Brain@home:

Moving and enhancing brain training for an active life

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Abstract: This statement describes an overview of the State of the Art in multi-domain cognitive computerized training to prevent the decline in cognitive functions of healthy elderly. Methodologies and outcomes of recent studies and reviews are summarized, providing useful indications for B@H research implementation.

Keywords: Aging, cognitive decline, cognitive functions, computerized cognitive training and VR

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1. Introduction

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The Brain@Home project aims to maintain/improve cognitive functions in healthy elderly, through engagement in brain training activities that promote independence and active ageing, thus preventing cognitive decline.

Main objectives are to:

- Develop a platform through which older persons can accede to a motivating, challenging and playful environment to engage in brain training and physical activity
- Build a hardware system using consumer-level portable devices for braintraining
- Construct a gaming platform for social-powered braintraining.
- Create a virtual community for older persons and caregivers, families, friends to share and disseminate knowledge and curiosities about interesting visits and travels
- Develop a system to store results and give access (web, mobile, etc) to this data and trends to users, caregivers and possibly to GP/family physicians.
- Examine improvements in different domains such as well being, quality of life, and cognitive status following the training program

Computerized cognitive training (CCT) will support the interventions. CCT received increasingly attention during the last few years in research and literature as valid tools for brain training and rehabilitation. Target users are cognitively healthy older adults aged over 65 years old who could face difficulties in everyday life activities due to age related cognitive decline.

This deliverable is the result of the Task 1.1 (WP 1) of the project, providing an overview of the state-of-the-art in multidomain cognitive training preventing the decline in cognitive performace of healthy older adults.

We will summarize the current literature about brain training in healthy ageing, by identifying:

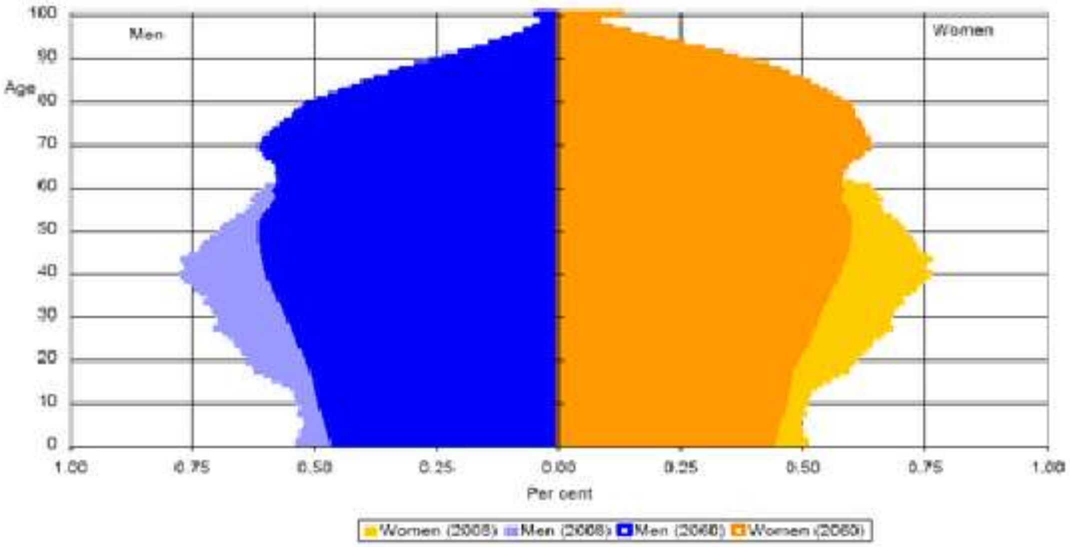
- specific cognitive functions to be trained and
- related cognitive exercise that could prevent decline.

Paragraph 1 will provide data about the incidence of ageing population. Paragraph 2 will describe the main cognitive functions most affected by ageing, as well as social and psychological changes that could be experienced by elderly people. Paragraph 3 will describe evidences provided from recent studies about the efficacy of computerized cognitive training (CCT) in healthy older population on cognition. Moreover, it will focus on the identification of studies concerning home-based cognitive training, by reporting data about population demographics, intervention design, study design and quality. Paragraph 4 will focus on the state-of-the-art of the use of Virtual Reality in studies on older adults.

2. Data about the incidence of ageing

Life expectancy at birth rose rapidly during the last century due to a number of factors, including reductions in infant mortality, rising living standards, improved lifestyles and better education, as well as advances in healthcare and medicine. As a result, the share of the population aged 65 years and over is increasing in every EU Member State. The population of the EU-28 on 1 January 2014 was estimated at 506.8 million. Young people (0 to 14 years old) made up 15.6 % of the EU-28's population, while persons considered to be of working age (15 to 64 years old) accounted for 65.8 % of the population. Older persons (aged 65 or over) had a 18.5 % share (an increase of 0.3 % compared with the previous year).

Population ageing is a long-term trend, which began several decades ago in Europe. This ageing is visible in the development of the age structure of the population and is reflected in an increasing share of older persons coupled with a declining share of working-age persons in the total population. The growth in the relative share of older people may be explained by increased longevity, a pattern that has been apparent for several decades as life expectancy has risen; this development is often referred to as 'ageing at the top' of the population pyramid (Eurostat).



Source: Eurostat, EUROPOP2008 convergence scenario

3. Cognitive and psychological changes associated with aging.

Aging is an irreversible process that causes, even in the absence of diseases, a decline of vital functions. With aging occur both biological and psychological changes. Regarding brain and mind, normal aging brain drives toward neuroanatomical and neurophysiological modifications and those changes account for alteration in cognitive functions. A growing number of studies have tried to correlate the biological changes with those behavioral; in particular, cognitive neuroscience is the field that try to make exact mapping between brain and behavior; nevertheless, these relations remain largely speculative due to the extreme complexity of both brain and cognition mechanisms. Moreover, changes in brain and cognition are not uniform across individuals: a question of great interest to aging researchers is what accounts for this variability. Many older people perform cognitive tasks in the same way as younger one, whereas some elderly show some kind of decline but enormous variability exists across individuals. Several characteristics have been established risks- and protective factors for cognitive decline. Those factors are biological, psychological and highly related to the lifestyle (Glisky E.L., 2007).

Interestingly, the brain has the ability to change its structure and its functionality depending on the activity of its neurons, for example related to stimuli received from the external environment, in reaction to traumatic injury, pathological changes and in relation to the individual's development process. This capacity, which is expressed in degrees and in different ways throughout the nervous system, is based on the so-called neuronal plasticity. Several studies have accumulated evidences regarding the presence, extend and nature of brain plasticity in elderly people.

Aging is associated with functional deficits in episodic memory, attention, language, visuo-spatial abilities, and executive functions (Optale et al., 2010). However, the basic cognitive functions most affected by age are attention, memory and executive functions. We provide an overview of the basic cognitive functions that show age-related decline, and some examples of tasks addressed to protect from decline.

3.1. Attention.

According to the great American psychologist William James (1890), attention is "the taking possession by the mind in clear and vivid form of one of the many objects or between the many possible trains of thought”. James highlighted two fundamental concepts related to the attention processes: firstly, the ability to select an object, therefore leaving out others. This capacity will be studied in detail through numerous subsequent studies and is called selective attention. Secondly, the James’s definition shows that the origin of the information may be external (in the environment) or internal (in terms of bodily sensations, states of mind, emotions etc.). It is clear how declines in attention can have broad-reaching effects on one’s ability to function adequately and efficiently in everyday life.

From a neuro-anatomical point of view, the attention is a property of a group of brain structures that are anatomically and functionally specific to the recognition of different types of stimuli. In humans, the activity of attentional mechanisms employs a set of different neural structures in which it is possible to recognize based on topographical criteria, almost two distinct sections. The first section is called “anterior attention system” and it comprises the cerebral cortex of the most medial part of the frontal lobe. The second section, the so-called “posterior attention system” is formed by the upper part of the midbrain from the rear portion of the thalamus and to the rear areas of the parietal cortex. The focus anterior attention system is involved in the recognition of stimuli that, in humans, involve a verbal activity. The posterior attention system is involved in the reaction of stimuli based on the visual recognition of the spatial location of an object and in the orientation abilities. These structures tend to act independently.

Different types of attention have been identified in a variety of ways by different researchers and theorists. However, the wide used division takes account of selective attention, divided attention, and sustained attention. *Selective attention* refers to the ability to attend to some stimuli while disregarding others that are irrelevant to the task. For example, in an everyday “visual search task”, people usually search in a shelf grocery (environment) the product to buy (target stimulus) that is surrounded by other similar products (distractors or non-target stimuli). The task is more difficult when the similarity of targets and distractors is high. Targets and distractors could be similar in perceptive features (i.e. products with similar packaging, colors, forms, positions etc.) or semantically similar i.e. when they belong to the same semantic category (fruits, vegetables, tools, etc.). *Divided attention* tasks require the processing of two or more sources of information or the performance of two or more tasks at the same time. For example, people may have to monitor stimuli at two different spatial locations, or they may be asked to make semantic judgments about visually presented words while simultaneously monitoring for the occurrence of an auditory presented digit. Humans regularly challenge these control processes when attempting to accomplish simultaneously multiple goals (i.e., multitasking), generating interference as the result of fundamental information processing limitations. It is clear that multitasking behavior has become ubiquitous in today’s technologically dense world, and substantial evidence has accrued regarding multitasking difficulties and cognitive control deficits in our aging population (Anguera 2013). For these reasons, divided attention has usually been associated with significant age-related declines in performance, particularly when tasks are complex. Moreover, the reaction times are usually crucial for multitasking: those abilities are associated with speeded information processing. As we age, we may notice that we require more time to respond to sensory input. There are many potential biological causes for our slower responses, including loss of myelin integrity, longer neural recovery times, decreased brain connectivity, and loss of neural synchrony (Anderson, 2013). Finally, *sustained attention* refers to the ability to maintain concentration on a task over an extended period. In general, older adults are not impaired on those tasks.

3.2. Memory.

Many older adults complain of increased memory lapses as they age, and a major focus of research has been to try to distinguish memory declines attributable to normal aging from those that are indicative of pathological aging, particularly dementia. In recent decades, there has been a significant increase in attention of the neurodegenerative diseases and several studies have highlighted the importance of early detection of such diseases that, by definition, have a sneaky and insidious onset. The largest increase of information provided by one party from both morphological and functional neuroimaging, and on the other by the greater understanding of the underlying neurobiological mechanisms, have allowed progress in this direction and the focus has increasingly concentrated towards the identification of prodromal stages degenerative diseases. From a clinical point of view, it is pivotal the early detection of prodromal phase of cognitive deficits in order to prevent the decline.

Like other human cognitive processes, memory is not a unitary process, rather it is made up of separate components with psychological, anatomical and physiological distinct characteristics and that can be functionally dissociated. Numerous observations have demonstrated the existence of a complex system of structures that interact each other but can separately work. For example, humans have a *short-term* and a *long-term storage*. These two complex systems differ in the amount of material that can retain, in the time within which the memory trace is lost, and finally in the modality of representation with which the information is stored. Usually, aging affect long-term memory, whereas short-term memory remains without impact. In the realm of long-term memory, the declarative memory refers *episodic memory* and *semantic memory*. Episodic memory refers to memory for personally experienced events that occurred in a particular place and at a particular time. It seems the most susceptible to brain damage and the most affected by normal aging. Semantic memory refers to one's store of general knowledge about the world, including information such as "George Washington was the first president of the United States" and knowledge of words and concepts. Such information is not tied to the space or time of learning, and its retrieval is generally prefaced with "I know." Finally, autobiographical memory involves memory for one's personal past and includes memories that are both episodic and semantic in nature. Usually, autobiographical memory shows a significant though gentle temporal gradient sparing childhood memories and selectively affecting ones that are more recent. Episodic memory problems experienced by older adults may involve deficient encoding, storage, or retrieval processes. Forgetfulness is a common complaint among older adults. Many situations (like start to talk about an argument and realize not to remember exact details, coming back home and suddenly blank on a familiar street name; find ourselves standing in the middle of the bedroom wondering what we went in there for etc) are common experiences in elderly and can be cause of concern and apprehension. There are many ways to improve memory skills, prevent memory loss, and protect from a decline.

We report some tasks that are demonstrated to be effective in elderly people in order to protect from memory loss. Encoding, immediate and delayed recall tasks using a list of words, pairs of words, prose memory and visual memory. It is possible to identify some variables that allow you to quantify the difficulty of an exercise, and that therefore will be varied related to the performance: first, the amount of proposed material. Second, the quality of the proposed material. Third, the retention interval between the encoding and the deferred reenactment of the material. Fourth, the quantity and quality of suggestions aimed at the retrieval: an important part of the rehabilitation process, as required by the Vanishing Cues technique consists in the gradual reduction of suggestions aimed at the retrieval, to make sure that the person face their own strategies that at first came from outside. The balance, timing and recording of aid given to the subject is one of the crucial points and yet difficult to quantify in the training process.

Finally, particular attention should be given to *working memory* as it forms a bridge between attentional abilities and mnesic ones. Many complex everyday tasks such as decision-making, problem-solving, and the planning of goal-directed behaviors require the integration and reorganization of information from a variety of sources. Working memory is the ability to active manipulation, reorganization, or integration of the contents.

3.3. Executive functions

Executive functions (EF) could be described, generally speaking, as a broad range of cognitive processes that control behavior. Thus, executive abilities exert control over cognitive functions (such as attention and memory) in terms of monitoring, cognitive flexibility, and inhibition. Executive functions are regulated by the frontal lobes, since executive deficits have been associated with damage to the most forward areas of the frontal lobes, but also with connected cortical and subcortical structures. Executive functions encompasses the ability to planning, monitoring and accomplish behaviors; the capacity to use and modify cognitive strategies during task performance and to adjust behavior as a function of new demands and external feedbacks (cognitive flexibility). Moreover, inhibitory control exerts by executive functions involves the abilities to prevent behavioral responses, which are inappropriate to the context. Therefore, EF exert an important role in all contexts in which individuals have to deal with novel situations, which could not be solved by relying on acquired experiences, but required instead formulation of new strategies. However, EF are also involved in updating previews experiences on the basis of current information.

It is clear the pivotal role of EF on everyday individuals functioning, considering their relevant influence on behavior. EF are considered high-level supervisory processes that control complex thoughts and behaviors. Individuals face everyday with new and complex situations, and they are always exposed to information that needs to be integrated in personal experience. Furthermore, EF are strictly related to others cognitive processes. Although executive functions, attention and memory are distinct theoretical constructs, they could be considered as somewhat interrelated. Specifically, executive functions exert an influence over attentive abilities through the supervisory attentional control (Norman & Shallice, 1986), which allows the subject to consciously direct attention towards different aspects of a complex situation. In such terms, the individual is able to manage and monitoring attentive resources throughout task execution. Thus, executive functions are closely linked to selective, divided and sustained attention.

Regarding memory abilities, executive functions are involved in strategic processes (retrieval and selection of information from memory). Another core aspect of EF regards working memory, which involves temporary storage and active manipulation of information (Baddeley & Hitch 1994). For example, working memory has a role in tasks in which individuals are required to use information to solve a problem.

Disorders of executive functions lead to a broad range of cognitive impairments and behavioural changes. Given that EF are necessary to several intentional activities, decline of EF abilities have inevitable consequences in everyday functioning, particularly when individuals have to face with novel complex situations. Difficulties could be experienced in the abilities to plan and modify sequence of actions, to solve problems, to provide judgements, to conceptualize and categorize.

There are many tasks, which are effective to improve executive functions. For example, tasks requiring the extraction of the main characteristics of stimuli (images or words) in order to categorize them adequately, involve abilities to abstraction and categorization. Some exercises, such as moving in to a maze, require involvement of visuo-spatial problem solving abilities in order to plan movements aimed to the reaching of the correct path and to predict consequences of actions. Also verbal problem solving capacities could be improved by means of task involving creativity, monitoring of behaviours, cognitive flexibility.

3.4. Psychological aspects.

The normal cognitive decline is intertwined to psychological changes, related to loss of social roles (usually represented by retirement) that may cause exclusion from opportunities and social roles. Social engagement has an important role: it refers to participation in social activities that maintain and create social ties and reinforce meaningful social roles (Berkman et al., 2000). Through social engagement, individuals construct social and emotional connections with the community. Psychology and sociology have tried to put forward theories that could clarify the phenomenon of elder psychological difficulties. Withdrawal from society, loss of goals and ambitions are very common phenomena. The elderly may perceive event such as retirement and widowhood as disengagement that permits with a gradual reduction of social roles covered in the past. To remain active, in terms of replacement and reconstruction of new roles at the expiration of the old ones, seems to drive towards a more adaptive, easiness and well-being conditions.

4. Computerized cognitive training in elderly: some evidences.

Many studies have provided evidences that cognitive interventions could provide cognitive gains in healthy older adults (Ball et al. 2002; Mahncke et al. 2006; Martin et al. 2011; Smith et al. 2009). Evidences about transfer effects of such gains are mixed, however some studies have provided results about transfers of cognitive improvements to new tasks which required processing different from the trained task (Basak et al., 2008; Bherer & Kramer, 2008; Mahncke et al., 2006; Smith et al., 2009). Particularly, computerized cognitive training (CCT) is a cost-effective alternative to traditional training programs (Kueider et al. 2012) and involves structural practice on standardized and cognitively challenging tasks (Clare et al., 2003). It has been argued that CCT have several advantages in terms of appealing interfaces, efficient delivery, content and difficulty adaptation to individual performances (Jak et al., 2013; Kueider et al., 2012).

Recently, Lampit, Hallock and Valenzuela (2014) published a systematic review and meta-analysis on the efficacy in enhancing cognitive performance in healthy older adults of Computerized cognitive training (CCT). The eligibility criteria for the review were subdivided in: i) Types of studies; ii) Types of participants; iii) Types of interventions and iv) Types of outcome measures.

Regarding the types of studies, peer reviewed articles reporting results from randomized controlled trials (RCTs) of the effects of CCT on one or more cognitive outcomes in healthy older adults were selected. Concerning participants, were included studies on participant aged ≥60 years and participants who lacked any major cognitive, neurological, psychiatric, and/or sensory impairment. Importantly, studies with Mild Cognitive Impairment (MCI) as an inclusion criterion were excluded. Eligible trials compared the effects of ≥4h of practice on standardized computerized tasks or video games with clear cognitive rationale, administered on personal computers, mobile devices, or gaming consoles, versus an active or passive control condition. Interventions that did not involve interaction with a computer were excluded. Finally, outcomes included performance on one or more cognitive tests that were not included in the training program, administered both before and after training. In particular, the review is limited to change in performance from baseline to immediately post-training on tests of global cognition, verbal memory, nonverbal memory, working memory, processing speed, attention, language, visuospatial skills and executive functions. Long-term outcomes, subjective measures (e.g. questionnaires), non-cognitive outcomes (e.g. mood, physical), imaging data, and activities of daily living outcome measures were excluded from the analysis.

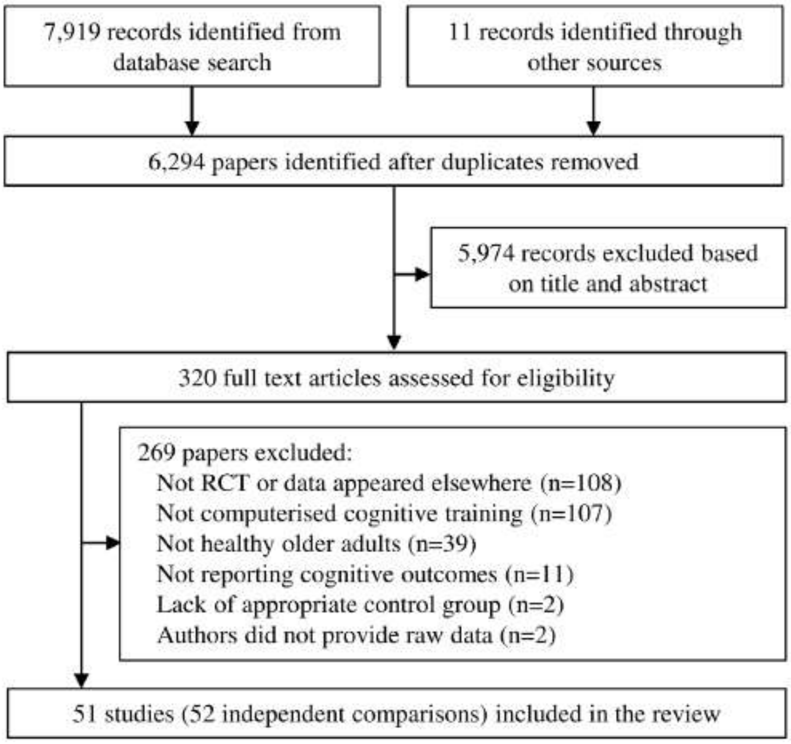


Figure 1. Summary of trial selection (Lampit et al., 2014)

A total of 51 articles included in the analysis of the review. Overall, the 52 datasets included in this review encompassed 4,885 participants (CCT, n=2,527, mean group size=49; controls n=2,358, mean group size=45) and reported 396 cognitive outcomes. Mean participant age ranged from 60 to 82 y, and about 60% of participants were women. The cohorts were largely from the US (N=24) or Europe (N=16), in addition to studies from Canada (N=3), Australia (N=2), Israel (N=1), China (N=1), Taiwan Special Administrative Region (N=1), Republic of Korea (N=1), and Japan (N=1). Type of CCT varied considerably across studies (Lampit et al. 2014, Table 1).

Twenty-four studies used multidomain training, nine used speed of processing (SOP) training, nine used WM training, six used attention training, and four were video games. Group (center-based) training was conducted in 32 (61.5%) of the studies, and 19 (36.5%) provided training at home.

The overall effect of CCT on cognition was small and statistically significant (g=0.28, 95% CI 0.18 to 0.39, $p < 0.001$). Twenty-three studies reported verbal memory outcomes.

The combined effect size was small and statistically significant (g = 0.16, 95% CI 0.03 to 0.29, p =0.02). Thirteen studies reported nonverbal memory outcomes. The combined effect size was small and statistically significant (g = 0.24, 95% CI 0.09 to 0.38, p =0.002). Twenty-eight studies reported working memory outcomes. The combined effect size was small and statistically significant (g = 0.22, 95% CI 0.09 to 0.35, p < 0.001). Thirty-three studies reported processing speed outcomes. The combined effect size was moderate and statistically significant (g = 0.31, 95% CI 0.11 to 0.50, p =0.002). Eleven studies reported attention-related outcomes. The combined effect size was small and non-significant (g = 0.24, 95% CI 20.01 to 0.50, p = 0.06). Twenty-nine studies reported outcomes with measures of executive functions. The combined effect size was negligible and statistically non-significant (g = 0.09, 95% CI 20.02 to 0.19, p = 0.096). Eight studies reported visuospatial outcomes. The combined effect size was small and statistically significant (g =0.22, 95% CI 0.15 to 0.29, p =0.01). Planned analyses of global cognition were not performed, as this outcomes was reported in only three studies.

In general, the review suggests some crucial aspects regarding some features that are associated with a better result regarding the efficacy of the treatments.

Domain-specific analyses found evidence of efficacy for nonverbal memory, processing speed, working memory, and visuospatial outcomes, but not for attention and executive functions. Analyses of verbal memory and executive outcomes were sufficiently powered, encompassing 23 and 29 trials. On the contrary, the therapeutic value of several commonly implemented CCT design choices come under question. For example, the review found that WM training alone was not effective in healthy older adults. The negative results for WM and executive outcomes likely represent deficits in the efficacy of CCT in healthy older individuals.

One of the attractions of home-based (often Internet-delivered) CCT is the ability to administer a customized and adaptive intervention in the individual's home, with potential for decreased implementation cost and the facility to target the frail and immobile. However, the analysis revealed a significant interaction between delivery setting and therapeutic outcome, whereby group-based delivery was effective and home-based delivery was not. The authors speculate about possible causes of this dissociation: potentially relevant practice variables when conducting group-based CCT include direct supervision by a trainer to help ensure adherence, treatment fidelity, and compliance, provision of motivational support and encouragement to master challenging tasks that are otherwise easy to avoid, problem solving of IT issues, and non-specific factors such as social interaction. The authors conclude that future studies may wish to investigate the value of combining initial group-based administration with more long-lasting home-based CCT, as well as test emerging technologies that allow remote clinical supervision and interaction via social media.

In order to deepen the status of the research about computerized cognitive home-based training in older adults, we summarize evidences provided by Lampit et al. (2014) by specifically selecting studies providing home-based training. To this aim, from a total of 52 studies, we chose only those providing home-based training programmes (i.e. studies in which training was delivered at home and participants underwent exercises autonomously). We considered studies published from year 2000. Thus, a total of 18 studies was selected (Table 1).

Overall, studies included 1545 participants (mean group size = 86). Mean participants age ranged from 60 to 82 years (females = 66%).

An active control group was used in 15 studies (83, 3%). According to Lampit et al. (2014), where studies presented data of both active and passive groups, only the active control group was used as a comparison to the intervention group. The remaining 3 studies used a passive control condition.

Lampit et al. (2014) used the Physiotherapy Evidence Database (PEDro) scale to assess the methodological quality and reporting of RCTs. Maximum PEDro score for this study was 9 (given that authors did not consider two items in the PEDro scale, which referred to blinding of therapists and participants). Overall, the average PEDro score of our dataset was 6.4/9 (SD = 1.42). Moreover, the authors assessed risk of bias for each study using the items recommended in the Cochrane's Collaboration's risk of bias tool (Higgins & Green, 2011) (note that authors considered only blinding of assessors to determine risk of bias in the blinding item due to impracticability of the blinding of therapists and participants in CCT trials).

With regard to the type of intervention, thirteen studies used multidomain CCT programmes, four used working memory training and one used attention training.

Five studies administered 3-4 training sessions per week; ten studies trained participants 5 times per week and three studies trained subjects more than 5 times per week. Session length ranged from 15 to 60 minutes each.

In Table 1 we reported the characteristics of home-based studies.

Total number of CCT sessions.
Length: Session length (minutes)Sessions/week: Number of sessions per week.
PEDro Score: Physiotherapy Evidence Database.
Ns: not specified.
*Anderson: MOCA score (1-30)
*Barnes: Converted from 3MSE to MMSE
*Bozoki: St.Louis University Mental Status Exam (1-30)

Table 1

Authors	Year	Journal	N	Mean age	Age range	Females (%)	MMSE score	CCT type	Program	Dose	Sessions	Length	Sessions/ week	Control	Control intervention	Risk of bias	PEDro score
Ackerman	2010	Psychol Aging	78	60.7	50-71 (final sample)	46.2		Multidomain	Wii Big Brain Academy	20	20	60	5	Active	Readings about 4 different topic domains	Low	4
Anderson	2013	Proc Natl Acad Sci U S A	67	63.0	55-70 final sample	58.2	27.4 *	Multidomain	PS Brain Fitness	40	40	60	5	Active	Educational DVDs (art, science, history, etc.) and answering multiple choice questions	High	6
Anguera	2013	Nature	31	65.8	60-85 (all groups)	64.5	≥ 26	Attention	In-house program	12	12	60	3	Active and passive	Active controls: matched for all factors except the presence of interference	High	5
Barnes	2013	JAMA Intern Med	63	74.3	ns	60.3	28.4*	Multidomain	PS Brain Fitness+InSight	36	36	60	3	Active	MA control: Educational DVDs (art, history, science) EX control: stretching	Low	8
Boot	2013	Front Psychol	40	72.5	54–86 (initial sample)	61	29	Multidomain	Brain Age 2 (Nintendo DS)	60	60	60	5	Passive	ns	High	7
Bozoki	2013	Arch Gerontol Geriatr	60	68.9	ns	58.4	27.3*	Multidomain	In-house program	30	30	60	5	Active	Online activities that simulated the look and feel of the games but with low level interactivity and no calibration of difficulty	High	5
Brehmer	2012	Front Hum Neurosci	45	63.8	60-70 (final sample)	60		WM	Cogmed	9	23	26	4	Active	Same CCT program as EG, but task difficulty remained constant at the same low starting level	High	8
Colzato	2011	Front Psychol	60	67.6	ns	46.7	28.8	Multidomain	In-house program	25	50	30	7	Active	Watching documentaries (politics,music,tourism,history) followed by multiple choise questions	High	5
Mahncke	2006	Proc Natl Acad Sci U S A	123	70.9*	60-87 (at posttraining)	50*	≥ 24	Multidomain	PS Brain Fitness	40	40	60	5	Active	Watching and listening to DVD-based educational lectures and other programs	High	7

Table 1

Authors	Year	Journal	N	Mean age	Age range	Females (%)	MMSE score	CCT type	Program	Dose	Sessions	Length	Sessions/ week	Control	Control Intervention	Risk of bias	PEDro score
McAvinue	2013	Front Aging Neurosci	36	70.4	64-79 (initial group)	63.9	28.1	WM	In-house program	14.75	25	35	5	Active	Non-adaptive version of the training program, which maintained all exercises at the easiest level	High	4
Miller	2013	Am J Geriatr Psychiatry	69	81.9	ns	67.7	28	Multidomain	Dakim Brain Fitness	15	40	23	5	Passive	Participants were instructed not to engage in any kind of cognitive training	High	6
Nouchi	2012	PLoS ONE	28	69.1	ns		28.5	Multidomain	Brain Age (Nintendo DS)	5	20	15	5	Active	Tetris (Nintendo)	Low	7
Peretz	2011	Neuroepidemiology	155	67.8	ns	62	29.0	Multidomain	CogniFit	16	36	25	3	Active	Computer games program with 12 classic computer games that engage cognitive processing (e.g. tennis, tetris, puzzles, snake). Similar to EG but no adaptive training features	Low	8
Richmond	2011	Psychol Aging	40	66.0	60-80 (recruited)	80	29.0	WM	In-house program	10	20	30	4	Active	Trivia learning regime (funtrivia.com, quizzles with low WM load)	High	6
Simpson	2012	Educ Gerontol	34	62.3	53-75 (final sample)	52.9	≥ 27	Multidomain	MyBrainTrainer	7	21	20	7	Active	Playing solitaire on the computer	High	7
Smith	2009	J Am Geriatr Soc	487	75.3	age-stratified treatment group (20% 65–69, 40% 70–79, 40% 80)	52.4	29.2	Multidomain	PS Brain Fitness	40	40	60	5	Active	DVD-based educational programs on history, art, and literature (quizzes after each training session)	Low	9
van Muijden	2012	Front Hum Neurosci	72	67.6	60-77	44.4	28.8	Multidomain	In-house program	25	49	30	7	Active	Online documentaries and answering quiz questions	High	6
von Bastian	2013	Mem Cognit	57	68.5	62-77	40.4	≥ 25	WM	In-house program	16	20	27	5	Active	Tasks with low working memory demands.	Low	7

Dose: Total number of training hours. Sessions: Total number of CCT sessions.
Length: Session length (minutes)Sessions/week: Number of sessions per week.
PEDro Score: Physiotherapy Evidence Database.
Ns: not specified.
*Anderson: MOCA score (1-30)
*Barnes: Converted from 3MSE to MMSE
*Bozoki: St.Louis University Mental Status Exam (1-30)

5. The use of Virtual Reality in studies on older adults populations

A growing number of studies have used Virtual Reality (VR) with different aims, from the development of assessment methods based on VR environments, to rehabilitation and training uses aimed to improve both motor and cognitive abilities in clinical ageing populations. Effectively, VR encompasses several application fields: medical-psychological (e.g. phobias), motor-function rehabilitation (post brain damage), assessment of navigational skills (Cushman & Duffy, 2008) cognitive training in neurological populations (Man et al., 2012; Optale et al., 2010) .

Concerning the literature about VR uses in clinical ageing population, some studies used VR to investigate the possibility of improvements in memory in older adults with memory deficits (Optale et al. 2010) and in adults with questionable dementia (Man et al. 2011), since VR systems has immersive and interactive therapeutic possibilities (Optale et al. 2010).

To the best of our knowledge, few studies implement cognitive training with the use of VR in healthy ageing population. Some studies involved the use of exergames such as Cay Anderson-Hanley at al. (2012) who examined the impact of a cyberciclying intervention over cognition, as compared to traditional one. They provided preliminary evidence that exergaming can lead to greater cognitive benefıt than traditional exercise alone. Eggenberger et al. (2015) used VR in a combined cognitive-physical training program in a sample of healthy adults, showing executive functions benefit improvements from simultaneous cognitive–physical training compared to an exclusively physical intervention.

However, few VR studies specifically targeted interventions to the enhancement of cognitive functioning in healthy ageing. As an example, the study of Legault et al (2013) uses VR to assess older adults abilities and to improve tracking speed, by means of a dynamic, immersive VR environment. Older adults (mean age 66 y.o.) underwent a perceptual cognitive training (3DMOT-type task, multiple object training) which requires to simultaneously track multiple moving items among many. Analysis of older adults performance in comparison with younger revealed that both groups obtain similar training gains, thus suggesting that perceptual-cognitive training can reduce age-related effects, since older adults showed learning function as younger adults.

Differently, some studies use a non-immersive type of Virtual Reality environment. Jebara et al. 2014 implemented non-immersive virtual reality as a tool to investigate the enactment effect on episodic memory in complex situations in a sample of healthy 65y.o. (mean age) adults. Specifically, authors tested the influence of action, in terms of the degree of interaction with the environment (active or passive navigation) and the source of itinerary choice (self or externally imposed), on episodic memory (EM) encoding. Participants have to navigate in a virtual town while they have to memorize all the events they experienced. Different conditions was developed by manipulating the amount of active navigation and decision of the itinerary. Authors then compared older adults and young adults performances on immediate and delay verbal and visuo-spatial memory tests (free recall, visuospatial recall, recognition) and found benefits of active navigation on episodic memory performance regardless of the age, suggesting that active navigation is beneficial to boostepisodic memory in aging.

Rose et al. (2015) instead uses non-immersive VR in a prospective memory (PM) training which required the use of VirtualWeek computer game, which is a computerized game that simulates going through the course of a day and remembering to perform intended actions at the appropriate times. Participant were trained in 12, 1h sessions over 1 month. Performance of older adults (mean age 67.4) was compared to an active (music training) control and a passive control group (no contacts). Authors found an enhancement of prospective memory ability following training relative to controls, suggesting PM plasticity is preserved in older adults. Moreover, training produced transfer to real-world outcomes including improvements in performance on real-world prospective memory.

6. Conclusions and indications.

Aging is associated with cognitive decline with functional deficit in episodic memory, attention, language, visuo-spatial abilities, and executive functions (Optale et al., 2010). With aging both biological and psychological changes occur, related to loss of social roles, usually represented by retirement that may cause exclusion from opportunities. Age-related cognitive impairments interfere with everyday life of healthy elderly leading to difficulties to cope with different tasks and situations.

Concerning the target users, given that no evidences were found about gender related differences in cognitive training in older adults, brain training interventions will be targeted to healthy ageing populations over 65 years old, without specific investigations about gender distribution.

Evidences from the literature lead us to focus on those cognitive functions most affected by age, which are: attention, memory and executive functions.

Some specific tasks are demonstrated to be effective in elderly people in order to protect from memory loss, for example those requiring encoding, immediate and delayed recall tasks using different list of words, pairs of words, prose memory and visual memory.

Moreover, visual search tasks and tasks requiring to monitor more than one source of information at the same time are generally used to stimulate selective and divide attention, respectively; exercise of mental reasoning and problem solving are targeted to executive functions abilities.

Analysis of the literature revealed that Computerized Cognitive Training (CCT) in older adults provides improvements in cognitive functioning. Specifically, a recent review of Lampit and colleagues (2014) suggested some important aspects about CCT in healthy older adults that should be taken into account for the study design. With regards to the domains trained, evidences suggest efficacy for nonverbal memory, processing speed, working memory and visuospatial abilities. Results seem to suggest less efficacy concerning attention and executive functions. However, we aim to study cognitive training including attentive and executive domains, which are interrelated one to each other and strongly involved in the ecological approach of B@H. Actually, the project aims to train functions involved in everyday activities.

Results from this review seem to suggest that home-based trainings are less effective than group-based training. Authors speculated that potentially relevant variables when conducting group-based CCT include direct supervision by a trainer to ensure adherence and compliance, provision of motivational support and encouragement, problem solving of IT issues, and non-specific factors such as social interaction. Such evidences lead us to provide some considerations about specific aspects of the CCT training:

1- the importance of combining an initial group-based treatment at the hospital with a following continuation of the training at home. The aim of this design is to integrate the initial approach of the trainer in the clinical setting with a more long-lasting home-based CCT.
2- The need of a remote clinical supervision, by maintaining/enhancing interactions between the trainer and the patient, with formal contacts. We could suggest at least one formal monitoring supervision per week, reinforced by some other possible informal contacts through the platform.
3- The advantage that the training may provide to the older adults, by developing a social environment in the platform where participants could interact. The idea is to let them share results, thus taking into account the need to support and maintain social engagements in healthy elderly.

Furthermore, results from this study provide specific evidences about the importance of correct CCT dose, suggesting about 45 min of stimulation no more than three times per week. Therefore, 36 sessions of CCT intervention may be provided, covering a period of about three months.

These considerations will support the consortium in the next tasks of the WP 1, focused both on the cognitive exercise design and on the research study protocol.

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