



Psychological interventions in psychosis in children and adolescents: a systematic review

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Abstract

Background Early onset psychosis (EOP), referring to psychosis with onset before the age of 18 years, is a more severe form of psychosis associated with worse prognosis. While medication is the treatment of choice, psychological interventions are also considered to have an important role in the management of symptoms and disability associated with this condition. The present review aimed to explore the effectiveness of such interventions.

Method An electronic search was conducted on the Embase, Medline, and PsychInfo databases for papers of randomized controlled trials (RCTs) referring to psychological interventions in EOP. References of identified papers were hand searched for additional studies. Identified studies were quality assessed.

Results Eight studies were included in the present review evaluating cognitive remediation therapy (CRT), cognitive behavioural therapy (CBT), a family intervention and psychoeducation. CRT was associated with improvement in cognitive function and CBT and CRT seem to also have a positive effect in psychosocial functioning. Symptom reduction appears to not be significantly affected by the proposed treatments.

Conclusions There is some evidence supporting the effectiveness of psychological interventions in EOP. However, most research on adolescents is focused on CRT and its effects on cognitive deficits. More studies on the effects of psychological interventions in EOP are needed.

Keywords Early onset psychosis · Cognitive remediation · Cognitive behavioural therapy · Psychoeducation · Adolescent · Family intervention

Introduction

Psychosis in childhood and adolescence, referred in this paper as early onset Psychosis (EOP), although rare, is associated with poor outcome and medical comorbidity [1]. Psychosis is an umbrella term for symptoms that can occur

in a range of disorders including depression, bipolar disorder, neurocognitive, and emerging personality disorders, and which are most characteristic of schizophrenia spectrum diagnoses, including schizophrenia, schizoaffective and delusional disorders [2, 3]. Symptoms are grouped into positive (i.e., beliefs and perceptions that can seem unfounded or unusual to others); negative (i.e., blunted affect, lack of motivation); disorganized (i.e., disorganized thinking, concentration and memory problems); and affective (high and low mood, mood dysregulation) [4]. Psychosis is also associated with significant cognitive deficits even after the successful treatment of its hallmark symptoms [5]. The global personal (early death, poor health and quality of life) and societal (cost of formal and informal care, lost productivity) burden of schizophrenia-spectrum psychosis is high [6]. The prevalence and incidence rates of schizophrenia-type psychosis are 1% and 0.1–0.4 per 1000 population per year, respectively [7], while the adolescent-onset cases account

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for less than 15% of all cases [8]. The highest incidence is during late adolescence and early adulthood.

Treatment guidelines [9–11] recommend cognitive behavioural individual (CBT for psychosis) and family-based interventions (FIp) at any stage of presentation, to reduce functional impairment and distress associated with psychotic symptoms, and to treat comorbid conditions [12]. A wider psychosocial care plan is recommended as part of the treatment offered. It has been suggested that young people who are 16 and older should be in specialized psychosis services. Intensive support is offered to young people in the first 2 years following a first episode of psychosis by early intervention psychosis services (EIP). This period is considered a ‘critical period’ for future outcomes [13].

Previous reviews [14, 15] on the effectiveness of psychosocial interventions in young people with psychosis show favorable outcomes for the addition of psychological interventions over medication only treatment. However, their results vary, as Armando and colleagues [14], favor cognitive remediation therapy (CRT) over other proposed treatments, whereas Bird and colleagues [15] mainly focus on the advantages of cognitive behavioural therapy (CBT). More importantly, neither review focuses on adolescents as both include samples up to the age of 30. To the authors’ knowledge, no previous review has specifically examined interventions for EOP only. The present review aimed to include only studies with adolescent samples also updating the previous reviews on all evaluated psychological treatments for this particular age group. Its main focus was to assess current evidence on the efficacy of psychological treatments in three aspects of the disorder: positive and negative symptom reduction, cognitive functioning and psychosocial functioning.

Methods

Search strategy

PRISMA guidelines were followed throughout the present review [16]. An electronic search was carried out on the PsychInfo, Medline and Embase databases on the 19th of January 2018. Keywords included “adolescent psychosis”, “adolescent schizophrenia”, “early onset psychosis”, “early onset schizophrenia”, “cbt”, “cognitive behavioural therapy”, “cognitive remediation therapy”, “family therapy”, and “psychological intervention”. Boolean operators OR and AND were used, as well as alternative English and American spellings. The titles and abstracts of the identified papers from the electronic search were screened and duplicates were removed. The references of the relevant identified papers were hand searched for additional relevant studies. The full search strategy is included in the “Appendix”. The

first author conducted the search and screened all of the abstracts. Co-authors reviewed the screened abstracts and read the included papers. Inclusion of papers was discussed within the team by applying the inclusion and exclusion criteria as described below.

Eligibility criteria

For the purpose of the present review, papers were only included if they followed a randomized controlled trial design (RCT), to ensure the highest result quality. In addition, the participants had to be aged between 12 and 18 and have a diagnosis of psychosis in accordance to the current classification system (either International Classification of Disorders—ICD or the Diagnostic and Statistical Manual—DSM). Papers were also included if they had mixed samples of diagnosed and at-risk patients. Finally, follow-up studies were only included if the original study was included as well to provide a clearer vision of the long-term outcomes of the treatment. Papers not in English, symposium abstracts, poster abstracts, and dissertations were excluded. Papers were also excluded if the sample included adults and data about the adolescent sample could not be extracted.

Outcome measures

Outcomes extracted from the papers included symptom reduction, cognitive functions ameliorations and changes in psychosocial functioning. All the papers were assessed for risk of bias using the Jadad scale for randomized controlled trials [17]. Studies’ characteristics are summarized by sample characteristics, country of origin, proposed treatment and comparison, treatment design, measures, outcomes, and Jadad score (Table 1).

Results

Identified studies

One hundred and twenty-nine papers were identified through the electronic search, of which 81 remained after duplicate removal. Five additional papers were added through hand searching reference lists of relevant articles. Screening based on title and abstract, resulted in 68 articles being excluded. Thirteen papers were screened at full text of which 5 were excluded based on the previously mentioned inclusion and exclusion criteria. One paper was revealed to not be an RCT [18], two were symposium abstracts [19, 20], one included adults [21], and one focused on at-risk participants [22]. A total of 8 papers were included in the present review.

Evidence from the reviewed papers suggests that a variety of psychological interventions were evaluated in EOP alongside medication treatments. Cognitive Remediation Therapy (CRT) was used in two of the studies [23, 24] and one of the follow-ups [25], while one more study [26] and its follow-up [27] followed the principles of cognitive remediation but in a computerized form, Computer-Assisted Cognitive Remediation (CACR). A psychoeducational approach was also evaluated one study [28] and its follow-up [29]. Finally, one study [30] focused on a combination of Cognitive Behavioural Therapy (CBT) and family intervention.

Outcomes

Evaluated outcomes depended on the proposed treatment. In studies employing CRT [23–27], the main outcome was cognitive deficits improvement, while CBT's, family therapy's [30] and the psychoeducational approach's [28, 29] main outcomes were related to psychosocial functioning. All eight studies report on psychotic symptom changes.

Psychotic symptoms

Psychotic symptoms appear to not be significantly affected by the proposed psychological treatments. While the initial study by Calvo and colleagues [28] reports a significant reduction of negative symptoms only in the psychoeducational group and no between group differences for positive symptom reduction, this distinction disappeared in the follow-up [29]. Similarly, Urban and colleagues [27] report marginally significant reductions in both the treatment and the comparison groups. Finally, Ueland et al. [25] and Browning et al. [30] report no significant between groups differences in this respect.

Psychosocial functioning

Psychosocial functioning results present a mixed outlook. While Browning and colleagues' pilot CBT and family therapy study [30] and Puig and colleagues' CRT study [24] report significant improvements only in the treatment group, Ueland and colleagues' CRT study [23] does not. Similarly, Holzer and colleagues' CACR study [26] reports significant improvements in both the experimental and control groups.

Cognitive functioning

Cognitive functioning is only explored in the CRT studies, all of which show improvements on different areas of cognitive ability. Holzer and colleagues [26] report significant ameliorations in visuospatial abilities in the treatment

group, which are retained at the 6-month follow-up [27], where additional improvements in executive functioning and reasoning are also observed. Puig and colleagues [24] also report significant improvements in executive functioning as well as in verbal memory and working memory. Finally, Ueland and colleagues [23] report improvements in executive functioning, attention and memory which are retained at the 1 year follow-up [25] as well as improvements in early visual information processing. However, in the follow-up study, the control group has also improved in those same cognitive functions over time.

Discussion

A number of psychological interventions have been proposed as complementary to standard care in psychosis. The present review is the first one evaluating their effectiveness specifically in adolescent samples on focusing on psychotic symptoms, cognitive functioning and psychosocial functioning. Our findings indicate that the aspect that has received most attention in EOP is cognitive functioning and there is evidence to suggest that CRT interventions have an effect in improving cognitive deficits. There is also some evidence for benefits on psychosocial functioning, while the effect of treatments in psychotic symptom reduction does not seem to be significant. Psychoeducation appears to aid in relapse prevention but this outcome was only explored in one of the studies [28].

Recent reviews [31] in adult literature support the view that it is essential to develop treatments aiming at achieving life goals and improving quality of life, in addition to treatments that target psychotic symptoms. Psychological treatments focusing on underlying psychological processes that are likely to be maintaining the distress and impairment associated with psychotic symptoms, are starting to develop. Based on the view that psychosocial mechanisms are common between non-clinical unusual experiences and clinical psychotic symptoms, it has been suggested that psychosis can be treated by applying normal psychological processes [32]. More specifically, in a CBT treatment study [33] that focused on personal goals such as taking the bus alone, results showed that patients learned new skills improving their self-esteem, which in turn led to better psychosocial functioning. Similarly, CBT could aim to promote flexibility in appraisals of personal experiences to reduce distress and disability [34]. Our findings, regarding psychosocial functioning measures, also seem to suggest that psychological interventions should take a similar direction. While most of the studies discussed do not report changes in symptomatology, they do report better scores in outcomes of psychosocial functioning. Thus, it could be argued that the development of effective psychological treatments that

target psychosocial functioning should be a separate focus of attention in EOP. This theoretical model of psychosis is applied in an ongoing research on the 12 to 18 population accessing community child and adolescent mental health services (CAMHS) with reported psychotic symptoms (The CUES + trial) [35]. Should such an approach prove helpful, this would indicate that psychological interventions could be developed for specific symptoms separately, for example for hallucinations or delusions.

Our findings, on the effectiveness of CRT in cognitive symptom reduction, also seem consistent with the adult literature on the subject. It has been proposed [36, 37] that the areas mostly benefiting by CRT in schizophrenia are memory and executive functioning. All of the included CRT studies show similar results. In addition, the adult literature supports that by improving the cognitive deficits of schizophrenia, social functioning improves as well [37]. This seems to be less clear in the younger age group. While Holzer and colleagues [26] report significant changes in psychosocial functioning, those are absent at follow-up [27]. Similarly, Puig and colleagues [24], report improvements in global functioning that are not retained at the 3-month follow-up. Finally, Ueland and colleagues [23], did not find any between group differences on psychosocial functioning. It is evident from these results that the relationship between cognitive deficits improvements and psychosocial functioning in EOP need to be further explored.

While it appears that cognitive functioning is the area benefitting the most from psychological interventions, this could be due to the fact that the majority of the studies used in the present review were on CRT [23–27], which explicitly targets cognitive deficits. There was only one pilot study included in the present review on CBT which limits our ability to draw conclusions on its benefits. Adult studies on CBT for schizophrenia have shown that CBT significantly helped improve negative and positive symptoms [38] and also helped accelerate remission from 6 weeks to 4 [39]. CBT controlled trials in adult populations also showed greater efficacy of CBT for command hallucinations in schizophrenia than standard care [40, 41]. The pilot study by Browning and colleagues [30] included in the present review also shows improvements in psychosocial functioning. Taking that into account, it is evident that more research on how CBT affects adolescents with psychosis should be undertaken. While having evidence supporting certain interventions in adult trials is encouraging, a specific focus on outcomes for adolescents is warranted as the higher degree of severity of the condition in younger people [2, 3] may affect their response to treatment. In addition, it is possible that adult interventions would have to be adapted when applied in an adolescent population. Research has shown that engagement with therapy might differ when taking into consideration developmental and cognitive factors [42]. The

language used would have to be adapted, as well as the pace and duration of the sessions due to younger people having more limited attention span compared to adults. Another issue to consider would be focusing on behavioural change using behavioural activation or social skills training [30], as they might be easier to engage in. Finally, working with adolescents gives therapists the opportunity to employ their parents as co-therapists, exploring their appraisals of illness [22], as well as developing mutual problem-solving skills and coping strategies [43]. Similarly, such interventions could include liaison with schools in developing relapse prevention plans.

In our systematic review, there are a few limitations that need to be considered. As previously mentioned, most of the included studies focused on CRT as a psychological intervention for children and adolescents with psychosis. While it appears that this particular intervention is very effective, mainly in improving cognitive functioning, this conclusion could be obscured due to the limited research in alternative interventions. In addition, the included studies use different types of psychological treatments as their comparison group, instead of using a treatment as usual control [19, 23, 24, 30]. This kind of design still allows for some comparison between groups, but it also introduces confounding factors in the treatment evaluation. Specifically, while conclusions can potentially be drawn for the primary outcome, secondary outcomes may be difficult to interpret. For instance, in the study by Ueland and colleagues [23], where CRT was offered as well as psychoeducation, it is difficult to pinpoint whether changes in cognitive functioning were due to the CRT alone or due to its combination with psychoeducation. Finally, the small sample sizes in all the studies might mean that some treatment effects may not have reached statistical significance and were, therefore, missed. Even so, larger scale studies in EOP are very hard to conduct due to the rarity and specific characteristics of these disorders.

Although the focus of our review necessitated the exclusion of studies of young adults with psychosis and, therefore, might have led to less generalizable conclusions, it was thought important to only include adolescent samples as extending upwards the age limit would take away the focus from the specific needs of the adolescent population. In this age range, cognitive and developmental factors need to be taken into consideration when designing psychological interventions [42]. Finally, outcome measures such as relapse and family burden, while frequently used in adult studies, were not researched in most of the studies in our review, apart from Calvo and colleagues [28]. There is evidence that family interventions are effective in reducing relapse in young adults at risk of psychosis [44], so it would be interesting for future studies focusing on adolescence to include those measures as well.

However, even when taking into account these particular limitations, the present review offers new insights into the use and benefits of psychological treatments in EOP. The emphasis given on the adolescent population by only including studies with 12–18 years helps conclude on what the effectiveness of psychological treatment is in this particular population. CRT and its effects are better researched in adolescents with psychosis, whereas other forms of therapy such as CBT and family therapy would benefit from further exploration. In addition, the inclusion of only RCTs ensures the high quality of the extracted results. This is further confirmed by the fact that most of the studies used have very high Jadad quality scores. Finally, the present review highlights the urgent need for effective psychological interventions alongside medication treatment to target residual debilitating symptoms in EOP. Our findings indicate that adding a psychological intervention to medication may lead to better cognitive functioning as well as better psychosocial outcomes.

In conclusion, psychological interventions seem to have an important role in improving cognitive deficits

and possibly psychosocial outcomes in EOP when added to medication treatment. Further research that focuses on adolescent patients is urgently needed, even if psychological treatments have been previously proven effective in adults. Evidence based psychological interventions in adolescents with EOP would be a very significant step towards reducing the burden and impairment associated with the condition and assist with their recovery.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical declaration The manuscript does not contain clinical studies or patient data.

Appendix

See Fig. 1 and Tables 1 and 2.

Fig. 1 Journal identification process [16]

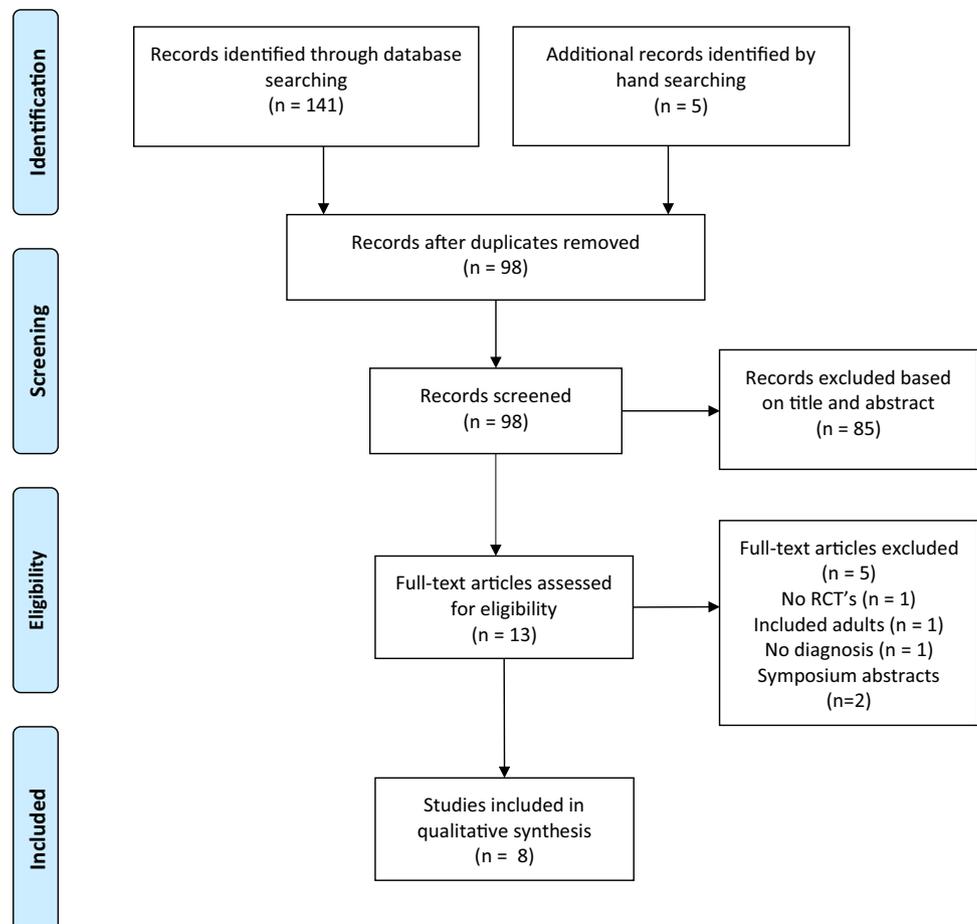


Table 1 Characteristics of used studies

References, Country	Study type	Age/N	N diagnosis	Intervention	Comparison	Treatment design	Measures (tool used)	Main outcomes	Jadad Score
Holzer et al. [26]	RCT	M: 15.4 N = 32 (20 diagnosed, 12 high risk)	DSM-IV diagnosis of a psychotic disorder At risk group Structured Interview for Prodromal Symptoms (SIPS) - Scale of Prodromal Symptoms (SOPS)	Computer assisted cognitive remediation (CACG) (N = 18)	Computer games (CG) (N = 14)	8-week trial, 45-min sessions, two sessions per week, targeting: (a) Attention skills (b) Visual motor skills (c) Conceptual skills (d) Memory (e) Logic	(a) Cognitive functioning (RBANS ^a —adolescent) (b) Symptoms, (PAINSS ^b) (c) Psychosocial functioning, (SOFAS ^c and HoNOSCA ^d)	(a) Visuospatial abilities significantly improved in the CACG group (b) Attention, memory and social functioning significantly improved in both groups (c) Higher motivation correlated with improvement in both groups	5
Urban et al. [27], Switzerland	Follow-up (6-month)	M: 15.2 N = 22 (16 diagnosed, 6 high risk)	Same as above	Computer assisted cognitive remediation (CACG) (N = 12)	Computer games (CG) (N = 10)	8-week trial, 45-min sessions, two sessions per week, targeting: (a) Attention skills (b) Visual motor skills (c) Conceptual skills (d) Memory (e) Logic	(a) Cognitive functions, defined as processing speed, working memory, long term memory, executive functions, reasoning and planning (b) Symptoms (CGI ^e)	(a) Significant improvement in executive functions (inhibition) and reasoning abilities in the CACG group (b) Marginally significantly less symptoms in both groups (c) No correlation between changes in symptom severity and cognitive functioning	5

Table 1 (continued)

References, Country	Study type	Age/N	N diagnosis	Intervention	Comparison	Treatment design	Measures (tool used)	Main outcomes	Jadad Score
Browning et al. [30], UK	Pilot RCT	14–17 N=30	ICD-10 Psychotic disorder diagnosis	Cognitive behavioural therapy (N=10) or Family Therapy (N=10) (along with standard care)	Standard care alone (N=10)	For CBT: 10 half-hour sessions, twice a week Family Therapy: 5 h long sessions over 4–10 weeks	(a) Symptoms (BPRS) (b) Psychosocial functioning (CGAS) (c) Satisfaction rates	(a) Significant improvement in symptoms and psychosocial functioning for both therapy groups (b) Improvements only in symptoms for the standard care group (c) No sufficient effect size for between group comparisons (d) The psychological therapies achieved a high satisfaction rate from both adolescents and parents	2

Table 1 (continued)

References, Country	Study type	Age/N	N diagnosis	Intervention	Comparison	Treatment design	Measures (tool used)	Main outcomes	Jadad Score
Puig et al. [24], Spain	RCT	12–18 N=51	DSM-IV schizophrenia or schizoaffective disorder	Cognitive remediation therapy (N=25)	Treatment as usual (N=26)	40 sessions, 2 per week, targeting: (a) Thinking flexibility (b) Information maintenance (c) Executive processes (d) Memory (e) Planning (f) Schema formation Manipulation	(a) Cognitive functions: verbal memory, working memory, working memory, processing speed, executive functions (part of the WISC [®] and COWAT [®]) (b) Symptoms (PANSS) (c) Real world day living (LSP [®]) (d) Real world functioning (VABS [®] and C-GAS) (e) Self-esteem (Rosenberg scale) (f) Caregiver burden (CBI [®])	(a) Significant improvements in verbal memory, working memory and executive functioning only in the CRT group (maintained at 3-month follow-up) (b) Greater improvements in daily living and global functioning in CRT (not maintained at the follow-up) (c) Greater improvement on caregiver burden in the CRT group	4
Calvo et al. [28], Spain	RCT	14–18 N=55	DSM-IV schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, major depressive disorder with psychotic features, brief psychotic disorder, or psychosis not otherwise specified	Psychoeducational intervention (N=27)	Non-structured group intervention (N=28)	One group for patients and a different one for parents, 12 sessions of 90 min each, every 15 days focusing on: (a) Better understanding of the disorder (b) Problem solving strategies (c) Written material about the disorder	(a) Hospital admissions, number of days in the hospital and number of visits to the ED (b) Symptoms (PANSS) (c) Social functioning (C-GAS) (d) Family psychological climate (FES ^m)	(a) Significant reduction of negative symptoms only in the PE group (b) Positive symptom reduction in both groups (c) Marginally significant less number of emergency visits in the PE group (d) No statistical differences in all other measures	4

Table 1 (continued)

References, Country	Study type	Age/N	N diagnosis	Intervention	Comparison	Treatment design	Measures (tool used)	Main outcomes	Jadad Score
Calvo et al. [29], Spain	Follow up (2 years)	14–18 N=55	Same as above	Psychoeducational intervention (N=27)	Non-structured group intervention (N=28)	One group for patients and a different one for parents, 12 sessions of 90 min each, every 15 days focusing on: (a) Better understanding of the disorder (b) Problem solving strategies (c) Written material about the disorder	(a) Hospital admissions, number of days in the hospital and number of visits to the ED (b) Symptoms (PANSS)	(a) Less visits to the ED in the PE group still after 2 years (b) Same improvement on negative, positive and total symptom scores for both groups (c) Significantly more improvement in the general symptoms in the PE group	4
Ueland and Rund [23], Norway	RCT	12–18 N=26	DSM 4 a diagnosis within the schizophrenia spectrum or other psychotic disorder	Cognitive remediation therapy (+psychoeducation) (N=14)	Treatment as usual (+psychoeducation) (N=14)	30 h individual training on: (a) Cognitive differentiation (b) Attention (c) Memory Social perception	(a) Cognitive functions: pre-attentional processing, early visual information processing, visual sustained attention, visual long-term memory, verbal learning, long term verbal memory and executive functioning (b) Symptoms (BPRS) (c) Psychosocial functioning (GAS) (d) Behavioural functioning (CBCL ⁿ)	(a) No significant group effect due to low power (b) Within group analyses showed improvement in 5 cognitive functions in the CRT group and 3 in the control (c) No significant differences in symptoms or social functioning	4

Table 1 (continued)

References, Country	Study type	Age/N	N diagnosis	Intervention	Comparison	Treatment design	Measures (tool used)	Main outcomes	Jadad Score
Ueland and Rund [25], Norway	Follow up (1 year)	12–18 N=26	Same as above	Cognitive remediation therapy (+psychoeducation) (N=14)	Treatment as usual (+psychoeducation) (N=14)	30 h individual training on: (a) Cognitive differentiation (b) Attention (c) Memory Social perception	(a) Cognitive functions: pre-attentional processing, early visual information processing, visual sustained attention, visual long-term memory, verbal learning, long term verbal memory and executive functioning (b) Symptoms (BPRS) (c) Psychosocial functioning (GAS) (d) Behavioural functioning (CBCL)	(a) Significant improvement in 8 out of 10 cognitive tasks for both groups (b) The CRT group significantly improved more in early visual information processing than the control, after controlling for IQ (c) No other significant differences between groups on the other measures	4

^aRepeatable battery for the assessment of neuropsychological status (Pearson 2012)

^bPositive And Negative Symptom Scale (Kay et al. 1987)

^cSocial and Occupational Functioning Scale (Rybarczyk 2011)

^dHealth of the Nation Outcome Scales Child and Adolescent Mental Health (Gowers et al. 1998)

^eThe Clinical Global Impressions Scale (Busner and Targum 2007)

^fBrief Psychiatric Rating Scale (Overall and Gorham 1962)

^g(Children's) Global Assessment Scale (Endicott et al. 1976)

^hWechsler Intelligence Scale (Wechsler 2014)

ⁱControlled Oral Word Association Test (Patterson 2011)

^jLife Skills Progression (Wollesen and Peifer 2006)

^kVineland Adaptive Behaviour Scale (Sparrow et al. 2005)

^lCaregiver Burden Inventory (Novak and Guest 1989)

^mFamily Environmental Scale (Moos and Moos 1994)

ⁿChild Behaviour Checklist (Achenbach 1992)

Table 2 Electronic search strategy

1. Psychotic-like experiences.mp
2. Adolescent psychosis.mp
3. Adolescent schizophrenia.mp
4. Early onset psychosis.mp
5. Early onset schizophrenia.mp
6. Children psychosis.mp
7. Children schizophrenia.mp
8. (At-risk youth AND psychosis).mp
9. Unusual experiences.mp
10. Cbt.mp
11. Cognitive remediation.mp
12. Cognitive behavioural therapy.mp
13. Cognitive behavioural therapy.mp
14. Family therapy.mp
15. Psychological intervention.mp
16. Psychological interventions.mp
17. Parenting.mp
18. Play therapy.mp
19. Child psychosis.mp
20. Child schizophrenia.mp
21. Psychoeducation therapy.mp
22. Metacognitive intervention.mp
23. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 or 19 or 20
24. 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 21 or 22
25. 23 AND 24

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