Cognitive Stimulation for Persons with Dementia: a Systematic Review and Meta-Analysis

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CME

Abstract

Objective: We aim to provide an up-to-date systematic review and meta-analysis of the effects of cognitive stimulation (CS) on cognition, depressive symptoms, and quality of life in persons with dementia. Factors affecting the treatment effect were examined.

Methods: A literature search was performed on databases of MEDLINE, EMBASE, PsycINFO, CINAHL Plus, and Cochrane Library up to 7 March 2019. Only randomised controlled trials investigating the effects of CS in persons with dementia were included. The outcome measures were cognitive function, depressive symptoms, and quality of life.

Results: 20 randomised controlled trials with a total of 1251 participants (intervention group: 674; control group: 577) were included for meta-analysis. Most participants had mild to moderate dementia. CS had a significant positive small-to-moderate effect on cognition (Hedges's $g = 0.313$, $p < 0.001$). Heterogeneity of CS was low to moderate ($Q=30.5854$, $df=19$, $p < 0.05$, $I^2 = 37.877\%$). Inconclusive results were found for depressive symptoms and quality of life.

Conclusion: CS has a significant positive effect on cognitive function, but its effect on depressive symptoms and quality of life was inconclusive. Future studies with more robust methodology establishing evidence of its efficacy are required.

Key words: Cognition; Dementia; Meta-analysis; Systematic review

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Introduction

Dementia is a neurocognitive disorder and a major public health issue¹ and causes difficulty in independent daily functioning.² Dementia has a high burden on morbidity and mortality. Both pharmacological and non-pharmacological treatments are the mainstay of treatment, but pharmacological treatment has potential adverse effects. There is a growing need for non-pharmacological interventions in dementia.³ Cognitive stimulation (CS) aims at stimulating cognitive and social functions globally by means of activities and discussions.⁴ CS emphasises information processing rather than acquiring knowledge and facts.⁵ CS can be operationally performed in groups or individually with an

integrative approach involving presentation of orientation information, structured discussions on various everyday topics and enjoyable activities within a socially engaged context.^{4,6,7} The mechanism of action for CS is based on the theories of cognitive reserve and neuronal plasticity, which are originated from reality orientation developed in 1966.⁸ CS stimulates cognitive functions globally, as various cognitive functions are utilised in a unified rather than an isolated manner.⁴ However, CS is heterogeneous in terms of formats, settings, and duration of treatment, with high content variability.

Two meta-analyses investigated the effects of CS in dementia.^{7,9} Both supported the efficacy of CS on cognition (with medium effect size) and on quality of life but not on depressive symptoms. However, other studies reported inconsistent results on cognitive function,¹⁰⁻¹² which may be due to the heterogeneity of CS in terms of formats, settings, and duration of treatment, as well as methodological quality of studies, sample size, and recruitment. Depressive symptoms and quality of life were not fully representative in the two meta-analyses. Applying stringent eligibility criteria (pre-defined control group, study design) in selection of studies enables more accurate summarisation of findings. Therefore, we aim to provide an up-to-date systematic review and meta-analysis of the effects of CS on cognition, depressive symptoms, and quality of life in persons with dementia. Factors affecting the treatment effect were examined.

Methods

Only randomised controlled trials (RCTs) with both parallel and cross-over designs were considered. For RCTs with cross-over design, only data before cross-over were included, as it was difficult to ascertain whether the washout period from previous intervention was adequate. CS interventions and reality orientation classified under the domain of CS interventions that fit in definition were included.⁴ Interventions with different formats (group or individual) and settings (inpatient, outpatient, institution, or home) were accepted. Studies with inactive control group (in form of no active treatment, waitlisted for intervention, or treatment as usual) were included to estimate the absolute effect of treatment.¹³ Studies with combined interventions (CS +/- other forms of cognitive intervention) were excluded.

Study subjects had to fulfil a diagnosis of dementia. Older studies using descriptive terms other than dementia were considered, but the diagnosis must be supported by cognitive assessment (eg, Mini-Mental State Examination). Studies with a mixed group of subjects (such as mild cognitive impairment and dementia) or subjects with comorbidity (such as delirium, substance misuse, or learning disabilities) were excluded.

Cognitive function had to be assessed using Mini-Mental State Examination or Alzheimer's Disease Assessment Scale-Cognitive Subscale. Depressive symptoms had to be assessed using the Cornell Scale for Depression in Dementia or the Hamilton Depression Rating Scale. Quality of life had to be measured using Quality of life in Alzheimer's Disease (QoL-AD). Outcomes immediately after the intervention were measured. Data on follow-up assessments were documented. Studies with no report or inadequate information to calculate the effect size of cognitive outcome were excluded.

A literature search was performed on databases of MEDLINE, EMBASE, PsycINFO, CINAHL Plus, and Cochrane Library (Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews) up to 7 March 2019. No limit was applied for language. Ongoing clinical trials were identified by searching ClinicalTrials.gov, EU Clinical Trials Register, and WHO International Clinical Trials Registry Platform up to 7 March 2019. Reference lists of the included studies and review articles of similar topics were searched to identify potentially eligible studies. Keywords used to identify articles related to CS-related clinical trials in dementia were: exp cognitive therapy/ or cognit* stimul* therap* or (cognit* adj (therap* or stimul* or train* or rehabilitat* or intervent* or enhanc* or enrich* or treat* or activit* or program* or method* or exercise*) or (CST or CS intervent*) or (memory adj (rehabilitat* or strateg* or exercise or train* or group* or enhanc*)) or (((non-drug or non-pharmacologic*) adj3 (treat* or intervent* or program* or method* or therap*)) and cognit*) or reality orient*; exp dementia/ or dement* or Alzheimer* or (frontotemporal lobar degeneration or frontolobar degeneration or frontal

lobar degeneration) or vascular cognitive impair* or lewy* bod* or ((memory adj (disorder or impair* or dysfunction)) or (cognitive adj (disorder or impair* or dysfunction)) or neurocognitive disorder); random* or controlled trial or clinical trial or RCT.

Eligible studies were identified by two authors independently. Duplicated records were removed. Studies that met the inclusion criteria or could not be excluded based on titles and abstracts were reviewed in full text. Any disagreements were resolved by discussion or by a third author. The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁴

The two authors independently extracted the data using a semi-structured form for each trial and cross-checked the results for accuracy. Disagreements regarding data extraction were resolved by consensus or by the third author. The corresponding authors of the studies were contacted for clarification or missing information.

The methodological quality of included RCTs was examined by the three authors independently according to the six domains of the Cochrane Collaboration's tool for assessing the risk of bias:¹⁵ (1) sequence generation, (2) allocation concealment, (3) blinding of the participants, (4) blinding of the assessors, (5) method of addressing incomplete outcome data, and (6) selective reporting. The methodological quality was classified as low, high, or uncertain risk of bias in each domain.

The treatment effect was examined using a meta-analysis by pooling data from the RCTs. For the outcome variables, a pooled effect size was calculated using a random effects model and presented as a standardised mean difference with 95% confidence intervals. The random effects model was used because the estimates of the treatment effect vary between trials because of real differences and sampling variability.¹⁶ Forest plots were generated with the Comprehensive Meta-Analysis v3 software.¹⁷ Significant heterogeneity between studies was indicated as $p < 0.1$ in the Q statistic and as $>50\%$ in the I^2 statistic.¹⁸

Subgroup analyses were performed to investigate heterogeneity and estimate treatment effects of CS on cognition for clinically relevant subgroups. Programme formats (individual and group), settings (home and non-home), and duration of treatment were assessed. For the latter, the cut-off point was set at 3 months as it was the median duration among the included studies.

Results

The literature search yielded 7594 results. A detailed PRISMA flow diagram of trials identification and selection is shown in Figure 1. A search of ongoing clinical trials, reference lists of review articles of similar topics, and included studies yielded further 2470 results. After exclusion of duplicates and irrelevant records, 263 articles required full-text review. After excluding the ineligible articles, 22 RCTs were included in the qualitative synthesis.

Figure 1. PRISMA flow diagram of selection of studies

Cognitive outcome immediately after CS was not available in two RCTs,^{12,19} despite follow-up through emails, and these two RCTs were excluded. Finally, 20 studies were included in the meta-analysis.^{11,20-38}

A total of 1343 participants (intervention group: 717, control group: 626) were included (Table 1). Their mean age ranged from 70.09 to 86.37 years. 18 studies reported sex distribution; most comprised predominantly female participants (51.9% to 100%). 15 studies used validated diagnostic guidelines including ICD-10, DSM-III, DSM-III-R, and DSM-IV. The diagnosis of dementia was made based on the Clifton Assessment Procedures for the Elderly and the Mini-Mental State Examination.^{20,29} 14 studies reported the subtypes of dementia, and nearly all of them included those with Alzheimer disease, except for one

study that included those with Parkinson dementia only.³⁰ 16 studies reported the severity of dementia (mainly mild to moderate dementia). 15 studies reported information on the use of cognitive enhancers: all and none of participants used cognitive enhancers in seven and two studies, respectively. Nearly all studies did not report information on the use of antidepressants.

The characteristics of the included RCTs are shown in Table 2. 20 were parallel studies and two were cross-over studies.^{20,30} CS was commonly carried out in outpatient and institution settings. Only two studies were carried out at home and another two in the hospital. CS therapy was conducted in three studies. Reality orientation was delivered in eight studies. Treatment as usual and no active treatment were the control condition in most studies.

Table 1. Characteristics of studies and participant demographics

Study	Setting	Country	Design	Mean $\pm$ SD patient age, y	% of female	Sample size, treatment: control	Diagnosis*	Mean $\pm$ SD or range Mini-Mental State Examination score	On cognitive enhancers (% of treatment: control)	On anti-depressants
Baines et al, ²⁰ 1987	Institution	United Kingdom	Cross-over (reality orientation/ reminiscence therapy)	80.9	-	5:5	Confused patients with moderate to severe impairment of cognitive functioning on Clifton Assessment Procedures for the Elderly	-	-	-
Baldelli et al, ²¹ 1993	Institution	Italy	Parallel	84.5 $\pm$ 6.4	100	13:10	Senile dementia of Alzheimer's type, mild to moderate in severity	20.62 $\pm$ 4.8	-	-
Baldelli et al, ²² 2002	Institution	Italy	Parallel	80 $\pm$ 7.4	70.1	71:16	Senile dementia of Alzheimer's type and vascular multi-infarct dementia	20.73 $\pm$ 2.92	-	-
Bottino et al, ²³ 2005	Outpatient	Brazil	Parallel	73.7 $\pm$ 6.39	69.2	6:7	ICD-10 and NINCDS-ADRDA Alzheimer's dementia, mild in severity	22.31 $\pm$ 3.61	Rivastigmine (100:100)	-
Breuil et al, ²⁴ 1994	Outpatient	France	Parallel	77.15 $\pm$ 7.08	60.7	29:27	DSM-III criteria of dementia, mild to moderate in severity; 92% Alzheimer's dementia, others Parkinson's dementia and multi-infarct dementia	>9	-	Allowed
Camargo et al, ²⁵ 2015	Outpatient	Brazil	Parallel	80.14 $\pm$ 6.04	36	7:7	DSM-IV criteria of Alzheimer's dementia, mild to moderate in severity	22.43 $\pm$ 2.82	Donepezil (100:100)	-
Chapman et al, ¹⁹ 2004	Outpatient	United States	Parallel	76.38 $\pm$ 7.86	54	17:20	NINCDS-ADRDA probable Alzheimer's dementia, mild to moderate in severity	20.87 $\pm$ 3.55	Donepezil (100:100)	-
Coen et al, ²⁶ 2011	Institution	Ireland	Parallel	79.8 $\pm$ 5.69	51.9	13:12	Mild to moderate dementia	16.88 $\pm$ 4.94	Cholinesterase inhibitors (14.3:30.8)	-
Cove et al, ²⁷ 2014	Outpatient	United Kingdom	Parallel	77.29 $\pm$ 6.99	46.8	24:23	DSM-IV criteria of dementia, mild to moderate in severity	22.81 $\pm$ 3.38	Dementia medications (66.7:56.5)	-
D'Onofrio et al, ²⁸ 2015	Outpatient	Italy	Parallel	77.36 $\pm$ 4.37	53.3	45:45	Alzheimer's dementia, mild to moderate in severity	18.91 $\pm$ 2.82	Rivastigmine patch (100:100)	No
Ferrario et al, ²⁹ 1991	Institution	Italy	Parallel	82.5 $\pm$ 5.2	42.1	13:6	Cognitive disturbance	18-25	No	-
Folkerts et al, ³⁰ 2018	Institution	Netherlands	Cross-over	76.59 $\pm$ 7.11	16.7	6:6	Movement Disorder Society diagnostic criteria of Parkinson's disease dementia	17.84 $\pm$ 5.31	No. of drugs (0.83 $\pm$ 0.98 : 1.00 $\pm$ 0.63)	No. of drug (0.83 $\pm$ 1.17 : 0.42 $\pm$ 0.66)

* NINCDS-ADRDA denotes National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association

Table 1. (cont'd)

Study	Setting	Country	Design	Mean $\pm$ SD patient age, y	% of female	Sample size, treatment: control	Diagnosis*	Mean $\pm$ SD or range Mini-Mental State Examination score	On cognitive enhancers (% of treatment: control)	On anti-depressants
Luttenberger et al, ³¹ 2012	Institution	Germany	Parallel	85.1 $\pm$ 5.1	83.3	31:30	ICD-10 criteria of Alzheimer's dementia / unspecified dementia	14.6 $\pm$ 5.4	Cholinesterase inhibitors/ memantine (18:8.7)	-
Middelstadt et al, ³² 2016	Institution	Germany	Parallel	86.37 $\pm$ 4.45	84.5	35:33	ICD-10/German Social Code Book XI/clinical diagnosis of mild to moderate dementia	16.92 $\pm$ 4.45	-	-
Onder et al, ³³ 2005	Home	Italy	Parallel	75.8 $\pm$ 7.1	72.4	70:67	NINCDS-ADRA criteria of probable Alzheimer's dementia, mild to moderate in severity	20.05 $\pm$ 3.15	Donepezil (100:100)	-
Orrell et al, ¹¹ 2017	Home	United Kingdom	Parallel	78.2 $\pm$ 7.49	46	134:139	DSM-IV criteria of mild to moderate dementia	21.22 $\pm$ 4.3	Cholinesterase inhibitors (76:76)	-
Requena et al, ³⁴ 2006	Outpatient	Spain	Parallel	76.96 $\pm$ 7.4	66	20:30	DSM-IIIIR and NINCDS ADRDA criteria of mild to moderate Alzheimer's dementia	21.88 $\pm$ 6.66	Donepezil (100:100)	-
Spector et al, ³⁵ 2001	Institution and day centre	United Kingdom	Parallel	85.7 $\pm$ 6.7	-	17:10	DSM-IV criteria of dementia	12.98 $\pm$ 4.74	-	-
Spector et al, ³⁶ 2003	Institution and day centre	United Kingdom	Parallel	85.3 $\pm$ 7.0	78.6	97:70	DSM-IV criteria of dementia, mild to moderate in severity	14.4 $\pm$ 3.8	No	-
Tsantali et al, ¹² 2017	Outpatient	Greece	Parallel	73.8 $\pm$ 5.25	-	17:21	NINCDS-ADRDA and DSM-IV criteria of Alzheimer's dementia, mild in severity	22.83 $\pm$ 1.23	Cholinesterase inhibitors (100:100)	-
Wallis et al, ³⁷ 1983	Inpatient	United Kingdom	Parallel	70.09 $\pm$ N/A	-	10:9	Clinical diagnosis of dementia	-	-	-
Yamagami et al, ³⁸ 2012	Institution	Japan	Parallel	85.21 $\pm$ 5.31	90.7	28:25	Mild to severe dementia	-	Donepezil (32.1:46.2)	-

The methodological quality of the included RCTs is summarised in Table 3. In most studies, all types of risk of bias were of low risk, except for blinding of participants and personnel. The risk of bias was uncertain in terms of random sequence generation, adequacy of allocation concealment, and blinding of assessors, because of insufficient information. Four RCTs had a high risk of bias because of having incomplete outcome data. None had a reporting bias. Overall, the methodological quality of included RCTs was moderate, because most types of risk of bias were of low risk, yet uncertain risk was evident for random sequence

generation and allocation concealment owing to insufficient information.

Meta-analysis of 1251 participants (intervention group: 674, control group: 577) in 20 studies indicated that CS had a significant positive small-to-moderate effect on cognition (Hedges's $g = 0.313$, 95% CI = 0.154-0.472, $p = 0.0001$, Figure 2). Heterogeneity of CS was low to moderate ($Q = 30.584$, $df = 19$, $p = 0.045$; $I^2 = 37.877\%$). Meta-analysis of 296 participants (intervention group: 165, control group: 131) in four studies indicated that CS had no significant effect on depressive symptoms

Table 2. Intervention and control characteristics of included studies

Study	Programme details	Duration and frequency of session	Duration of programme	Format	Control
Baines et al, ²⁰ 1987	Reality orientation: use of orientation board, writing materials, old and current newspaper/photos; sensory stimulation	30 minutes, 5 times per week	4 weeks	Group	No treatment
Baldelli et al, ²¹ 1993	Reality orientation	60 minutes, 3 times per week	3 months	Group	No active intervention
Baldelli et al, ²² 2002	Reality orientation	60 minutes, 5 times per week	1 month	Group	Treatment as usual (physical therapy)
Bottino et al, ²³ 2005	Temporal and spatial orientation, talking about lives, sharing life experiences, discussing interesting themes, simulation of daily activities	90 minutes, once per week	5 months	Group	Treatment as usual (medications)
Breuil et al, ²⁴ 1994	Stimulation of different cognitive functions through theme related objects/pictures	60 minutes, 2 times per week	5 weeks	Group	Treatment as usual
Camargo et al, ²⁵ 2015	Reality orientation: stimulate personal, temporal, and spatial orientation, discussing on personal and social events, social engagement	30-60 minutes, once per week	6 months	Individual	Treatment as usual (medications)
Chapman et al, ¹⁹ 2004	Cognitive-communication stimulation: group discussion on present events, personal interests and sharing of past events	90 minutes, once per week	8 weeks	Group	Treatment as usual (medications)
Coen et al, ²⁶ 2011	Cognitive stimulation therapy	45 minutes, 2 times per week	7 weeks	Group	Routine activities
Cove et al, ²⁷ 2014	Cognitive stimulation therapy	45 minutes, once per week	14 weeks	Group	Waiting list group
D'Onofrio et al, ²⁸ 2015	Reality orientation: orientation and stimulation of different cognitive functions (memory, attention, logic, verbal fluency)	90 minutes, once per week	6 months	Individual	Treatment as usual (medications)
Ferrario et al, ²⁹ 1991	Reality orientation	60 minutes, 5 times per week	24 weeks	Group	No treatment
Folkerts et al, ³⁰ 2018	NEUROvitalis senseful: range of activities and the use of sensory stimulation to stimulate various cognitive functions	60 minutes, 2 times per week	8 weeks	Group	Usual care
Luttenberger et al, ³¹ 2012	Discussion of meaningful topics, group songs, cognitive activities (eg, combining numbers, sentences and words, photo puzzle, word association), performs tasks in daily activities, psychomotor games and activities	120 minutes, 6 times per week	12 months	Group	Usual activities

Table 2. (cont'd)

Study	Programme details	Duration and frequency of session	Duration of programme	Format	Control
Middelstadt et al, ³² 2016	NEUROvitalis senseful: range of activities (eg, city map game, word and pictures) and the use of sensory stimulation to stimulate various cognitive functions and facilitate conversations about personal experiences and opinions	60 minutes, 2 times per week	8 weeks	Group	Usual care
Onder et al, ³³ 2005	Reality orientation delivered by caregivers: orientation, topics of general interest, attention, memory, visuospatial exercise with the aid of calendars, clocks, and notes	30 minutes, 3 times per week	25 weeks	Individual	Treatment as usual (medications)
Orrell et al, ¹¹ 2017	Cognitive stimulation therapy delivered by caregivers	30 minutes, 3 times per week	25 weeks	Individual	Treatment as usual
Requena et al, ³⁴ 2006	Covered different areas: orientation, bodily awareness, family and society, self care, reminiscing, household activities, animals, people and things; related images were shown and questions were asked	45 minutes, 5 times per week	12 months	Group	Treatment as usual (medications)
Spector et al, ³⁵ 2001	Orientation, multisensory stimulation, reminiscing techniques, recognising and naming people and objects	45 minutes, 2 times per week	7 weeks	Group	Usual activities
Spector et al, ³⁶ 2003	Cognitive stimulation therapy	45 minutes, 2 times per week	7 weeks	Group	Usual activities
Tsantali et al, ¹² 2017	Free discussion with clinician, copying figure, naming images, leisure activities (craft, music, puzzles)	90 minutes, 3 times per week	16 weeks	Individual	Treatment as usual (medications)
Wallis et al, ³⁷ 1983	Reality orientation: orientation, comments on surroundings, use of objects	30 minutes, 5 times per week	3 months	Group	Treatment as usual (occupational therapy)
Yamagami et al, ³⁸ 2012	Brain activating rehabilitation: enhancing social communication and cognition through orientation techniques and topic-specific activities	60 minutes, 2 times per week	12 weeks	Group	No treatment

(Hedges's $g = 0.557$, 95% CI = -0.213 to 1.326, $p = 0.156$, Figure 2). Meta-analysis of 582 participants (intervention group: 304, control group: 278) in five studies indicated that CS had no significant effect on quality of life (mean difference = 0.551, 95% CI = -0.889 to 1.992, $p = 0.453$, Figure 2).

Subgroup analysis of the format of CS indicated no significant difference between individual format (in four studies) and group format (in 16 studies) [Hedges's $g = 0.263$ vs 0.317 , $p = 0.701$, Figure 3]. Subgroup analysis of the setting of CS indicated no significant difference between home setting and non-home setting (Hedges's

Table 3. Risks of bias of studies included in meta-analysis using Cochrane's criteria*

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of assessors	Incomplete outcome data	Selective reporting
Baines et al, ²⁰ 1987	?	?	-	+	+	+
Baldelli et al, ²¹ 1993	?	?	-	?	+	+
Baldelli et al, ²² 2002	?	?	-	?	+	+
Bottino et al, ²³ 2005	+	+	-	+	+	+
Breuil et al, ²⁴ 1994	?	?	-	+	+	+
Camargo et al, ²⁵ 2015	-	-	-	?	+	+
Coen et al, ²⁶ 2011	?	?	-	+	+	+
Cove et al, ²⁷ 2014	+	?	-	+	+	+
D'Onofrio et al, ²⁸ 2015	+	+	-	+	+	+
Ferrario et al, ²⁹ 1991	?	?	-	?	+	+
Folkerts et al, ³⁰ 2018	+	+	-	-	+	+
Luttenberger et al, ³¹ 2012	+	?	-	+	-	+
Middelstadt et al, ³² 2016	+	+	-	?	+	+
Onder et al, ³³ 2005	+	?	-	+	+	+
Orrell et al, ¹¹ 2017	+	+	-	+	-	+
Requena et al, ³⁴ 2006	?	?	-	?	+	+
Spector et al, ³⁵ 2001	+	+	-	-	-	+
Spector et al, ³⁶ 2003	+	+	-	+	+	+
Wallis et al, ³⁷ 1983	+	?	+	+	-	+
Yamagami et al, ³⁸ 2012	?	?	-	?	+	+

* '+' denotes low risk of bias, '-' high risk of bias, and '?' uncertain risk of bias

$g = 0.269$ vs 0.323 , $p = 0.749$, Figure 3). Subgroup analysis of the duration of CS indicated no significant difference between ≤ 3 months and > 3 months (Hedges's $g = 0.246$ vs 0.323 , $p = 0.639$, Figure 3).

Egger's regression tests showed no significant publication bias for the main analyses ($p = 0.555$), suggesting symmetry in the funnel plot. Sensitivity analysis was performed by omitting studies that used terms other than dementia as diagnosis^{20,29} and studies that had a high risk of selection bias²⁵ and/or detection bias.^{30,35} There was no significant change in the primary results of cognition, with similar Hedges's g .

Discussion

In the present meta-analysis, CS had a significantly positive treatment effect (Hedges's $g = 0.313$) on cognition in dementia subjects, compared with inactive controls (including no active treatment, waitlisted for intervention, and treatment as usual). The effect size was smaller than

that in other studies (0.41^7 and 0.44^9). This is because the present meta-analysis included the largest number of studies and participants and thus had higher power in estimating the effect of CS, particularly a multicentre RCT with nearly 300 participants was included.¹¹ Eight and eleven of the studies were not available in two previous reviews.^{7,9} We used more stringent eligibility criteria. CS was compared with a consistent pre-defined control group, and only RCTs were included. Definitions for various CS interventions were strictly followed during article selection.⁴

CS had no significant effect on depressive symptoms. This is because participants might have mild depressive symptoms at baseline (as reflected by the mean score of Cornell Scale for Depression in Dementia) in most included studies^{30,35,36} and hence the effect of CS, if any, was not apparent. In addition, only four studies that assessed depressive symptoms with appropriate tools were included in meta-analysis. More evidence is needed before any conclusion is reached.

Figure 2. Forest plot of the effect of cognitive stimulation versus control on (a) cognition, (b) depressive symptoms, and (c) quality of life in persons with dementia

Figure 3. Forest plot of subgroup analysis of the effect of cognitive stimulation in terms of (a) format, (b) setting, and (c) duration of programme

CS had no significant effect on quality of life, although two previous meta-analyses reported a significant improvement in the self-reported quality of life.^{7,9} This may be due to different types of assessment scales used. The previous meta-analyses used the EuroQol-5-Dimensions and the Quality of Well-being, which are not comprehensive enough to detect the disease-specific changes. We used QoL-AD, which is a valid and reliable scale specifically for assessing the quality of life in persons with (different stages) of dementia.^{39,40} However, our results on quality of life were not representative because only five studies were included in meta-analysis.

Subgroup analyses suggested no significant subgroup differences in terms of format, setting, and duration of programme. This may be due to the uneven distribution of covariates (the number of trials and study participants in each subgroup). In addition, the investigated characteristics were not exclusive. Other unidentified factors might account for the difference in treatment effect. Participants-related factors could potentially affect the effect size, but meaningful subgroup analyses could not be conducted. For instance, subtypes of dementia could not be investigated, as many studies did not provide related information or analyse separately.

There are some limitations in the present study. The overall quality of the evidence was limited by the methodological quality of included studies. Though the study by Orrell et al¹¹ is the largest clinical trial so far with around 300 participants, the high non-adherence to assigned intervention may cause bias. Heterogeneity could not be explained by the results of subgroup analyses. Nearly all studies were carried out in non-Asian populations; differences in the cultural and social backgrounds could affect the generalisability of the research findings. Meta-analysis on specific cognitive function was not performed. Although there were a few included studies reported assessment in specific cognitive domains such as communication, executive function, and orientation, the high variability of the measurement tools used and scarcity of data make meta-analysis on specific cognitive function of limited value. The impact of various subtypes of dementia on the effectiveness of CS was not addressed. Owing to CS characteristic of involving communication and verbal expression, the effects of CS on different subtypes of dementia may be variable. The underlying pathophysiological mechanisms for respective dementia subtypes may predispose to the differences in the effectiveness of treatment. However, a number of studies did not classify dementia into different subtypes, whereas some studies recruited participants with mixed entities. Therefore, separate meta-analysis for dementia subtypes could not be performed. Stratification of participants by different subtypes of dementia according to consistent diagnostic criteria is suggested for future studies. The sustainability of effect after CS remains uncertain. Given the limited data available together with the arbitrary time points on follow-up assessments, meta-analysis for follow-up assessment was not attempted as it is of limited value

with a potential of arriving at an implausible conclusion.

Conclusions

CS has a significant positive effect on cognitive function, but its effect on depressive symptoms and quality of life was inconclusive. The quality of evidence was limited by the methodological quality of included studies and unexplained heterogeneity. Future studies with more robust methodology establishing evidence of its efficacy are required. Stratification of participants by different subtypes of dementia according to consistent diagnostic criteria is recommended. Separate meta-analysis for dementia subtypes is recommended to improve the ability to combine results.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest. Dr Gloria Wong is the Director of Training of the CST-HK programme.

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Data Availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

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