Review

Cognitive remediation for negative symptoms of schizophrenia: A network meta-analysis

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HIGHLIGHTS

- This is the first study on the effect of Cognitive Remediation (CR) on negative symptoms in people with schizophrenia.
- The results demonstrate a small to moderate effect of CR on negative symptoms (effect size $g = -0.30$).
- Negative symptom reduction is maintained at follow-up (effect size 95% $g = -0.36$).
- Studies with more robust methodology show a larger negative symptom reduction (effect size $g = -0.40$).
- There were no differences in drop-out rates between individuals randomized to CR and the control conditions suggesting that this intervention is acceptable.

ARTICLE INFO

ABSTRACT

Cognitive remediation (CR) is a treatment targeting cognitive difficulties in people with schizophrenia. Recent research suggested that CR may also have a positive effect on negative symptoms. This meta-analysis investigates the effect of CR on negative symptoms.

A systematic search was used to identify all randomized-controlled trials of CR in people with schizophrenia reporting negative symptoms outcomes. Levels of negative symptoms at baseline, post-therapy and follow-up, sample demographics and treatment length were extracted. Study methodological quality and heterogeneity were addressed. Negative symptoms standardized mean change was calculated using Hedges's g and used as the main outcome.

The search identified 45 studies reporting results for 2511 participants; 15 studies reported follow-up outcomes. CR was associated with a reduction of negative symptoms (most conservative model $g = -0.30$; 95% CI: -0.36, -0.22) at post-therapy compared with treatment as usual and this effect was larger at follow-up ($g = -0.36$; 95% CI: -0.51, -0.21). Drop-out rate was comparable between conditions. Network meta-analysis confirmed CR was superior to TAU and TAU plus active control or adjunctive treatment. No evidence of publication bias was found. Studies with more rigorous methodology were associated with larger negative symptom reduction ($g = -0.40$; 95% CI: -0.51 to -0.30).

Although negative symptoms have not been considered a primary target for CR, this intervention can have small to moderate beneficial effects on this symptom cluster. Future research should explore in detail the active mechanisms responsible for negative symptom reduction and the relationship between cognitive and negative symptoms in schizophrenia.

Contents

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1. Introduction

Cognitive remediation (CR) is a behavioural intervention aiming to improve cognitive processes in neuropsychiatric disorders. CR relies largely on learning principles such as repeated and personalised task practice, tailored feedback and the teaching of compensatory methods to overcome cognitive related problems. The consolidated notion of widespread cognitive difficulties in people with schizophrenia prompted the application of this intervention in this illness domain (Keshavan, Vinogradov, Rumsey, Sherrill, & Wagner, 2014; Vinogradov, Fisher, & de Villers-Sidani, 2012). To date a relatively large number of studies that appear in the literature, systematic reviews and meta-analyses suggest that CR has beneficial effects on both cognition and functioning with small to moderate effect sizes (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). The most recent meta-analysis also suggests that CR has a small effect on symptoms; however, this study considered only global symptoms and did not distinguish between different dimensions (Wykes et al., 2011).

Schizophrenia is a heterogeneous condition comprising different symptom clusters. The most reported symptom dimensions in the literature are positive and negative symptoms. While antipsychotic medications have proven beneficial for the management of positive symptoms, pharmacological treatments have still not provided convincing benefits for negative symptoms (Fusar-Poli et al., 2014). Negative symptoms have often been found to contribute to long term illness features including poor community and social functioning and to negatively influence recovery and general health outcomes (Ventura et al., 2015).

Research has suggested that negative symptoms may partially overlap with cognitive difficulties. Negative symptoms have been shown to correlate with poor cognitive resources, difficulties in the generation and execution of cognitive strategies, slow responses on simple attention tasks, poor abstract reasoning and impaired set shifting (Heydebrand et al., 2004), while positive symptoms appear to correlate only with inhibition difficulties (Waters, Badcock, Maybery, & Michie, 2003). Reviews and longitudinal studies have further confirmed the association between negative symptoms and cognitive impairment in people with schizophrenia (Rund, 1998). Evidence from animal models also suggests that similar neural pathways may underlie the processes involved in components of both negative symptoms and cognitive impairments (Karlsson et al., 2009; Labrie, Lipina, & Roder, 2008).

The primary target of CR is cognition but most interventions consider cognitive improvement as a means to achieve higher functioning levels (Wykes, Reeder, et al., 2007; Wykes, Newton, et al., 2007). There are also reports that CR has a small effect on the symptoms of schizophrenia (Wykes et al., 2011). The majority of these studies converge in suggesting that this effect is more evident for negative compared to positive symptoms (Cella, Reeder, & Wykes, 2014; Farreny, Aguado, Ochoa, Haro, & Usall, 2013; Sanchez et al., 2014).

1.1. How CR may impact on negative symptoms of schizophrenia

Strauss and Gold (2012) suggested that problems in the domain of working memory may negatively influence motivation and the experience of pleasure. These authors hypothesised that working memory problems may have a negative impact on representing and accessing past experiences with a subsequent negative effect on estimates of future enjoyment and motivation.

A similar mechanism of action is through improving reward sensitivity. People with schizophrenia have difficulties in using feedback, particularly positive feedback, to modify their behaviour (Strauss, Waltz, & Gold, 2014). Lack of response to positive feedback can be associated with a number of negative symptoms such as apathy, anhedonia, amotivation and social withdrawal (Gold, Waltz, Prentice, Morris, & Heerey, 2008). Recent research showed that CR can improve reward sensitivity in people with schizophrenia and indicated that sensitivity to feedback is inversely associated with negative symptoms severity (Cella, Bishara, et al., 2014).

CR may also affect negative symptoms by influencing executive functions. The behavioural components of negative symptoms, linked to withdrawal and poor motivation, may depend on poor planning and difficulties in sequencing actions to complete a complex task. The association between improvement in executive function and reduction in negative symptoms has been highlighted in a recent study suggesting that CR may exert an indirect effect on negative symptom via executive function (Farreny et al., 2013).

It is possible that CR may exert an effect on negative symptoms by improving self-esteem and confidence. Studies showed that cognitive problems in people with schizophrenia are associated with reduced self-esteem (Cella, Swan, Medin, Reeder, & Wykes, 2014) and that CR benefits on cognition are often associated with a self-esteem boost (Kidd et al., 2014; Ostergaard Christensen et al., 2014). Increased self-esteem after CR may counter negative symptoms by challenging defeatist beliefs, avoidant behaviour and poor motivation.

Despite a number of positive reports of potential mechanisms of action there is still no systematic evidence showing that CR can be beneficial for negative symptoms and there is no indication of its effect size. With a restricted number of interventions available that benefit negative symptoms it is important to investigate the putative advantage that a well-established intervention, such as CR, may have on this symptom cluster. For this reason the current study sets out to assess the potential usefulness of CR for negative symptoms.

In this study we first determine the clinical effectiveness (i.e. effect sizes) of CR compared to treatment as usual and active control using a pairwise and network-meta analysis approach at end of therapy and at follow-up. Secondly, we evaluate the role of moderating factors including age, gender, study methodological quality and therapy duration. Lastly, we will determine the acceptability of this treatment option and evaluate treatment retention rates.

2. Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. The study protocol was published online on the PROSPERO database on November 12th 2014 (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014529).

2.1. Literature search

2.1.1. Electronic searches
Multiple systematic searches were conducted using the following databases: MEDLINE, Embase, Web of Science, PsycInfo and Cochrane Collaboration Controlled Trials Register. The following search terms were used as either key terms or keywords: ("cognitive" or "cognit*") AND ("training" or "remediation" or "rehabilitation" or "enhancement") AND "schizophrenia" AND ("random" or "randomized control trial" or "clinical trial").

2.1.2. Other resources
References of recent meta-analyses were inspected to identify papers potentially missed by the electronic search. Members of the Cognitive Remediation Experts Workshop group were contacted regarding outstanding CR trials.

2.2. Studies included

All relevant studies were considered eligible if they included: randomisation; an appropriate comparison group (i.e. treatment as usual or another active treatment); >75% of participants had a diagnosis of schizophrenia or schizoaffective disorder (see participants section for details); received a form of CR (see intervention section for definition) appropriate intervention; assessed negative symptoms using a validated measure.

2.3. Participants

Adults (aged 18+) with a diagnosis of schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorder (American Psychiatric Association, 2013), Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978) or International Classification of Diseases (World Health Organisation,

1992). Studies including participants with other diagnosis in the psychosis spectrum were included only if participants with a diagnosis of schizophrenia or schizoaffective disorders were >75% of the participants considered.

2.4. Intervention

The intervention is a course of CR conducted according to principles including massed practice, errorless learning and scaffolding and had to target one or more cognitive domains as primary targets. Both computerised and pencil and paper CR were considered. We did not consider CR interventions primarily focussed on psychoeducation related to cognitive problems.

2.5. Negative symptom assessment

Only studies using a validated symptom assessment measures providing an assessment of negative symptoms were used. These include the Positive and Negative Symptom Scale (PANSS) (Kay, Fiszbein, & Opler, 1987), Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) and the Symptom Assessment for Negative Symptoms (SANS) (Andreasen, 1982).

2.6. Data collection

Two authors (TD, CE) independently reviewed the list of papers retrieved from the electronic searches according to the pre-defined inclusion criteria. Any disagreement was resolved with discussion after an independent review of the list of papers by a third author (MC). The study selection process is reported in the supplementary material (Appendix A).

2.7. Data extraction and management

Two authors (TD, CE) independently extracted the data from the list of included papers. For papers that only reported partial data (e.g. not reporting both pre and post treatment values for negative symptoms) original authors were contacted via email and asked to provide the unpublished scores necessary for the analysis. Authors were given 8 weeks to reply to the request and reminded once. Partial data from authors who did not provide the missing information were not considered in the analysis. Studies excluded due to missing data were explored with regards to their main characteristics (sample size, type of treatment, duration of treatment, main findings) to exclude possible biases.

2.8. Risk of bias assessment

Three authors (CE, TD, MC) independently assessed the quality of all papers using the Clinical Trials Assessment Measure (CTAM) (Wykes, Steel, Everitt, & Tarrier, 2008) if there was disagreement a fourth author provided guidance (TW) and a consensus reached. This tool evaluates study methodological rigour (e.g. randomisation, blinding, analyses). All agreed ratings were sent to the study authors for approval. In cases where authors disagreed, supplementary evidence was requested. Only five study authors failed to reply. Comments received from the authors were used to modify the rating.

2.9. Measures of treatment effect

We considered both acute (i.e. end of treatment) and maintenance (i.e. at follow-up) effectiveness. For continuous measures, effect sizes were calculated as bias-corrected standardized mean change values (i.e. Hedges's g and 95% confidence interval) and computed so that a negative value indicates a favourable outcome (i.e., symptom reduction) (Hedges & Olkin, 1985). For categorical variables (e.g. dropout rates) odds ratio (OR) with 95% confidence intervals (CI) were

calculated. Individual trials were first investigated by pairwise, head-to-head meta-analyses, and then tested in the network meta-analysis. Network meta-analysis can be considered a generalization of pairwise meta-analysis that compares all pairs. This approach was used to evaluate the effectiveness of CR compared with TAU and TAU plus active control. By comparing three conditions network meta-analysis can consider both the direct and indirect effect of an intervention (See Appendices C, D and G for additional details).

2.10. Unit of analysis issues

Effectiveness was estimated by comparing baseline data with data at the end of treatment. Treatment retention was estimated by comparing baseline with follow-up data. Treatment duration, age and gender were assessed as acute effectiveness moderators with meta-regression. Follow-up duration was assessed as a moderator of treatment retention.

2.11. Missing data

For studies with missing data, we contacted the study team. If the missing information was not provided, the study was excluded from the analysis.

2.12. Assessment of heterogeneity

Heterogeneity was assessed with Cochran's Q and I2 statistics (Huedo-Medina, Sanchez-Meca, Marin-Martinez, & Botella, 2006). Significant Q statistics (i.e. $p < 0.05$) was interpreted as suggestive of heterogeneity. For I2, values between 30 and 60% represent moderate heterogeneity; 75–100% represent considerable heterogeneity. Additional assessment of heterogeneity was conducted using Baujat plots (Baujat, Mahe, Pignon, & Hill, 2002). To control for models adequacy and outliers identification we used radial and standardized residuals plots (Viechtbauer, 2010) (See Appendix G).

2.13. Assessment of reporting biases

Publication bias was evaluated using the Egger's regression test and a funnel plot of the effect sizes against the standard error (SE). Publication bias was adjusted using the trim-and-fill procedure (Duval & Tweedie, 2000). In case of statistically significant results, fail-safe n was calculated. This is the minimum number of additional null studies necessary to make the result no longer statistically significant (Rosenthal, 1991). An effect size can be regarded as robust if the fail-safe number exceeds 5 K + 10, where K is the number of studies included in the meta-analysis (Rosenthal, 1991). We also used the Rosenberg (2005) method, which calculates the number of studies averaging null results that would have to be added to the given set of observed outcomes to reduce significance level of the (weighted) average effect size (based on a fixed-effects model) to a target alpha level (e.g., 0.05).

2.14. Data synthesis

The bias-corrected standardized mean change score (Hedges' g), standard error and variance were calculated with the Comprehensive Meta-Analysis version 2.2 (http://www.meta-analysis.com/). Subsequent pairwise meta-analyses based on Hedges' g, and network meta-analysis were carried using R version 3.0.2 (R Core Team, 2013; Viechtbauer, 2010).

The results of both fixed- and random-effects models were reported for the pairwise meta-analyses. Fixed-effects models are aimed at making a conditional inference only about the studies included in the meta-analysis and can provide valid inferences under heterogeneity (Viechtbauer, 2010). The random-effects model provides an inference about the average effect in the entire population of studies from which the included studies are assumed to be a random selection. Between studies variance and variance of the effect size parameters across the population were estimated with the tau-squared statistics using Empirical Bayes estimator. We calculated the 95% CI for the heterogeneity using the Q-Profile method, to assess the extent and relevance of heterogeneity (Viechtbauer, 2010). The significance level threshold was set at $p < 0.05$.

2.15. Sensitivity analysis

Sensitivity analysis was performed to evaluate the robustness of the meta-analysis results. The RCTs considered at high risk of bias (i.e. CTAM score < 65) were compared with to those considered at low risk (i.e. CTAM score > 65) (as in Wykes et al., 2011).

Table 1
Results of pairwise meta-analyses: effects of cognitive remediation on negative symptoms versus comparison condition.

Outcome	K studies	N participants	Model	Original model											Trim and fill analysis				
				Hedges' g	95%CI		z	p	Q	I²	p	AIC	BIC		Estimated missing study	New estimate	95%CI		p
					lower	upper											lower	upper	
Negative symptoms																			
At	45	2511	FE	−0.34	−0.42	−0.27	−8.59	<0.01	59.88		0.06	31.76	33.57		0				
post-treatment	45	2511	RE	−0.35	−0.44	−0.25	−7.23	<0.01	59.88	28%	0.06	32.12	35.74		0				
	42	2318	RE (−out)	−0.30	−0.36	−0.22	−7.88	<0.01	32.28	0%	0.83	8.37	11.85		0				
At follow-up	15	808	FE	−0.47	−0.61	−0.33	−6.54	<0.01	49.60		0.01	42.29	43.00		0				
	15	808	RE	−0.52	−0.80	−0.23	−3.57	<0.01	49.60	74%	0.01	28.44	29.86		0				
	14	737	RE (−out)	−0.36	−0.51	−0.21	−5.18	<0.01	11.65	0%	0.56	6.89	8.17		0				
Dropout				Relative risk															
At post−	42	2435	FE	0.89	0.75	1.06	−1.29	0.20	37.55		0.62	100.9	102.7		2	0.88	0.74	1.04	0.14
treatment	42	2435	RE	0.89	0.75	1.06	−1.29	0.19	37.55	0%	0.62	102.9	106.4		2	0.88	0.74	1.04	0.14
	40	2317	RE (−out)	0.90	0.78	1.05	−1.36	0.18	25.43	0%	0.95	90.18	93.56		1	0.90	0.75	1.07	0.23

FE: fixed-effects model.
RE: random-effects model with Bayes estimator.
RE (−out): random-effects model with Bayes estimator after exclusion of outliers.
*$p < 0.01$.

3. Results

3.1. Search results

The literature search produced 487 papers from 387 independent studies. Two-hundred and twelve of these were excluded as not fitting the entry criteria. From the remaining pool of 175 reports, after full paper screening, we were able to include data from 45 independent studies (see Appendix A). The studies included 2511 participants with a mean age of 35.1 (*SD* 6.7) and mostly men (i.e. 71%). Most studies were carried out in the United States ($N = 14$), although 15 countries were represented. The control group was treatment as usual (TAU) in 18 studies and TAU with addition of active control or adjunctive treatment (e.g., computer games or cognitive behavioural therapy) for 26 studies. Negative symptoms were measured with the PANSS in 34 studies, BPRS in 6 and SANS in 5. All studies included data on participants at baseline and after treatment; 15 included data on participants at follow-up.

3.2. Bias rating

Overall, the studies included had a medium to high risk of bias (see Appendix B). Scores on the CTAM ranged between 27 and 87, with 47% of studies scoring below 65.

3.3. Treatment efficacy

One thousand three-hundred and three participants were randomized to Cognitive Remediation and 1208 to the control group. Table 1 summarizes the results of the pairwise comparisons. Cognitive Remediation was effective in reducing levels of negative symptoms at post-treatment (Fig. 1). Mean effect size (Hedges' g) on negative symptoms was -0.39 (95%CI: -0.47 to -0.30) in the fixed-effects model with no significant differences with the random-effects (i.e. for AIC and BIC largely below 10). The fail-safe number was estimated at 1178 using Rosenthal (1991), and at 819 using Rosenberg (2005). These values are both higher than the robustness threshold ($5 \times 45 + 10 = 235$).
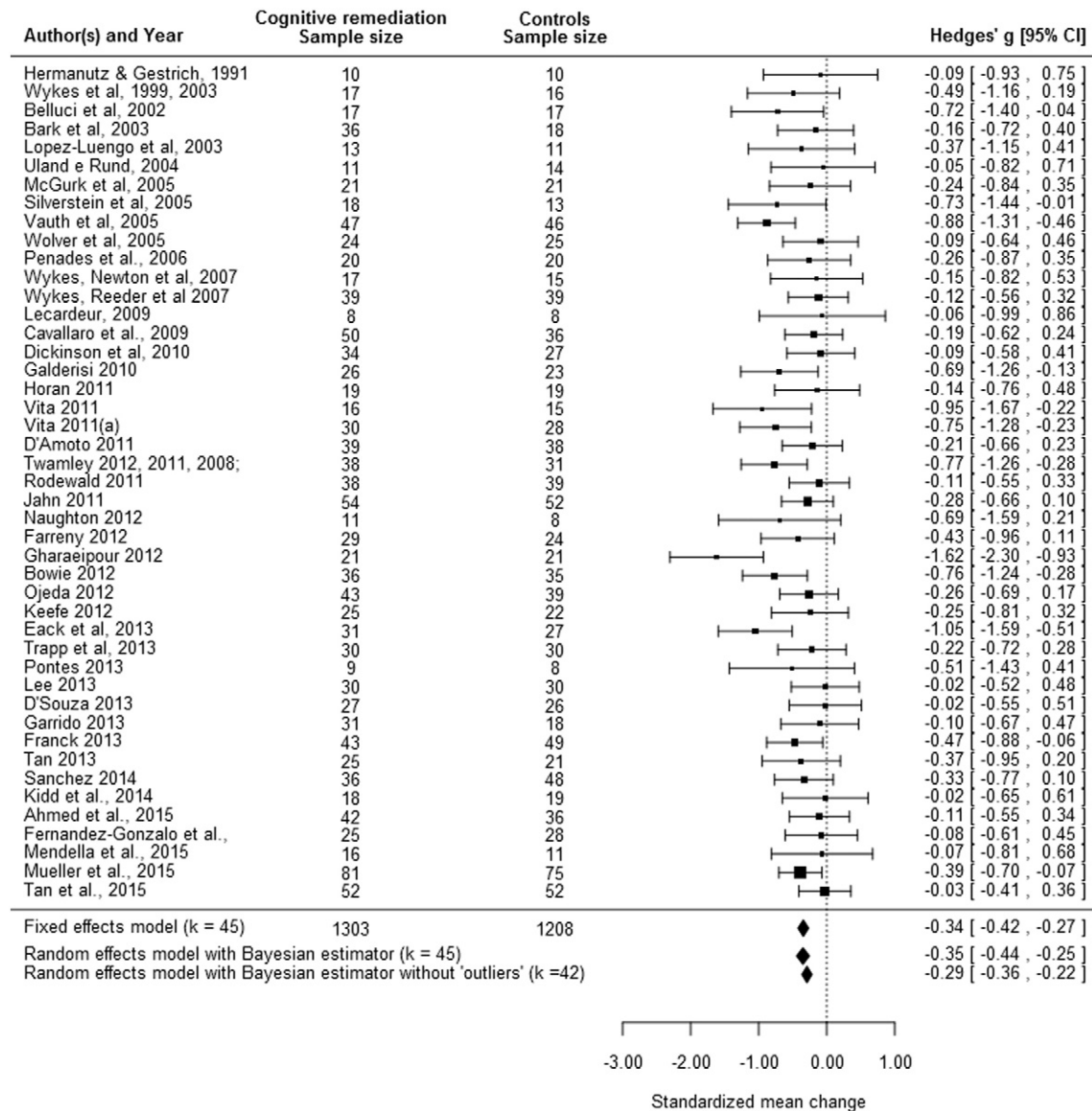

Fig. 1. Forest plot of the effectiveness of cognitive remediation in the treatment of negative symptoms in schizophrenia (k = 45). Reported the results of the fixed- and the random-effects models with empirical Bayes estimator with and without outliers.

In the random-effects model, heterogeneity was low (I^2 lower than 30%), the funnel plot was reasonably symmetric (Fig. 2), and no trimming was suggested. Radial plot, the standardized residuals plot, and the Baujat plot for the random-effects model converged in indicating three outliers (Eack, Mesholam-Gately, Greenwald, Hogarty, & Keshavan, 2013; Gharaeipour & Scott, 2012; Vauth et al., 2005) (see Appendix C Figs. C1, C2, C3). A random-effects model was recalculated without the outliers, with small change in the effect size (-0.30 [-0.36 to -0.22]) and reduction in heterogeneity ($I^2 = 0$%; 95%CI: 0% to 22%).

Studies with higher methodological quality showed a larger effect size compared to those with low: CTAM score < 65 ($N = 21$) fixed-effects model effect size $= -0.27$ (95% CI: -0.39 to -0.15); CTAM score ≥ 65, $n = 24$, fixed-effects model effect size $= -0.40$ (95% CI: -0.51 to -0.30).

3.4. Effects at follow-up

Effectiveness of CR on negative symptoms was maintained at follow-up, with no decrement of the effect size in all models (Table 1). The model without outliers had zero heterogeneity ($I^2 = 0$%; 95%CI: 0% to 63%).

3.5. Network meta-analysis

Compared to TAU, CR was superior to TAU + other treatments in both the fixed-effects and random-effects models (Fig. 3). The network was close (see Appendix D). Q-statistics showed that this result is consistent across studies: whole network ($Q = 67.36$; $df = 44$; $p = 0.013$); within designs ($Q = 56.36$; $df = 41$; $p = 0.055$); between designs ($Q = 11.0$; $df = 3$; $p = 0.01$).

3.6. Treatment moderators

Treatment duration had a very small impact on the estimated effect size, with studies with longer duration providing a slightly larger effect size: $\beta = -0.01$ (95%CI: -0.013 to -0.003); $t = -2.23$; $p = 0.03$ (see Appendix E). In the model with duration of treatment as a moderator, heterogeneity was low (Test for Residual Heterogeneity: $Q = 49.91$;

$df = 39$; $p = 0.11$; $I^2 = 23$%; 95%CI: 0% to 55%). Age (coefficient $= 0.01$; -0.01 to 0.02), gender ratio (coefficient $= -0.03$; -0.08 to 0.02), sample size (coefficient $= 0.0$; -0.01 to 0.01) had no impact on the effect size.

Studies using the PANSS had lower but more precise effect size (-0.35; -0.46 to -0.24; $t = -6.46$, $p < 0.001$) than studies using the BPRS (-0.40; -0.70 to -0.11; $t = -2.77$, $p = 0.008$) or the SANS (-0.38; -0.66 to -0.09; $t = -2.68$, $p = 0.01$).

None of the moderators considered had an impact on the effect size at follow-up.

3.7. Treatment acceptability

Data on dropout were available in 42 studies, including 2435 patients (1264 randomized to CR and 1171 randomized to the control condition). There were no differences in drop-out rates between individuals randomized to CR and the control conditions (Fig. 4). In the random-effects model the funnel plot was reasonably symmetric (see Appendix F) and the Egger test was negative. However, the trim-and-fill procedure suggested that 2 studies might be added, still with no difference between groups (Table 1). In the random-effects model the heterogeneity was low: $I^2 = 0$% (95%CI: 0% to 37%); $Q = 37.55$; $df = 41$; $p = 0.62$. Radial plot, the standardized residuals plot, and the Baujat plot for the random-effects model converged in indicating two outliers (see Appendix F).

The analysis repeated without the outliers did not alter these estimates: $RR = 0.90$ (95%CI: 0.78 to 1.05) and $I^2 = 0$% (0% to 8%).

4. Discussion

The current meta-analysis is the first systematic study of the effect of CR on negative symptoms in people with schizophrenia. The results demonstrate a small to moderate effect of CR on negative symptoms at post-therapy with this effect being maintained at follow-up. The result of the network meta-analysis comparison corroborated the effectiveness of CR not only in comparison to TAU but also in relation to the active control condition. Overall, the best model had a 95% CI ranging between -0.36 and -0.22, corresponding to a number needed to treat between 5 and 8.

Methodological quality is important when considering the reliability of meta-analytic findings. We found that it did influence negative
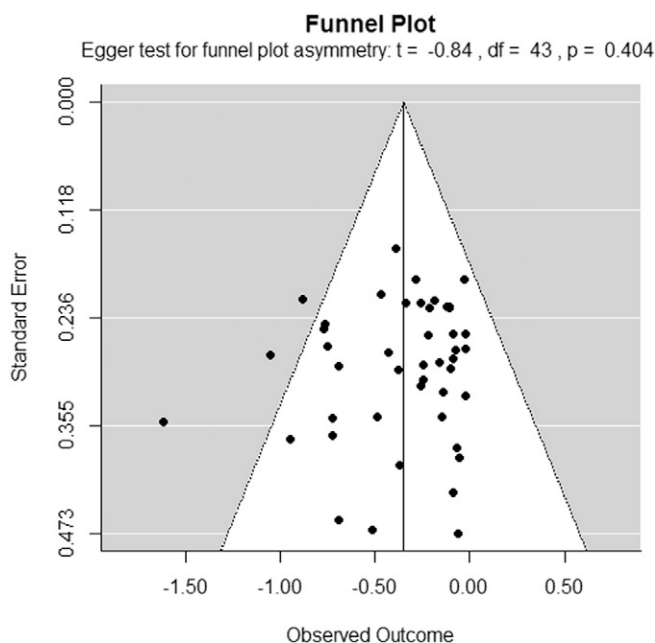

Fig. 2. Funnel plot of the effect sizes against the standard error for the random-effect model with empirical Bayes estimator (using data from 45 studies). The results of the Egger test for funnel plot asymmetry are reported at the top.
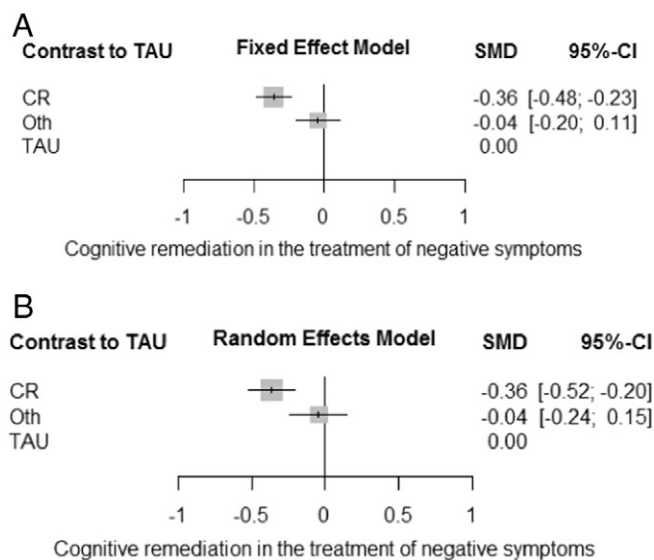

Fig. 3. Shows effect size, using Fixed (Panel A) and Random (Panel B) effect models, for CR on negative symptoms compared to Oth (other active therapy) and TAU (treatment as usual).

symptom reduction but unusually studies with better methodology had a higher effect size and a narrower 95% CI. This provides further confidence in the reliability of our results as effect sizes tend to increase with poorer methods due to higher risk of bias. On the contrary our results suggest that we have minimised the risk of methodological bias.

Amongst studies with high methodological rigour (i.e. CTAM score over 65) five had an effect size above 0.7 and may warrant closer inspection to highlight possible mechanisms responsible for negative symptom reduction. These are Twamley, Vella, Burton, Heaton and Jeste (2012), Vita, De Peri, Barlati, Cacciani, Cisima et al. (2011), Vita, De Peri, Barlati, Cacciani, Deste et al. (2011), Bowie, McGurk, Mausbach, Patterson and Harvey (2012), Eack et al. (2013). These programmes delivered between 24 and over 100 h of therapy over a period of time spanning between 12 weeks and 2 years. One common characteristic amongst these programmes is supporting practice on cognitive tasks with rehabilitation activities (e.g. supported employment) or

opportunities to reflect on how to apply CRT skills in everyday life. These programs also required frequent personal contact with a facilitator or therapist. It is likely that by providing these elements these programs facilitated learning consolidation making new cognitive skills accessible in everyday life. These in turn might have reduced the influence of behavioural negative symptoms such as poor motivation or lack of social behaviour. Programs using supported practice and other methods to maximise transfer of therapy learned skill to everyday life and those who used a therapist or a facilitator may be more likely to have an impact on negative symptoms.

Most studies considered were underpowered to detect the reported effect size. To detect an effect size of d = 0.30 with two-tailed $p < 0.05$ and 80% power, a study would require a sample of over 120 participants per group. This may explain why most studies did not report statistically significant differences. Future studies aiming to assess the effectiveness of CR on negative symptoms should consider
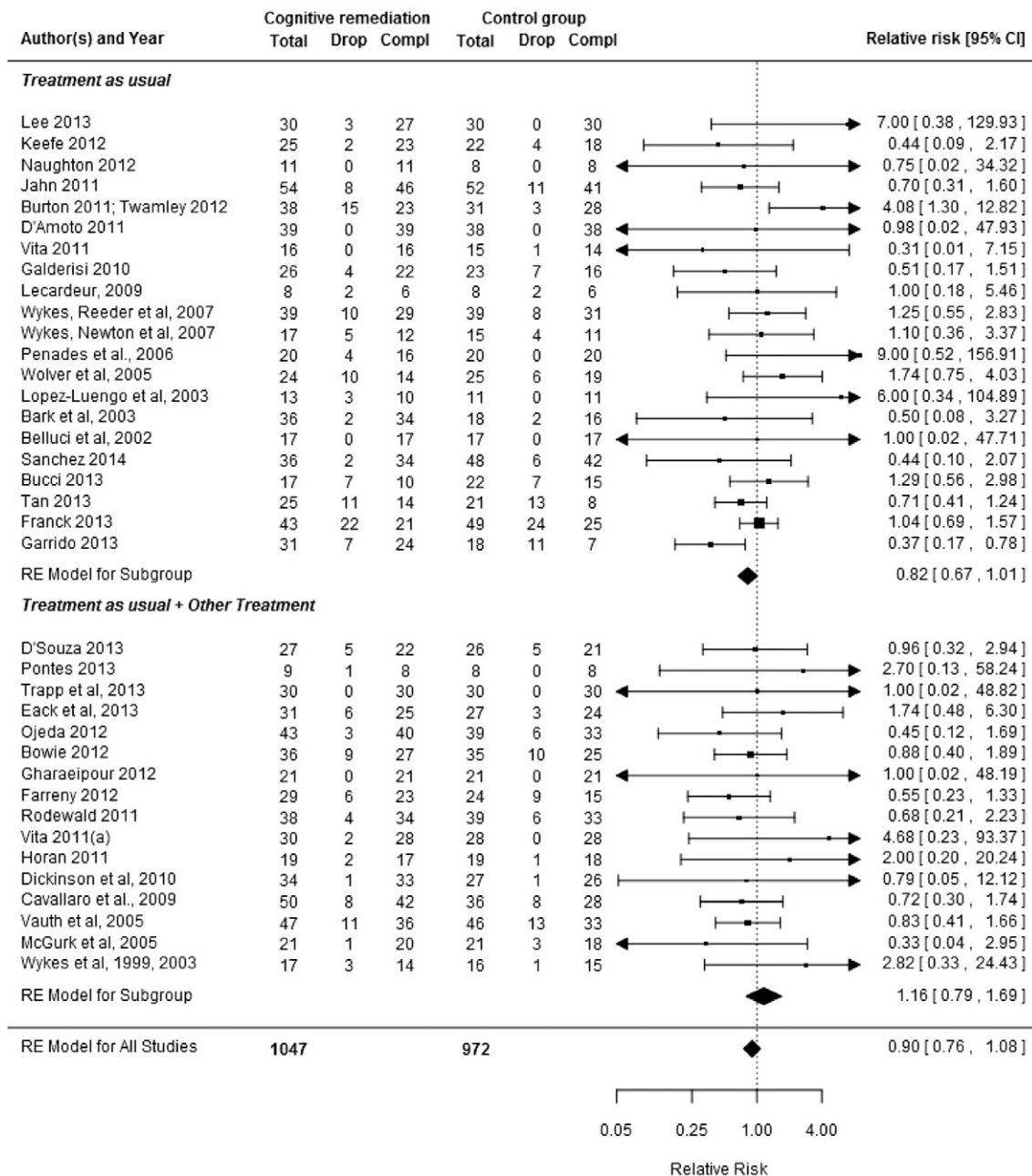

Fig. 4. Forest plot of studies' dropout pairwise analysis.

the power of their study to detect the benefits given the results of this meta-analysis.

We did not find that CR length influenced negative symptom reduction. With only 18% of the studies having a treatment length over 12 weeks this result may be influenced by a skewed distribution and limited variability. Intervention frequency is also important in determining the optimal "dose" of CR and this is also a parameter that differs across the interventions considered. There is currently limited agreement on how to optimise CR protocols to maximise outcomes and future studies should focus on characterising the resource-benefit trade-off so that this information can be used to develop interventions that are fit for purpose.

Given the lack of consideration of negative symptom change in the context of CR there is limited information available in the literature on potential moderators. One study showed that younger people may achieve larger benefit on cognitive measures after CR compared to older participants (Wykes et al., 2009). We explored the potential moderating role of age on negative symptom reduction but we did not find it to have an effect. Similarly there is limited information in relation to mediators and active ingredients of CR that may contribute to negative symptom reduction. A recent study suggested that improvement in executive functioning after CR may be associated with negative symptom reduction (Farreny et al., 2013). CR may exert a positive effect on negative symptom also via its non-specific components including the contact with a therapist and the behavioural activation consequent to session attendance (Vinogradov, Fisher, & Nagarajan, 2013); however these suggestions require more empirical grounding.

Negative symptoms are not traditionally considered a primary target for CR. The current study demonstrated that it may have similar effect sizes to other available pharmacological and behavioural interventions designed to tackle negative symptoms directly (Fusar-Poli et al., 2014). The drop-out rate also suggests that CR is acceptable and tolerated by service users and further recommends this approach as viable and safe. This is an area that would require further research. Nonetheless, these results are promising and point to CR as a useful intervention for reducing the negative symptoms of schizophrenia.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.cpr.2016.11.009.

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