Cognitive Computerized Training for Older Adults and Patients with Neurological Disorders: Do the Amount and Training Modality Count? An Umbrella Meta-Regression Analysis

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Abstract

Numerous applications have been created to train cognition and challenge the brain; a process known as computerized cognitive training (CCT). Despite potential positive results important questions remain unresolved: the appropriate training duration, the efficacity of CCT depending on its type (commercial or developed in-house for the rehabilitation of specific patients) and delivery mode (at-home or on-site), and the patients most likely to benefit such intervention. This study aims to perform an umbrella meta-analysis and meta-regression to determine if the type of CCT, the delivery mode, the amount of training, and participants' age at inclusion influence the improvement of the cognitive function. To do so we performed a umbrella meta-analysis. One hundred studies were included in this analysis representing 6,407 participants. Statistical improvements were found for the different conditions after the training. We do not find statistical difference between the type of intervention or the delivery mode. No dose-response relationship between the total amount of training and the improvement of cognitive functions was found. CCT is effective in improving cognitive function in patients suffering from neurological conditions and in healthy aging. There is therefore an urgent need for health care systems to recognize its therapeutic potential and to evaluate at a larger scale their integration into the clinical pipeline as preventive and rehabilitation tool.

Keywords: Cognitive Brain Training, mHealth, rehabilitation

Introduction

Cognitive impairments are common symptoms of most neurological diseases[1–4] and cognitive decline is associated with aging.[5] Various cognitive training programs have been developed for decades to try to preserve, increase, restore, or slow down the decrease of cognitive functions. Such kind of interventions have been validated to improve cognition of young healthy people,[6] healthy older adults,[7] and patients with Mild Cognitive Impairment (MCI).[8] Cognitive interventions have also been developed and successfully tested in patients with various neurological disorders such as stroke,[9] Multiple Sclerosis (MS),[10] and Parkinson's disease (PD).[11] However classic center-based[12] cognitive training programs may be difficult to implement since they require the presence of healthcare professionals, additional travels to the centre and may seem boring and repetitive for the patients.[13] The development and generalization of computer and mobile technologies offer new possibilities in the management of cognitive deficits in various populations.[14] In parallel to this rapid growth, the industry of software and mobile apps is exploding. Health-related apps make up an important part of this market, and numerous solutions (including online platforms, and mobile apps) have been developed to 'train' cognition and challenge the brain, what is called computerized cognitive training (CCT). CCT is a digital health application that enables consumers to access interactive cognitive exercises from a personal computer or mobile. These exercises can be designed to enhance general cognition or specific cognitive functions (i.e., learning and memory, attention, processing speed, executive functioning). The advantage over classic center-based cognitive training is that they can be performed as well in center as at home, the exercise level is continuously adapted based on the score obtained in the exercises or based on (self-administered) cognitive tests, and adherence can be monitored remotely.[15]

Currently two types of approaches are possible to perform CCT; using commercially available solutions,[16] part of which are not primarily developed for clinical applications, or solutions that have been developed in-house specifically for rehabilitation of patients with specific disorders. A lot of studies have been performed to validate the use of CCT, these works have been synthesized in different systematic reviews and meta-analyses in various conditions such as aging,[17,18] MCI,[19] stroke,[20] PD,[21] and MS.[22] Despite these analyses, important clinical issues remain unknown such as defining the appropriate duration and frequency of the intervention, the best type of intervention and delivery mode, and the patients most likely to benefit from this type of intervention. Another important question, not been answered yet, is to determine if training performed independently at home is as efficient as centre-based training. Most of the interventions are indeed performed in centres under the supervision of clinicians while one of the potential advantages of such solutions is that they could be used to train patients in home-environment without requiring the continuous presence of healthcare professionals and frequent travels to the center. Therefore this study aims to perform an umbrella meta-analysis to determine if the type of CCT (commercial vs. specific), the delivery mode (at-home or on-site), the amount of training, and participants' age at inclusion influence the improvement of the cognitive function.

Methods

We performed a second analysis of the meta-analyses by synthesizing evidence from multiple meta-analyses performed in this field. We performed an omnibus meta-analysis, which pooled all primary studies across all potential moderators, followed by individual meta-analyses for various potential moderators, to synthesize the effect size across the first order meta-analyses.[24] The protocol of the present study was registered in the international prospective register of systematic reviews PROSPERO (registration number CRD42020167321). This systematic review and omnibus meta-analysis were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[25] For the present study, no ethics committee approval was necessary.

Search strategy and selection criteria

We searched the PubMed electronic database, Web of Sciences, Embase, Scopus, and Sciences Direct for relevant meta-analyses published up to the 31st of March 2022. MeSH terms and free words referring to brain training ("cognitive training", "brain training", "memory training", "reasoning training", "attention training", "processing speed training"), games ("video games", "exergames", "computer training", "games", "mobile games", "cognitive games") and meta-analysis were used as keywords. The search was limited to meta-analyses published in English in peer-reviewed journals.

The inclusion and exclusion criteria were as follows. No time period threshold was used because CCT is a fairly recent paradigm. A PICOS approach (Population, Intervention, Control, Outcome, and Study design) was used for the inclusion and exclusion criteria, which were predetermined and assessed by the study team from the selected meta-analysis.

- Population: For studies in older adults: cognitively healthy participants (defined in the study as an MMSE ≥ 27.5/30) aged above 60 years old. For studies in patients with neurological diseases: stroke patients and patients with MS, PD and MCI, denoted later in the text as conditions.
- Intervention: Studies using CCT to perform cognitive training. The duration of the training must be a minimum of 1 month.[26] Studies using action-video games, active-video games or a combination of cognitive and physical rehabilitation exercises (i.e., dual-task paradigms) were not included. Indeed, although these types of intervention could also improve cognitive functions,[27] we decided to focus in present study on CCT dedicated to train and challenge specifically cognitive functions to reduce heterogeneity across the different types of intervention and training.
- Control: Active brain training or brain-stimulating activities (e.g., reading, board games, etc.)

- Outcome: Outcomes included performance on one or more cognitive tests, administered both before and after training that provide any validated measure of cognitive functions. The outcomes were categorized according to their transfer-level. The transfer effect refers to the capability of using the knowledge and skills learned in one task to improve performance in similar or different task. We defined three types of transfer: direct transfer (performance at tests that are similar or identical to the exercises of the CCT), near transfer (performance at tests assessing cognitive functions trained during the CCT) and far transfer (performance in tasks that are different from the training tasks in nature or in appearance).[28] Due to an incomplete description of the content of exercises used during CCT, it was sometimes difficult to determine if tests used to assess cognitive function were similar or not to the task trained during the CCT and, because of that, to define the type of transfer for those studies. Therefore, we end up with lot of studies classified as 'mixed' transfer. The assessment of the type of transfer, according to the tests used, was made independently by the two authors (B.B. and M.K.). In case of disagreement, the final decision was made after discussion between the two authors.
- Study design: Randomized Controlled Trials (RCTs).

A flow diagram of the study selection with the screened meta-analyses and the selection process is presented in Figure 1.

Quality assessment

The Physiotherapy Evidence Database Scale (PEDro) was used to assess methodological quality of included studies. The PEDro scale is an 11-item scale designed for rating methodological quality of RCTs. Each satisfied item contributes one point to the total PEDro score (item 1 omitted for score calculation, range=0 –10 points).[29] Total PEDro scores of 0-3 are considered 'poor quality', 4-5 'moderate quality' and 6-10 'good quality'.

Data extraction

The following information was extracted from the included studies: characteristics of the participants (age, severity of the disease and/or MMSE, when available), type of intervention (commercial or specific), duration of the intervention (total duration of the training, number of weeks, duration of one session), delivery mode (at-home or on-site), type of assessment and transfer, and results of the cognitive assessment. Summary of the included studies is presented in Table 1.

Statistical analysis

The measure of treatment effect was the effect size (standardized mean difference (SMD)), defined as the between-group difference in mean values divided by the pooled SD computed using the Hedge's g method (see Eq. 1)

$$g = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\left((n_1 - 1) \times {s_1}^2 + (n_2 - 1) \times {s_2}^2\right) / (n_1 + n_2 - 2)}} \qquad \text{Eq.1}$$

where X is the mean, n the sample size and s the variance.

In most of the studies, several tests are used to evaluate the different cognitive functions of the participants. The results of the different tests were combined, using weighted mean, to produce a single SMD according to Cochrane's recommendation.[30] A positive SMD implies better therapeutic effects over time in the intervention group compared to the control group.

To assess the risk of publication bias, funnel plots were checked for asymmetry[31] and Egger's test for the intercept was applied for the different conditions evaluated.[32]

To assess the potential effect of the type of CCT and the delivery mode on the results we performed sub-group analysis.

To ease the visualization of the different parameters of the included studies (type of intervention, transfer, delivery mode, and condition), we used network meta-analysis to plot the results. The distribution of the available evidence was assessed using a network geometry graph in which the size of the nodes was proportional to the number of trials included for each intervention and the width of the continuous line connecting nodes corresponding to the number of trials directly comparing the interventions.[33]

Random-effects meta-regression analysis quantified the association of changes in cognitive functions and the amount of training and the age of the participants. Studies were weighted by the inverse of the sum of the within- and between-study variance.[34]

Statistical analyses were performed at an overall significance level of 0.05, carried out in RStudio (version 1.2.1335), using R version 3.6.1

Results

Eight meta-analysis were included in this umbrella meta-analysis (older adults [17,18,35], MS [22], MCI [19], stroke [20,36], and PD [21]) to finally include 100 studies in this meta-analysis (48 with older adults [37–84], 17 with patients with MS [85–101], 15 with patients with MCI [102–116], 14 with patients after a stroke [117–132] and 6 with patients with PD [133–138]), representing in total 6,407 participants (see Supplementary Figure 1). The quality of the studies has been assessed using the PEDro scale [139], we did not take into consideration the question about the blinding of the therapist, since the intervention are not performed with therapists, the mean score is 6.6 (1.4) out of 9. A one-way ANOVA was performed to compare the effect of the conditions on study quality. The ANOVA revealed that there was not a statistically significant difference in PEDro scores between at least two groups ($F(4,97) = 2.212$, $p = 0.073$).

Characteristics of the participants, type of intervention, delivery mode, training duration and frequency and type of transfer and individual PEDro scores are presented in Table 2. Description of the interventions, tests used to assess cognitive function are further detailed in Supplementary Table 1. To ease the visualization of the amount of studies assessing the different modalities (type of intervention, type of transfer, delivery mode, initial cognitive function and condition) we plotted network graphs (Figure 2).

First, we checked for potential publications bias, the funnel plot is presented in Supplementary Figure 2 and did not show significant asymmetry (Egger's intercept= 0.67, p = 0.75).

By far the most represented participants are older adults (*n* = 3,438; 70.1±4.7 years old; MMSE = 28.4±0.6), followed by patients with stroke (*n* = 842; 60.3±6.8 years old; MMSE = 21.9±3.1), MS (*n* = 738; 45.8±5.2 years old; MMSE = 26.3±3.3), MCI (*n* = 590; 73.1±3.3 years old; MMSE = 27.1±0.9) and PD (*n* = 255; 68.0±4.7 years old; MMSE = 26.4±3.7).

Concerning the type of CCT, there are slightly more studies carried out using commercial solutions (*n* = 56) compared to specific ones (*n* = 45). It is important to note that there are differences depending on the condition investigated with 70% of the studies in stroke done with specific solutions, 67% in PD, 53% in MCI, 41% in older adults, and only 30% in MS. The repartition of the commercial solutions used (tested in at least 3 studies) is presented in Supplementary Figure 3. The three most used apps are RehaCom (n = 11), Posit Sciences (n = 8) and Lumosity (n = 6).

Concerning the delivery mode, most of the studies (60 %) were done on site (clinical centers), 31% at home and 9% using a combination. Again, results show important differences between conditions. For older adults and MS the ratio between on-site and at-home is 50/50 while for MCI (76%), PD (67%) and stroke (73%) most of the studies are performed on-site.

On average the studies includes a median number of 20 [P25 = 13 ; P75 = 32] sessions of 45 minutes [P25 = 30 ; P75 = 60] over a 6 weeks period [P25 = 5 ; P75 = 12]. The total amount of training is 15 hours [P25 = 10 ; P75 = 20]. There is no difference in the total amount of training (p = 0.42) between conditions (Figure 3) but well for the average duration of one training session (p = 0.016). After adjusting for multiple testing (Bonferroni's correction), the median duration of one session is indeed longer in MCI (60 min [P25 = 52 ; P75 = 67]) compared to stroke (30 min [P25 = 30 ; P75 = 52], $p = 0.047$). There is also a difference in the number of weeks of training ($p = 0.025$), after adjusting for multiple testing, the median duration of the intervention being longer in MCI (12 weeks [P25 = 6 ; P75 = 16]) compared to stroke (5 weeks [P25 = 4 ; P75 = 8], $p = 0.019$).

In all the included studies the overall effect of training is moderate (g = 0.25 [95%CI 0.21 – 0.29], $p < 0.001$, fixed effect model due to low heterogeneity [$I^2 = 34\%$]). We then analyse the different conditions individually, the effect of training on cognition was moderate in stroke (g = 0.48 [95%CI -0.17 – 0.79], $p = 0.002$), small but still significant in patients with MS (g = 0.37 [95%CI 0.23 – 0.52], $p < 0.001$), MCI (g = 0.31 [95%CI 0.15 – 0.47], $p < 0.001$), PD (g = 0.30 [95%CI 0.03 – 0.57], $p = 0.028$) and older adults (g = 0.21 [95%CI 0.13 – 0.28], $p < 0.001$). Forest plot summarizing the effect of training on global cognition for the different conditions is presented in Figure 4.

Concerning the type of intervention, we compared the studies using specific solutions versus commercial solutions and did not find significant differences between the two types of solutions (g = 0.25 [0.16 – 0.34] for commercial solutions and g = 0.22 [0.13 – 0.32] for specific ones, $p = 0.69$) on the cognitive improvement. We then compared the delivery mode and did not find significant difference either (g = 0.23 [0.02 – 0.60] for at-home training and g = 0.30 [0.11 – 0.53] for on-site training, $p = 0.33$). Finally, we compared the type of transfer, note that due to the small number of studies assessing direct transfer (n = 4) we only compared the near (n = 47) and far (n = 14) effects and the combination of both (n = 31). There is no statistically significant difference for the three types of transfer evaluated (g = 0.25 [0.14 – 0.36] for near effect, g = 0.25 [0.09 – 0.41] for far effect and g = 0.27 [0.18 – 0.35] for the combination, $p = 0.67$).

We then performed meta-regression to determine if the amount of training influences the cognitive outcomes. As we did not find any difference for the type of CCT, delivery mode or transfer type, we performed the meta-regression including all the studies. We did not find any significant association between the total amount of training (β = -0.0043, SE = 0.0024, p = 0.07), the number of weeks of training (β = -0.0006, SE = 0.0087, p = 0.95), or the average duration of one session and the improvement in cognitive outcomes (β = 0.0001, SE = 0.0016, p = 0.95). There is no association with the age of the participant (β = -0.0041, SE = 0.0031, p = 0.19). The results for the different conditions are presented in Table 3 and summarized in Figure 5. Individual results for the different cognitive functions are presented in Supplementary Tables 2-6.

Discussion

To the authors' best knowledge this is the first study comparing the efficacy of CCT in different populations with neurological disorders, in healthy older adults or with MCI. The main result of our analysis is that CCT can be used to train cognitive function in various conditions ranging from normal aging to neurological diseases. First, let's discuss the clinical implications of our findings. Interestingly we did not observe statistically significant differences either comparing specific and commercially available CCT or comparing the delivery mode. CCT, commercial or specific, could therefore be interesting tools to integrate in prevention and rehabilitation.[140] It must be noted here that commercial solutions are more easily available than the specific ones, which may explain why there are more used in research and in clinics. Note that for stroke and PD we observed more usage of specific solutions compared to other conditions. That may be due to the fact that those patients may experience some specific limitations (motor or cognitive) which may limit the use of commercial solutions.

From a practical point of view, we did not observe a difference in the average total amount of training between the five conditions investigated. Based on our analysis including all the conditions, the median duration of an intervention improving significantly cognitive functions is 15 hours over 6 weeks (3 sessions/week). The meta-regression analyses do not show a relationship between the total amount of training, the number of weeks of training, or the duration of one single session and cognitive improvements whether for all participants or when studying conditions individually. It must be pointed out here that the dose-response relationship in cognitive training has not been investigated much and is not obvious.[63,141–143] This could be explained by the fact that the interventions protocol are heterogeneous[144] and that the difference may only be observed in the long term and for far transfer effect,[145] while most of the research is focusing on the immediate or short term effect.[146]

Interestingly we observed statistically significant differences in the median duration of one session with longer sessions found in MCI (60 min) compared to stroke patients (30 min), the duration of the intervention in weeks was also shorter in stroke patients compared to MCI. We could not determine if this difference is related to clinical aspects (e.g., fatigue, lower dexterity level, etc.) or to the specificity of the patient care.

The findings of this study have to be seen in light of some limitations. First, as seen in Supplementary Table 1, there is a huge variety of tests used to assess different cognitive functions and numerous training applications being used (both commercial and specific ones) whose main objectives, type of exercises and/or graphical interface may be somewhat different. This high heterogeneity make comparison between studies more complicated. Therefore, we decided to calculate a global cognitive effect by combining results of the different cognitive tests for each study. In addition, results for the different cognitive functions are presented in Supplementary Materials but are unpowered due to the smaller number of studies per cognitive function. It would then be interesting for further studies to analyse the specific effects and the potential dose-response relationship for the different cognitive functions.[147]

Due to an incomplete description of the content of exercises used during CCT, it was sometimes difficult to determine if tests used to assess cognitive functions were similar or not to the task trained during the CCT and, because of that, to define the type of transfer for those studies. Therefore, we end up with a lot of studies classified as 'mixed' transfer. The absence of difference in the subgroup analysis according to the type of transfer may thus be biased by the high number of studies classified as 'mixed effects'. Also, only few studies investigated far-transfer effects and the neural mechanisms involved. Given the fact that far-transfer effects occur when two different tasks share an underlying processing component and neuroanatomical areas or neural circuits,[148] it would be interesting in the future to have more studies focusing on change in brain function after CCT training to investigate this particular aspect.

Another important limitation is the relatively small number of studies, and therefore of patients, included for PD (6 studies representing 255 patients), therefore the results for PD must be interpreted carefully.

We focused our analysis on the effect of the dose of training and later checked if the age of the participants or the conditions could influence the results. But other parameters may influence the ability to train the cognition such as sex,[149] genetic factors,[150] depression,[151] and fatigue[152], and other aspects such as the familiarity with the use of new technologies can influence the ease of use of CCTs and adherence.

We could also assume that the amount of rehabilitation exercises and participation in physical activities may influence cognition. It has indeed been demonstrated that other types of activities such as aerobic training, alone or combined with cognitive exercises, can increase cognition in aging,[153,154] MCI,[155] MS,[156] stroke[157]. Note that for PD the results are still unclear.[158] The participation in cultural, social activities and other stimulating activities are also positively associated with cognitive functions.[159,160] Therefore it would be interesting to evaluate the part of improvement attributable to the cognitive training and the part attributable to other activities. Finally, most of the participants have a relatively good and preserved cognitive function (as evaluated by a median MMSE score of 28). Further studies are therefore needed to determine if such kinds of training are feasible and effective in patients with lower cognitive function and determine the minimal cognitive level required to achieve significant improvement.

Conclusions

This study highlights the potential of CCT for prevention and rehabilitation of cognitive decline. The development and widespread use of computer and mobile technology now make it possible to integrate different cognitive interventions into CCT. Despite the fact that the effects were small to moderate, such kind of solutions have several advantages: easily accessible thanks to the large availability of mobile technology (smartphones, tablets), more fun and engaging than traditional exercises, allowto record the scores of the patients and follow their improvements, do not require the continuous presence of trained healthcare specialist which offers the possibility to implement this kind of solution in areas with fewer healthcare professionals and/or for patients living far from rehabilitation centers.[161] Our results show no difference in cognitive improvements between trainings performed at home and on site and support the possibility to perform the training at home with a remote monitoring. In the absence of pharmaceutical treatment to prevent or slow down cognitive decline and due the low accessibility to classical center-based cognitive interventions, there is an urgent need to assess the therapeutic potential of CCT and to evaluate at a larger scale their integration into the clinical pipeline.

Authors' contribution

BB gathered literature sources. BB wrote the initial manuscript with critical input from MK. BB and MK contributed to writing and approved the final version of the manuscript.

Conflicts of Interest

None declared

Abbreviations

MCI: Mild Cognitive Impairment

MS: Multiple Sclerosis

PD: Parkinson's disease

CCT: Computerized Cognitive Training

RCT: randomized controlled trial

MMSE: Mini-mental state examination

SMD: standardized mean difference

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