# Computerized Cognitive Training in People with Depression: A Protocol for a Systematic Review and Meta-Analysis

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**Protocol**

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## Abstract

# Background

People with depression often present with concurrent cognitive impairment. Computerized cognitive training (CCT) is safe and efficacious strategy to maintain or enhance cognitive performance in a range of clinical populations. However, its efficacy in people with depression and how it varies across populations and design factors is currently unclear.

# Methods

We searched MEDLINE, EMBASE and PsycINFO from inception to 29 June 2020 for randomised controlled trials examining the efficacy of CCT vs any control condition on cognitive, mood, psychiatric symptoms, psychosocial functioning and daily function in adults with depression. Eligible samples include studies specifically targeting people with major depressive disorder as well as those with other diagnoses where at least 50% of the sample meets clinical criteria for depression, with the exception of major psychiatric disorders or dementia. The primary outcome is change in overall cognitive performance. Multivariate analyses will be used to examine effect sizes on each outcome category as well as possible effect modifiers and correlations between categories. Risk of bias will be assessed using the Cochrane risk of bias tool version 2.

# Discussion

To the best of our knowledge, this will be the first systematic review and meta-analysis of narrowly-defined CCT across clinical populations with depression. We aim to investigate not only whether CCT is efficacious for cognition, but also how such effects vary across design factors, what other clinically relevant outcomes might respond to CCT and the extent to which they differ across populations.

# Systematic review registration:

Submitted and pending evaluation with PROSPERO.

## Background

Cognitive impairment is a core feature of depression [1], common not only in symptomatic but also remitted states [2], and only partially responsive to common antidepressants [3]. A history of depression is one of the most robust dementia risk factors, associated with approximately 80% higher risk of developing dementia in late life [4] and given its relatively high prevalence, may independently account for about 8% of dementia cases worldwide [5]. Moreover, depression is one of the most common comorbidities in chronic diseases, may interfere with management and lead to poorer functional

outcomes [6]. Therefore, interventions that effectively target cognition alongside other symptoms in people with depression may have an important role in not only maintaining everyday function [7], but also in delaying or preventing cognitive decline and dementia [4, 8].

Computerised cognitive training (CCT) is a key component of cognitive remediation and has received increasing interest for targeting cognitive and functional outcomes in depression and a range of other mental disorders [7, 9]. CCT is different from other approaches by focusing on repeated and controlled practice on cognitively demanding tasks targeting one or more cognitive domains, as opposed to explicit learning of compensatory strategies [7, 9]. CCT is inherently safe, typically adaptive to individual needs, provides ongoing feedback and can be delivered inexpensively in a range of healthcare and community settings. Meta-analyses of randomised controlled trials (RCTs) investigating CCT by itself or in combination with other strategies have reported small-to-moderate effect sizes for not only cognition but also for psychosocial and functional outcomes in schizophrenia [10, 11], psychosis [12] and mild cognitive impairment [13]. However, effect size estimates are often heterogeneous and vary across populations, outcomes or intervention design factors such as training content, dose and supervision [10, 11, 14].

The efficacy of CCT in people with depression has been previously investigated in two systematic reviews with meta-analysis. Motter and colleagues [15] reported moderate effect sizes on measures of symptom severity, daily functioning and attention, as well as large effect sizes on working memory and global cognition. Effect sizes for executive functions and verbal memory were small and imprecise. Although the review inclusion criteria were specified to RCTs of CCT, at least three of the nine included studies were not randomised trials [16–18] and one provided memory strategy training rather than CCT [19]. More recently, Chan and colleagues [20] investigated the effects of different cognitive interventions on depression outcomes in older people with mild cognitive impairment or dementia. The review included seven CCT studies, which reported large and statistically significant effect size on depressive symptoms. However, none of the included studies specifically targeted people with depression, and mean baseline scores were below the cut-off for depressive disorder in all studies.

Therefore, while results of preliminary meta-analyses as well as those in other populations are encouraging, the potential of CCT as an effective intervention for cognition and function in people with depression has yet to be systematically and robustly evaluated. Moreover, investigations of the extent to which design factors such as population characteristics, concurrent pharmacological or psychological treatments, intervention strategies, control comparisons and study quality may relate to clinical outcomes are required in order to inform clinical guidelines [7].

# Objectives

The aim of this review is to evaluate the efficacy of CCT on cognitive, mood, psychosocial and functional outcomes in adults with depression. Specifically, we aim to:

1. Investigate the efficacy of CCT on cognitive, mood, psychosocial outcomes and daily function in comparison to active or passive control.
2. Examine study and intervention design factors that could moderate CCT effects across studies in each domain.
3. Evaluate the strength and quality of the evidence for CCT in depression.
4. Suggest recommendations for future research and practice in the field.

## Methods

This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines [21]. The PRISMA-P checklist is provided as Additional file 1.

# Eligibility criteria

Consistent with our previous systematic reviews of CCT [13, 14, 22] we will include studies that meet the following criteria:

# Types of studies

RCTs studying the effects of CCT on one or more cognitive, mood, psychosocial or functional outcome in people with depression. Eligible studies will provide neuropsychological testing or clinical outcome measures (e.g., depression scales) at baseline and post CCT intervention. Randomised crossover trials will be included but only the first treatment phase will be considered and used for analysis. Non-randomised trials will be excluded. Unpublished RCTs or those published as conference abstracts, theses or monographs will be eligible if data needed for analysis and appraisal can be obtained from the authors.

# Types of participants

Eligible participant groups will be relatively broad in order to ensure results are relevant across clinical settings as well as to examine whether efficacy varies across populations, including those with other chronic disorders [6]. Therefore, included studies would have recruited adults (aged ≥ 18 years, including older adults) with depression at baseline, established according to standard diagnostic criteria (e.g., Research Diagnostic Criteria, DSM-5, ICD-10), diagnostic interviews, expert clinical diagnosis or median score greater than a cut-off on an established clinical measure (e.g., BDI ≥ 14, GDS-30 ≥ 10), at any clinical stage. These may include, for example, samples of treatment-resistant or recurrent depression, those on chronic pharmacological treatment, in- or outpatients, or mixed samples. There will be no limitations for studies where some or all the sample uses concurrent antidepressant medications. Studies who sampled people from a broader clinical sample (e.g., mixed psychiatric samples, mild cognitive impairment, multiple sclerosis) meeting criteria for depression will be included. However, studies recruiting solely from a psychiatric sample other than depression (e.g., all included patients with schizophrenia) will be excluded. In the case of mixed psychiatric samples, if ≥ 50% of the sample

includes people with other major psychiatric disorders or receiving antipsychotic medication, the study will be included only if data for those without the concurrent disorder or medication use can be obtained from the report or authors. Similarly, if ≥ 50% of the sample includes people with dementia, the study will included only if data for participants without dementia can be obtained as CCT is unlikely to be efficacious in dementia [13]. In all other cases, will we try to obtain separate data but will not categorically exclude the study if otherwise eligible. A clinical panel including a consultant psychiatrist (CGD), old age psychiatrist (NTL), neurologist (CF) and neuropsychologist (HMG) will review and approve inclusion decisions.

# Types of interventions

Minimum of 3 hours [23] of practice on standardized computerized tasks or video games with clear cognitive rationale, administered on personal computers, mobile devices or gaming consoles. Studies combining CCT with other non-pharmacological interventions (e.g., psychotherapy, physical exercise, brain stimulation) or with pharmacological interventions will be eligible as long as the CCT condition is the only key difference between the two groups. That is, studies will be included only if the contrast between arms allows to delineate the effect of CCT from the composite intervention; thus, studies comparing e.g., CCT + antidepressant to CCT + placebo will be excluded as such designs do not provide useful information regarding the effects of CCT.

# Types of comparators

Eligible control conditions include wait-list, no-contact and active (e.g., sham CCT, recreational activities) control groups. Alternative treatments (e.g., pharmacological, physical exercise) will be eligible if provided similarly to both groups. All eligible controls in multi-arm studies will be included.

# Types of outcomes

Eligible outcomes are change in performance from baseline to post-intervention in non-trained measures of cognition (global or domain-specific), assessed through standardised neuropsychological tests or close equivalents (e.g., a computer-based version of a common neuropsychological test). Additional outcomes include validated measures of mood, psychiatric symptoms (e.g., anxiety, neuropsychiatric symptoms), subjective cognitive function and daily functioning. Outcomes will be excluded if they were used as (or closely resemble) training tasks or if they were exploratory in nature (i.e., do not resemble common neuropsychological tests). In studies reporting more than one outcome measure per category, all eligible outcome measures will be included and pooled within studies (see *Data synthesis*). The primary outcome will be overall cognitive performance, defined as the mean effect size across all cognitive outcomes in a study [10, 13, 14, 22]. Secondary outcomes are domain-specific cognitive performance, classified according to the CHC-M framework [24], global cognition, subjective cognition, mood, other psychiatric symptoms, psychosocial functioning and daily function.

# Search strategy

We searched MEDLINE, EMBASE and PsycINFO through the OVID interface for eligible articles from inception to 29 June 2020. No restrictions on language or type of publication will be applied. The electronic search will be complemented by hand-searching the references of included articles and previous reviews as well as clinical trial registries. The full search strategy is provided as Additional file 2.

# Study selection

Literature search results will be uploaded to a single Covidence library. Duplicates will be removed and articles identified from other sources will be added. Initial screening for eligibility based on titles and abstracts will be conducted by two independent reviewers. Full-text screening of potentially relevant articles will be conducted by two independent reviewers. Disagreements at each stage will be resolved by consensus or by involvement of a senior reviewer (AL). The final list of included studies will be reviewed by at least two members of the clinical panel (CGD, NTL, CF and HMG).

# Data extraction

Data will be extracted to a piloted Excel spreadsheet by one reviewer and a senior reviewer (AL or HMG) will check data entry. Any disagreements will be resolved by consensus or by involvement of a third reviewer if necessary. If any additional information is needed, we will contact the corresponding authors of the studies. The following data items will be extracted:

- Study information: first author, year of publication, study location
- Population: mean age, percent female, clinical characteristics at baseline (diagnostic criteria, mean depression scores, clinical stage), co-morbid disorders, medication use, mean MMSE score or equivalent (older samples only)
- Intervention: type of CCT, program used, training content, delivery format (supervised or unsupervised), total training duration (hours), session frequency (sessions/week), session length (minutes), total number of sessions, intervention duration (weeks), adjacent treatments
- Comparator: type of control, control group activity
- Outcome: name of measure, summary data for each group (e.g., mean, standard deviation, sample size) at baseline and post intervention, cognitive or clinical domain

Intention-to-treat data will be preferred if reported. Data will be extracted as means and standard deviation for each time point or change scores. If such information is not available, data in other formats (e.g., effect sizes and confidence intervals) will be used if the article provides sufficient information to reliably calculate standardised mean difference. If these data are unavailable, authors will be contacted to obtain missing data.

# Risk of bias assessment

Risk of bias in individual RCTs will be assessed using the revised Cochrane Risk of Bias tool (RoB 2) [25]. Low, high or some concerns risk of bias will be determined for each of the following domains:

1. Bias arising from the randomization process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result
6. Overall bias

Studies with “some concerns” or “high” risk of bias in domains 3 or 4 will be considered as having some concerns or high risk of bias, respectively. Two independent reviewers will assess the risk of bias and disagreements will be resolved by consensus or consulting a third reviewer if necessary.

# Data synthesis

Analyses will be conducted using the packages metafor, metaSEM, robumeta and clubSandwich for R. Between-group differences in change from baseline to post-intervention will be converted to standardized mean differences and calculated as Hedges’ *g* with 95% confidence interval for each eligible outcome measure. Pooling of outcomes across studies will be conducted using random-effects models. All eligible outcomes per analysis will be used, accounting for dependency structure of effect sizes within studies [26, 27]. Sensitivity analyses for the primary outcome will be conducted by comparing results from multilevel and robust variance estimation models. Analyses of secondary outcomes will be contingent on the availability of at least three studies for analysis.

Heterogeneity across studies will be quantified using $tau^2$ and additional expressed as a proportion of overall observed variance using the $I^2$ statistic [28, 29]. Prediction intervals will be calculated to assess the dispersion of effects across settings [30]. Provided sufficient statistical power for investigations of heterogeneity [31], potential moderators will be investigated using meta-regression models. Additional meta-regressions will examine the relationship between cognitive, mood and functional effect sizes. If warranted, potential interactions across moderators will be tested on an exploratory basis using multivariate meta-regressions.

# Meta-bias(es)

Small-study effect will be assessed by visually inspecting funnel plots of effect size vs standard error [32]. If at least 10 studies are available, small study effect will be formally tested using a multivariate analogue of the Egger’s test [33] i.e., a meta-regression using standard error as covariate. Subgroup analysis of the primary outcome will be conducted based on overall RoB 2 scores.

# Confidence in cumulative evidence

The strength of the evidence will be assessed and summarized qualitatively based on risk of bias for individual studies, precision of the effect estimates, heterogeneity across studies (including prediction intervals) and evidence for small study effects, with additional sensitivity analyses conducted if warranted.

## Discussion

Depressive symptoms and their associated cognitive impairments are prevalent and heterogeneous. Our eligibility criteria allow for the inclusion of different presentations and definitions of depression in clinical practice, while including only RCTs of narrowly-defined CCT. Combined with our multivariate analysis approach, these criteria will allow us to examine clinical and intervention design factors as sources of heterogeneity and potential effect modifiers. As such, we aim to examine not only whether CCT is efficacious, but also for what outcomes, in whom, and intervention and study design elements appear to be most promising in future trials and clinical practice.

## Abbreviations

**BDI**
Beck Depression Inventory
**CCT**
Computerised cognitive training
CHC-M
Cattell-Horn-Carroll-Miyake
**DSM-5**
Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
**GDS**
Geriatric Depression Scale
**ICD-10**
International Statistical Classification of Diseases, 10th Revision
**MMSE**
Mini-Mental State Examination
**RCT**
Randomised controlled trial

## Declarations

# Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of data and materials

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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# Authors' contributions

AL led the drafting of the manuscript. AL, NHL, AR, CGD, CF, NTL, and MHG contributed to the design of the systematic review. CGD, CF, NTL, and MHG contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

# Acknowledgements

Not applicable.

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