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The Timecourse of Global Cognitive Gains from Supervised Computer-Assisted Cognitive Training: A Randomised, Active-Controlled Trial in Elderly with Multiple Dementia Risk Factors

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Abstract

BACKGROUND: Home-based computerised cognitive training (CCT) is ineffective at enhancing global cognition, a key marker of cognitive ageing.

OBJECTIVES: To test the effectiveness of supervised, group-based, multidomain CCT on global cognition in older adults and to characterise the dose-response relationship during and after training.

DESIGN: A randomised, double-blind, longitudinal, active-controlled trial.

SETTING: Community-based training centre in Sydney, Australia

PARTICIPANTS: Eighty nondemented community-dwelling older adults (mean age = 72.1, 68.8% females) with multiple dementia risk factors but no major neuropsychiatric or sensory disorder. Of the 80 participants admitted to the study, 65 completed post-training assessment and 55 were followed up one year after training cessation.

INTERVENTIONS: Thirty-six group-based sessions over three months of either CCT targeting memory, speed, attention, language and reasoning tasks, or active control training comprising audiovisual educational exercises.

MEASUREMENTS: Primary outcome was change from baseline in global cognition as defined by a composite score of memory, speed and executive function. Secondary outcome was 15-month change in Bayer Activities of Daily Living from baseline to one year post-training.

RESULTS: Intention-to-treat analyses revealed significant effects on global cognition in the cognitive training group compared to active control after three weeks of training (ES = 0.33, P=.039) that increased after 3 months of training (ES = 0.49, P=.003) and persisted three months after training cessation (ES = 0.30, P=0.023). Significant and durable improvements were also noted in memory and processing speed. Dose-response characteristics differed among cognitive domains. Training effects waned gradually but residual gains were noted twelve months post-training. No significant effects on activities of daily living were noted and there were no adverse effects.

CONCLUSIONS: In older adults with multiple dementia risk factors, group-based CCT is a safe and effective intervention for enhancing overall cognition, memory and processing speed. Dose-response relationships vary for each cognitive domain, vital information for clinical and community implementation and further trial design.

Key words: Cognitive training, global cognition, memory, speed, dose-responsiveness.

Introduction

Advanced age is commonly accompanied by simultaneous decline in several cognitive abilities, often a precursor of functional impairment and dementia (1). Composite measures of global cognition (GC) summarise performance across multiple cognitive domains and are predictors of key outcomes such as well-being (2), falls (3) mobility (4), and incidence of dementia (5), and have recently been recommended for use in dementia prevention trials (6). The clinical significance of interventions aimed at combating age-related cognitive decline may therefore depend on effectiveness across multiple cognitive domains (7).

Computerised cognitive training (CCT) is a safe, scalable and inexpensive way of delivering mentally challenging exercises for the purpose of cognitive enhancement (8), but effects tend to be bound to the targeted cognitive domains. For example, speed training may improve performance on untrained processing speed tasks, but not on memory or reasoning tasks (9). For this reason it is likely that multidomain CCT may be required in order to enhance GC, as found in schizophrenic patients (10). Trials in healthy elderly, however, have so far failed to produce positive effects on GC (11, 12). These have been home-based programs, reliant on participants to engage with the technology and adhere to a regimen without therapist oversight, advice or encouragement. By contrast, physical exercise studies in older adults suggest that supervised training in a group format may produce superior outcomes compared to home-based training, especially at the outset (13).

We therefore tested for the first time the efficacy of trainer-led multidomain CCT on GC in healthy elderly, and further charted the evolution of cognitive gains

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during training as well as their decay during the 12-months post-training period.

Methods

Setting

This randomised active-controlled trial was conducted at a training centre in Sydney, Australia. Participants were recruited through newspaper advertisements and word of mouth from the neighbouring suburbs. This study was approved by the Human Research Ethics Committee at the University of New South Wales, Sydney. The trial was prospectively registered with anzctr.org.au (identifier ACTRN12611000702910).

Participants

Eligible participants were older adults (aged ≥65 years) who were fluent in English, physically able to use a computer and able to attend the training centre for 3 sessions per week. Participants were excluded for history, diagnosis or treatment for dementia, diagnosis or treatment for depression in last 6 months, stroke in last 12 months, major neurological and/or psychiatric disorder requiring current treatment, lack of personal informant, already undertaking a CCT program or current alcohol abuse. Further exclusion criteria included Mini Mental State Examination (MMSE) ≤23, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) > 3.3, or Geriatric Depression Scale (15-item GDS) ≥8. All participants provided written informed consent prior to eligibility screening.

Dementia risk factors

For each participant we computed a dementia risk factor sum (DRFS) based on a single point for any of the following: age ≥ 85 years, education ≤10years, any cardiovascular risk factor (current or past smoker, hypercholesterolemia, hypertension, ischemic heart disease, atrial fibrillation or diabetes), physical inactivity by CHAMPS estimated caloric all cause activity <1843 (14), family history of dementia, subjective memory complaint based on GPCOG questionnaire (15), or baseline memory domain score below 1.5SD of age-matched norms. The maximum theoretical DRFS is therefore 12. The average DFRS in our sample was 3.22 (SD 1.59), ranging from 1 – 9. All subjects therefore carried at least one recognised dementia risk factor and 47% had 3-4 risk factors.

Randomisation and Masking

Participants were randomised using a simple computer-generated randomisation sequence in a 1:1 ratio to either CCT or active control (AC) group. Randomisation was conducted by the principal investigator (MV) and was concealed from the rest of the research team until the first day of training. Assessors were blinded to group allocation and participants were blinded to the study hypotheses. On-going participant blinding achieved by describing CCT as a "diversified set of cognitive exercises", and AC as "comprehension and memory exercises." Both interventions were administered in a supervised group format of one trainer to ten participants (maximum) during three 30-45 minute sessions per week for a total of 36 sessions over 12-weeks, in a designated training room. A member of the study team (AL) supervised all training sessions.

Interventions

Computerised Cognitive Training (CCT)

We designed and administered a CCT program based on 24 exercises from the COGPACK package, Version 8.1 (Marker Software) to cover the five cognitive domains: memory, attention, response speed, executive functions and language. Each exercise contained 4-8 levels of increasing difficulty. The exercises were administered according to a predefined order that ensured equal (≈20%) allocation of training time on each cognitive domain. The identical COGPACK training regimen can be obtained for inspection and replication purposes from http://rng.org.au/wp-content/uploads/2013/08/Lampit-et-al-CCT-Sessions.zip

Active Control (AC)

This control intervention was developed for general sensory-motor stimulation, computer use, socialisation, motivation, simple learning and memory demands, and other non-specific effects inherent to supervised CCT and was used in a previous trial conducted by our group (16). Participants viewed seven National Geographic videos per session on computer and answered multiple-choice questions immediately after each presentation. An electronic library of the 390 videos and associated multiple-choice questions are available from the corresponding author.

Outcome Measures

The primary outcome was change across four cognitive domain composites (memory, information processing speed, executive functions and global cognition) over six timepoints: baseline and after 9 and 36 training sessions (FU1 and 2, respectively), as well as 3, 12 and 52 weeks after training cessation (FU3, 4 and 5 respectively).

Memory and information processing speed z-score

composites were obtained from the Mindstreams battery (17). Executive function z-score composite was defined as the average of Mindstreams Stroop Interference test and CANTAB Stockings of Cambridge problems solved in minimum moves score. Global Cognition Score was obtained by averaging these three z-domain scores. Mindstreams tests have three alternate forms that provide good test-retest reliability, are sensitive to differences between healthy elderly and those with mild cognitive impairment, and have been used widely in RCTs (18). The CANTAB Stockings of Cambridge test is a validated measure of planning and spatial problem solving (19).

In addition, at three of the five FU assessments we evaluated the language domain by averaging performance in the Controlled Oral Word Association Test (COWAT) (20), and short forms of the Boston Naming Test (21) (baseline and FUs 2, 4 and 5). Computerised adaptations of the Recognition Memory Test (22) and WAIS-IV Matrix Reasoning (23) were also administered at these timepoints (baseline and FUs 2, 4 and 5). These four tests were included in the more expansive post hoc Global Cognitive Score. Finally, we administered the Bayer Activities of Daily Living Scale (24) at baseline and follow-up 5. One test was initially planned but not implemented because of poor usability with our participants (Mindstreams Visual-Spatial Orientation test), and one test (Cogscreen) could not be implemented because of technical issues. These changes were documented in the trial registry.

Statistical Analysis and Sample Size

In order to assess the efficacy of CCT over the six timepoints, we conducted linear mixed-modeling repeated-measures (MMRM) analyses using SPSS version 21 (IBM Statistics). Our model included main effects for Group and Time and a Group X Time interaction term. Each cognitive domain score was tested separately. MMRM incorporates a model for missing data values and so avoids discrete imputation or omission of cases (25). All analyses are therefore intention-to-treat (ITT).

Within-group effect sizes (Cohen's d) were calculated by subtracting mean baseline scores from mean score at each time point divided by standard deviation at baseline. Bias-corrected net effect size (NES) were estimated by subtracting Cohen's d of the AC group from that of the CCT group, and then applying a bias correction factor 1-(3÷4[(nCCT – nAC – 2) – 1]) (26). Absolute differences between CCT and AC for outcomes at each follow-up time point were also calculated along with the associated 95% confidence interval.

During the conduct of the trial we reduced our registered sample size requirement from N = 100 to N = 80 (40 participants in each group) due to unavoidable pragmatic and logistical reasons. Our original anticipated power of 0.80 to detect a net effect size of 0.56 was therefore lowered to 0.70.

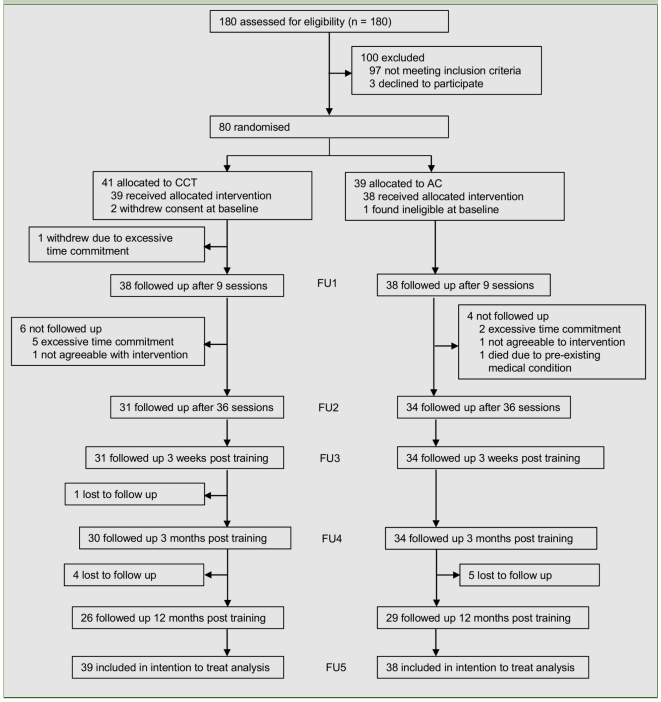
Results

Participants, Attrition & Protocol Adherence

Participants were enrolled from July 12, 2011, through April 10, 2012, and data collection was completed on July 5, 2013. A total of 80 older participants were enrolled into the trial. Of these, 77 participants (39 in the CCT group and 38 in the AC group) completed baseline assessment and are included in all intention-to-treat (ITT) analyses. Twelve participants withdrew during the intervention period (8 in the CCT group, 4 in the AC group, 2-sided $\chi 2$ p = 0.347), and 10 additional participants (five in each group) were lost to longitudinal follow-up (see Figure 1). No baseline sociodemographic or clinical differences were noted between dropouts and those who completed intervention. There were also no systematic differences in protocol adherence in the CCT group (35.1 sessions, 97.5%) compared to AC training (34.7 sessions, 96.4%, p-value = 0.581).

At baseline, the age range of participants was 65 to 90 years (mean age 72.1, SD = 6.2), 68.8% were female, MMSE scores ranged from 24 to 30 (mean MMSE 28, SD = 1.6), 28.5% had 10 or fewer years of education, and the average NART-r IQ was 112.5 (SD = 11). All subjects had

Figure 1. Study design and participant flow



FU1=after 9 training sessions, FU2=after 36 training sessions, FU3=3 weeks after training cessation, FU4=3 months after training cessation, FU5=12 months after training cessation.

Table 1. Baseline characteristics

Demographics	CCT (n = 39)	AC (n=38)	P -value
Age (years)	72.2 (7.1)	71.9 (5.3)	.815
Female Sex, No. (%)	29 (74)	24 (63)	.289
Native English Speakers, No. (%)	30 (78)	29 (76)	.950
NART-r (SD) pFSIQ*	112.6 (10.1)	112.3 (11.0)	.896
Prior computer use	35 (89.7)	36 (94.7)	.414
Dementia risk factors			
Subjective memory complaints†, No. (%)	27 (69.2)	27 (71.1)	.861
Hypertension, No. (%)	12 (30.8)	20 (52.6)	.052
Hypercholesterolemia, No. (%)	14 (35.9)	14 (36.8)	.931
Diabetes, No. (%)	1 (2.6)	5 (13.2)	.083
Ischemic Heart Disease, No. (%)	2 (5.1)	6 (15.8)	.125
Atrial Fibrillation, No. (%)	3 (7.7)	4 (10.5)	.665
Physical inactivity‡, No. (%)	10 (25.6)	11 (28.9)	.802
Low education (≤10 years), No. (%)	11 (28.2)	11 (28.9)	.501
Family history, No. (%)	8 (20.5)	9 (23.7)	.789
Past smoking, No. (%)	23 (59.0)	21 (55.3)	.742
Current smoking, No. (%)	2 (5.1)	0 (0)	.157
DRFS (SD)	3.0 (1.6)	3.44 (1.6)	.221
Clinical			
IQCODE score (SD)	3.05 (0.12)	3.1 (0.13)	.111
GPCOG examination score (SD)	7.92(1.3)	8.05 (1.0)	.631
MMSE (SD)	28.2 (1.4)	27.8 (1.8)	.267
B-ADL (SD)	1.58 (0.52)	1.63 (0.65)	.702
GDS (15-item) (SD)	1.7 (1.4)	1.3 (1.5)	.225
Quality of life			
QOLS (SD)	88.8 (9.8)	89.7 (9.2)	.690
SF36 physical component (SD)	72.0 (18.0)	74.6 (17.4)	.522
SF36 mental component (SD)	83.0 (9.9)	82.6 (11.1)	.868

Data are n (%) or mean (SD). CCT=computerised cognitive training. AC=active control. DRFS=dementia risk factor score. GDS=geriatric depression scale. IQCODE=informant questionnaire on cognitive decline in the elderly. GPCOG=general practitioner assessment of cognition. MMSE=mini mental state examination. NART=national adult reading test (revised). B-ADL=Bayer activities of daily living. QOLS=quality of life scales. SF36=short form health survey. *IQ-equivalent. † defined as 4 points or less in the GPCOG questionnaire(52). ‡ defined as CHAMPS (51) estimated caloric all cause activity score <1843.

at least one established dementia risk factor, the most prevalent being subjective memory complaints (68.9% in women; 70.1% men – see Table 1 for further details). There were no significant demographic or cognitive differences between the groups at baseline (see Table 1).

Strength and Durability of Effects on Global Cognition

Linear mixed-modelling repeated-measures ITT analysis revealed an overall significant Group X Time interaction on GC favouring CCT across the 15-month trial period (F-value=3.297, p=0.006). As shown in Figure 2, GC improved significantly from baseline in the CCT group compared to AC after nine sessions (FU1: Net Effect Size, NES=0.33). The effect increased after 27 additional sessions (FU2: NES=0.49). This gain diminished by about one-third three weeks after cessation (FU3: NES=0.32), but a significant medium-sized effect was maintained three months post training (FU4: NES=0.30). A small NES was noted one year after training finished (FU5: NES=0.21).

To further evaluate efficacy on GC, on a post hoc basis we computed a more expansive Global Cognition Score that included two language domain tests, as well as additional memory and executive function tests that were administered only at follow-ups 2, 4 and 5 because of lack of alternate forms (see Methods section). The overall Group X Time interaction remained significant (F-value=9.004, p<0.001), and produced stronger effect size estimates at specified timepoints (FU2 NES = 0.65; FU4 NES=0.47; FU5 NES=0.36).

Domain-specific Effects

Linear mixed-modelling repeated-measures ITT analyses revealed significant Group X Time interactions

Table 2. Cohen's d effect size for CCT and AC groups (95% confidence interval)

		CCT		AC		Bias Corrected Net ES	p-value
		d	95% CI	d	95% CI		
Global Cognition	FU1	0.70	(0.24 to 1.16)	0.37	(-0.09 to 0.82)	0.33	
	FU2	1.12	(0.61 to 1.62)	0.62	(0.15 to 1.09)	0.49	
	FU3	1.19	(0.68 to 1.7)	0.87	(0.39 to 1.36)	0.32	0.006
	FU4	1.34	(0.81 to 1.86)	1.04	(0.54 to 1.53)	0.30	
	FU5	1.27	(0.72 to 1.81)	1.05	(0.54 to 1.57)	0.21	
Memory Domain	FU1	0.28	(-0.17 to 0.73)	0.20	(-0.26 to 0.65)	0.09	
	FU2	0.87	(0.38 to 1.36)	0.38	(-0.09 to 0.84)	0.49	
	FU3	0.66	(0.18 to 1.14)	0.40	(-0.07 to 0.87)	0.26	0.011
	FU4	0.68	(0.19 to 1.16)	0.51	(0.04 to 0.98)	0.17	
	FU5	0.84	(0.32 to 1.36)	0.68	(0.18 to 1.18)	0.16	
Information Processing Speed	FU1	0.62	(0.16 to 1.09)	0.22	(-0.23 to 0.67)	0.40	
	FU2	0.73	(0.23 to 1.22)	0.52	(0.05 to 0.99)	0.21	
	FU3	1.01	(0.5 to 1.52)	0.69	(0.21 to 1.16)	0.32	
	FU4	1.19	(0.67 to 1.72)	0.87	(0.39 to 1.35)	0.32	0.037
	FU5	1.00	(0.46 to 1.54)	0.86	(0.36 to 1.37)	0.13	
Executive Function Domain	FU1	0.71	(0.24 to 1.17)	0.46	(0 to 0.92)	0.24	
	FU2	0.94	(0.44 to 1.44)	0.49	(0.02 to 0.96)	0.45	
	FU3	1.02	(0.52 to 1.52)	0.87	(0.38 to 1.35)	0.15	0.397
	FU4	1.18	(0.66 to 1.69)	0.90	(0.41 to 1.4)	0.27	
	FU5	1.01	(0.48 to 1.53)	0.80	(0.3 to 1.3)	0.20	
Language Domain	FU2	0.76	(0.28 to 1.25)	0.55	(0.08 to 1.02)	0.21	
	FU4	0.71	(0.22 to 1.20)	0.52	(0.08 to 0.99)	0.18	0.067
	FU5	1.01	(0.48 to 1.54)	0.90	(0.38 to 1.41)	0.11	
Extended Global Cognition	FU2	1.24	(0.73 to 1.75)	0.59	(0.11 to 1.06)	0.65	
	FU4	1.33	(0.80 to 1.85)	0.86	(0.38 to 1.34)	0.47	<0.001
	FU5	1.35	(0.80 to 1.89)	0.98	(0.47 to 1.49)	0.36	

Bias-corrected net effect size (NES) is difference between two effects after correction. F-value refers to linear mixed model with Time (six repeated measures), Group and Group X Time terms in model. P-value refers to Group X Time interaction. FU1=after 9 training sessions, FU2=after 36 training sessions, FU3=3 weeks after training cessation, FU4=3 months after training cessation, FU5=12 months after training cessation.

favouring CCT on two of four composite scores, namely, the memory domain (p=0.011) and the processing speed domain (p=0.037), as well as a trend on the language domain (p=0.067). There were no significant findings for the executive function domain (see Table 2).

Dose Response and Decay of CCT Therapeutic Effects

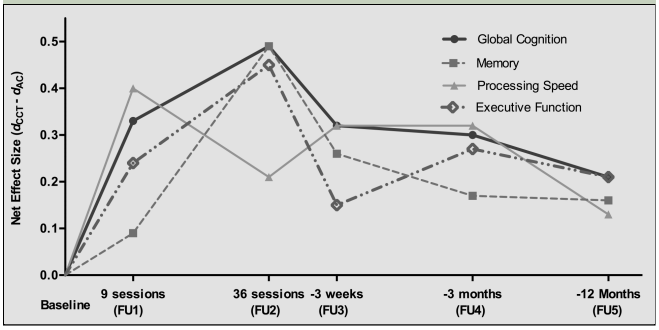
As opposed to GC, the effect on memory domain (see Figure 2) was negligible after nine sessions (FU1: NES=0.09), but reached a similar effect to GC after 36 sessions (FU2: NES=0.49). These gains more than halved three weeks after stopping training (FU3: NES=0.26) and continued to diminish one year later (FU4: NES=0.17; FU5: NES=0.16). CCT effects on the processing speed domain showed a unique pattern (Figure 2). The therapeutic effect peaked after nine sessions (FU1: NES=0.40), and then declined after 36 sessions (FU2: NES=0.21). However, medium-sized effects favouring CCT were maintained throughout the three-month post training period (FU3: NES=0.49; FU4: NES=0.32), diminishing by approximately a half one-year after training stopped (FU5: NES=0.13).

Longitudinal Effect on Activities of Daily Living

One year after training cessation there was no significant Group X Time interaction improvement on Bayer Activities of Daily Living scale, resulting from a small positive effect size in the CCT group (ES 0.20) and no change in the AC group (ES 0.00; NES=0.20, F = 0.162 p= 0.689).

No adverse effects related to the intervention were recorded throughout the study period.

Figure 2. Net effect sizes (NES) for domain summary scores across the 15-month trial period as measured after 9 and 36 training sessions (FU1 and 2, respectively), as well as 3, 12 and 52 weeks after stopping training (FU3-5). NES calculated as Cohen's d [(post mean -pre mean) ÷ pooled baseline standard deviation] for CCT minus AC group, and then applying a bias correction factor (1-(3÷4[(nCCT – nAC – 2) – 1]) 26



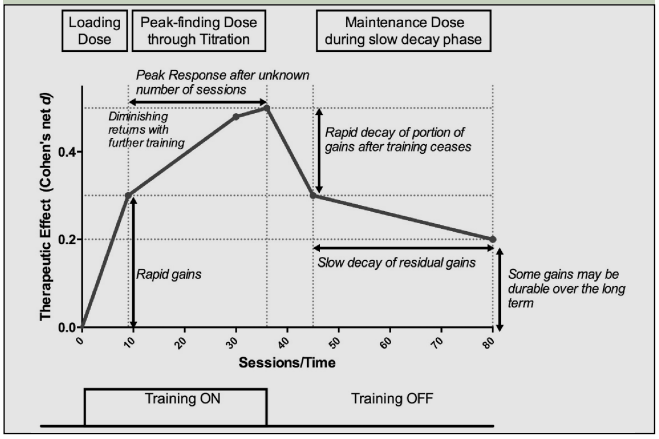
Discussion

Clinical Implications

In cognitively unimpaired older adults with multiple dementia risk factors, 36 hours of trainer-led, group-based multidomain CCT over 12 weeks produced moderate and statistically significant effects on memory and processing speed, as well as on composite measures of global cognition. The magnitude of the net effect size on GC at the end of 36 hours of training is sufficient (NES 0.49) to be of clinical interest. Some of these benefits were preserved as far as 12 months after completing training, but as expected, decayed relative to combined retest and non-specific effects in the active control group. This comparison group was a most rigorous control, designed to take into account sensorimotoric, mnemonic, attentional, motivational, social and trainer-related stimulation. Further strengthening these outcomes was selection of cognitive tests that were functionally dissimilar to the training tasks.

For the first time in this population type, we also examined cognitive outcomes at multiple time points during and after CCT, providing new insights into dose-response relationships. Memory effects, for example, continue to display a steep upward trajectory even after 36 training sessions, but decay rapidly following training offset, in contrast to processing speed effects which peak after 9 sessions but are largely resistant to decay for at least 3 months following the end of training. Accordingly, our data may suggest a new way for framing multidomain CCT based on the common medical ideas of 'loading dose', 'titration' and 'maintenance dose' (see Figure 3). Initially, we observed steep therapeutic response curves, characterised by large gains from relatively few training sessions, a period conceptualised as loading dose. Thereafter, global gains continue to rise but follow a logarithmic function, where individuals will experience diminishing returns as they approach peak therapeutic response. Due to individual variability, a peak-response finding procedure may be advantageous at this point (titration). Following the offset of training, therapeutic gains decay quickly, but some residual effects on GC can persist for at least 3-months. It is during this time that booster training is indicated and forms the third maintenance phase. Mechanistic and applied research in this field may benefit by clearly distinguishing between these three therapeutic phases. This information will aid design of next generation CCT technology, as well as provide guidance for clinicians and researchers.

Figure 3. Therapeutic heuristic for multidomain supervised Computerised Cognitive Training in older individuals



Sessions refer to number of consecutive CCT sessions implemented three times a week, and time to the equivalent period after stopping training. Three main phases are distinguished: loading dose, during which rapid therapeutic effects may be seen; titration, during which the trainer identifies peak therapeutic response beyond which further training is inefficient; and maintenance, during which rapid decay of gains are lost but residual therapeutic effects may be conserved especially with use of booster sessions.

Previous trials of non-computerised cognitive interventions have reported improved GC in healthy or mildly impaired older adults (27, 28). However, these employed single-blinded wait-list control designs and the NES in these trials were considerably smaller than reported here. Interestingly, two recent well-designed RCTs in the elderly have failed to detect GC effects following CCT (11, 12). Similar to our study, these used multi-domain CCT and a comparable number of training sessions, but unlike our study, CCT was self-administered at home rather than in a trainer-supervised group setting. This raises the possibility that expert supervision involving feedback, motivational support and emphasis of applicability of training to everyday life may be a key factor moderating CCT outcomes.

Limitations

Our study has two main limitations. First, whilst efficacy on GC may be a necessary condition for primary

dementia prevention, it is not sufficient. For this purpose, robust and simultaneous effects on daily function are required (7), but such effects are hard to establish in non-demented cohorts (6, 29) and require substantially larger sample sizes and a longer follow-up period (7). Indeed, we found only small and non-significant effects using the Bayer ADL measure at our 12-month post training assessment (NES=0.2). This finding is in line with the lack of significant IADL effects in the first two years of the large ACTIVE trial (9) although such effects were found in five years post-training in one of the groups compared to no-contact control (30). The overarching clinical challenge for CCT researchers is therefore to demonstrate far transfer to everyday function, an issue closely related to development of validated tools sensitive enough to detect treatment-related functional change in asymptomatic and preclinical individuals (29).

Second, our results do not indicate which CCT software package is optimal for enhancing GC in this population. We used COGPACK, which has a relatively rich history within the cognitive rehabilitation setting (10) and is convenient for research purposes. However, COPGACK relies on now dated technology that lacks useful auditory exercises and relies on a trainer rather than an automated algorithm to create the training regimen and adapt training content. Accordingly, there is great scope for improving beyond these outcomes with new software that takes into account underlying dose-response functions. The field would also benefit from head-to-head comparisons of CCT programs with clear structural differences.

Conclusions

Despite a rapidly growing body of evidence, a clear understanding of the optimal practice parameters, dose-response relationships and key moderating factors underlying CCT efficacy in the aged remain elusive. We found that group-delivered multidomain CCT is effective at improving global cognitive performance in older individuals over the long term, and moreover, this outcome was based on a complex pattern of dose-dependent gains during training and time-dependent decay following training offset. This information will be vital to the design of next generation CCT technology, as well as for helping clinicians and researchers make the most this intervention.

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