode of illness.

One of the main learning points is that there are fundamental differences in the conceptualisation of the notions explored and their assessment by different measures (7). There is no consistency in reporting dissociation scale scores in the papers included in this review and therefore a cross-sectional comparison of the outcomes was not possible. Although the articles included report studies conducted in different countries, the search strategy was limited to those published in English. Although the population samples used for these studies include a wide range of ages and sources, the potential influence exercised by the cultural factor onto the dissociative experiences suggests that the results communicated by the Western studies may not always fully translate to other cultural settings (6). The small sample size studies (19, 22) and the cross-sectional design (6, 19–24) limited the generalizability of findings and the possibility to extract causal relationships among the variables studied. Another factor that could have influenced the findings, could be the recruitment methodology: approached by clinicians based on diagnoses (17, 19–

TABLE 6 Results and limitations.

Nr	Author/ Year	Results	Limitations
1	Longden et al. (2020)	• Dissociative phenomena are significantly related to positive symptoms and disorganisation. • Associations with negative symptoms were of smaller magnitude or nonsignificant. • The effects considered in the review were observed across both clinical and nonclinical samples.	• Impact on the magnitude of effects due to patients being likely more symptomatic than nonclinical participants; • Fundamental differences in the constructs assessed by different measures; • The search strategy was limited to peer-reviewed English-language studies; • The same studies examined multiple psychotic experiences within the same sample
2	Farrelly et al. (2016)	No results available as this paper presents the protocol for a study to assess the feasibility and acceptability of a brief cognitive behavioural therapy intervention for individuals who have depersonalisation symptoms in the context of psychotic symptoms.	
3	Hwu et al. (1981)	• The prevalence of the derealisation syndrome at initial evaluation is not different between the clinical (patients with schizophrenia) and the non-clinical groups.	not reported
4	Perona-Garcelan et al. (2008)	• The attention of subjects with hallucinations was more self-focussed than the nonclinical group; • A positive correlation ($p<0.05$) between self-focusing and dissociative experiences in subjects with hallucinations; • Depersonalisation - the only factor predicting auditory hallucinations ($F[1,66] = 113.366$, $p = 0.000$); • Patients recovered from hallucinations had a significantly higher mean DES-II score than the nonclinical control group ($T = 11.130$, $p = 0.009$); • The subjects with psychotic disorder who had never had hallucinations, had a significantly higher score on the DES-II scale than the subjects in the nonclinical control group ($T = 5.668$, $p = 0.007$). • Absorption - the patients recovered from hallucinations and those who had never had hallucinations had significantly higher scores than the nonclinical control group ($T = 18.465$, $p = 0.012$; $T = 8.586$, $p = 0.007$, respectively);	• Small sample size; • Limited in generalizability; • Only used single dissociative instruments.
5	Perona-Garcelan et al. (2012)	• Significant differences between the groups ($p < .001$) regarding depersonalisation, absorption and metacognitive variables • Both absorption and depersonalisation were positively associated with all Metacognition Questionnaire -30 subscales, and also with the total score ($p < .01$). • The variable with the most predictive power for hallucinations (scores on the PANSS) of all those used in this study was depersonalisation [$F(1, 122) = 101.472$, $p < .001$].	• Unable to establish any causal relationships between the variables studied; • Uncontrolled variable (schizophrenic patients were on antipsychotic medication while the rest of the subjects were not) that could affect the dependent variables; • Under reported symptoms; • Potential bias by the relationship between anxiety and depression and the dissociative variables; • Difficulties in understanding some of the items.
6	Wright et al. (2020)	• Metacognitive ability was a significant predictor of functional capacity, $R2 = 0.23$, $F(1, 131) = 38.98$, $p<.001$; and functional outcome, $R2 = 0.104$, $F(1, 133) = 15.39$, $p<.001$; and subjective recovery outcome in FEP $R2 = 0.39$, $F(3, 57) = 11.55$, $p<.001$. • Metacognitive control was a significant predictor of functional capacity, $R2 = 0.11$, $F(1, 130) = 16.16$, $p<.001$. • Metacognitive experience was a significant predictor of functional capacity, $R2 = 0.101$, $F(1, 131) = 14.6$, $p<.001$; and functional outcome, $R2 = 0.03$, $F(1, 132) = 4.15$, $p=.04$. • The FEP group demonstrated more accurate metacognitive experience (appraisal of experience), and higher scores on metacognitive monitoring compared to controls.	• The authors combined FEP and healthy control group in order to increase sample size and range of scores; • Individuals who typically engage in research studies tend to be higher-functioning, caution should be taken when applying these results to a lower functioning group.
7	Rosen et al. (2017)	• A highly positive correlation ($p<0.001$) between absorption and hallucinations, thought disorder; • 2 subtypes of absorption within the sample: Cluster One-Attenuated Ego Boundaries	• Small sample size; • Results based largely on self report - limited generalizablity

(Continued)

TABLE 6 Continued

(Continued)

TABLE 6 Continued

Nr	Author/ Year	Results	Limitations
		(AEB) - 55 participants both clinical and non-clinical (48%); Cluster Two - Stable Ego Boundaries (SEB) - 60 participants (52%). • A significant increase in PANSS positive, cognitive, excitement, depression factor scores in the AEB cluster compared to the SEB cluster; no significant differences between cluster groups in PANSS negative factor scores.	
8	Úbeda-Gómez et al. (2015)	• Distress caused by the voices correlated positively with self-focussed attention (private and public) ($p< 0.001$) and negatively with mindfulness ($p<0.001$); • A negative correlation was also found between mindfulness and self-focussed attention - private ($p<0.05$) and public ($p<001$); • Public self-focus was the only factor predicting distress caused by the voices [$R2 = 0.25$, $F(1, 50) =17.66$, $p<.001$;	•No causal relationships because of being a correlational study; •Not clearly isolated differences among groups with regard to the variables involved.
9	Humpston et al. (2016)	• Detachment and absorption predicted levels of delusional ideation and anomalous perceptual experiences; • Compartmentalisation did not predict psychosis-like experience; • Detachment and absorption are largely distinct from psychosis-like experience and do not reflect similar constructs.	•Not possible to determine the direction of causality; •The results may not always fully translate to other cultural settings.
10	Lynch et al. (2018)	Participants reported that through art therapy, they were able to build up relationships, connect with others, sustain participation and therapeutic engagement and experience therapeutic change.	•The service users were not involved in the design or execution of the study; •Not all participants brought artwork to discuss during the interview.
11	Bacon & Kenedy (2014)	• A model of the Theory of Structural Dissociation of the Personality (TSDP) suggests that the difference between psychosis and dissociation is circumstantial, dependent on the structural dissociation and mental level of an individual's personality (or parts thereof) at that time. It validates suggestions of a continuum-based approach to psychosis and dissociation as traumatic reactions.	•Difficult to disentangle the authors own beliefs from the experiences and understandings of the participants; •Factors such as participant nationality, profession and recruitment organisation may have influenced the findings.

(Continued)

TABLE 6 Continued

Nr	Author/ Year	Results	Limitations
12	Ross & Keyes (2009)	The authors predicted that the dissociative subtype of schizophrenia affects in the range of 25–40% of individuals meeting DSMIV-TR diagnostic criteria for schizophrenia. They diagnosed dissociative schizophrenia in 22% of the 50 cases interviewed. The percentage of cases assigned to the proposed dissociative subtype was within the range of the research-based prediction.	•The interviews were conducted by foreigners using translators; •Vague histories given by the participants; •Potential memory problems due to institutionalisation, ECT and medications; •Limited size of sample; •The lack of knowledge of dissociation making questions unclear to the participants.
13	Lysaker et al. (2020)	• No statistics reported; • Deficits in metacognition commonly occur in schizophrenia and are related to basic neurobiological indices of brain functioning; • The capacity for metacognition in schizophrenia is positively related to a broad range of aspects of psychological and social functioning when measured concurrently and prospectively; • Metacognitive Reflection and Insight Therapy (MERIT) has the potential to treat fragmentation and promote recovery.	•Difficulty measuring the extent of metacognitive deficit; •Lack of long term, longitudinal studies.
14	Lysaker et al. (2018)	•Review of major theories of alterations in self- experience in schizophrenia; • Results: The authors argue that research on metacognition suggests that reduction in metacognitive function may partially explain the occurrence of these difficulties and also explain how their resolution contributes to recovery.	
15	Kumar et al. (2018)	•50% reduction of PSYRATS score on the items related to the beliefs about origins of voices, intensity of distress, interference with life and controllability; •May be effective in patients who are not receiving antipsychotic treatment.	•Limited generalizability of the findings; •No discussion about the impact of the disappearance of the psychotic experiences; •No standard measure to assess the subjective rating of patient about recovery; •No tool for

(Continued)

TABLE 6 Continued

Nr	Author/ Year	Results	Limitations
			assessment of patient's metacognitive capacities.
16	Perivolioitis et al. (2009)	• Psychological intervention can be adapted to successfully treat patients with schizophrenia who lack insight; • The cognitive formulation of negative symptoms provides a useful roadmap; • The importance of experiential learning in driving both behaviour change and belief modification.	•Under reporting symptoms and guarded
17	Pec et al. (2020)	The metacognitive approach might provide operational definitions for psychoanalytic concepts in schizophrenia related to self-disturbance and the emotional, cognitive, and social disruptions associated with psychoanalytic understanding of fragmentation.	
18	Bob & Mashour (2011)	• Significant overlaps between the symptomatology and experimental data regarding dissociative processes and schizophrenia. • Although direct evidence is lacking, the investigation of dissociative processes may be beneficial for understanding certain types of schizophrenia.	
19	Ross (2006)	It proposes a dissociative subtype of schizophrenia.	

21, 23, 25, 26), advertisement within the local community (6, 21), random selection from an urban university medical centre and neighbouring communities (22); from research registers (17). Many factors such as participant nationality, profession, recruitment organisation may have influenced the findings and for this reason they cannot be considered representative (5).

8 Conclusion

Dissociation is a complex phenomenon involving different mechanisms that can modulate both the psychopathological processes underlying psychosis and recovery. The idea of integrative dissociation, suggested by Bacon and Kennedy (5), actually opens up the way to a new conceptualisation of dissociation, with potential impact on therapeutic intervention.

The process of reviewing the existing scientific literature in the field of dissociation and recovery from psychosis has been useful for charting the direction that future research projects will take. The putative association which we have raised, between dissociation and recovery from psychosis, has not previously been researched.

The literature is extremely diverse and dissociation is a phenomenon with many facets, difficult to measure unitarily, but which can be conceptualised very specifically through its processes. As a future project, a review of the different conceptual- definitions of dissociation, would seem of value given the diversity of its conceptualisation in the material presented.

Further research is needed to observe what happens to dissociative phenomena throughout the evolution of psychosis and not just in the acute phase of this illness. This work could helpfully include qualitative, patient experience studies and outcome research using tools identified in this review.

This overview of the literature should be considered a preliminary attempt to explore dissociation in recovery as we believe it to be a topic of clinical interest in a time of change in how therapeutic interventions are provided within the mental health services. It would be of interest to replicate the survey and evaluate also the factors which we did not include in this review.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

CC: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. RM: Writing – review & editing, Validation, Conceptualization. SC: Writing – review & editing, Investigation, Formal analysis. MZ: Writing – review & editing, Investigation, Formal analysis. RK: Writing – review & editing, Investigation, Formal analysis. KR: Writing – review & editing, Validation. CS: Writing – review & editing, Validation, Supervision. JW: Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Effect of computerized cognitive remediation therapy on mental time travel in patients with schizophrenia— a pilot randomized controlled trial

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Objective: To investigate the intervention effect of computerized cognitive remediation therapy (CCRT) on mental time travel (MTT) in patients with schizophrenia(SCZ).

Methods: From August 2020 to July 2021, 60 patients with SCZ were randomly allocated to either the study or the control group. The control group was treated with conventional drugs alone. The study group received CCRT and medical therapy for 40 minutes three times a week for 4 weeks. The participants underwent the MTT test before and after the training.

Results: A total of 28 patients in the study group and 26 patients in the control group were included in the analysis. Before training, there was no significant difference in the concretization ratio of recalling past and imagining future events between the study group and the control group ($P > 0.05$). After 4 weeks of training, the specific event ratio of the study group was higher than that of the control group ($P < 0.01$). In terms of the emotional titer of the events, the concreteness of the positive events in the study group was higher than that of the neutral events and negative events ($P < 0.01$). The concreteness of negative events was higher than that of neutral events ($P < 0.01$).

Conclusion: CCRT can improve the MTT ability of SCZ patients, which is manifested by an increase in the concretiveness of recalling past and imagining future events.

KEYWORDS

schizophrenia, computer cognitive remediation therapy, mental time travel, remember the past, imagine the future

1 Introduction

Schizophrenia(SCZ) is a chronic severe mental illness with a worldwide prevalence of approximately 1% (1). Patients suffer from attention disorder, memory disorder, executive dysfunction and other cognitive impairment, including mental time travel (MTT) (2). MTT refers to an individual's ability to recall the past or imagine the future. The ability to mentally relive past events is called a mental time travel pointing to the past (recalling the past), while the ability to mentally pre-experience future events is called a mental time travel pointing to the future (imagining the future). Projecting oneself into the past (recalling the past, i.e., autobiographical memory) is closely related to projecting oneself into the future (wanting to go to the future) (3). MTT plays an important role in our daily life. For example, it can help people achieve goals, cope with stress, and make decisions (4). Deficits in MTT affect the ability to recall of specific events and imagine the future, which may lead to problems such as impaired problem-solving and decreased overall functionality (5, 6). Therefore, the study of MTT in SCZ has important clinical significance.

Existing studies on MTT indicate that there is a deficit in MTT in patients with SCZ, which is manifested in issues in remembering the past and imagining the future. In terms of remembering the past, people with SCZ recall fewer events and lack details (7). Regarding the future, people with SCZ have difficulties in imagining it in detail (8), and the deficits are more pronounced than those related to remembering the past (9). Presently, researchers are exploring ways to improve MTT ability, one of which is cognitive correction training. Computerized cognitive remediation therapy (CCRT) is a brain-training method used in the study of SCZ and affective disorders using a series of targeted tasks to enhance learning and improve patients' cognitive abilities (10). Over the past 20 years, the number of trials investigating the efficacy of CCRT in SCZ spectrum disorder has increased significantly (11), and there is evidence that CCRT improves cognitive function in patients with SCZ, and that the benefits persist long after treatment has ended, particularly in memory, attention, and executive functioning (12).

Two recent meta-analyses examined the CCRT approach. One study found that CCRT had a small to moderate effect on attention, working memory, positive symptoms, and depressive symptoms (13). The second study evaluated the effects of CCRT on cognition, function, and clinical outcomes in patients with SCZ in 67 studies and found that CCRT treatment had significant improvements in small to moderate effects in all three areas (14).

So far, the current research mainly focuses on cognitive function, and there are few reports on mental time travel of patients with SCZ. The purpose of this study was to evaluate the efficacy of CCRT on MTT in patients with SCZ. Our main hypothesis is that CCRT will improve MTT ability in patients with SCZ.

2 Materials and methods

2.1 Materials

2.1.1 Study design

This was a longitudinal, randomized, single-blind trial conducted at the Second People's Hospital of Guizhou Province and Guiyang Lindong Hospital (the Intensive Medical Association of the Second People's Hospital of Guizhou Province). This study has been approved by the ethical review of the Second People's Hospital of Guizhou Province with the number [2020-SEYWYH-017]. All subjects gave informed consent to the study and signed informed consent form before starting the training.

2.1.2 Participants

From August 2020 to July 2021, 60 inpatients diagnosed with SCZ were recruited from the Second People's Hospital of Guizhou Province and Guiyang Lindong Hospital. Inclusion criteria were (1) SCZ that meets the diagnostic criteria of the International Classification of Diseases-10th Revision (ICD-10), with the Positive and Negative Syndrome Scale (PANSS) score not exceeding 60 points; (2) no history of neurological diseases; (3) no history of drug or alcohol dependence; (4) no electroconvulsive therapy within the past three months; (5) age of 18–50 years; (6) patients primary or higher education; (7) the intelligence quotient (IQ) of ≥70. Exclusion criteria comprised (1) mental retardation; (2) organic mental illness; (3) no cooperation due to declined or impulsive excitement; (4) severe anxiety, depression, or substance abuse; (5) auditory or visual perception impairment; (6) physical function diseases or other drug adverse reactions, not allowing patients to conduct computer game training in time; (7) pregnant or lactating women. In the end, 2 refused to participate, 4 were dislodged with a change in condition, and a total of 54 patients participated in the study. Experimental flow is shown in Figure 1.

2.1.3 Randomization and blinding

Participants were randomly assigned 1:1 (the study group and control group), and randomization was conducted independently by psychiatrists not involved in the study after completing all

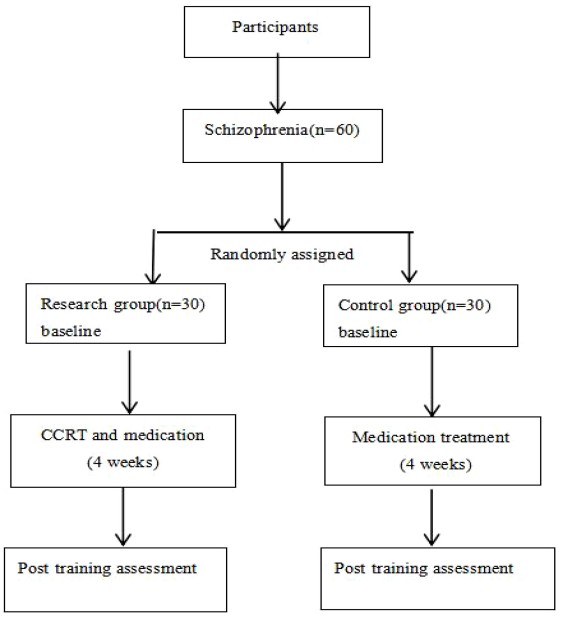

FIGURE 1
Flow chart of the study design.

baseline assessments. A table of random numbers was used to generate randomization, and the two groups were balanced in terms of age, sex, education, and disease course, as would be expected from random assignment. The patients and research personnel who are responsible for data collection, end-point evaluation, and statistical analysis will be blinded to the allocation of the two intervention arms. However, it is impractical to blind the attending physicians due to the nature of the treatment. Therefore, clinicians and researchers will not be blinded to the treatment allocation.

2.2 Methods

2.2.1 Tools

2.2.1.1 Sociodemographic data

We collected patients' basic information, including age, sex, name, years of education, course of disease, medication dosage, etc.

2.2.1.2 MTT measurement

The MTT measurement adopted in this study was adapted from the Autobiographical Memory Test(AMT)developed by Williams et al (15). The AMT consists of 10 different validities (5 positive cue words, 5 negative cue words). Subjects were asked to name a specific event related to the cue word within one minute. The criteria for concreteness event were: a specific time and place, and an event lasting no more than 1 day. Emotional titer is a dimension of emotion, which is divided into positive, neutral and negative. The emotional titer of events includes positive events, negative events and neutral events. The MTT measurement consists of two main parts: remembering the past and imagining the future (3). In this test, participants were asked to remember specific events in the past or imagine possible events in the future based on cue words, For example, the following question could be asked: "Can you describe a specific event or scene that has or has not occurred before but may occur in the future and is related to the cue word (e.g., a garden)." According to Ozdes et al. this paper has 15 cue words for recall and imagery respectively, including 5 each for positive, neutral and negative (4). For each cue word, participants had 1 minute to think and then describe the event. The Participants' responses were recorded and then transcribed into words to judge the concretiousness of the described events and classify them into: (1) specific events, recalled or imagined events that occurred within a specific time of day; (2) Extensibility events, events lasting longer than one day;(3) A class event is a class of things that may occur frequently; (4) A semantically relevant description, which is not a thing, but may be an expression of a state or feeling; (5) No answer or can't think of anything. The composition ratio of specific events to all described events was calculated as the main index of this test, and the composition ratio of recalled specific events and future specific events was divided according to the time direction, and the composition ratio of positive, neutral and negative specific events was divided according to the emotional titer of cue words. In order to ensure the reliability of the score, two raters scored the data of some participants at the same time, and the consistency coefficient of the raters was 0.85, indicating good consistency.

2.2.1.3 Mini-international neuro-psychiatric interview

Studies have shown that MINI has good reliability as well as high inter-investigator agreement, and has been widely used in multicenter clinical drug studies and clinical practice (16). Patients with SCZ and their psychotic symptoms were diagnosed and controlled, respectively, by MINI with attending psychiatrists. The reliability and validity of neuropsychiatric interviews were good.

2.2.1.4 Revised Wechsler Adult Intelligence Scale in China

IQ is an estimate of adult intelligence (17), which was assessed using the Chinese-revised Wechsler Adult Intelligence Scale based on four main subtests, including general knowledge, arithmetic, similarity, and number breadth. First, the rough score of each subtest was measured and then converted into the scale score. Then, the scale score of the four subtests was added, followed by dividing the total number by 4 and multiplying by 11. Finally, the corresponding IQ value was queried according to the norm table of different ages.

2.2.1.5 Verbal fluency test

A verbal fluency test was used to detect speech priming (18). The subjects had 60 seconds to name the animal that came to mind. If the name of the animal was repeated, no score would be given. The number of correct animal names was the main index, which was positively correlated with the score.

2.2.1.6 Alphanumeric span test

The alphanumeric span test was used to test working memory (19). Trained doctors read out combinations of characters (e.g., A, B, C, butyl, pente, and heptyl) and numbers (e.g., 123456789). The subjects were asked to first rank the numbers from the smallest to the largest and then answer the characters according to "A, B, C, butyl, pente, and heptyl." The correct number was the main detection index.

2.2.1.7 PANSS

The PANSS was used to assess the severity of psychiatric symptoms. PANSS has seven standards: 1 — none, 2 — very light, 3 — mild, 4 — moderate, 5 — heavy, 6 — severe, and 7 — extremely severe (20).

2.2.2 Intervention methods

The control group was treated with conventional drugs for 4 weeks. The study group received CCRT and 40 minutes of training 3 times a week, 12 times for 4 weeks, in addition to conventional drug therapy. It is supervised by an experienced therapist with a ratio of 1:4 participants. The therapist taught the participants to use CCRT for the first two weeks, and the subsequent treatment was mostly done by the participants alone. CCRT equipment is provided by Beijing Dixin Technology Co., LTD, and involved cognitive flexibility, working memory, and planning to perform three therapeutic tasks. Each treatment task consisted of 6–10 different cognitive correction exercises, and each cognitive correction training program consisted of 10–30 training tasks of varying difficulty. Specific content included continuous matching, quick matching,

finding differences, shopping planning, picture classification, and emotion management. Before the initial treatment, the computer will evaluate the subjects and give the training plan. The subjects will undergo cognitive training under the guidance of the therapist. In each training, the content of 3 modules will appear, and the computer will automatically match the corresponding progress and difficulty according to the subjects' achievements in the training module. Special staff will call to remind subjects in advance on the day of treatment, and those who complete the 4-week training will be rewarded to improve their compliance.

2.2.3 Sample size

According to relevant studies, this paper conducted technical tests on the sample size selection. Specifically, the effect value was set as 1, the significance level as 0.05, and the statistical testing force as 0.9. The minimum sample size was calculated as 23 for each group through G*power software, and the sample size of each group was finally determined to be 30 people considering the loss rate of 10%.

2.2.4 Statistical methods

SPSS 22.0 was used for data analysis. A t-test and χ^2 test were used to compare the two groups of general data. 2 (group: study group, control group) × 2 (time point: before intervention, after intervention) × 2 (time direction: memory, imagination) × 3 (emotional titer: positive, neutral, and negative) repeated measures of ANOVA were performed, and η^2 was used to represent the effect size, the greater the value, the greater the degree of difference. Test level $\alpha = 0.05$.

3 Results

3.1 Demographic and clinical information

A total of 60 patients with SCZ participated in the study: 30 in the study group and 30 in the control group. Within 4 weeks of treatment, one patient in the MTT group was excluded due to discharge, another one was excluded due to aggravation of the disease, two patients in the control group were excluded due to inability to adhere to the evaluation, and two patients were excluded due to recurrence of the disease. Finally, 28 patients in the study group and 26 patients in the control group could complete the training after enrollment. Both groups were given risperidone, olanzapine, aripiprazole, and other drugs, which were converted into equivalent doses of chlorpromazine. Antipsychotic dose, general psychopathological symptoms, positive symptoms, negative symptoms, education level, sex, age, and IQ were not significantly different between the two groups (Table 1).

3.2 Comparison of MTT concreteness between the two groups before and after intervention

The concrete descriptive results of MTT in the two groups before and after the intervention are shown in Table 2. In the two groups, the task to remember past and imagine future specific events was repeated by 2 (group: study group, control group) × 2 (time point: before intervention, after intervention) × 2 (time direction: remember, imagination) × 3 (emotional titration: positive, neutral, and negative). The results showed that the main effect was significant [$F(1, 52) = 24.76$, $P < 0.01$, $\eta^2 = 0.323$], and the specific event ratio in the study group was higher than that in the control group. The time point main effect was significant [$F(1, 52) = 139.21$, $P < 0.01$, $\eta^2 = 0.728$], and the specificity of the test after training was higher than that before training. The time direction main effect was significant [$F(1, 52) = 24.20$, $P < 0.01$, $\eta^2 = 0.318$], and the specificity of remembering past events was higher than that of imagining the future. The main effect of emotional titer was significant [$F(1, 52) = 127.57$, $P < 0.01$, $\eta^2 = 0.833$]. Further analysis showed that the concreteness of positive cue words was higher than that of neutral and negative cue words, and that of negative cue words was higher than that of neutral words ($P < 0.01$). Group and the interaction between before and after the test significantly [$F(1, 52) = 85.56$, $P < 0.01$, eta squared = 0.622]. Simple

TABLE 1 Demographic and clinical information of participants.

Project	Study (n = 28)	Control (n = 26)	t/χ^2	P
Male/Female	14:14	14:12	0.074[a]	0.785
Age(years)	37.43 ± 8.48	41.58 ± 8.70	−1.775[b]	0.082
IQ	79.16 ± 5.96	78.90 ± 9.49	0.120[b]	0.905
Education(years)	9.54 ± 3.32	9.69 ± 3.80	−0.162[b]	0.872
Duration of illness (years)	11.38 ± 7.30	11.29 ± 6.93	0.045[b]	0.965
General psychopathology	26.39 ± 2.38	26.39 ± 2.17	0.013[b]	0.989
Positive symptoms	8.50 ± 1.29	8.15 ± 1.85	0.803[b]	0.426
Negative symptoms	14.50 ± 2.53	15.58 ± 2.77	−1.492[b]	0.142
PANSS	49.39 ± 4.21	50.12 ± 3.64	−0.672[b]	0.505
Medication (CPZ mg/d)	191.51 ± 119.09	220.00 ± 149.63	−0.777[b]	0.441

[a]represents the value of χ^2, and [b]represents the value of t.

TABLE 2 Descriptive statistical results of mental time travel concreteness in both groups after 4 weeks of intervention (x ± s).

Point in time	Emotional titer	Study (n = 28)		Control (n = 26)	
		pre-training	post-exercise	pre-training	post-exercise
remember	positive	0.11 ± 0.07	0.28 ± 0.13	0.13 ± 0.06	0.15 ± 0.11
	neutral	0.03 ± 0.05	0.08 ± 0.10	0.02 ± 0.04	0.02 ± 0.03
	negativity	0.06 ± 0.07	0.12 ± 0.10	0.06 ± 0.05	0.07 ± 0.07
imagine	positive	0.09 ± 0.07	0.33 ± 0.09	0.09 ± 0.06	0.12 ± 0.09
	neutral	0.02 ± 0.03	0.03 ± 0.05	0.02 ± 0.03	0.01 ± 0.03
	negativity	0.05 ± 0.07	0.10 ± 0.01	0.03 ± 0.04	0.06 ± 0.07

effect analysis showed that there was no significant difference between the two groups before training, and the concreteness of the study group was significantly higher than that of the control group after CCRT training ($P < 0.01$).

4 Discussion

The mental time travel ability of schizophrenic patients is defective (21), affecting cognitive, emotional, and behavioral processes (22). It is difficult to recall the past and imagine the future, which makes it difficult for people to make decisions, solve problems, plan for the future, and make reasonable time estimates for activities of daily living. At present, some scholars have begun to explore the methods that can improve mental time travel ability, including life review training, autobiographical memory training and cognitive training (23, 24). Although life review therapy and autobiographical memory training were used in patients with SCZ, the above-mentioned studies have limitation. Due to the obvious decline in memory in some patients, there is resistance to life review training and autobiographical memory training, and most patients have poor compliance. This study adopted CCRT therapy, making full use of the advantages of computer technology in task standardization, material enrichment, objective evaluation, difficulty adjustment, and other aspects, to maximize the adaptability and compliance of treatment.

After four weeks of CCRT treatment, The results show that CCRT has a certain effect on the concreteness of past and future events in patients with SCZ. This is similar to Blairy's findings (25), which found that cognitive training improved the ability to recall specific events, and cognitive correction therapy was mentioned as an effective intervention to improve autobiographical memory. Therefore, this study extends on the basis of Blairy's research. In addition, Garrido and Linke found that CCRT can improve the attention, memory, executive function and other cognitive fields of SCZ patients (26, 27). CCRT improves working memory, attention and executive function and problem-solving abilities of patients with SCZ and thus improve the ability to recall the past and imagine the future (28, 29).

This study shows that CCRT can be an effective intervention for the MTT of patients with SCH. This provides preliminary evidence for the role of CCRT in MTT in patients with SCZ. CCRT is a behavioral training method that has been shown to have a relatively good therapeutic effect on improving cognitive deficits in SCZ patients (30). Compared with other methods that can be used to improve cognitive impairment in patients with SCZ, CCRT has advantages such as high patient acceptance, simple operation, low safety risks, extensive data and easy access. Therefore, as a new therapy, CCRT has become one of the cognitive rehabilitation intervention tools for SCZ patients at home and abroad.

5 Strengths and limitations

Regarding the strengths of this study, We are the first to use the CCRT method to improve the effect of patients with schizophrenia on the MTT. There are still some shortcomings in this study, which should be further explored in future studies. The limitations of this study are as follows. First, the clinical training period of this study was relatively short, and the long-term effect was not tracked. Future studies can extend the training time to further explore the effects of CCRT on MTT, cognition, and clinical symptoms of patients with SCZ. Second, no follow-up evaluation was conducted, and future clinical studies should include follow-up evaluation as much as possible, such as three months and six months after the completion of training. Finally, the health study group was not included. Whether the treatment for CCRT is likely to improve the ability to remember the past and imagine the future to a healthy level needs to be further explored. Future research directions can include the health group for comparison.

6 Conclusion

CCRT can provide an effective, simple and economical way to improve SCZ. In the future, it could be integrated into the overall treatment of people with mental illness, which could be a key part of recovery and relapse prevention for people with mental illness.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

This study was approved by the ethics review of the Second People's Hospital of Guizhou Province with the number. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JC: Investigation, Data curation, Writing – review & editing, Writing – original draft. CZ: Writing – review & editing, Project administration, Methodology, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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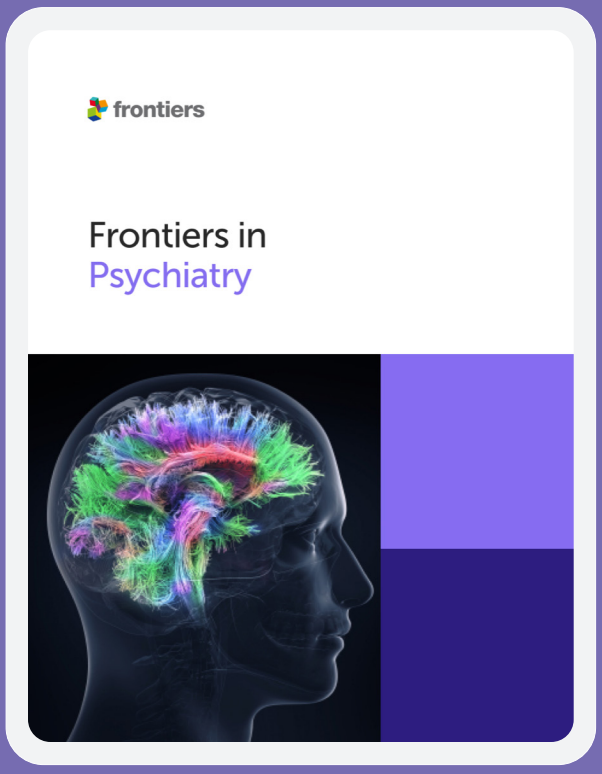

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