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REVIEW

Enhancing Cognitive Functioning in Healthly Older Adults: a Systematic Review of the Clinical Significance of Commercially Available Computerized Cognitive Training in Preventing Cognitive Decline

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Abstract Successfully assisting older adults to maintain or improve cognitive function, particularly when they are dealing with neurodegenerative disorders such as Alzheimer's disease (AD), remains a major challenge. Cognitive training may stimulate neuroplasticity thereby increasing cognitive and brain reserve. Commercial brain training programs are computerized, readily-available, easy-to-administer and adaptive but often lack supportive data and their clinical validation literature has not been previously reviewed. Therefore, in this review, we report the characteristics of commercially available brain training programs, critically assess the number and quality of studies evaluating the empirical evidence of these programs for promoting brain health in healthy older adults, and discuss underlying causal mechanisms. We searched PubMed, Google Scholar and each program's website for relevant studies reporting the effects of computerized cognitive training on cognitively healthy older adults. The evidence for each program was assessed via the number and quality (PEDro score) of studies, including Randomized Control Trials (RCTs). Programs with clinical studies were subsequently classified as possessing Level I, II or III evidence. Out of 18 identified programs, 7 programs were investigated in 26 studies including follow-ups. Two programs were identified as possessing Level I evidence, three programs demonstrated Level II evidence and an additional two programs demonstrated Level III evidence. Overall, studies showed generally high methodological quality (average PEDro score = 7.05). Although caution must be taken regarding any potential bias due to selective reporting, current evidence supports that at least some commercially available computerized brain training products can assist in promoting healthy brain aging.

Keywords Computerized cognitive training · Brain training · Cognition · Dementia · Alzheimer's disease

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Introduction

There has been a recent increase in interest in the maintenance of brain function well into late life, yet helping older adults to maintain or improve brain health and cognition remains a challenge (Brayne 2007). High prevalence of age-related cognitive decline and neurodegenerative disorders such as Alzheimer's disease (AD) add considerable difficulty to this task (Schonknecht et al. 2005; Reitz et al. 2011). Current treatment for AD is only palliative (Casey et al. 2010), and clinical evidence to support prophylactic or delaying strategies is minimal. Lifestyle strategies, including appropriate physical and mental activities, good diet and social engagement for the purposes of improving/maintaining cognition, functional independence and quality of life have been the focus of many recent studies (Ruthirakuhan et al. 2012; Shah et al. 2014; Ngandu et al. 2015). Concurrently, there has been increased

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interest amongst older adults in cognitive interventions and activities to maintain and improve brain function. This is clear from the estimated computer-based brain health and fitness market in 2009, which was estimated to be $295 million worldwide, representing a growth of nearly 35% compared with 2008 (Fernandez 2010).

The concept of cognitive interventions for older adults is not new, and evidence for neural plasticity, including brain response to increasing cognitive activity has accumulated (Johansson 2004; Pascual-Leone et al. 2005). Plasticity is the brain's lifelong ability for physical and functional change in response to sensing, perceiving and learning; thus building experience that in turn promotes learning throughout life (Merzenich and Jenkins 1999; 1993). Cognitive reserve or behavioural brain reserve is the brain's ability to respond or compensate against brain injury/degeneration. Subjects with high cognitive reserve exhibit more tolerance of AD pathology (Stern 2006, 2012) and also show a 50% reduction in the incidence of dementia (Valenzuela and Sachdev 2006). Importantly, Stern has argued that engaging in mentally stimulating activities may stimulate plasticity and thereby increase cognitive reserve (Stern 2012).

Supporting this, observational studies have found that high levels of cognitive activity appear to be beneficial in preserving cognition and reducing the risk of dementia amongst older adults (Verghese et al. 2003). For example, healthy older people with greater early and mid-life cognitive activity have lower brain amyloid deposition, a hallmark of AD pathology, as measured using carbon 11-labelled Pittsburgh compound-B positron emission tomography (PiB-PET, Landau et al. 2012). Further, cognitive training intervention studies using paper and pencil as well as computer modalities have been found to improve targeted cognitive domains of memory, processing speed and reasoning in both typically and atypically aging older adults (Ball et al. 2002a; Mahncke et al. 2006; Engvig et al. 2010). These and other studies support the concept that computer-based training can be beneficial to cognitively normal older adults, as well as those with mild cognitive impairment (MCI) or AD (Günther et al. 2003; Barnes et al. 2009; Tárraga et al. 2006; Galante et al. 2007). Although cognitive training can maintain or promote neuroplasticity (Mowszowski et al. 2010) and may provide benefits in preventing/slowing progression of cognitive decline (Gates et al. 2011; Woodward and Brodaty 2007), it may not necessarily reverse the disease trajectory.

Cognitive training (and similar constructs, such as cognitive stimulation and cognitive rehabilitation) typically involve structured, frequent and repeated engagement in standardized cognitively demanding tasks targeting specific cognitive domains such as attention, memory and problem-solving (Bahar-Fuchs et al. 2013; Gates et al. 2011). Previous reviews of the literature evaluating the efficacy of computer-based commercially available cognitive training programs for healthy older adults have not systemically evaluated the quality of individual studies and did not review follow-up studies (Lampit et al. 2014; Shao et al. 2015; Kueider et al. 2012). Therefore, the potential benefits of commercial computerized cognitive training in enhancing cognition in healthy older adults remains unclear. This is important, as the extant literature includes studies that vary in both methodological approach and quality. Furthermore, the potentially differential benefits between the many cognitive training programs available has not been systematically evaluated, leaving clinicians with inadequate information from which to base recommendations for their patients at risk of cognitive decline.

Until recently, there have been few randomized controlled trials (RCTs) using commercial computerized cognitive training programs in cognitively healthy older adults. However, there has been an increase in this research over the last five years (Nouchi et al. 2012; Barnes et al. 2013; Ballesteros et al. 2015a). The time is therefore appropriate for a systematic review of the evidence for efficacy of commercially available computerized brain training programs in improving specific cognitive domains in older adults. In this review, we rigorously categorized studies according to their scientific and methodological merit. In addition, we discuss underlying mechanisms in context of the potential benefits of cognitive training in enhancing cognition in the elderly population.

Methodology

The search process was completed in two steps. In step one, relevant commercial cognitive training programs were identified and in step two, studies related to the programs were identified and subsequently reviewed systematically. Briefly, information regarding the availability of brain training software programs was originally obtained using World Wide Web search engines. Search terms initially used were commercial brain/cognitive training programs, computerized brain/cognitive training programs and software for brain/cognitive training. In the next step, for the scientific validation literature of identified programs, we searched for human clinical trials in PubMed and Google Scholar (using exact phrase as article title) along with the following search terms: "cognitive stimulation" OR "brain training" OR "cognitive rehabilitation" OR "cognitive enhancement" OR "brain fitness software" OR "cognitive retention therapy" OR "computerized cognitive behavioural therapy" with and without the related software programs. Exclusion criteria were reviewed manually in final eligible studies. In addition, we searched each product's website for relevant software information and any published clinical studies including internal white paper studies eligible for this review. The search was performed and updated through September 2015.

Study Selection

Eligible studies were published in English, peer reviewed reports of clinical trials evaluating the effects of previously identified computerized brain training on formal outcome measures of specific cognitive domains in cognitively intact, healthy older adults, aged ≥ 50 years. Internal white paper studies were also eligible for inclusion. Relevant follow-up studies were included to identify maintained/long term efficacy of any observed cognitive benefits. Articles for detailed review were excluded if they were: (1) conference abstracts (2) studies of populations other than cognitively healthy older adults (3) studies on rehabilitation for psychiatric or any other neurodegenerative ailments including dementia (4) articles involving training using video games (5) review articles and (6) studies without cognition as primary outcome measure. Moreover, if studies already satisfied the criteria for providing a higher level of evidence, then trials of the same commercial program providing a lower evidence level were not reviewed.

Data Extraction

Two reviewers (TS and MW) independently screened the titles and abstracts along with the relevant websites to identify eligible articles. Disagreements between the reviewers about study inclusion were resolved through discussion. Specifically, the following data were extracted onto a template (see Table 2): study source, sample size, age and intervention duration, intensity and frequency with main study outcomes at post-intervention and follow-up. We included the significance levels (p value) and effect sizes [eta-squared (η^2)/partial eta-squared ($p\eta^2$)/Cohen's *d*] for immediate post-intervention data including the cognitive outcome measures of processing speed, attention, reasoning, language, memory, executive functions and working memory. For studies that did not report effect sizes but where the required data were available, Cohen's *d* values were calculated (Cohen 1988).

Risk of Bias

The risk of bias was assessed along with the overall methodological quality using the Physiotherapy Evidence Database (PEDro) scale. The PEDro scale has a maximum score of 10 and interpretive guidelines for study quality are as follows: >6 = high; 5–6 = moderate and <5 = poor quality (Maher et al. 2003; Walser et al. 2009). The trials were initially rated by TS and independently evaluated by MW and HRS. Any disagreements on the assessments among the authors were resolved through discussion. Besides collecting systematic evidence of publication bias, we additionally documented the role of company or authors who designed the cognitive training programs used in reviewed articles or relevant study funding by the companies that designed respective programs.

Data Synthesis and Analysis

For the current review, we assessed 1) the number of published clinical trials for each program and 2) the methodological quality of each study in an approach adapted from a series of systematic reviews of the efficacy of cognitive intervention for acquired brain injury by Cicerone et al. (for a review please see Cicerone et al. 2011). Cicerone et al. (2011) classified interventions as demonstrating Level I evidence if there was at least one supportive RCT or quasi-randomized study, regardless of blinding. Interventions were classified as having Level II evidence if there were supportive non-randomized studies, and interventions with Level III evidence included studies without control conditions or absence of direct statistical comparison of treatment conditions. Overall, the inclusion of non-randomized, retrospective and baseline studies, studies without control group or single-subject designs and lack of discussion on the quality of the study methodology were some of the limitations of the criteria by Cicerone et al. (2011). For the present study, therefore we adapted this approach to be more stringent and include information on both the quantity and quality of each study (provided by the PEDro scale).

Specifically, we required at least two well-designed RCTs or quasi-randomized studies, one of which must be of high quality (PEDro score in the high range) and second at least of moderate quality (PEDro score in the moderate range) for classification as Level I evidence. Programs with clinical trials providing Level II evidence required only one well-designed RCT of high quality (PEDro score in the high range). Programs with one or more moderate/poorly designed RCT (Pedro score in the moderate to poor range) and other methodological approaches (e.g., internal "white paper" studies) were classified as providing Level III evidence. Randomized trials without a formally identified control group (active/inactive) were excluded. Follow-up studies were not considered as independently contributing to Level classification, but were reviewed to assess whether the observed cognitive benefits were sustained over time. Finally, in order to assess the methodological quality of each RCT, we used the PEDro scale.

Results

Figure 1 illustrates the flow of studies into review. In step one, 32 commercial brain training programs were identified, out of which 14 programs were found to be recommended for younger population, rehabilitation, cognitively declined or other neurological conditions or were paper and pencil based and

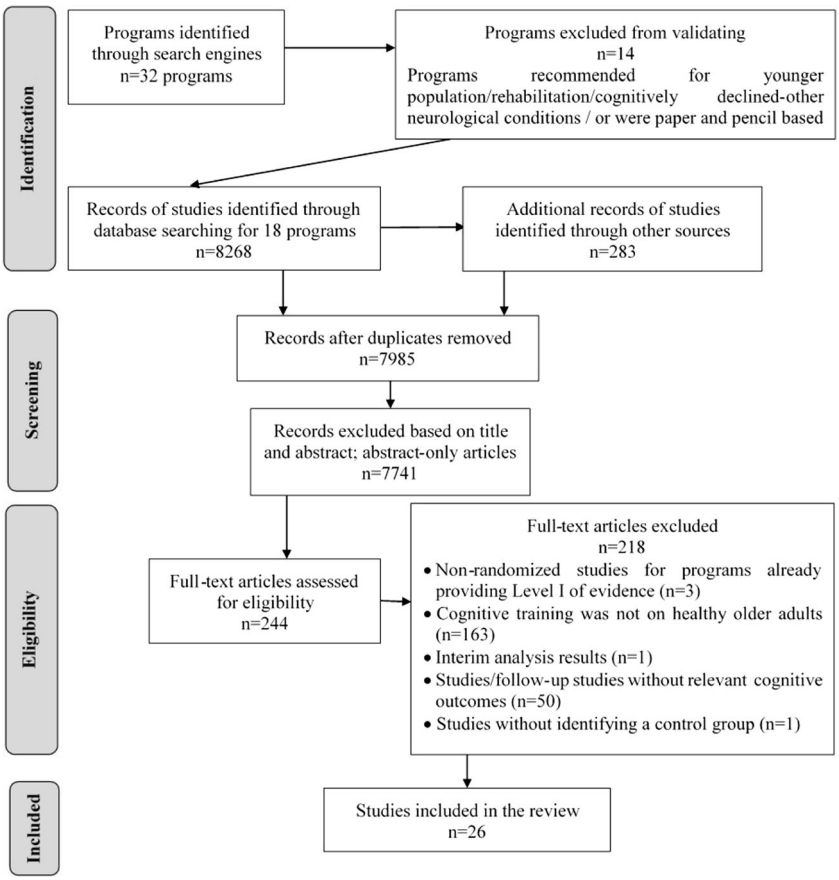

Fig. 1 Flow of studies into review

hence, excluded. Step two was then conducted to identify studies that used each of the remaining 18 programs identified for cognitive training. A total of 7985 studies were retrieved after removing duplicates. In total, 244 full text publications were identified and assessed for eligibility. Based on the inclusion/exclusion criteria, 26 supporting studies including follow-ups were reviewed.

Evidence of Quality and Characteristics

The characteristics of all clinical trials relevant for each program are summarized in Table 1. Out of the 18 programs initially identified, relevant articles were retrieved for only seven programs. Programs with no clinical trials, i.e. without any empirical evidence ($n = 11$) were removed from assessment. Twenty-six eligible articles including follow-up studies were reviewed and all subsequent studies without follow-ups ($n = 18$) evaluated. The mean PEDro score for all studies ($n = 18$) was 7.05 indicating high methodological quality overall, with most studies classified as high ($n = 12$) or moderate ($n = 6$) quality and no studies classified as poor quality.

Twelve studies were either conducted or funded by the program's respective company. Two studies were allowed free access to respective programs to conduct the research, and four studies were conducted independently of the product company. We scored the ratings of independent funding ($n = 6$, includes 2 studies in which companies allowed program access) versus company funded ($n = 12$) studies. When compared, the PEDro ratings showed moderate to high quality studies in both categories (average PEDro score for independently funded studies = 6.3 and average PEDro score for company funded studies = 7.4).

Study Characteristics

Study characteristics and program features are summarized in Table 2 and 3 respectively. The products described below are listed as per the classification Levels.

Programs With Clinical Trials Providing Level I Evidence

Studies classified as delivering Level I evidence (at least two well-designed RCTs or quasi-randomized studies, one with high quality and second at least of moderate quality as rated on the PEDro score) were available for programs from Posit

Table 1 Evidence quality and characteristics for studies included in this review

Program identified with eligible trials	Level of evidence	Study	PEDro score[a]	Author/s designed program/company employee	Study funded by company
Posit science	I	Mahncke et al. (2006)	8	Yes	Yes
		Smith et al. (2009)	9	Yes	Yes
		Ball et al. (2002a)	9	Yes	NA
		Wolinsky et al. (2013)	9	Yes	NA
		Berry et al. (2010)	8	Yes	Yes
		Edwards et al. (2013)	5	Yes	NA
		O'Brien et al. (2013)	7	Yes	NA
		Barnes et al. (2013)	7	Allowed program access	
		Anderson et al. (2013)	7	NA	not funded by company
		Leung et al. (2015)	5	NA	not funded by company
		Peretz et al. (2011)	9	Yes	Yes
Cognifit		Shatil (2013)	5	Yes	NA
		Shatil et al. (2014)	6	Yes	NA
Cogmed		Brehmer et al. (2011)	7	Allowed program access	
Brain age	II	Nouchi et al. (2012)	9	Yes	NA
My brain trainer		Simpson et al. (2012)	7	NA	not funded by company
Dakim	III	Miller et al. (2013)	5	Yes	Yes
Lumosity		Ballesteros et al. (2014)	5	NA	not funded by company

PEDro Physiotherapy Evidence Database, *NA* not available

[a] PEDro score: >6 = high; 5–6 = moderate and <5 = poor methodological quality

science and Cognifit. These programs are discussed in the section below.

Posit Science®

Posit science was evaluated in 10 studies, including 8 high quality RCTs. The interventions include a number of cognitive training programs, including modules for memory, processing speed and reasoning. Posit also produces the Brain Fitness Program (BFP, six exercises), which was developed to improve auditory processing and memory. The principle behind the BFP is based on the SAAGE™ (Speed, Accuracy, Adaptivity, Generalizability, Engagement) design protocol (Brainhq.com) for spanned acoustic stimuli (Mahncke et al. 2006) including engaging mechanisms promoting brain plasticity (Recanzone et al. 1992, 1993; Xerri et al. 1999). Another Posit program is the Cortex – Insight program (IP, 5 exercises), which focuses on visual processing and memory. The IP is based on the principle of "Useful Field of View" (UFOV), defined as the area over which the participant can see details quickly and accurately without moving one's eyes or head (Ball and Owsley 1993; Owsley et al. 1998; Sanders 1970). Interventions based on UFOV are designed to improve driving and visual processing and attention skills (Ball et al. 1988, 2002b; Edwards et al. 2005, 2006). At present, Posit Science have replaced its programs by an online training system known as BrainHQ (Brainhq.com).

Multiple peer-reviewed articles evaluating Posit Science programs have fulfilled the gold standard for clinical trials (Ball et al. 2002a; Mahncke et al. 2006; Smith et al. 2009; Brainhq.com). The landmark study "The Advanced Cognitive Training for Independent and Vital Elderly" (Ball et al. 2002a), ACTIVE trial is one of the largest, multicentre, RCT on cognitive training in healthy older adults. Besides cognition, this trial also examined the long-term benefits of cognitive interventions on the daily functioning of older individuals who were living independently. The study recruited 2832 participants aged 65 years or older and randomly assigned them into one of three intervention groups targeting memory, reasoning or speed of processing, as well as a control group that did not receive any training. The intervention consisted of 10 one-hour training sessions over six weeks. Memory training focused on improving verbal episodic memory through the use of mnemonic strategies. Reasoning training consisted of working with trainers to learn and practice skills related to inductive reasoning and problem solving. Speed of processing training included a computer-based training procedure that required the participants to identify a central visual target and locate another peripheral stimulus. Results indicated that training resulted in improved memory, reasoning and processing speed, with maximum benefits observed in the speed of

Table 2 Published randomized clinical trials that have tested computerized software programs to enhance cognition/memory in cognitively intact older adults

Program/Company, study (References)	*n*, Age	Groups	Cognitive training sessions	Duration	Control condition	Reported results
BFP/Posit Science, (Mahncke et al. 2006)	$n = 182$, 60–87 years	1. Experimental 2. Active control 3. No contact control	40 sessions, one hour/day, 5 days/week	8-10 weeks	Educational DVDs or no contact	Training improved processing speed: $p < 0.001$, $d = 0.25$; RBANS: $p = 0.019$, $d = 0.25$ and word recognition: $p = 0.022$, $d = 0.25$. Sustained benefits at 3 months follow-up.
BFP/Posit Science, IMPACT trial (Smith et al. 2009)	$n = 487$, 65–80 years	1. Experimental 2. Active control	40 sessions, one hour/day, 5 days/week	8-10 weeks	Educational DVDs	Training improved processing speed: $p < 0.001$, $d = 0.87$; RBANS: $p = 0.02$, $d = 0.23$; word recall: $p < 0.05$, $d = 0.28$; delayed word recall: $p < 0.05$, $d = 0.20$; digit span: $p < 0.05$, $d = 0.26$; letter number sequencing: $p < 0.05$, $d = 0.23$ and CSRQ: $p = 0.001$, $d = 0.33$.
BFP/Posit Science, IMPACT trial (Zelinski et al. 2011)	$n = 415$, >65 years	3-month follow-up study	–	–	–	Training gains declined over the 3-month no-contact period.
Insight/Posit Science, ACTIVE trial (Ball et al. 2002a)	$n = 2832$, 64–94 years	1.Reasoning training 2.Processing speed training (Insight not completely developed) 3.Memory training 4. Control	10 sessions, 60–75 min/session	4-5 weeks	No contact	Each intervention significantly improved the targeted cognitive domain, sustained benefits until 2 years. Training improved memory: $p < 0.001$, $d = 0.25$; reasoning: $p < 0.001$, $d = 0.48$ and processing speed: $p < 0.001$, $d = -1.46$.
Posit Science, ACTIVE trial (Wolinsky et al. 2006b)	$n = 2147$, >65 years	2-year follow-up study	–	–	–	Only the speed of processing training protected against extensive clinically relevant decline in HRQoL.
Posit Science, ACTIVE trial (Wolinsky et al. 2006a)	$n = 1804$, >65 years	2 and 5 year follow-up study	–	–	–	At 2 years post-training, processing speed intervention showed less decline in HRQoL; at 5 year post-training all three intervention groups were protective at a lower threshold of age related extensive declines in HRQoL.
Posit Science, ACTIVE trial (Willis et al. 2006)	$n = 67\%$ retention from ACTIVE study	5-year follow-up study	–	–	–	Maintained cognitive benefits at 5 years of the ACTIVE trial intervention; reasoning training showed less functional decline in IADL.
Posit Science, ACTIVE Trial (Rebok et al. 2014)	$n = 44\%$ retention from ACTIVE study	10-year follow-up study	–	–	–	All three interventions showed less difficulty with IADL; reasoning and processing speed interventions maintained their effects on their targeted cognitive domains; memory training intervention did not maintain memory performance at 10 years follow-up.
Insight-Road tour module/Posit Science, (Wolinsky et al. 2013)	$n = 681$, 50–64 years and ≥65 years	1.Processing speed training 2. Active control	10 h	1.5 months	Computerised crossword puzzles	Training improved UFOV: $d = -0.322$ to -0.579; Trails A: $d = -0.204$ to -0.265; Trails B: $d = -0.225$ to -0.320; SDMT: $d = 0.263$ to 0.351 and Stroop Word: $d = 0.240$ to 0.271. All intervention groups had $p < 0.05$.
Insight-Sweep seeker module/Posit Science,	$n = 32$, 60–89 years	1. Cognitive training 2. Control	10 h; 40 min sessions, 3–5 sessions/week	3-5 weeks	No training	Training improved perception-medium: $d = 0.85$; perception-high: $d = 0.88$;

Table 2 (continued)

Program/Company, study (References)	*n*, Age	Groups	Cognitive training sessions	Duration	Control condition	Reported results
(Berry et al. 2010)						discrimination: $p < 0.01$, $d = 0.91$ and working memory: $p < 0.05$, $d = 0.81$. Transfer of benefits from perceptual discrimination training to working memory; EEG-early visual processing during stimulus encoding predicted working memory accuracy improvements.
Insight/Posit Science, (Edwards et al. 2013)	$n = 75$, 59–95 years	1. Insight training 2. Control	20 sessions, twice/week	12 week	No training	Training improved performance in the UFOV: $p = 0.043$, $d = 0.63$.
Insight/Posit Science, (O'Brien et al. 2013)	$n = 22$, 65–82 years	1. Speed of processing training 2. Control	Upto 20 h; 70 min twice/week	10 weeks	No training	Training improved attention: $p = 0.01$, $p\eta^2 = 0.31$ with changes in event related potentials in the form of increased N2pc amplitude: $p = 0.025$; $p\eta^2 = 0.227$ and P3b amplitude $p = 0.023$; $p\eta^2 = 0.419$.
BFP & Insight/Posit Science, (Barnes et al. 2013)	$n = 126$, >65 years	1. MA-I/EX-I 2. MA-I/EX-C 3. MA-C/EX-I 4. MA-C/EX-C	36 sessions, Insight for the first 6 weeks–18 sessions; BFP for the last 6 weeks–18 sessions; 1 h three times/week	3 months	MA-C: educational DVDs; EX-C: stretching and toning	Global cognitive scores improved significantly over time: $p < 0.001$; no significant differences between the intervention and the active control group.
BFP/Posit Science, (Anderson et al. 2013)	$n = 104$, 55–75 years	1. Cognitive training 2. Active control	40 sessions; 1-h/day, 5 days/week	8 weeks	Educational DVD's	Training improved memory: $p < 0.001$, $d = 0.79$; processing speed: $p = 0.021$, $d = 0.68$ and speech-in-noise perception: $p < 0.01$, $d = 0.72$.
BFP/Posit Science, (Anderson et al. 2014)	$n = 62$, 55–70 years	6-month follow-up study	–	–	–	Maintained gains in processing speed but not memory and speech-in-noise recognition.
BFP/Posit Science, (Leung et al. 2015)	$n = 209$, >60 years	1. Cognitive training 2. Active control	39 sessions, 1-h per sessions, 3 times/week	13 weeks	Educational video programs	Training improved attention: $p = 0.026$, $d = 0.31$ and working memory: $p = 0.012$, $d = 0.35$.
Personal Coach/Cognifit, (Peretz et al. 2011)	$n = 155$, >50 years	1. Cognitive training 2. Computer games	36 sessions, 20–30 min/session; 3 sessions/week	3 months	Played conventional computer games	Training-specific improvement in visuospatial working memory: $p = 0.0001$, $d = 0.43$; learning: $p = 0.0012$, $d = 0.51$ and attention: $p = 0.0019$, $d = 0.63$.
Cognifit, (Shatil 2013)	$n = 118$, 65–93 years	1.Physical activity 2.Cognitive training 3. Combined 4. Active Control	Cognitive training – 32 h, 48 min sessions, three times/week	4 months	Book reading	The cognitive training and the combined group improved on: hand-eye coordination: $p < 0.001$, $d = 0.80$; processing speed: $p < 0.001$, $d = 0.71$; visual scanning: $p = 0.021$, $d = 0.77$; global visual memory: $p = 0.003$; $d = 0.64$ and naming: $p < 0.05$, $d = 0.82$.
Cognifit, (Shatil et al. 2014)	$n = 140$, 60–87 years	1. Television based cognitive training 2. Active control	24 sessions, 20 min sessions, three times per week	8 weeks	Non-cognitive applications	Improvement in working memory and executive functions in the training group. Digit Span Forward: $p < 0.01$; $d = 0.58$. Digit Span Reverse: $p < 0.01$; $d = 0.58$. Digit Span Total: $p < 0.001$; $d = 0.70$. Trail Making Test Part B: $p < 0.05$; $d = -0.40$. Trail Making Test Total: $p < 0.05$; $d = -0.40$.
Cogmed QM/Cogmed, (Brehmer et al. 2011)	$n = 23$, 60–70 years	1. Adaptive training 2. Active control	25 sessions, 25 min/day, 5 days/week	5 weeks		Improved working memory, attention, episodic memory, less everyday cognitive problems;

Table 2 (continued)

Program/Company, study (References)	*n*, Age	Groups	Cognitive training sessions	Duration	Control condition	Reported results
					Fixed, low level cognitive training practice	BOLD decrease in frontal, parietal and temporal regions, higher neural efficiency. Span Board Backward: $p = 0.04$; $p\eta^2 = 0.18$. Paced Auditory Serial Addition Task: $p = 0.02$; $p\eta^2 = 0.22$.
Brain Fitness/Dakim, (Miller et al. 2013)	$n = 69$, 81.8 ± 6.1 years	1. Intervention 2. Control	20-25 min/day, 5 days/week, 43 sessions at 2 months and 81 sessions at 6 months	6 months	Wait –list	Training improved delayed memory: $p = 0.01$, $d = 0.67$; 40 sessions over 6 months resulted in improved immediate memory: $p = 0.001$; delayed memory: $p = 0.004$ and language: $p = 0.03$.
Brain age/Nintendo, (Nouchi et al. 2012)	$n = 32$, 69.1 ± 0.31 years	1. Brain age 2. Tetris	15 min/day, 5 days/week	1 month	Played Tetris	Improved executive functions and processing speed assessed using Frontal Assessment Battery at Bedside: $p = 0.001$, $\eta^2 = 0.13$; Trail Making Test Type B: $p = 0.006$, $\eta^2 = 0.13$; Symbol Search: $p = 0.014$, $\eta^2 = 0.12$ and Digit Symbol Coding: $p = 0.005$, $\eta^2 = 0.19$.
My brain trainer, (Simpson et al. 2012)	$n = 34$, 53–75 years	1. My brain trainer 2. Active Control	20 min daily	21 days	Played Solitaire	Improved processing speed at post - training and at three weeks follow-up as assessed on Simple Reaction Time: $p = 0.024$, $p\eta^2 = 0.154$ and Complex Reaction Time: $p = 0.007$, $p\eta^2 = 0.170$.
Lumosity, (Ballesteros et al. 2014)	$n = 60$, 57–80 years	1. Experimental group 2. Control	20 sessions; 1-h sessions	10-12 weeks	Three meetings; 2-h in duration discussing aging and interests	Training improved processing speed: $p < 0.001$, $p\eta^2 = 0.83$; Cross-Modal Oddball Attention Task: $p < 0.05$, $p\eta^2 = 0.05$; immediate memory: $p < 0.05$, $p\eta^2 = 0.14$ and delayed memory: $p < 0.001$, $p\eta^2 = 0.45$.
Lumosity, (Mayas et al. 2014)	$n = 27$, 57–77 years	1. Experimental group 2. Control	20 sessions; 1-h sessions	10-12 weeks	Three meetings; 2-h in duration discussing aging and interests	Improved alertness: $p = 0.04$, $d = 0.9$ and reduced distraction: $p = 0.05$, $d = 0.43$ in the exercise group
Lumosity, (Ballesteros et al. 2015a)	$n = 40$, 57–80 years	3-month follow-up study	–	–	–	No sustained cognitive benefits; maintained benefits in subjective wellbeing only

BFP Brain Fitness Program, *DVD* Digital Video Disc, *d* Cohen's *d*, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *IMPACT* The Improvement in Memory with Plasticity-Based Adaptive Cognitive Training, *CSRQ* Cognitive Self Report Questionnaire-25, *ACTIVE* The Advanced Cognitive Training For Independent And Vital Elderly, *HRQoL* Health-Related Quality of Life, *IADL* Instrumental Activities Of Daily Living, *UFOV* Useful Field Of View, *SDMT* Symbol Digit Modalities Test, *EEG* Electroencephalogram, $p\eta^2$ Partial eta squared, *MA-I* Mental Activity-Intervention, *EX-I* Exercise-Intervention, *EX-C* Exercise-Control, *MA-C* Mental Activity-Control, *BOLD* Blood-Oxygen-Level-Dependent, η^2 Eta squared

processing training group. The IP was originally developed as part of this ACTIVE trial for training of processing speed and was later revised to include additional tasks (Jobe et al. 2001; Ball et al. 2013). Thus, the program was not fully developed in the ACTIVE trial.

Following the initial validation trial, ACTIVE participants were reassessed on multiple occasions over 10 years. Initially they received a booster training of 4 hours after 11 and 35 months post-baseline, and displayed additional improvements in the reasoning and speed of processing intervention groups. However, the memory group participants did not show further benefit. Notably, however, a five-year follow-up on 67% of ACTIVE participants demonstrated persistence of the benefits obtained in all three intervention groups. Further, these participants displayed a slower decline in instrumental activities of daily living {IADL, (Willis et al. 2006)} with the reasoning group showing the greatest resistance to IADL loss. It was additionally noted that the speed of processing training was protective against clinical decline in health-related quality of life at two and five years post-training (Wolinsky et al. 2006a, b). More recently, a 10-year follow-up study of the ACTIVE trial participants found that each of the cognitive intervention groups reported less decline in self-reported IADL when compared to the control group. However, reasoning and speed, but not memory training, resulted in improved targeted cognitive abilities (Rebok et al. 2014).

Results from other studies using Posit software have generally supported findings from the ACTIVE trial. For example, Edwards and colleagues studied 97 adults (61–95 years), and found that while speed of processing training produced no immediate transfer effects to other cognitive domains, it may have contributed to enhanced speed in performing IADLs (Edwards et al. 2002). In addition, studies using the IP and BFP programs have produced promising results. For example, a study of 32 healthy older adults using the "sweep seeker" module from the IP for 40 min, 3–5 sessions/week for 3–5 weeks reported direct transfer of benefits from perceptual discrimination training to working memory performance in older adults. The study also used electroencephalography and reported that early visual processing during stimulus encoding predicted improved working memory (Berry et al. 2010). In another study of 22 participants, an increase in the amplitudes of event related potentials related to selective attentional processing were reported following speed of processing training for 10 weeks (O'Brien et al. 2013). Finally, in yet another study using IP on 75 older adults, the UFOV performance was enhanced after 3 months of training with 20 sessions (Edwards et al. 2013). The "road tour" module of IP also showed improved processing speed and executive functions (Wolinsky et al. 2013).

Mahncke and colleagues administered the BFP to 187 participants randomized into a training group, a contact control group or a no-contact control group, and found training produced gains in independent measures of cognition (Mahncke et al. 2006). Briefly, the intervention group was given intensive training on the BFP with a duration and frequency of 60 min sessions for 5 days per week (total 40 sessions) for 8 to 12 weeks. The contact control group were given an educational DVD whereas the no-contact control group did not receive any intervention. The study showed significant improvements in directly trained tasks underlying speed of processing and forward recognition memory span. An obtained effect size of 0.25 suggested significant generalization of improvements to non-related standardised memory tests from the Repeatable Battery for the Assessment of Neuropsychological Status. Memory enhancement was found to be sustained after 3 months of no contact at a follow-up assessment. The study also reported that older adults had no difficulty in using the program on the computer. Based on this study, Smith and colleagues carried out another landmark study, "The Improvement In Memory With Plasticity Based Adaptive Cognitive Training" {(Smith et al. 2009), IMPACT study}. The cohort included 487 healthy community-dwelling adults aged 65 years and older, and used a similar training approach to the initial study led by Mahncke and colleagues. The study found improved neuropsychological function broadly, but with the greatest benefits observed in auditory memory/attention. However, training gains declined at 3-month follow-up which indicated that booster training sessions may be required to maintain training-induced benefits (Zelinski et al. 2011). Recent studies support the above findings in the form of improved attention, working memory, processing speed and transfer of training benefits to everyday problem solving and reasoning with altered occipital-temporal white matter integrity (Strenziok et al. 2014; Leung et al. 2015; Anderson et al. 2013, 2014).

Of interest, one RCT study evaluated the utility of Posit Science programs in combination with physical activity. The mental activity and exercise (MAX) trial used a 2x2 factorial design and 126 older adults with cognitive complaints were divided into four groups, and underwent intensive physical and/or cognitive training. All groups including the control group underwent 12 weeks of home-based mental activity (1 h/day, 3 days/week) plus class-based physical activity 1 h/day, 3 days/week, (Barnes et al. 2013). Cognitive training comprised of 18 sessions of IP (visual stimulation) for the first 6 weeks followed by 18 sessions of BFP (auditory stimulation) for the last 6 weeks. Thus each group had 36 sessions of mental training (as just described, whereas the control group watched educational DVDs 3 times a week) and 36 sessions of physical training; either active (aerobic) or control (stretching and toning), giving a total of 72 sessions. Improved global cognition was found in all the groups including the control group, and there were no intervention-specific benefits, a possible reason being that the amount of activity may be more important than the type i.e. more training sessions may be required to see an effect when used in combination. Details for three non-randomized studies that used Posit Science

softwares in combination with physical activity were not included in the review (Frantzidis et al. 2014; Shah et al. 2014; Bamidis et al. 2015).

Cognifit™

Cognifit™ interventions were evaluated in 3 studies including 1 high and 2 moderate quality studies. Its software includes four different versions: Cognifit personal coach for brain health, Mindfit which is a CD-ROM version, Cognifit senior driver for maintaining driving skills of seniors and the Mindfit "back on track" version. Mindfit aims to train 14 cognitive skills through 21 exercises. Feedback is provided by progression charts and personal coaching via an individualised training system (ITS™) and is recommended for rehabilitation. A study using the Mindfit program for cognitive remediation on gait performance reported improved processing speed in the sedentary elderly (Verghese et al. 2010). As attention and executive functions are associated with slow gait and falls in the elderly, this study showed that the benefits of cognitive training can be transferred to untrained domain of mobility. RCTs have been conducted using ITS™ on individuals with multiple sclerosis, dyslexia and other disorders showing improved cognition. Mindfit has also been reported to enhance memory, attention, executive functions and processing speed in chronic insomnia patients (Haimov et al. 2008).

A study by Peretz and colleagues in 155 healthy older adults using the Cognifit personal coach reported that although both the training and an active control condition improved cognition per se, the training was more effective for visuospatial working memory, learning and attention (Peretz et al. 2011). Another randomized double-blind study was conducted using Cognifit along with a physical activity intervention, using a four-condition design on 118 healthy older adults (Shatil 2013). Participants were randomized into physical activity, brain training, a combination of both, or a control group. The brain training and combined groups displayed enhanced memory, processing speed including hand-eye coordination, the authors concluded that the mechanism of action behind the benefits observed in the combined group was likely due to the brain training rather than the physical activity component. For older adults without computer facilities, Cognifit's television compatible software version showed improved working memory and executive functions in healthy older adults (Shatil et al. 2014).

Programs with Clinical Trials Providing Level II Evidence

Studies providing Level II (that is, only a single relevant well-designed RCT with PEDro score in the high range) evidence used brain training programs from Cogmed, Brain age 2 and My brain trainer.

Cogmed

Cogmed (Cogmed.com) was evaluated in one RCT of high quality. The Cogmed coach version initially trains for 30 sessions with assistance and motivation. There is a six-month follow-up interview and training with another 100 sessions over a year. In a RCT of 23 healthy older adults Cogmed training resulted in improved memory performance (Brehmer et al. 2011). The study administered 25 sessions of adaptive training (individually adjusted task difficulty to bring individuals to their performance maximum) within five weeks, and included an active control group that performed low-level fixed cognitive training. Specifically, improvements were observed in the adaptive training group for working memory, but also in the untrained cognitive domains of attention and episodic memory. In addition, functional magnetic resonance imaging [blood-oxygen-level-dependent (BOLD) fMRI] was performed to assess in-scanner task-associated neural activations seen during working memory performance. No significant group differences in brain activation patterns at baseline or post-intervention were seen, in the low-task difficulty condition. However, greater decreases in neocortical brain activity and greater increases in subcortical activity were found in the adaptive training group under high-task difficulty conditions, post-intervention. This was interpreted as indicating that the high-load task was less executively demanding and required less neural activity to attain the same baseline performance level in the adaptive training group. Overall, the study findings showed behavioural training gains as a result of adaptive cognitive training which was associated with changes in neural activity while performing a challenging working memory task.

Brain Age 2

Brain Age 2 from *Nintendo*® (Brainage.com) was evaluated in one high quality RCT. It trains individuals to solve simple maths problems, count currency, draw pictures and unscramble letters. It is administered via a handheld device and has a touch screen with a pen. This product is extremely popular in the market and its most appealing feature is considered to be its portability. Brain age 2 has been tested in healthy elderly and young adults (Nouchi et al. 2012, 2013). An RCT on 32 healthy older adults using brain age versus another popular game "Tetris" for 15 min/day for 5 days/week for 4 weeks reported improved executive functions and processing speed (Nouchi et al. 2012). However, no transfer effects were

Table 3 List of computerized brain fitness programs and their features (in alphabetical order)

Program	Website	Specifications	Training exposure	Web references
BFP/Insight	www.positscience.com www.brainhq.com	NP, BFP - SAAGE™ design protocol, Insight - UFOV technology/web based	BFP - 60 min for 5 days/week for 8–10 weeks, total 40 sessions; Insight - 60–90 min of 10 sessions for 2–3 times/week	(Brainhq.com)
Brain Age 2	www.brainage.com www.brainage2.com	Increases blood flow to the prefrontal cortex/played on a palm device	Few minutes per day	(Brainage.com; Brainage2.com)
Cogmed	www.cogmed.com	NP/CD-ROM/web based	30-45 min, 1 session for 5 days/week for 5 weeks	(Cogmed.com)
Cognifit	www.Cognifit.com,	NP/web based	20 min, 3 times/week	(Cognifit.com)
Dakim (m) Power	www.dakim.com	Use it or lose it?/web based	20-25 min, 3–5 times/week	(Dakim.com)
Lumosity	www.lumosity.com	NP/web based	Full workout in 10 min/day/daily 30 min sessions	(Lumosity.com)
My Brain Trainer	www.mybraintrainer.com	Elementary cognitive tasks to stimulate neurons, increases blood flow to the brain/web based	10 min twice per day, daily	(Mybraintrainer.com)

BFP Brain Fitness Program, *NP* Neuroplasticity, *SAAGE* Speed, Accuracy, Adaptability, Generalizability and Engagement, *UFOV* Useful Field of View, *CD-ROM* Compact Disc-Read Only Memory

observed in other outcome measures of global cognition or attention.

My Brain Trainer

My brain trainer (Mybraintrainer.com) was evaluated in a single RCT of high quality. It is a program that includes exercises for neuronal stimulation that aims to increase cerebral blood flow and the number of neural receptors, and to enhance the synthesis and uptake of neurotransmitters. A randomized single blind trial have been conducted using my brain trainer's 21-day online exercises on 34 participants between 53–75 years of age with an active control group that played solitaire card game. The study reported improved processing speed (Simpson et al. 2012).

Programs With Clinical Trials Providing Level III Evidence

Studies providing Level III evidence (that is one or more moderate/poorly designed RCT with Pedro score in the moderate to poor range and other methodological approaches) used brain training programs from Dakim and Lumosity.

Dakim

Dakim (Dakim.com) was evaluated in a single trial of relatively moderate quality (PEDro score = 5). It comes as software or as a plug in and play touch screen system with five levels of challenging exercises. Individual 25-min sessions includes exercises from each of the following domains: memory, critical thinking, visuospatial, calculation and language. It has over 100 exercises lasting for over 300 h with regular updates. In a RCT of 69 healthy older adults using this program, the intervention group showed improved memory and language after completing 40 sessions in two months (Miller et al. 2013). The study also reported benefits at six months follow-up. In addition, an unpublished clinical trial on more than 100 participants reported improved memory retention and delayed recall (Dakim.com).

Lumosity

Lumosity (Lumosity.com) was evaluated in a single RCT classified in the moderate range of the PEDro scale. It is based on the principle of neuroplasticity and recommends 15 min of daily training. The website has online neuropsychological assessments for various cognitive domains with about 10 million members in its community. It includes a brain grade test for speed, memory, attention, flexibility and problem solving. While not yet the subject of an RCT, a white paper reported a study of 23 healthy adults who trained with lumosity for 20 min per day for five weeks reported improved working memory, visual attention and executive functions (Scanlon et al. 2007; Hardy and Scanlon 2009). Later, a RCT using lumosity reported cognitive gains, increased alertness and wellbeing in healthy older adults (Ballesteros et al. 2014; Mayas et al. 2014). A follow-up study three months later

showed that only subjective well-being was maintained, indicating that booster sessions of brain training may be required for the maintenance of cognitive benefits (Ballesteros et al. 2015a). Moreover, lumosity's online brain exercises involving visual working memory when used as an assessment parameter for cognition, identified subjects at risk of cognitive decline (Geyer et al. 2015). A web-based RCT ($n = 4715$, 18–80 years) reported improved processing speed, memory, problem solving abilities and concentration after participants completed lumosity exercises for 15 min, 5 days per week for 10 weeks (Hardy et al. 2015). However, the study also included younger participants. Only one study was validated for lumosity as separate articles reported findings from the data of a single RCT (Ballesteros et al. 2014, 2015a, b; Mayas et al. 2014).

Discussion

This review gives details of 7 commercial computerized brain training programs and summarizes 26 clinical trials including follow-up studies conducted in healthy older adults. Overall, most studies had at least adequate methodological quality (67% of studies were rated as high quality using PEDro classification, see Table 1). In addition to classifying the methodological quality of individual studies, this review also classified the overall level of research evidence found for each training program. Results indicated that two programs (Posit science and Cognifit) met criteria for Level I evidence (multiple well-designed RCTs). Three additional programs (Cogmed, Brain age 2 and My brain trainer) met criteria for Level II evidence (at least one high quality, well-designed RCT). Finally two products (Dakim and Lumosity) were classified as possessing Level III evidence (some supportive research, but moderately designed RCT).

Programs with clinical trials providing Level I evidence (13 studies, see Table 1) administered training sessions that ranged from 4 weeks to 16 weeks. Briefly, seven studies reported improved processing speed, 3 studies reported improved attention with either small, medium or large effect sizes and five studies reported improved memory/working memory with small to medium effect size. One study reported improved reasoning with small effect size whereas only two studies reported significantly improved executive functions with a small effect size.

Programs with clinical trials providing Level II evidence (3 studies, see Table 1) administered training sessions that ranged from 21 days to 5 weeks. Results from all three studies reported improved processing speed with a medium to large effect size whereas one study reported improved memory with large effect size. One study also reported improved attention with a large effect size. Only one study reported improvement in executive functions with medium effect size.

Programs with clinical trials providing Level III evidence (2 studies, see Table 1) administered training sessions that ranged from 10 weeks to six months. Results from one study reported improved processing speed with a large effect size whereas two studies reported improved memory with medium to large effect size. One study reported improved attention with small effect size.

The RCTs conducted using Posit Science interventions (IP and BFP) include large sample sizes. According to the ACTIVE trial, the benefits of cognitive training for even a relatively short period of time appear to be sustained over 2, 5 and possibly 10 years post-intervention when occasional booster sessions were included. The ACTIVE trial is the largest and most frequently cited RCT reporting cognitive benefits, following 10 sessions of training. The ACTIVE trial reported generalisation of benefits to health-related quality of life and IADLs, with the follow-up study at 10 years post-intervention showing sustained benefits, including resistance to IADL decline. Thus, although it is difficult to compare any two programs side by side, there is evidence that at least some of these programs enhance memory, processing speed, executive functions and reasoning capabilities in older adults.

When used in combination with physical activity, computerized brain training have shown mixed results. The MAX trial (Barnes et al. 2013) used both physical and mental training but did not demonstrate intervention specific benefits. One of the reasons for this may be that the training conditions used for the control group may have provided similar benefits to the intervention training program. Moreover, the cognitive training sessions shown to be effective are 10 sessions for the IP and 40 sessions for the BFP. The cognitive training thus differed (i.e., 36 sessions in the MAX trial) from the recommended sessions and this could have led to undetected training benefits. On the other hand, the study led by Evelyn Shatil (Shatil 2013) using Cognifit program together with physical activity showed improved hand-eye coordination, global visual memory and processing speed in the cognitive training and the combined group. The exercise group alone did not show cognitive gains. Another study on 224 elderly participants showed that a combination of physical activity in the form of walking and resistance training along with auditory and visual stimulation using the BPF and IP programs (total 160 combined sessions in four months) improved verbal episodic memory in healthy older adults (Shah et al. 2014). Furthermore, improved verbal memory in the combined group was associated with increased brain glucose metabolism in the left primary sensorimotor cortex at 16 weeks post-intervention. In addition, a study using the Greek version of BFP together with exercise reported increased neuropsychological synchronisation in the intervention group (Frantzidis et al. 2014). This study used 24–40 training sessions of the BFP. Although the exercise component and the study design differed in these studies, it is possible that all observed

benefits could be the result of the greater number of training sessions. Some studies lack the inclusion of stand-alone training such as that in the study by Franzidis and colleagues (Frantzidis et al. 2014), which means that the combined effects cannot be compared with isolated training effects. Overall, further evidence is required to determine if computerized brain training programs show synergistic benefits when used in combination with exercise.

Despite the positive cognitive outcomes reviewed here, there are still significant limitations to the current evidence and areas needing further study. One such limitation is the fact that the measurement of cognition remains limited in many studies, with little or no measurement of cognitive domains with demonstrated promise in predicting real-world functioning in older adults {e.g. prospective memory; (Woods et al. 2012)}. Assessments of executive functions considered as one of the reliable predictors of IADL in older adults (Lewis and Miller 2007) is also lacking in majority of the studies. Inclusion of assessments testing a broad array of cognitive domains would enhance our understanding regarding the potential transfer of effects to untrained cognitive domains. Additionally, although brain training has been tested in combination with exercise as discussed above, more studies are required that also consider combination with other lifestyle factors such as social engagement and diet.

Another major limitation is the lack of measuring candidate blood, cerebrospinal fluid (CSF) or brain imaging AD biomarkers in many of the studies providing Level I and Level II evidence. The inclusion of such parameters could have helped to elucidate the possible mechanisms of action behind the benefits observed using such neuroplasticity-based tailored programs. In a study testing the BFP on 6 MCI patients versus 6 controls using fMRI, it was shown that activation in the left hippocampus increased significantly in the training MCI group (Rosen et al. 2011). One could speculate that similar brain changes happen in trials involving cognitively intact healthy older adults. The trial by Cogmed QM targeted working memory and used fMRI to measure brain activity under two difficult conditions (Brehmer et al. 2011). The study showed that although there were no training related changes in working memory, a pattern of increased neural efficiency in the form of decreased neocortical brain activity and increased subcortical activity was observed in the intervention group. Moreover, the gains were transferred to non-targeted tasks of attention and episodic memory. Performance gains in the training group increased from week 1 through week 4 and remained stable thereafter. The active control group received the same training as the experimental group, with the main difference being that of task difficulty was fixed at a lower level. This would indicate that the intensity of the training is also important in addition to the type of training performed. However, the results are limited by a small sample size, and replication in a larger cohort is needed. The use of brain imaging in future clinical studies of cognitive training would help indicate its mechanism(s) of action, thus paving a way for investigating strategies for the therapeutic management of AD. Studies providing relevant evidence to the significant question yet to be adequately addressed regarding the mechanism(s) by which the cognitive training interventions reviewed here may produce positive cognitive effects is further discussed below.

Potential Mechanisms Underlying Cognitive Benefits of Cognitive Training

Animal studies show that cognitive stimulation can result in molecular, synaptic and neural alterations in the brain (reviewed in Buonomano and Merzenich 1998). Virtual reality based games can alter neurochemical levels in the brain (Koepp et al. 1998), suggesting potential mechanisms for cognitive rehabilitation by these programs (Cameirão et al. 2010). For example, intervention studies incorporating brain training have reported increased levels of serum brain derived neurotropic factor (Anderson-Hanley et al. 2012; Vinogradov et al. 2009). The brain derived neurotropic factor plays an important role in memory processing. However, as mentioned in the discussion above, in humans, the most powerful and commonly used measure to assess the effects of brain training is neuroimaging. Brain imaging conducted after training has shown changes in activity in certain brain regions while performing specific tasks, along with long-term global changes (Buschert et al. 2010). Engvig and colleagues showed that 8 weeks of training with the Method of Loci (paper and pencil based memory training) resulted in improvements in memory (Engvig et al. 2010). These improvements correlated positively with increases in the cortical thickness of the lateral orbitofrontal cortex bilaterally, as well as the right fusiform cortex. The same group found that the training caused changes in white matter microstructure: diffuse tensor imaging was used to show higher levels of fractional anisotropy in the frontal cortex of the older adults who had undergone the intensive memory training, compared to the control group. This indicated that training may protect against age-related decreases in myelination (Engvig et al. 2012). Other studies of the same Method of Loci training found that training increased brain activity in the occipito-parietal and frontal cortex as assessed using PET (Nyberg et al. 2003), and that memory improvements after 5 weeks of training correlated with increases in choline and creatine signals in the hippocampus, as measured using magnetic resonance spectroscopy (Valenzuela et al. 2003).

Computer based games also appear to influence changes seen in brain activity. For example, a PET study ($n = 8$, males, 19–32 years of age in the training group) measuring regional cerebral glucose metabolic rate after 4–8 weeks of playing the computer game Tetris for 30–45 min, 5 times/week reported a

decrease in glucose metabolic rate in cortical surface regions, alongside a 7-fold increase in performance in the game (Haier et al. 1992). Another study using fMRI reported increased brain activity in the middle frontal gyrus and superior and inferior parietal cortices after practicing working memory tasks (Olesen et al. 2003). A recent study using manual "gist reasoning" cognitive training on 37 cognitively normal elderly individuals for 1 h sessions, 3 times/week for 12 weeks reported increased global and cerebral blood flow in the default mode and central executive network, with increased white matter integrity in the left uncinate region (Anand et al. 2011; Chapman et al. 2013). The study used 3 MRI-based measurements namely arterial spin labelling MRI, functional connectivity and diffusion tensor imaging. Using similar neuroimaging techniques, it will be interesting to determine whether the use of computerized brain training exercises results in similar or greater training benefits than those obtained with the paper and pencil/video games based training.

Considering that the brain is adaptive in nature, a computerized brain training program that is adaptable and challenging may alter neural activity involving the specific targeted cognitive domains to be trained, as well as the brain regions involved in executing the tasks. One possible explanation is that, as the training becomes adaptive and the brain becomes accustomed to performing the trained tasks, neural activity in these regions would eventually decrease. It is also possible that if the training is too challenging, other brain regions may be involved as a compensatory mechanism resulting in increased neural activity in these regions. Another explanation to this mechanism is that decreased neural activity may demonstrate that the subjects are performing well in the trained tasks thus using a limited (minimum necessary) number of neural circuits. In contrast, subjects finding the training difficult, i.e. "poor performers" may display increased neural activity (Haier et al. 1992). A study ($n = 17$) by Small and colleagues (Small et al. 2006) investigated the benefits of a combination of memory training, exercise, stress reduction and diet on cognition and cerebral glucose metabolism using PET scan. The study reported a 5% decrease in activity in the left dorsolateral prefrontal cortex and improvement in word fluency in the intervention group. It is possible that the changes observed in the brain's left hemisphere could be due to the verbal emphasis in the program's memory training exercises as explained by the study authors. However, inclusion of comparative single intervention groups would further help to conclusively determine whether all and/or any one component of the program resulted in training benefits. In summary, it has been hypothesised that processes requiring attention show decreased brain activity and task specific brain regions are associated with increased brain activity after training (Buschert et al. 2010). Interestingly, a lifetime of cognitive activity has been shown to result in lower Aβ deposition levels in the human brain (Landau et al. 2012). It would be tempting to speculate that besides alterations in neural activity, computerized brain training may alter levels of brain and/or blood Aβ peptide in humans; high levels of which are thought to form toxic oligomers that have key roles in promoting neurodegeneration in AD.

The studies discussed above indicates that mentally challenging activities may trigger brain changes beneficial for enhancing cognition. Out of the many cognitive domains assessed, many studies on computerized brain training interventions have reported an improvement in the targeted cognitive domain of verbal episodic memory. Of note, this is a major domain that is affected in MCI and AD (Petersen et al. 2001). However, one of the greatest challenges faced by brain training programs is to prove the claims that the benefits extend to other non-targeted and untrained cognitive domains. The controversial study by Owen and colleagues challenged the support behind the widely held belief that commercially available computerized brain training programs improve general cognition (Owen et al. 2010). The six-week web-based study included 11,430 participants trained to improve reasoning, memory, planning, visuospatial skills and attention. The study reported improvements in the targeted domains, yet there were no transfer effects to other cognitive domains. Although the study received global focus, it was criticised due to its training duration which was only 10 min/day, three times/week for six weeks and the lack of face to face cognitive training. The study cohort also included younger people (age range 18–69). Further clinical trials need to be carried out to address the transfer effect query which may also be answered more definitively by inclusion of brain imaging biomarkers in such studies.

Mental Activities versus Computerized Cognitive Training

The concept of benefits to cognition being obtained from leisure-time mentally stimulating activities was initially obtained from observational studies based on self-reported questionnaires (Verghese et al. 2003; Wilson et al. 2007; Scarmeas et al. 2001; Fratiglioni et al. 2004). Recent studies (such as many of those listed in Table 2) have shown that computerized programs could result in superior benefits when compared to activities carried out by control groups. An active control group usually engages in routine leisure activities like book reading, puzzles, surfing the internet or watching YouTube documentaries on a computer. The study by Mahncke and colleagues (Mahncke et al. 2006) included an "active computer" control group as well as a "no contact" control group versus the intervention group. Besides demonstrating the cognitive benefits in the intervention group, the study also showed that the control groups did not differ statistically from one another, in other words, no placebo effect was found. On the other hand, the study by Peretz and colleagues (Peretz et al. 2011) included a computer games

group versus the computerized cognitive training group, and demonstrated cognitive benefits in both groups compared to baseline cognitive performance, with superior benefits in the cognitive training group (Peretz et al. 2011). Another one year RCT involving 191 healthy older adults aged 65–75 years reported that intensive use of personal computers with standard software applications did not result in any cognitive benefits when compared to three types of control groups (Slegers et al. 2009). These findings support the concept that simple mental activities do not provide the cognitive benefits of the specialised software based brain training exercises. Therefore, a tailored program which is adaptable, continuously challenging and not monotonous, with fixed intensity, duration and frequency is more beneficial than routine mental activities. Most of the training programs follow the same design principle of targeting, adaptivity, novelty, engagement and completeness in their exercises. Such an approach is usually absent in routine mental activities. Tasks that have been performed many times in the past simply revitalize the existing circuits and do not challenge the brain to work in new ways. Thus, in order for the brain to be exercised effectively, the activities are required to be novel, well-tailored to the individual, and continually challenging. A total of 11 programs initially selected did not show clinical significance as there were no studies to provide any Levels of evidence. While it is possible that these other programs are equally effective, given that they are mostly based on the same neuroplasticity principle, they could differ/target specific cognitive domains only, and thus need to be empirically validated in independent clinical studies.

The limitations of this review need to be acknowledged. Studies evaluating cognitively impaired older adults with a comparative study control group were not reviewed. Thus, it is unknown whether the results reviewed for healthy older adults can also be extended to cognitively impaired subgroups. Furthermore, it was also difficult to extract information solely concerning those programs recommended for older adults as most of these programs are recommended to be used by all age groups. Additionally, differences between on-line brain training games and software designed exercises still needs to be clearly demarcated. However, this is only possible if each brain training component comes with particular specifications. Most important and as discussed earlier, findings of company funded/affiliated studies should be further validated in more independent studies. Lastly, although we did not include video games in the review, some of the programs may utilise a similar format, however it was not possible to verify the contents of each of the programs.

Future Directions

Cognitive training interventions show the potential to enhance brain health. The majority of the programs discussed here support the notion that the human brain is plastic in later life, and can benefit from specifically designed brain training programs (Baltes et al. 1988; Baltes and Lindenberger 1988; Schaie and Willis 1986; Willis 1987). Level 1 clinical trials and their programs identified in this review have been clinically endorsed for their ability in enhancing memory, processing speed, reasoning and executive functions. However, the molecular evidence concerning how or where these software programs alter neuronal or synaptic plasticity is lacking. Assessments using blood, CSF and brain imaging biomarkers of AD would considerably enhance clinical validation of such brain training programs. This would also enable greater understanding of the connection between computerized brain exercises and human cognition. The Stanford Centre on Longevity and the Max Planck Institute for Human Development, Berlin produced a consensus statement for the public concerning the state of science of such programs in May 2009. It states that "software based cognitive training and brain games have been shown to improve users' performance on trained tasks. The important caveat is that very few training programs have shown evidence that such gains translate into improved performance in the complex realm of everyday life. A program might train in memorizing lists of words, for example, but this particular skill is not likely to help you remember where you left your car keys or the time of an upcoming appointment. We strongly support research on software-based training and encourage interested people to participate in clinical trials investigating its potential." This statement indicates that clinical research needs to determine whether the benefits measured by neuropsychological testing translate into cognitive benefits in day to day real life situation. The statement also mentions that "learning stimulates the brain and contributes to one's general sense of competence."

Finally, other avenues of cognitive enhancement such as social engagement must also be explored: as many elderly people are not motivated to learn new technology and follow complex commands while spending their time in front of computers. However, even if such brain training programs are scientifically validated and people are keen to use them, there are questions that still need to be addressed, such as how much time needs to be spent on such programs, how much time is practical or necessary to obtain optimum benefits in old age? Elderly people are encouraged to be active both physically and mentally as this will surely enhance their quality of life and assist in retaining their independence as they age. Due to the expanding interest in such programs, yet without any debate or validation studies concerning whether these programs are effective in preventing/delaying AD onset, the choice on the market continues to expand with the launching of more and more new programs. Economically, a delay of AD onset by 5 years can save $13.5 billion by 2020 and $67.5 billion by 2040 in Australia alone (AccessEconomics 2004). Therefore there is an urgent need for further clinical validation studies of

such programs, particularly those with clinical trials that have already shown cognitive benefits and are described as providing Level I and II evidence in this article.

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