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Review Article

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

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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...
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 Wilkiss, 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).
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.,...
| Study                        | Study design            | Original paper | Title                                                                 | Moderator investigated                              | Participants                        | Sample size N |
|-----------------------------|-------------------------|----------------|----------------------------------------------------------------------|----------------------------------------------------|-------------------------------------|---------------|
| 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? Social skills training and computer-assisted cognitive remediation in schizophrenia. | Age, duration of illness                         | Mean age (SD): 32.96 (11.57) Male (%): 70.5% | 112           |
| McGurk and Mueser, 2008, USA| Secondary analysis of two RCTs (McGurk et al., 2005 and McGurk et al., 2015) | McGurk et al., 2015 | 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) |
| 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) |
| Frack et al., 2013, UK      | RCT                     | /              | Remediation of memory disorders in schizophrenia                      | Age; intellectual symptoms                         | 33.54 (6.9) | 73% | 138 (65) |
| Bark et al., 2003, USA      | Secondary analysis of RCT (Medalia et al., 2000) | Medalia et al., 2000 | /                                                                  | Medication; demographics (age, gender); and symptoms | 36.77 | 59.26% | 54 (36) |
| Wykes et al., 1999, UK      | RCT                     | /              | /                                                                  | Medication                                        | 38.55 | 75.75% | 33 (17) |
| Wykes et al., 2007, UK      | RCT                     | /              | /                                                                  | Medication; COMT allele                             | 36 (NR) | 73% | 85 (43) |
| Bosia et al., 2007, Italy   | RCT                     | /              | /                                                                  | Demographics (sex, age, education); illness duration; medication; cognition; symptoms and functioning | 39.5 (8.5) | 65.5% | 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 | Baseline negative symptoms and executive function | 40.6 (7.6) | 68% | 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 | | | |

(continued on next page)
| Study                        | Study design                        | Original paper | Title                                                                 | Moderator investigated | Participants |
|-----------------------------|-------------------------------------|----------------|----------------------------------------------------------------------|------------------------|--------------|
| Panizzutti et al., 2013, USA| Secondary analysis of 2 RCTs        | Fisher, 2009   | Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia | COMT allele            | Mean age (SD): 33.6 (13.1) Male (%): 70.8% Sample size N (CR): 48 (48) |
|                             |                                     | Fisher, 2015   | Neuroplasticity-based auditory training via laptop computer improves cognition in young individuals with recent onset schizophrenia |                        |              |
| Penades et al., 2016, Spain | Secondary analysis of RCT           | Penadés, 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 cognitive performance; symptoms; cognition; functioning; self-reported cognitive and functioning problems; intelligence) | Mean age (SD): 36.22 Male (%): 74% Sample size N (CR): 50 (17) |
| Twamley et al., 2011, USA   | Secondary analysis of RCT           | Twamley, 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) | Mean age (SD): 47.3 (9.8) Male (%): 69% Sample size N (CR): 89 |
| Bell et al., 2008, USA      | RCT                                 | /              | Neurocognitive enhancement therapy with vocational services: work outcomes at two-year follow-up | Baseline community function | Mean age (SD): 40 Male (%): 54% Sample size N (CR): 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 | Mean age (SD): 40 Community functioning: 40.35 (10.48) Male (%): 48% Sample size N (CR): 175 (99) |
| Burton and Twamley, 2015, USA| Secondary analysis of RCT           | Twamley, 2012  | Compensatory Cognitive Training for psychosis: effects in a randomized controlled trial | Neurocognitive insight | Mean age (SD): 46.3 (9.7) Male (%): 65.2% Sample size N (CR): 69 |
| Burton et al., 2015, USA    | Secondary analysis of RCT           | Twamley, 2012  | Compensatory Cognitive Training for psychosis: effects in a randomized controlled trial | COMT allele            | Mean age (SD): 48 (8.6) Male (%): 65.9% Sample size N (CR): 41 (20) |
| Evensen et al., 2017, Norway| RCT                                 | /              | Global functioning, self-esteem | Global functioning, self-esteem | Mean age (SD): 33.2 (8.0) Male (%): 61.8% Sample size N (CR): 148 (64) |

(continued on next page)
| Study                        | Study design            | Original paper      | Title                                                                 | Moderator investigated                                                                 | Participants                                                                 |
|-----------------------------|-------------------------|---------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Fiszdon et al., 2006, USA   | RCT                     |                     | Fiszdon et al., 2016                                               | Intellectual (pre-morbid and morbid)                                                     | Mean age (SD) 42.82 (8.66) Male (%) 80% Sample size N 152 (72)               |
| Davidson et al., 2016, USA  | Secondary analysis of RCT (Fiszdon et al., 2016) |                     | Fiszdon et al., 2016                                               | Learning potential                                                                     | CR = 47.3 (9.1) TAU = 48.9 (9.9) CR = 78.4% TAU = 62.5% Sample size N 75 (50) |
| 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) Male (%) 64% Sample size N 58                   |
| Kurtz et al., 2009, USA     | Secondary analysis of RCT (Kurts et al., 2010) |                      | Kurtz et al., 2007                                               | Computer-assisted cognitive remediation in schizophrenia: what is the active ingredient? | Cognitive, symptoms 32.4 (11.2) Male (%) 69% Sample size N 36                |
| Kurtz et al., 2008, USA     | RCT                     |                     | Kurts et al., 2007                                               | Planning and problem-solving training for patients with schizophrenia: a randomized controlled trial. | Cognition, symptoms, functioning     | 34.6 (10.0) Male (%) 72% Sample size N 46                                    |
| Rodewald et al., 2014, Switzerland | Secondary analysis of RCT (Rodewald et al. 2011) |                     | Rodewald et al., 2011                                             | 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% |
| Subramaniam et al., 2017, USA | RCT                     |                     | Subramaniam et al., 2017                                          | Brain Structure (White matter integrity)                                                | HC = 41.41 (1.74) SZ = 45.59 (10.25) HC = 66.71% SZ = 68.75% N = 28          |
| Fisher et al., 2015, USA    | RCT                     |                     | Fisher et al., 2015                                              | Motivation                                                                             | Computerized auditory training = 21.70 (3.26) Computerized auditory training = 72.09% |
| Vinogradov et al., 2009, USA | Secondary analysis of RCT (Twamley et al., 2012) |                     | Vinogradov et al., 2009                                          | Medication (Serum anticholinergic activity)                                             | Computer game = 20.74 (3.37) Computer game = 76.74%                         |
| Dickinson et al., 2010, USA | Secondary analysis of RCT (Fiszdon et al., 2016) |                     | Dickinson et al., 2010                                           | Cognitive remediation for individuals with psychotic efficacy and mechanisms of treatment effects | Age                                 | 38.10% Sample size N 63 (35)                                                  |
| Fiszdon et al., 2004, USA   | RCT                     |                     | Fiszdon et al., 2016                                             |                                                                                       | Control = 46.9 (6.6) Control = 48.5 (8.8)                                    |
| Lewandowski et al., 2011, USA | Secondary analysis from 2 RCT |                     | Lewandowski et al., 2011                                         | Durability and mechanism of effects of cognitive enhancement therapy.                    | Symptom NET + WT = 41.9 (9.9) NET + WT = 76% Control = 33.21 (6.89)           |
|                            |                         |                     | Back et al., 2009                                               | Cognition enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. | Diagnosis                           | 25.9 (6.3) Male (%) 68% Sample size N 58                                    |

(continued on next page)
Table 1 (continued)

| Study               | Participants                                                                 | Intervention                                                                 |
|---------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| McGurk et al., 2009, USA |                                                                                   |                                                                             |
|                    |                                                                                   |                                                                             |
| Sanchez et al., 2014, Spain |                                                                                   |                                                                             |
|                    |                                                                                   |                                                                             |
| Bellucci et al., 2003, Australia |                                                                                   |                                                                             |
|                    |                                                                                   |                                                                             |
| Thomas et al., 2018, USA |                                                                                   |                                                                             |
|                    |                                                                                   |                                                                             |
| Gomar et al., 2015, Spain |                                                                                   |                                                                             |
|                    |                                                                                   |                                                                             |
| 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 |
|                    |                                                                                   |                                                                             |
| Corbera et al., 2017, USA | 1.282 (2.40) 112 9.34 | Outpatients Cognitive remediation Computer skills training Working memory, functioning and symptoms |
| McGurk and Mueser, 2008, USA | NR 76 NR | Cognitive training + vocational rehabilitations Vocational rehabilitations Cognitive functioning; symptoms |
| Wykes et al., 2009, UK | Young = 11.85 Older = 10.8 | Memory: 75 PT; 68 FU 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 | 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 RECODE 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 |
| 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 |
Table 1

| Study            | Participants | Total included in analysis (dropouts; interventions) | Years of illness (mean) | Intervention | Control intervention | Primary outcome measures | Secondary outcome measures |
|------------------|--------------|------------------------------------------------------|-------------------------|--------------|----------------------|--------------------------|---------------------------|
| Wykes et al., 2007, UK | 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                      | Function-specific computer-aided exercises + standard rehabilitation treatment | Standard rehabilitation treatment | Symptoms; functioning; cognitive flexibility; sustained attention | NR |
| Farreny et al., 2016, Spain | NR           | NR                                                   | 17.6                    | REPYFLEC | Stimulating activities focused on leisure and socialisation | Neurocognition functioning symptoms | NR |
| Farreny et al., 2013, Spain | NR           | NR                                                   | NR                      | REPYFLEC | Leisure activities | Neurocognition functioning symptoms | NR |
| Panizzuti et al., 2013, USA | NR           | NR                                                   | 12.9                    | Posit science auditory training | Computer game | Neurocognition functioning symptoms | Global cognition | NR |
| Pendas et al., 2016, Spain | 13.34        | NR                                                   | 12.84                   | Cognitive remediation therapy | Social skills training and healthy control group | Cognition | NR |
| Twamley et al., 2011, USA | 13.3 (1.8)   | 89                                                   | 12.7                    | Compensatory Cognitive Training (CCT) + standard pharmacotherapy | Standard pharmacotherapy | Cognition; functioning, symptoms | NR |
| Bell et al., 2008, USA | NR           | 72                                                   | NR                      | 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) | 174                     | NR                      | 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                    | Compensatory Cognitive Training + standard pharmacotherapy | Standard pharmacotherapy | Cognition and functioning | NR |
| Burton et al., 2015, USA | 13.1 (1.7)   | 41                                                   | 23.8                    | Compensatory Cognitive Training + standard pharmacotherapy | Standard pharmacotherapy | Cognition, functioning, symptoms | NR |
| Evensen et al., 2017, Norway | NR           | 148                                                  | NR                      | Vocational rehabilitation augmented + CR | Vocational rehabilitation augmented + CBT Work therapy | Self-esteem; global functioning; depression; employment status | NR |
| Fisdon et al., 2006, USA | 13.38 (3.03) | 151                                                  | NR                      | Neurocognitive enhancement therapy with work therapy | Neurocognitive enhancement therapy with work therapy | Cognitive functioning | NR |
| Study                                      | Participants | Intervention | Primary outcome measures | Secondary outcome measures |
|-------------------------------------------|--------------|--------------|--------------------------|----------------------------|
| Davidson et al., 2016, USA                | 75           | CR = 12.5 (1.8) | Cognition and social functioning | Cognition and symptoms, social cognition, symptoms and reward sensitivity |
| Keshavan et al., 2011, USA                | 50           | NR           | Cognition and social functioning | Cognition and symptoms, social cognition, symptoms and reward sensitivity |
| Kurtz et al., 2009, USA                   | 36           | 13.4 (1.9) | Cognition, functioning, symptoms | Self-assessed cognitive performance and symptoms |
| Kurtz et al., 2008, USA                   | 23           | 13.4 (1.9) | Cognition, functioning, symptoms | Self-assessed cognitive performance and symptoms |
| Rodewald et al., 2014, Switzerland        | 75           | Problem-solving training = 14.7 (2.9) | Cognition and symptoms, social cognition, symptoms and reward sensitivity | Cognition and symptoms, social cognition, symptoms and reward sensitivity |
| Subramaniam et al., 2014, USA             | 96           | NR           | Cognition and symptoms, social cognition, symptoms and reward sensitivity | Cognition and symptoms, social cognition, symptoms and reward sensitivity |
| Fisher et al., 2015, USA                  | 86           | 13.4 (1.9) | Cognition, functioning, symptoms | Self-assessed cognitive performance and symptoms |
| Fiszdon et al., 2004, USA                 | 94           | NET + WT = 13.3 | Work Therapy | Cognition, symptoms and self-esteem |
| Lewandowski et al., 2011, USA             | 58           | Control = 9.66 (2.28) | Computer-assisted cognitive rehabilitation + TAU | Cognition, symptoms and self-esteem |
| Thomas et al., 2015, USA                  | 46           | Control = 10.68 | Cognition, social and cognitive rehabilitation + TAU | Cognition, symptoms and self-esteem |
| Thomas et al., 2016, USA                  | 13.8          | 11.83 (2.08) | Cognition, auditory perception, and symptoms | Cognition, auditory perception, and symptoms |

(continued on next page)
| Study design | Original paper | Clinical Trial Assessment Measure scores | Treatment description | Total score |
|--------------|----------------|------------------------------------------|-----------------------|-------------|
| Secondary analysis of two RCTs (Pyke et al., 2007) | McGurk et al., 2005 | 10 / 10 / 29 / 29 | Secondary analysis of RCT (Maxwell et al., 2004) | 36 / 36 / 66 / 66 |
| Secondary analysis of RCT (McGurk et al., 2003) | McGurk et al., 2005 | 7 / 7 / 16 / 16 | Secondary analysis of RCT (Pyke et al., 2007) | 11 / 11 / 17 / 17 |
| Secondary analysis of RCT (Barnett et al., 2012) | Burton et al., 2015 | 10 / 10 / 29 / 29 | Secondary analysis of RCT (Subramaniam et al., 2009) | 36 / 36 / 66 / 66 |
| Secondary analysis of RCT (Twamley et al., 2012) | Burton et al., 2015 | 10 / 10 / 29 / 29 | Secondary analysis of RCT (Subramaniam et al., 2009) | 36 / 36 / 66 / 66 |
| Secondary analysis of RCT (Fiszdon et al., 2016) | Fiszdon et al., 2006 | 10 / 10 / 29 / 29 | Secondary analysis of RCT (Subramaniam et al., 2009) | 36 / 36 / 66 / 66 |
| Secondary analysis of RCT (Kurt et al., 2009) | Kurt et al., 2009 | 10 / 10 / 29 / 29 | Secondary analysis of RCT (Subramaniam et al., 2009) | 36 / 36 / 66 / 66 |
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 old, 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 lenticular subregion (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, Ramsey 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 | 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                             |
|                  |         |                 | Farreny et al., 2016, Penades et al., 2016, Twamley et al., 2011       | YES                         | Younger improve more than older in negative symptoms and functioning     |
|                  |         |                 | Wykes et al., 2009                                                   | YES                         | Older improve more than younger in memory                                 |
|                  |         | 1               | Wykes et al., 2009                                                   | YES                         | Older improve more than younger in self-esteem                            |
|                  |         | 1               | Twamley et al., 2011                                                 | YES                         | Older improve more than younger in working memory                         |
|                  |         | 1               | Wykes et al., 2009, Penades et al., 2016, Twamley et al., 2011       | YES                         | Older improve more than younger in verbal learning                        |
|                  |         | 1               | Dickinson et al., 2010                                               | NO                          | /                          |
|                  |         | 1               | Thomas et al., 2018                                                  | YES                         | /                          |
|                  |         | 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 |
|                  | Genetic variable | 1            | Ramsay et al., 2018                                                  | NO                          | People with Met on active treatment had better outcomes in cognitive flexibility and functioning |
|                  |         | 1               | Bosia et al., 2007                                                   | YES                         | Association between COMT gene and response in global cognition            |
|                  |         | 1               | Panizzutti et al., 2013                                             | YES                         | /                          |
|                  |         | 1               | Buron et al., 2015                                                   | NO                          | /                          |
|                  | Cognition and functioning | IQ | Fiskdon et al., 2006                                               | YES                         | Lower IQ associated with cognitive gains                                  |
|                  |         | 1               | Frank 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       |
|                  |         | 2               | Kurtz et al., 2009, Kurz et al., 2008                                | YES                         | Higher baseline cognition larger improvement in functioning                |
|                  | Baseline cognition | 1          | Farreny et al., 2016, Penades et al., 2016, Twamley et al., 2011     | YES                         | Higher baseline cognition larger improvement in negative symptoms          |
|                  |         | 2               | Rodewald et al., 2014                                               | YES                         | Higher baseline cognition larger improvement in cognition                  |
|                  |         | 1               | Twamley et al., 2011                                                 | YES                         | Lower baseline cognition larger improvement in cognition                   |
|                  |         | 3               | Farreny et al., 2013, McGurk et al., 2009, Ramsay et al., 2018       | NO                          | /                          |
|                  | Cognitive insight | 1          | Twamley et al., 2011, Buron and Twamley, 2015, Farreny et al., 2016, Kurz et al., 2008 | YES                         | Greater self-reported cognitive problems at baseline associated with larger improvements in cognition |
|                  |         | 1               | Evenen et al., 2017, Twamley et al., 2011                           | YES                         | Higher baseline functioning associated with a larger improvement in functioning |
|                  | Baseline functioning | 2          | Farreny et al., 2016, Kurz et al., 2008                               | YES                         | Higher baseline functioning associated with higher rates of competitive employment |
|                  |         | 1               | Evenen et al., 2017, 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)
| Type of features | Factors         | How many papers | Papers                                                                 | Association with CR outcomes | Outcomes                                                                                     |
|------------------|-----------------|-----------------|------------------------------------------------------------------------|-----------------------------|-----------------------------------------------------------------------------------------------|
| Psychological    | Motivation      | 1               | Fisher et al., 2015                                                   | YES                         | Higher baseline motivational system functioning larger improvements in global cognition and verbal memory |
|                  | Self-esteem     | 1               | Rodewald et al., 2014                                                 | NO                          | Higher baseline self-esteem associated with higher competitive employment and lower unemployment |
|                  | Illness-related | Symptoms        | Farreny et al., 2013, Twamley et al., 2011, Farreny et al., 2016, Farreny et al., 2016 | YES | Higher negative and positive symptoms at baseline associated with greater improvement in functioning |
|                  |                 | 2               | 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                                                   | NO                          | 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, Perades et al., 2016, Rodewald et al., 2014, Sanchez et al., 2014, Wykes et al., 1999, Thomas et al., 2018 | YES | People on a lower antipsychotic dose were more likely to complete therapy and improve |
|                  | Medication      | 2               | Twamley et al., 2011, Rodewald et al., 2014, Thomas et al., 2018, Vinogradov et al., 2009, Wykes et al., 1999, Wykes et al., 2007, Perades et al., 2016, Sanchez et al., 2014, Gomar et al., 2015 | YES | People on a lower antipsychotic dose were more likely to complete therapy and improve |
|                  | Diagnosis       | 1               | Twamley et al., 2011                                                  | YES                         | People with schizoaffective disorder had greater improvement in subjective quality of life compared to those with schizophrenia |
|                  | Comorbid disorders | 1               | Lewandowski et al., 2011                                             | NO                          | Comorbid substance abuse was associated with worse employment outcomes |
|                  | Duration of illness | 1               | McGurk et al., 2009                                                   | YES                         | Physical comorbid condition (e.g. metabolic deficits) was not associated with employment outcomes |
|                  |                  | 1               | McGurk et al., 2009                                                   | NO                          | People with shorter illness duration had better outcomes |
|                  | Hospitalisation | 1               | Perades 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 (Rudewald 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, Rudewald 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; Rudewald 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 (Rudewald 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 (Ttwamley et al., 2011) suggesting that participants with schi-
zoaffective disorder reported greater CR-associated improvement, in
subjective quality of life, compared with those with a diagnosis of schizophre
nia. 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 voca
ional 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;
Ttwamley 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 mod-
erators 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 methodo-
logical 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 re-
search implications for the field to consider.

4.1. Research implications

While it is well known that positive findings are more likely to be
published (Mlinaré 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. How-
ever, it is likely that negative results were found as often but not reported
contributing to a “skewed view” of the moderators’ landscape. Future re-
search 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 evi-
dence consolidation. This will require large datasets and clear hy-
pothesis-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 po-
tential, motivation, self-esteem, and working alliance. These are hy-
pothesis-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 me-
chanisms 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 persona-
лёisation 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 con-
sider 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 execu-
tive 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 prio-
rities. One, more research-based and more interested in the underlying
mechanism of CR, while the other more clinical and focussed on im-
proving 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 parti-
cipants taking part in CR studies, it may be difficult to generalise the
findings to female and younger or older people. In addition, we in-
cluded 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 as-
sessment. This is a potential source of bias as it may mean that
assessor blinding was not rigorously implemented and that parti-
cipants 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-normalled
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 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.

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