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The effect of Computerized Cognitive Training on cognitive outcomes in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis

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Key words: Mild cognitive training (MCI), computerised, cognitive training, cognitive outcomes, meta-analysis.

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Abstract:

Objectives To determine the effect of computerised cognitive training (CCT) on improving cognitive function for older adults with mild cognitive impairment (MCI).

Design Systematic review and meta-analysis.

Data Sources PubMed, Embase, Web of Science and the Cochrane Library were searched through January 2018.

Eligibility Criteria Randomised controlled trials (RCTs) comparing CCT with control conditions in those with MCI aged 55+ were included.

Data extraction and synthesis Two independent reviewers extracted data and assessed the risk of bias. Effect sizes (Hedges' g and 95% CIs) were calculated and random effects meta-analyses were performed where three or more studies investigated a comparable intervention and outcome. Heterogeneity was quantified using the I^2 statistic.

Results 18 studies met the inclusion criteria and were included in the analyses, involving 690 participants. Meta-analysis revealed small to moderate positive treatment effects compared to control interventions in 4 domains as follows: Global Cognitive Function (g = 0.23, 95% CI = 0.03, 0.44), Memory (g = 0.30, 95% CI = 0.11, 0.50), Working Memory (g = 0.39, 95% CI = 0.12, 0.66) and Executive function (g = 0.20, 95% CI = -0.03, 0.43). Statistical significance was reached in all domains apart from executive function.

Conclusions This meta-analysis provides evidence that CCT improves cognitive function in older people with MCI. However, the long-term transfer of these improvements and the potential to reduce dementia prevalence remains unknown. Various methodological issues such as heterogeneity in outcome measures, interventions and MCI symptoms and lack of intention-to-treat (ITT) analyses limit the quality of the literature and represent areas for future research.

Strengths and limitations of this study

1. This is a comprehensive systematic review and meta-analysis evaluating the effects of computerised cognitive training in older adults with mild cognitive impairment on cognitive outcomes.
2. We excluded studies that did not utilise strict clinical diagnostic criteria for MCI to reduce the heterogeneity often found between participants in MCI studies.
3. Data for four main cognitive domains most significantly affected by MCI and targeted by cognitive interventions were extracted from individual studies (global cognitive function, episodic memory, working memory and executive function) and where appropriate composite measures were calculated for meta-analyses.
4. The studies included in the systematic review are generally of moderate quality, however several methodological issues may limit the interpretation of results.
5. A lack of follow up data makes it impossible to draw conclusions regarding long term effects or impact on the prevalence of dementia.

INTRODUCTION

There are currently estimated to be over 46 million people worldwide living with dementia. This number is expected to grow to approximately 131.5 million by 2050.[1] There is therefore an urgent need to develop therapeutic treatments that may delay or prevent dementia in population groups considered 'at risk'.[2] Interventions that delay the onset of AD by an average of two years would decrease the worldwide prevalence rate by 22.8 million cases, [3] which in turn, would ease the huge burden placed on individuals, families and society. For these reasons, evidence-based interventions that reduce the risk of dementia are urgently required.

Mild Cognitive Impairment (MCI) refers to an intermediate stage between normal age-related cognitive decline (ARCD) and dementia. [4] Although many older adults experience a degree of deterioration in cognitive performance, MCI is described as a greater than the expected cognitive decline for an individual's age and education, but without notable interference in everyday functioning.[5] Within the older adult population, the estimated prevalence rate of MCI ranges from 15-20%. [6] Although MCI can present with a variety of symptoms, when memory loss is the predominant symptom it is termed "amnestic MCI" and is frequently seen as a prodromal stage of Alzheimer's disease. [6] When individuals have impairments in domains other than memory it is classified as non-amnestic single- or multiple-domain MCI and these individuals are believed to be more likely to convert to other types of dementia. [6]

The lack of therapeutic benefit or delay in progression from MCI to AD with pharmacological interventions has meant that the focus has shifted towards non-pharmacological interventions. [7] Cognitive remediation is the term used for interventions designed to mediate cognitive decline and can be typically identified as involving one of three different approaches: cognitive stimulation (CS), cognitive rehabilitation (CR) and cognitive training (CT). Interventions based on CS and CR are more focused on individuals with established dementia, often with the aim of overcoming specific difficulties with daily living and improving general quality of life. In comparison, CT can be used for

subjects without significant cognitive or functional difficulties, and is therefore well suited for individuals with MCI.

CT refers to interventions that aim to improve cognitive domains through repeated practice on theoretically driven skills and strategies. [8] Each CT exercise aims to target one or two specific domains in an adaptive manner with a possibility of transfer effects whereby performance in other untrained cognitive domains is also improved. [9]

Computerised cognitive training (CCT) utilises computers for the delivery of the intervention and differs from traditional CT, which usually incorporates face-to-face contact with a professional and paper-and-pencil paradigms. [8] CCT has several advantages including cost-effectiveness, increased accessibility and ability to customise the content and difficulty of the training. [10-12] Research involving older adults has found that CCT programs are associated with high satisfaction levels, and that they are also a feasible option for individuals with MCI, with equal or better adherence rates when compared to traditional CT. [10 13] In addition, evidence suggests that studies utilising CCT show a pattern of stronger effect sizes and enhanced generalisation of benefits compared to traditional strategy training in MCI. [14] A previous meta-analysis found that CT is not effective in people with established dementia. [15] However, there is growing interest as to whether CCT has the potential to prevent or slow the progression from MCI to dementia particularly given the association between higher participation in mental activity and reduced dementia risk. [16]

Studies investigating the effectiveness of CT in improving cognitive performance in people with MCI have demonstrated small to moderate improvement but existing research suffers from methodological concerns and limitations. [14 17-19] CT research in individuals with MCI has been criticised for the failure to include an appropriate control group, [20-22] use of subsets of participants from previous studies, [23] and pooling of MCI data with that from non-impaired adults[24] as well as those with probable AD. [25-27] Another issue raised in treatment studies has been the use of ecologically valid outcome measures. For example, the inclusion of functional outcome measures is important to monitor progression from MCI to dementia but given that individuals with MCI are, by

definition, not significantly impaired in functioning, it is a challenge to measure the functional effects of the intervention. [17]

CCT is far from a single construct and factors such as the content, platform, context and dose of training may differ. [28] Unfortunately, despite increasing scientific scrutiny, there is a limited understanding as to which, if any, dimensions are associated with cognitive benefit. Ideally, critical analysis of research using CCT for MCI would reveal insight into which specific components of CCT are necessary for it to be effective, however, it is important to establish the overall effect of CCT on individuals with MCI.

Systematic reviews and meta-analyses of cognitive interventions in MCI have reported mixed results, [19 29-34] and when exploring the effect of cognitive training in MCI have largely not distinguished between studies evaluating computerised and non-computerised training. This makes it difficult to draw conclusions, specifically on the efficacy of CCT in MCI. For example, a systematic review by Ge et al summarised the findings of CCT studies among people with MCI, however no meta-analyses were performed and the review included non-randomized controlled studies, studies that combined CCT with other interventions and studies not using Petersen's core MCI diagnosis criteria, making it challenging to draw rigorous conclusions. [35] A previous meta-analysis by Hill et al (2017) specially explored the effectiveness of CCT in MCI on cognition and behavioural outcomes, [32] however the field is progressing rapidly, as highlighted by Ge et al's observation that 42% of the studies in their review were published between 2016 and 2017, [35] and further relevant studies have been published subsequently. [32 36-38] Another more recently published meta-analysis by Gates et al only included studies where the intervention period lasted for more than 12 weeks and excluded a significant number of studies with shorter training duration. [39] Thus, it is necessary to conduct an updated meta-analysis to include more recent articles and all intervention durations.

This paper investigates the effect of CCT on improving cognitive outcomes in individuals diagnosed with MCI using random effects meta-analyses. To address some of the problems identified in the literature, only peer-reviewed Randomised controlled trials (RCTs) were selected and cognitive outcome measures were extracted for analysis. Variables that may moderate the effect of CCT, such as the type of programme or dose of the intervention, were reviewed. The purpose of the current review was to: a) evaluate the effect of CCT in older adults with MCI on cognitive outcomes; b) evaluate the content and methodological quality of the intervention studies; and c) suggest future directions in CCT research in this group based on findings.

MATERIALS AND METHODS

Search strategy and selection criteria

A literature search was completed during January 2018 of four online literature databases and trial registers: PubMed, Embase, Web of Science and Cochrane library. The search terms are shown in supplementary table 1. Previous meta-analyses and systematic reviews of cognitive interventions in MCI were also searched. Furthermore, reference lists of included studies were manually scanned for additional relevant papers.

Inclusion and exclusion criteria

Types of studies: Published, peer-reviewed studies with an RCT design investigating the use of CCT interventions in older people with MCI were considered for inclusion. Studies were included if sufficient data were available for calculation of effect sizes in each treatment arm (unavailable information was requested from authors and included if obtained). The date of publication was not limited, but only studies published in English were included.

Participants: Inclusion criteria were a mean age of participants greater than 55 years, a diagnosis of MCI using core criteria according to Petersen [4] and no other psychiatric diagnosis or neurological disorder. The number of participants in each arm needed to be at least five. Studies with non-impaired older people or those with probable AD were excluded unless separate data for participants with MCI was provided.

Types of interventions: Studies were included if they compared any CCT intervention, administered on a personal computer or gaming console, to an active or non-active control. Computerised training had to represent the primary intervention, not simply one of multiple broader non-computerised cognitive interventions, in order to be included. Active controls were classified as interventions that controlled for non-specific therapeutic effects, whereas non-active control groups included waiting list conditions, treatment as usual (TAU) or a non-matched minimal intervention. Each study was

independently screened, selected for inclusion and its data extracted by independent researchers. Any disagreements were resolved through discussion with another author.

Types of outcome measures: We focused on cognitive domains that are reported to be most significantly affected by MCI and targeted by cognitive interventions, namely episodic memory, executive function, working memory/attention and general cognitive function .[40] Available data from all relevant cognitive outcomes was extracted. Cognitive outcomes used in the included studies and their classification into the main cognitive domains are shown in supplementary table 2.

Risk of bias assessment

The Cochrane Collaboration Risk of Bias tool was used to assess study methodological quality[41]. Risk of bias was assessed in multiple domains: sequence generation, allocation concealment, blinding of participants and investigators, incomplete outcome data and selective reporting of outcomes. In each of these categories, the methodological quality of each assessed domain was rated as 'low risk', 'unclear' or 'high risk'. Studies were excluded if unsure or high risk in all assessed domains.

Statistical analysis

Intervention and control groups' post-intervention outcome scores were compared using Review Manager (RevMan) software version 5.3. The programme uses Hedges' adjusted g [42] to calculate a standardised mean difference (SMD) which is adjusted for small sample bias. Pooling of standardized mean Hedges' g estimates of <0.30, ≥ 0.30 and < 0.60, and ≥ 0.60 were considered small, moderate, and large, respectively. Meta-analyses were performed where three or more studies investigated a comparable intervention and outcome using a random effects model. Heterogeneity was quantified using the I^2 statistic, considered as low, moderate, or large when at 25%, 50%, or 75%, respectively. [43] Where a study reported multiple outcome measures for one cognitive domain (e.g., within memory function), a composite measure was calculated to provide a single quantitative measure for meta-analysis. [44] Publication bias was examined using funnel plots. We also performed subgroup

analysis and meta-regression using the "metafor" program in R (https://www.R-project.org/), for example we compared the effectiveness of single and multi-domain training. Furthermore, we subgrouped studies with a training dose of less than 10 hours and more than 30 hours to see if there is a dose-response correlation. We also compared studies with active vs. non-active control conditions, following a reviewer's suggestion. Sensitivity analyses were performed to identify potential sources of heterogeneity. Further details of statistical methods are found in the supplementary material (see supplementary appendix 1).

Patient and public involvement

There was no direct patient or public involvement in this review.

RESULTS

Description of studies

The Preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist was used to guide reporting of results.[45]

Following the initial literature review a total of 8893 studies were found. Of these 8875 were excluded and 18 studies met inclusion criteria. Figure 1 presents a flowchart of study selection. The total number of participants included was 690 and the brief summary characteristics of each study are presented in table 1 and detailed in supplementary table 3. Sample sizes ranged from 12 to 106, and dropout rates ranged from 0% to 32%. One study was excluded from the meta-analysis because of suspected inclusion of participants with probable AD based on the reported average Mini–Mental State Examination (MMSE) score. [46] Another two studies were excluded from the meta-analysis as post-intervention cognitive data could not be obtained. [47 48]

Thirteen studies reported outcomes assessing memory, five studies reported outcomes assessing working memory, 11 studies reported outcomes assessing executive function, and 11 studies reported global cognitive functioning outcomes (see table 2.).

Quality of studies

The quality of each study was evaluated in regard to certain methodological aspects and summarised in supplementary figure 1. 11 of the 18 studies did not report blinding of participants.

Participant characteristics

The total number of participants from all studies included was 690 (CCT: n=351, mean group size: n=20, control: n=339, mean group size: n=19). The average age of participants in both conditions was 73.4 years. 52.5% of all participants were male. The disparity and lack of reporting of the ratio of

participants' years of education precluded mean calculations, although the available data suggests most participants had at least secondary school education. The pooled average baseline score for the MMSE was 26.9 in both groups, although the range of scores indicated heterogeneity within participants.

Cognitive Training Interventions

Interventions were mostly delivered on a personal computer (PC), using commercially available or purpose built CT packages, with two studies utilising a video game on a games console. [13 38] All interventions were specifically designed to improve various aspects of cognition. The most common type of intervention used was multi-domain (11/18 studies), where the programme targeted two or more cognitive domains. In the seven single domain intervention studies, three evaluated memory training and executive function training while one used working memory training. The dose and duration of the CT intervention was variable, with the total length of training ranging from 4 hours [49] to 80 hours [50] and the duration of training from 2 weeks[51] to 26 weeks. [50]

Outcome Measures

Supplementary Table 2 summarises the 60 different cognitive outcome measures used by studies included in the meta-analyses. A considerable variability in measures reported was also noted; only three outcome measures were reported three or more times; seven studies used the MMSE as a measure of global cognition, three studies used Paired-associates learning (PAL) to measure memory and in four studies used the Trail Making Test (TMT) as a measure of executive function.

Meta-analysis of specific outcomes

Separate meta-analyses were conducted on four different cognitive domains. The most commonly tested domains were memory, with thirteen studies exploring this domain. The results of the meta-analyses are presented in table 2.

Global Cognition function

Overall, there was a significant benefit of CCT on global cognition compared to the control group. The meta-analysis revealed a small but statistically significant pooled effect size of 0.23 (95% CI [0.03, 0.44], z= 2.22, p = 0.03) with low heterogeneity between studies (I^2 = 6%) (see figure 2.). The funnel plot did not reveal significant asymmetry (see supplementary figure 2.). The effect size across active-controlled trials (n=7, g=0.23, 95% CI [-0.05, 0.51], I^2=27%) was smaller than that of trials with non-active control groups (n=4, g=0.31, 95% CI [-0.06, 0.68], I^2=0%) (see supplementary figure 3-4.), but was not statistically significantly different (z = -0.11, *p* = 0.91).

Memory

The pooled effect size of CCT on memory outcomes, when compared with control conditions, was moderate and statistically significant (g = 0.30, 95% CI = [0.11, 0.50], z = 3.03, *p* = 0.002), with moderate heterogeneity between studies (I^2 = 46%) (see figure 3.). The funnel plot did not reveal significant asymmetry (see supplementary figure 5.). The effect size across active-controlled trials (n=8, g=0.36, 95% CI [0.11, 0.61], I^2=52%) was larger than that of trials with passive control groups (n=5, g=0.20, 95% CI [-0.14, 0.54], I^2=43%) (see supplementary figure 6-7.), but was not statistically significantly different (z = -0.32, *p* = 0.75). However, there was moderate heterogeneity across studies in both analyses.

Due to the moderate heterogeneity between studies, a sensitivity analysis was also conducted, in which one study at a time was removed and the others analysed to estimate whether the results could have been markedly affected by a single study. The combined Hedges' g were consistent and without apparent fluctuation, with a range from 0.23 [0.07, 0.39] to 0.35[0.15, 0.55].

Working Memory

The meta-analysis revealed a statistically significant moderate effect size of 0.39 in favour of CCT compared with controls (95% CI [0.12, 0.66], z = 2.85, p = 0.004) with low heterogeneity between studies (I^2 = 0%) (see figure 3.). The funnel plot did not reveal significant asymmetry (see

supplementary figure 5.). Due to there being fewer than three non-active we did not compare the effect size between active-controlled trials and non-active trials.

Executive function

The overall effect of CCT on executive function compared with control conditions was small and non-significant. The meta-analysis revealed a pooled effect size of 0.20 (95% CI [-0.03, 0.43], z= 1.74, p = 0.08) with high heterogeneity between studies (I^2 = 51%) (see figure 3.). The funnel plot did not reveal significant asymmetry (see supplementary figure 5.). The effect size across active-controlled trials (n=7, g=0.13, 95% CI [-0.08, 0.35], I^2=20%) was smaller than for the non-active control groups (n=4, g=0.32, 95% CI [-0.23, 0.87], I^2=74%) (see supplementary figure 8-9.), but was not statistically significantly different (z = 0.95, *p* = 0.35).

Considering the large heterogeneity between studies (I^2 = 51%), a sensitivity analysis was also conducted as described above. The combined Hedges' g were consistent and without apparent fluctuation, with a range from 0.12 [-0.05, 0.28] to 0.35 [0.03, 0.48].

A priori subgroup analysis

A priori, we stipulated that meta-analysis would only be performed if three studies report outcomes in the same cognitive domain and so subgroup analysis could only compare single and multi-domain memory training. Similarly, only global cognition could be used for subgroup analysis to compare the training interventions less than ten hours and more than thirty hours. Our subgroup analyses and meta-regression suggested that there is no difference between multi-domain CCT and single-domain CCT (z = 0.09, *p* = 0.93), although the former had a significant effect (g = 0.30, 95% CI (0.08, 0.53)) while the latter was non-significant (g = 0.31, 95% CI (-0.19, 0.81)) (see supplementary figure 10-11). There is also no clear evidence for a dose-response relationship. Our subgroup analysis found that studies that provided more than 30 hours of CCT had a smaller overall effect on global cognitive function (g = 0.20, 95% CI (-0.31, 0.71)) compared to studies providing less than 10 hours of CCT (g=

0.30, 95% CI (-0.01, 0.61) (see supplementary figure 12-13). We did not perform a meta-regression for training dose because fewer than ten studies were included. The subgroup analyses need to be interpreted with caution due to the small number of studies and heterogeneity, however, they illustrate the lack of clear factors that are associated with efficacy.

DISCUSSION

Main findings

Based on results from 18 RCTs, it is likely that CCT is a viable intervention for improving cognition in older people with MCI. There were small to moderate positive effect sizes found in all domains, with statistical significance reached for global cognitive function (g=0.23, 95% CI = [0.03, 0.44]), memory (g=0.30, 95% CI=[0.11, 0.50]) and working memory (g=0.39, 95% CI=[0.12, 0.66]), but not executive function (g=0.20, 95% CI=[-0.03, 0.43]). The largest effect sizes were found for working memory and memory (although statistically significant heterogeneity was found for the latter domain). This is unsurprising given its central focus in most interventions and promising given this is the primary complaint in most cases of MCI.

The present meta-analyses updated the literature search and added eight new studies[23 36-38 51-54]compared with the previous study conducted by Hill et al[32]. The present findings are largely in keeping with the results of Hill et al [32] that demonstrated positive effect sizes for global cognition (g=0.38, 95% CI=[0.14–0.62]), memory (g=0.42, 95% CI =[0.21, 0.63]), working memory (g=0.74, 95% CI =[0.32, 1.15]) and executive function (g=0.20, 95% CI=[-0.05, 0.44]). However, our results are in contrast with the results reported by Gates et al which found that there were no clear effects of CCT on cognition for people with MCI [39]. Methodological reasons for this inconsistency may be that Gates et al only included studies with a minimum intervention period of 12 weeks and included a broader range of participants at risk of cognitive decline. As a result, fewer studies (eight) met their eligibility criteria, of which two studies did not require a strict MCI diagnosis [46 47] and one used self or informant–reported cognitive complaints.[55]

The current meta-analysis employed strict eligibility criteria to overcome the methodological issues reported in the literature [56 57] such as inappropriate control groups and CCT being combined with other interventions. The combination of an overall large sample size (N=690) and stringent eligibility criteria make this meta-analysis a useful contribution to the growing evidence for the efficacy of CCT

in MCI. Nevertheless, various methodological issues were identified that limit the ability to make recommendations for the optimal format, frequency or intensity of CCT. Further, the lack of longitudinal studies make it unclear whether observed post-intervention benefits contribute in any way to the goal of delaying or preventing the progression from MCI to dementia.

Validity of observations and limitations

Sources of bias

Several methodological issues were identified. Studies were rarely double-blinded, and whilst it may be considered impractical to blind therapists and participants given the nature of the intervention, this nevertheless introduces the risk of expectation bias and exaggerated results. In addition, data concerning dropouts were rarely included in the analyses and ITT analysis was only used in two studies.[49 58] Whilst most of the remaining studies reported no significant differences at baseline for those who dropped out, these differences may have only become apparent post-intervention, and baseline differences may have been more obvious with the large number of participants in the meta-analysis. Thus, the absence of ITT may have introduced an attrition bias.

Further bias may have arisen due to the decision in this study not to differentiate between amnestic and non-amnestic forms of MCI. This classification is an example of the heterogeneity of MCI symptoms. This heterogeneity is supported in descriptions by Petersen [59] and in the results of a study revealing MCI as a highly nuanced and complex clinical entity. [60] This may lead to considerably different intervention effects between participants and render it difficult to evaluate the efficacy of the cognitive intervention and the generalisability of the current results.

This meta-analysis calculated composite effect sizes when multiple outcome measures were provided for the same domain in each study. Whilst this method maximises the amount of data drawn from the reviewed studies, it also has certain limitations. Firstly, this approach necessitated an arbitrary measure of correlation between outcome measures, in this case set at 0.5. This may be

inaccurate, with outcome measures being more or less heterogeneous. Unfortunately, data on composite heterogeneity was not available, however, choosing between outcome measures to decide which best represents a particular domain would have posed a significant risk of selection bias. This partly stems from the fact that 'gold standard' tests for the different cognitive domains have not been identified.

Another limitation of the present meta-analysis is the lack of registration on Prospero. The registration could ensure that the protocol and results are available to other researchers for replication and updating. [61] However unfortunately at the stage of registration of our protocol, data extraction was complete and the study was therefore ineligible to be registered on Prospero.

The literature suggests multiple factors may influence the efficacy of cognitive interventions. [62] An aim of the current analysis was to provide insight regarding CCT design choices and training outcomes to inform decisions on interventions to use both clinically and in future studies. Of note, the sub-groups analyses and meta-regression did not find any significant differences between studies with active and non-active control conditions for any domain, or between multi-domain and single-domain CCT. Due to the limited number of studies and heterogeneity of interventions and outcome measures, it is difficult to make clear recommendations for the optimal form of CCT.

This meta-analysis has demonstrated efficacy of CCT in MCI patients for a very specific outcome: performance on a neuropsychological test immediately post-intervention. Whilst promising, this is far removed from the goal of slowing progression to or preventing dementia in MCI patients. There was a lack of follow-up data, with only three studies [50 53 63] including long-term outcome measures, so no conclusions can be drawn regarding the longevity of the small to moderate effects or the transfer of immediate effects. In addition, benefits on neuropsychological testing may not translate to clinically meaningful benefits in everyday function. Barnett and Ceci [64] describe the immediate

outcomes measured here as 'near transfer' and the long-term transfer to untrained cognitive abilities as 'far transfer'. If there is any possibility of dementia being prevented or delayed using CCT then 'far transfer' of some sort is likely necessary. A review by Zelinski [65] outlines how 'far transfer' from cognitive training has been observed in aging population, though this is not specific to CCT or MCI. Demonstration of 'far transfer' as a result of cognitive training in healthy adults is very rare and there is increasing evidence that even 'near transfer' is difficult to demonstrate convincingly. [66] More research into long-term transfer effects of CCT in patients with MCI is vital in determining its potential to reduce the dementia burden.

Suggestions for future research

The discussion highlights factors limiting the reliability and transferability of the results of the meta-analysis. These limitations may be potentially overcome by more RCTs examining long-term cognitive outcomes to assess transfer of CCT to everyday life and provide more insight on whether CCT can influence progression to dementia. It is feasible to conduct large and longitudinal studies of CCT, as it can be delivered online and therefore be easily and widely available. The standardization of outcome measures between RCTs would also avoid problems associated with heterogeneity and overall higher methodological quality of RCTs would reduce bias.

Conclusion

This meta-analysis has demonstrated support for the hypothesis that CCT improves cognitive function in older people with MCI. However, the long-term transfer of these improvements and relevance to reducing dementia prevalence remains unknown. Various methodological issues such as heterogeneity in outcome measures, interventions and MCI symptoms and lack of ITT analyses are significant limitations of the literature. Long-term outcomes are the next priority for CCT in MCI patients to further explore its efficacy with respect to influencing dementia progression.

Contributors

HZ, RB, JDH, RG, HW, XY and RJH all contributed to the conception and design of the review. HZ, BH, CJT, JDH read and screened abstracts and titles of potentially relevant studies. HZ, RB, and JDH read the retained papers and were responsible for extracting data and rating their quality independently. HZ drafted the paper with all the authors critically reviewing it and suggesting amendments prior to submission. All the authors had access to all the data in the study and can take responsibility for the integrity of the reported findings.

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Competing interests

None declared.

Patient consent

Not required.

Provenance and peer review

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Data sharing statement

Details of excluded papers are available from the first author on request.

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Table 1. Characteristics of studies using computerised cognitive training in persons with MCI

Author and Year	CCT Group N, age, education	Control Group N, age, education	CCT type	Total hours
Barban et al 2016[67]	N = 46, Age = 74.4 (5.7), Edu = 9 (4.3)	N = 60, Age = 72.9 (6.0), Edu = 11 (4.7)	Multi domain	24
Ciarmiello et al 2015[52]	N = 15, Age = 71.2 (7.7), Edu = 9.3 (3.0)	N = 15, Age = 72.0 (7.1), Edu = 7.8 (2.6)	Multi domain	24
Djabelkhjr et al 2017[36]	N = 10, Age = 75.2 (6.4), Edu = 60.0% of college level	N = 10, Age = 78.2 (7.0), Edu = 44.4% of college level	Multi domain	18
Fiatarone et al 2014[50]	N = 24, Age = >55, Edu = n/s	N = 27, Age = >55, Edu = n/s	Multi domain	80
Finn & McDonald 2011[68]	N = 8, Age = 69.0 (7.7), Edu = 13.3 (2.2)	N = 8, Age = 76.4 (6.5), Edu = 12.0 (2.8)	Multi domain	25
Finn & McDonald 2015[69]	N = 12, Age = 72.8 (5.7), Edu = 13.8 (3.0)	N = 12, Age = 75.1 (7.5), Edu = 13.7 (2.8)	Memory	n/s
Gagnon & Belleville 2012[51]	N = 12, Age = 67.0 (7.8), Edu = 15.0 (4.6)	N = 12, Age = 68.4 (6.0), Edu = 13.1 (5.7)	Attentional control	6
Gooding et al 2016 study 1[70]	N = 31, Age = 75.6 (8.8), Edu = 15.1 (2.6)	N = 10, Age = 75.6 (8.8), Edu = 15.1 (2.6)	Multi domain	30
Gooding et al 2016 study 2[70]	N = 23, Age = 75.6 (8.8), Edu = 15.1 (2.6)	N = 10, Age = 75.6 (8.8), Edu = 15.1 (2.6)	Multi domain	30
Hagovska et al 2016[71]	N = 40, Age = 68.0 (4.4), Edu = 75% of secondary education	N = 40, Age = 65.9 (6.2),Edu = 70% of secondary education	Multi domain	10
Han et al 2017[37]	N = 23, Age = 73.7 (4.8), Edu = 13.5 (3.2)	N = 20, Age = 74.5 (6.4), Edu = 12.7 (3.7)	Memory	4

Author and Year	CCT Group N, age, education	Control Group N, age, education	CCT type	Total hours
Herrera et al 2012[63]	N = 11, Age = 75.1 (2.0), Edu = 46% of secondary school or more	N = 11, Age = 78.2 (1.4), Edu = 63% of secondary school or more	Multi domain	24
Hughes et al 2014[13]	N = 10, Age = 78.5 (7.1), Edu = 13.8 (2.4)	N = 10, Age = 76.2 (4.3), Edu = 13.1 (1.9)	Multi domain	36
Hyer et al 2016[53]	N = 34, Age = 75.1 (7.4), Edu = 70% secondary	N = 34, Age = 75.2 (7.8), Edu = 66% secondary	Working memory	16.7
Lin et al 2016[54]	N = 10, Age = 72.9 (8.2), Edu = 90.0% of college level	N = 11, Age = 73.1 (9.6), Edu = 54.5% of college level	Processing speed	24
Rosen et al 2011[23]	N = 6, Age = 70.7 (10.6), Edu = 16.7 (0.8)	N = 6, Age = 78.0 (7.9), Edu = 18.3 (1.5)	Processing speed	36
Rozzini et al 2007[72]	N = 15, Age = 63-78,Edu = n/s	N = 22, Age = 63-78, Edu = n/s	Multi domain	60
Savulich et al 2017[38]	N = 21, Age = 75.2 (7.4), Edu = 15.9 (1.3) (Age left school)	N = 21, Age = 76.9 (8.3) Edu = 16.0 (2.1) (Age left school)	Memory	8

Notes: MMSE: Mini Mental State Examination, n/s: not stated

Table 2 Results of Meta-analysis of computerised cognitive training (CCT) on cognitive domains

Analysis of CCT	No. of studies	N Tx*/control	Pooled Effect size g (95% CI)	Overall effect: Z (P value)	Heterogeneity: I^2 % (P value)
Global Cognition	11	258/245	0.23 (0.03, 0.44)	z= 2.22, p = 0.03	6% p = 0.39
Memory	13	245/232	0.30 (0.11, 0.50)	z = 3.03, p = 0.002	46% p = 0.04
Working Memory	5	82/83	0.39 (0.12, 0.66)	z = 2.85, p = 0.004	0% p = 0.81
Executive Function	11	171/182	0.20 (-0.03, 0.43)	z= 1.74, p = 0.08	51% p = 0.03

*Tx = training group.

Figure 1 Flow chart of the study selection process

Figure 2 Forest plot demonstrating the efficacy of CCT on global cognition function

Figure 3 Forest plot demonstrating the efficacy of CCT on memory, working memory and executive function

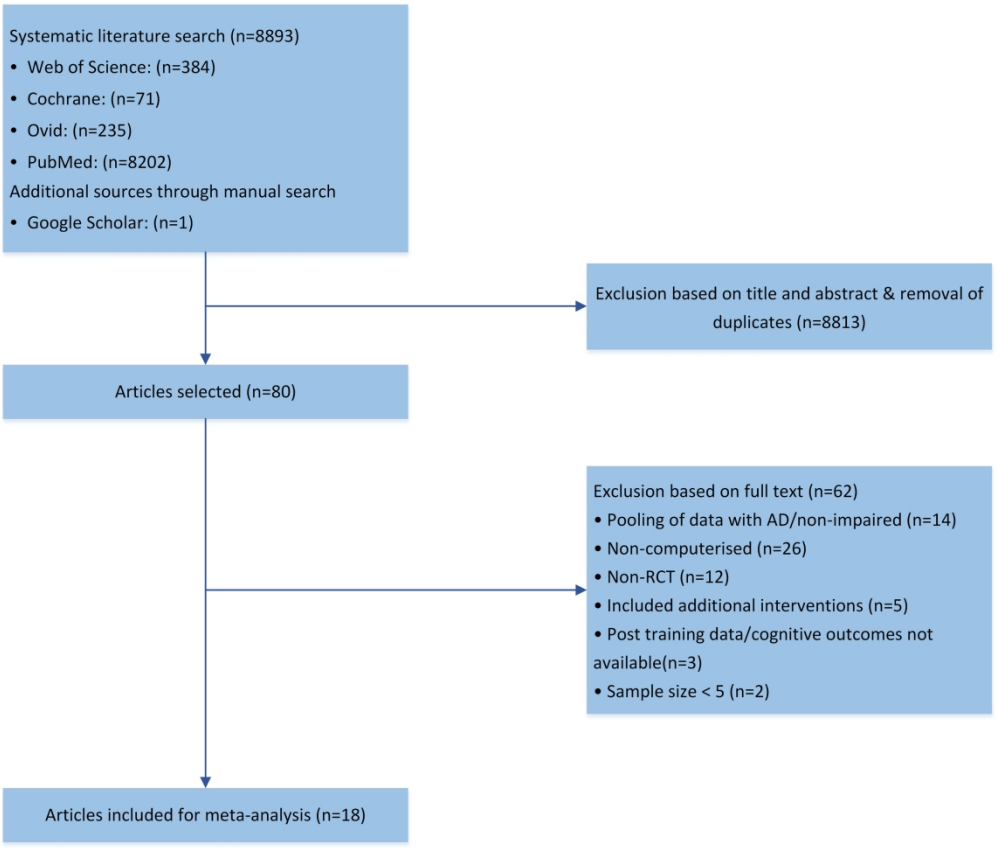

Figure 1. Flow chart of the study selection process

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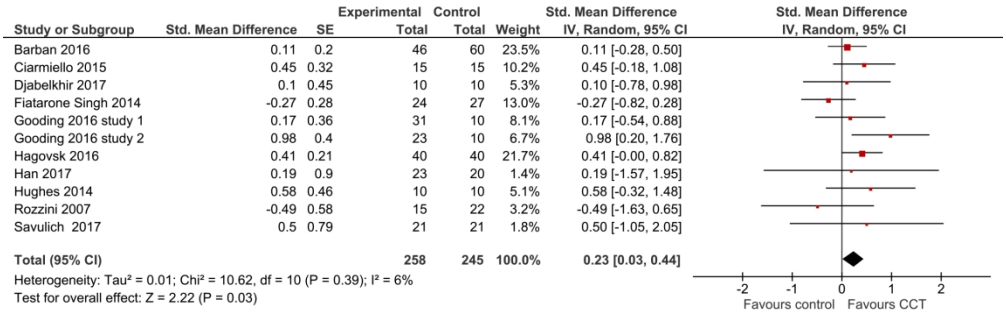


Figure 2 Forest plot demonstrating the efficacy of CCT on global cognitive function

195x62mm (300 x 300 DPI)

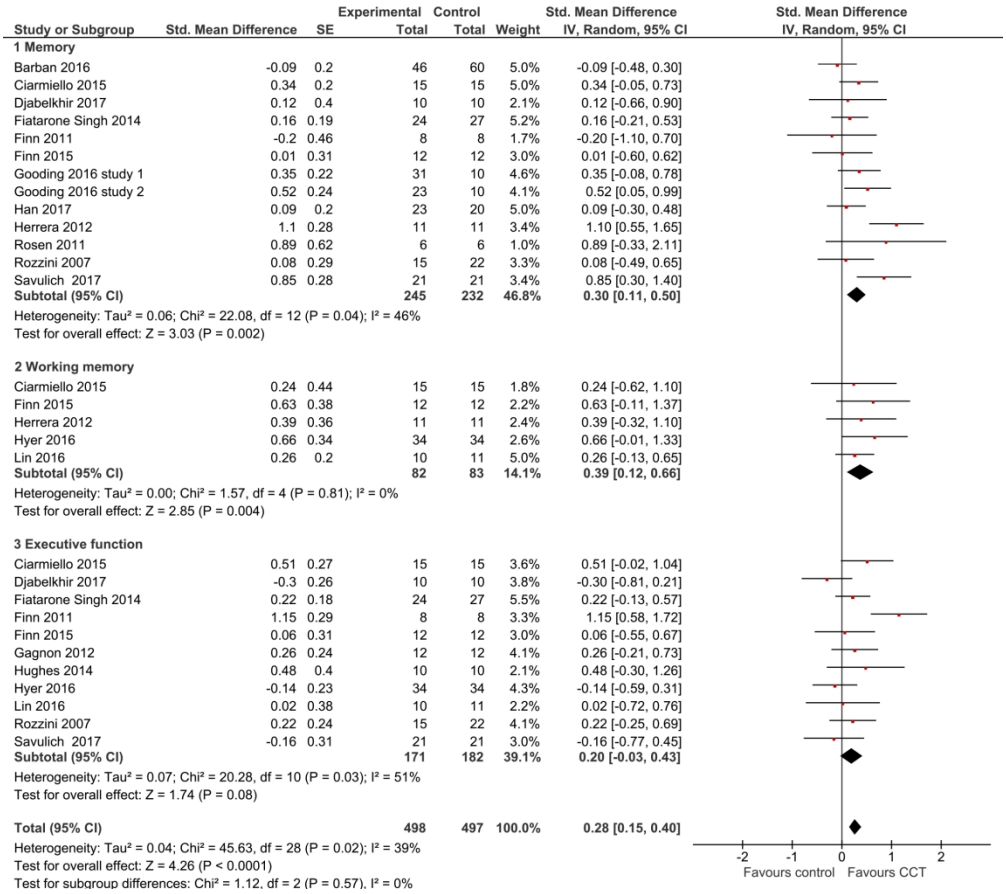
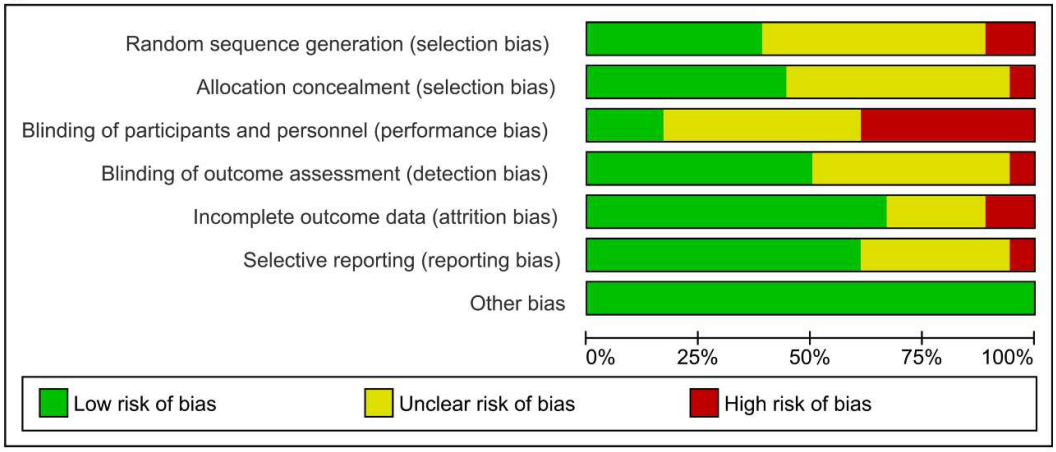


Figure 3 Forest plot demonstrating the efficacy of CCT on memory, working memory and executive function

195x173mm (300 x 300 DPI)

Supplement to: Zhang H, Huntley J, et al. The efficacy of Computerized Cognitive Training on cognitive outcomes in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis.

A.



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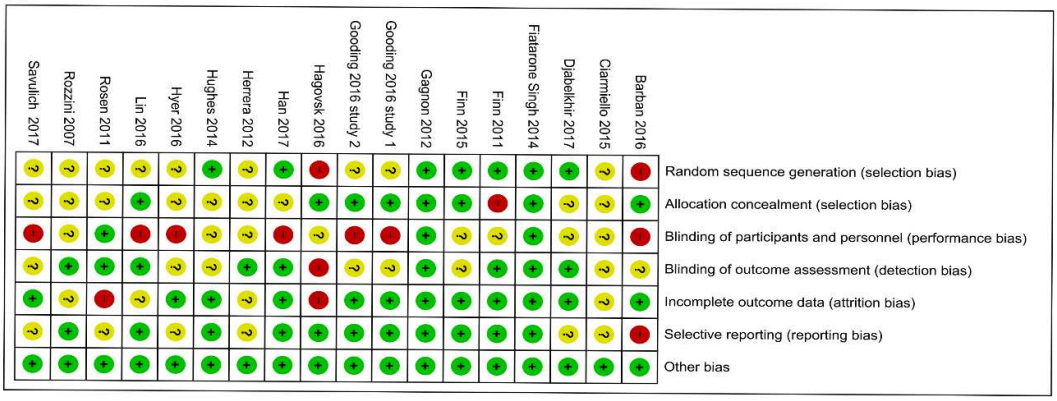
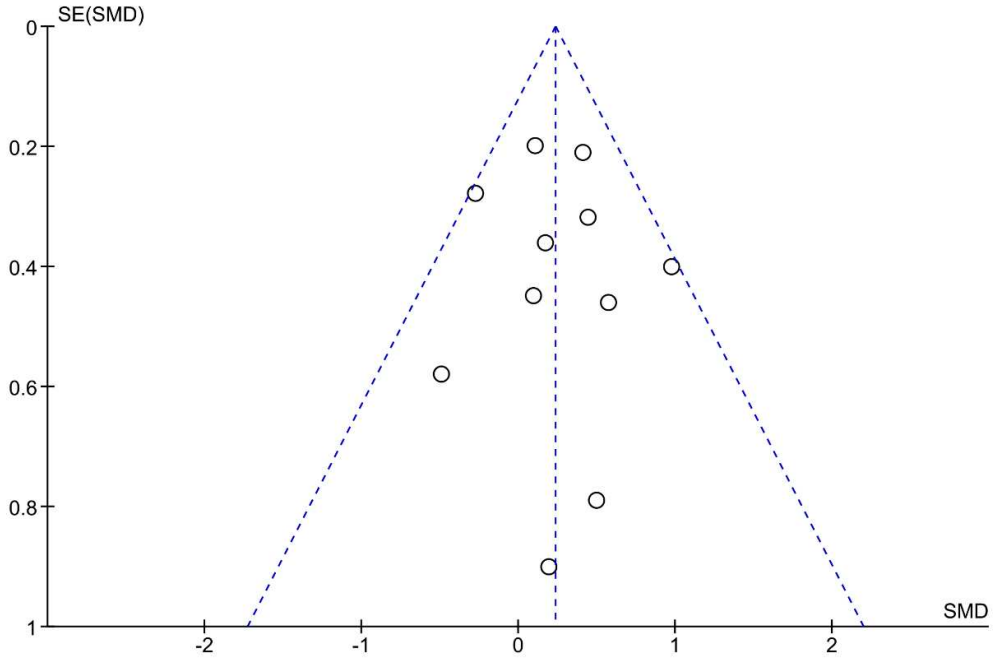
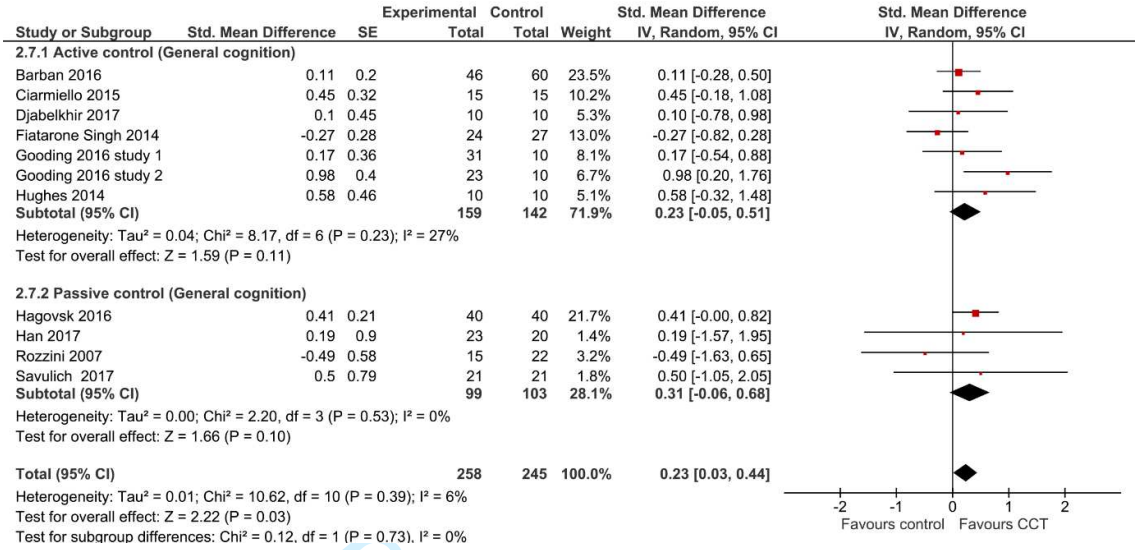


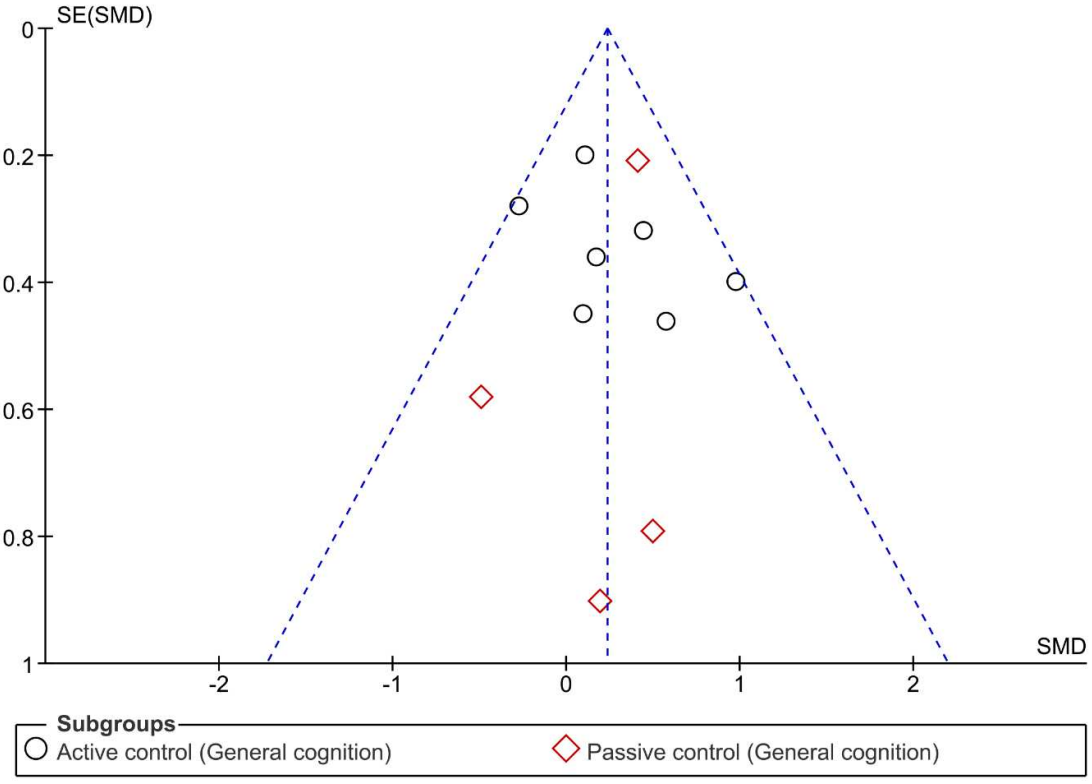
Supplementary Figure 1 (A-B). Summary of risk of bias for included studies. (A). Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. (B). Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



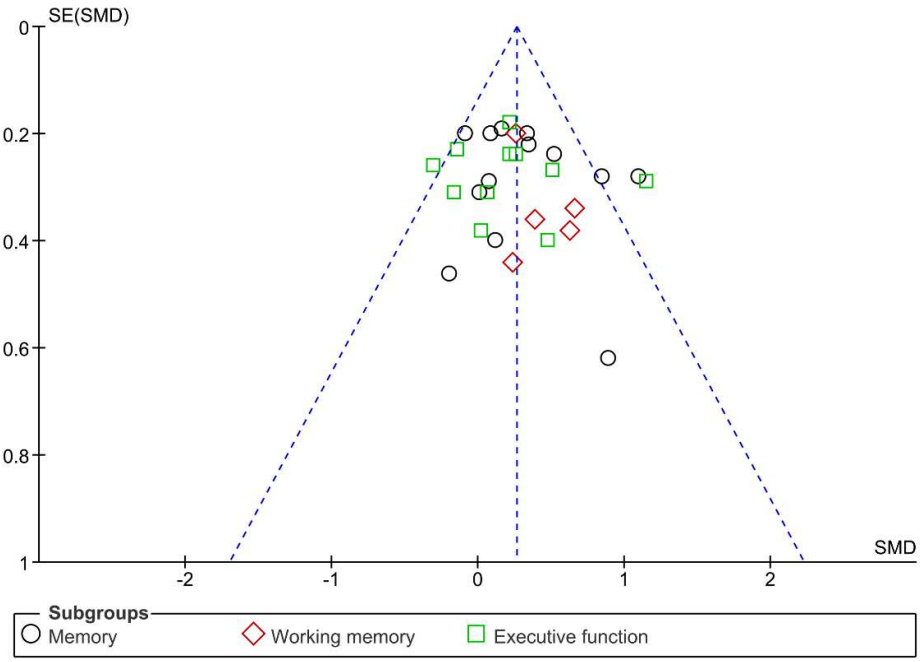
Supplementary Figure 2. Funnel plot demonstrating bias of CCT on global cognitive function



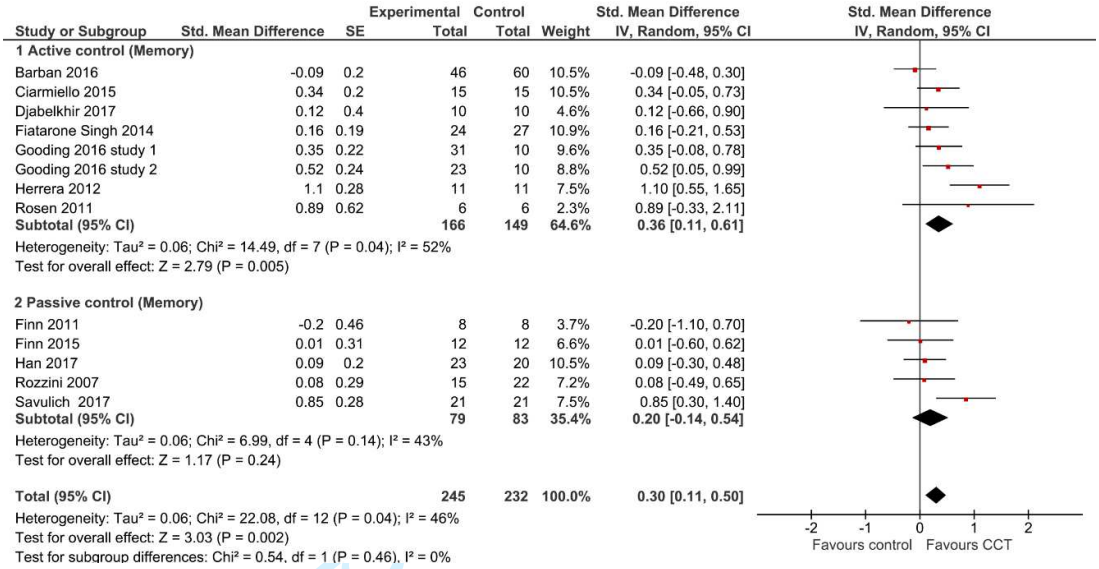
Supplementary Figure 3. Forest plot demonstrating efficacy of CCT on global cognition stratified by the type of control group



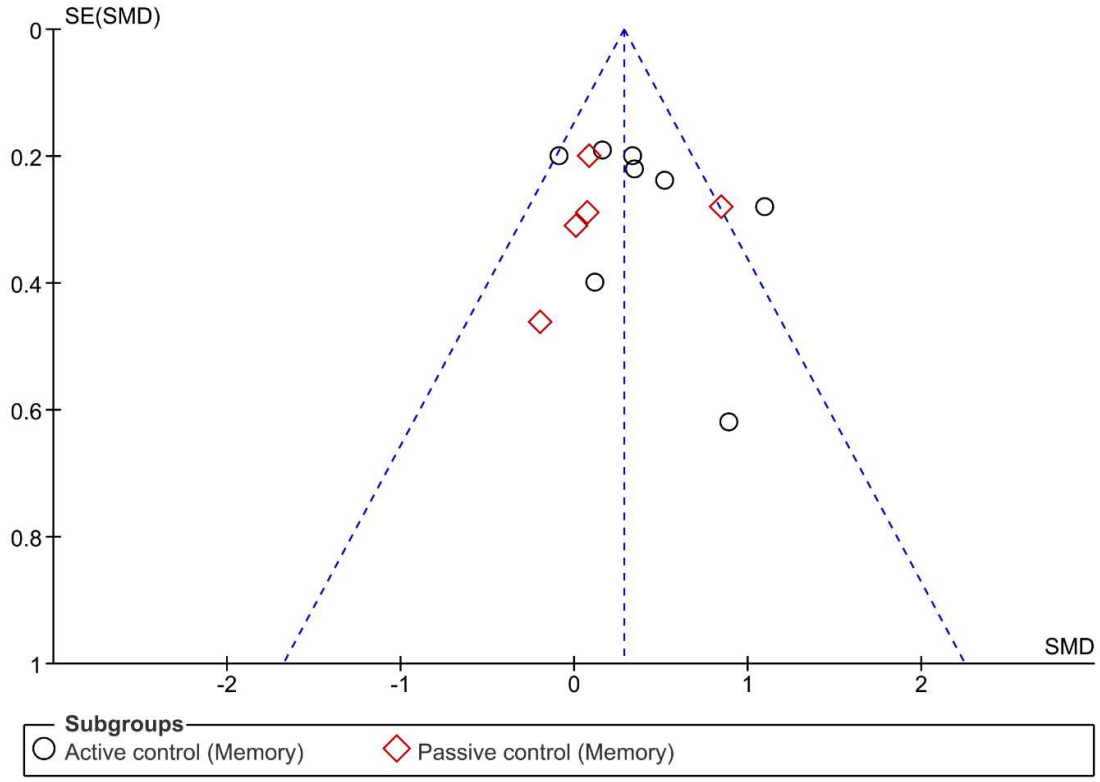
Supplementary Figure 4. Funnel plot demonstrating bias of CCT on global cognition stratified by the type of control group



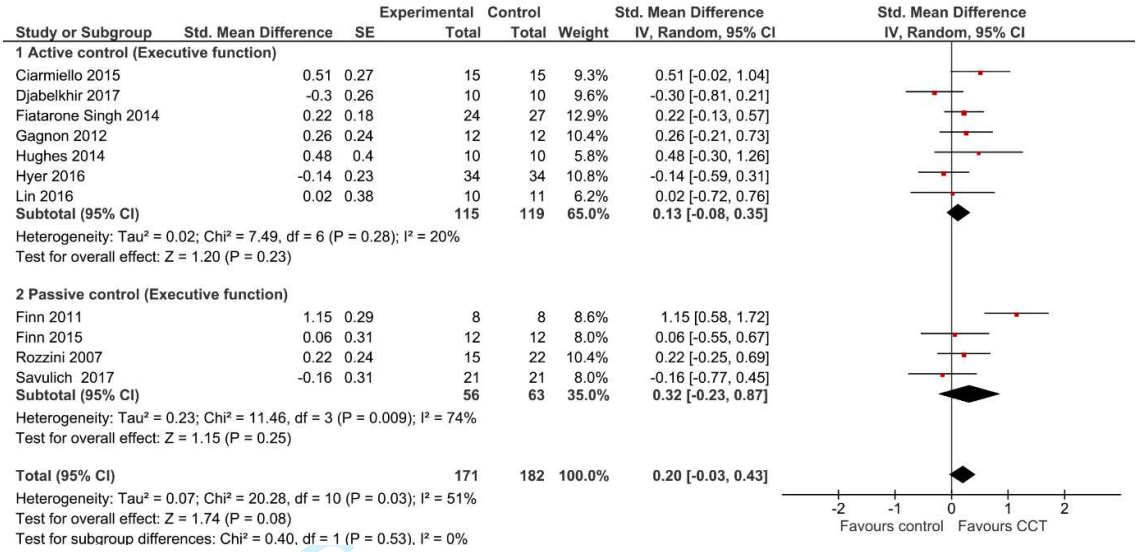
Supplementary Figure 5. Funnel plot demonstrating bias of CCT on memory, working memory and executive function



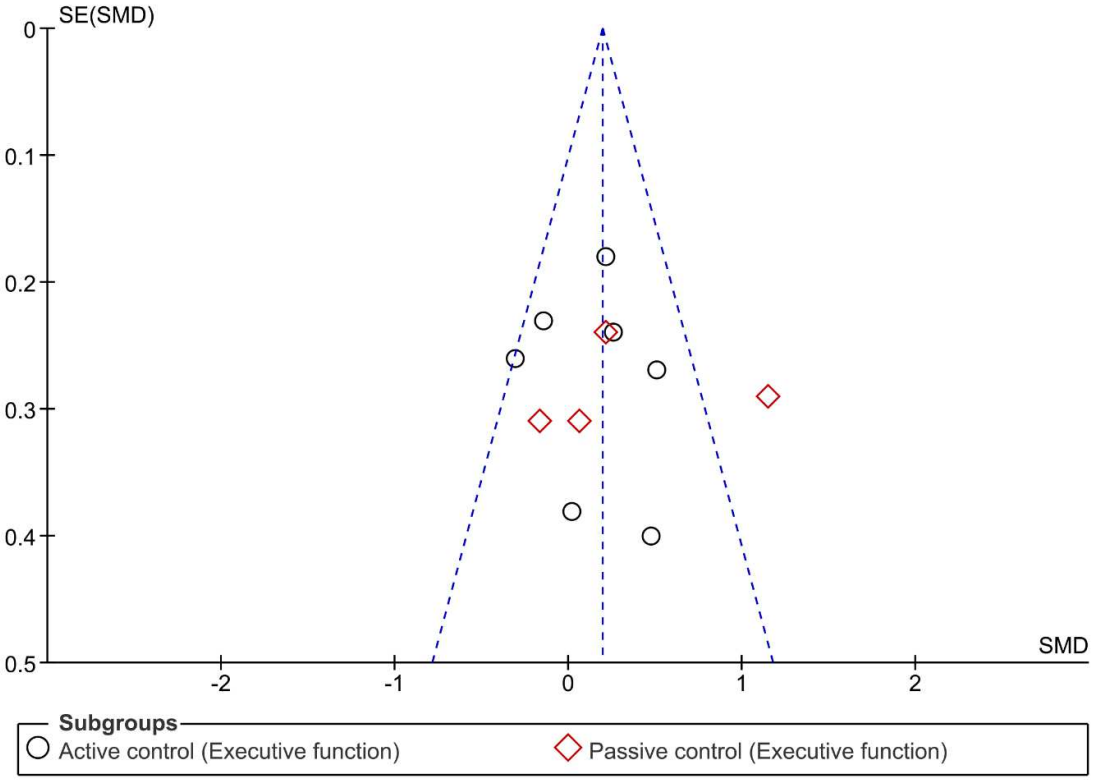
Supplementary Figure 6. Forest plot demonstrating efficacy of CCT on memory stratified by the type of control group



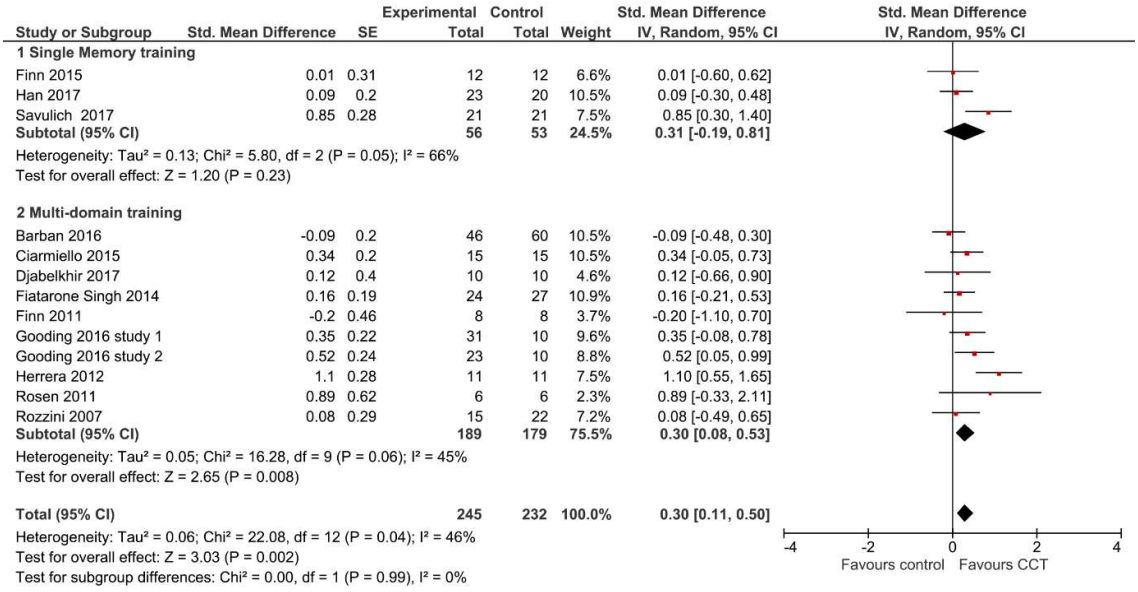
Supplementary Figure 7. Funnel plot demonstrating bias of CCT on memory stratified by the type of control group



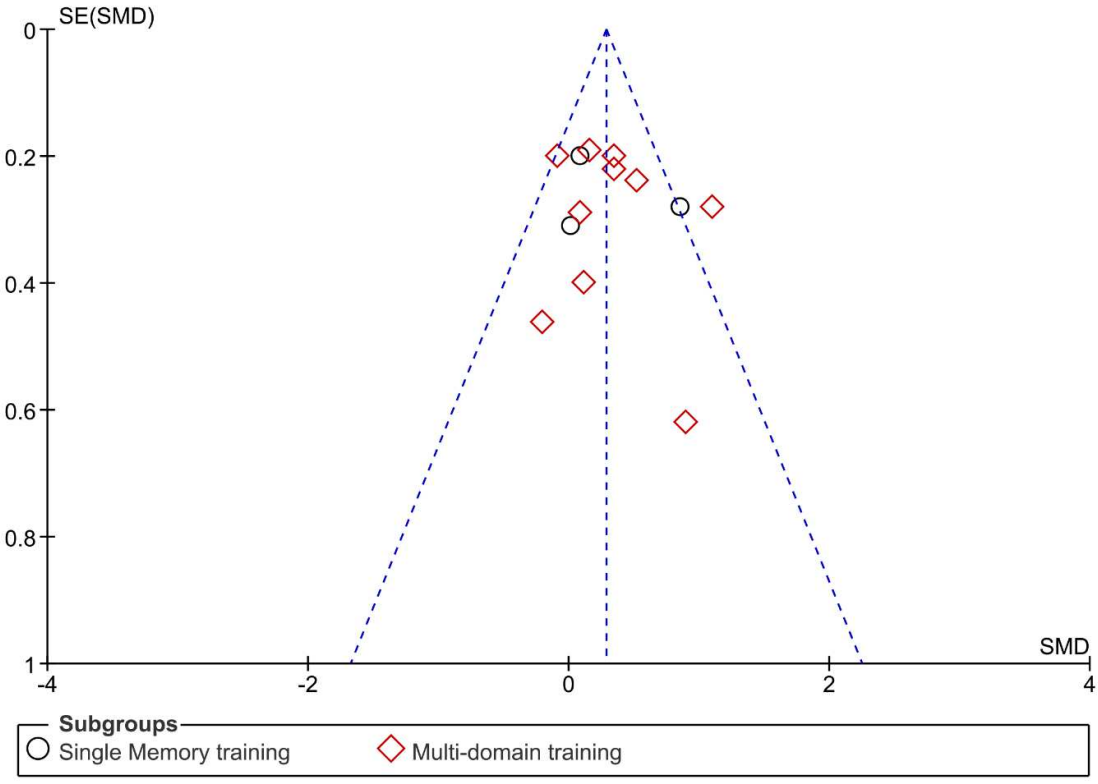
Supplementary Figure 8. Forest plot demonstrating efficacy of CCT on executive function stratified by the type of control group



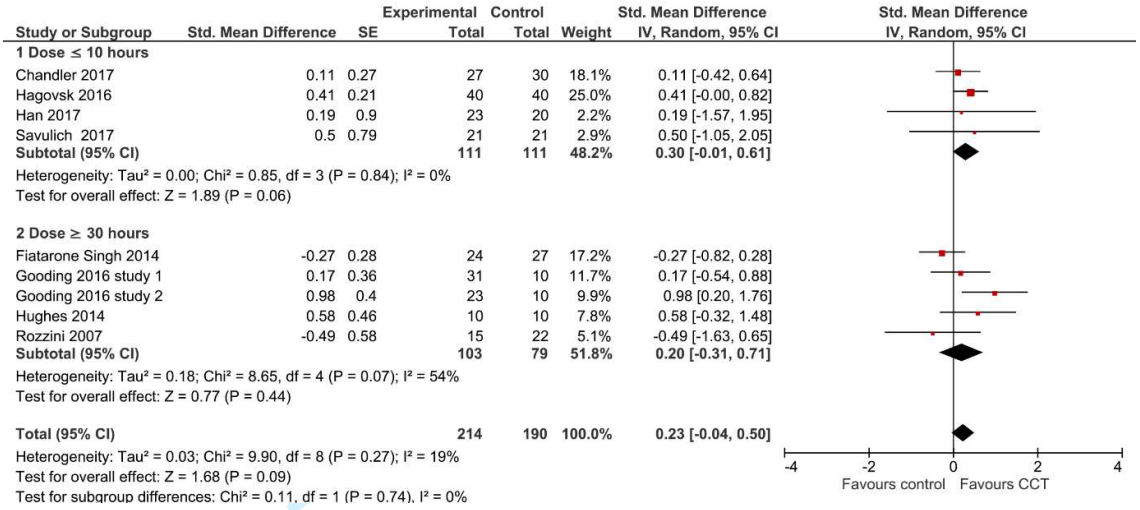
Supplementary Figure 9. Funnel plot demonstrating bias of CCT on executive cognition stratified by the type of control group



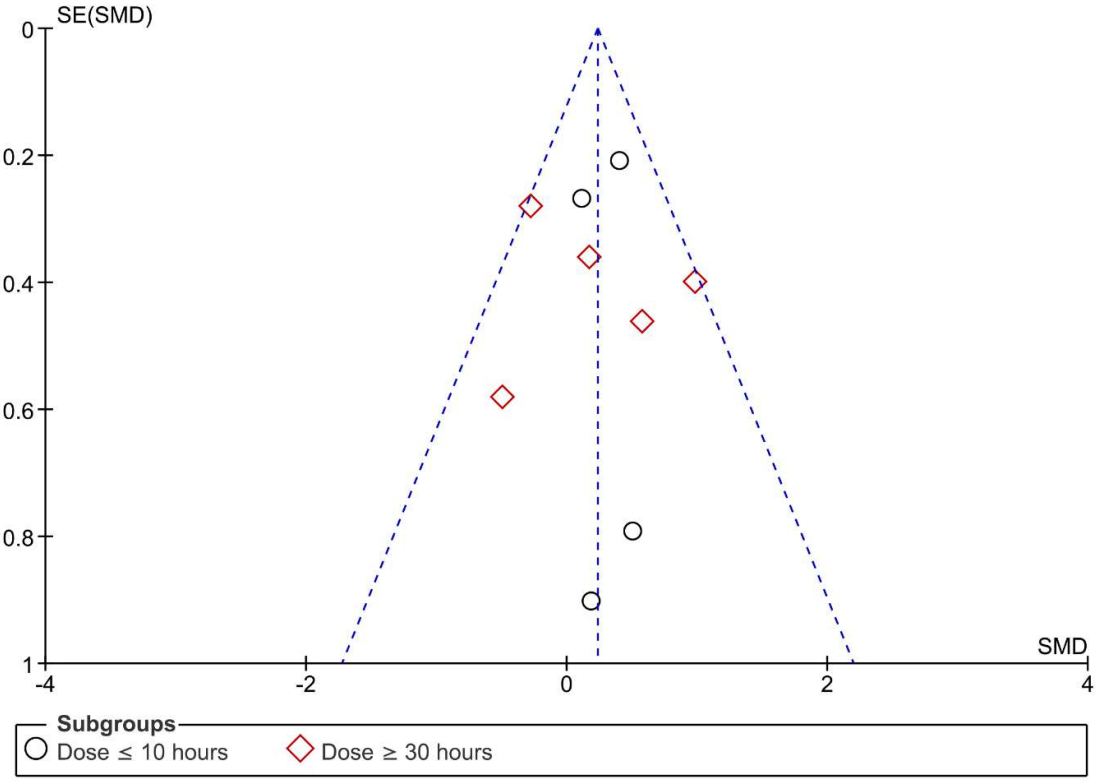
Supplementary Figure 10 Forest plot demonstrating efficacy of CCT on memory stratified by single memory domain or multi-domain intervention



Supplementary Figure 11 Funnel plot demonstrating bias of CCT on memory stratified by single memory domain or multi-domain intervention



Supplementary Figure 12 Forest plot demonstrating efficacy of CCT on global cognition stratified by dose of the intervention



Supplementary Figure 13 Funnel plot demonstrating bias of CCT on global cognition stratified by dose of the intervention

Supplement to: Zhang H, Huntley J, et al. The efficacy of Computerized Cognitive Training on cognitive outcomes in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis.

Supplementary Table 1 Search terms used for literature search

Supplementary Table 2 Brief description of the specific outcome measures included in the meta-analysis

Supplementary Table 3 Detailed Characteristics of studies using computerised cognitive training in persons with MCI

Supplementary Appendix 1 Statistical methods

Supplementary Table 1. Search terms used for literature search

Intervention Terms	"cognitive stimulation" OR "cognitive rehabilitation" OR "cognitive training" OR "cognitive therapy" OR "cognitive retraining" OR "cognitive support" OR "cognitive intervention" OR "cognitive exercise" OR "cognitive strategy" OR "cognitive aid" OR "memory function" OR "memory rehabilitation" OR "memory therapy" OR "memory aid" OR "memory group" OR "memory training" OR "memory retraining" OR "memory support" OR "memory stimulation" OR "memory strategy" OR "memory management" OR "brain training" OR "brain rehabilitation" OR "brain stimulation" OR "brain retraining" OR "brain exercise" OR "neuropsychological training" OR "neuropsychological therapy" OR "neuropsychological strategy" OR "neuropsychological aid" OR "neuropsychological stimulation" OR "neuropsychological rehabilitation" OR "neuropsychological exercise" OR "neuropsychological intervention" OR "neuropsychological retraining" OR "neuropsychological support" OR "psychostimulation" OR "executive training" OR "executive stimulation" OR "executive rehabilitation" OR "attention training" OR "attentional training" OR "attentional rehabilitation" OR "global stimulation" OR "reality orientation"
Study Terms	"RCT" OR "controlled trial" OR random*
Subject Terms	"Mild cognitive impairment" OR "memory impairment" OR "cognitive impairment" OR "memory disorder" OR "cognitive disorder" OR "memory dysfunction" OR "cognitive dysfunction" OR "MCI" OR "AAMI" OR "MCD" OR "mild cognitive disorder"

Supplementary Table 2. Brief description of the specific outcome measures included in the meta-analysis

Outcome measure	Domain	Brief Description	Study
Mini Mental State Examination (MMSE)	GEN COG	A 30-point questionnaire used to estimate severity of cognitive impairment including orientation and memory functions	Barben et al, 2016 Ciarmiello et al. 2015 Djabelkhir et al 2017 Han et al 2017 Hagovska et al. 2015 Rozzini et al 2007 Savullich et al 2017
Modified Mini Mental State Examination (mMMSE)	GEN COG	This instrument included all items from the standard MMSE, plus the Wechsler Adult Intelligence Scale–Revised Digit Span subtest and additional attention/calculation and general knowledge, language, and construction items.	Gooding et al 2016 study 1&2
Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)	GEN COG	Measuring severity of cognitive dysfunction associated with Alzheimer's disease, and is widely used in pharmacological studies of dementia and MCI. Higher scores indicate more dysfunction.	Fiatarone Singh et al 2014
Computerised Assessment of Mild Cognitive Impairment (CAMCI)	GEN COG	A battery of tests to assess cognitive performance including domains of attention, executive functioning, memory and processing speed	Hughes et al 2014
Milan Overall Dementia Assessment (MODA)	GEN COG	The MODA is a paper and pencil test, composed of three sections: an autonomy scale, a section testing orientation and a section testing a wide range of cognitive domains.	Ciarmiello et al. 2015
16-item free and cued reminding test	MEM	Participants search a card containing four pictures of items with matched category cues before subjected to tests of free and cued recall	Herrera et al 2012 Djabelkhir et al 2017
BEM-144 recall test	MEM	A 12-word immediate recall test from BEM-144 memory battery	Herrera et al 2012
Description of the visual recognition memory task (DMS48)	MEM	Participants asked to remember a sample before making a delayed forced-choice match to original sample	Herrera et al 2012 Ciarmiello et al. 2015

Outcome measure	Domain	Brief Description	Study
Doors Recognition subtest	MEM	Participants are shown a variety of different coloured doors which they must remember and later recognise from a selection of similar doors	Herrera et al 2012
MMSE - Recall Test	MEM	Participants presented with stimuli before being asked to recall as many as possible	Herrera et al 2012
Paired-associates learning (PAL)	MEM	Visual patterns revealed in different boxes before participant tested on where pattern originally located	Finn & McDonald 2011 Finn & McDonald 2015 Savullich et al 2017
Pattern Recognition Memory (PRM)	MEM	Test of visual pattern recognition in a forced discrimination paradigm	Finn & McDonald 2011
Recall of Rey's Complex Figure	MEM	Subjects shown complex figure and then tested on their delayed recall of the figure	Herrera et al 2012 Rozzini et al 2007
Rey's figure copy	MEM	Participants are to reproduce a drawing by i) copying (reproduction) and ii) memory (recall) using a 18-point scoring system	Rozzini et al 2007
List Learning Memory Sum from ADAS-Cog	MEM	List learning assessed across the three memory recall trials of the ADAS-Cog. Higher scores indicate better memory.	Fiatarone Singh et al 2014
Benton Visual Retention Test-Revised (BVRT-R)	MEM	BVRT-R is a visual memory test which assesses visual perception and visual constructional abilities as participants are required to draw from memory simple designs. Higher scores indicate better function.	Fiatarone Singh et al 2014 Savullich et al 2017
The Logical Memory subtest of the Wechsler Memory Scale 3rd edition (immediately and delayed)	MEM	The logic memory is used to measure both immediate (I) and delayed (II) memory for verbal information. Participants are presented with a simple narrative and are required to recall as many details of the story as they can immediately after presentation. Higher scores indicate better memory.	Fiatarone Singh et al 2014
Rey Auditory Verbal Learning Test (RAVLT)	MEM	RAVLT includes a list of 15 words to be recalled immediately after each of the 5 verbal presentations and after a 30-min delay	Barben et al, 2016 Ciarmiello et al. 2015
Prose memory	MEM	A subset of The Memory Assessment Scales, is an auditory verbal prose recall task which requires the subject to recall a short story. Subjects are asked to recall the story from memory and are then asked nine questions about details of the story.	Ciarmiello et al. 2015

Outcome measure	Domain	Brief Description	Study
visuospatial memory test (VST)	MEM	From the Cognitive Efficiency Profile	Djabelkhir et al 2017
Buschke Selective Reminding Test (BSRT)	MEM	The test provides 12 words which are selectively rehearsed by the subject until they are memorized. That is, only those words not recalled on the immediately preceding trial are presented. The subject then attends to an interference task or verbal list. Subsequently, after a delay, the subject is asked to recall the words.	Gooding et al 2016 study 1&2
WMS-R Visual Reproductions (VR) I and II subtests	MEM	VR assesses visual memory. Cards with printed designs is shown to the participants. Following each exposure and a 30 minutes delay, subjects draw what they remember of the design.	Gooding et al 2016 study 1&2
WMS-R Logical Memory (LM)Subtests I and II subtests	MEM	LM. The examiner reads two stories, stopping after each reading for an immediate free recall. And a 30 minutes delayed recall.	Gooding et al 2016 study 1&2
Short Story	MEM	Participants are asked to recall a short story	Rozzini et al 2007
The Word List Memory Test (WLMT)	MEM	Word list task that contains 10 semantically unrelated words The words are presented to the subject one at a time and are read aloud Three trials are administered in this fashion, with the order of the 10 words being randomized for each trial The examiner records the order of recall and notes any intrusions that might occur The primary Indices of Interest are the number of words recalled on each trial	Han et al 2017
The Word List Recall Test (WLRT)	MEM	Words, displayed one at a time for one second each. Participants read each of the words, and try to remember them without taking notes.	Han et al 2017
WLRcT(The Word List Recognition)	MEM	A word list was designed so that half its words would denote targets when any of a number of target classes were defined. After scanning this list for targets, subjects were unexpectedly tested on their ability to recognize the words they had scanned.	Han et al 2017

Outcome measure	Domain	Brief Description	Study
RBANS Memory Score	MEM	It consists of 12 subtests, which yield five Index scores (i.e., Attention, Language, Visuospatial/Constructional, Immediate Memory, and Delayed Memory) and a Total Scale score.	Rosen et al 2011
Dot counting test	WM	The task dot counting requires examinees to count the dots as quickly as possible by the fastest means possible.	Lin et al 2016
1-back test	WM	In the 1-Back task, participants are presented a sequence of stimuli one-by-one. For each stimulus, they need to decide if the current stimulus is the same as the one presented 1 trials ago.	Lin et al 2016
Digit Span Test	WM	Sequence of digits is read aloud. Subjects asked to immediately recall digits in the correct order. If correct, a sequence with an additional digit is presented.	Herrera et al 2012 Ciarmiello et al 2015
LNS (Letter-Number Sequencing)	WM	The task involves listening to and remembering a string of digits and letters read aloud at a speed of one per second, then recalling the information by repeating the numbers in chronological order, followed by the letters in alphabetical order.	Hyer et al 2016
Spatial Span	WM	Participants tested on ability to remember the location of objects on a spatial grid.	Hyer et al 2016
Spatial Span (Corsi test)	WM	Corsi is a short term memory task conceptually similar to the digit span test. the experimenter (the person who carries out the study) shows nine blocks arranged in front of the participant, the experimenter taps a sequence of blocks (for example, the experimenter taps a sequence of 3 different blocks, one after another), the participant needs to tap the blocks that the experimenter showed, in the same order, steps 1-3 are repeated multiple times with different lengths of blocks.	Ciarmiello et al. 2015
Spatial working memory (SWM)	WM	A test that requires retention and manipulation of visuospatial information to collect 'tokens' and fill a column	Finn & McDonald 2011

Outcome measure	Domain	Brief Description	Study
Symbol Span	WM	This subtest assesses visual working memory using novel visual stimuli. Beginning with two symbols, abstract visual symbols are exposed for 5 seconds. In the test phase, the participant has to correctly recall not only the correct symbols from distractor items, but also the order in which they were presented from left to right. The number of symbols presented increases by one at intervals as the test progresses. Higher scores indicate better visual working memory.	Finn & McDonald et al 2015
Word span	WM	Participants tested on ability to remember a list of words in order.	Ciarmiello et al. 2015
Alpha span task	WM	In the alpha span test, short lists of words are presented and the participant's task is to mentally reorder the words and give them back in correct alphabetical order.	Ciarmiello et al. 2015
Intra-/extra-dimensional set shifting (IED)	EXE	A test of rule acquisition and reversal. It is computerised analogue of the Wisconsin Card Sorting test and measured the total errors made	Finn & McDonald 2011
Modified Dual Task	EXE	Participants completed a modified dual task consisting of a visual detection task (responding to an appearance of a stimuli) and alpha-arithmetic task (responding 'true' or 'false' to equations of letters and numbers e.g. 'U-1 = T') simultaneously and were recorded in accuracy of responses in each task	Gagnon & Belleville 2012
Raven's coloured matrices	EXE	60 patterns present in order of difficulty. Subjects asked to identify the missing element that completes a pattern.	Rozzini et al 2007
Telephone Search Dual Task	EXE	Participants complete the telephone search test whilst simultaneously counting audible tones.	Gagnon & Belleville 2012
Telephone Search Test	EXE	Participants circle key stimuli while searching entries in a simulated classified telephone directory.	Gagnon & Belleville 2012
Trial making test	EXE	The task requires participants to 'connect the dots' in two parts, firstly numerically and secondly, alphanumerically.	Gagnon & Belleville 2012, Hughes et al 2014, Djabelkhir et al 2017 Hyer et al 2016

Outcome measure	Domain	Brief Description	Study
Verbal fluency	EXE	Participants generate as many words in one minute from a given letter.	Rozzini et al 2007, Djabelkhir et al 2017
Visual Elevator Test	EXE	Participants count up and down according to visual stimuli in an elevator, the time-per-direction-change score was calculated.	Gagnon & Belleville 2012
Raven's progressive matrices - non-verbal test (PM47)	EXE	The Raven Standard Progressive Matrices (PM47) assess the measure the test taker's reasoning ability.	Ciarmiello et al. 2015
Rey–Osterrieth complex figure test (ROCF)	EXE	ROCF is a neuropsychological assessment in which examinees are asked to reproduce a complicated line drawing, first by copying it freehand (recognition), and then drawing from memory (recall). The test therefore permits the evaluation of different functions, such as such as visuospatial abilities, memory, attention, planning, working memory and executive functions.	Ciarmiello et al. 2015
Categorical verbal fluency (animals)	EXE	Participants generate as many animal names as possible in one minute.	Fiatarone Singh et al 2014 Djabelkhir et al 2017
Number sequencing Number-Letter switching	EXE	In Number Sequencing, the participant is asked to draw a line connecting numbers in order from low to high as quickly as possible without making mistakes, and is a measure of attention. In Number-Letter switching, the task is to switch between connecting numbers and letters, in order, from lowest to highest, e.g., 1-A, 2-B, 3-C etc., and is a measure of cognitive flexibility.	Finn & McDonald et al 2015
Tracking A, Tracking B	EXE	Two tracking tasks requiring participants to (1) track numbers (from 24-1) in reverse order (Tracking A), and (2) months forward (January – December) and numbers in reverse (Tracking B).	Hughes et al 2014
Useful field of view (UFOV)	EXE	UFOV is a computerized test assessing visual processing speed and attention.	Lin et al 2016
Verbal fluency	EXE	Phonemic and categorical fluency	Lin et al 2016
Cognitive control	EXE	Set shifting and flanker tasks	Lin et al 2016

Outcome measure	Domain	Brief Description	Study
Cross-modality dual task (Divided)	EXE	Participants were subjected to a dual-task simultaneously consisting of a visual detection (as above) with a digit span task (orally recalling a list of digits) and recorded span items recalled correctly in %.	Gagnon & Belleville 2012
The CANTAB CRT(speed)	EXE	It is used to assess motor speed and thus acts as a control measure of general alertness to help interpret other cognitive tasks. An arrow will appear on either the left or right side of a computer screen. After the arrow appears, the participant is instructed to press a corresponding left or right button, using a response box, as quickly as possible.	Savullich et al 2017
WAIS-III Similarities	EXE	WAIS Similarities is a subtest from the WAIS-III used to measure verbal conception formation and abstractive thinking. Higher scores indicate better function.	Fiatarone Singh et al 2014
WAIS-III Matrices	EXE	WAIS Matrices is a perceptual subtest of the Wechsler Adult Intelligence Scale–III and is used to assess executive functions posing four types of non-verbal reasoning tasks including pattern completion, classification, abstraction and serial reasoning, and all items require visual perception, organization, and synthesis of visual spatial information. Higher scores indicate better function.	Fiatarone Singh et al 2014
COWAT	EXE	Combined Oral Word Association Test is a language-based task assessing association fluency, and is often used as a measure of executive functioning. The most commonly used letters are F, A, and S. or C, F, and L, based upon word prevalence rates. Higher scores indicate better function.	Fiatarone Singh et al 2014
SDMT (Attention/speed)	EXE	Symbol Digit Modalities Test measures divided attention, visual scanning, tracking, and motor speed. It uses a substitution format presenting symbols with matching numbers, and participants are required to provide name the numbers corresponding to each given symbol. Higher scores indicate better function.	Fiatarone Singh et al 2014

Notes: General cognition (GEN COG), episodic memory (MEM), working memory (WM), executive function (EXE)

Supplementary Table 3. Detailed Characteristics of studies using computerised cognitive training in persons with MCI

Author and Year	Treatment Group N, % male, mean age, mean education, MMSE (SD)	Control Group N, ratio of male, mean age, mean education, MMSE (SD)	CCT type for EC and type of CC	Frequency, duration and total hours	Drop-out (%)	Cognitive Training Intervention	Assessment interval (time pre or post intervention)	Included for meta-analysis
Barban et al 2016	N = 46 Ratio = 54.3% Age = 74.4 (5.7) Edu = 9 (4.3) MMSE = 27.3 (2.1)	N = 60 Ratio = 51.7% Age = 72.9 (6.0) Edu = 11 (4.7) MMSE = 28.1 (1.4)	EC: multi domain training. CC: passive(rest)	60 minute sessions, 2 sessions per week for 3 months. Total = 24 hours	n/s	Computerised software: 'SOCIABLE' using touch screen. Multi-component - CT including Memory, attentional Executive Function, orientation, logical reasoning, constructional Praxis, language.	Before and after training, follow-up (n/s)	Yes
Chandler et al 2017	N = 27 Ratio = 73.3% Age = 77.4 (7.2) Edu = 16.2 (2.6) MMSE = 26.7 (3.0)	N = 30 Ratio = 50.0 % Age = 76.2 (7.0) Edu = 16.0 (2.4) MMSE = 25.8 (3.2)	EC: Auditory memory training CC: Active(Memory Support System (MSS))	Frequency: n/s Duration: n/s Total = 10 hours	EC:4 CC:3 Total:10.94 %	"Auditory Brain Training" software: 6 adaptive modules exercises to recognize and differentiate sounds, match or repeat sounds, remember increasingly difficult directions, and remember details from stories.	n/s	No*

Author and Year	Treatment Group N, % male, mean age, mean education, MMSE (SD)	Control Group N, ratio of male, mean age, mean education, MMSE (SD)	CCT type for EC and type of CC	Frequency, duration and total hours	Drop-out (%)	Cognitive Training Intervention	Assessment interval (time pre or post intervention)	Included for meta-analysis
Ciarmiello et al 2015	N = 15 Ratio = 35.7% Age = 71.2 (7.7) Edu = 9.3 (3.02) MMSE = 27.9 (1.8)	N = 15 Ratio = 46.7% Age = 72.0 (7.1) Edu = 7.8 (2.6) MMSE = 27.8(1.9)	EC: multi domain CC: semi-active (meeting with psychologist – no computer)	45 minute sessions, 2 days per week for 4 months. Total = 24 hours.	EC: 0 CC: 0 0%	Computerised training with multiple difficulty levels. Includes dual-task training, executive function training, working memory updating, visual exploration, spatial orienting tasks.	Before and after training follow-up (n/s)	Yes
Djabelkhjr et al 2017	N = 10 Ratio = 30.0 % Age = 75.2 (6.4) Edu = 60.0% (6) (of college level) MMSE = 27.7 (1.9)	N = 10 Ratio = 40.0 % Age = 78.2 (7.0) Edu = 44.4% (4) (of college level) MMSE = 27.4 (2.0)	EC: multi-domain CC: Active(multi-component)	90 mins per session 1 sessions/week, 12 weeks. Total = 18 hours.	EC: 1 CC: 0 Total: 5%	'KODRO' (Altera-Group, Paris, France), a web-based platform with several applications (ie, appointment and event reminding, cognitive games, communication, entertainment, videos and a library).	Before and after training. Follow-up (n/s)	Yes
Fiatarone et al. 2014	N = 24 Ratio = n/s Age = >55 Edu = n/s MMSE = 28.0 (2.0)	N = 27 Ratio = n/s Age = >55 Edu = n/s MMSE = 27.0 (2.0)	EC: multi domain CC: active (sham)	75 minute sessions, 2 or 3 days per week for 26 weeks. Total = 80 hours.	EC: 2 CC: 3 Total: 9.8%	COGPACK program: Computer-based multimodal and multi domain exercises targeting memory, executive function, attention, and speed of information processing	At baseline and 6 months and at least 72 hours after the previous training session Follow-up: at	Yes

Author and Year	Treatment Group N, % male, mean age, mean education, MMSE (SD)	Control Group N, ratio of male, mean age, mean education, MMSE (SD)	CCT type for EC and type of CC	Frequency, duration and total hours	Drop-out (%)	Cognitive Training Intervention	Assessment interval (time pre or post intervention)	Included for meta-analysis
							18 months	
Finn & McDonald 2011	N = 8 ratio = 37.5% age = 69.0 (7.7) Edu = 13.3 (2.2) MMSE = 28.5 (2.3)	N = 8 ratio = 62.5% age = 76.4 (6.5) Edu = 12.0 (2.8) MMSE = 27.5 (2.4)	EC: Multi-domain CC: Waiting list (Passive)	30 minute sessions, 4-5 sessions a week for an average of 11.43 weeks. Total = 25 hours	EC: 4 CC: 5 Total: 32%	Lumosity Inc CCT package. Four broad cognitive domains targeted: attention, processing speed, visual memory and cognitive control	Before and after training Follow-up (n/s)	Yes
Finn & McDonald 2015	N = 12 ratio = 66% age = 72.8 (5.7) Edu = 13.8 (3.0) MMSE = 27.8 (1.3)	N = 12 ratio = 75% age = 75.1 (7.5) Edu = 13.7 (2.8) MMSE = 27.8 (1.9)	EC: Single memory domain CC: Passive	2 sessions per week for 4 weeks Total = n/s	EC: 4 CC: 3 Total:22.6%	Repetition-lag training to improve recollection memory	First and last training session Follow-up (n/s)	Yes

Author and Year	Treatment Group N, % male, mean age, mean education, MMSE (SD)	Control Group N, ratio of male, mean age, mean education, MMSE (SD)	CCT type for EC and type of CC	Frequency, duration and total hours	Drop-out (%)	Cognitive Training Intervention	Assessment interval (time pre or post intervention)	Included for meta-analysis
Gagnon & Belleville 2012	N = 12 ratio = n/s age = 67.0 (7.8) Edu = 15.0 (4.6) MMSE = 28.1 (1.2)	N = 12 ratio = n/s age = 68.4 (6.0) Edu = 13.1 (5.7) MMSE = 27.8 (1.5)	EC: Single domain(attentional control) CC: Active	60 minute sessions, 3 times a week for 2 weeks. Total = 6 hours	EC: 1 CC: 1 Total: 8%	Programme targeting attentional control using Variable Priority (VP) training in a dual task with selected priorities and feedback.	One week pre and after intervention Follow-up (n/s)	Yes
Gooding et al 2016 study 1	N = 31 ratio = 58.1% age = 75.6 (8.8) Edu = 15.1 (2.6) MMSE = n/s	N = 10 ratio = 58.1% age = 75.6 (8.8) Edu = 15.1 (2.6) MMSE = n/s	EC: Multi-domain CC: Active	60 min sessions, two days per week for 16 weeks Total = approx. 30 hours	EC: 12 CC: 1 Total: 20.3%	Posit Science's BrainFitness – repeated drill-and-practice adaptive exercises involving memory, attention and executive functions.	Before and after training Follow-up (n/s)	Yes
Gooding et al 2016 study 2	N = 23 ratio = 58.1% age = 75.6 (8.8) Edu = 15.1 (2.6) MMSE = n/s	N = 10 ratio = 58.1% age = 75.6 (8.8) Edu = 15.1 (2.6) MMSE = n/s	EC: Multi-domain CC: Active	60 min sessions, two days per week for 16 weeks Total = approx. 30 hours	EC: 12 CC: 1 Total: 20.3%	Posit Science's BrainFitness – repeated drill-and-practice adaptive exercises involving memory, attention and executive functions.	Before and after training Follow-up (n/s)	Yes

Author and Year	Treatment Group N, % male, mean age, mean education, MMSE (SD)	Control Group N, ratio of male, mean age, mean education, MMSE (SD)	CCT type for EC and type of CC	Frequency, duration and total hours	Drop-out (%)	Cognitive Training Intervention	Assessment interval (time pre or post intervention)	Included for meta-analysis
Hagovska et al 2016	N = 40 ratio = 55% age = 68.0 (4.4) Edu = 75% of secondary education MMSE = 26.0 (2.6)	N = 40 ratio = 48% age = 65.9 (6.2) Edu = 70% of secondary education MMSE = 26.0 (1.5)	EC: Multi domain + balance training CC: Passive(just balance training)	30 minute sessions, 2 times a week for 10 weeks. Total = 10 hours	EC: 0 CC: 2 Total: 2.5%	CogniPlus training program Battery contains subprograms for attention, Working Memory, long-term memory, executive functions, spatial processing and visuomotor coordination.	Before and after training Follow-up (n/s)	Yes
Han et al 2017	N = 23 Ratio = 56.5% Age = 73.7 (4.8) Edu = 13.5 (3.2) MMSE = 25.7 (3.2)	N = 20 Ratio = 50.0% Age = 74.5 (6.4) Edu = 12.7 (3.7) MMSE=24.5 (2.4)	EC: single memory training CC: Passive (Usual Care)	30 min per session 1 hour per day 2 sessions/week, 4 weeks. Total = 4 hours	EC:3 CC:5 Total: 16%	USMART program involving spaced retrieval-based memory training, using a self-administered application on an iPad tablet.	Week 0, 5 Follow-up (n/s)#	Yes
Herrera et al 2012	N = 11 ratio = 54% age = 75.1 (2.0) Edu = 46% of secondary school or more MMSE = 27.4 (0.5)	N = 11 ratio = 45% age = 78.2 (1.4) Edu = 63% of secondary school or more MMSE = 27.2 (0.4)	EC: Multidomain CC: Active	60 minute sessions, 2 days a week for 12 weeks. Total = 24 hours	0%	Several computer-based training exercises designed to improve memory and attention	0, 12 weeks ± 15 days Follow-up: at 24 weeks	Yes

Author and Year	Treatment Group N, % male, mean age, mean education, MMSE (SD)	Control Group N, ratio of male, mean age, mean education, MMSE (SD)	CCT type for EC and type of CC	Frequency, duration and total hours	Drop-out (%)	Cognitive Training Intervention	Assessment interval (time pre or post intervention)	Included for meta-analysis
Hughes et al 2014	N = 10 ratio = 20% age = 78.5 (7.1) Edu = 13.8 (2.4) MMSE = 27.2 (1.9)	N = 10 ratio = 40% age = 76.2 (4.3) Edu = 13.1 (1.9) MMSE = 27.1 (1.8)	EC: Multidomain CC: Active	90 minute sessions, once a week for 24 weeks. Total = 36 hours	0%	Group-based Nintendo Wii sports package. Group-based Interactive video gaming	0, 24 weeks ± 1 weeks Follow-up: (n/s)	Yes
Hyer et al. 2016	N = 34 ratio = 50% age = 75.1 (7.4) Edu = 70% secondary MMSE = n/s	N = 34 ratio = 44% age = 75.2 (7.8) Edu = 66% secondary MMSE = n/s	EC: Single domain (working memory) CC: Active (Sham)	25 days of 40 min sessions, completed over 5 to 7 weeks. Total = 16.7 hours	EC: 4 CC: 5 Total: 11.7%	Cogmed – adaptive WM training	Before and after training Follow-up: 3 months after intervention	Yes
Lin et al 2016	N = 10 Ratio = 50.0% Age = 72.9 (8.2) Edu = 90.0% of college level MMSE = n/s	N = 11 Ratio = 54.5% Age = 73.1 (9.6) Edu = 54.5% of college level MMSE = n/s	EC: Single domain speed-of-processing CC: active control(mental leisure activities)	1 hour per day 4 days per week for 6 weeks in their homes. Total = 24 hours	EC:2 CC:1 Total: 12.5%	INSIGHT online program: (vision-based speed-of-processing) which included five training tasks: eye for detail, peripheral challenge, visual sweeps, double decision, and target tracker.	Before and after training Follow-up (n/s)#	Yes

Author and Year	Treatment Group N, % male, mean age, mean education, MMSE (SD)	Control Group N, ratio of male, mean age, mean education, MMSE (SD)	CCT type for EC and type of CC	Frequency, duration and total hours	Drop-out (%)	Cognitive Training Intervention	Assessment interval (time pre or post intervention)	Included for meta-analysis
Optale et al 2010	N = 15 ratio = 59.1% age = 78.5 (10.9) Edu = 5.3 (2.4) MMSE = 22.9 (5.0)	N = 16 ratio = 31.25% age = 81.6 (5.0) Edu = 6 (3.5) MMSE = 21.0 (4.8)	EC: Single domain - Memory CC: Active	30 minute sessions, 3 times a week for 3 months. Total = 58.5 hours	EC: 3 CC: 2 Total: 16.1%	A Virtual Reality-based memory training programme	Before and after training Follow-up: 3 months after intervention	No**
Rosen et al 2011	N = 6 ratio = n/s age = 70.7 (10.6) Edu = 16.7 (0.8) MMSE = 29.3 (1.2)	N = 6 ratio = n/s age = 78.0 (7.9) Edu = 18.3 (1.5) MMSE = 27.8 (2.3)	EC: processing speed and accuracy in auditory processing CC: computer-based activities(Active)	100 minute sessions, 5 times a week for 8 weeks. Total = 36 hours	0%	processing speed and accuracy in auditory processing	Before and after training Follow-up (n/s)	Yes

Author and Year	Treatment Group N, % male, mean age, mean education, MMSE (SD)	Control Group N, ratio of male, mean age, mean education, MMSE (SD)	CCT type for EC and type of CC	Frequency, duration and total hours	Drop-out (%)	Cognitive Training Intervention	Assessment interval (time pre or post intervention)	Included for meta-analysis
Rozzini et al 2007	N = 15 ratio = n/s age = 63 - 78 Edu = n/s MMSE = 26.0 (1.6)	N = 22 ratio = n/s age = 63 - 78 Edu = n/s MMSE = 26.4 (1.9)	EC: Multidomain and medication CC: Medication only (Passive)	60 minute session, 5 days a week for 4 weeks in 3 discrete blocks. Total = 60 hours	0%	Cognitive exercises based on Neuropsychology Training combined with a cholinesterase inhibitor	Before and after training Follow-up (n/s)	Yes
Savulich et al 2017	N = 21 Ratio = 52.4% Age = 75.2 (7.4) Edu = 15.9 (1.3) (Age left school) MMSE = 26.6 (2.9)	N = 21 Ratio = 66.7% Age = 76.9 (8.3 Edu = 16.0 (2.1) (Age left school) MMSE = 26.8 ± 2.2	EC: a novel memory game CC: negative (clinic visits as usual)	1 hour per session, 8 hours within 4 weeks. Total = 8 hours.	0 %	Gameshow program: Computer-based episodic memory training.	At a maximum of 4 weeks after the baseline testing session Follow-up (n/s)	Yes

Notes: MMSE: Mini Mental State Examination, SD: Standard deviation, n/s: not stated, EC: Experimental condition, CC: Control condition. *Excluded from meta-analysis due to immediate cognitive outcomes not stated, ** Excluded from meta-analysis due to suspected inclusion of individuals with AD.

Supplementary Appendix 1

Statistical methods

Effect size calculation

Effect sizes were calculated using RevMan software version 5.3. Standardised mean differences were calculated using Hedges' adjusted g[1]. Pre-intervention standard deviations were used as these are most likely to be comparable across studies and therefore provide the most accurate estimate of effect size.[3]

The Hedges' adjusted g formula used in RevMan is as follows:

$$g = [M_{post\ intervention} - M_{post\ control}/SD_{pre\text{-}pooled}]*[1- 3/(4N-9)]$$

Where $N = n_{intervention\ group} + n_{control\ group}$

and

$$SD_{pre\text{-}pooled} = \sqrt{[((n_{intervention\text{-}1})\ SD_{pre\ intervention}^2 + (n_{control\text{-}1})\ SD_{pre\ control}^2)/\ N-2]}$$

Meta-analyses

Meta-analyses were performed using RevMan software version 5.3. A random effects method as described by DeSirmonian and laird[4] was used, adjusting standard errors of the effect sizes in each study to account for the heterogeneity for intervention effects observed between different studies.

The pooled effect size of each meta-analysis was calculated by attributing a weight to the average effect size in each study according to sample size. The z statistic was used to evaluate whether the pooled effect size was significantly different to no effect.

Heterogeneity was quantified using the I^s statistic.

Composite measure calculation

Composite scores were calculated where a study reported multiple outcomes falling within a particular outcome domain (e.g. objective cognitive performance). This approach was pragmatic in allowing one score to represent each intervention in the meta-analysis regardless of the number of outcomes reported. In turn this prevents more weight being given to studies with multiple outcomes.[2]The variance of the sum of variables was calculated as described below.

Using the example of a study with two relevant outcomes, there will be two effect sizes, namely y_1 and y_2. The overall mean effect size for the composite measure will be:

$\bar{y} = 1/2(y_1 + y_2)$

The variance of this mean is calculated as follows:

$V_{\bar{y}} = \frac{1}{4} (V_{Y1} + V_{y2} + 2r * \sqrt{V_{Y1}} * \sqrt{V_{y2}})$,

where r is the correlation coefficient describing to what extent y_1 and y_2 co-vary.

If the correlation is set at 0, the outcomes are essentially treated as independent of each other and if the correlation is set at 1, the variance is an average of each outcome's variance. The former will lead to an underestimate of the variance and overestimate of precision while the latter will have the opposite effect. Consequently, in the absence of existing literature to identify a suitable correlation, we reported composite effect sizes calculated using a correlation of 0.5.

1. Hedges LV, Olkin I. Statistical methods for meta-analysis. New York, Academic Press 1985.

2. Borenstein M, Hedges LV, Higgins JPT, et al. Introduction to Meta-Analysis. Chichester, John Wiley & Sons, Ltd 2009.

3. Morris S. Estimating Effect Sizes From Pretest-Posttest-Control Group Designs. Organ. Res. Meth 2008;11 (2):364-386.

4. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7(3):177-188

PRISMA checklist

Section/topic	Checklist item	Page number/ Figure/Table
Title		
Title	Identify the report as a systematic review, meta-analysis, or both.	**1**
Abstract		
Structured summary	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**2-3**
Introduction		
Rationale	Describe the rationale for the review in the context of what is already known.	**4-6**
Objectives	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**6**
Methods		
Protocol and registration	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**n/a**
Eligibility criteria	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**8**
Information sources	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**8**
Search	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Supplementary**

Section/topic	Checklist item	Page number/ Figure/Table
		Table 1
Study selection	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**9**
Data collection process	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**9**
Data items	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**n/a**
Risk of bias in individual studies	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**9**
Summary measures	State the principal summary measures (e.g., risk ratio, difference in means).	**9**
Synthesis of results	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**9**
Risk of bias across studies	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**9**
Additional analyses	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**10**
Results		
Study selection	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**Figure 1**

Section/topic	Checklist item	Page number/ Figure/Table
Study characteristics	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**Table 1** **11-12**
Risk of bias within studies	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**Supplementary Figure 1**
Results of individual studies	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**Figs 2-3**
Synthesis of results	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**13-14**
Risk of bias across studies	Present results of any assessment of risk of bias across studies (see Item 15).	**Supplementary Figure 1**
Additional analysis	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**13-14**
Discussion		
Summary of evidence	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**16**
Limitations	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**16-17**
Conclusions	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**19**
Funding		
Funding	**Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the**	**n/a**

Section/topic	Checklist item	Page number/ Figure/Table
	systematic review.	

The PRISMA for Abstracts Checklist

TITLE	CHECKLIST ITEM	REPORTED ON PAGE #
1. Title:	Identify the report as a systematic review, meta-analysis, or both.	3
BACKGROUND		
2. Objectives:	The research question including components such as participants, interventions, comparators, and outcomes.	3
METHODS		
3. Eligibility criteria:	Study and report characteristics used as criteria for inclusion.	3
4. Information sources:	Key databases searched and search dates.	3
5. Risk of bias:	Methods of assessing risk of bias.	3
RESULTS		
6. Included studies:	Number and type of included studies and participants and relevant characteristics of studies.	3
7. Synthesis of results:	Results for main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If meta-analysis was done, include summary measures and confidence intervals.	3
8. Description of the effect:	Direction of the effect (i.e. which group is favoured) and size of the effect in terms meaningful to clinicians and patients.	3
DISCUSSION		
9. Strengths and Limitations of evidence:	Brief summary of strengths and limitations of evidence (e.g. inconsistency, imprecision, indirectness, or risk of bias, other supporting or conflicting evidence)	3
10. Interpretation:	General interpretation of the results and important implications	3
OTHER		
11. Funding:	Primary source of funding for the review.	NA
12. Registration:	Registration number and registry name.	NA