Schizophrenia Research: Cognition 19 (2020) 100160

Contents lists available at ScienceDirect

Schizophrenia Research: Cognition

journal homepage: www.elsevier.com/locate/scog

Review Article

A systematic review of moderators of cognitive remediation response for people with schizophrenia

Benedetta Seccomandi[a,*], Dimosthenis Tsapekos[c], Katie Newbery[a,b], Til Wykes[a,b], Matteo Cella[a,b]

[a] Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AF, UK
[b] South London & Maudsley NHS Foundation Trust, Maudsley Hospital, London SE5 8AZ, UK
[c] Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, UK

ARTICLE INFO

Keywords:
Cognitive remediation
Cognition
Moderator
Schizophrenia
Psychosis

ABSTRACT

Background: There is evidence that cognitive remediation (CR) is moderately effective in improving cognitive and functional difficulties in people with schizophrenia. However, there is still a limited understanding of what influence different treatment responses.
Aim: To identify moderators influencing CR response in people with schizophrenia.
Methods: This systematic review follows PRISMA guidelines. Searches were conducted up to January 2019 on PubMed and PsychInfo to identify randomized controlled trials of CR reporting analyses of moderators of treatment response. All papers were assessed for methodological quality and information on sample size, intervention and control condition, moderators, outcomes, effect of moderator on outcomes and demographic characteristics from each study was extracted and critically summarised.
Results: Thirty-six studies were included, considering 2737 participants. Study participants consisted on average of people in their late-thirties, mostly men, with over 10 years of illness. The review identified moderators that could be grouped into five categories: demographics, biological, cognitive and functional, psychological, and illness-related characteristics. The assessment of methodological quality showed that many studies had a high risk of bias.
Conclusions: There was no high-quality replicated evidence which identifies reliable moderators of CR response. Many moderators were not replicated or presented in single, underpowered studies. Studies also investigated moderators independently despite their potential to overlap (e.g. age and education). Future research should concentrate on evaluating, with sound studies, the role moderators may play in affecting CR treatment response. This information can inform who will benefit most from the therapy and help to improve the benefits of CR.

1. Introduction

Cognitive impairment is a core feature of schizophrenia with a negative prognostic value for global functioning, social skills, poorer self-care, and independent living skills (Allott et al., 2011; Bowie et al., 2008; Bowie and Harvey, 2006; Green et al., 2000). In addition, cognitive deficits reduce the potential benefit of rehabilitation programs, even when high-quality rehabilitation is provided, contributing to higher rates of institutionalization (Bell and Bryson, 2001; McGurk and Meltzer, 2000; Wykes, 1994). It is for these reasons that cognitive training techniques were developed, in the hope that improving cognition would lead to lasting functional outcome improvements.

Cognitive remediation (CR) is "an intervention targeting cognitive deficit using scientific principles of learning with the ultimate goal of improving functional outcomes" (Cognitive Remediation Experts Workshop, 2012, p. 1). In the meta-analysis conducted by Wykes et al. (2011), CR was found to have a moderate but durable effect on global cognition and functional outcomes. In addition, functioning was improved most when CR was combined with other forms of rehabilitation.

Although CR is an effective approach, there is evidence that as many as one in four participants receiving this intervention will not improve (Murthy et al., 2012; Wykes et al., 2011). While many studies have focussed on the evaluation of CR efficacy, only a limited number have considered how individual characteristics, clinical presentation, and other factors may affect treatment response (Fiszdon et al., 2005; Medalia and Richardson, 2005; Twamley et al., 2011; Vita et al., 2013). Wykes and Spaulding (2011) suggested that these types of studies are important to improve the personalisation agenda of CR even if the results are negative. Systematic evidence on mediators and moderators may allow tailoring therapy according to patients' characteristics in

* Corresponding author at: Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, London SE5 8AF, UK.
E-mail address: benedetta.seccomandi@kcl.ac.uk (B. Seccomandi).

https://doi.org/10.1016/j.scog.2019.100160
Received 10 May 2019; Received in revised form 14 August 2019; Accepted 17 August 2019
Available online 05 September 2019

order to maximise its potential benefits.

To date, there is no systematic review of the putative factors which may affect CR response, although some have been suggested in the literature. For instance, a number of studies have suggested that the individuals most likely to benefit from CR are younger (McGurk and Mueser, 2008; Wykes et al., 2009), with fewer symptoms (Wykes et al., 2011) and, more severe cognitive difficulties (Pillet et al., 2015; Wykes et al., 2011). However, these characteristics have been identified in single studies using underpowered samples. There is limited converging evidence, with some studies suggesting that higher or lower levels of a characteristic (e.g. functioning) may be important in influencing therapy outcomes (Farreny et al., 2016; Twamley et al., 2011). Further, studies have considered therapy moderators and mediators in relation to different therapy outcomes (e.g. different cognitive domains, functioning, motivation) contributing to the limited consensus in identifying reliable factors that can be used to tailor CR.

Despite the limited evidence, a number of authors (Demily and Franck, 2008; Levaux et al., 2009; Medalia et al., 2018; Silverstein and Wilkniss, 2004) have highlighted the importance of developing a more individualized treatment to improve therapy response. Franck et al. (2013) attempted to personalise CR by adapting training on modules participants received in relation to their initial cognitive assessment (e.g. receiving more training for the most compromised domain). These authors compared the personalised approach to general CR training but found no differences between the two methods suggesting that this personalisation method may not bring about benefits.

While personalisation is increasingly found important, there is no systematic evidence in the literature summarizing relevant findings that may be able to guide future studies. The current review aims to identify potential individual factors at baseline, moderators, that may predict treatment outcomes and that may be used to tailor CR and improve its benefits.

2. Methods

2.1. Research evidence identification

For this review, we followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The review protocol was registered on a public database (e.g. https://www.crd.york.ac.uk/prospero/) on the 27th of February 2018. Searches were conducted up to the 16th of January 2019 on PsycInfo and PubMed databases. We also searched potentially relevant websites including ResearchGate and Mendeley.

In order to identify any additional relevant papers, the reference lists of included studies, relevant and recent reviews (e.g. Wykes and Huddy, 2009; Wykes et al., 2011; Best and Bowie, 2017; Cella et al., 2017), and relevant articles in this field were also inspected.

2.2. Literature search

A broad search string strategy was adopted including the following terms: “exp. schizophrenia” OR “exp. psychosis” OR “exp. schizoaffective disorder” AND “cognitive enhancement” OR “cognitive rehabilitation” OR “cognitive remediation” OR “cognitive training”.

2.3. Inclusion criteria

Eligible studies:

- Randomized controlled trials.
- Assessed the relationship of one or more baseline moderators to CR treatment response. Moderators, according to Baron and Kenny (1986), are all those factors that identify for whom and under which circumstances treatments have different effects (e.g. age, cognitive profile).
- Included participants over the age of 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 et al., 1978) or International Classification of Diseases (World Health Organization, 1992).
- The sample considered had at least 75% of participants with a diagnosis of schizophrenia or schizoaffective disorders.
- The study was in English language.
- The CR interventions adopted use principles such as massed practice, errorless learning, and scaffolding to improve cognition and/or social cognition and/or functioning. All modes of administration (computer, pen and paper, individual, group, presence or absence of therapist) were considered.

2.4. Exclusion criteria

We excluded all study designs that were not randomized controlled trials (e.g. case studies and opinion papers) or were a combination of randomized and non-randomized controlled trials [e.g. the study conducted by Greenwood et al., 2011]. We also excluded studies where the focus of the intervention was psychoeducation about cognitive difficulties.

2.5. Study selection and data extraction

Two authors (BS and DT) independently conducted a screening of all titles and abstracts to identify eligible studies. Disagreements during the selection process were resolved by consultation with a third author (MC).

For all the included studies the following information was extracted:

- sample size for the experimental and control condition;
- demographic characteristics including age, gender, years of education, and duration of illness;
- details of the intervention and control condition;
- type of moderator considered;
- study primary and secondary outcomes;
- reported effect of the moderator on the outcome.

2.6. Quality assessment

All included studies were assessed for methodological rigor using the Clinical Trials Assessment Measure (CTAM) (Wykes et al., 2008). This is a 15-item measure of trial methodology specifically developed for psychological treatment studies. The maximum score is 100 and studies with a CTAM score < 65 are considered at higher risk of bias (Wykes et al., 2008). All studies were independently rated by two authors (BS and KN) and discrepancies resolved by consultation with a third author (MC). CTAM scores were checked with the study authors and adjusted according to their feedback if provided.

3. Results

As shown in the PRISMA diagram (Fig. 1), the literature search identified thirty-six eligible studies, including 2737 participants. A summary of the studies characteristics is reported in Table 1.

3.1. Sample characteristics

Participants had a mean age of 37.7 years (SD 7.3; range 21.2–48.1), and the majority were men (mean = 66.6%; SD 9.4; range 38.1% - 80.5%), with 13.2 years of education (SD 3.8; range 9.7–30.4). Participants had an average illness duration of 12.6 years (SD 7.8; range 1.7–24.5).

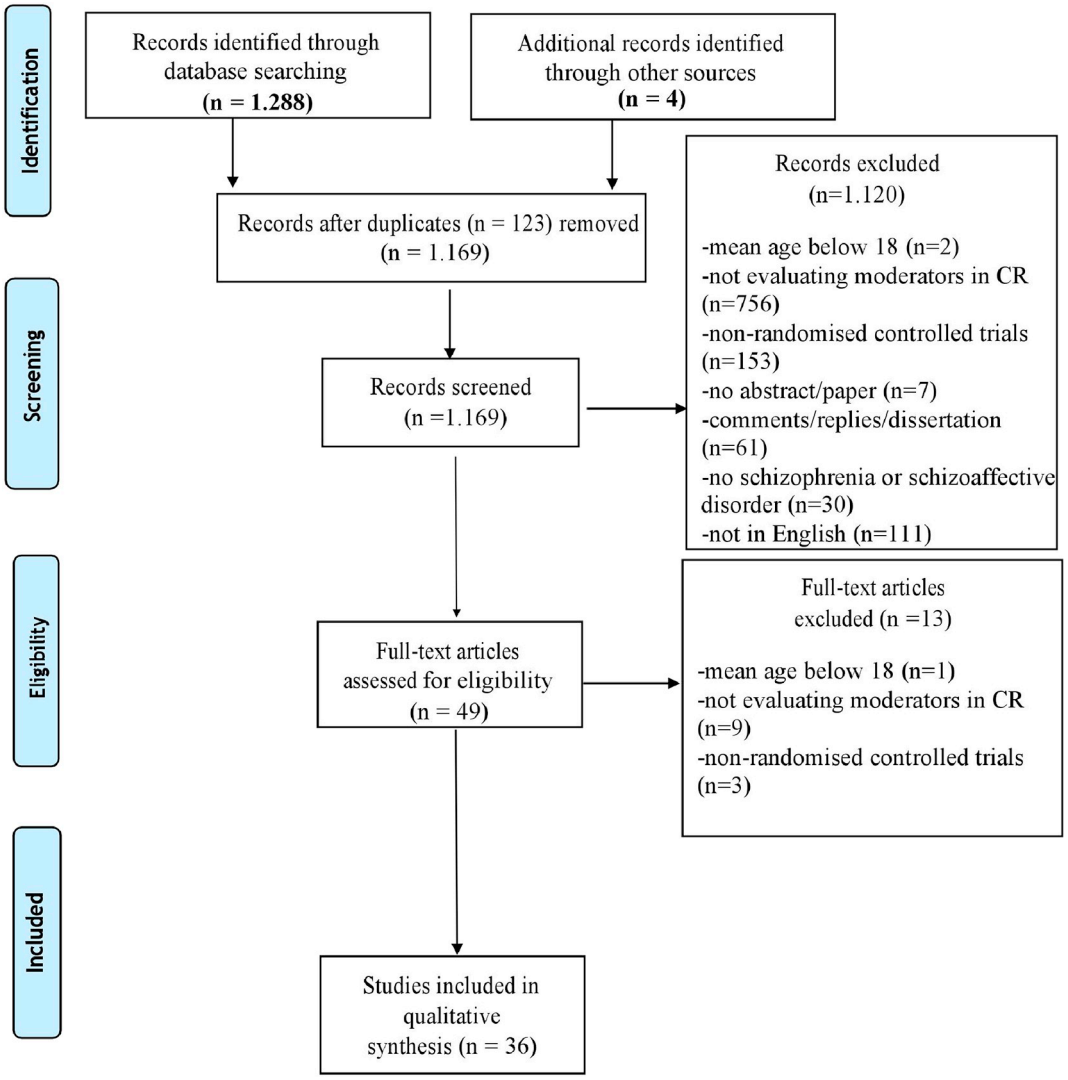

Fig. 1. Systematic search PRISMA diagram.

3.2. Study characteristics

The mean sample size was 76 [(SD 36.9); range 32–175; CR group mean = 41 (SD 18.9); Control group mean = 41.4 (SD 22)]. Most studies were carried out in the United States (N = 23); five studies took place in Spain, four in the United Kingdom and the remaining four in Italy, Australia, Norway, and Switzerland.

3.3. Therapy characteristics

Nineteen studies provided CR alone, five combined CR with another active condition (e.g. vocational rehabilitation, social cognitive training) and twelve combined CR with treatment as usual.

3.4. Control condition

Twenty-one studies had an active control condition (e.g. computer game, leisure activities), twelve had treatment as usual or waiting list, two had two control conditions (one active and one passive) and another one had an active control condition and a control group including healthy people.

3.5. Trial quality

The Clinical Trial Assessment Measure scores for each study are summarised in Table 2. The mean score was 66.1 (SD 11.7; range 44–90) out of a maximum of 100. Only 21 (53%) studies scored above the cut-off of 65, indicating a low risk of bias (Wykes et al., 2008). Problems were sample size (33% were too small) with only three studies having adequately calculated power (7.3%), group allocation was not masked (35%), lack of independent randomization (60%), and lack of treatment fidelity assessment (83%).

3.6. Moderators affecting treatment response

Twenty studies evaluated at least one moderator; seven assessed two, four evaluated three and, five studies investigated more than three moderators. Taken together, they identified moderators falling into five broad categories: demographic; biological; cognitive and functional; psychological and illness-related aspects. Results for each category are summarised in Table 3.

3.7. Demographic characteristics

A number of papers reported that gender (Farreny et al., 2016; Twamley et al., 2011; Wykes et al., 1999), education (Farreny et al.,

Table 1
Characteristics of the included studies.

Study	Study design	Original paper	Title	Moderator investigated	Participants		
					Mean age (SD)	Male (%)	Sample size N (CR)
Corbera et al., 2017, USA	Secondary analysis of RCTs (Kurtz et al., 2007, 2015)	Kurtz et al., 2007	Computer-assisted cognitive remediation in schizophrenia: what is the active ingredient?	Age, duration of illness	32.96 (11.57)	70.5%	112
		Kurtz et al., 2015	Social skills training and computer-assisted cognitive remediation in schizophrenia.				
McGurk and Mueser, 2008, USA	Secondary analysis of two RCTs (McGurk et al., 2005 and McGurk et al., 2015)	McGurk et al., 2005	Cognitive training and supported employment for persons with severe mental illness: one-year results from a randomized controlled trial	Age	NR	55.26%	76 (37)
		McGurk et al., 2015	Cognitive enhancement treatment for people with mental illness who do not respond to supported employment: a randomized controlled trial				
Wykes et al., 2009, UK	Secondary analysis of RCT (Wykes, Reeder, Landau et al., 2007)	Wykes, Reeder, Landau et al., 2007	Cognitive remediation therapy in schizophrenia: a randomized controlled trial	Age	36 (NR)	73%	85 (43)
Franck et al., 2013, UK	RCT	/	/	Age; intellectual	33.54 (6.9)	73%	138 (65)
Bark et al., 2003, USA	Secondary analysis of RCT (Medalia et al., 2000)	Medalia et al., 2000	Remediation of memory disorders in schizophrenia	Symptoms	36.77	59.26%	54 (36)
Wykes et al., 1999, UK	RCT	/	/	Medication; demographics (age, gender); and symptoms	38.55	75.75%	33 (17)
Wykes et al., 2007, UK	RCT	/	/	Medication	36 (NR)	73%	85 (43)
Bosia et al., 2007, Italy	RCT	/	/	COMT allele	NR	68%	50 (27)
Farreny et al., 2016, Spain	Secondary analysis of RCT, Farreny et al., 2012	Farreny et al., 2012	REPYFLEC cognitive remediation group training in schizophrenia Looking for an integrative approach	Demographics (sex, age, education); illness duration; medication; cognition; symptoms and functioning	39.5 (8.5)	65.5%	62 (29)
Farreny et al., 2013, Spain	Secondary analysis of RCT, Farreny et al., 2012	Farreny et al., 2012	REPYFLEC cognitive remediation group training in schizophrenia looking for an integrative approach	Baseline negative symptoms and executive function	40.6 (7.6)	68%	62 (29)
Panizzutti et al., 2013, USA	Secondary analysis of 2 RCTs (Fisher et al., 2009, 2015)	Fisher et al., 2009	Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia	COMT allele	33.6 (13.1)	70.8%	48 (48)
		Fisher et al., 2015	Neuroplasticity-based auditory training via				

(*continued on next page*)

Table 1 (*continued*)

Study	Study design	Original paper	Title	Moderator investigated	Participants		
					Mean age (SD)	Male (%)	Sample size N (CR)
			laptop computer improves cognition in young individuals with recent onset schizophrenia				
Penades et al., 2016, Spain	Secondary analysis of RCT (Penadés et al., 2013)	Penadés et al., 2013	Brain effects of cognitive remediation therapy in schizophrenia: a structural and functional neuroimaging study.	Demographic variables (age; education; duration of illness; number of hospitalisations) medication; baseline brain structure; baseline symptoms; baseline cognitive performance	36.22	74%	50 (17)
Twamley et al., 2011, USA	Secondary analysis of RCT (Twamley et al., 2012)	Twamley et al., 2012	Compensatory Cognitive Training for psychosis: effects in a randomized controlled trial	Demographic variables (age; gender; education; diagnosis; duration of illness); medication; symptoms; cognition; functioning; self-reported cognitive and functioning problems; intelligence	47.3 (9.8)	65%	89
Bell et al., 2008, USA	RCT	/	/	Baseline community function	40	54%	77 (38)
Bell et al., 2014, USA	Secondary analysis from RCT	Bell et al. 2008	Neurocognitive enhancement therapy with vocational services: work outcomes at two-year follow-up.	Baseline community function	CR high community functioning = 40.35 (10.48) CR low community functioning = 40.07 (8.96) SE high community functioning = 42.51 (10.69) SE low community functioning = 41.28 (10.28)	CR high community functioning = 48% CR low community functioning = 55% SE high community functioning = 53% SE low community functioning = 72%	175 (99)
Burton and Twamley, 2015, USA	Secondary analysis of RCT (Twamley et al., 2012)	Twamley et al., 2012	Compensatory Cognitive Training for psychosis: effects in a randomized controlled trial	Neurocognitive insight	46.3 (9.7)	65.2%	69
Burton et al., 2015, USA	Secondary analysis of RCT (Twamley et al., 2012)	Twamley et al., 2012	Compensatory Cognitive Training for psychosis: effects in a randomized controlled trial	COMT allele	48 (8.6)	65.9%	41 (20)
Evensen et al., 2017, Norway	RCT	/	/	Global functioning, self-esteem	CBT = 33.2 (8.0) CR = 32.4 (7.9)	CBT = 61.8% CR = 79.4%	148 (64)
Fiszdon et al., 2006, USA	RCT	/	/	Intellectual (pre-morbid and morbid)	42.82 (8.66)	80%	152 (72)
Davidson et al., 2016, USA	Secondary analysis of RCT (Fiszdon et al., 2016)	Fiszdon et al., 2016	Cognitive remediation for individuals with psychosis: efficacy and mechanisms of treatment effects	Learning potential	CR = 47.3 (9.1) TAU = 48.9 (9.9)	CR = 78.4% TAU = 62.5%	75 (50)

Table 1 (*continued*)

Study	Study design	Original paper	Title	Moderator investigated	Participants		
					Mean age (SD)	Male (%)	Sample size N (CR)
Keshavan et al., 2011, USA	Secondary analysis of RCT (Eack et al., 2009)	Eack et al., 2009	Cognitive enhancement therapy for early-course schizophrenia: effects of a two-years randomized controlled trial.	Cortical reserve	25.72 (5.94)	64%	58
Kurtz et al., 2009, USA	Secondary analysis of RCT (Kurts et al., 2007)	Kurts et al., 2007	Computer-assisted cognitive remediation in schizophrenia: what is the active ingredient?	Cognition, symptoms	32.4 (11.2)	69%	36
Kurtz et al., 2008, USA	RCT	/	/	Cognition, symptoms, functioning	34.6 (10.0)	72%	46
Rodewald et al., 2014, Switzerland	Secondary analysis of RCT (Rodewald et al. 2011)	Rodewald et al. 2011	Planning and problem-solving training for patients with schizophrenia: a randomized controlled trial.	Cognition, symptoms, motivation	Problem-solving training = 28.0 (7.0) Basic cognition training = 29.5 (7.4)	Problem-solving training = 84% Basic cognition training = 77%	77
Subramaniam et al., 2017, USA	RCT	/	/	Brain Structure (White matter integrity)	HC = 41.41 (11.74) SZ = 45.59 (10.25)	HC = 60.71% SZ = 68.75%	HC (*N* = 28) SZ (*N* = 48)
Fisher et al., 2015, USA	RCT	/	/	Motivation	Computerized auditory training = 21.70 (3.26) Computer game = 20.74 (3.37)	Computerized auditory training = 72.09% Computer game = 76.74%	121 (63)
Vinogradov et al., 2009, USA	Secondary analysis of RCT (Twamley et al., 2012)	Twamley et al., 2012	Compensatory Cognitive Training for Psychosis: Effects in a Randomized Controlled Trial	Medication (Serum anticholinergic activity)	43.86 (10.29)	71%	49 (25)
Dickinson et al., 2010, USA	Secondary analysis of RCT (Fiszdon et al., 2016)	Fiszdon et al., 2016	Cognitive remediation for individuals with psychosis: efficacy and mechanisms of treatment effects	Age	CR = 46.9 (6.6) Control = 48.5 (8.8)	38.10%	63 (35)
Fiszdon et al., 2004, USA	RCT	/	/	Symptoms	NET + WT = 41.9 (9.9) WT = 43.2 (8.0) Control = 33.21 (6.89)	NET + WT = 76% WT = 80%	94 (45)
Lewandowski et al., 2011, USA	Secondary analysis from 2 RCT	Hogarty et al., 2006 Eack et al., 2009	Durability and mechanism of effects of cognitive enhancement therapy. Cognitive enhancement therapy for early- course schizophrenia: effects of a two-year randomized controlled trial.	Diagnosis	25.9 (6.3)	69%	58 (31)
McGurk et al., 2009, USA	RCT	/	/	Cognition, demographic variables (substance abuse and medication comorbidity)	VR + CR = 45.5 (9.58) VR = 42.44 (8.52)	VR + CR = 61% VR = 56%	34
Sanchez et al., 2014, Spain	RCT	/	/	Medication, symptoms	REHACOP = 33.60 (9.4) Control = 36.92 (10.5)	REHACOP = 75% Control = 77.1%	92 (38)

Table 1 (*continued*)

Study	Study design	Original paper	Title	Moderator investigated	Participants		
					Mean age (SD)	Male (%)	Sample size N (CR)
Bellucci et al., 2003, Australia	RCT	/	/	Self-esteem	42.0	47.1%	32
Thomas et al., 2018, USA	RCT	/	/	Age, symptoms, medication, illness duration	35.14 (12.57)	47.5%	46 (24)
Gomar et al., 2015, Spain	RCT	/	/	Age, medication	TAU = 45.40 (9.77) Control active = 46.13 (10.11) CRT = 46.68 (9.97)	68.5%	130 (43)
Ramsay et al., 2018, USA	Secondary analysis of RCT (Fisher et al. 2015)	Fisher et al. 2015	Neuroplasticity-based auditory training via laptop computer improves cognition in young individuals with recent onset schizophrenia	Brain structure, baseline cognition and symptoms	22.27 (4.13)	65.9%	44 (22)

Study	Participants			Intervention			Primary outcome measures	Secondary outcome measures
	Mean years of education (SD)	Total included in analysis (dropouts; interventions)	Years of illness (mean)	Setting (inpatients, outpatients)	Treatment intervention	Control intervention		
Corbera et al., 2017, USA	12.82 (2.40)	112	9.34	Outpatients	Cognitive remediation	Computer skills training	Working memory, functioning and symptoms	NR
McGurk and Mueser, 2008, USA	NR	76	NR	NR	Cognitive training + vocational rehabilitations	Vocational rehabilitations	Cognitive functioning; symptoms	NR
Wykes et al., 2009, UK	Young = 11.85 Older = 10.8	Memory: 75 PT; 68FU Flexibility: 72 PT; 64 FU Planning: 74 PT; 67 FU Self-esteem: 75 PT; 67 FU Symptoms: 79 PT; 69 FU Social functioning: 77 PT; 74 FU	NR	NR	Cognitive remediation (paper and pencil) + treatment as usual	Treatment as usual	Memory, cognitive flexibility and planning	Social functioning, symptoms, self-esteem
Franck et al., 2013, UK	NR	92	NR	Outpatients	Cognitive remediation therapy	RECOS program	BADS (Behavioural Assessment of Dysexecutive Syndrome)	Cognition and clinical measures
Bark et al., 2003, USA	10.99	NR	NR	Inpatients	Cognitive remediation exercises + standard hospital care	Treatment as usual	Cognitive functioning; symptoms	NR
Wykes et al., 1999, UK	12.35	33	NR	Outpatients	Cognitive Remediation Therapy + standard rehabilitation treatment	Intensive occupational therapy	Working memory; cognitive flexibility and planning	Social functioning, symptoms, and self-esteem.
Wykes et al., 2007, UK	NR	NR	NR	NR	Cognitive remediation therapy	Treatment as usual	Working memory; cognitive flexibility and planning	Social functioning, symptoms, self-esteem
Bosia et al., 2007, Italy	NR	49	NR	Outpatients	Function-specific computer-aided exercises + standard rehabilitation treatment	Standard rehabilitation treatment	Symptoms; functioning; cognitive flexibility; sustained attention	NR

Table 1 (*continued*)

Study	Participants			Intervention			Primary outcome measures	Secondary outcome measures
	Mean years of education (SD)	Total included in analysis (dropouts; interventions)	Years of illness (mean)	Setting (inpatients, outpatients)	Treatment intervention	Control intervention		
Farreny et al., 2016, Spain	NR	NR	17.6	Outpatients	REPYFLEC	Stimulating activities focused on leisure and socialisation	Neurocognition functioning symptoms	NR
Farreny et al., 2013, Spain	NR	NR	NR	Outpatients	REPYFLEC	Leisure activities	Neurocognition functioning symptoms	NR
Panizzutti et al., 2013, USA	NR	NR	12.9	Outpatients	Posit science auditory training	Computer game	Global cognition	NR
Penades et al., 2016, Spain	13.34	NR	12.84	Outpatients	Cognitive remediation therapy	Social skills training and healthy control group	Cognition	NR
Twamley et al., 2011, USA	13.3 (1.8)	89	12.7	Outpatients	Compensatory Cognitive Training (CCT) + standard pharmacotherapy	Standard pharmacotherapy	Cognition; functioning, symptoms	NR
Bell et al., 2008, USA	NR	72	NR	Outpatients	Neurocognitive enhancement therapy + vocational program	Vocational program	Competitive employment rates and hours of competitive employment	NR
Bell et al., 2014, USA	CR high community functioning = 12.26 (1.57) CR low community functioning = 12.20 (2.04) SE high community functioning = 13.57 (2.68) SE low community functioning = 12.57 (2.44)	174	NR	Outpatients	Neurocognitive enhancement therapy + vocational program	Vocational program	Competitive employment rates and hours of competitive employment	NR
Burton and Twamley, 2015, USA	12.9 (1.7)	43	23.3	Outpatients	Compensatory Cognitive Training + standard pharmacotherapy	Standard pharmacotherapy	Cognition and functioning	NR
Burton et al., 2015, USA	13.1 (1.7)	41	23.8	Outpatients	Compensatory Cognitive Training + standard pharmacotherapy	Standard pharmacotherapy	Cognition, functioning, symptoms	NR
Evensen et al., 2017, Norway	NR	148	CBT = 8.1 CR = 5.9	NR	Vocational rehabilitation augmented + CR	Vocational rehabilitation augmented + CBT	Self-esteem; global functioning; depression; employment status	NR
Fiszdon et al., 2006, USA	13.38 (3.03)	151	NR	Outpatients	Neurocognitive enhancement therapy with work therapy	Work therapy	Cognitive functioning	NR
Davidson et al., 2016, USA	CR = 12.5 (1.8) TAU = 12.1 (2.3)	75	NR	Outpatients	Cognitive remediation	Treatment as usual	Cognition	NR
Keshavan et al., 2011, USA	NR	50	3.26	NR	Cognitive enhancement therapy	Enriched supportive therapy	Cognition and social cognition	NR
Kurtz et al., 2009, USA	13.4 (1.9)	36	8.7	Outpatients	Cognitive remediation	Computer-skills training	Cognition, functioning, symptoms	NR
Kurtz et al., 2008, USA	13.4 (1.9)	23	9.6	Outpatients	Cognitive remediation	Computer-skills training	Functioning	NR

Table 1 (*continued*)

Study	Participants			Intervention			Primary outcome measures	Secondary outcome measures
	Mean years of education (SD)	Total included in analysis (dropouts; interventions)	Years of illness (mean)	Setting (inpatients, outpatients)	Treatment intervention	Control intervention		
Rodewald et al., 2014, Switzerland	Problem-solving training = 14.7 (2.9) Basic cognition training = 15.6 (3.7)	75	Problem-solving training = 5.0 Basic cognition training = 3.8	Inpatients	Training of planning and problem-solving ability (PLAN)	Basic cognitive training	Cognition	NR
Subramaniam et al., 2017, USA	HC (*N* = 28) SZ = 45.59 (10.25)	HC = 15.15 (2.67)	HC (N = 28)	24.52	Outpatients	Targeted Cognitive training + Social Cognitive Training	Targeted Cognitive training	Cognition and symptoms,
Fisher et al., 2015, USA	Computerized auditory training = 12.88 (1.60) Computer game = 12.86 (2.10)	86	NR	Outpatients	Computerized auditory training	Computer game	Cognition, symptoms, functioning and reward anticipation	NR
Vinogradov et al., 2009, USA	13.08 (2.20)	49	NR	Outpatients	Neuroplasticity-Based Computerized Auditory Training	Computer game	Cognition and symptoms	NR
Dickinson et al., 2010, USA	CR = 12.2 (1.8) Control = 12.8 (1.3)	63	NR	NR	Computer-assisted cognitive remediation	Computer game	Cognition and functioning	Self-described cognitive performance and symptoms
Fiszdon et al., 2004, USA	NET + WT = 13.3 (2.1) WT = 13.5 (2.2) Control = 9.66 (2.28)	94	NR Control = 10.68	Outpatients	Cognitive Remediation Therapy + work therapy	Work Therapy	Memory	NR
Lewandowski et al., 2011, USA	NR	58	3.2	Outpatients	Cognitive enhancement therapy	Enriched supportive therapy	Cognition, social cognition, symptoms and social adjustment	NR
McGurk et al., 2009, USA	VR + CR = 12.22 (2.73) VR = 11.75 (1.81)	34	NR	Outpatients	Vocational Services Program + Cognitive Remediation Program	Vocational Services Program	Cognition, symptoms, comorbidity and employment	NR
Sanchez et al., 2014, Spain	REHACOP = 9.23 (2.7) Control = 10.24 (2.8)	84	NR	Inpatients	Neuropsychological rehabilitation (REHACOP) + TAU	Group activities including drawing, reading the daily news, and constructing objects using different materials	Cognition, symptoms and functioning	NR
Bellucci et al., 2003, Australia	12.6	NR	NR	NR	Computer-assisted cognitive rehabilitation (CACR)	Wait-list	Cognition, symptoms and self-esteem	NR
Thomas et al., 2018, USA	11.83 (2.08)	46	15.68	Outpatients	Computerized targeted cognitive training + TAU	TAU	Cognition, auditory perception, and symptoms	NR
Gomar et al., 2015, Spain	TAU = 10.33 (2.65) Control active = 9.53 (3.08) CRT = 9.30 (2.86)	130	TAU = 23.38 (8.63) Control active = 22.58 (9.10) CRT = 24.30 (8.52)	Inpatients	Computerized CRT	TAU Computerized typing program and computerized games	Cognition (executive function and memory)	Other cognitive tests and functioning
Ramsay et al., 2018, USA	12.64 (2.54)	44	1.70	Outpatients	Targeted cognitive training	Computer games	Symptoms and cognition	NR

Table 2
Clinical Trial Assessment Measure scores.

Study	Study design	Original paper	Clinical Trial Assessment Measure scores						
			Sample (maximum 10)	Allocation procedure (maximum 16)	Assessment (maximum 32)	Comparison (maximum 16)	Analysis (maximum 15)	Treatment description (maximum 11)	Total score (maximum 100)
Corbera et al., 2017, USA	Secondary analysis of RCTs (Kurtz et al., 2007, 2015)	Kurtz et al., 2007	2	10	29	10	9	6	66
		Kurtz et al., 2015	7	10	29	10	11	3	70
McGurk and Mueser, 2008, USA	Secondary analysis of two RCTs (McGurk et al., 2005 and McGurk et al., 2015)	McGurk et al., 2005	2	16	26	6	15	6	71
		McGurk et al., 2015	7	16	29	16	11	11	90
Wykes et al., 2009 UK	Secondary analysis of RCT (Wykes, Reeder, Landau et al., 2007)	Wykes, Reeder, Landau et al., 2007	10	16	29	6	15	11	87
Franck et al., 2013, UK	RCT	/	7	10	26	10	5	3	61
Bark et al., 2003, USA	Secondary analysis of RCT (Medalia et al., 2000)	Medalia et al., 2000	2	10	6	16	9	6	49
Wykes et al., 1999, UK	RCT	/	5	16	16	6	15	11	69
Wykes et al., 2007, UK	RCT	/	10	16	29	6	15	11	87
Bosia et al., 2007, Italy	RCT	/	2	10	26	16	5	3	62
Farreny et al., 2016, Spain	Secondary analysis of RCT, Farreny et al., 2012	Farreny et al., 2012	2	16	26	10	11	6	71
Farreny et al., 2013, Spain	Secondary analysis of RCT, Farreny et al., 2012	Farreny et al., 2012	2	16	26	10	11	6	71
Panizzutti et al., 2013, USA	Secondary analysis of 2 RCTs (Fisher et al., 2009, 2015)	Fisher et al., 2009	7	13	26	10	9	6	71
		Fisher er al., 2015	7	10	26	10	15	11	79
Penades et al., 2016, Spain	Secondary analysis of RCT (Penadés et al., 2013)	Penadés et al., 2013	2	16	6	10	11	6	51
Twamley et al., 2011, USA	Secondary analysis of RCT (Twamley et al., 2012)	Twamley et al., 2012	7	13	26	6	15	6	73
Bell et al., 2008, USA	RCT	/	7	16	6	10	15	6	60
Bell et al., 2014, USA	Secondary analysis from RCT	Bell et al., 2008	7	16	6	10	15	6	60
Burton and Twamley, 2015, USA	Secondary analysis of RCT (Twamley et al., 2012)	Twamley et al., 2012	7	13	26	6	15	6	73
Burton et al., 2015, USA	Secondary analysis of RCT (Twamley et al., 2012)	Twamley et al., 2012	7	13	26	6	15	6	73
Davidson et al., 2016, USA	Secondary analysis of RCT (Fiszdon et al., 2016)	Fiszdon et al., 2016	2	16	6	6	11	6	47
Evensen et al., 2017, Norway	RCT	/	7	10	16	10	5	0	48
Fiszdon et al., 2006, USA	RCT	/	7	10	3	16	5	3	44
Keshavan et al., 2011, USA	Secondary analysis of RCT (Eack et al., 2009)	Eack et al., 2009	7	16	6	10	11	6	56
Kurtz et al., 2009, USA	Secondary analysis of RCT (Kurts et al., 2007)	Kurts et al., 2007	2	10	29	10	9	6	66
Kurtz et al., 2008, USA	RCT	/	7	10	26	10	5	6	64
Rodewald et al., 2014, Switzerland	Secondary analysis of RCT (Rodewald et al. 2011)	Rodewald et al. 2011	7	10	26	10	5	6	64
Subramaniam et al., 2017, USA	RCT	/	7	10	16	10	5	3	51
Fisher et al., 2015, USA	RCT	/	7	10	26	10	15	6	74
Vinogradov et al., 2009, USA	Secondary analysis of RCT (Twamley et al., 2012)	Twamley et al., 2012	7	13	26	6	15	6	73

(*continued on next page*)

Table 2 (*continued*)

Study	Study design	Original paper	Clinical Trial Assessment Measure scores						
			Sample (maximum 10)	Allocation procedure (maximum 16)	Assessment (maximum 32)	Comparison (maximum 16)	Analysis (maximum 15)	Treatment description (maximum 11)	Total score (maximum 100)
Dickinson et al., 2010, USA	Secondary analysis of RCT (Fiszdon et al., 2016)	Fiszdon et al., 2016	7	16	29	10	9	11	82
Fiszdon et al., 2004, USA	RCT	/	7	16	6	10	15	6	60
Lewandowski et al., 2011, USA	Secondary analysis from two RCTs (Hogarty et al., 2006 and Eack et al., 2009)	Hogarty et al., 2006	7	10	16	10	9	6	58
		Eack et al., 2009	7	16	6	10	11	6	56
McGurk et al., 2009, USA	RCT	/	2	13	26	10	11	3	65
Sanchez et al., 2014, Spain	RCT	/	7	13	26	10	5	6	67
Bellucci et al., 2003, Australia	RCT	/	2	10	26	6	15	6	65
Thomas et al., 2018, USA	RCT	/	2	13	6	6	15	6	48
Gomar et al., 2015, Spain	RCT	/	7	16	26	16	11	6	82
Ramsay et al., 2018, USA	Secondary analysis from one RCT (Fisher et al. 2015)	Fisher et al., 2015	7	10	26	10	15	11	79

2016; Penades et al., 2016; Twamley et al., 2011) and age (Farreny et al., 2016; Franck et al., 2013; Gomar et al., 2015; Penades et al., 2016; Wykes et al., 1999) were not significant moderators of the effect of CR on therapy outcomes. However, of the studies finding age as a moderator of therapy response, three reported that younger participants benefited more than older in several cognitive domains (Corbera et al., 2017; McGurk et al., 2007; Wykes et al., 2009), negative symptoms and functioning (Wykes et al., 2009). In contrast, four studies found that older participants showed larger improvements in cognition (Thomas et al., 2018; Twamley et al., 2011), self-esteem (Wykes et al., 2009) and, functioning (Dickinson et al., 2010) compared to younger. However, in the study conducted by Dickinson et al. (2010), age was not found as a moderator of the effect of CR on cognition and symptoms.

The generalisability of the demographic factors considered is subject to limitations. There is limited variability in terms of gender [males were the 75.8% (Wykes et al., 1999), 65.5% (Farreny et al., 2016), 68.6% (Twamley et al., 2011)]. Education was measured using different methods [years of education (Penades et al., 2016; Twamley et al., 2011), level of education (Farreny et al., 2016)]. These aspects are likely to affect the quality of the findings and limit the possibility of drawing reliable conclusions. Similarly, in the studies exploring participants' age, each study compared participants from a different age range [under 45 years old and age 45 years old or over, mean age is not reported (McGurk and Mueser, 2008); 17–65 years old, mean 36 (Wykes et al., 2009); younger than 25-older than 40, mean 33 (Corbera et al., 2017); 21–69 years old, mean 45 (Twamley et al., 2011); over age 44 vs. under age 45, mean 35.1 (Thomas et al., 2018); 18–60 years of age, mean 39.5 (Farreny et al., 2016); 18–45 years old, mean 33.5 (Franck et al., 2013); age <55 years, mean 36 (Penades et al., 2016); 19–64 years old, mean 38.6 (Wykes et al., 1999); 21–60 years old, mean 47.7 (Dickinson et al., 2010); 20–65 years old, mean 46 (Gomar et al., 2015)], making it difficult to compare different results. Another limitation is that these studies have a very narrow range to carry out an analysis, for example, in the study conducted by Dickinson et al. (2010) while the age range was 21–60 years old, the majority of participants (within one standard deviation above or below mean) were between 40.3 and 53.5 years limiting how these results will apply to those at the extremes of the distribution. In addition, seven studies analysed age as a continuous variable (Dickinson et al., 2010; Farreny et al., 2016; Franck et al., 2013; Penades et al., 2016; Thomas et al., 2018; Twamley et al., 2011; Wykes et al., 1999) while three studies (Corbera et al., 2017; McGurk and Mueser, 2008; Wykes et al., 2009) considered it as a categorical variable.

3.8. Biological features

The studies included highlighted several potential biological moderators including brain structure and genetic variability. Cortical reserve was identified as a moderator although studies used different measures of this concept. Grey matter volume (Keshavan et al., 2011), cortical thickness (Penades et al., 2016), integrity of the right fronto-occipital fasciculus, right corticospinal tract and, bilateral medial lemnisci (Subramaniam et al., 2017) were all found to moderate CR outcomes including social cognition, verbal and non-verbal memory, attention/vigilance and executive function. However, Ramsay et al. (2018) reported that baseline thalamic volume did not moderate improvements in cognition and subcortical volume after CR.

Our searches found two studies investigating genotype as a putative moderator of treatment response. These found differential improvement across variants of the COMT gene in favour of global cognition (Panizzutti et al., 2013), cognitive flexibility and functioning (Bosia et al., 2007). By contrast, Burton et al. (2015) suggested no significant effect of the COMT genotype on CR response.

Overall the total samples of these brain and genetic studies was small. No study assessed the possibility that the association between

Table 3
Summary of identified moderators.

Type of features	Factors	How many papers	Papers	Association with CR outcomes YES/NO	Outcomes
Demographics	Gender	3	Farreny et al., 2016 Twamley et al., 2011 Wykes et al., 1999	NO	/
	Education	3	Farreny et al., 2016 Penades et al., 2016 Twamley et al., 2011	NO	/
	Age	3	Corbera et al., 2017 McGurk and Mueser, 2008 Wykes et al., 2009	YES	Younger improve more than older in cognition
		1	Wykes et al., 2009	YES	Younger improve more than older in negative symptoms and functioning
		1	Twamley et al., 2011	YES	Older improve more than younger in memory
		1	Wykes et al., 2009	YES	Older improve more than younger in self-esteem
		1	Dickinson et al., 2010	YES	Older improve more than younger in functioning
		1	Thomas et al., 2018	YES	Older improve more than younger in verbal learning
		4	Farreny et al., 2016 Franck et al., 2013 Penades et al., 2016 Wykes et al., 1999 Dickinson et al., 2010 Gomar et al., 2015	NO	/
Biological	Brain structure	1	Keshavan et al., 2011	YES	Higher cortical reserve positively moderated social cognition
		1	Penades et al., 2016	YES	Greater cortical thickness in the temporal and frontal lobes, linked with greater improvement in verbal memory and non-verbal memory
		1	Subramaniam et al., 2017	YES	Greater integrity of white matter in the right front-occipital fasciculus predicted improvements in attention/vigilance Greater integrity of right corticospinal tract and bilateral medial lemnisci predicted improvements in executive functioning
		1	Ramsay et al., 2018	NO	/
	Genetic variable	1	Bosia et al., 2007	YES	People with Met on active treatment had better outcomes in cognitive flexibility and functioning
		1	Panizzutti et al., 2013	YES	Association between COMT gene and response in global cognition
		1	Burton et al., 2015	NO	/
Cognition and functioning	IQ	1	Fiszdon et al., 2006	YES	Lower IQ associated with cognitive gains
		1	Franck et al., 2013	YES	Higher IQ associated with lower cognitive gains
		1	Twamley et al., 2011	NO	/
	Learning potential	1	Davidson et al., 2016	YES	Learning potential predicted improvement in verbal and visual memory
	Baseline cognition	2	Kurtz et al., 2009 Kurtz et al., 2008	YES	Higher baseline cognition larger improvement in functioning
		1	Farreny et al., 2016	YES	Higher baseline cognition larger improvement in negative symptoms
		1	Penades et al., 2016	YES	Higher baseline cognition larger improvement in cognition
		2	Rodewald et al., 2014 Twamley et al., 2011	YES	Lower baseline cognition larger improvement in cognition
		1	Twamley et al., 2011	YES	Lower baseline cognition larger improvement in functioning
		3	Farreny et al., 2013 McGurk et al., 2009 Ramsay et al., 2018	NO	/
	Cognitive insight	1	Twamley et al., 2011	YES	Greater self-reported cognitive problems at baseline associated with larger improvements in cognition
		1	Burton and Twamley, 2015	NO	/
	Baseline functioning	2	Farreny et al., 2016 Kurtz et al., 2008	YES	Higher baseline functioning associated with a larger improvement in functioning
		1	Evensen et al., 2017	YES	Higher baseline functioning associated with higher rates of competitive employment
		1	Twamley et al., 2011	YES	Lower function at baseline associated with larger gains on functioning
		2	Bell et al., 2008 Bell et al., 2014	YES	People with poor community function receiving NET + VOC achieved better competitive employment rates and worked more hours than people only in the VOC No different outcomes between the conditions in people with higher community function

(*continued on next page*)

Table 3 (*continued*)

Type of features	Factors	How many papers	Papers	Association with CR outcomes YES/NO	Outcomes
Psychological	Motivation	1	Fisher et al., 2015	YES	Higher baseline motivational system functioning larger improvements in global cognition and verbal memory
		1	Rodewald et al., 2014	NO	/
	Self-esteem	1	Evensen et al., 2017	YES	Higher baseline self-esteem associated with higher competitive employment and lower unemployment
		1	Bellucci et al., 2003	NO	/
Illness-related	Symptoms	2	Farreny et al., 2013 Twamley et al., 2011	YES	Higher negative and positive symptoms at baseline associated with greater improvement in functioning
		1	Twamley et al., 2011	YES	Higher negative and positive symptoms at baseline associated with greater improvement in cognition
		1	Farreny et al., 2016	YES	Higher disorganized PANSS scale associated with greater improvement in cognition
		1	Farreny et al., 2016	YES	Lower scores for the PANSS excited scale, positive and negative symptoms associated with higher functioning improvements and negative symptoms reduction
		1	Ramsay et al., 2018	YES	Lower baseline symptoms associated with improvements in cognition and left thalamic volume
		9	Bark et al., 2003 Fiszdon et al., 2004 Kurtz et al., 2009 Kurtz et al., 2008 Penades et al., 2016 Rodewald et al., 2014 Sanchez et al., 2014 Wykes et al., 1999 Thomas et al., 2018	NO	/
	Medication	2	Twamley et al., 2011 Rodewald et al., 2014	YES	People on a lower antipsychotic dose were more likely to complete the therapy and improve
		1	Thomas et al., 2018	YES	Higher antipsychotic loads associated with better improvement in verbal learning
		1	Vinogradov et al., 2009	YES	Serum anticholinergic activity associated with lower therapy gains
		1	Wykes et al., 1999	YES	People on atypical antipsychotic had larger effects on cognition compared to those on typical antipsychotics
		1	Wykes et al., 2007	YES	People who received clozapine or typical medication had larger response compared to those on atypical medications
		3	Penades et al., 2016 Farreny et al., 2016 Sanchez et al., 2014 Gomar et al., 2015	NO	/
	Diagnosis	1	Twamley et al., 2011	YES	People with schizoaffective disorder had greater improvement in subjective quality of life compared to those with schizophrenia
		1	Lewandowski et al., 2011	NO	/
	Comorbid disorders	1	McGurk et al., 2009	YES	Comorbid substance abuse was associated with worse employment outcomes
		1	McGurk et al., 2009	NO	Physical comorbid condition (e.g. metabolic deficits) was not associated with employment outcomes
	Duration of illness	1	Corbera et al., 2017	YES	People with shorter illness duration had better outcomes
		4	Farreny et al., 2016 Penades et al., 2016 Twamley et al., 2011 Thomas et al., 2018	NO	/
	Hospitalisation	1	Penades et al., 2016	NO	/

brain structure and COMT genotype and CR response could have been confounded by the effect of antipsychotic medications, despite the noted influence of drugs on brain structure and dopaminergic system (Bosia et al., 2014).

3.9. Cognition and functioning

Our search identified different cognitive and functional aspects as possible moderators. These include cognitive difficulties insight, baseline cognition, IQ, learning potential and baseline functioning.

Twamley et al. (2011) found that higher self-reported cognitive problems at baseline was associated with larger improvements in cognition after CR. Conversely, Burton and Twamley (2015) found no difference between people with good or poor cognitive difficulties awareness.

Nine studies evaluated baseline cognition with six finding significant effects and three no effect on CR outcomes (Farreny et al., 2013; McGurk et al., 2009; Ramsay et al., 2018). However, those that found significant effects reported an association with different outcomes. In four studies higher baseline cognition was associated with larger improvement in functioning (Kurtz et al., 2009; Kurtz et al., 2008), negative symptoms (Farreny et al., 2016) and cognition (Penades et al., 2016) after CR. Conversely, two studies reported that lower initial cognition was associated with larger cognitive improvements (Rodewald et al., 2014; Twamley et al., 2011) and functioning (Twamley et al., 2011) after CR.

Of the three studies investigating IQ, one found lower IQ was related to smaller gains (Fiszdon et al., 2006), one that higher premorbid IQ was related to fewer gains (Franck et al., 2013) and one reported no difference (Twamley et al., 2011).

Our search identified only one study evaluating learning potential which predicted improvement in verbal and visual memory (Davidson et al., 2016).

Of the six studies investigating baseline functioning, three noted that better functioning was associated with a larger improvement in functioning (Farreny et al., 2016; Kurtz et al., 2008) higher competitive employment and lower unemployment (Evensen et al., 2017). In contrast, Twamley et al. (2011) found that people with lower function showed larger gains; with this finding confirmed by Bell et al. (2008). In a more recent study by Bell et al. (2014), people with poor community function receiving CR plus supported employment program had better competitive employment rates and worked more hours than people who only received a supported employment program alone. However, for participants with higher community function at entry to the study CR conferred no extra benefit (Bell et al., 2014).

The main limitation of this set of studies was the relatively small sample sizes which meant that although they found a significant, the effect size reliability is low. Outcomes were measured with different tests, making the comparison complicated (e.g. in baseline cognition studies Kurtz et al. (2008) measured verbal learning and memory with the California Verbal Learning Test, whereas Twamley et al. (2011) used Hopkins Verbal Learning Test; in functioning, Farreny et al. (2016) used Life Skills Profile, Kurtz et al. (2008) the University of California San Diego Performance-based Skills Assessment and, Twamley et al. (2011) Quality of Life Interview; in IQ research, Fiszdon et al. (2006) used the Information subtest of the Wechsler Adult Intelligence Scale, Franck et al. (2013) French National Adult Reading Test).

3.10. Psychological features

Our search identified two psychological factors investigated as possible moderators: motivation, and self-esteem. For motivation, Fisher et al. (2015) reported that an individual's baseline motivation (assessed by anticipatory and consummatory of pleasure) was associated with improvements in global cognition and verbal memory after therapy. But, Rodewald et al. (2014), found that motivation (considered both as negative symptoms and intrinsic motivation) had no effect on improvement in problem-solving ability.

Two studies evaluated self-esteem with one showing that higher self-esteem at baseline was associated with better competitive employment and lower unemployment (Evensen et al., 2017) and the other found no influence on cognitive gains (Bellucci et al., 2003).

It is, however, important to highlight that an accurate comparison between motivation studies is difficult because each study considered a different facet of motivation and measuring motivation is complex. The studies conducted by Bellucci et al. (2003) and Evensen et al. (2017) also have a modest sample size and an active control group (vocational rehabilitation services) that might have influenced the results.

3.11. Illness-related features

We identified six illness-related factors as possible moderators: symptoms, medication, diagnosis, comorbid disorders, duration of illness and number of hospitalisations. In terms of symptoms, some studies found that higher baseline symptoms severity was associated to larger improvements in functioning (Farreny et al., 2013; Twamley et al., 2011) and cognition (Farreny et al., 2016; Twamley et al., 2011). But others reported that lower baseline symptoms severity was related to better functioning (Farreny et al., 2016), negative symptoms (Farreny et al., 2016), cognition and subcortical volume preservation (Ramsay et al., 2018) after therapy. Another nine studies (Bark et al., 2003; Fiszdon et al., 2004; Kurtz et al., 2009; Kurtz et al., 2008; Penades et al., 2016; Rodewald et al., 2014; Sanchez et al., 2014; Thomas et al., 2018; Wykes et al., 1999), found no association between baseline symptoms profile and CR outcomes.

Again, these studies had limitations: used different PANSS factor models and participants in different studies had different levels of symptoms. For example, Twamley et al. (2011) used the PANSS three-factor structure from Kay et al. (1987) but considered only the Positive (mean 16.0) and Negative dimensions (mean 15.6). Ramsay et al. (2018) used the same factor structure but considered Positive (mean 12.65), Negative (mean 17.18) and General symptoms (mean 33.32) scores. Farreny et al. (2013) used both PANSS three- and five-factor (Wallwork et al., 2012), analysing only Negative symptoms (mean 2.7). Farreny et al. (2016), instead, considered a 5-factor structure by Wallwork et al. (2012); Positive (mean 6.8), Negative (mean 16), Disorganized (mean 8.4) Depressed (mean 6.8) and Excited (mean 5.8).

There were also inconsistencies in how medication influenced therapy outcomes with two studies reporting that those on a lower dose of antipsychotic medication were more likely to complete the therapy (Twamley et al., 2011) and show improvement on problem-solving (Rodewald et al., 2014). One study, however, showed the opposite with higher medication levels being associated with improvements in verbal learning (Thomas et al., 2018). Gomar et al. (2015) did not find that antipsychotic dose moderated CR outcomes. Vinogradov et al. (2009) found that serum anticholinergic activity, an index of individual's anticholinergic burden, contributed by the cumulative effect of drugs and their metabolites, was associated with poorer CR response. A study by Wykes et al. (1999) showed that people who received atypical antipsychotic medications showed larger effects on cognition after CR compared to those who had been prescribed typical antipsychotics, but this difference was not maintained at follow-up. In a further study, Wykes et al. (2007) reported that people who received either clozapine or typical antipsychotic achieved better results after therapy in comparison with those who received other atypical medications. Finally, three studies showed that medication levels before therapy did not predict CR response for cognition, functioning or symptoms improvements (Farreny et al., 2016; Penades et al., 2016; Sanchez et al., 2014). It is, however, important to highlight that a comparison between these studies is difficult because each study used different medications (e.g. first- and second-generation of antipsychotics).

Diagnosis and additional comorbid disorders are other illness-related aspects identified as possible moderators. We found only one

study (Twamley et al., 2011) suggesting that participants with schizoaffective disorder reported greater CR-associated improvement, in subjective quality of life, compared with those with a diagnosis of schizophrenia. However, Lewandowski et al. (2011) did not find the diagnosis as a moderator. McGurk et al. (2009), comorbid substance abuse was related to worse employment outcomes, after CR plus vocational rehabilitation and vocational rehabilitation alone, while the presence of a physical comorbid condition (e.g. metabolic deficits) was not associated with work outcomes.

The effects of illness duration on CR outcomes were mixed: with superior CR benefits reported for individuals with shorter illnesses length reported by Corbera et al. (2017) but no associations found in four other studies (Farreny et al., 2016; Penades et al., 2016; Thomas et al., 2018; Twamley et al., 2011). Penades et al. (2016) reported that the number of hospitalisations (mean 1.76) had no effects on CR outcomes. However, there is large variability in participants' illness duration across these studies making, again, comparisons difficult with average illness length ranging from 9.3 to 20.5 years. There were also differences in the way these studies analysed illness duration with the only study that found an effect considered it as categorical, unlike all other studies that considered illness duration as continuous and found negative results.

4. Discussion

The aim of this study was to review the literature to identify moderators of CR treatment response which can be used to understand why different participants achieve different outcome after CR.

This review identified 18 moderators considered to have an effect on CR; however, we found no high-quality replicated evidence for any of these. The majority of the studies reviewed lacked adequate power to conduct moderation analysis and half of the studies had poor methodological quality are considered at high risk of bias. The variability in the CR approaches and control groups considered might have also played a role in the lack of findings convergence. Studies also measured the same outcomes in different ways, particularly cognition but also functioning, with measures spanning from capacity to role functioning. Further, the studies included in this review considered a large number of moderators for a large number of outcomes. This created a vast amount of research questions which may make the current set of results at risk of reporting false positives. In addition, different individual potential predictors were investigated independently despite the possibility for a combined effect on CR (e.g. learning potential, education, and age).

To move the personalisation agenda of CR forward evidence on moderators needs to be stronger, replicated and based on appropriately powered research. In the section below, we have highlighted some research implications for the field to consider.

4.1. Research implications

While it is well known that positive findings are more likely to be published (Mlinarić et al., 2017), it is recognised that negative findings play an important role in shaping knowledge advancement. The majority of the studies we reviewed reported positive results. This may be because positive results are more often reported and mentioned in papers. However, it is likely that negative results were found as often but not reported contributing to a “skewed view” of the moderators' landscape. Future research should consider more routine reporting of negative findings.

As the results of this review show, there is no strong evidence for any of the moderators identified. While this is likely to be due to the lack of rigorous studies, it also shows that the field has, so far, focussed on exploratory studies to identify potential moderators. While this is a necessary first step, what the field needs now is replication and evidence consolidation. This will require large datasets and clear hypothesis-driven studies to test specific moderators and estimate more precisely their effect size on outcomes of interest.

It is also important to consider the mechanisms by which a moderator may act on therapy. Like other psychological therapies, CR relies on factors implicated in learning such as age, IQ, learning potential, motivation, self-esteem, and working alliance. These are hypothesis-based moderators and can be investigated based on a coherent theoretical framework. For example, there is evidence that people with schizophrenia have low self-esteem and that this has a negative impact on engagement and may have a detrimental effect on outcomes (Cella and Wykes, 2017; Huddy et al., 2012). Self-esteem also affects the perception that people with schizophrenia have about their cognitive difficulties (Cella et al., 2014). Moderators linked to hypothesised mechanisms of action may be more likely to show consistent trends and be used to understand mechanisms of CR effectively.

Research showed that people with schizophrenia have unique type and severity profiles of cognitive impairment (Silverstein, 2000). As CR targets cognitive difficulties, it is unclear whether different profiles of cognitive impairment would require different therapies regimes. Using an analogy from medication prescribing, one may hypothesise that more severe impairment may require higher therapy intensity (e.g. dose) or frequency. However, as psychological therapy, CR may respond to a different type of personalisation not necessarily to do with therapy dose and frequency but with ingredient types or dose. It may be that adapting or calibrating training to a particular profile of cognitive impairment may help to improve treatment response. A recent attempt at personalisation in this sense has not proven to be successful (Franck et al., 2013) but personalisation in this study was done only on one cognitive domain (e.g. executive function). It may be that training programs need to consider personalisation on multiple cognitive domains.

As research on personalisation progresses, it is also important to consider what outcome is the personalisation aiming to improve. A recent study compared different CR training methods targeting executive and perceptual processes (Best et al., 2019). Personalisation for perceptual processes programs may be very different to executive programs and research in these two areas may reflect different priorities. One, more research-based and more interested in the underlying mechanism of CR, while the other more clinical and focussed on improving outcomes for people with schizophrenia.

4.2. Limitations

The studies included have several limitations that can be grouped in main areas:

(i) *Generalisability*: While the results in this study are based on a sample's characteristics which reflect people with schizophrenia presenting to clinical services, the generalisability of these findings may be subject to limitations. For instance, the majority of the included studies consider samples with a high proportion of male participants and with a restricted range of age (21.2–48.1 years old). While these are likely to be the most common demographics associated with participants taking part in CR studies, it may be difficult to generalise the findings to female and younger or older people. In addition, we included only English-language publications and the majority of the studies considered took place in United States. These aspects may limit the generalisability of our results to other countries and cultures.

(ii) *Methodological quality*: The majority of the studies considered lacked independent randomization and/or treatment fidelity assessment. This is a potential source of bias as it may mean that assessor blinding was not rigorously implemented and that participants may have received treatment of variable quality within the same study. Caution should be used in drawing firm conclusions from these studies.”

(iii) *Measure heterogeneity*: Studies measured the same outcomes using different methods tools, making the comparison and an overall conclusion about the effect of moderators difficult. Future research would benefit for using standardized assessments and well-normed neurocognitive, functional, and symptoms batteries.

(iv) *Ratio for study selection*: This review only considered studies that mentioned the assessment of moderators in the abstract. This search strategy might therefore have missed relevant papers where the moderators were assessed but not reported. These moderation analyses were likely to be negative. In addition, it was difficult to ascertain if any moderators were hypothesis-driven or opportunistic as most studies did not have pre-registered analysis plans.

(v) Heterogeneity of CR therapy and type of control: The results heterogeneity found in this review may be due to differences in the CR intervention used. These include differences in intervention length, mode of administration (paper and pencil, computer, individual, group), focus of training (single versus multi-domain as well as drill-and-practice versus drill plus strategy training) and whether the intervention is administered as a stand-alone or part of a broader rehabilitation program.

There is also heterogeneity in the control groups with some studies having active control groups (e.g. computer games), others a passive control condition (e.g. treatment as usual), and some studies both. For instance, Farreny et al. (2016) used a CR strategy-based training focus on executive function and metacognition, in a group format, with a duration of 16 weeks and consisting of 32 sessions and did not found age as a moderator of CR benefits. On the other hand, Wykes and Huddy (2009), used CR plus treatment-as-usual, 3 days per week until 40 sessions were completed, in an individual format, and with treatment-as-usual as control group and found age as a moderator of treatment response.

In the future, it might be useful to conduct studies using large datasets produced by aggregating data from existing trial to reduce the effect of different therapy programs and control groups. This is what the National Institute for Mental Health is aiming to do by developing the Database of Cognitive Training and Remediation Studies (DoCTRS) (for example of DoCTRS database use Cella et al., 2017). These data would allow to test mechanisms and moderators of CR with an adequate statistical power and limit the influence of individual studies procedures and control groups on CR outcomes.

5. Conclusion

Even though there is evidence of substantial individual differences in response to CR (Murthy et al., 2012; Wykes et al., 2011), we still have a limited understanding of what causes variability in CR response. This review highlighted five categories of moderators that might influence CR response. We did not find strong evidence in support of any of them. Many significant effects were in opposite directions and most studies were small. The importance of this work is in summarizing the evidence so far accumulated in the field and suggesting moderators to be investigated in future studies. A recommendation is for appropriately powered and hypothesis driven moderation studies. While this may be difficult to achieve in one study, merging data from existing trials may provide the solution. Achieving clear evidence on the role of moderators in CR and using this information for understanding who will benefit more from the therapy relies largely on future studies adhering to good quality methodology and more shared efforts to identify key factors to investigate.

Declaration of competing interest

The authors did not declare any conflicts of interest.

Acknowledgments

This research was supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust (NIHR CLAHRC-2013-10022). The authors would also like to acknowledge the support of the National Institute for Health Research (NIHR) Biomedical Research Centre in Mental Health at the South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry, Psychology and Neuroscience at King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

References

Allott, K., Liu, P., Proffitt, T.M., Killackey, E., 2011. Cognition at illness onset as a predictor of later functional outcome in early psychosis: systematic review and methodological critique. Schizophr. Res. 125 (2–3), 221–235.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub.

Bark, N., Revheim, N., Huq, F., Khalderov, V., Ganz, Z.W., Medalia, A., 2003. The impact of cognitive remediation on psychiatric symptoms of schizophrenia. Schizophr. Res. 63 (3), 229–235.

Baron, R.M., Kenny, D.A., 1986. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J. Pers. Soc. Psychol. 51 (6), 1173.

Bell, M.D., Bryson, G., 2001. Work rehabilitation in schizophrenia: does cognitive impairment limit improvement? Schizophr. Bull. 27 (2), 269–279.

Bell, M.D., Zito, W., Greig, T., Wexler, B.E., 2008. Neurocognitive enhancement therapy with vocational services: work outcomes at two-year follow-up. Schizophr. Res. 105 (1–3), 18–29. https://doi.org/10.1016/j.schres.2008.06.026.

Bell, M.D., Choi, K.-H., Dyer, C., Wexler, B.E., 2014. Benefits of cognitive remediation and supported employment for schizophrenia patients with poor community functioning. Psychiatr. Serv. 65 (4), 469–475. https://doi.org/10.1176/appi.ps.201200505.

Bellucci, D.M., Glaberman, K., Haslam, N., 2003. Computer-assisted cognitive rehabilitation reduces negative symptoms in the severely mentally ill. Schizophr. Res. 59 (2–3), 225–232.

Best, M.W., Bowie, C.R., 2017. A review of cognitive remediation approaches for schizophrenia: from top-down to bottom-up, brain training to psychotherapy. Expert. Rev. Neurother. 17 (7), 713–723.

Best, M.W., Milanovic, M., Iftene, F., Bowie, C.R., 2019. A randomized controlled trial of executive functioning training compared with perceptual training for schizophrenia Spectrum disorders: effects on neurophysiology, neurocognition, and functioning. Am. J. Psychiatr. 176 (4), 297–306.

Bosia, M., Bechi, M., Marino, E., Anselmetti, S., Poletti, S., Cocchi, F., Cavallaro, R., 2007. Influence of catechol-O-methyltransferase Val158Met polymorphism on neuropsychological and functional outcomes of classical rehabilitation and cognitive remediation in schizophrenia. Neurosci. Lett. 417 (3), 271–274.

Bosia, M., Zanoletti, A., Spangaro, M., Buonocore, M., Bechi, M., Cocchi, F., Cavallaro, R., 2014. Factors affecting cognitive remediation response in schizophrenia: the role of COMT gene and antipsychotic treatment. Psychiatry Res. 217 (1–2), 9–14. https://doi.org/10.1016/j.psychres.2014.02.015.

Bowie, C.R., Leung, W.W., Reichenberg, A., McClure, M.M., Patterson, T.L., Heaton, R.K., Harvey, P.D., 2008. Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. Biol. Psychiatry 63 (5), 505–511.

Burton, C.Z., Twamley, E.W., 2015. Neurocognitive insight, treatment utilization, and cognitive training outcomes in schizophrenia. Schizophr. Res. 161 (2–3), 399–402. https://doi.org/10.1016/j.schres.2014.12.002.

Burton, C.Z., Vella, L., Kelsoe, J.R., Bilder, R.M., Twamley, E.W., 2015. Catechol-O-methyltransferase genotype and response to Compensatory Cognitive Training in outpatients with schizophrenia. Psychiatr. Genet. 25 (3), 131–134. https://doi.org/10.1097/YPG.0000000000000085.

Cella, M., Wykes, T., 2017. The nuts and bolts of cognitive remediation: exploring how different training components relate to cognitive and functional gains. Schizophr. Res. 203, 12–16.

Cella, M., Swan, S., Medin, E., Reeder, C., Wykes, T., 2014. Metacognitive awareness of cognitive problems in schizophrenia: exploring the role of symptoms and self-esteem. Psychol. Med. 44 (3), 469–476.

Cella, M., Preti, A., Edwards, C., Dow, T., Wykes, T., 2017. Cognitive remediation for negative symptoms of schizophrenia: a network meta-analysis. Clin. Psychol. Rev. 52, 43–51.

Corbera, S., Wexler, B.E., Poltorak, A., Thime, W.R., Kurtz, M.M., 2017. Cognitive remediation for adults with schizophrenia: does age matter? Psychiatry Res. 247, 21–27. https://doi.org/10.1016/j.psychres.2016.10.084.

Davidson, C.A., Johannesen, J.K., Fiszdon, J.M., 2016. Role of learning potential in cognitive remediation: construct and predictive validity. Schizophr. Res. 171 (1–3), 117–124. https://doi.org/10.1016/j.schres.2016.01.044.

Demily, C., Franck, N., 2008. Cognitive remediation: a promising tool for the treatment of schizophrenia. Expert. Rev. Neurother. 8 (7), 1029–1036.

Dickinson, D., Tenhula, W., Morris, S., Brown, C., Peer, J., Spencer, K., Bellack, A.S., 2010. A randomized, controlled trial of computer-assisted cognitive remediation for schizophrenia. Am. J. Psychiatry 167 (2), 170–180. https://doi.org/10.1176/appi.ajp.2009.09020264.

Evensen, S., Ueland, T., Lystad, J.U., Bull, H., Klungsoyr, O., Martinsen, E.W., Falkum, E., 2017. Employment outcome and predictors of competitive employment at 2-year follow-up of a vocational rehabilitation programme for individuals with schizophrenia in a high-income welfare society. Nord. J. Psychiatry 71 (3), 180–187. https://doi.org/10.1080/08039488.2016.1247195.

Farreny, A., Aguado, J., Ochoa, S., Haro, J.M., Usall, J., 2013. The role of negative symptoms in the context of cognitive remediation for schizophrenia. Schizophr. Res. 150 (1), 58–63. https://doi.org/10.1016/j.schres.2013.08.008.
Farreny, A., Aguado, J., Corbera, S., Ochoa, S., Huerta-Ramos, E., Usall, J., 2016. Baseline predictors for success following strategy-based cognitive remediation group training in schizophrenia. J. Nerv. Ment. Dis. 204 (8), 585–589. https://doi.org/10.1097/NMD.0000000000000509.
Fisher, M., Loewy, R., Carter, C., Lee, A., Ragland, D., Niendam, T., Vinogradov, S., 2015. Neuroplasticity-based auditory training via laptop computer improves cognition in young individuals with recent onset schizophrenia. Schizophr. Bull. 41 (1), 250–258. https://doi.org/10.1093/schbul/sbt232.
Fiszdon, J., Bryson, G., Wexler, B., Bell, M., 2004. Durability of cognitive remediation training in schizophrenia: performance on two memory tasks at 6-month and 12-month follow-up. Psychiatry Res. 125 (1), 1–7. https://doi.org/10.1016/j.psychres.2003.10.004.
Fiszdon, J.M., Cardenas, A.S., Bryson, G.J., Bell, M.D., 2005. Predictors of remediation success on a trained memory task. J. Nerv. Ment. Dis. 193 (9), 602–608.
Fiszdon, J., Choi, J., Bryson, G., Bell, M., 2006. Impact of intellectual status on response to cognitive task training in patients with schizophrenia. Schizophr. Res. 87 (1–3), 261–269. https://doi.org/10.1016/j.schres.2006.04.011.
Franck, N., Duboc, C., Sundby, C., Amado, I., Wykes, T., Demily, C., Vianin, P., 2013. Specific vs general cognitive remediation for executive functioning in schizophrenia: a multicenter randomized trial. Schizophr. Res. 147 (1), 68–74. https://doi.org/10.1016/j.schres.2013.03.009.
Gomar, J.J., Valls, E., Radua, J., Mareca, C., Tristany, J., del Olmo, F., McKenna, P.J., 2015. A multisite, randomized controlled clinical trial of computerized cognitive remediation therapy for schizophrenia. Schizophr. Bull. 41 (6), 1387–1396. https://doi.org/10.1093/schbul/sbv059.
Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the “right stuff”? Schizophr. Bull. 26 (1), 119–136.
Greenwood, K., Hung, C.-F., Tropeano, M., McGuffin, P., Wykes, T., 2011. No association between the catechol-O-methyltransferase (COMT) val158met polymorphism and cognitive improvement following cognitive remediation therapy (CRT) in schizophrenia. Neurosci. Lett. 496 (2), 65–69.
Bowie, & Harvey, P. D. (2006). Cognitive deficits and functional outcome in schizophrenia. Neuropsychiatr. Dis. Treat., 2(4), 531.
Huddy, V., Reeder, C., Kontis, D., Wykes, T., Stahl, D., 2012. The effect of working alliance on adherence and outcome in cognitive remediation therapy. J. Nerv. Ment. Dis. 200 (7), 614–619. https://doi.org/10.1097/NMD.0b013e31825bfc31.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
Keshavan, M.S., Eack, S.M., Wojtalik, J.A., Prasad, K.M., Francis, A.N., Bhojraj, T.S., Hogarty, S.S., 2011. A broad cortical reserve accelerates response to cognitive enhancement therapy in early course schizophrenia. Schizophr. Res. 130 (1–3), 123–129. https://doi.org/10.1016/j.schres.2011.05.001.
Kurtz, M., Wexler, B., Fujimoto, M., Shagan, D., Seltzer, J., 2008. Symptoms versus neurocognition as predictors of change in life skills in schizophrenia after outpatient rehabilitation. Schizophr. Res. 102 (1–3), 303–311. https://doi.org/10.1016/j.schres.2008.03.023.
Kurtz, M., Seltzer, J., Fujimoto, M., Shagan, D., Wexler, B., 2009. Predictors of change in life skills in schizophrenia after cognitive remediation. Schizophr. Res. 107 (2–3), 267–274. https://doi.org/10.1016/j.schres.2008.10.014.
Levaux, M.-N., Vezzaro, J., Larøi, F., Offerlin-Meyer, I., Danion, J., Van der Linden, M., 2009. Cognitive rehabilitation of the updating sub-component of working memory in schizophrenia: a case study. Neuropsychol. Rehabil. 19 (2), 244–273.
Lewandowski, K.E., Eack, S.M., Hogarty, S.S., Greenwald, D.P., Keshavan, M.S., 2011. Is cognitive enhancement therapy equally effective for patients with schizophrenia and schizoaffective disorder? Schizophr. Res. 125 (2–3), 291–294. https://doi.org/10.1016/j.schres.2010.11.017.
McGurk, S.R., Meltzer, H.Y., 2000. The role of cognition in vocational functioning in schizophrenia. Schizophr. Res. 45 (3), 175–184.
McGurk, Mueser, K., 2008. Response to cognitive rehabilitation in older versus younger persons with severe mental illness. Am. J. Psychiatr. Rehabil. 11 (1), 90–105. https://doi.org/10.1080/15487760701853136.
McGurk, S.R., Twamley, E.W., Sitzer, D.I., McHugo, G.J., Mueser, K.T., 2007. A meta-analysis of cognitive remediation in schizophrenia. Am. J. Psychiatry 164 (12), 1791–1802. https://doi.org/10.1176/appi.ajp.2007.07060906.
McGurk, S., Mueser, K., DeRosa, T., Wolfe, R., 2009. Work, recovery, and comorbidity in schizophrenia: a randomized controlled trial of cognitive remediation. Schizophr. Bull. 35 (2), 319–335. https://doi.org/10.1093/schbul/sbn182.
Medalia, Richardson, 2005. What predicts a good response to cognitive remediation interventions? Schizophr. Bull. 31 (4), 942–953. https://doi.org/10.1093/schbul/sbi045.
Medalia, A., Saperstein, A.M., Hansen, M.C., Lee, S., 2018. Personalised treatment for cognitive dysfunction in individuals with schizophrenia spectrum disorders. Neuropsychol. Rehabil. 28 (4), 602–613.
Mlinarić, A., Horvat, M., Šupak Smolčić, V., 2017. Dealing with the positive publication bias: why you should really publish your negative results. Biochem. Med. 27 (3), 1–6.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann. Intern. Med. 151 (4), 264–269.
Murthy, N., Mahncke, H., Wexler, B., Maruff, P., Inamdar, A., Zucchetto, M., Alexander, R., 2012. Computerized cognitive remediation training for schizophrenia: an open label, multi-site, multinational methodology study. Schizophr. Res. 139 (1–3), 87–91. https://doi.org/10.1016/j.schres.2012.01.042.
Panizzutti, R., Hamilton, S.P., Vinogradov, S., 2013. Genetic correlate of cognitive training response in schizophrenia. Neuropharmacology 64, 264–267. https://doi.org/10.1016/j.neuropharm.2012.07.048.
Penades, R., Pujol, N., Catalan, R., Masana, G., Garcia-Rizo, C., Bargallo, N., Junque, C., 2016. Cortical thickness in regions of frontal and temporal lobes is associated with responsiveness to cognitive remediation therapy in schizophrenia. Schizophr. Res. 171 (1–3), 110–116. https://doi.org/10.1016/j.schres.2016.01.006.
Pillet, B., Morvan, Y., Todd, A., Franck, N., Duboc, C., Grosz, A., Krebs, M.-O., 2015. Cognitive remediation therapy (CRT) benefits more to patients with schizophrenia with low initial memory performances. Disabil. Rehabil. 37 (10), 846–853.
Ramsay, I.S., Fryer, S., Boos, A., Roach, B.J., Fisher, M., Loewy, R., Mathalon, D.H., 2018. Response to targeted cognitive training correlates with change in thalamic volume in a randomized trial for early schizophrenia. Neuropsychopharmacology 43 (3), 590–597. https://doi.org/10.1038/npp.2017.213.
Rodewald, K., Holt, D.V., Rentrop, M., Roesch-Ely, D., Liebrenz, M., Funke, J., Kaiser, S., 2014. Predictors for improvement of problem-solving during cognitive remediation for patients with schizophrenia. J. Int. Neuropsychol. Soc. 20 (4), 455–460. https://doi.org/10.1017/S1355617714000162.
Sanchez, P., Pena, J., Bengoetxea, E., Ojeda, N., Elizagarate, E., Ezcurra, J., Gutierrez, M., 2014. Improvements in negative symptoms and functional outcome after a new generation cognitive remediation program: a randomized controlled trial. Schizophr. Bull. 40 (3), 707–715. https://doi.org/10.1093/schbul/sbt057.
Silverstein, S.M., 2000. Psychiatric rehabilitation of schizophrenia: unresolved issues, current trends, and future directions. Appl. Prev. Psychol. 9 (4), 227–247. https://doi.org/10.1016/S0962-1849%2800%2980002-5.
Silverstein, S.M., Wilkniss, S.M., 2004. At issue: the future of cognitive rehabilitation of schizophrenia. Schizophr. Bull. 30 (4), 679–692.
Spitzer, R.L., Endicott, J., Robins, E., 1978. Research diagnostic criteria: rationale and reliability. Arch. Gen. Psychiatry 35 (6), 773–782.
Subramaniam, K., Gill, J., Fisher, M., Mukherjee, P., Nagarajan, S., Vinogradov, S., 2017. White matter microstructure predicts cognitive training-induced improvements in attention and executive functioning in schizophrenia. Schizophr. Res. https://doi.org/10.1016/j.schres.2017.06.062. No Pagination Specified.
Thomas, M.L., Bismark, A.W., Joshi, Y.B., Tarasenko, M., Treichler, E.B., Hochberger, W.C., Light, G.A., 2018. Targeted cognitive training improves auditory and verbal outcomes among treatment refractory schizophrenia patients mandated to residential care. Schizophr. Res. 202, 378–384. https://doi.org/10.1016/j.schres.2018.07.025.
Twamley, Burton, Vella, 2011. Compensatory cognitive training for psychosis: who benefits? Who stays in treatment? Schizophr. Bull. 37 (Suppl. 2), S55–S62. https://doi.org/10.1093/schbul/sbr059.
Vinogradov, S., Fisher, M., Warm, H., Holland, C., Kirshner, M.A., Pollock, B.G., 2009. The cognitive cost of anticholinergic burden: decreased response to cognitive training in schizophrenia. Am. J. Psychiatry 166 (9), 1055–1062. https://doi.org/10.1176/appi.ajp.2009.09010017.
Vita, A., Deste, G., De Peri, L., Barlati, S., Poli, R., Cesana, B.M., Sacchetti, E., 2013. Predictors of cognitive and functional improvement and normalization after cognitive remediation in patients with schizophrenia. Schizophr. Res. 150 (1), 51–57.
Wallwork, R., Fortgang, R., Hashimoto, R., Weinberger, D., Dickinson, D., 2012. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophr. Res. 137 (1–3), 246–250.
World Health Organization, 1992. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. vol. 1 World Health Organization.
Wykes, T., 1994. Predicting symptomatic and behavioural outcomes of community care. Br. J. Psychiatry 165 (4), 486–492.
Wykes, T., Huddy, V., 2009. Cognitive remediation for schizophrenia: it is even more complicated. Curr. Opin. Psychiatry 22 (2), 161–167. https://doi.org/10.1097/YCO.0b013e328322fbf4.
Wykes, T., Spaulding, W.D., 2011. Thinking about the future cognitive remediation therapy—what works and could we do better? Schizophr. Bull. 37 (suppl_2), S80–S90.
Wykes, T., Reeder, C., Corner, J., Williams, C., Everitt, B., 1999. The effects of neurocognitive remediation on executive processing in patients with schizophrenia. Schizophr. Bull. 25 (2), 291–307. https://doi.org/10.1093/oxfordjournals.schbul.a033379.
Wykes, T., Reeder, C., Landau, S., Everitt, B., Knapp, M., Patel, A., Romeo, R., 2007. Cognitive remediation therapy in schizophrenia: randomised controlled trial. Br. J. Psychiatry 190, 421–427. https://doi.org/10.1192/bjp.bp.106.026575.
Wykes, T., Steel, C., Everitt, B., Tarrier, N., 2008. Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. Schizophr. Bull. 34 (3), 523–537.
Wykes, T., Reeder, C., Landau, S., Matthiasson, P., Haworth, E., Hutchinson, C., 2009. Does age matter? Effects of cognitive rehabilitation across the age span. Schizophr. Res. 113 (2–3), 252–258. https://doi.org/10.1016/j.schres.2009.05.025.
Wykes, T., Huddy, V., Cellard, C., McGurk, S., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am. J. Psychiatr. 168 (5), 472–485.