The Key Components of Successful Cognitive Remediation for Schizophrenia: A Systematic Review and Network Meta-Analysis

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Abstract

Cognitive remediation (CR) is an evidence-based treatment targeting cognitive deficits in people with schizophrenia. CR aims at improving real-world functioning. A recent expert consensus established (1) cognitive exercises, (2) administration through a trained therapist, (3) strategy training, and (4) procedures to generalize cognitive improvements as core components for CR treatments to be effective in achieving this goal. This study examined the available literature to determine which combination of these components is associated with the greatest improvements in functional outcomes. The databases PubMed, Cochrane Library, and PsycInfo were searched for randomised control trials that included participants diagnosed with schizophrenia, implemented cognitive exercises, and included a functional outcome measure. A Bayesian random effect network meta-analysis (NMA) was conducted to compare the different combinations of CR components with each other. Study quality was appraised using the Risk of Bias tool 2.0. The NMA included 51 studies (4183 participants) and revealed that combining all four components was the configuration that was associated with the greatest improvement in functional outcome at post-treatment and had the highest likelihood (90.88%) of being the most effective component configuration. Meta-regressions identified administrator training and psychiatric rehabilitation as two moderators of the influence of CR on functional outcome at post-treatment. Our results (1) accentuate the importance of integrating all four components for CR to be effective, (2) the importance to differentiate between isolated cognitive exercises and CR and (3) point at the importance of strategy training while questioning the centrality of cognitive exercises in CR.

The Key Ingredients of Successful Cognitive Remediation for Schizophrenia: A Systematic Review and Network Meta-Analysis

Schizophrenia is a severe mental disorder affecting over 20 million people worldwide (James et al., 2018). It is marked by a broad range of symptoms including hallucinations, delusions, disorganized speech, apathy, and cognitive deficits (Patel et al., 2014). There is considerable heterogeneity in the symptoms patients experience, for a majority, however, they result in impairments in independent living as well as occupational and social functioning (Leung et al., 2008), which are arguably the costliest outcomes of schizophrenia (Harvey & Strassnig, 2012). As such, functional recovery has become an important treatment goal (Kern et al., 2009), with 14% (Jääskeläinen et al., 2013) to 38% (Castelein et al., 2021) of patients regaining sufficient real-world functioning. These statistics are promising as they show the possibility of living a fulfilling life even when diagnosed with schizophrenia.

Cognitive Impairment

Cognitive impairments are a distinct core feature of schizophrenia (Fatouros-Bergman et al., 2014; Heinrichs & Zakzanis, 1998; Kahn & Keefe, 2013; Schaefer et al., 2013), which are experienced by roughly 70-75% of the affected individuals (Heinrichs et al., 2013). Impairments range from basic cognitive functions such as attention and processing speed to higher-order functions such as executive functions, problem-solving, or social cognition (Heinrichs & Zakzanis, 1998; Mihaljeviü-Peleš et al., 2019). Cognitive deficits are consistently associated with real-world functioning (Fett et al., 2011; Fu et al., 2017; Galderisi et al., 2018; Green et al., 2004) and seem to be the strongest predictors of diminished real-world functioning (Bowie et al., 2010; Green & Harvey, 2014). For instance, impoverished working memory might render a person unable to do his/her chores (e.g., shopping) independently. Similarly, a combination of deficiencies in attention, processing speed, and social cognition might negatively impact a person's capability to interact with others and consequently impede the development of meaningful interpersonal connections. As impaired cognition plays a central role in schizophrenia, recovering crucial functioning has been a focus of research over the past decades culminating in the creation of cognitive remediation (Wykes & Spaulding, 2011).

Cognitive Remediation – An Umbrella Term

Cognitive remediation (CR) is inspired by cognitive rehabilitation for individuals with brain injury (Green & Harvey, 2014; Medalia & Choi, 2009) and is defined as "a behavioural training intervention targeting cognitive deficits (attention, memory, executive function, social cognition, or metacognition), using scientific principles of learning, with the ultimate goal of improving functional outcomes. Its effectiveness is enhanced when provided in a context (formal or informal) that provides support and opportunity for extending to everyday functioning" (Cognitive Remediation Expert Working Group, Florence, Italy, April 2010). This broad definition of CR encapsulates different interventions that have been under scientific scrutiny (Barlati et al., 2013). Historically, there used to be a conceptual differentiation between restorative and compensatory approaches, while more modern approaches tend to incorporate components of both approaches. Compensatory approaches utilize strategies, either internal self-management strategies (e.g., self-talk while performing a task or the "chunking" of information) or external strategies such as environmental living aids (e.g., notes in the apartment) to compensate for the cognitive impairments of people with schizophrenia (Allott et al., 2020). Restorative approaches, on the other hand, attempt to directly improve the cognitive deficits through cognitive training, which involves the repeated practice of cognitive exercises (Barlati et al., 2013). In the following, cognitive training always denotes a combination of cognitive exercises used in the context of CR and does not represent a synonym for CR.

Restorative Approaches – Differences in Cognitive Exercises

Restorative approaches can be described along two dimensions: target and modality (Best & Bowie, 2017). The target of a given cognitive exercise describes what cognitive function the exercise attempts to train (e.g., attention or working memory). The modality refers to the context of how cognitive exercises are administered.

Targets of Restorative CR – The Content. Different cognitive exercises utilized in restorative CR approaches target either (1) primary perceptual skills (*bottom-up*), such as auditory perception (Popov et al., 2011), (2) higher-order cognitive functions (*top-down*), e.g., executive functions (Eack et al., 2010), or (3) aim at improving global cognition (*broad and non-targeted).* While the latter non-targeted approaches attempt to improve cognition as a whole, bottom-up and top-down approaches have an underlying theoretical rationale of how they are improving cognition. The rationale of bottom-up approaches is that improvements in the perceptual signal-to-noise ratio lead to improvements in higher-order cognitive functions (Popov et al., 2011). Top-down approaches aim to improve the reduced functioning of frontal cortical neural networks, which is reasoned to result in a positive downward cascade along the perceptual hierarchy (Best & Bowie, 2017). At the time of writing there exists a gap in the evidence comparing the different target approaches directly. Experiments that directly compared top-down and bottom-up approaches seem to indicate that top-down and bottom-up approaches improve different cognitive areas but it is unclear whether the two target approaches do impact functional outcomes differently (Jahshan et al., 2018; Lindenmayer et al., 2017). Additionally, cognitive exercises can differ in a few other characteristics apart from the target such as (1) duration, (2) intensity, and whether (3) the exercises are computerized, (4) adaptive, or (5) personalized.

Modalities of CR – The Context of Administration. While all restorative approaches include cognitive exercises, the overall modality of administration, as examined in the literature, is best approached as a spectrum. On the one end of the spectrum are studies that examine CR offering cognitive exercises in isolation without any additional measures (Fisher, 2009). This sparse approach to CR holds the promise of distributing treatment at a low cost to a wide range of people. In theory, sole internet access could allow people to start the treatment. On the other end are integrated approaches such as *Integrated Psychological Therapy* (Roder et al., 2006), where the cognitive exercises are embedded into a comprehensive psychiatric rehabilitation program. Cognitive exercises are administered by a trained and supervised therapist, who helps to establish goals and maintain motivation. Repeated cognitive exercises are augmented by compensatory strategy training and acquired improvements in the training are gradually applied to more real-world tasks, e.g., vocational training or social skill training. In between the two ends lies a broad variety of contexts in which cognitive exercises are administered. They can differ in (1) who administered the exercises and what training the administrator received, (2) what kind of strategy training was implemented, if any, and (3) the types of additional procedures implemented to facilitate the transmission of cognitive improvements to real-world functioning if any.

Contemporary Evidence

Over the past two decades, meta-analyses have examined the efficacy of CR in general (McGurk et al., 2007; Vita et al., 2021; Wykes et al., 2011). One of the most replicated findings is that CR has a small to moderate effect on improving global cognition (g = 0.28 - 0.45; Grynszpan et al., 2011; Kambeitz-Ilankovic et al., 2019; McGurk et al., 2007; Wykes et al., 2011). Similarly, CR seems to positively affect functional outcomes (d = 0.16 - 0.42; Kambeitz-Ilankovic et al., 2019; McGurk et al., 2007; Wykes et al., 2011) and these improvements appear constant over time (d = 0.37; Wykes et al., 2011). The majority of meta-analytic evidence emphasizes the effectiveness of CR and proponents of CR argue for the integration of the treatment into general health care services (Vita et al., 2021). It is reasoned that CR should be considered the treatment of choice for individuals with schizophrenia, compared to CBT and pharmacological interventions, if the desired outcome is improved functioning (Best & Bowie, 2017).

Heterogeneity in Approaches

Contrary to experts in the field, recent APA guidelines for the treatment of schizophrenia rate the evidence base of CR as low (Keepers et al., 2020). The aforementioned discussed heterogeneity in CR approaches is argued to be a key factor in explaining why there is no broader support for the treatment as (1) the collection of a vast amount of treatments under the same term led to heterogeneity in research outcomes and (2) the precise working mechanisms of the treatment remain unclear (Best & Bowie, 2017). Bowie et al. (2020) posit that CR is often misdefined and equated with isolated computerized cognitive training, the effectiveness of which remains controversial to this day (Harvey et al., 2018).

A Shift in Focus

To address the issue a shift in research focus from efficacy to efficiency in the form of moderator and mediator analyses for treatment characteristics (McGurk et al., 2007; Vita et al., 2021; Wykes et al., 2011) and participant characteristics (Reser et al., 2019; Seccomandi et al., 2020) occurred. While some participant characteristics were suggested as moderators, such as premorbid IQ, baseline cognition and training task progress (Reser et al., 2019), all identified variables lack support through replicated high-quality evidence (Seccomandi et al., 2020). Regarding treatment characteristics, analyses showed that approaches that combined restorative (repeated cognitive exercises) and compensatory components (strategy training) led to larger improvements in functioning (McGurk et al., 2007; Wykes et al., 2011).

Furthermore, exploratory analyses (Van Duin et al., 2019; Vita et al., 2021; Wykes et al., 2011) revealed that studies implementing CR in combination with additional psychiatric rehabilitation produce significantly larger functional improvements than those without. Notably, computerized cognitive exercises alone was not found to increase community functioning (Prikken et al., 2019) and as such the evidence highlights the importance of the right modality for the administration of CR to be effective in influencing real-world functioning.

Consensus: The Core Components of CR

With regard to these findings, a working expert group (Bowie et al., 2020) agreed on four components, which they argue to be essential for CR to improve daily life functioning. These four components are (1) cognitive exercises, (2) facilitation by a trained therapist, (3) procedures to develop problem-solving strategies, and (4) procedures to facilitate transfer to real-world functioning. Improvements in functioning are not only assumed to be enhanced when “provided in a context (formal or informal) that provides support and opportunity”, but the context is portrayed to be an essential ingredient for successful treatment. Furthermore, it was proposed that isolated cognitive exercises without additional psychosocial treatment should not be considered CR altogether (Bowie et al., 2020; Harvey et al., 2018).

The first evidence directly testing the four key components comes from a recent meta-analysis by Vita et al. (2021). The study is an inclusive update on the last broad meta-analysis conducted by Wykes et al. (2011), including 130 studies and 8851 participants. They showed that interventions, defined as cognitive remediation, are effective in improving cognition (d = 0.29) and global functioning (d = 0.22) in people living with schizophrenia. Notably, a decline in the effectiveness of CR was observed over the last 10 years. Possible explanations might be (1) improvements in study methodologies or (2) improvements in control conditions, such as treatment as usual. Here it is argued that the inclusion of over 50 different CR approaches in the analysis led to the dilution of the overall effectiveness of CR. Furthermore, a subgroup analysis indicated that studies, which included all four components, reported significantly improved functional outcomes, even when methodological adequacy was considered (Vita et al., 2021). Similarly, an active therapist, strategy training, and psychiatric rehabilitation were shown to significantly influence functional outcomes separately. However, the inclusion of cognitive exercises did not influence functional outcomes. Vita et al. (2021) argued that this might be the case because cognitive exercises were included in a large proportion of the analyzed interventions.

The major limitation of this evidence is that a subgroup analysis does not present the ideal statistical method to explore the optimal configuration of the four components for CR to be effective, as different configurations of the four components could not be compared directly to each other. While integrating all four components seems to be more effective compared to other approaches in general, it is not clear how the inclusion of all four components compares to other configurations, as they were chunked together. It is conceivable that not all components are necessary and that the inclusion of, for instance, three components might yield similar results to the inclusion of all four components. The inclusion of some component combination might create a synergetic effect, which could lead to possible improvements in cost-effectiveness and applicability of CR. For example, providing cognitive exercises with strategy training administered by a trained therapist would be cheaper compared to integrating the treatment in additional psychiatric rehabilitation.

Research Question

This study attempts to closely examine which configuration of the four components is associated with the largest improvements in functional outcomes in people with schizophrenia. There was a particular focus on approaches to CR that entail some form of cognitive exercises for two reasons. First, a focus on approaches that include cognitive exercises allows ascertaining the necessary conditions for cognitive exercises to influence real-world functioning. Even though cognitive exercises are often considered the heart of CR treatments (Bowie et al., 2020), to the author’s knowledge, this was not directly examined at this point in time. Secondly, a narrowed approach allows the closer examination of differences in implemented cognitive exercises, e.g., the proposed cognitive target. A closer look at cognitive exercises specifically seems important as we argue that the missing influence of cognitive exercises on functional outcome found by Vita et al. (2021) is not due to the lack in the heterogeneity of their sample but rather due to the heterogeneity of cognitive exercises across all included CR approaches. Here it is argued that the broad inclusion criteria, and resulting sample size, in the meta-analysis by Vita et al. (2021) were the optimal conditions to answer the question whether the inclusion of cognitive exercises does influence the effect of CR on functional outcomes.

Objectives

1. What is the ideal configuration of the four proposed core components of CR to improve functional outcomes in people with schizophrenia?
2. Do treatment-characteristics of cognitive remediation and of cognitive exercises, such as cognitive target, treatment duration, intensity, or personalization moderate the influence of cognitive remediation on functional outcome?

Method Section

A protocol was developed, according to the template provided by PROSPERO (National Institute for Health, n.d.), before conducting the systematic review and network meta-analysis, which was not pre-registered in the PROSPERO databank. The review was conducted according to the guidelines provided by the Cochrane Handbook (Higgins et al., 2021) and reported in line with the PRISMA statement (Page et al., 2021), the PRISMA extension for network meta-analyses (Hutton et al., 2015), as well as the JARS-Quant guidelines (Appelbaum et al., 2018).

Eligibility Criteria

The inclusion process focused on published peer-reviewed studies that implemented a randomized control trial (RCT) including a control group as described further below or compared two or more eligible interventions directly. No further restrictions were set for the study design. Eligible studies had to be available in English, German or Dutch. We defined the inclusion criteria according to the PICO guidelines, an abbreviation for population, intervention, comparison, and outcome. The PICO guidelines present a framework for the development of precise research questions (Huang et al., 2006).

Population

Populations were eligible when all included participants were diagnosed with a schizophrenia spectrum disorder (regardless of the diagnostic criteria system). Transdiagnostic populations were excluded.

Intervention

Studies were eligible when they compared any form of cognitive exercises against any kind of control group. Cognitive exercises were defined along the lines of Gates & Valenzuela (2010) and Bowie et al. (2020), as containing (1) the repeated practice of (2) standardized tasks, that (3) have an inherent problem to solve and (4) target specific cognitive domains. Additionally, eligible studies had to mention the intention to improve cognitive functioning. There were no restrictions on the mode of delivery, treatment duration, or intensity. The specifics of the implemented treatment and setting were purposefully left broad to include a wide range of different treatment modalities.

Studies examining compensatory CR approaches (e.g., Cognitive Compensatory Training (Twamley, 2010)) were excluded as they do not implement cognitive exercises as defined previously, but rather attempt to circumvent the cognitive deficits through strategy training or environmental living aids. Similarly, trials that investigated purely social cognition training (SCT) approaches and metacognitive training (MCT) were excluded as the training does not involve the repetitive practice of cognitive exercises.

Control Condition

No exclusion criteria for control conditions were set. Extracted control groups were categorized as either (1) treatment as usual, such as waiting lists, missing details, and only case management or drug treatment, (2) active control treatments, such as multidisciplinary rehabilitative programs or active evidence-based treatments, (e.g., cognitive-behavioral therapy), or (3) active non-specific interventions, when the control was matched with the experimental conditions on different dimensions to reduce possible confounds. For example, this could take the form of teaching control groups spreadsheet skills for the same amount of time as the treatment group practiced cognitive tasks to account for computer exposure or time spend on tasks in general.

Outcome Measures

The primary outcome of interest was changes in global functioning from baseline to post-intervention. Studies were eligible if they included any form of functional outcome measure, which were broadly defined and included measures of real-world functioning, global functioning, occupational functioning, social functioning, and residential functioning. Next to self-rater, caregiver-rater, and investigator-rater scales, direct, as well as indirect measures in the form of functional capacity measures were eligible for inclusion.

Search Strategy

A broad systematic literature search was conducted on PsychInfo, PubMed (MEDLINE), and Cochrane Library by one researcher (T.B.). All articles published and available on the search engines up until the 4th of May 2021 were searched. The search strategy utilized the combination of synonyms for “cognitive exercises”, “schizophrenia”, “psychosis”, “randomized control trial”, and “functional outcome” (for full search strings implemented see Appendix A). An additional search, with “severe mental illness” as a synonym for schizophrenia, was conducted on the 23rd of May 2021. Reference lists of included articles were scanned to identify additional eligible studies.

Data Extraction

The data extraction was performed by one researcher (T.B). Data was collected in an excel spreadsheet and double-checked before the analysis. Authors were not contacted in case of missing information. Information on (1) publication descriptors, (2) study design and inclusion criteria, (3) participant characteristics (i.e. means and standard deviations for age, contact with services (in years), education (in years), premorbid IQ, and symptom severity), (4) intervention characteristics (i.e. information on the cognitive exercises implemented, such as intensity and duration as per protocol, computerization, adjustment of task difficulty, personalization of cognitive exercises, cognitive exercises as part of comprehensive psychiatric rehabilitation, the cognitive target of the cognitive exercises, implementation of strategy training or procedures for generalization, implementation of bridge groups, who administered the exercises, their expertise level, and if the person was trained or supervised) and (5) outcome measures were extracted. Participant characteristics and outcome measures were extracted separately for each treatment arm if accessible. Outcome measures were extracted at baseline, post-treatment, and the latest available follow-up. Raw data in the form of groupwise means and standard deviations/standard errors were prioritized, however, when such measures were not reported, F-values, effect sizes, or p-values were extracted.

Risk of Bias assessment

The Risk of Bias tool 2.0. (Higgins et al., 2019) was utilized as an assessment framework of the risk of bias within each study, covering possible bias (1) due to deviation from intended interventions, (2) due to missing outcome data, (3) in the measurement of outcome, and (4) in the selection of the reported results. The tool contains several signaling questions that were answered on a 5-item scale. Based on the answers, an overall risk-of-bias judgement of either (1) low risk of bias, (2) some concerns, or (3) high risk of bias was calculated.

Data Manipulation

In line with previous publications (Vita et al., 2021; Wykes et al., 2011), global functioning scores were obtained by first calculating the adjusted effect size Hedges' *g* (Higgins et al., 2021) of each individual reported outcome measure and subsequent aggregation of the separate effect sizes into one composite score, in case more than one functional outcome measure was reported. The formulas for the computation of the composition scores can be found in Appendix B).

Network Meta-Analysis

A network meta-analysis (NMA) was conducted to compare the different component configurations to each other. Unlike conventional pairwise meta-analyses, an NMA permits the comparison of more than two interventions at the same time by integrating *direct evidence* (observations obtained from direct treatment comparisons) and *indirect evidence* (observations obtained when two interventions were compared to the same comparator, an "anchor") to estimate the relative effect sizes (mixed effect size estimates) of each included treatment compared to one another (Salanti, 2012). The inclusion of indirect evidence can add precision to existing direct evidence and estimations of effect sizes between treatments that were never directly compared can be computed. Additionally, an NMA allows the computation of ranking scores, which present probabilistic evidence of what might be the most effective treatment (Jansen et al., 2011).

To evaluate to what extent different component configurations influence functional outcome at post-treatment and follow-up compared to control groups and one another, included treatment arms were categorized based on the reported implemented combination of (1) repeated cognitive exercise with (2) a therapist, (3) strategy training, and (4) procedures to generalize cognitive improvement to functioning. A study was considered to utilize a therapist as an administrator if it was specifically reported. Research assistants, on-screen instructions, or missing information on the education of the administrator were categorized as no therapist being present. Similarly, strategy training was assumed to be included when it was reported. Procedures to generalize differ widely between studies and next to the direct reporting of generalization procedures, vocational/ occupational therapy, bridge groups, and additional psychiatric rehabilitation were considered generalization procedures. Bridge groups are discussion groups where acquired improvements in cognition and acquired strategies are related to real-world scenarios and how these new skills could be helping in real-life events (Medalia & Bowie, 2016).

To complement the first network, a second network was created in which the different treatment arms were categorized according to the CR program they implemented (e.g., Integrated Psychological Therapy, RehaCom, Brain Fitness etc.). This allowed the comparison of the extracted CR programs directly to one another and assess their influence on functional outcome.

The Bayesian Approach

A Bayesian approach to NMA was implemented, by utilizing the “gemtc” package (van Valkenhoef et al., 2012) in the statistical software environment R 4.0.3 (R Core Team, 2021). A core idea of the Bayesian approach to statistics is that a prior belief (the *prior distribution*) about a given outcome, such as the effectiveness of a treatment, can be combined with the observed outcome of an experiment (the *likelihood distribution*). The result is an updated belief of what the actual effect of a treatment is (the *posterior distribution*), which is then used for further statistical inferences (Béliveau et al., 2019; Jansen et al., 2011).

Model Compilation

A hierarchical Bayesian random effect model was adopted to account for expected between-study variance (Efthimiou et al., 2016; Shim et al., 2019). An uninformed prior distribution, which assumes that all potential outcomes are equally likely, was chosen to avoid biasing the posterior distribution (Jansen et al., 2011; Shim et al., 2019). The 'gemtc' package utilizes Markov Chain Monte Carlo (MCMC) simulations (using the Just Another Gibbs Sampler (JAGS) (Plummer, 2019)), to estimate the best fit posterior distribution. The optimal convergence of the simulation was adjusted and assessed by (1) checking the MCMC error, (2) deviance information criterion (DIC), and the evaluation of the trace and density plots (Shim et al., 2019). The 'gemtc' package accounts for multi-arm trials (van Valkenhoef et al., 2012).

SUCRA score

Next to the pairwise comparisons, a surface under the cumulative ranking curve (SUCRA) was calculated. The SUCRA score presents a numeric representation of the likelihood of each component configuration to be the best among the included configurations (Mbuagbaw et al., 2017).

Assumptions – Transitivity & Consistency

To conduct an NMA, and for indirect comparisons to be valid, the transitivity and consistency assumptions must hold. The transitivity assumption states that the synthesis of studies is only appropriate when there is sufficient similarity of potential effect modifiers between the nodes as well as within the nodes (Salanti, 2012). Put differently, there should be as little as possible difference between the included trials, and their respective populations, apart from the characteristic researched (Cipriani et al., 2013), in our case treatment characteristics. The a priori investigation of the distributions of possible effect modifiers within and across each node a priori is recommended (Efthimiou et al., 2016; Jansen et al., 2011). The following potential effect modifiers were identified in the literature and their distributions were reviewed by one researcher: (1) years of education, (2) premorbid IQ, (3) symptom severity, (4) age of participants, (5) baseline functioning, (6) and duration of illness

(Radhakrishnan et al., 2016; Seccomandi et al., 2020; Vita et al., 2021; Wykes et al., 2011). As no specific decision rules exist in the literature, a roughly normal distribution of a potential effect modifier was considered sufficient to consider the modifier similar enough across studies.

Consistency is the statistical extension of transitivity and postulates that direct and indirect evidence have to agree (Efthimiou et al., 2016; Salanti, 2012). The consistency assumption was checked by employing the node split method (Dias et al., 2010). Here first each mixed effect size estimate is split into its respective direct and indirect evidence components. Then direct and indirect effect size estimates are computed. Subsequently, statistical comparisons determine whether there is a significant difference between the two estimates. If significant differences exist, the consistency assumption does not hold.

Meta-Regression

A meta-regression was performed, utilizing the ‘metafor’ package (Viechtbauer, 2010). The influence of the four components separately was examined, as well as specific characteristics of cognitive exercises. Regarding the four components the following treatment characteristics were examined: the inclusion of strategy training, the implementation of generalization procedures, the combination of CR and psychiatric rehabilitation, the implementation of bridge groups, and whether the administrator of the cognitive exercises was (a) a therapist, (b) trained and/or (c) supervised.

With respect to the second research question the influence of the following treatment-characteristics of cognitive remediation and cognitive exercises on functional outcomes were explored: the target of the implemented cognitive exercises (categorized as described by Best & Bowie (2017) into top-down, bottom-up and non-targeted)**,** the treatment duration, the amount of CR sessions, the intensity measured in sessions per week, the administration in a group or not, computerization, adjustment of task difficulty, and personalization.

Sensitivity Analyses

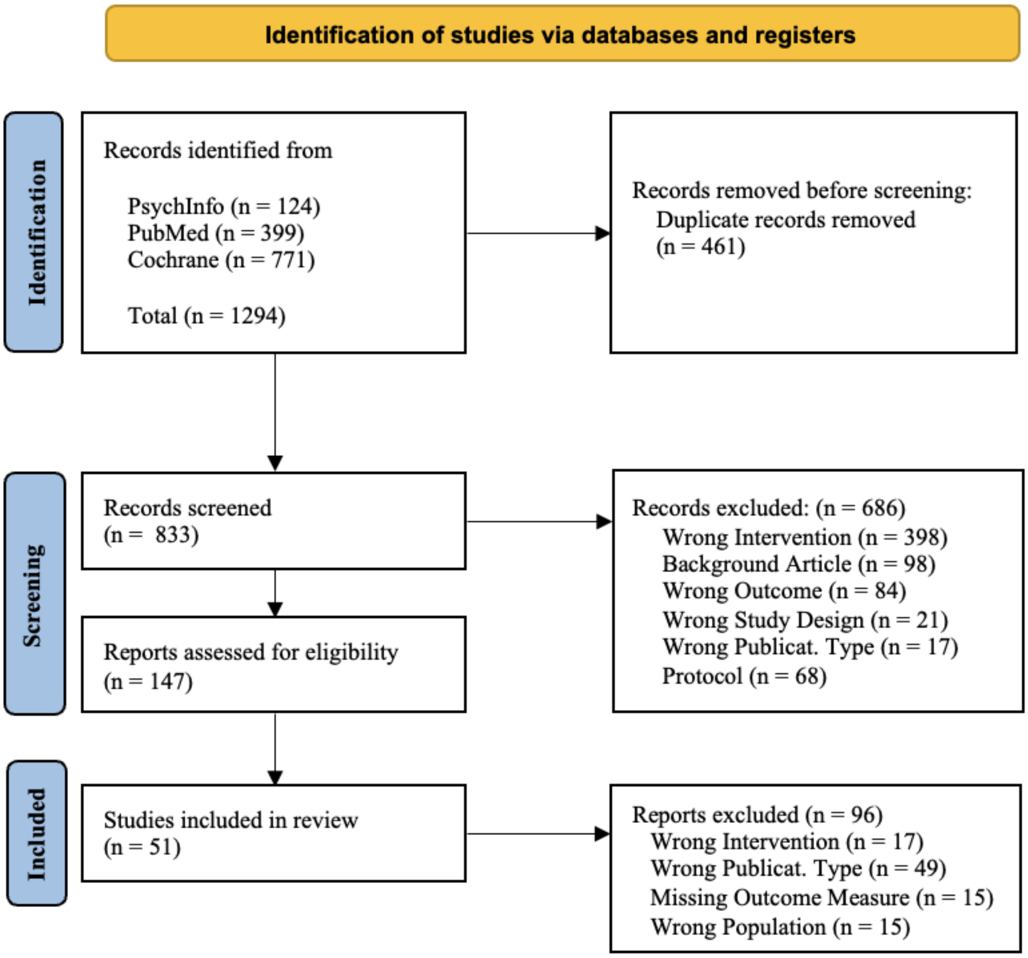
The potential effects of different steps in the analysis on the outcome of this NMA were examined using sensitivity analyses. First, if some extracted studies were excluded from the final analysis, the analysis was rerun with the inclusion of all extracted studies. Secondly, another analysis was run in which all control groups were assigned to one node instead of being split into three different control groups. Third, a series of analyses were run to control the exclusion of several treatment arms from the NMA due to limitations of the 'gemtc' package, which prevents the comparisons of nodes to themselves. Therefore, when a three-arm study compared two treatments that were assigned to the same node (e.g., CT) one treatment arm had to be excluded from the analysis. Those arms were excluded randomly, and different combinations were used to check for the influence of these decisions. Lastly, the influence of the risk of bias assessment score on the study outcome was examined employing a meta-regression.

Result Section

A total of 1294 articles were identified (first search: 1235, second search: 59) of which the title and abstract of 833 articles were scanned after duplicate deletion. 147 studies were eligible and exported for the full text screening. The data of 51 articles, which included 4183 participants and 57 treatment arms, was extracted (Figure 1). Lastly, the reference lists of included studies were searched. An overview of study characteristics can be found in Appendix C and the summary of sample characteristics in Table 1.

Figure 1

Prisma Flow Chart



Note. The Prisma flow chart shows (1) how many records were identified initially and (2) how many identifications were excluded and for what reason at which step in the data extraction process.

Table 1

Average of Included Treatment-Arms

Characteristics	Mean	Range	Number of treatment arms [a]	Proportion of studies
Participant characteristics				
Age (years)	38.4	16.8 - 51.3	57	100
Duration of illness (years)	14.6	1.6 - 29.7	34	59.6
Education (years)	11.9	9.0 - 15.1	46	80.7
Percentage of women	33	7 - 75	53	92.9
Treatment characteristics				
Administration by a therapist			44	77.2
Therapist received training			28	49.12
Therapist received supervision			13	22.8
Strategy training			37	64.91
Generalization procedures			38	66.7
Number of sessions	36.9	10 - 130	43	75.4
Duration of training in weeks	16.86	3 - 104	57	100
Type of cognitive exercises:				
Non-targeted			36	63.2
Top-down			12	21.1
Bottom-up			7	12.3
Delivery format:				
Computerized			39	68.4
Personalized			9	15.8
Group setting			19	33.3

Note. Treatment and participant characteristics of all eligible studies reported on treatment-arm level

[a] Number of treatment arms that reported a given characteristic

Assumptions and outliers

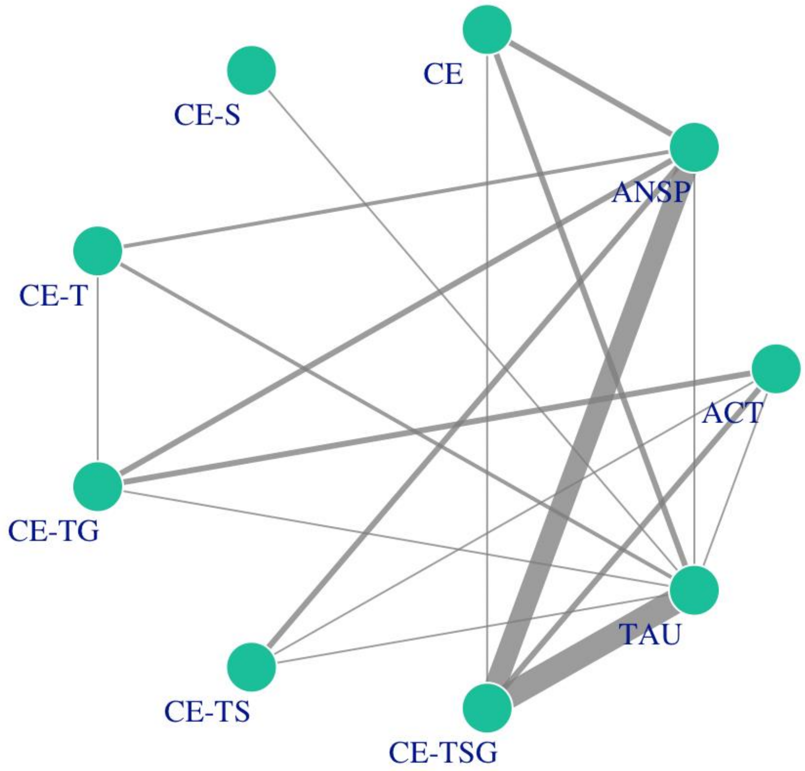
The transitivity assumption was assumed to hold after reviewing the distributions of possible effect modifiers across and within the network nodes. The node split method (Appendix D) pointed at the existence of inconsistency in the pairwise comparison of cognitive exercises administered by a therapist and added strategy training (CE-TS) and active control. The consistency assumption hold for all other pairwise comparisons. One study (Aloi et al., 2018) was excluded from the meta-analysis as it was unclear if the standard deviation or the standard error was reported and as a result, the effect size could not be calculated.

Network Geometry

The main network consisted of 46 two-arm and five three-arm studies. With 29 arms the most common configuration of treatment components was cognitive exercises administered by a therapist, with added strategy training and generalization procedures (CE-TSG). Cognitive exercises alone (CE) were present in six arms, cognitive exercises with a therapist (CE-T) in five arms, cognitive exercises with a therapist and added strategy training (CE-TS) in five arms, cognitive exercises with a therapist and generalization procedures (CE-TG) in seven arms and cognitive exercises with strategy training alone (CE-S) in one arm (Figure 2). An active control treatment (ACT) was used in seven arms, an active non-specified control (ANSP) in 22 arms, and treatment as usual (TAU) in 21 arms (A short description of the control group of each study can be found in Appendix C).

Figure 2

Network Plot: Component Configurations



Note. Nodes present the different component configurations. Lines between the nodes are called *bridges* and indicate existing direct comparisons between the nodes they connect. The width of bridges increases with the number of direct comparisons. *CE:* Cognitive exercises only, *CE-S:* Cognitive exercises + strategy training, *CE-T:* Cognitive exercises + therapist, CE-TG*:* Cognitive exercises + therapist + generalization procedures, *CE-TS*: Cognitive exercises + therapist + strategy training, *CE-TSG:* Cognitive exercises + therapist, + strategy training + generalization procedures, *TAU:* Treatment as usual, *ACT*: Active control treatments, *ANSP:* Active non-specified control

Post-Treatment Functional Outcome

Cognitive exercises administered by a therapist with added strategy training and generalization procedures (CE-TSG) was the only component configuration that showed significantly superior effect sizes compared to TAU (*g* = 0.35, 95% CrI [0.19, 0.51]), to ANSP (*g* = 0.44, 95% CrI [0.27 – 0.61]), and to ACT (*g* = 0.37, 95% CrI [0.10 – 0.65]) at post-treatment (Figure 3). Furthermore, CE-TSG was the only component configuration that was significantly better than another component configuration, namely cognitive exercises administered by a therapist and added generalization procedures (CE-TG) (*g* = 0.29, 95% CrI [0.01 – 0.58]). Otherwise, only cognitive exercises administered by a therapist and added strategy training (CE-TS) showed significant improvements in functional outcomes compared to ANSP (*g* = 0.36, 95% CrI [0.05 – 0.67]) at post-treatment. Cognitive exercises alone (CE), cognitive exercises with strategy training (CE-S), cognitive exercises administered by a therapist (CE-T), cognitive exercises administered by a therapist and added generalization procedures (CE-TG) were not found to influence functional outcomes at post-treatment significantly compared to TAU, ACT, or ANSP. Figure 4 presents a forest plot that shows the different pairwise comparisons of the component configurations against treatment as usual at post-treatment.

Figure 3

League Table – Pairwise Comparisons

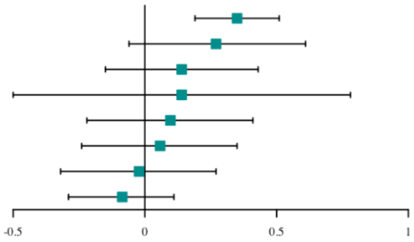
CE-TSG								
0.08 (-0.25, 0.40)	**CE-TS**							
0.21 (-0.08, 0.50)	0.13 (-0.27, 0.54)	**CE**						
0.21 (-0.46, 0.87)	0.13 (-0.59, 0.86)	0.001 (-0.71, 0.71)	**CE-S**					
0.25 (-0.06, 0.57)	0.18 (-0.24, 0.60)	0.04 (-0.36, 0.44)	0.04 (-0.67, 0.76)	**CE-T**				
0.29 (0.01, 0.58)	0.22 (-0.16, 0.60)	0.08 (-0.29, 0.46)	0.08 (-0.62, 0.80)	0.04 (-0.32, 0.39)	**CE-TG**			
0.35 (0.19, 0.51)	0.27 (-0.06, 0.60)	0.14 (-0.15, 0.43)	0.14 (-0.51, 0.79)	0.10 (-0.22, 0.41)	0.06 (-0.24, 0.35)	**TAU**		
0.37 (0.10, 0.65)	0.29 (-0.07, 0.67)	0.16 (-0.22, 0.54)	0.16 (-0.54, 0.87)	0.12 (-0.27, 0.51)	0.08 (-0.22, 0.38)	0.02 (-0.27, 0.31)	**ACT**	
0.44 (0.27, 0.61)	**0.36 (0.05, 0.67)**	0.23 (-0.06, 0.51)	0.23 (-0.45, 0.91)	0.18 (-0.13, 0.49)	0.14 (-0.13, 0.41)	0.09 (-0.12, 0.29)	0.07 (-0.23, 0.35)	**ANSP**

Note. The figure shows all the relative mixed effect sizes (Hedge's *g*) and 95% credible intervals (CrI) for each pairwise comparison. Bold values represent significant pairwise comparisons and indicate favorable outcomes for the column-defining component configuration. Configurations are ordered according to their SUCRA score in descending order from left to right. *CE:* Cognitive exercises only, *CE-S:* Cognitive exercises + strategy training, *CE-T:* Cognitive exercises + therapist, CE-TG*:* Cognitive exercises + therapist + generalization procedures, *CE-TS*: Cognitive exercises + therapist + strategy training, *CE-TSG:* Cognitive exercises + therapist, + strategy training + generalization procedures, *TAU:* Treatment as usual, *ACT*: Active control treatments, *ANSP:* Active non-specified control

Figure 4

Forest Plot – Component Configurations compared to Treatment as usual

Network Node	Number of arms	Mean Difference (95% CrI)
CE-TSG	29	0.35 (0.19, 0.51)
CE-TS	5	0.27 (-0.06, 0.61)
CE	6	0.14 (-0.15, 0.43)
CE-S	1	0.14 (-0.5, 0.78)
CE-T	5	0.097 (-0.22, 0.41)
CE-TG	7	0.058 (-0.24, 0.35)
ACT	7	-0.022 (-0.32, 0.27)
ANSP	22	-0.086 (-0.29, 0.11)



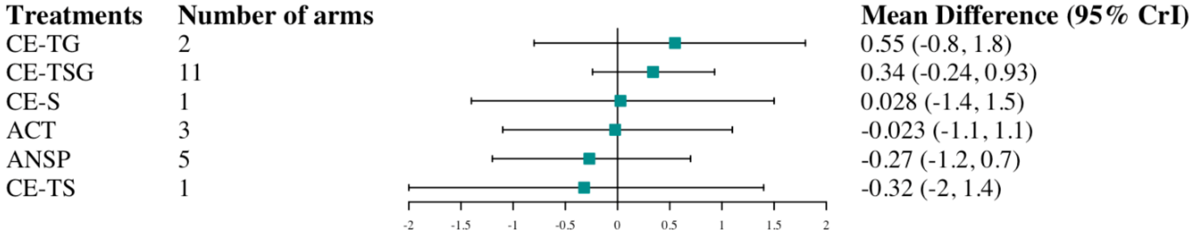
Note. A forest plot presenting the different pairwise comparisons of the different component configurations against treatment as usual at post-treatment. *CE:* Cognitive exercises only, *CE-S:* Cognitive exercises + strategy training, *CE-T:* Cognitive exercises + therapist, CE-TG*:* Cognitive exercises + therapist + generalization procedures, *CE-TS*: Cognitive exercises + therapist + strategy training, *CE-TSG:* Cognitive exercises + therapist, + strategy training + generalization procedures, *TAU:* Treatment as usual, *ACT*: Active control treatments, *ANSP:* Active non-specified control

Follow-Up Functional Outcome

A second NMA inspected the impact of different component configurations on functional outcome at follow-up. 15 out of the included studies reported functional outcome at an average follow-up time of 40.37 weeks (range: 5 to 104) and 16 treatment arms were included in this follow-up NMA. No differences between any component configuration compared to TAU, ANSP, or ACT at follow-up were found. Figure 5 shows the results of the pairwise comparisons of the component configurations against treatment as usual at follow-up.

Figure 5

Forest Plot – Component Configurations compared to Treatment as Usual at Follow-Up



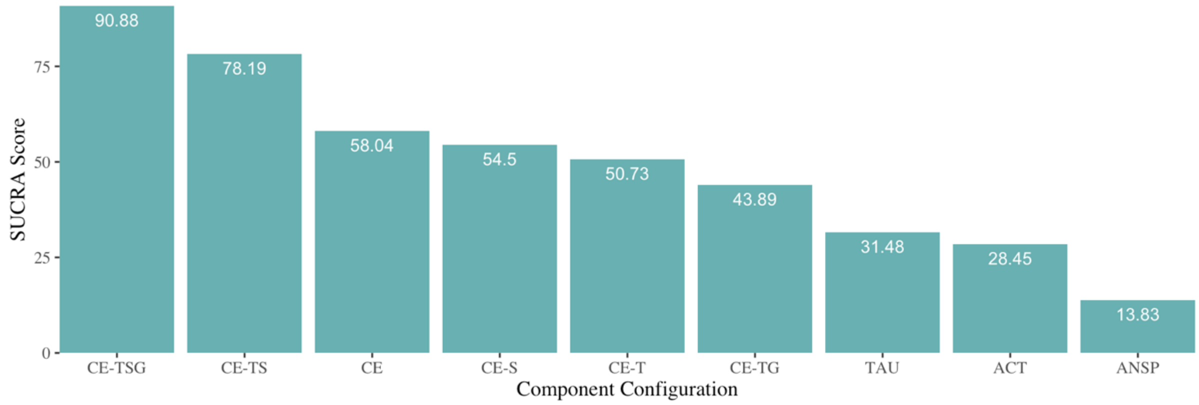
Note. A forest plot presenting the pairwise comparisons of the component configurations against treatment as usual at follow-up. *CE-S:* Cognitive exercises + strategy training, CE-TG*:* Cognitive exercises + therapist + generalization procedures, *CE-TS*: Cognitive exercises + therapist + strategy training, *CE-TSG:* Cognitive exercises + therapist, + strategy training + generalization procedures, *TAU:* Treatment as usual, *ACT*: Active control treatments, *ANSP:* Active non-specified control

SUCRA Score

The SUCRA scores suggested that the inclusion of all four components, CE-TSG, had the highest likelihood of being the best component configuration for improving functional outcome in patients with schizophrenia at post-treatment (SUCRA = 90.88%), followed by CE-TS (SUCRA = 78.19%), CE (SUCRA = 58.04%), CE-S (SUCRA = 54.5%), CE-T (SUCRA = 50.73%), CE-TG (SUCRA = 43.89%) (Figure 6).

Figure 6

SUCRA plot.



Note. The surface under the cumulative ranking curve (SUCRA) presents a numeric representation of the likelihood of each component configuration to be the best among the included. *CE:* Cognitive exercises only, *CE-S:* Cognitive exercises + strategy training, *CE-T:* Cognitive exercises + therapist, CE-TG*:* Cognitive exercises + therapist + generalization procedures, *CE-TS*: Cognitive exercises + therapist + strategy training, *CE-TSG:* Cognitive exercises + therapist, + strategy training + generalization procedures, *TAU:* Treatment as usual, *ACT*: Active control treatments, *ANSP:* Active non-specified control

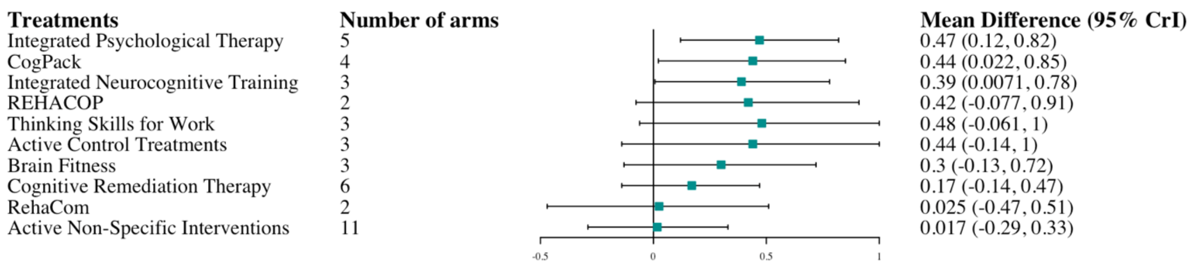
Additional Network Meta-Analyses

A third NMA was conducted to compare all CR programs that were used in more than two studies. The included CR programs were Cognitive Remediation Therapy (CRT) (k = 6), Integrated Psychological Therapy (IPT) (k = 5), CogPack (k = 4), Brain Fitness (k = 3), Integrated Neurocognitive Training (INT) (k = 3), Thinking Skills for Work (k = 3), 2 REHACOP (k = 2), and RehaCom (k = 2). Descriptions of the different CR programs can be found in Appendix E.

IPT (*g* = 0.47, 95% CrI [0.12, 0.82]), CogPack (*g* = 0.44, 95% CrI [0.02, 0.85]), and INT (*g* = 0.39 95% CrI [0.01, 0.78]) were found to significantly improve functional outcomes at post-treatment compared to treatment as usual. These results hold for IPT (*g* = 0.45, 95% CrI [0.13, 0.77]) and CogPack (*g* = 0.42, 95% CrI [0.07, 0.77]) when being compared to active non-specified control groups. No other treatment was significantly better than any of the control conditions. Figure 7 presents the results of the pairwise comparisons of the different CR programs against treatment as usual at post-treatment.

Figure 7

Forest Plot – CR programs comparted to treatment as usual



Note. A forest plot showing the pairwise comparisons of included CR programs and treatment as usual at post-treatment.

Sensitivity Analyses

Sensitivity analyses found that the results remained relatively stable over all the sensitivity analyses. CE-TSG remained the component configuration that was associated with the largest changes in functional outcome across all analyses. The inclusion of the outlier accentuated the results at post-treatment. CE-TSG produced significantly larger outcomes compared to TAU (g = 0.56, 95% CrI [0.26, 0.86]) and ANSP (g = 0.49, 95% CrI [0.16, 0.82]). In the main network, four arms had to be removed randomly. Different configurations of removal showed that this exclusion did not influence the results. Network inconsistency only existed in the network in which one study was excluded. Sensitivity analyses did not replicate the inconsistency of the main network.

Meta-Regression

Multiple meta-regressions were conducted to examine the influence of different treatment-characteristics on functional outcome at post-treatment. The results of separate meta-regressions revealed that the addition of strategy training (β = 0.23, 95% CI [0.04, 0.41], p = 0.018), psychiatric rehabilitation (β = 0.22, 95% CI [0.04, 0.39], p = 0.015) and training of the therapist (β = 0.23, 95% CI [0.01, 0.45], p = 0.038), were the only separate regressors that statistically significantly influenced functional outcome at post treatment. When all moderators were added to a single meta-regression model, none of the included moderators remained significant. Generalization procedures, the implementation of bridge groups, the inclusion of a therapist or not, as well as supervision of the therapist did not have a significant effect on functional outcome at post-treatment.

Regarding the second research question, none of the inspected moderators were significant. Neither the target of the implemented cognitive exercises, personalization of the cognitive exercises, if cognitive exercises were adaptive, treatment duration, treatment intensity, number of overall sessions, and administration in a group were significant.

Risk of Bias Assessment

The risk of bias assessment showed that 25 of the included studies had a low risk of bias, 17 some concerns and 15 high risks of bias. The randomization process was the only domain that showed unproportionally often some concerns because it was seldom reported if participants were blind to allocation. A meta-regression showed that risk of bias did not moderate functional outcomes significantly ($\beta = -0.14$, 95% CI [-0.31, 0.04], $p = 0.136$).

Discussion

The first aim of this study was to examine what combination of the four components identified by Bowie et al. (2020) presents the optimal combination for cognitive remediation to improve real-world functioning in people with schizophrenia. The results of the current analysis indicated that cognitive remediation improved functional outcomes most effectively at post-treatment if (1) cognitive exercises are (2) administered by a therapist, (3) combined with strategy training, and (4) with generalization procedures. The second aim was to investigate if treatment-related characteristics of cognitive remediation moderate the impact of cognitive remediation treatment on functional outcomes. A specific focus lied on the characteristics of the implemented cognitive exercises. While no facet of cognitive remediation treatment or cognitive exercises moderated the impact of cognitive remediation treatment on functional outcome, the combination of cognitive remediation treatment with psychiatric rehabilitation as a procedure to generalize, the training of the administrator and the addition of strategy training did.

The Importance of Integration and Differentiation

The results of our main NMA highlight (1) the importance of integrating all four components and (2) point at the necessity to differentiate between different interventions coined as cognitive remediation. By utilizing a novel statistical approach, namely a network meta-analysis, we found that integrating all four components (CE-TSG) was the only component configuration that showed significant improvements compared to all three control groups and was over 90% likely to be the best configuration of the four components, which accentuates earlier findings by Vita et al. (2021). This finding presents an entry in a line of meta-analyses that showed that cognitive remediation treatment is associated with improved functional outcomes (McGurk et al., 2007; Van Duin et al., 2019; Vita et al., 2021; Wykes et al., 2011). Further, it adds to the current body of research by demonstrating that cognitive remediation programs that include cognitive exercises are effective in improving functional outcomes (d = 0.35) on par with social cognition training (d = 0.41 - 0.82*;* Nijman et al., 2020) or purely compensatory approaches to CR (g = 0.46; Allott et al., 2020) if cognitive exercises are administered under the right circumstances. The importance of integrating all four components is further accentuated by our alternative network, which compared different cognitive remediation programs directly. The alternative NMA indicated that one cognitive remediation program that integrated all four components inherently, namely *Integrated Psychological Therapy* (IPT), improved functional outcomes significantly more compared to treatment as usual and active non-specific conditions. Another cognitive remediation program, namely *Integrated Neurocognitive Training* (INT), which evolved out of IPT, was also found to improve functional outcomes more compared to treatment as usual. IPT is a group-based cognitive remediation approach that combines cognitive exercises and social cognitive training with psychosocial rehabilitation (Roder et al., 2006). IPT is divided into 5 subprograms that are administered in sequential order. The subprograms are (1) cognitive differentiation (neurocognition), (2) social perception, (3) verbal communication, (4) social skills, and (5) interpersonal problem-solving. The earlier subprograms address basic cognitive functions (e.g., executive functioning) in group-based problem-solving exercises, along which alternative strategies are taught. Inherently, IPT presents a gradual approach that is including all four components and helps participants to generalize cognitive improvements and acquired strategies to real-world situations and skills.

Contrary to integrated approaches, sole cognitive exercises without other additional components did not improve functional outcomes significantly compared to any of the control groups. In line with Bowie et al. (2020), we argue that isolated cognitive exercises and cognitive remediation programs that include all four components should be regarded as separate interventions as the former do not influence functional outcomes at post-treatment. Additionally, it is suggested to update the definition of cognitive remediation to clearly implicate certain components as necessary for cognitive remediation programs to reliably improve functional outcomes. Contrary to the consensus by Bowie et al. (2020), the largest meta-analysis on cognitive remediation by Vita et al. (2021) included isolated cognitive exercises, even though these are not deemed cognitive remediation. Here it is concluded that there exists a dichotomy in the current state of knowledge on what is cognitive remediation and its official definition, which is necessary to be resolved for cognitive remediation to find its way into the health care services and to be adopted by clinicians.

The Four Components – A Closer Look

While out NMA showed the importance of the presence of all four components in cognitive remediation treatment, the conducted meta-regression implicated certain characteristics of the four components that moderated the influence of cognitive remediation treatments on functional outcomes, which are addressed in the following.

The meta-regression revealed that not all generalization procedures have an impact on functional outcomes but only psychiatric rehabilitation. Similar to Vita et al. (2021), transfer procedures overall were not moderating the effectiveness of cognitive remediation in improving functional outcomes, while psychiatric rehabilitation was identified as a moderator. The latter finding was frequently reported in earlier publications (McGurk et al., 2007; Van Duin et al., 2019; Vita et al., 2021; Wykes et al., 2011). One implication could be that the effectiveness of generalization procedures is increasing when the procedures are less conceptual and closer to real-world situations. Bridge groups, whose implementation did not moderate the effectiveness of CR in improving functional outcomes, are an example of a more conceptual approach. Here, study participants discuss and generate potential activities in groups to connect their cognitive improvements and learned strategies to daily life (Medalia & Bowie, 2016). An example of a generalization procedure that is closer to real-world scenarios is presented by Iwata et al. (2017), who administered their CR program in the context of comprehensive psychiatric rehabilitation. All study participants received a variety of additional treatment services such as social skill training, individual work therapy, recreational group activities or community meetings for up to 30 hours per week. Participants had ample opportunities to practice their newly acquired cognitive skills and strategies in a more environmentally valid fashion.

Similarly, administration by a therapist itself did not influence functional outcome, however, reported training of the administrator influenced functional outcome positively. These findings glue two incoherent reports about the importance of a therapist in the literature together (Kambeitz-Ilankovic et al., 2019; Vita et al., 2021). On the one hand, Kambeitz-Ilankovic et al. (2019) reported that the sole inclusion of supportive guidance did not influence functional outcome, while Vita et al. (2021) reported that the inclusion of a *trained* therapist significantly impacted functional outcome. Our analysis replicated both findings and as such accentuates the importance of administrator training. A possible explanation poses that training enables an administrator to identify cognitive impairments (e.g., memory deficits), and link them to problems experienced in daily life such as (1) forgetting the places of items around the house, (2) memorizing one's phone number, (3) what groceries one wanted to buy (4) or remembering a person's name. Furthermore, trained administrators can then make informed decisions on the right strategies to train, such as (1) keeping objects in a specific place, (2) chunking, (3) writing a list, or (4) repeating the name a few times internally. Training might also facilitate the development of a good working alliance which was found to influence social functioning significantly (Melau et al., 2015).

Lastly, our results accentuate the superiority of cognitive remediation interventions that integrate strategy training compared to approaches that do not, similar to earlier publications (McGurk et al., 2007; Van Duin et al., 2019; Vita et al., 2021). Next to the inclusion of all four components, only the combination of (1) cognitive exercises with (2) a therapist and (3) strategy training (CE-TS) was significantly better than treatment as usual and showed a trend towards significance compared to the other control conditions. Furthermore, interventions that included all four components (CE-TSG) were also significantly better than interventions that included all components but strategy training. While the importance of strategy training is widely recognized (Bowie et al., 2020; McGurk et al., 2007; Van Duin et al., 2019; Vita et al., 2021), the exact reasons for how it is influencing the relation between cognitive impairments and functional outcomes remains an open question. One explanation is given by Cella et al. (2015) who proposed that strategy training and increasing individuals awareness of their difficulties might be increasing metacognitive capacities, such as metacognitive knowledge. Furthermore, it is reasoned that helping people to become aware of deficiencies in their use of strategies and facilitating the acquisition of new strategies might help them to cope with problems they encounter in daily life as people with schizophrenia are often cognitively very rigid and possess only a small strategy skillset (Cella et al., 2015).

Characteristics of Cognitive Exercises

Regarding our second research question, no facet of cognitive remediation, or implemented cognitive exercises, could be identified that influenced treatment effectiveness.

Neither the number of overall cognitive remediation sessions, the overall duration of treatment, treatment intensity, group administration, computerization, adjustment of task difficulty, or personalization affected functional outcomes. Furthermore, there seemed to be no difference in the efficiency of different cognitive targets, such as bottom-up, top-down, and non-targeted. This finding is in line with evidence that showed no difference in the effectiveness between top-down and bottom-up approaches (Jahshan et al., 2018) and it aligns with the notion that improvements of general cognition are independent of the area trained, suggesting generalizations of treatment effects to other cognitive areas (Pfammatter et al., 2006). The current study presents the first direct meta-analytic evidence for comparing different theoretical rationales to cognitive exercises. However, Best & Bowie (2017) argued that it is challenging to discern the effectiveness of bottom-up versus top-down as both approaches are often confounded by study designs and the implementation of different components. This became apparent throughout the data extraction. Similarly, it was difficult to distinguish which theoretical rationale underlies which CR program and as such the results should be considered with caution. Similarly, earlier publications (Vita et al., 2021; Wykes et al., 2011) identified none but one characteristic of cognitive exercises as a moderator variable. While Vita et al. (2021) found an effect of duration of treatment after utilizing a large sample, this was neither replicated here nor earlier (Wykes et al., 2011). Given that the current sample was smaller, we might have lacked the statistical power to detect the small effect.

The Role of Cognitive Exercises

The missing identification of any moderator variable among the extracted treatment-characteristics of cognitive exercises was surprising, as it was assumed that the missing influence of cognitive exercises on the impact of cognitive remediation on functional outcomes (Vita et al., 2021) could be explained by the implemented cognitive target or personalization of exercises. As this is not the case the question arises what the role of cognitive exercises in cognitive remediation is. As the current review included studies that used cognitive exercises only, we could not compare component configurations that excluded cognitive exercises with those that integrated them. Therefore, the question of whether cognitive exercises contribute to the effectiveness of cognitive remediation can only be addressed indirectly. However, our results add another perspective and weight to a body of cumulating evidence which is questioning the exact role of cognitive exercises in the context of cognitive remediation (Allott et al., 2020; Cella et al., 2015; Vita et al., 2021). The historical rationale of restorative approaches is that improvements in cognition help the acquisition of real-world functioning or directly influence it. The finding that cognitive impairments can lead to impairments in social functioning (Green et al., 2004) seems often to be taken as an indication that the reverse might also be true. Broad cognitive deficits seem to predict around 60% of the real-world functioning variance (Fett et al., 2011) and ample evidence shows that CR in the right circumstances results in improvements in domains of real-world functioning, as we demonstrated in this study. Causation is implied, which manifests itself in the continuous attempt to show that isolated cognitive exercises improve real-world outcomes without any extra additions. However, most evidence is correlational in nature and is not evidence of causality (Penadés et al., 2010).

There exists evidence that the association between cognition and functioning is multifaceted and bilateral in nature. For instance, Stiekema et al. (2020) showed that cognitive adaptation training (CAT), which is not designed to improve cognitive functioning, improved executive functioning and visual attention next to improvements in daily functioning. Furthermore, while some compensatory approaches utilize repeated cognitive exercises, this is not the case for all of them and Allott et al. (2020) showed that even these purely compensatory approaches are effective in improving certain domains of functioning.

This indicates that functioning is also improved when repeated cognitive exercises are not present. Still, it should be noted that approaches combining cognitive exercises and strategy approaches were found to be superior compared to strategy approaches alone (Van Duin et al., 2019).

The fact that there are improvements in cognition and functioning without cognitive exercises involved, and that there is an inconsistency in the literature regarding moderators associated with cognitive exercises, challenges the centrality of cognitive exercises as the key ingredient of cognitive remediation. At the same time, the evidence seems to strengthen the importance of strategy training. This notion is in line with several findings (Galderisi et al., 2018; Ho et al., 2013) that established the moderating role of functional capacity between real-world functioning and cognition. One suggestion is that cognitive exercises are not a necessary condition for improvements in functional outcomes to occur, but they might rather present a first learning environment for the acquisition of strategies that are then gradually trained and shifted to real-world situations. The gradual nature of cognitive remediation would also be in line with the effectiveness of psychiatric rehabilitation compared to other generalization measurements (e.g., bridge groups) as they often closely resemble real-world scenarios.

Strength and Limitations

The utilization of a network meta-analysis presents a novel technique in data aggregation and allowed the inclusion of indirect evidence in the inferential process. Furthermore, it enabled the relative comparison of different configurations of the assumed active ingredients of cognitive remediation. There can be reasonable confidence in the findings as this study included a large sample. The narrower inclusion criteria allowed more specific inferences and reduced potential confounding factors. The risk of bias did not influence the results significantly.

One limitation of this study is that only one person extracted and classified the data, while with respect to the PRISMA guidelines two raters would have been optimal to achieve ideal confidence in the results. Furthermore, while confidence in the results is high due to a large sample size, caution should be taken when interpreting data as some comparisons contained less direct evidence than others. This is represented in the higher variance in evidence of many pairwise comparisons. Similarly, the inconsistency in the main network is attributed to one node only containing one treatment arm. While it is possible for nodes to contain only one treatment arm, inconsistency in the network mandates caution when evaluating the research results. Another limitation is the computation of a composite score as the outcome, as self-rater and observer rater measures were eligible as functional outcome measures. However, only objective measures of real-world functioning, such as observer rater measures were found to correlate with real-world functioning, which is not the case for self-rater measures of functioning (Fiszdon et al., 2016). Similarly, to the National Institute of Mental Health – Measurement and Treatment Research to Improve Cognition in Schizophrenia initiatives (NIMH-MATRICS) consensus cognitive battery for measuring cognition in people with schizophrenia, there should be a consensus on how real-world functioning is assessed. Lastly, our evidence is limited by what was reported in the included articles. Studies were classified into different nodes according to which components were reported. Therefore, some studies might have been allocated to nodes they do not belong to as some components might have not been reported. A solution for this issue would be to contact the researchers of a given study to obtain missing data. However, this was not possible within the time frame of this master thesis.

Future Research

The current evidence informs future research in a variety of ways. The evidence shows the necessity to combine cognitive exercises with the other three components to improve functional outcomes. As such future research should allocate more resources to investigate integrated approaches. Rather than focusing on isolated cognitive exercises, nuances of the different components should be closely examined. For instance, questions such as “what are successful generalization procedures” or “how much training and trainer expertise is necessary for an administrator to administer CR effectively” should be considered.

Lastly, there is a lack of conclusive evidence for whether cognitive exercises are improving the effectiveness of CR. A larger network meta-analysis that compares CR programs that include cognitive exercises and those without, such as some social cognition training or compensatory approaches (e.g., CAT and CCT), could shed light on whether cognitive exercises present a necessary or sufficient condition for the effectiveness of CR.

Conclusion

This current study accentuates that cognitive remediation is a viable option in the treatment of schizophrenia and represents an entry in a line of reviews and meta-analyses that revealed the effectiveness of different approaches to cognitive remediation. Our results indicate that cognitive remediation programs that utilize cognitive exercises are effective in improving functional outcomes when administered by a trained therapist, are combined with strategy training and procedures to generalize cognitive improvements to real-world functioning. Isolated cognitive exercises were not found to influence functional outcomes and it is suggested to differentiate between cognitive remediation and isolated cognitive exercises. We could not identify any characteristic of cognitive exercises that moderate their effectiveness in improving functional outcomes. However, our results accentuated the importance of integrating strategy training in cognitive remediation treatments and point at the necessity to closely examine what the exact role of cognitive exercises in cognitive remediation is.

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Appendix A

Full search string

The following is the complete search string used to search the databases PubMed, PsychInfo, and Cochrane.

Search 1: Schizophrenia/ Psychosis

PubMed

((“Cognitive”[tiab] OR “Cognition”[tiab] OR “Neurocognitive”[tiab] OR “Memory”[tiab] OR “Attention”[tiab] OR “Verbal Learning”[tiab] OR “Visual Learning”[tiab] OR “Vigilance”[tiab] OR “Reasoning”[tiab] OR “Problem Solving”[tiab] OR “Speed of Processing”[tiab] OR “Brain”[tiab] OR “Executive Function”[tiab] OR “Executive Functioning”[tiab])

AND

(“Training”[tiab] OR “Intervention”[tiab] OR “Remediation”[tiab] OR “Rehabilitation”[tiab] OR “Enhancement”[tiab] OR “Retraining”[tiab]))

AND

(“randomly” OR “randomized” OR “randomised” OR “RCT” OR “Clinical Trial”)

AND

(“Schizophrenia”[tiab] OR “Psychosis”[tiab])

AND

(“functional outcome” OR “daily functioning” OR “daily function” OR “everyday functioning” OR “everyday function“ OR “real-world functioning” OR “Real-world function” OR “activities of daily life” OR “activities of daily living” OR “ADL” OR “IADL” OR “occupational functioning” OR “occupational function” OR “social function” OR “social functioning” OR “Psychosocial functioning” OR “Psychosocial function” OR “Functional Independence” OR “ Independent Living”)

PsychInfo and Cochrane Search String

In title and abstract:

((“Cognitive” OR “Cognition” OR “Neurocognitive” OR “Memory” OR “Attention” OR “Verbal Learning” OR “Visual Learning” OR “Vigilance” OR “Reasoning” OR “Problem Solving” OR “Speed of Processing” OR “Brain” OR “Executive Function” OR “Executive Functioning”) AND (“Training” OR “Intervention” OR “Remediation” OR “Rehabilitation” OR “Enhancement” OR “Retraining”))

AND

(“Schizophrenia” OR “Psychosis”)

AND

In complete text:

(“randomly” OR “randomized” OR “randomised” OR “RCT” OR “Clinical Trial”)

AND

(“functional outcome” OR “daily functioning” OR “daily function” OR “everyday functioning” OR “everyday function“ OR “real-world functioning” OR “Real-world function” OR “activities of daily life” OR “activities of daily living” OR “ADL” OR “IADL” OR “occupational functioning” OR “occupational function” OR “social function” OR “social functioning” OR “Psychosocial functioning” OR “Psychosocial function” OR “Functional Independence” OR “ Independent Living”)

Search 2: (Severe Mental Illness)

PubMed

(“Cognitive”[tiab] OR “Cognition”[tiab] OR “Neurocognitive”[tiab] OR “Memory”[tiab] OR “Attention”[tiab] OR “Verbal Learning”[tiab] OR “Visual Learning”[tiab] OR “Vigilance”[tiab] OR “Reasoning”[tiab] OR “Problem Solving”[tiab] OR “Speed of

Processing"[tiab] OR "Brain"[tiab] OR "Executive Function"[tiab] OR "Executive Functioning"[tiab])

AND

("Training"[tiab] OR "Intervention"[tiab] OR "Remediation"[tiab] OR "Rehabilitation"[tiab] OR "Enhancement"[tiab] OR "Retraining"[tiab])

AND

("randomly" OR "randomized" OR "randomised" OR "RCT" OR "Clinical Trial")

AND

("severe mental illness")

AND

("functional outcome" OR "daily functioning" OR "daily function" OR "everyday functioning" OR "everyday function" OR "real-world functioning" OR "Real-world function" OR "activities of daily life" OR "activities of daily living" OR "ADL" OR "IADL" OR "occupational functioning" OR "occupational function" OR "social function" OR "social functioning" OR "Psychosocial functioning" OR "Psychosocial function" OR "Functional Independence" OR " Independent Living")

PsychInfo and Cochrane

In title/abstract:

("Cognitive" OR "Cognition" OR "Neurocognitive" OR "Memory" OR "Attention" OR "Verbal Learning" OR "Visual Learning" OR "Vigilance" OR "Reasoning" OR "Problem Solving" OR "Speed of Processing" OR "Brain" OR "Executive Function" OR "Executive Functioning")

AND

("Training" OR "Intervention" OR "Remediation" OR "Rehabilitation" OR "Enhancement" OR "Retraining")

AND

("severe mental illness")

AND

In full-text:

("randomly" OR "randomized" OR "randomised" OR "RCT" OR "Clinical Trial")

AND

("functional outcome" OR "daily functioning" OR "daily function" OR "everyday functioning" OR "everyday function" OR "real-world functioning" OR "Real-world function" OR "activities of daily life" OR "activities of daily living" OR "ADL" OR "IADL" OR "occupational functioning" OR "occupational function" OR "social function" OR "social functioning" OR "Psychosocial functioning" OR "Psychosocial function" OR "Functional Independence" OR " Independent Living")

Appendix B

Composite score computation

The following formulas were used to calculate the composite score of functional outcomes.

Mean Effect Size:

$$\underline{Y} = \frac{1}{m}(\sum_{d}^{m} Y_d)$$

Variance:

$$V_{\underline{Y}} = (\frac{1}{m})^2(\sum_{d=1}^{m} V_i + \sum_{d \neq e} r_{de}\sqrt{V_d}\sqrt{V_e})$$

The correlation r_{de} was assumed to be 1.

Appendix C

Descriptive table of included studies

Table C3

Descriptive Table of Included Studies

Study	Sample Size	Proportion of women	Mean Age	Functional Outcome Mean (SE)	Type of Cognitive Exercises	Node	CR program	Control Group	Description Control Group	ROB
Ahmed, (2015)	78	0.13	40.50	0.25 (0.03)	Bottom-Up	CE-TSG	Brain Fitness	ANSP	Computer games; healthy behaviors discussion group	Low
Aloi, (2018)	46	0.30	51.05	4.13 (0.10)	Non-Targeted	CE-TSG	IPT	TAU	Treatment as usual	Some Concerns
Au, (2014)	90	0.37	36.14	-0.05 (0.03)	Non-Targeted	CE-TG	Captain's Log Software	ACT	Integrated supported employment + timed TV watching	Low
Bowie, (2012)	114	NA	40.57	-0.10 (0.03)	Non-Targeted	CE-TSG	Thinking Skills for Work	ACT	Functional Adaptation Skill Training	Low

Study	Sample Size	Proportion of women	Mean Age	Functional Outcome Mean (SE)	Type of Cognitive Exercises	Node	CR program	Control Group	Description Control Group	ROB
Bryce, (2018)	56	0.30	41.03	-0.08 (0.07)	Top-Down	CE-TS	CogPack	ANSP	Computer Games	Low
Cassetta, (2018)[a]	83	0.39	40.21	0.52 (0.22)	Bottom-Up	CE & CE	WM & PS	TAU	No-training control	Low
Cavallaro, (2009)	100	NA	33.62	0.16 (0.03)	Non-Targeted	CE-TG	CogPack	ACT	Standard rehabilitation treatment + domain-non-specific enhancement therapy	Some Concerns
D'Amato, (2011)	77	0.25	32.86	-0.10 (0.03)	Non-Targeted	CE-T	RehaCom	TAU	Standard treatment	Some Concerns
Dickinson, (2010)	69	0.29	47.66	0.19 (0.04)	Non-Targeted	CE-TSG	CACR-D	ANSP	Computer games with a therapist	Low

Study	Sample Size	Proportion of women	Mean Age	Functional Outcome Mean (SE)	Type of Cognitive Exercises	Node	CR program	Control Group	Description Control Group	ROB
Fernandez -Gonzalo, (2015)	53	0.36	30.48	-0.03 (0.07)	Non-Targeted	CE-TSG	NPT-MH	ANSP	Non-specific computer training	High
Fisher, (2015)	121	0.26	21.24	-0.05 (0.02)	Bottom-Up	CE	AT	ANSP	Computer games	High
Fiszdon, (2016)	75	0.27	47.81	0.14 (0.03)	Non-Targeted	CE-S	NET	TAU	Treatment as usual	High
Galderisi, (2010)	60	NA	39.74	0.95 (0.06)	Non-Targeted	CE-TSG	SSANIT	ANSP	Structured leisure activities	Some Concerns
García-Fernández, (2019)	110	0.30	25.32	0.13 (0.03)	Non-Targeted	CE-TG	RehaCom	ANSP	Computerized active control group	High

Study	Sample Size	Proportion of women	Mean Age	Functional Outcome Mean (SE)	Type of Cognitive Exercises	Node	CR program	Control Group	Description Control Group	ROB
Garrido, (2013)	67	0.27	33.30	0.92 (0.03)	Non-Targeted	CE-TSG	CRT-G	ANSP	Watching videos	Low
Gomar, (2015)[a]	130	0.39	46.07	-0.01 (0.04)	Non-Targeted	CE	FesKits	ANSP & TAU	Computerized active control & treatment as usual	Some Concerns
Iwata, (2017)	60	0.75	34.36	0.64 (0.04)	Non-Targeted	CE-TSG	Thinking Skills for Work	TAU	Treatment as usual including social skill training, psychoeducation, individual work therapy	High
Jahshan, (2018)[a]	99	0.22	51.27	0.19 (0.06)	Top-Down	CE-T & CE-T	Brain Fitness & CogPack	ANSP	Computer game control	Some Concerns
Katsumi, (2019)	44	0.41	37.75	0.30 (0.06)	Non-Targeted	CE-TSG	NEAR	TAU	Treatment as usual	High

Study	Sample Size	Proportion of women	Mean Age	Functional Outcome Mean (SE)	Type of Cognitive Exercises	Node	CR program	Control Group	Description Control Group	ROB
Kukla, (2018)[a]	75	0.07	50.24	0.27 (0.06)	Non-Targeted	CE-TG	CBT + CR	ACT & TAU	Work-focused CBT & Vocational support	Low
Kurtz, (2015)	64	0.27	36.60	0.16 (0.03)	Non-Targeted	CE-TG	COG REM	ANSP	Computer literacy course	High
Lee, (2013)	66	0.45	43.49	0.36 (0.04)	Non-Targeted	CE-TG	Cog Trainer	ANSP	Usual rehabilitation	Low
Linden-mayer, (2013)	59	0.19	43.28	-0.41 (0.05)	Top-Down	CE-TG	CogPack + MRIGE	CR approach	CogPack	High
Lu, (2012)	126	0.39	37.50	-0.01 (0.04)	Top-Down	CE-T	CRT	ANSP	Timed treatment as usual	High

Study	Sample Size	Proportion of women	Mean Age	Functional Outcome Mean (SE)	Type of Cognitive Exercises	Node	CR program	Control Group	Description Control Group	ROB
Lystad, (2017)	131	0.30	32.72	-0.13 (0.02)	Non-Targeted	CE-TSG	Thinking Skills for Work	ACT	Cognitive behavioral therapy	High
Mahncke, (2019)	150	0.19	42.90	0.02 (0.12)	Non-targeted	CE	CRT-M	ANSP	Computer games	Low
Matsuda, (2018)	62	0.44	37.1	0.40 (0.04)	Non-targeted	CE-TSG	JCORES	TAU	Treatment as usual	Low
Mueller, (2015)	156	0.31	34.22	0.29 (0.02)	Non-Targeted	CE-TSG	INT	TAU	Treatment as usual	Some Concerns
Mueller, (2017)	61	0.22	35.51	-0.11 (0.05)	Non-Targeted	CE-TSG	INT	TAU	Treatment as usual	Some Concerns

Study	Sample Size	Proportion of women	Mean Age	Functional Outcome Mean (SE)[b]	Type of Cognitive Exercises	Node	CR program	Control Group	Description Control Group	ROB
Mueller, (2020)	58	0.41	31.83	1.00 (0.05)	Non-Targeted	CE-TSG	INT	TAU	Treatment as usual	Low
O'Reilly, (2019)	65	0.16	40.96	-0.01 (0.04)	Non-Targeted	CE-TSG	CRT-OR	TAU	Treatment as usual	Low
Omiya, (2016)	17	0.59	41.00	1.22 (0.14)	Top-Down	CE-TS	FEP	ACT	Regular psychotherapy	High
Peña, (2016)	104	0.28	39.00	0.39 (0.02)	Non-Targeted	CE-TSG	REHACOP	ANSP	Occupational group activities	Low
Poletti, (2010)	100	0.40	34.29	0.60 (0.02)	Top-Down	CE-TSG	CogPack-P	ANSP	Computer-aided non-domain-specific activity	Low

Study	Sample Size	Proportion of women	Mean Age	Functional Outcome Mean (SE)	Type of Cognitive Exercises	Node	CR program	Control Group	Description Control Group	ROB
Popova, (2014)	80	0.34	37.28	0.25 (0.07)	Bottom-Up	CE	AT+WM	TAU	Treatment as usual	High
Puig, (2014)	51	0.53	16.75	0.37 (0.05)	Non-Targeted	CE-TSG	CRT	TAU	Treatment as usual	Some Concerns
Rakitzi, (2016)	48	0.33	32.55	0.50 (0.08)	Non-Targeted	CE-TSG	IPT	ANSP	Timed treatment as usual	Some Concerns
Ran & Chen, (2004)	121	0.41	37.30	0.64 (0.02)	Non-Targeted	CE-TSG	CET	ACT	Enriched Supportive Therapy	High
Reeder, (2017)	93	0.35	38.30	0.55 (0.18)	Non-Targeted	CE-TSG	CIRCuITS	TAU	Treatment as usual	Low

Study	**Sample Size**	**Proportion of women**	**Mean Age**	**Functional Outcome Mean (SE)**	**Type of Cognitive Exercises**	**Node**	**CR program**	**Control Group**	**Description Control Group**	**ROB**
Rodewald, (2011)	89	0.19	28.74	0.04 (0.04)	Non-Targeted	CE-TSG	Plan-A-Day	CE	Basic cognition training	Some Concerns
Ruiz-Iriondo, (2019)	77	0.31	43.69	0.25 (0.03)	Non-Targeted	CE-TSG	IPT	TAU	Treatment as usual	Some Concerns
Sánchez, (2014)	92	0.24	35.55	0.43 (0.03)	Non-Targeted	CE-TSG	REHACOP	TAU	Treatment as usual	Low
Silver-stein, (2014)	105	0.26	43.90	0.10 (0.03)	Bottom-Up	CE-T	Attention Shaping	TAU	Treatment as usual	High
Tan, (2016)	104	0.35	46.30	0.36 (0.03)	Top-Down	CE-TS	CRT	ANSP	Music and dance therapy	Low

Study	Sample Size	Proportion of women	Mean Age	Functional Outcome Mean (SE)	Type of Cognitive Exercises	Node	CR program	Control Group	Description Control Group	ROB
Vita, (2011)[a]	84	0.31	39.00	0.85 (0.04)	Top-Down	CE-TSG & CE-TSG	CogPack & IPT	ANSP	Occupational Therapy	Low
Vita, (2011)b	32	0.17	37.25	0.57 (0.07)	Non-Targeted	CE-TSG	IPT	ANSP	Non-cognitive-oriented group psychosocial intervention	Some Concerns
Wykes, (1999)	33	0.24	38.49	0.26 (0.09)	Top-Down	CE-TS	CRT	ANSP	Non-cognitive-oriented group psychosocial intervention	High
Wykes, (2007)	40	0.35	18.18	0.01 (0.05)	Top-Down	CE-TS	CRT	TAU	Treatment as usual	Some Concerns
Wykes, (2007)b	85	0.27	36.00	-0.05 (0.03)	Top-Down	CE-TSG	CRT	TAU	Treatment as usual	Some Concerns

Study	Sample Size	Proportion of women	Mean Age	Functional Outcome Mean (SE)	Type of Cognitive Exercises	Node	CR program	Control Group	Description Control Group	ROB
Zhu, (2020)	157	0.46	43.69	0.24 (0.02)	Top-Down	CE-TSG	CRT-Z	TAU	Treatment as usual	Low
Zimmer, (2007)	66	0.25	38.17	0.84 (0.04)	Non-Targeted	CE-TSG	IPT	TAU	Treatment as usual	Low

Note. ACT: Active Control Treatment, *ANSP*: Active Non-Specified Control, *AT*: Auditory Training, *AT+WM:* Auditory Training+ Working Memory Training, *CACR-D*: Computer-assisted cognitive Remediation by Dickinson et al. (2010), *CET*: Cognitive Enhancement Therapy, *CRT*: Cognitive Remediation Therapy, *CogPack-P*: CogPack by Poletti et al. (2010), *COG REM*: cognitive remediation, *CRT-G*: Cognitive Remediation Therapy, *CRT-M*: Cognitive Remediation Therapy by Mahncke et al. (2019), *CRT-OR*: Cognitive Remediation by O'Reilly et al. (2019), *CRT-Z:* Cognitive Remediation Therapy by Zhu et al. (2020), *FEP-J:* Frontal/Executive Program-Japanese version, *INT*: Integrated Neurocognitive Training, *IPT*: Integrated Psychological Therapy, *JCORES:* Japanese Cognitive Rehabilitation Programme for Schizophrenia, *NEAR*: Neuropsychological Educational Approach to Remediation, NET: Neurocognitive Enhancement Training, *NPT-MH*: NeuroPersonalTrainer, *PS:* Processing Speed Training, *REHACOP:* Neuropsychological Rehabilitation, *SSANIT:* social skills and neurocognitive individualized training, *TAU:* Treatment as Usual, *WM:* Working Memory Training, *CE:* Cognitive exercises only, *CE-S:*

Cognitive exercises + strategy training, *CE-T:* Cognitive exercises + therapist, CE-TG*:* Cognitive exercises + therapist + generalization procedures, *CE-TS*: Cognitive exercises + therapist + strategy training, *CE-TSG:* Cognitive exercises + therapist, + strategy training + generalization procedures, *TAU:* Treatment as usual, *ACT*: Active control treatments, *ANSP:* Active non-specified control, *CR program*: Cognitive remediation program, *ROB*: Risk of bias score

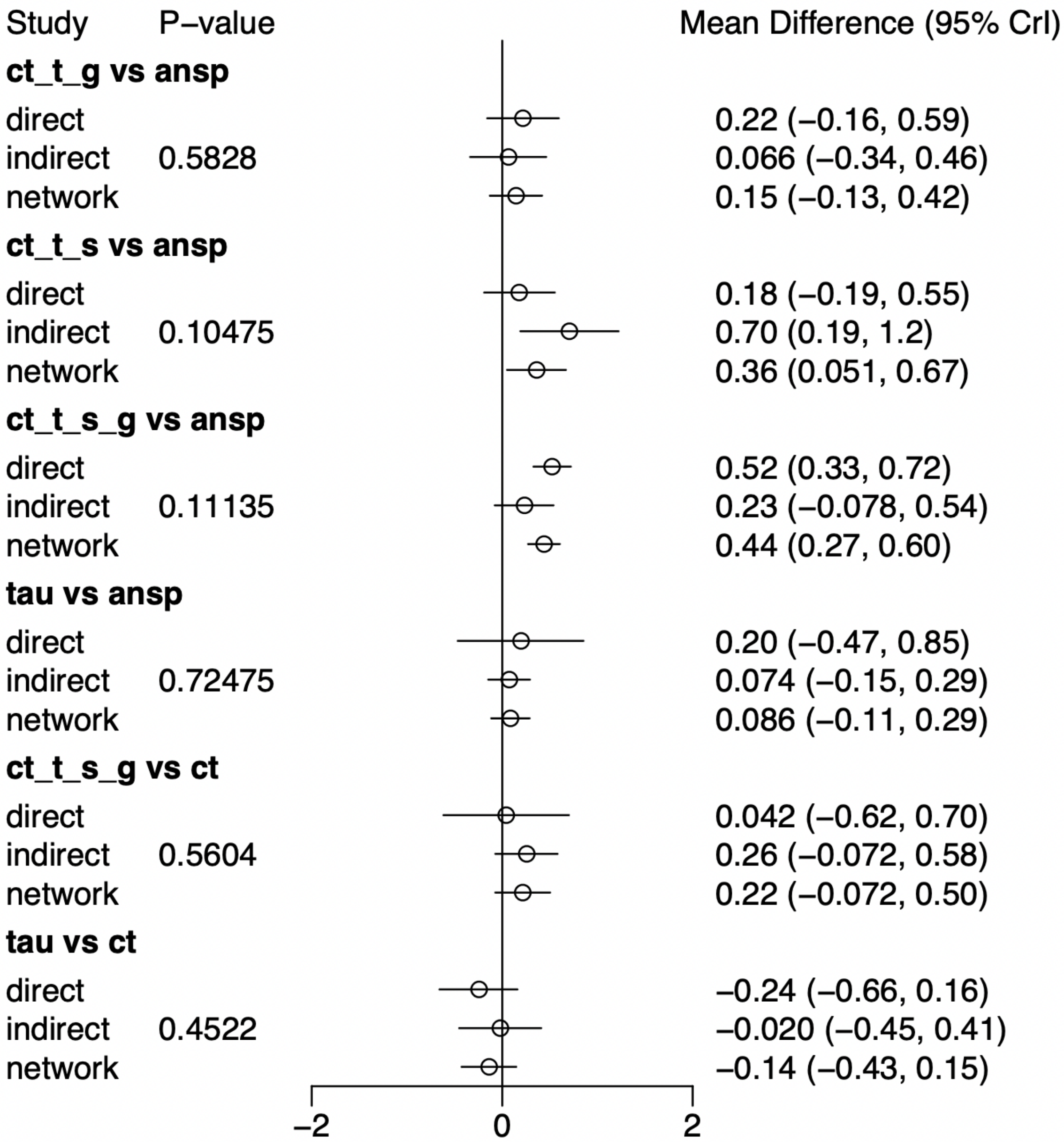
[a] Three-arm studies

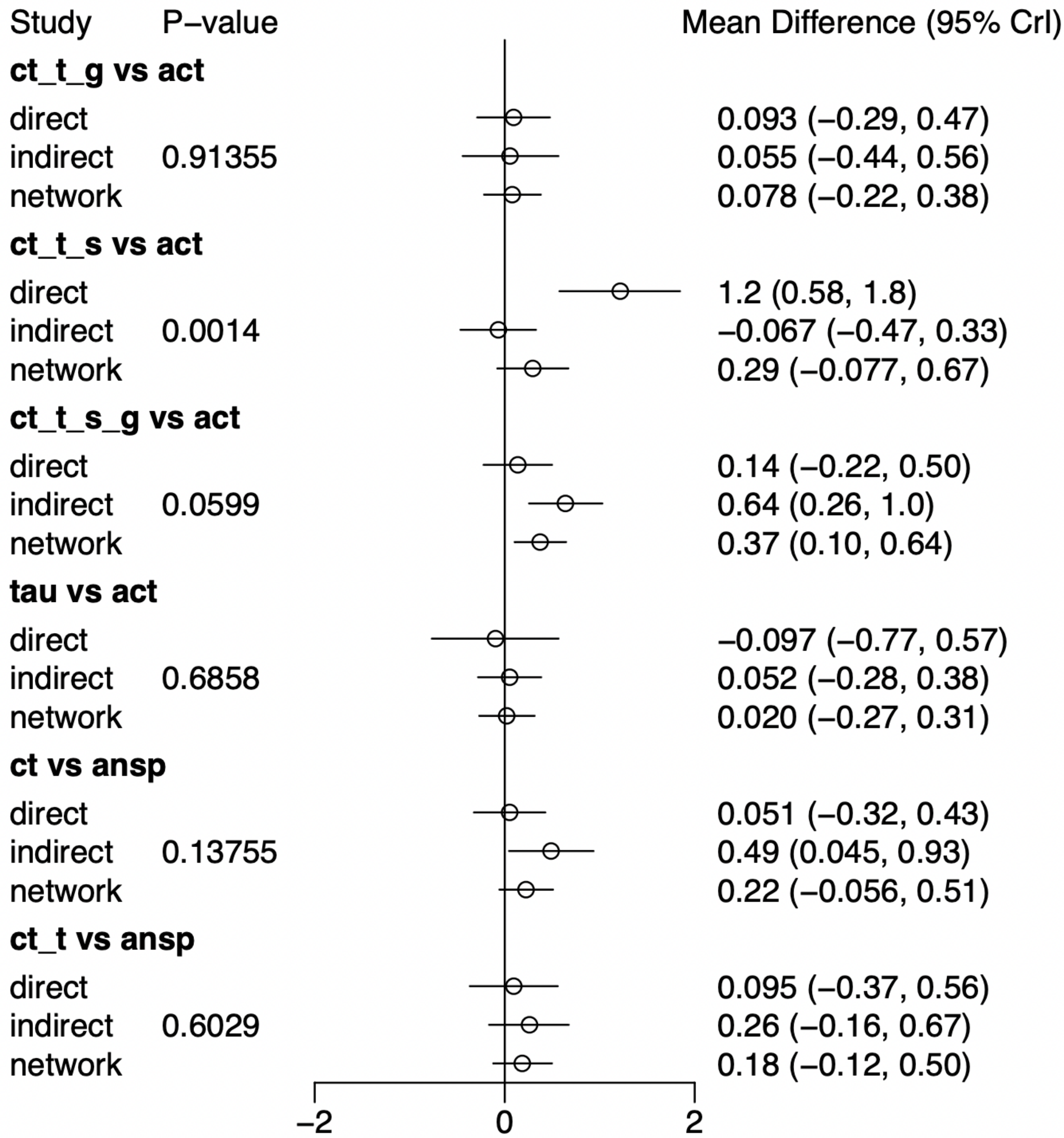
[b] Composite functional outcome score

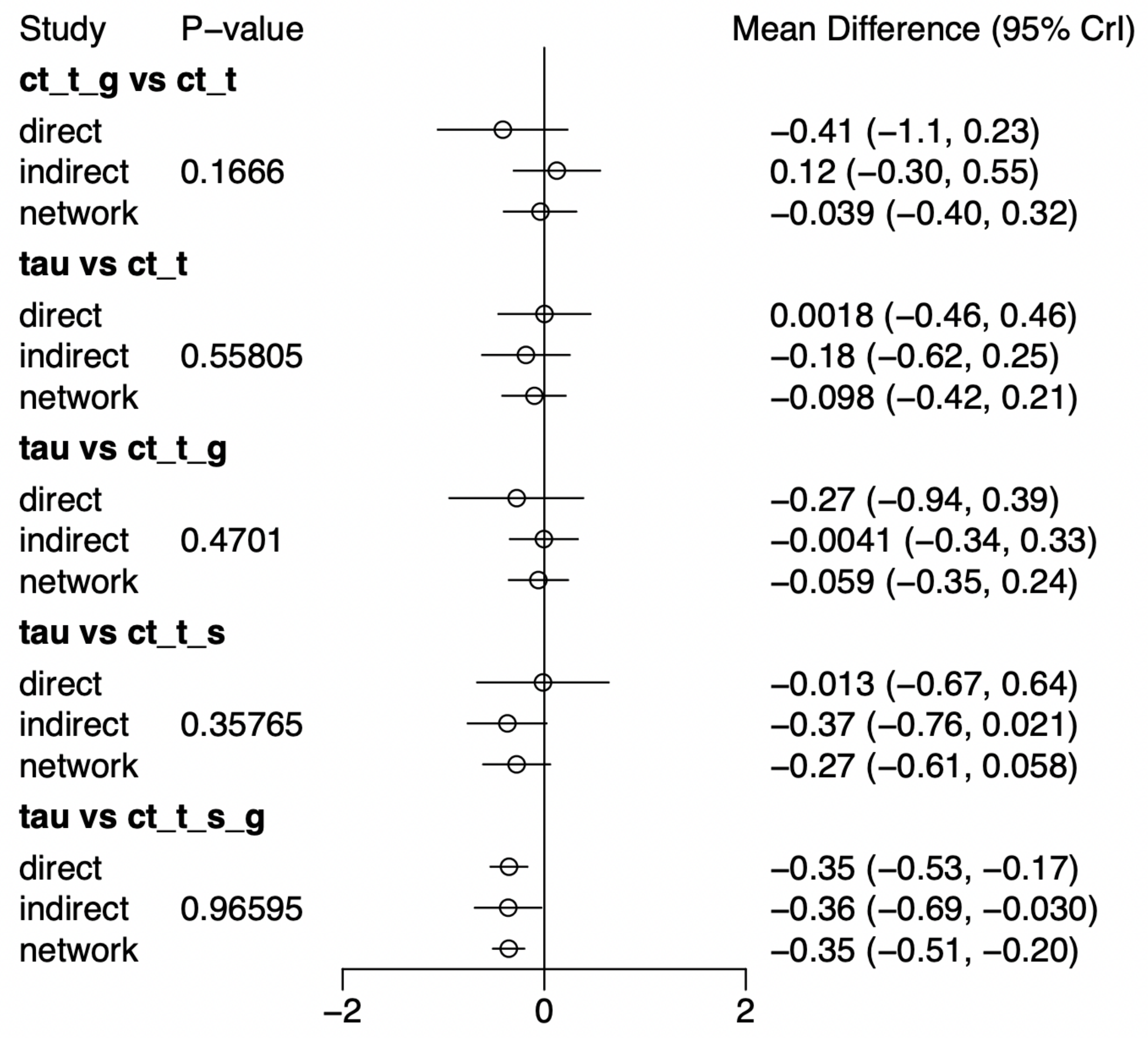
Appendix D

Assessment of consistency assumption

The consistency assumption was tested by using the node split method (Dias et al., 2010),which splits the mixed relative effect sizes of each pairwise comparison, into a direct and an indirect effect size estimate. A significant p-value (< 0.05) indicates significant differences between the two estimates and followingly inconsistency.




Study P−value Mean Difference (95% CrI)
ct_t_g vs act
direct 0.093 (−0.29, 0.47)
indirect 0.91355 0.055 (−0.44, 0.56)
network 0.078 (−0.22, 0.38)
ct_t_s vs act
direct 1.2 (0.58, 1.8)
indirect 0.0014 −0.067 (−0.47, 0.33)
network 0.29 (−0.077, 0.67)
ct_t_s_g vs act
direct 0.14 (−0.22, 0.50)
indirect 0.0599 0.64 (0.26, 1.0)
network 0.37 (0.10, 0.64)
tau vs act
direct −0.097 (−0.77, 0.57)
indirect 0.6858 0.052 (−0.28, 0.38)
network 0.020 (−0.27, 0.31)
ct vs ansp
direct 0.051 (−0.32, 0.43)
indirect 0.13755 0.49 (0.045, 0.93)
network 0.22 (−0.056, 0.51)
ct_t vs ansp
direct 0.095 (−0.37, 0.56)
indirect 0.6029 0.26 (−0.16, 0.67)
network 0.18 (−0.12, 0.50)
−2 0 2



Note. ct: Cognitive exercises, *ct_t_g*: cognitive exercises + therapist + generalization procedures, *ct_t_s:* Cognitive exercises + therapist + strategy training, *ct_t_s_g:* Cognitive exercises + therapist + strategy training, *tau:* treatment as usual, *act:* Active control group, *ansp:* active non-specific control, ct_t: Cognitive exercises + therapist,

Appendix E

Description of the Different CR Programs compared in the Alternative Network

Table E1

Description of different CR programs

CR program	Description
Integrated Psychological Therapy	Integrated Psychological Therapy combines neuro- and social cognitive remediation with psychosocial rehabilitation measures. The manualized treatment is administered in groups of 5-12 people and encapsulates five subprograms that are sequentially administered to participants. The five subprograms are: (1) cognitive differentiation, (2) social perception, (3) verbal communication, (4) social skills, (5) interpersonal problem-solving. The subprograms increase in their complexity and difficulty (Roder et al., 2011).
Integrated Neuropsychological Therapy	Integrated Neurocognitive Therapy developed out of IPT and aims to target all neuro- and social cognitive MATRICS domains. This group-based treatment is divided into 4 modules that all target different domains, however, possess the same structure. Early sessions emphasize psychoeducation about the domains and connecting the relevance to real-world situations. Participants then learn individualized strategies which are practiced through repeated exercises using partially computerized exercises (Mueller et al., 2015).
REHACOP	REHACOP is a structured paper-pencil based cognitive remediation program, that gradually trains domains such as attention, memory, processing speed, or executive functioning, through increasingly more demanding cognitive exercises. The treatment included three modules that focus on psychoeducation, social skill training and activities of daily living. Along with the exercises, basic cognitive strategies are taught that are trained along with the different cognitive exercises (Sánchez et al., 2014).
Thinking Skills for Work	The Thinking Skills for Work Program aims at integrating cognitive remediation and supported employment services and is divided into 4 modules. The components are (1) assessment, (2) 24 hours of computerized cognitive exercises across a variety of cognitive domains (e.g., attention, processing speed, memory, and executive functioning), (3) job search, and (4) job support (McGurk et al., 2005).

CR program	Description
Brain Fitness	Brain Fitness is a web-based software library that encapsulates cognitive exercises that focus on basic auditory-visual processing (Fisher et al., 2015). The software can be combined with other treatment components but can also be used as a complete isolated cognitive exercise.
RehaCom	REHACOM, is a computer-assisted treatment software for cognitive functions. Exercises are gradual and cover a variety of cognitive domains (D'Amato et al., 2011). The software can be combined with other treatment components but can also be used as a complete isolated cognitive exercise.
Cognitive Remediation Therapy	Cognitive Remediation Therapy is a manualized treatment of 40 individual sessions that combines the training of strategies with the practice of cognitive skills. The treatment consists of three modules: (1) cognitive flexibility, (2) working memory and (3) planning, which consist of paper and pencil based cognitive exercises, which being gradually increase in difficulty (Wykes, Reeder, et al., 2007).
CogPack	CogPack is a computer software that encapsulates cognitive exercises including attention, memory, learning, and executive functioning (Bryce et al., 2018). The software can be combined with other treatment components but can also be used as a complete isolated cognitive exercise.

Note. The table contains short descriptions of the different CR programs in the alternative network. *CR program*: Cognitive remediation intervention