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Effectiveness of Cognitive Rehabilitation in Improving Symptoms and Restoring Cognitive Functions in Patients with Depression: An Updated Meta-Analysis of Randomized Controlled Trials

ABSTRACT

Objective: Patients with depression often experience cognitive impairments. Cognitive rehabilitation, as an adjunctive intervention, may help to improve symptoms and restore functions in these patients. This study explores the effectiveness of cognitive rehabilitation in improving symptoms and restoring cognitive functions in patients with depression.

Methods: The following databases were systematically searched for relevant randomized controlled trials (RCTs): PubMed, Embase, and the Cochrane Central Register of Controlled Trials. Two reviewers independently screened the studies. The search was conducted from the inception of the databases to April 10, 2024. Standardized mean differences (SMDs) with 95% CIs, confidence interval were calculated using RevMan v. 5.3 software, and heterogeneity was assessed using Cochran's Q test and the I^2 statistic.

Results: A total of 14 RCTs involving 700 patients were included in this meta-analysis. Compared with the control group, there was no significant difference in the severity of depression after cognitive rehabilitation intervention, with a pooled SMD of −0.14 (95% CI: −0.32 to 0.05; $P = .15$; $I^2 = 30\%$). Among the 4 studies reporting attention-related data, cognitive rehabilitation significantly improved attention function in patients with depression compared with the control group, with an SMD of −0.63 (95% CI: −0.99 to −0.27; $P < .001$; $I^2 = 0\%$). In 6 studies, data showed significant improvement in verbal learning ability in patients with depression after cognitive rehabilitation intervention, with an SMD of −0.33 (95% CI: −0.60 to −0.05; $P = .02$; $I^2 = 48\%$). Executive function outcomes were reported in 6 studies, whereas working memory outcomes were reported in 7 studies, both before and after the intervention. No significant differences were observed between the groups, with SMDs of −0.45 (95% CI: −1.09 to 0.19; $P = .17$; $I^2 = 78\%$) in executive function and −0.38 (95% CI: −0.82 to 0.07; $P = .10$; $I^2 = 67\%$) in working memory post-intervention. Subgroup analysis suggested that cognitive rehabilitation training had a close to statistically significant improvement effect on depression severity in European regions, whereas no significant impact was observed in other regions.

Conclusion: Cognitive rehabilitation shows certain value in improving attention and verbal learning in patients with depression as an adjunctive treatment, but its effectiveness in improving depressive symptoms, executive function, and working memory remains inconclusive. Future large-sample RCTs are needed to further explore this aspect.

Keywords: Depression, cognitive function, executive function, meta-analysis

Introduction

Depression has become a major global health issue significantly affecting the quality of life and social functioning of patients. According to the latest data from the World Health Organization, approximately 320 million people suffer from depression worldwide, making it one of the leading causes of disability.[1] Apart from its direct impact on mental health, depression is closely associated with various physical health issues, including heart disease,

Lijun Liu[1#]
Keqiang Wang[2#]
Dongmei Xu[1]
Yuhong Wang[2]
Xiaomei Xu[2]
Qian Wang[1]
Xinfu Wang[2]

[1]*Department of Mental Rehabilitation, Rongjun Hospital of Hebei Province, Baoding, China*
[2]*Department of Clinical psychiatry, Rongjun Hospital of Hebei Province, Baoding, China*

[#]*These authors contributed equally to this study*

Corresponding author:
Xinfu Wang
✉ wangxinfu2020@126.com

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diabetes, and stroke, further escalating the overall health risks for patients.[2] The clinical manifestations of depression are diverse and mainly characterized by persistent feelings of sadness, loss of interest or pleasure in daily activities, fatigue, diminished self-worth, and a pessimistic outlook on the future.[3] Additionally, many patients may experience secondary symptoms (e.g., anxiety, sleep disturbances, and appetite changes), exacerbating their distress and discomfort. Importantly, depression often coexists with cognitive impairments, manifested as difficulties in concentration, memory deficits, and compromised decision-making, executive function, and cognitive flexibility. These cognitive deficits not only exacerbate the clinical symptoms of depression but also further impair patients' social functioning and quality of life, influencing treatment outcomes and rehabilitation.[4]

Depression is a multifactorial condition involving neurobiology, psychosociology, and genetics. Neurotransmitter imbalances, particularly in serotonin and dopamine, and alterations in brain structures in the prefrontal cortex and amygdala are linked to depression symptoms.[5,6] Although using pharmacotherapy (e.g., selective serotonin reuptake inhibitors and tricyclic antidepressants) is common, it often has side effects and is not always effective.[7,8] This has led to interest in non-pharmacological treatments such as cognitive rehabilitation, which aims to enhance cognitive functions and emotional regulation.[9] Non-pharmacological treatments encompass a range of interventions, including cognitive behavioral therapy, mindfulness-based cognitive therapy, exercise, and brain stimulation therapies (e.g., transcranial magnetic stimulation). These interventions target various aspects of depression, from cognitive distortions to neuroplasticity, and have been shown to offer benefits either as standalone treatments or in conjunction with medication. Recent studies suggest that cognitive rehabilitation can significantly improve depressive symptoms, cognitive functions, and quality of life.[10]

Despite the potential value of cognitive rehabilitation in depression treatment, current research findings regarding its effectiveness are inconsistent. Some studies support its efficacy as a treatment for depression, whereas others indicate ambiguous effects or efficacy in specific populations only.[11,12] Moreover, existing research data are largely based on outdated information, necessitating further updates and validations. Thus, although cognitive rehabilitation shows promise as a non-pharmacological intervention in depression treatment, there are gaps and insufficient information in the literature. This study aims to address these issues by conducting an updated meta-analysis to comprehensively evaluate the effectiveness of cognitive rehabilitation in improving symptoms and restoring cognitive functions in patients with depression, providing clearer and more up-to-date evidence for clinical practice.

MAIN POINTS

- *Cognitive rehabilitation significantly improved attention function in patients with depression compared with the control group.*
- *The meta-analysis found no significant difference in the severity of depression between the cognitive rehabilitation intervention group and the control group.*
- *Data from 6 studies indicated significant improvement in verbal learning ability in patients with depression following cognitive rehabilitation.*
- *No significant differences were observed in executive function and working memory between the intervention and control groups.*
- *Subgroup analysis suggested a close to statistically significant improvement in depression severity from cognitive rehabilitation in European regions, whereas no significant impact was observed in other regions.*

Material and Methods

Search Strategy and Literature Selection

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines recommended by the Cochrane Collaboration.[13] The primary electronic databases, PubMed, Embase, and the Cochrane Central Register of Controlled Trials, were selected for literature retrieval. The search was conducted from the inception of the databases to April 10, 2024, with no language restrictions. The search strategy was formulated by combining Medical Subject Headings (MeSH), Emtree, and free-text terms. The main key terms used in the search strategy were "depression," "cognitive rehabilitation," "cognitive training," "computerised cognitive training," "personalised optimised training," "working memory training," and "randomised controlled trials." These key terms were connected using the Boolean operator "AND" to ensure that all articles included in the search contained all these main concepts. Within each main topic, MeSH/Emtree and free-text terms were combined using the Boolean operator "OR" to capture a comprehensive range of relevant studies. The search was performed with a focus on titles and abstracts to enhance relevance. Additionally, references from relevant studies were manually searched to expand the search scope. All electronic records were imported into reference management software for automatic deduplication, followed by a manual check. After removing duplicate records, 2 reviewers independently conducted literature screening based on titles and abstracts. Any discrepancies were resolved by a third reviewer.

Inclusion and Exclusion Criteria

Based on the classic participants, interventions, comparisons, outcomes, and study design (PICOS) principle, the inclusion criteria for this study were as follows: (1) the patients were diagnosed with depression or had a history of depression and temporarily recovered; (2) the intervention group received cognitive rehabilitation training; (3) the control group received either standard treatment methods (positive control) or a placebo (sham, negative control); (4) the outcome measures included depression symptom scores and cognitive functions (e.g., attention, executive function, verbal learning, and working memory), requiring an assessment in any of these areas but not mandating the use of a specific score; and (5) only randomized controlled trials (RCTs) were included. The exclusion criteria were as follows: (1) duplicate or identical studies; (2) irrelevant study types (e.g., case-control studies, observational studies, and literature reviews); (3) studies with unavailable or unobservable data for the predefined outcome measures; and (4) interventions or controls that did not meet the predefined requirements.

Data Extraction and Risk of Bias Assessment

After determining the final included studies, 2 independent reviewers extracted information and data from them using a pre-defined table. This information mainly included study details (e.g., authors, publication year, country, intervention-control settings, outcome measures, and follow-up period), population characteristics (e.g.,

inclusion criteria, sample size, age, gender, marital status, and education), and study results. Subsequently, the reviewers independently assessed the risk of bias in the included studies according to the *Cochrane Handbook for Systematic Reviews of Interventions*. Any discrepancies were resolved by a third senior researcher. The main aspects of Cochrane's risk assessment included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, selective reporting, and other biases from different sources. The risk of bias was categorized into 3 levels: low risk, high risk, and unclear.

Statistical Analysis

Meta-analysis was conducted using RevMan v. 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Standardized mean differences (SMDs) and their corresponding 95% CIs were used to calculate statistical indicators for continuous variables, as SMDs can accommodate different indicators and units. This method standardizes the effect sizes, allowing for a comprehensive comparison across studies. Cochran's Q test and the I^2 statistic were used to assess the heterogeneity among studies. When heterogeneity was low ($P > .1$ or $I^2 < 50\%$), a fixed-effects model was used for meta-analysis; otherwise, a random-effects model was used. The significance level (α) was set at 0.05. Funnel plots were used to assess publication bias, and subgroup analyses were performed to examine variations in the effects of cognitive rehabilitation on patients with depression in different groups.

Results

A total of 5004 electronic records were identified through the search strategy, comprising 3888 from PubMed, 1086 from Embase, and 30 from Cochrane. Three additional records were identified through manual searches. After removing 1681 duplicate records, 3326 were screened based on titles and abstracts, from which 35 potentially relevant articles were selected. After a full-text review, 21 articles were excluded due to irrelevant outcome measures, intervention methods, lack of usable data, or they were non-randomized controlled studies, leaving 14 articles for inclusion in the meta-analysis.[14-27] (Figure 1).

Characteristics of the Included Studies

A total of 14 studies involving 700 patients were included in this study: 8 studies were conducted in Europe, 5 in the Asia-Pacific region, and 1 in North America. The basic information of the included studies is presented in Table 1. Nearly all studies (85.7%) were single-center, RCTs. Various intervention methods were employed (e.g., computerized cognitive training, personalized optimized training, and working memory training). Control groups received routine rehabilitation, computer games, sham interventions, among others. The outcomes explored in the studies included depression symptoms, cognitive

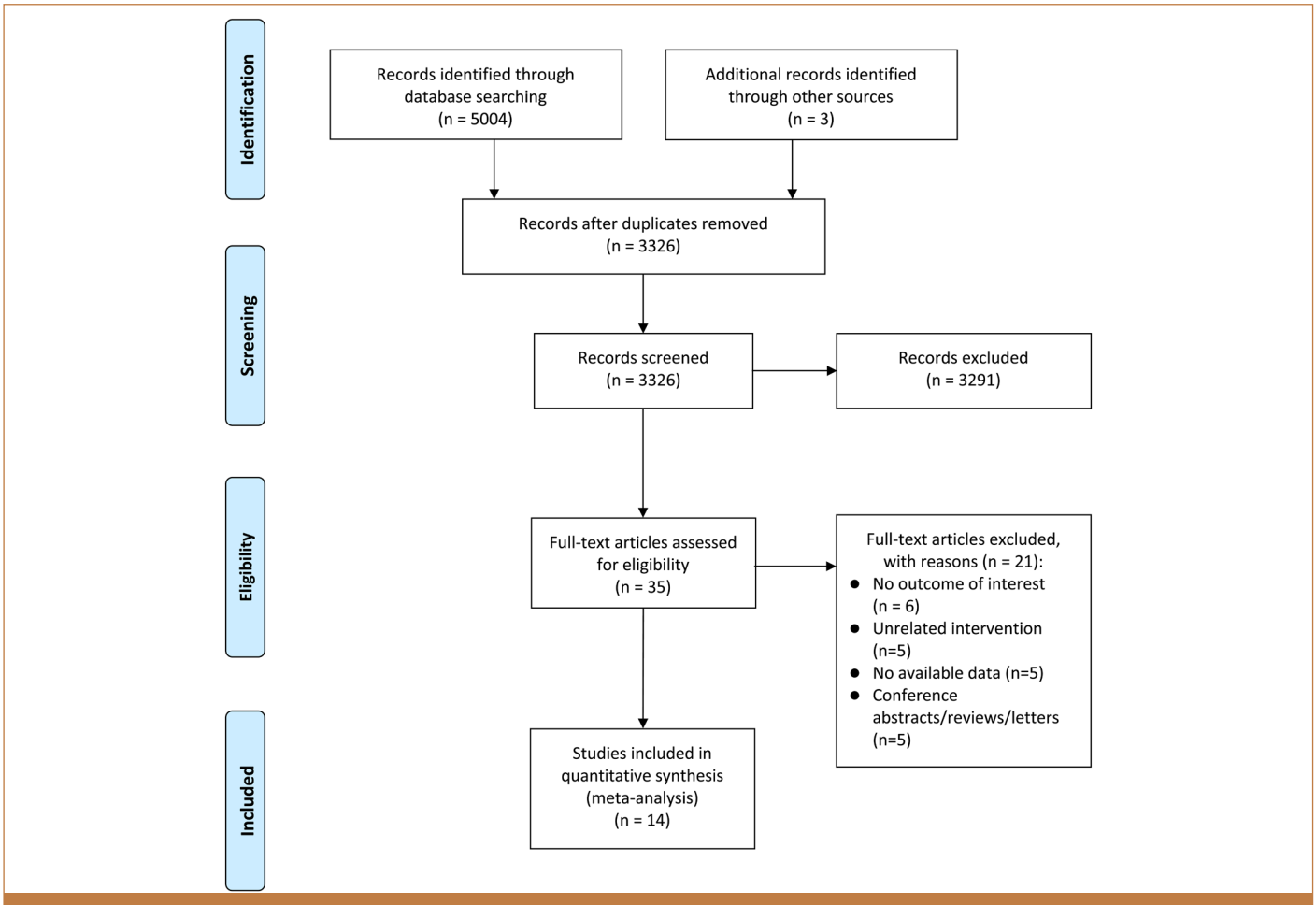

Figure 1. PRISMA flow diagram outlining the study selection procedure.

Table 1. Main Characteristics of the Included Studies

Author, year	Country	Design	Intervention	Control	Outcomes	Indicators	Intervention Duration	Follow-up Duration
Amano, 2023[14]	Japan	Single-center	Cognitive behavioral therapy	Talking control	Future thinking, depression, dysfunctional cognition, word fluency	Response time, GRID-HAMD17, BDI-II, DAS, WFT	16 weeks	12 months
Au, 2021[15]	China	Single-center	Compensatory cognitive + training occupational therapy	Occupational therapy	Psychiatric symptoms, depression, anxiety, stress, memory	BPRS-E, CAMPROMPT-C, DASS	NR	NR
Hauschildt, 2022[16]	Germany	Single-center	Metacognitive training	Euthymic therapy	Depressive symptoms, dysfunctional cognition, subjective appraisal	HAMD-17, BDI, DAS, MCQ-30	NR	3 months
Hawighorst, 2023[17]	Australia	Single-center	Personalized training	Standard training	Cognition, emotion, social cognition	PDQ-5-D, MADRS, PANAS-X, WAIS-ACS	8 weeks	3 months
Hoorelbeke, 2016[18]	Belgium	Single-center	Internet-delivered cognitive control training	Low cognitive load training	Depression, emotion, general function, quality of life, resilience, remission from depression	RRS, BDI-II, CERQ, WHODAS, QLDS, RS, RDQ	2 weeks	3 months
Katayama, 2023[19]	Japan	Single-center	Cognitive behavioral training	Talking control	Neuroimaging, depression, negative and positive automatic thoughts,	MRI, GRID-HAMD17, Beck Depression Inventory, ATQ-R	16 weeks	12 months
Klojčnik, 2021[20]	Slovenia	Single-center	Computerized cognitive remediation therapy+standard rehabilitation	Standard rehabilitation	Attention, executive functions, depression	TAP, TOL, BRIEF-A, BDI-II	10 weeks	Post-intervention
Listunova, 2020[21]	Germany	Multi-center	Individualized cognitive remediation therapy	Passive control	Information processing, attention, learning and memory, executive functions, subjective cognitive deficits, premorbid intelligence	TMT-A, ZST, WAF, CVLT, FGT, INHIB, TMT, TOL, NBV, FLei, MWT	5 weeks	Post-intervention
Moshier, 2017[22]	USA	Single-center	Cognitive control training+BBAT	Peripheral vision training+BBAT	Depression, rumination	BDI-II, MADRS, RRS	4 weeks	Post-intervention
Semkovska, 2017[23]	Ireland	Single-center	Neurocognitive remediation therapy	Computer games	Premorbid intelligence, computer expertise, neurocognitive function, executive function, depression	NART, CPS, Digit Symbol Substitution, d2 Selective attention test, Digit Span, Logical memory-I & II, ROCF, DE-KEFS, HRSD, BDI-II	5 weeks	Post-intervention
Trapp, 2016[24]	Germany	Single-center	Cognitive remediation therapy	Standard drug and non-drug (cognitive behavioral, occupational, sports, relaxation, and music therapy) antidepressive treatment	Attention, executive function, working memory, memory, depression	CPT, TMT, WCST, WMS, Digit Span, Logical memory, BDI-II, HAMD	4 weeks	Post-intervention
Wanmaker, 2015[25]	Netherlands	Single-center	Working memory training	Bogus training	Rumination, working memory, depression, anxiety	RRS, WMS, IST, Digit Span, BDI-II, STAI	4 weeks	Post-intervention
Woolf, 2024[26]	Australia	Multi-center	Psychoeducation and computer-based cognitive training	Waitlist control	Depression, verbal learning and memory, executive function, sleep, quality of life, wellbeing	HAMD, DASS, PHQ-9, HVLT, RBANS, TMT, PSQI, WHO-QoL, WHO Wellbeing Index	10 weeks	13-14 weeks
Zetsche, 2024[27]	Germany	Single-center	Computerized cognitive control training	Placebo training	Rumination, depression, disability	RRS, CES-D, WHODAS	2 weeks	3 months

ACS, Wechsler Adult Intelligence Scale Advanced Clinical Solutions Social Perception Subtest; ATQ-R, Automatic Thoughts Questionnaire-revised; BBAT, Brief Behavioral Activation Therapy; BDI, Beck Depression Inventory; BPRS-E, Brief Psychiatric Rating Scale (Expanded version) score; BRIEF-A, Behavior Rating Inventory of Executive Function-Adult; CAMPROMPT-C, Chinese version of the Cambridge Prospective Memory Test Score; CERQ, Cognitive Emotion Regulation Questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale; CPS, Computer Proficiency Scale; CPT, continuous performance test; CVLT, California Verbal Learning Test; DAS, Dysfunctional Attitude Scale; DASS, Chinese version of the Depression Anxiety Stress Scale score; DE-KEFS, Delis-Kaplan Executive Function System; FGT, Figural Memory Test; GRID-HAMD17, GRID-Hamilton Depression Rating Scale; HVLT, Hopkins Auditory Verbal Learning Test; INHIB, inhibition test; IST, Internal Shift Task; MADRS, Montgomery-Asberg Depression Rating Scale; MCQ, Metacognition Questionnaire; MRI, magnetic resonance imaging; MWT, Mehrfachwahl-Wortschatz-Intelligenz test; NART, National Adult Reading Test; NBV, N-Back-verbal; PANAS, Positive and Negative Affect Schedule; PHQ, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QLDS, Quality of Life in Depression Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RDQ, Remission of Depression Questionnaire; ROCF, Rey-Osterrieth Complex Figures; RS, Resilience Scale; STAI, State-Trait Anxiety Inventory; TAP, Test for Attentional Performance; TMT, Trail Making Test; TOL, Tower of London; WAF, Vienna Test System; WAIS- RRS, Ruminative Response Scale; WCST, Wisconsin Card Sorting Test; WFT, word fluency test; WHODAS, WHO Disability Assessment Schedule; WHO-QoL, World Health Organization Quality of Life Index; WMS, Wechsler Memory Scale; ZST, Zahlen-Symbol-Test; NR, Not Reported; PDQ-5-D, Perceived Deficits Questionnaire for Depression-5-items.

functions, future thinking, and anxiety. The evaluation criteria used varied across studies, with depression scores primarily assessed using the GRID-Hamilton Depression Rating Scale (GRID-HAMD 17), Beck Depression Inventory-II (BDI-II), Ruminative Response Scale (RRS), and Trail Making Test-A (TMT-A).

The characteristics of the patients in the included studies are summarized in Table 2. The sample sizes of the intervention groups ranged from 10 to 49, and for the control groups, they ranged from 10 to 63. Mean ages in the intervention and control groups ranged from 34.3 to 76.2 years and from 34.4 to 76.0 years, respectively. The proportion of men varied from 18% to 76% in the intervention group and from 16.7% to 63.3% in the control group. Married individuals comprised 31.6%-56.5% of the intervention group and 16.2%56.5% of the control group. Employment rates ranged from 45% to 100% in the intervention group and from 52.6% to 89.5% in the control group. Mean years of education were 9.3-16.3 years in the intervention group and 8.7-15.5 years in the control group. One study[15] included patients not only with depression but also with schizophrenia.

Risk of Bias Assessment

Details regarding the risk of bias are shown in Figure 2. Over half of the studies (57.1%) reported the random sequence generation method, but many did not explicitly describe allocation concealment. Seven studies might have a high risk of bias due to the lack of blinding of participants, but most studies (71.4%) employed a single-blind setting for the assessment process. All RCTs showed a low risk of bias in outcome data, selective reporting, and other types of bias.

Meta-Analysis

Twelve studies reported depression symptom scores for both groups post-intervention. As shown in Figure 3, there was no significant difference in depression severity post-intervention between the cognitive rehabilitation group and the control group, with an SMD of −0.14 (95% CI: −0.32-0.05; $P = .15$; $I^2 = 30\%$). The funnel plot shows a symmetrical distribution of study results, suggesting no significant publication bias (Figure 4). The results of the secondary outcome meta-analysis are shown in Figure 5. In 4 studies reporting attention-related data, cognitive rehabilitation significantly improved attention in patients with depression compared with the control group,

Table 2. Main Characteristics of the Included Population

Author, year	Participants (diagnostic criteria)	Sample Size	Age, years	Male, %	Married, %	Employed, %	School Education, years
Amano, 2023[14]	Patients with MDD aged 20-69 years (DSM-4)	16/15	38.0 ± 7.4/36.9 ± 10.1	47.4/47.4	52.6/47.4	100.0/89.5	16.3 ± 2.1/15.5 ± 1.4
Au, 2021[15]	Patients with depression or schizophrenia (ICD-10)	10/12	52.3 ± 12.3/52.7 ± 13.8	60.0/16.7	NR	NR	9.3 ± 9.5/8.7 ± 8.5
Hauschildt, 2022[16]	Patients with depression in acute intensive psychiatric inpatient care (MINI)	38/37	41.5 ± 12.9/38.8 ± 12.7	28.9/37.8	31.6/16.2	NR	11.2 ± 1.9/11.7 ± 1.6
Hawighorst, 2023[17]	Adult patients with recurrent or remitted MDD (DSM-5)	49/63	47.6 ± 13.3/40.4 ± 17.1	NR	NR	NR	13.7 ± 2.8/14.7 ± 3.0
Hoorelbeke, 2016[18]	Patients with remitted depression	34/34	46.1 ± 10.8/47.8 ± 12.2	35.3/32.4	NR	NR	NR
Katayama, 2023[19]	Outpatients aged 20-69 years with single or recurrent MDD episodes (DSM-4)	16/13	38.5 ± 6.7/38.5 ± 8.8	43.8/46.2	NR	87.5/76.9	16.3 ± 2.2/15.5 ± 1.1
Klojčnik, 2021[20]	Patients with depression who had previously been diagnosed with depressive episodes (ICD-10)	10/10	43.6 ± 11.5/47.0 ± 9.2	NR	NR	NR	12.3 ± 3.0/11.2 ± 2.8
Listunova, 2020[21]	Patients with MDD in partial remission with cognitive deficits (DSM-4, MINI, HAM-D)	20/19	45.9 ± 11.3/44.9 ± 10.3	25.0/31.6	40/31.6	45.0/52.6	NR
Moshier, 2017[22]	Patients with MMD aged 18-65 years (DSM-4)	21/13	36.3 ± 14.4/34.4 ± 15.4	52.4/38.5	NR	NR	NR
Semkovska, 2017[23]	Patients with a past history of MDD but currently in a remission aged 18-65 years (DSM-4)	11/11	45.9 ± 6.7/46.9 ± 9.3	18.0/18.0	NR	NR	12.3 ± 1.5/11.2 ± 2.2
Trapp, 2016[24]	Patients with MDD (DSM-4 and ICD-10)	23/23	34.3 ± 11.6/36.9 ± 12.1	39.1/26.1	56.5/56.5	69.6/78.3	12.4 ± 2.9/12.5 ± 2.9
Wanmaker, 2015[25]	Patients with a current depression episode or anxiety disorder aged 18-68 years (DSM-4)	49/49	46.6 ± 12.3/47.4 ± 11.7	38.8/63.3	NR	NR	NR
Woolf, 2024[26]	Patients aged ≥65 years with current depressive symptoms or history of MDD within 5 years (MINI)	21/19	76.2 ± 8.1/76.0 ± 6.8	76.0/63.0	NR	NR	14.5 ± 3.3/13.3 ± 3.7
Zetsche, 2024[27]	Patients aged 18-65 years with a current major depressive episode (DSM-5)	30/34	39.2 ± 13.1/38.5 ± 12.7	26.7/32.3	NR	NR	NR

Values are expressed as mean ± standard deviation or percentages (intervention/control groups). DSM, Diagnostic and Statistical Manual of Mental Disorders; HAM-D, the 24-item Hamilton Rating Scale for Depression; ICD, International Classification of Diseases; MDD, major depression disorder; NR:, not reported; MINI, Mini International Neuropsychiatric Interview.

Figure 2. Evaluation of risk of bias of the included studies.

with an SMD of −0.63 (95% CI, confidence interval: −0.99 to −0.27; $P < .001$; $I^2 = 0\%$). In 6 studies, data showed a significant improvement in verbal learning ability in patients with depression after cognitive rehabilitation, with an SMD of −0.33 (95% CI: −0.60 to −0.05; $P = .02$; $I^2 = 48\%$). A total of 6 and 7 studies reported executive function and working memory, respectively, before and after intervention. Meta-analysis showed no statistically significant difference between the groups in executive function and working memory post-intervention, with SMDs of −0.45 (95% CI: −1.09 to 0.19; $P = .17$; $I^2 = 78\%$) and −0.38 (95% CI: −0.82 to 0.07; $P = .10$; $I^2 = 67\%$). The funnel plot indicates symmetrical data distribution in the attention and verbal learning outcomes, whereas potential publication bias may have existed in executive function and working memory outcomes (Figure 6).

Subgroup Analysis

Subgroup analysis was conducted to evaluate the impact of different regions on the relationship between cognitive rehabilitation and depressive symptoms in patients, as well as heterogeneity. The results are shown in Supplementary Figure 1A. In European regions, cognitive rehabilitation training had a slight improvement effect on the severity of depressive symptoms in patients, with an SMD of −0.22 (95% CI: −0.45 to 0.00; $P = .05$; $I^2 = 32\%$), reaching the pre-set statistical threshold. However, studies conducted in other regions showed no significant effect of cognitive rehabilitation training on depressive symptoms in patients, with an SMD of 0.05 (95% CI: −0.28 to 0.38; $P = .78$; $I^2 = 23\%$). It is worth noting that no significant heterogeneity was found among the studies before and after subgroup analysis. No evident publication bias was found in the subgroup analysis (Supplementary Figure 1B).

Discussion

This meta-analysis integrated the latest clinical evidence, systematically analyzing the impact of cognitive rehabilitation as an auxiliary training method on symptom improvement and cognitive function recovery in patients with depression. It also methodologically assessed the quality of the included studies. The main findings of this study are as follows: (1) compared with the control group, there was no significant improvement in depression scores post-intervention in patients receiving cognitive rehabilitation training, with no statistically significant difference between the groups; (2) cognitive

Study or Subgroup	Cognitive rehabilitation Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Amano 2023	18.9	12.3	16	18.5	12	15	7.1%	0.03 [−0.67, 0.74]
Au 2021	22	12.1	12	21.3	16.8	10	5.0%	0.05 [−0.79, 0.89]
Hauschildt 2022	14.29	9.94	28	15	11.35	19	10.4%	−0.07 [−0.65, 0.52]
Hawighorst 2023	18.19	12.2	16	13.33	9.07	15	6.9%	0.44 [−0.28, 1.15]
Hoorelbeke 2016	4.5	5.1	34	9.29	7.28	34	14.5%	−0.75 [−1.25, −0.26]
Katayama 2023	7.6	5.2	14	12.9	9	13	5.8%	−0.71 [−1.49, 0.08]
Klojčnik 2021	22.5	6.26	10	22.8	6.27	10	4.6%	−0.05 [−0.92, 0.83]
Moshier 2017	22	11.8	21	18.2	14.6	13	7.3%	0.29 [−0.41, 0.98]
Semkovska 2017	8.3	7.6	11	7.3	8.6	10	4.8%	0.12 [−0.74, 0.98]
Trapp 2016	16.04	12.32	23	18.22	12.89	23	10.5%	−0.17 [−0.75, 0.41]
Woolf 2024	4.05	3.22	21	6.4	5.4	19	8.8%	−0.52 [−1.16, 0.11]
Zetsche 2024	29.48	11.12	30	27.84	8.08	34	14.5%	0.17 [−0.32, 0.66]
Total (95% CI)			**236**			**215**	**100.0%**	**−0.14 [−0.32, 0.05]**

Heterogeneity: Chi² = 15.75, df = 11 (P = 0.15); I² = 30%
Test for overall effect: Z = 1.43 (P = 0.15)

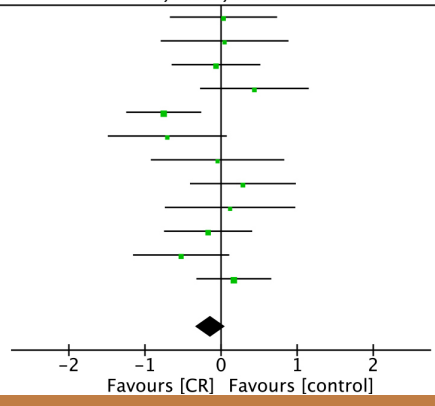

Figure 3. Forest plot of depressive symptom after cognitive rehabilitation. SD, Standard Deviation; CI, Confidence Interval.

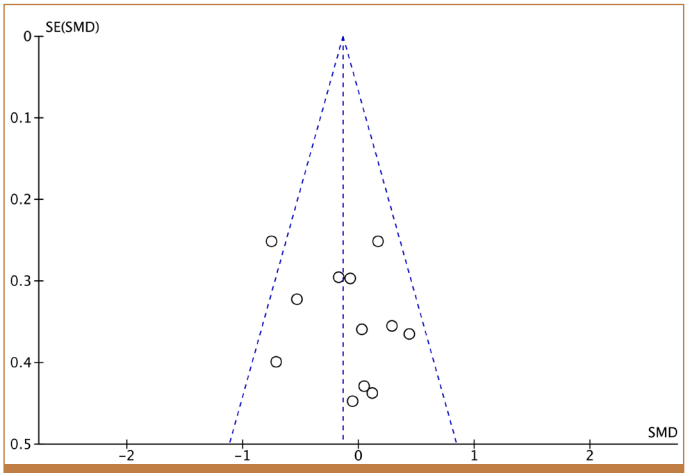

Figure 4. Funnel plot of analyses of depressive symptoms.

rehabilitation training contributed to the improvement of attention and verbal learning functions in patients with depression; and (3) cognitive rehabilitation training did not significantly affect the executive function and working memory of patients with depression. This study aimed to provide evidence and reference for using cognitive rehabilitation as a training method to help improve cognitive function in patients with depression.

The current meta-analysis has similarities and differences with previous related studies, but our study has certain advantages in methodology and inclusion criteria. First, previous meta-analyses have already suggested that cognitive rehabilitation has some efficacy in improving depressive symptoms. Woolf et al[28] and Legemaat et al[29] found that cognitive training and remediation had minor but statistically significant effects on depressive symptoms in patients with major depressive disorder (MDD). However, most of these studies are relatively old, with limited numbers of included studies, limiting the generalizability and timeliness of their conclusions. Recently, a meta-analysis also reached conclusions similar to ours, indicating that cognitive rehabilitation had no significant effect on the severity of depressive symptoms in patients.[30] However, differences in analysis methods and inclusion criteria have resulted in variations in scope and conclusions between our study and this meta-analysis. Our study includes a substantial number of recent studies, enhancing the timeliness and reliability of our results. The study also extends beyond MDD to encompass a broader spectrum of depressive symptoms and types, offering a comprehensive evaluation of the efficacy of cognitive rehabilitation across diverse patient populations with depression. Despite our meta-analysis providing more robust, up-to-date evidence supporting the efficacy of cognitive rehabilitation in improving depressive symptoms and restoring cognitive function, there are still challenges and research gaps. For example, there is a lack of unified standards and guidelines on the specific intervention content, optimal implementation methods, and the sustained and long-term effects of cognitive rehabilitation.

Cognitive functions, including attention, memory, executive function, and working memory, are often significantly impaired in patients with depression. In recent years, an increasing number of studies have focused on the relationship between cognitive training and cognitive function in patients with depression.[31] Although our meta-analysis shows that cognitive training has a certain recovery effect on attention and verbal learning in patients with depression, the exact mechanisms behind these results still need further exploration. Cognitive training may produce positive effects through various pathways, including changes in neural plasticity, the learning and application of cognitive strategies, and improvement in emotion regulation.[32] Recent neuroimaging studies have found that cognitive training can promote improvements in brain network connectivity in patients with depression, especially in the prefrontal–amygdala network involved in emotion regulation and cognitive control.[33] These improvements in brain networks may help to promote attention and verbal learning abilities, thereby alleviating cognitive impairments in patients with depression. Delving deeper into the results of this meta-analysis, the recovery effects of cognitive training on working memory and executive function in patients with depression are not significant. This is consistent with some previous research results on cognitive training but is different from some of the latest studies. This difference may partly originate from the heterogeneity in the studies, including variations in study design, sample selection, cognitive training programs, and evaluation criteria.

Additionally, variability in baseline depression scores, influenced by the diversity in scoring methods used across studies, was not explicitly detailed in Table 2. First, there are relatively few studies on working memory and executive function, limiting the statistical power, and affecting the stability and accuracy of the results. Second, different evaluation indicators in each study may have led to result heterogeneity, making comparison and synthesis analysis more difficult. Moreover, publication bias may have affected the results of our meta-analysis. Despite our efforts to include all available studies, published research results tend to be positive or significant, leading to an overly optimistic estimation of the effects of cognitive training.

The results of this study provide important insights for clinical practice, particularly regarding the potential role and limitations of cognitive rehabilitation in the treatment of depression. Although our meta-analysis did not reveal a comprehensive improvement effect of cognitive rehabilitation on depressive symptoms, it showed positive outcomes in attention and verbal learning. Although cognitive rehabilitation did not lead to extensive improvement in depressive symptoms, its positive effects on attention and verbal learning remain clinically significant. These cognitive functions are fundamental in daily life and social interactions, and enhancing them can greatly improve the quality of life and social functioning of patients with depression.

Our study underscores the complexity and variability of cognitive impairments among individuals with depression. Clinicians need to consider the specific types and degrees of cognitive impairments in each patient when designing individualized treatment plans. Furthermore, although cognitive rehabilitation did not produce positive effects in all cognitive function domains, it provided a supplementary strategy for the treatment of depression. Combined with other treatment methods (e.g., pharmacotherapy and psychotherapy), cognitive rehabilitation can be an important component of a comprehensive treatment plan to more fully meet the needs of patients with depression. These findings underscore the importance of exploring and optimizing the content, methods, and duration of cognitive rehabilitation to achieve broader and more lasting effects.

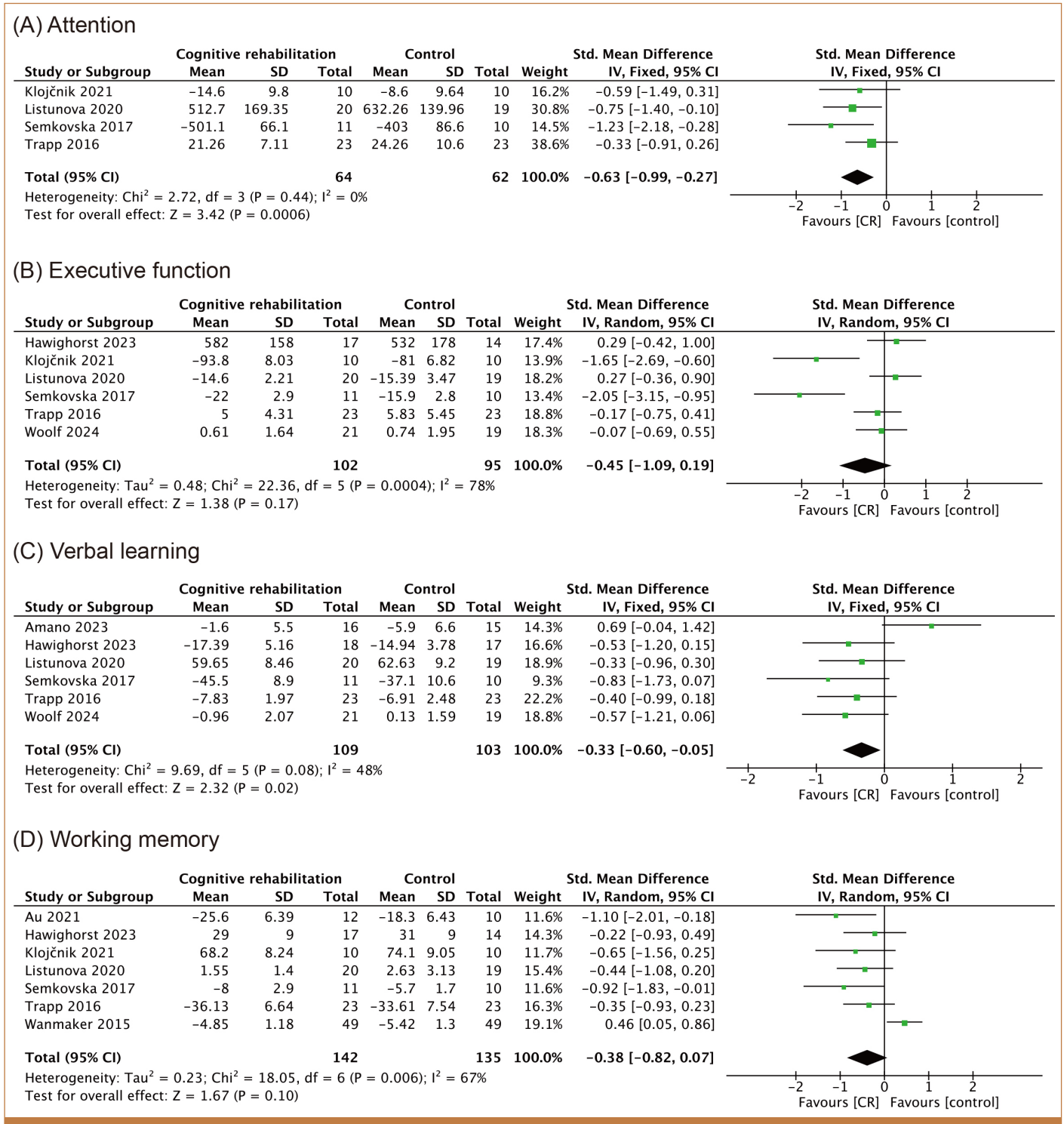

Figure 5. Forest plots of secondary outcomes after cognitive rehabilitation. (A) attention; (B) executive function; (C) verbal learning; (D) working memory.

Additionally, future research needs to validate our findings and explore the role of cognitive rehabilitation, its long-term effects, and potential mechanisms across diverse patient groups. The subgroup analysis revealed regional variations in the effects of cognitive rehabilitation training on depression severity. Several factors may have contributed to these differences: cultural attitudes toward mental health and therapy, healthcare system structures, socioeconomic conditions, and genetic or biological variations among populations. These findings highlight the importance of tailoring cognitive rehabilitation interventions to specific regional and cultural contexts. Clinically, this emphasizes the need for individualized, context-sensitive approaches to cognitive rehabilitation, considering the unique characteristics of different populations and regions to maximize effectiveness.

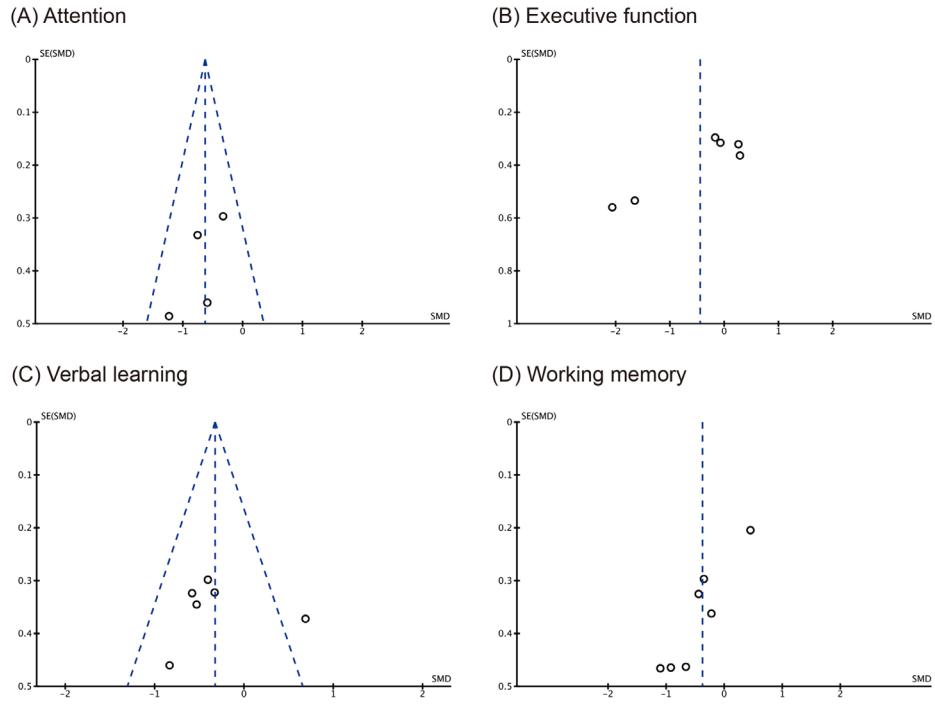

Figure 6. Funnel plots of analyses of secondary outcomes. (A) attention; (B) executive function; (C) verbal learning; (D) working memory.

This study may have some limitations. First, although we included a relatively large number of recent studies, the number of reports on secondary outcomes was limited. This may have restricted our understanding of the effects of cognitive rehabilitation on other cognitive functions in patients with depression. Second, there were significant differences among the studies in follow-up periods, intervention measures, and control measures, which may have introduced uncertainty and heterogeneity in the results of the study. These differences may have limited the comparison and synthesis analysis between studies, thereby affecting our accurate evaluation of the effects of cognitive rehabilitation. Third, from the perspective of methodological quality, most studies could not blind the participants due to design issues. This may have introduced bias into the results, as both participants and researchers could have had expectation effects when aware of the type of intervention received. Additionally, the sample sizes of each included study were relatively small, and most were conducted at single centers. This could have restricted the external validity and generalizability of the study findings, as these studies may have not fully reflected a broader population of patients with depression.

Conclusion

In conclusion, this study explored in depth the effects of cognitive rehabilitation on improving cognitive function and symptoms in patients with depression. Although we found that cognitive rehabilitation has positive effects on attention and verbal learning, its improvement effects on other cognitive functions and depressive symptoms are limited. These findings emphasize the role and limitations of cognitive rehabilitation as a potential supplementary treatment method in the treatment of depression. Future research should focus on addressing the current problems and limitations in the research to more comprehensively and accurately evaluate the potential value and practical application of cognitive rehabilitation in the treatment of depression.

Ethics Committee Approval: *Not applicable.*

Informed Consent: *Verbal/Written informed consent was obtained from the patients/patient who agreed to take part in the study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – L.L., K.W.; Design – L.L., K.W.; Materials – Q.W., X.W.; Data Collection and/or Processing – D.X., Y.W., X.X., Q.W., X.W.; Analysis and/or Interpretation – D.X., Y.W., X.X.; Literature Search – D.X., Y.W., X.X., Q.W., X.W.; Writing – L.L., K.W.; Critical Review – L.L., K.W., D.X., Y.W., X.X., Q.W., X.W.*

Acknowledgment: *Not applicable.*

Declaration of Interests: *The authors have no conflict of interest to declare.*

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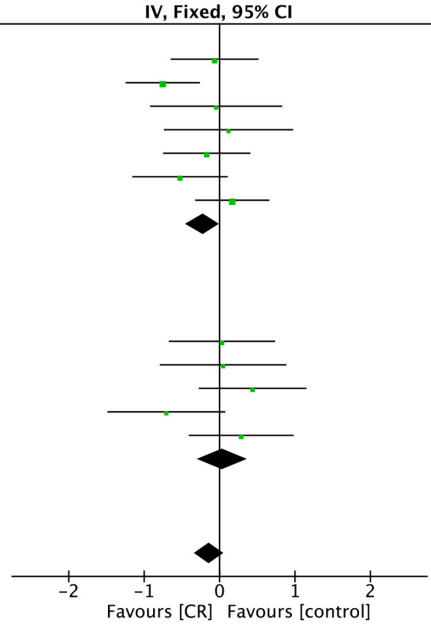

Study or Subgroup	Cognitive rehabilitation Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.1.1 Europe								
Hauschildt 2022	14.29	9.94	28	15	11.35	19	10.4%	−0.07 [−0.65, 0.52]
Hoorelbeke 2016	4.5	5.1	34	9.29	7.28	34	14.5%	−0.75 [−1.25, −0.26]
Klojčnik 2021	22.5	6.26	10	22.8	6.27	10	4.6%	−0.05 [−0.92, 0.83]
Semkovska 2017	8.3	7.6	11	7.3	8.6	10	4.8%	0.12 [−0.74, 0.98]
Trapp 2016	16.04	12.32	23	18.22	12.89	23	10.5%	−0.17 [−0.75, 0.41]
Woolf 2024	4.05	3.22	21	6.4	5.4	19	8.8%	−0.52 [−1.16, 0.11]
Zetsche 2024	29.48	11.12	30	27.84	8.08	34	14.5%	0.17 [−0.32, 0.66]
Subtotal (95% CI)			**157**			**149**	**68.0%**	**−0.22 [−0.45, 0.00]**
Heterogeneity: Chi^2 = 8.83, df = 6 (P = 0.18); I^2 = 32%								
Test for overall effect: Z = 1.92 (P = 0.05)								
1.1.2 Others								
Amano 2023	18.9	12.3	16	18.5	12	15	7.1%	0.03 [−0.67, 0.74]
Au 2021	22	12.1	12	21.3	16.8	10	5.0%	0.05 [−0.79, 0.89]
Hawighorst 2023	18.19	12.2	16	13.33	9.07	15	6.9%	0.44 [−0.28, 1.15]
Katayama 2023	7.6	5.2	14	12.9	9	13	5.8%	−0.71 [−1.49, 0.08]
Moshier 2017	22	11.8	21	18.2	14.6	13	7.3%	0.29 [−0.41, 0.98]
Subtotal (95% CI)			**79**			**66**	**32.0%**	**0.05 [−0.28, 0.38]**
Heterogeneity: Chi^2 = 5.18, df = 4 (P = 0.27); I^2 = 23%								
Test for overall effect: Z = 0.28 (P = 0.78)								
Total (95% CI)			**236**			**215**	**100.0%**	**−0.14 [−0.32, 0.05]**
Heterogeneity: Chi^2 = 15.75, df = 11 (P = 0.15); I^2 = 30%								
Test for overall effect: Z = 1.43 (P = 0.15)								
Test for subgroup differences: Chi^2 = 1.74, df = 1 (P = 0.19), I^2 = 42.5%								

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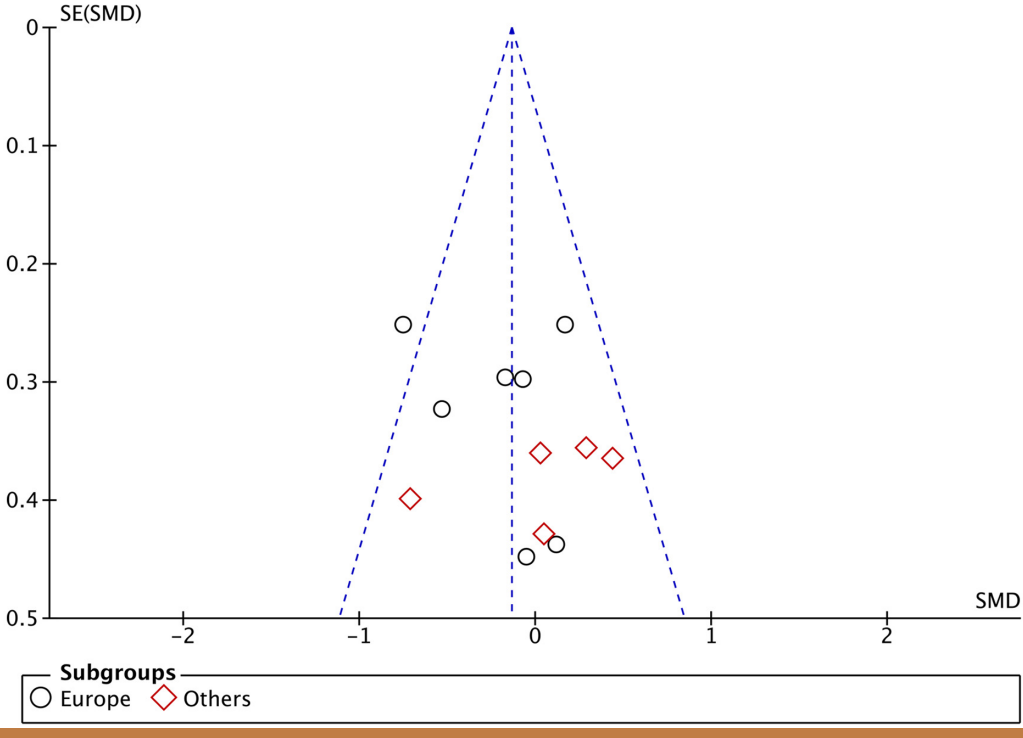

Supplementary Figure 1. The forest plots of secondary outcomes after cognitive rehabilitation. SMD, Standard mean difference.

Section and Topic	Item #	Checklist Item	Location Where Item is Reported
TITLE			
Title	1	Identify the report as a systematic review.	Line 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	N/A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Line 87
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Line 94
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Line 122
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Line 101
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Line 107
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Line 118
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Line 137
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Line 137
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Line 137
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Line 142
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Line 152
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Line 152
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Line 152
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Line 152
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Line 152
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Line 152
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Line 152
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Line 152
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			

Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Line 154
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	Line 177
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Line 202
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Line 177
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Line 213
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Line 213
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Line 247
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Line 213
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Line 260
	23b	Discuss any limitations of the evidence included in the review.	Line 359
	23c	Discuss any limitations of the review processes used.	Line 359
	23d	Discuss implications of the results for practice, policy, and future research.	Line 326
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Line 4
Competing interests	26	Declare any competing interests of review authors.	Line 4
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71