Neuroscience and Biobehavioral Reviews 44 (2014) 206–220

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

A review of physical and cognitive interventions in aging

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ARTICLE INFO

Article history:
Received 17 December 2013
Received in revised form 14 March 2014
Accepted 25 March 2014
Available online 4 April 2014

Keywords:
Cognitive health
Aging
Physical training
Cognitive training
Neuroplasticity
Neuroimaging
Functional brain connectivity
Neurophysiology
Interventions
Exergames
Brain health promotion

ABSTRACT

Maintaining a healthy brain is a critical factor for the quality of life of elderly individuals and the preservation of their independence. Challenging aging brains through cognitive training and physical exercises has shown to be effective against age-related cognitive decline and disease. But how effective are such training interventions? What is the optimal combination/strategy? Is there enough evidence from neuropsychological observations, animal studies, as well as, structural and functional neuroimaging investigations to interpret the underlying neurobiological mechanisms responsible for the observed neuroplasticity of the aging brain? This piece of work summarizes recent findings toward these questions, but also highlights the role of functional brain connectivity work, an emerging discipline for future research in healthy aging and the study of the underlying mechanisms across the life span. The ultimate aim is to conclude on recommended multimodal training, in light of contemporary trends in the design of exergaming interventions. The latter issue is discussed in conjunction with building up neuroscientific knowledge and envisaged future research challenges in mapping, understanding and training the aging brain.

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http://dx.doi.org/10.1016/j.neubiorev.2014.03.019
0149-7634/

1. Introduction

Growing older, may lead to wiser states of mind, but it may also lead to cognitive decline that interferes with our daily routines. Physical and cognitive interventions in elderly adults have challenged this deteriorating process and seem to be responsible for the induced neural change. These interventions target group (*elderly individuals, aged > 60 years old*) exhibits an augmented representation in the general population of western societies as a result of life expectancy increase along with a downwards trend in birth rates. The percentage of this group of people will reach 20% in 2025 and at least 30% in 2060 within the general population (Atchley and Barusch, 2004; FUTURAGE project, 2011). However, the physical and cognitive deterioration that occurs during aging poses challenges (social and financial) such as the need for social integration, as well as the financial burden resting on the public health systems which is associated to age-related disease, disability and dependency (Hertzog et al., 2008). Understanding age-associated changes in cognition is challenging and in proximity to the cognitive, mental and physical health issues of the elderly individuals.

Memory is probably the first of cognitive functions to exhibit various patterns of decline, i.e. episodic memory (Buckner, 2004; Grady, 2012; Hedden and Gabrieli, 2004), metamemory (Woodruff-Park, 1997), and the ability to retrieve both verbal and non-verbal material (Davis et al., 2003; Grady et al., 2006). Despite the fact that implicit memory is preserved in healthy older adults, in elders with Mild Cognitive Impairment (MCI) and even in Alzheimer's disease (AD) patients (Ballesteros and Reales, 2004; Ballesteros et al., 2012; Mitchell and Bruss, 2003; Wiggs et al., 2006), processing speed (Charness, 2008), as well as, attentional control and working memory, which fall under the umbrella term *executive functions* (Andrés and Van der Linden, 2000; Grady, 2012; Hahn and Kramer, 1995) exhibit robust declines. These deteriorations are associated to age-related changes at the neural (structural and functional) level as well. For instance, structural changes in the striatum and the prefrontal cortex such as reduced brain volume and thinning of the cortex are commonly observed in the aging brain (Haug and Eggers, 1991; Raz et al., 2004). Moreover, reduced connectivity between frontal and posterior areas of the human brain may account for the decline in attentional function observed with age (Grady, 2012). Nevertheless, it is plausible that the synaptic connectivity, and not the neural loss, is responsible for the age-related cognitive decline (Duan et al., 2003; Morrison and Baxter, 2012).

An adequate cognitive status and physical well-being play crucial roles in daily activities such as driving and managing finances, and adequate work performance (Callahan et al., 2003; Charness, 2008; Charness and Czaja, 2006; Drag and Bieliauskas, 2010; Wegman and McGee, 2004; for a meta-analysis of physical performance and daily functioning see Heyn et al., 2008). Consequently, the independent living promotion as well as the participation of senior citizens in the job market and society, call for evidence-based interventions focused on maintaining cognitive function and physical well-being during the silver ages (Ferri et al., 2005). At the same time, a greater integration between the cognitive functions and related brain areas should be envisaged in a multi-disciplinary way in view of emerging pilot studies and advances in structural and functional imaging, brain networks, electrophysiological evidence and multi-level modeling.

This review summarizes recent work in the efficacy of non-pharmaceutical interventions to enhance cognitive performance and prevent or at least slow down the age-related cognitive decline. We discuss several of the most pressing issues with respect to the use of cognitive and physical training to promote healthy aging, in an attempt to summarize and sketch the likely neurobiological mechanisms responsible for the positive effects of such type of interventions. Evidence is drawn from studies focusing on neuropsychological evaluation, but also structural and functional neuroimaging approaches and associated interpretations. Our review also highlights recent approaches with functional brain connectivity work, which is considered as an emerging discipline for the forth-coming research agenda in healthy aging and the study of the underlying cognitive decline mechanisms across the life span. The emerging picture is complemented by evidences from electrophysiological recordings and neurobiological mechanisms. Based on all of these, the ultimate aim of this review is to focus on recommending combined cognitive and physical training, and the emergence of contemporary trends in the design of *exergaming* interventions. The phrase *exergaming* or *exergames* derives from the combination of 'exercise' and 'games' and relates to computer games that involve deliberate intense physical activity (Mueller et al., 2003). The latter issue is discussed in view of the aforementioned neuroscientific evidence and the envisaged future research challenges in mapping, understanding and training the aging brain.

1.1. What is cognitive intervention?

The terms *cognitive training, mental activity, cognitive stimulation, cognitive rehabilitation and cognitive exercise* have interchangeably referred to the general notion of cognitive intervention (Buschert et al., 2010; for reviews see Clare and Woods, 2004; Gates and Valenzuela, 2010).

Clare and Woods (2004) have attempted to clarify the terminology associated with cognitive interventions, by proposing two main categories; *cognitive stimulation/reality orientation* and *cognitive training/cognitive rehabilitation*. The former category may include procedures designed to provide general cognitive stimulation and enhance people's social skills. This category of intervention usually consists of structured group activities and discussions, and is theoretically driven by the use-it-or-lose-it (Hultsch et al., 1999) and the cognitive-enrichment theories (Hertzog et al., 2008). Namely, this category does not target a specific cognitive process, but rather it involves activities that require general cognitive resources. The latter category refers to interventions designed to train specific cognitive processes (Clare and Woods, 2004), and are based on theories of neuroplasticity (Buschert et al., 2010; Mahncke et al., 2006b; Pascual-Leone et al., 2011).

There is an ongoing debate regarding the effectiveness of the aforementioned categories of cognitive interventions as a counter

Table 1
Main characteristics of cognitive rehabilitation versus cognitive training.

Intervention types	Cognitive rehabilitation	Cognitive training
Target population	People with cognitive deficits	Healthy individuals and people with cognitive deficits
Intervention approach	Biopsychosocial	Cognitive
Purpose	Improve daily functioning and the patient's quality of life	Indirectly improve user's quality of life by enhancing cognitive function
Individualization level	High	Low. It is designed for groups of people with similar characteristics
Administration	Health professionals and care-givers. Individual sessions	Self-administered Individual and group sessions

measure for cognitive decline (Hertzog et al., 2008; Salthouse, 2006). However, a common ground among most researchers is that the cognitive training/cognitive rehabilitation intervention exhibits positive effects with properly designed experimental controlled studies. In this review we will focus on this specific category (see Table 1). *Cognitive rehabilitation* can be precisely defined as a holistic biopsychosocial approach (McLellan, 1991) that takes into account the person's emotional, cognitive and social deficits which stem from disease or injury (Prigatano, 1999). This type of intervention improves daily functioning, and the patient's quality of life (Wilson, 1997). On the other hand, *cognitive training*, also termed as *cognitive exercise* (Gates and Valenzuela, 2010) can be defined as a standardized set of exercises (Clare and Woods, 2004; Martin et al., 2011), which involves repeated practice and increasing levels of difficulty, and taps into specific cognitive functions.

Cognitive rehabilitation is usually coined for interventions that target a pathological population with cognitive deficits; cognitive training/exercise is used in interventions that target both healthy people and patients with cognitive deficits (Clare and Woods, 2004). The level of individualization differentiates among these two types of intervention. The cognitive rehabilitation follows a highly individualized approach, which demands the involvement of health professionals, and care-givers (Wilson, 1997). In cognitive training, the only individualized aspect is the difficulty of the exercises, which is automatically adjusted according to the participants' performance. Consequently, cognitive training is a more flexible approach with both individual (Bernhardt et al., 2002; Koltai et al., 2001; Moore et al., 2001) and group participation (Davis et al., 2001; Farina et al., 2002). The involvement of care-givers and health professionals in cognitive training is not a necessary condition/prerequisite (Quayhagen et al., 2000).

1.2. What is physical intervention?

Physical training interventions usually involve quite a wide range of activities (Colcombe and Kramer, 2003). For the World Health Organization (WHO), physical activity for elderly individuals includes "recreational or leisure-time physical activity, transportation (e.g. walking or cycling), occupational (if the person is still engaged in work), household chores, play, games, sports or planned exercise, in the context of daily, family, and community activities" (WHO, 2010). According to the definitions provided by the Institute of Medicine and the American College of Sports Medicine (ACSM) though, physical activity refers to "body movement that is produced by the contraction of skeletal muscles and that increases energy expenditure" while exercise "refers to planned, structured, and repetitive movement to improve or maintain one or more components of physical fitness" (Chodzko-Zajko et al., 2009). Table 1 familiarizes the reader with the utilized terminologies and summarizes the recommendations for each type of physical activity from the two aforementioned main sources, namely, the WHO and the ACSM.

The benefits of physical activity and exercise on the body have been well-established by research (Rooney, 1993) and are nowadays much promoted by associations and agencies working with elderly individuals, as well as, governments and world organizations (e.g. the World Health Organization (WHO), 2010). The relationship between physical activity and mental health or cognition has only recently been strongly emphasized (Fratiglioni et al., 2004; Van Gelder et al., 2004). The key question, which remains to be answered, is the causality of this relationship, namely whether decreased physical activity that precedes cognitive decline could be either the cause of the decline per se or be the result of the prodromal cognitive impairment (Eggermont et al., 2006). In order to explore this causality, but also intervene non-pharmacologically, intervention studies incorporating physical activity and exercise have been deployed in numerous settings and under different conditions. Most interventions execute one (e.g. aerobic when focusing on cardiovascular fitness) or combinations of more than one categories (see Table 2, e.g. aerobic exercise training (AET) and resistance exercise training (RET) plus balance). The main parameters to control within such an intervention are the duration of training (how long the actual training lasts), the length of exercise intervention (how many weeks/months) and the outcome measure tools (e.g. cardiovascular improvement, senior fitness test, etc., Colcombe and Kramer, 2003).

During the past decade though, a renewed interest was noticed in using technological assistance, including user interface feedback loops, so as to physically (but also mentally) train healthy elderly individuals. Researchers and practitioners in the field of aging introduced elderly audiences to cognitive training and stimulation games which are now enjoyed within the context of computer and/or game consoles; and in a further step toward *mens sana in corpore sano*, to provide physical stimulation or rehabilitation exercises in the relaxed form of *exergaming* (Bamidis et al., 2011; Billis et al., 2010). The games that assist in achieving and improving spiritual and physical fitness have shaped a newer type of interventions, the so-called *Silver Gaming Interventions.*

Numerous recent studies have investigated how exergaming/silvergaming can be specifically applied to the needs of seniors, and the impact of such programs on specific issues as diverse as intergenerational interactions (Khoo et al., 2010) and geriatric depression (Rosenberg et al., 2010). The majority of these studies though have yet featured very small numbers of participants, in focused pilot studies and focus group environments. This line of research is certainly growing though and has been the subject of recent meta-analyses (Powers et al., 2013) and systematic reviews (Kueider et al., 2012).

2. Neuropsychological evidence for benefits of cognitive and physical interventions on brain health

In this section, we revisit evidence for the beneficial effects of each intervention, i.e. cognitive and physical. In line with the Ancient Greek proverb *Healthy mind in a healthy body*, the combined physical and cognitive training researches the separate and the combined effects of this intervention on cognitive performance of healthy elderly individuals. Although a limited number of studies analytically compare the effects of each training type (i.e. cognitive or physical activity) with those of the combined training (Fabre et al., 2002; Oswald et al., 2006; Shatil, 2013) research

Table 2
Definitions and types of physical activity together with recommended guidelines from WHO and ACSM.

Source	Type of physical activity	Recommendations
World Health Organization (WHO)	Aerobic physical activity	150 min of moderate-intensity throughout the week, or 75 min of vigorous-intensity or an equivalent combination (of moderate- and vigorous-intensity activity)
	Balance enhancement/prevention of falls	3 or more days per week
	Muscle-strengthening activities	Should be done involving major muscle groups, on 2 or more days a week
American College of Sports Medicine (ACSM)	Aerobic exercise training (AET) refers to exercises in which the body's large muscles move in a rhythmic manner for sustained periods	Frequency: At least 2 days/week
	Resistance exercise training (RET) is exercises that cause muscles to work or hold against an applied force or weight	Frequency: At least 2 days/week
		Intensity: Between moderate: (5–6) and vigorous: (7–8) intensity on a scale of 0–10
		Type: Progressive weight training program or weight bearing calisthenics (8–10 exercises involving the major muscle groups of 8–12 repetitions each), stair climbing, and other strengthening activities that use the major muscle groups
	Flexibility exercise refers to activities designed to preserve or extend range of motion (ROM) around a joint	Frequency: At least 2 days/week
		Intensity: Moderate (5–6) intensity on a scale of 0–10
		Type: Any activities that maintain or increase flexibility using sustained stretches for each major muscle group and static rather than ballistic movements
	Balance training refers to a combination of activities designed to increase lower body strength and reduce the likelihood of falling	Because of a lack of adequate research evidence, there are currently no specific recommendations regarding specific frequency, intensity, or type of balance exercises for older adults. However, the ACSM Exercise Prescription Guidelines recommend using activities that include the following: (1) progressively difficult postures that gradually reduce the base of support (e.g., two-legged stand, semi-tandem stand, tandem stand, one-legged stand), (2) dynamic movements that perturb the center of gravity (e.g., tandem walk, circle turns), (3) stressing postural muscle groups (e.g., heel stands, toe stands), or (4) reducing sensory input (e.g., standing with eyes closed)

production and, therefore, scientific evidence in this direction is growing rapidly over the last few years.

2.1. Beneficial effects of cognitive interventions

The protective effect of complex mental activity for dementia observed in prospective observational studies (Valenzuela and Sachdev, 2006) can infer causality when translated into experimental designs. A large body of research examining diverse cognitive interventions has met this challenge. There is growing evidence acknowledging the cognitive benefits of *multimodal interventions*. Multimodal interventions generally consist of "complex interventions or lifestyle changes, and may include a social component as well as a cognitive one" (Lustig et al., 2009). Playing strategy video games (Basak et al., 2008; Glass et al., 2013), acting (Noice et al., 2004; Noice and Noice, 2009), performing problem solving in social contexts (Stine-Morrow et al., 2008), taking a computer course (Klusmann et al., 2010) or receiving multiple cognitive stimulation (Tranter and Koutstaal, 2008) has resulted in improved cognitive performance in controlled trials. Note that other novel interventions such as the use of a user-sensitive home-based Information and Communication Technology (ICT-based home environments) and networking to avoid social isolation improve cognitive performance and aspects of wellbeing in older adults (Waterworth et al., 2012). Though promising, these interventions stimulate cognitive activity in a broader sense rather than specifically tackling certain cognitive functions. In contrast, cognitive exercise (Gates and Valenzuela, 2010) *ability training* (Ranganath et al., 2011) or *process-based training* (Lustig et al., 2009) – have addressed specific cognitive functions. Cognitive exercise uses repeated high-intensity practice of theory-driven tasks which adapt in difficulty to user performance (Gates and Valenzuela, 2010).

The rationale is that neuronal processes are plastic i.e., have the potential to rewire and reorganize (Mahncke et al., 2006a; Smith et al., 2009; for a review see Chklovskii et al., 2004). Thus, neuronal processes may be improved in their efficiency by structured intensive training. An additional assumption is that trained processes underlie higher-order cognitive functions and everyday activities. Hence, training-induced enhancement of those processes is not only expected to improve trained tasks but also to transfer to superficially unrelated tasks and everyday functions. Recent demonstrations of such a training-induced transfer have been made available for intelligence tests (Jaeggi et al., 2008, 2010; Karbach and Kray, 2009; Schmiedek et al., 2010; Schweizer et al., 2011), visual and verbal episodic memory tests (Buschkuehl et al., 2008; Schmiedek et al., 2010; Zelinski et al., 2011), reading (Chein and Morrison, 2010; Loosli et al., 2012), driving (Edwards et al., 2009) as well as performance and self-report measures of instrumental activities of daily living (Ball et al., 2007; Willis et al., 2006).

2.2. Beneficial effects of physical interventions

Prospective observational studies robustly demonstrated that physically active people have a reduced risk of cognitive decline

(Sofi et al., 2011) and dementia (Hamer and Chida, 2009). The positive association between aerobic exercise or cardiovascular fitness and executive functions (Barnes et al., 2003; Colcombe and Kramer, 2003; Gordon et al., 2008) has been considered one of the most consistent findings. However, an unequivocal causal relationship can only be established by research designs which manipulate physical activity. In the most recent meta-analysis by Hindin and Zelinski (2012), aerobic exercise interventions have shown moderate to medium-sized effects on executive function and memory. Additionally, resistance training has improved executive function (Liu-Ambrose et al., 2010) and memory (Cassilhas et al., 2007). Consequently, combined aerobic and resistance exercise trainings result in the most beneficial effects on cognition (Colcombe and Kramer, 2003; Smith et al., 2010).

This raises questions regarding the mechanisms responsible for cognitive augmentation. Multiple pathways have been proposed, yet most of them remain far from being understood. Beside the reduction of risk factors for cognitive decline (e.g. cardiovascular disease, insulin resistance, hypertension and inflammation (Carroll and Dudfield, 2004; Pedersen, 2006) or amyloid plaque (Adlard et al., 2005), exercise-induced molecular cascades affecting neuronal plasticity may play a role, especially for short-term exercise effects (for reviews see Cotman et al., 2007; Dishman et al., 2006; Lista and Sorrentino, 2010). The latter pathway is primarily based on findings from basic research with animal models, which studies the brain microenvironment and how physical and cognitive functions (of aged mice) can be restored by neuronal integrity that may be mediated by growth/neurotrophic factors (Park et al., 2013a).

On the behavioral level this is reflected in increased learning and memory performance (Lista and Sorrentino, 2010). The combination of aerobic and resistance exercise may be most potent in enhancing neuronal plasticity because different neurotrophins are presumably stimulated by each exercise type. While aerobic exercise has been shown to up-regulate the brain derived neurotrophic factor (BDNF; Neeper et al., 1995), resistance exercise appears to stimulate immune-globulin factor 1 production (Cassilhas et al., 2007). Both neurotrophins are thought to facilitate different plasticity mechanisms like neurogenesis, synaptogenesis and angiogenesis through partly interacting pathways (Cotman et al., 2007).

Human studies are consistent with the neurotrophin-induced plasticity enhancing pathways (Burdette et al., 2010; Cheeran et al., 2008; Cirillo et al., 2009; Colcombe et al., 2004, 2006; Erickson et al., 2010, 2011; Pereira et al., 2007; Voss et al., 2010). For example, a study by Erickson et al. (2011) indicates that exercise increases the volume of the hippocampus, a region relevant for learning and memory. This increase was in turn positively associated with changes in serum levels of BDNF and in spatial memory performance. Taking these outlined findings a step further leads to the question of how a combination of exercise-enhanced plastic potential with cognitive exercise programs aiming at an induction of positive plastic change might jointly impact cognition.

2.3. Combining cognitive and physical exercise

It has been proposed that the physical and cognitive exercise might interact to induce larger functional benefits (Hötting and Röder, 2013; Kempermann et al., 2010; Kraft, 2012; Lustig et al., 2009). Several interventional studies yielded consistent results in line with this hypothesis by demonstrating larger benefits on cognitive test performance for combined physical and cognitive activity than for each activity alone (Anderson-Hanley et al., 2012; Maillot et al., 2012; Mortimer et al., 2012). Those studies comprise an observational cross-sectional (Eskes et al., 2010), a longitudinal (Karp et al., 2006), as well as two controlled interventional designs (Fabre et al., 2002; Oswald et al., 2006). For example, Oswald et al. (2006) allocated elderly individuals ($n = 375$) to six groups including a control ($n = 103$), a cognitive intervention alone ($n = 57$), a physical exercise alone ($n = 32$) and a combined cognitive plus physical exercise group ($n = 32$). In contrast to all other groups, the combined cognitive plus physical exercise group showed large and highly significant effects on cognitive function as long as 5 years after the 30 session training intervention. Despite the above, there exist some recent studies where no additional or synergistic effects could be shown of the combination of both interventions (see for example Barnes et al., 2003; Legault et al., 2011; Shatil, 2013). However, Fissler et al. (2013) attribute this negative finding to the fact that, those studies investigated the effect of combined interventions, but separated each component in time; that is, no simultaneous cognitive and physical activities were trialed which might be crucial for interaction effects.

More recently, Kattenstroth et al. (2013) experimented with a six months dance intervention and claimed that even moderate levels of physical activity can in combination with rich sensorimotor and cognitive engagement (as well as other social and emotional challenges) ameliorate a wide spectrum of age-related decline.

Finally, in a recent short review Kraft (2012) puts across the concept of an enriched environment that facilitates both physical activity and challenging cognitive tasks as a basis to systematically assess possible interventions for successful aging. In that review, recent physical intervention findings on brain mechanisms are revisited in view of their effects on higher cognitive function following a combined systems and molecular approach; it is argued that since the physical/cognitive combination may generate more synergistic beneficial changes than either one individually, there is a need to take both into account when designing effective interventions that ought to take advantage of the presumed compensatory mechanisms of elderly individuals.

Additional support for this comes also from other neurodegenerative diseases. For example, Parkinson's Disease (PD) patients, in parallel to the severe motor deficits, suffer from cognitive decline and decreased mental flexibility (Tomer et al., 2002). Although the onset of PD can be earlier than the age of 60, it is noteworthy to mention it here; especially in the context of the connection between the motor system's involvement as well as the underlying functional brain connections in healthy aging and cognitive decline (see also Section 3.5.3).

3. Neuroimaging evidence for benefits of cognitive and physical interventions on brain health

In this section we collect evidence for the likely benefits of cognitive and physical interventions as these are manifested in recent neuroimaging (structural and functional) studies. We aim to outline the likely neurobiological mechanisms that underlie the process of maintaining brain health and healthy aging. Emphasis is drawn on different study threads, namely, structural/functional neuroimaging, as well as, the more recent notion of functional brain connectivity, across different thematic blocks, namely, age-related cognitive decline/neurodegeneration, and training, distinctly physical and cognitive training, as well as, combined training.

3.1. Evidence for age-related neurodegeneration

Normal aging has been linked to structural and neurophysiological changes within the brain as well as to cognitive decline. For instance, aging has been consistently correlated with frontal and hippocampal tissue loss, as well as, frontal, temporal, parietal, occipital and cerebellar white matter loss (Jernigan et al., 2001). Hippocampal volume loss in elderly individuals is considered as a marker of cognitive decline. Driscoll et al. (2003)

compared elderly subjects (*aged 60–85 years old*) to younger ones (*aged 20–39 years old*), and found that the elders demonstrated smaller hippocampal volumes, impaired memory task performance and lower n-acetylaspartate/creatine (NAA/Cr) ratios in the frontal white matter and the hippocampus. In that study, hippocampal volumes and NAA/Cr ratios were correlated in elderly subjects with performance on cognitive tasks. NAA is a brain-specific metabolite involved in myelin turnover. NAA/Cr ratio is considered an indicator of neuronal health with lower ratios indicating neurodegeneration (Moffett et al., 2007). Studies on aging have focused on the hippocampus since it is a key structure for memory processes (Kesslak et al., 1991; Piolino et al., 2008). Its functional importance has been indicated in humans with hippocampal resections who exhibited impaired performance on spatial memory tasks (Astur et al., 2002). Hippocampal atrophy in particular, may be accelerated in those who progress from MCI to dementia (Eckerstrom et al., 2008; Kesslak et al., 1991). Thus, it was considered plausible that interventions which aim at preventing hippocampal atrophy and neuro-degeneration may also prevent age-related cognitive/memory impairments and associated structural and functional brain changes. For instance, Hampstead and colleagues have conducted relevant research on memory training and found that mnemonic strategy training partially restores hippocampal activity in MCI older adults (Hampstead et al., 2012a,b). The longitudinal pattern of such regional brain volume changes yielded differential diagnosis of healthy aging from cognitive decline (MCI in specific) when comparing magnetic resonance imaging (MRI) scans of normal aged individuals (*n = 120, aged 64–86 years old*) and elderly MCI patients (*n = 18, matched on age*) (Driscoll et al., 2009). The latter research revealed a decline over 10 years in brain volume of all regions. The ventricular cerebrospinal fluid (CSF), frontal gray matter, as well as, frontal and parietal areas showed accelerated decline with aging. Also, subjects with MCI over 10 years, had greater volume losses in the ventricular CSF, gray matter, hippocampus, orbitofrontal, middle temporal, and perirhinal cortices.

3.2. Physical activity, cognitive function, healthy aging

Physical exercise may induce transient and permanent changes at the structural and functional levels in the aging brain as witnessed by structural and functional brain imaging techniques, or electrophysiological measures of brain activity (Erickson et al., 2011; Erickson and Kramer, 2009; Hillman et al., 2008; Kramer et al., 2006; Liu-Ambrose et al., 2012; Ruscheweyh et al., 2011; Voelcker-Rehage et al., 2010).

Also, aerobic exercise in aging humans has been positively associated neuroanatomically to cognitive functions such as mental flexibility (Gordon et al., 2008) and memory (Ruscheweyh et al., 2011). For example, Ruscheweyh et al. (2011) assessed healthy elderly individuals (*n = 62*) for levels of physical activity, aerobic fitness, episodic memory score, and brain MRI, at baseline and after a six months intervention of medium or low-intensity physical activity. It was reported that increases in total physical activity were positively associated with an increase in memory scores and was positively associated with increases in local gray matter volume in prefrontal and cingulate cortex.

At a structural level, Colcombe et al. (2003) showed that cardiovascular fitness in elderly individuals moderated the age-related decline of white and gray matter in frontal, temporal and parietal regions associated with executive functions. Erickson et al. (2009) examined the MRIs of non-demented elderly individuals (*n = 165*) and found associations between high fitness levels and large left and right hippocampi which correlated with better spatial memory performance.

Colcombe et al. (2004) used functional magnetic resonance imaging (fMRI) on high-fit participants as compared to low-fit participants and associated the enhanced cardiovascular functions that occur after aerobic training to greater task-relevant activity in prefrontal and parietal areas as well as in the anterior cingulate cortex, brain areas that engage in attentional control. Liu-Ambrose et al. (2010) studied senior women who had undergone 12 months of resistance training and reported that the functional changes localized on the anterior portion of the left middle temporal gyrus and the left anterior insula extending into lateral orbital frontal cortex co-occurred with improved task performance. Hippocampal volume increase was observed for elderly individuals after an aerobic exercise training (Erickson et al., 2011). Ruscheweyh et al. (2011) reported a correlation between the increase of total physical activity and better episodic memory in elderly individuals after both a low and medium intense physical training. This relation was also positively associated with increases (as measured in MRIs) in local gray matter volume in prefrontal and cingulate cortex, as well as, neurotrophic factors (BDNF levels; see below).

Finally, Bezzola et al. (2011) used MRI voxel-based morphometry to investigate training-induced gray matter changes in golf novices at younger ages (*aged 40–60 years old*) and demonstrated that 40 h of golf practice, performed as a leisure activity is still capable of inducing gray matter increases in a task-relevant cortical network encompassing sensorimotor regions and areas belonging to the dorsal stream.

3.3. Cognitive training, cognitive function, healthy aging

Beneficial changes at structural and functional levels in the aging brain can also occur due to cognitive training (Lustig et al., 2009). At the structural level, the beneficial changes have been related with increased brain volume, cortical thickness and density, as well as, with increased coherence of white matter tracts. For instance, Engvig et al. (2010) trained visuo-motor skills and abstract information learning and reported the increase of structural brain modifications. They studied the structural images of elderly subjects (*n = 22*) and controls (*n = 20*) who participated in an eight-week intensive memory training program. They employed a visualization mnemonic technique (MoL) which was shown to improve serial verbal recollection memory. The training group demonstrated cortical thickening in the right insula compared to the controls. In the case of split-half analysis, the training-related cortical thickening was expanded in the left lateral orbitofrontal cortex, right lateral orbitofrontal cortex and fusiform cortex. Thus, the specific memory training program improved memory performance and induced cortical thickening that further positively correlated with memory improvement. The areas that were reported in cortical thickening are regarded to be involved in the control of goal-directed behavior.

Moreover, Kirchhoff et al. (2012) used fMRI and trained elderly individuals (*n = 16*) toward employing self-initiated encoding strategies in order to improve their recognition memory. The training resulted in increased brain activation in the medial superior frontal gyrus, right precentral gyrus and left caudate during intentional encoding. Moreover, brain regions such as prefrontal and left lateral temporal areas, involved during semantic processing, also demonstrated increased brain activity that correlated with recognition memory performance.

Finally, in a recent study involving a large sample of healthy elderly individuals (*n = 167*), Ruscheweyh et al. (2013) investigated the interrelation between executive functioning and brain morphology by analyzing brain structure (MRI) by means of voxel-based morphometry; they confirmed the hypothesis that age-related regional brain volume loss and age-related cognitive changes are linked. As expected, improved task performance was associated with increased local gray matter volume in task-specific patterns in the prefrontal, but also in the insular cortex which was previously underestimated in its executive functional role.

3.4. Physical exercise in combination with cognitive training, cognitive function, healthy aging

From a functional neuroimaging perspective, the combination of cognitive training with physical activity was studied by Boyke et al. (2008) through learning a three-ball cascade juggling. The juggling task involved the interplay between visual, sensory and motor functions while it practiced coordination control. fMRI measurements on elderly individuals (*n* = *50*), who were divided into a training and a control group matched on age and gender, were obtained prior to the intervention. The training group was instructed to practice in three-ball cascade learning for three months. Post fMRI measurements were performed when skilled or almost-skilled performance was attained. The researchers revealed an increase in the right side of the hMT/V5 (middle temporal area of the visual cortex), as well as, increases of the brain gray matter regarding the left frontal cortex, the cingulate cortex, the left hippocampal area and the area of right precentral gyrus. These findings were evident only in the training group, while their statistical significance was eliminated after a 3-month follow-up evaluation period. The brain areas that benefited are generally implicated in complex visual motion processing and reward systems. Despite the lack of sustained findings, this study highlights the feasibility of the mature brain to adapt its structure through neurogenesis according to learning complex cognitive and/or physical training demands. Holzschneider et al. (2012) investigated the relationship between individual cardiorespiratory fitness level before and after a 6-month cycling program and spatial navigation training in a sample of middle-aged men and women (*aged 40–55 years old*). They reported associated patterns of greater activity in an extended neural circuitry, including the hippocampus, retrosplenial cortex, cuneus, precuneus, parahippocampal gyrus, caudate nucleus, insula, putamen, and further frontal, temporal, occipital and cingulate regions. Finally, Hötting et al. (2013) studied middle-aged individuals (*n* = *33, aged 40–55 years old*) and the effects of cognitive training (spatial vs. perceptual training) and physical training (endurance training vs. non-endurance training) on spatial learning by means of fMRI, and concluded that functional neural changes can be induced by cognitive interventions and these seem to be stronger than effects of physical exercise.

Finally, in recent research the body-cognitive relationship was investigated through behavioral and electrophysiological measures (Dotan Ben-Soussan et al., 2013). Quadrato Motor Training (QMT), a training paradigm designed to increase attention, coordination and creativity was used in an attempt to uncover the underlying mediating neuronal mechanism for movement induced cognitive change. It was shown that cognitive performance is positively correlated with alpha activity and whole-body training induces cognitive improvement (measured as a decrease in reaction times), and increases frontal alpha coherence. Moreover, the fact that alpha seems to be decreased in patients with cognitive decline (Alexander et al., 2006), spinal cord injury (Thuraisingham et al., 2007) and brain trauma (Klados et al., 2014), invigorates the positive correlation of alpha activity and cognitive performance (for a review on the interpretation of alpha activity see Bazanova and Vernon, 2013). Although this research involved female students (*n* = *27, aged 20–35 years old*), its relevance to the questions tackled within the healthy aging work is apparent. In addition, addressing the likely crucial motor characteristics, in other words what may be the mediating motor related aspects important for the positive effects to occur, is pivotal. For example, movement complexity and information load (Dotan Ben-Soussan et al., 2013) seem to be important to working memory, in addition to the combination of cognitive and motor aspects and intensity which have been usually addressed.

3.5. Evidence from functional brain connectivity network (FCN) studies

3.5.1. Rationale for using FCNs

Evidence reviewed above shows that cognitive and physical training can lead to changes in specific brain regions, which can be observed at the functional level as well. However, recent studies (Langer et al., 2013) on young adults suggest that we need to look at a higher level of organization if we want to understand how the brain works. The complex nature of the brain and the processing of parallel informational streams cannot be explained only through increased (or decreased) activations in some function-specific regions. That is, human brain networks are organized in a manner that confers high efficiency of information processing. Still, it is unclear how the architecture and the type of functional brain networks are related to and if these networks can be modified by brain training.

One way to approach the higher level of brain organization is to investigate the synchronous firing of regions and the dynamic organization of the functional networks within the cortex. For example, Esposito et al. (1999) has revealed that the functional connectivity among regions can change over the years, although retaining the ability to become reactivated. In the rest of this section, and due to the lack of adequate studies assessing functional connectivity in association with training (cognitive and/or physical), we review what FCN studies can reveal about changes over the years or else across the life span.

3.5.2. Functional brain connectivity across the life span

The brain's functional connectivity can be measured using various modalities like Electroencephalography (EEG), (Astolfi et al., 2007), Magnetoencephalography (MEG) (Stam, 2004), fMRI (Wang et al., 2007), Positron Emission Tomography (PET) (Savic and Lindstrom, 2008), incorporating various algorithms (Lithari et al., 2012a), under various conditions like the resting state (Lithari et al., 2012b) or during cognitive tasks (Klados et al., 2013) and in various pathologies like schizophrenia (Micheloyannis et al., 2006), epilepsy (Liao et al., 2010) and dementia (Stam et al., 2007). Apart from the neuronal changes occurring with age, the gradual deterioration of functional integrity between different brain areas, due to the loss of white matter fibers, can also cause some cognitive deficits during the lifespan (O'Sullivan et al., 2001). For instance, Gong et al. (2009) recruited healthy participants (*n* = *95, aged 19–85 years old*), in order to explore the age-related alternations of functional integration. They reported a positive correlation among age and the network's cost (FCN cost), thereby suggesting a decline of global connectivity during aging, and a negative correlation between local efficiency and age, which suggests loss of the network's resilience to the damage caused by a node removal. Moreover, regional efficiency seemed to be positively correlated to age in frontal and temporal regions, while the opposite appears to be the case in the parietal and occipital neocortex. Zuo et al. (2010) explored the resting state functional homotopic connectivity, by employing healthy individuals (*n* = *213, aged 7–85 years old*). They found a nonlinear positive quadratic relationship (U-pattern) among age and global homotopic connectivity, which decreases after childhood, reaches the global minimum at the age of 53 and then starts increasing again. Regarding the regional homotopic connectivity the results support that there are some regions, like anterior cingulate gyrus and parieto-occipital cortex, which are linearly correlated with age; other regions, like medial orbital gyrus, occipital cortex and cerebellum, which have a positive or negative (inversed U-pattern) quadratic relationship with aging; and some other regions, like putamen and parahippocampal gyrus seem to have a cubic relationship with age.

Finally, in a recent study, Poza et al. (2013) analyzed changes in magnetoencephalographic (MEG) activity across the life span of healthy subjects (*n* = *220, aged 7–84 years*) through complexity measures (Shannon entropy and Euclidean distance approaches) in order to assess changes in MEG oscillations during brain development. They found an increasing quadratic relationship between entropy and age. Such results suggest that human brain development is accompanied by several changes in the irregularity and statistical complexity patterns. Approaches like these may provide new insights into the neural dynamics across life span.

3.5.3. Functional brain connectivity in healthy aging and cognitive decline

Normal and pathological cognitive decline is characterized by alterations of long range connectivity and large scale organization. Indeed, changes in resting state functional connectivity within the default mode network (DMN) concern a wide spectrum of brain conditions ranging from healthy aging (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008), to MCI (Bai et al., 2009; Petrella et al., 2011) and to AD (Gili et al., 2011; Greicius et al., 2004). Damoiseaux et al. (2008) showed that the intrinsic activity of the DMN is related to normal aging and is linked to the observed decline in cognitive functions. The DMN response to cognitive tasks is actually considered to be unique (Fox and Raichle, 2007). Elderly (*n* = *22*) and younger (*n* = *10*) subjects were scanned at a rest state (eyes closed) and the former showed a decreased activity in the superior and middle frontal gyrus, posterior cingulate, middle temporal gyrus, and the superior parietal region (Damoiseaux et al., 2008). Correlations of FCN findings in healthy aging with cognitive assessments (Wen et al., 2011) showed that the efficiency of the whole brain network of cortical connections was associated with processing execution, speed and visuo-spatial functions. Specifically, stronger connectivity in the superior frontal gyrus and posterior cingulate cortex (PCC) were associated with better executive function. Greater processing speed was significantly correlated with better connectivity of nearly all cortical regions.

Recently, literature was enriched with the first longitudinal study that provided evidence for the plasticity of the FCN underlying memory training (Langer et al., 2013). WM performance was uniquely correlated with power in the theta frequency, which was in turn increased by WM training. The network's small-world topology[1] was also correlated with WM performance. Training shifted network characteristics in the direction of high performers and displayed an increased small-worldness within a distributed fronto-parietal network.

Very recent related research has examined brain networks capable of transferring cognitive enhancement (as a result of cognitive interventions) to everyday cognitive functioning by shedding light onto the notion of "far transfer", that is training aiming to enhance untrained abilities that share only few cognitive and perceptual elements with training (Strenziok et al., 2014). In the latter exploratory work employing 42 healthy older adults, cognitive training and far transfer has been associated with altered attentional control demands mediated by the dorsal attention network and trained sensory cortex. The findings of this work highlighted the link between cognitive training and a "top–down control of sensory processing by the dorsal attention network" (Strenziok et al., 2014) and emphasized that altered brain connectivity may also serve as a marker for evaluating the success of training.

Finally one can mention at this point the exciting new prospects emerging for this direction in the newly funded large European Project called Human Brain project (2013, https://www.humanbrainproject.eu/documents/10180/17646/Vision+Document/8bb75845-8b1d-41e0-bcb9-d4de69eb6603). It is intended the project will provide a spatial reference system of the human brain, as well as, major connectivity constraints and key pathways between brain regions. Inevitably the basis of the aforementioned evidence will keep growing in the next few years. Admittedly though, existing evidence and production of this research stream is only at its infancy, especially when it comes to how the functional networking capacity of the brain changes in healthy aging, as a result of physical, cognitive or combined exercises. Thus, we shall attempt to draw some indirect evidence in this direction by revisiting some of the FCN findings in pathological aging.

3.5.4. Functional brain connectivity in pathological aging and cognitive decline

Cognitive decline findings within the elder population have been shown a decade ago in a resting-state study, which observed decreased activity in the DMN in AD patients when compared with age-matched healthy controls (Greicius et al., 2004) thereby concluding that the DMN appears to be affected by aging, but even more so by pathology, that is, Alzheimer's disease. Damoiseaux et al. (2012) investigated the modulation of default mode subnetworks (e.g. anterior vs posterior, ventral vs dorsal) by comparing AD patients (*n* = *21*) to healthy elderly controls (*n* = *18*) through the assessment of connectivity changes over time. AD patients showed decreased connectivity at baseline in the posterior DMN (precuneus) and increased connectivity in the anterior (frontal pole) and ventral (precuneus) DMN when compared to healthy controls. At follow-up (two to four years), functional connectivity decreased across all default mode sub-networks in AD patients (anterior in superior frontal gyrus, ventral in the lingual gyrus and/or precuneus cortex, posterior in middle temporal gyrus). Hence, it was suggested that though regions of the posterior DMN disengage, while at the same time anterior and ventral regions of the DMN enhance their connectivity in the early stages of the disease, eventually connectivity deteriorates within all systems in analogy to the disease progression. For instance, He et al. (2008) found the small-world architecture to be altered when comparing AD patients (*n* = *92*) to healthy controls (*n* = *97*); the AD patients showed increased characteristic path length (L) and clustering coefficient (CC), which implied altered integration and segregation properties. The path length increases that characterized AD were considered as the declined communication efficiency between distant brain regions; such disruptions are thought to underlie impairments in high-level cognitive functions.

In addition to the above, MCI, a transitional state between normal aging and dementia (Petersen et al., 1999) attracts considerable interest in early interventions and it is critical to well characterize its nature as well as its early biomarkers. Gili et al. (2011) observed that though MCI patients exhibit decreased functional connectivity in extended cortical regions (e.g. between the posterior (PCC) and anterior (ACC) cingulate cortex, the PCC and frontal cortex, the medial prefrontal (mPFC) and PCC, as well as, ACC and between the mPFC and frontal cortex), the decrease in functional connectivity in MCI is less severe than in AD. In a similar vein, Petrella et al. (2011) distinguished MCI who undergo cognitive decline and convert to AD from those who remain stable over a two to three year follow-up period. Those findings suggested that MCI converters exhibited more severe decreased functional connectivity compared to non-converters and that MCI and AD were characterized by

[1] The typology of small-world networks is that with many short-distant connections, and a few long-distant ones. Most of such a network's nodes have limited connections with the others, but importantly only a few nodes have a considerably higher number of connections – these are called 'hubs' (see Lithari et al., 2012a).

intermediate and severe decreases respectively in resting state functional connectivity. Shu et al. (2012) demonstrated a significant correlation between network topological features and cognitive functions in MCI patients. In comparison to control subjects, the global topological organization of white matter networks was significantly disrupted in patients with multi-domain MCI (MD-MCI) (memory and cognitive deficits), but not in those with single domain MCI (SD-MCI) (e.g. memory deficit). Relative to SD-MCI, MD-MCI patients exhibited connectivity impairment in the frontal, temporal and parietal cortices and had decreased network efficiency with the most pronounced differences located in the frontal cortex.

4. Electrophysiological findings on brain health

Electrophysiological recordings are usually conducted by means of (resting-state) Electroencephalogram (EEG) or Event Related Potentials (ERPs), with subsequent analysis usually focusing on different brain signal frequency bands in connection with (or without) topographical/anatomical correlates. To this extent, it has been known for quite some time, that physiological aging is accompanied by EEG spectral slowing, since the amplitude of alpha oscillation decreases and gives rise to theta and delta oscillations (Klimesch, 1999; Rossini et al., 2007). Apart from a decrease of the alpha energy, the peak frequency is also decreased and its (topographical) localization is shifted anteriorly (Chiang et al., 2011). Physiological aging is also accompanied by synchronization alterations (Frantzidis et al., 2014). These modifications are induced by compensation effects during task performance (Cabeza et al., 2002; Ho et al., 2012). Attendance of two types of acoustic stimuli (target vs non-target) demonstrated that compensation phenomena involve the bilateral activations of frontal and temporo-frontal brain regions in order to preserve optimal performance during cognitive processing. The additional recruitment was mainly observed within the theta frequency range and was accompanied by a decrease of phase-locking and phase coherence (Ho et al., 2012). Compensation also occurs during anticipation and attention of forthcoming visual stimuli (Deiber et al., 2013). Senior citizens showed diminished alpha activity when compared to younger participants. Existence of visual cues prior to the stimuli onset motivated the participants to employ anticipation mechanisms. Beta band analysis revealed that for elderly subjects to do this, they need to recruit extended brain regions in comparison with healthy elderly. What is more, smaller event-related desynchronization implies an age-related attentional decline (Deiber et al., 2013).

Although elderly interventions were traditionally not studied in light of neurophysiological analysis, recent literature production witnesses a growing interest in this direction as well. Thus, a recent study employed multi-tasking training through an adaptive, custom-designed, three-dimensional video game, namely, NeuroRacer (Anguera et al., 2013), and elderly individuals (*n* = *46, aged 60–85 years*). Neurophysiological evaluation (pre- and post-) of the training program involved estimation of the frontal midline theta (4–7 Hz) and anterior–posterior theta coherence, which were previously associated with cognitive control. The results demonstrated that participants of the multi-tasking group improved in both electrophysiological outcomes when compared with the control participants. Such electrophysiological outcomes imply the increased prefrontal activation as a likely training-induced neuroplasticity mechanism. Another recent study employed Speed of Processing (SOP) training to provide electrophysiological evidence of neuroplasticity-based benefits regarding selective attention (O'Brien et al., 2013). SOP training is a process-based approach since it does not target on mere strategy implementation, but trains selective attention as a whole neural circuit (Jonides, 2004). Therefore, training benefits are not only restricted in selective attention, but are also transferred to other cognitive domains such as functional performance, independent living, driving ability, and depression (O'Brien et al., 2013). The training program was computerized and adaptive to the user abilities, providing feedback and reward while it was embedded in a video game environment, consisting of five exercises targeting at perception, processing speed, attention and memory. The study enrolled healthy senior citizens (*n* = *22, aged* > *65 years old*). The neurophysiological evaluation was performed through ERPs, targeting at the N2pc and P3b ERP peak components. The N2pc component reflects attention allocation during visual search, while P3b measures the attentional capacity employed toward target categorization. Participants enrolled to the training group demonstrated statistically significant N2pc amplitude increase, whereas controls did not demonstrate any alteration. Similarly, training participants demonstrated increased P3b component amplitudes after training, whereas there were no statistically significant alterations for the control group.

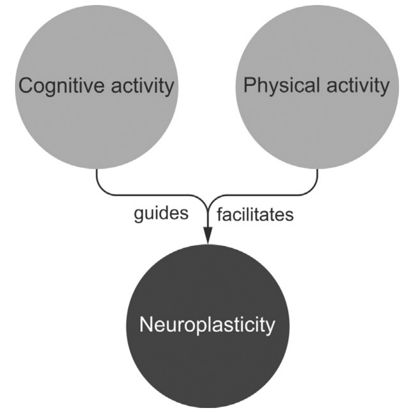

Fig. 1. Guided plasticity facilitation framework.
Figure is adapted from Fissler et al. (2013).

5. Models of neurobiological mechanisms in healthy aging and the case of combined physical and cognitive interventions

What might be the advantage of combined physical and cognitive exercise and can we use this knowledge to make the exercise protocols more effective? We postulate that the advantage is largely based on the brain's ability to adapt to new environmental challenges by plastic reorganization of the cortex. From an evolutionary perspective, physical and cognitive challenges were highly interwoven (Kempermann et al., 2010). The dissociation in current society (playing computer games or desk work) is a rather recent development making a genetic adaptation to this lifestyle improbable. It is therefore reasonable to assume that the neurobiological mechanisms triggered by physical and cognitive exercise go hand in hand to induce plastic change.

With the human brain being the most complex human organ, the challenge of positive neuroplastic change includes not only the regulation (facilitation and attenuation) of the plastic potential (neurogenesis and synaptogenesis) but also the guidance of functionally beneficial plastic changes (positive plasticity) in order to improve cognitive function. We assume, that physical exercise increases the potential for neurogenesis and synaptogenesis while cognitive exercise guides it to induce positive plastic change (Fissler et al., 2013, see Fig. 1).

Indeed, there have been many studies showing an exercise-induced up-regulation of neurotrophic factors, neurogenesis and synaptogenesis in animal models (for reviews see Cotman et al., 2007; Dishman et al., 2006; Lista and Sorrentino, 2010). Importantly, Geibig et al. (2012) recently showed that post-stroke physical exercise increased the number of newborn neurons in the adult mouse dentate gyrus but did not affect the percentage of functionally integrated neurons. Trachtenberg et al. (2002) demonstrated that the lifetime of synaptic spines of the mouse barrel cortex varies greatly with only 60% of the synapses being stable for more than 8 days. What is the difference between the stable and the transient synapses? One possible explanation is that synapses are generated at random locations and their stabilization depends on their activation. Activated synapses stabilize while inactive synapses disappear. This hypothesis is supported by the fact that the synaptic turnover increases in deprived sensory areas while it stays rather stable in non-deprived areas of the mouse barrel cortex (Trachtenberg et al., 2002). Therefore, the survival of the newly generated synapse – and thus the integration into the pre-existing neuronal network – depends on the activation of the synapse. Repeated cognitive exercise activating brain areas that are involved e.g., in working memory performance during a time window of enhanced neurogenesis and synaptogenesis should lead to functional integration of the newborn neurons and synapsis into the respective brain circuits and therefore lead to enhanced cognitive performance.

6. Drawing the threads together and suggesting future research

The protective effects of cognitive training for cognitive decline and dementia which formed classical knowledge found in prospective observational studies have been lately enriched with more convincing neuroscientific evidence. However, in addition to that, the currently available knowledge is supportive of physical exercise having beneficial effects on cognition by enhancing neuroplasticity, thereby preventing cognitive decline and pathological aging and promoting healthy aging. Recent studies have suggested that combining physical and cognitive training might result in a mutual enhancement of both interventions. Moreover, new data suggest that to maintain the neuro-cognitive benefits induced by physical exercise, an increase in the cardiovascular fitness level must be maintained (Hötting and Röder, 2013). We propose that simultaneous physical and cognitive exercise induce more beneficial cognitive effects than pure cognitive and physical interventions alone, especially when these are provided in a socially challenging and attractive way in the form of (computer based) exergames (Konstantinidis et al., 2012). To test this hypothesis, activities which are both, physically and cognitively challenging (e.g. dancing or other containing new learning or novelty elements) should be compared to pure aerobic and cognitive exercise (Park et al., 2013b). A recent study by Anderson-Hanley et al. (2012) also provides a hint to the benefits of simultaneous physical and cognitive exercise as an exergame, which incorporates cognitive demands such as imagery and decision-making. This has yielded greater cognitive benefits than traditional physical exercise alone. Similarly, Mortimer et al. (2012) showed beneficial effects on cognitive functions as well as increases in brain volume as a consequence of Tai Chi, which can be conceptualized as simultaneous physical and cognitive exercise. Importantly, a pure physical exercise group did not reveal any changes in brain and cognitive measures indicating that the combination of physical and cognitive challenge is crucial.

This notion is in line with a recent piece of work by Fissler et al. (2013) in which elderly training interventions are split into four categories, namely, process-based cognitive trainings (PCTs), which much improve performance only in cognitive tests similar to the training tasks with very limited effects on cognitive ability; novelty interventions, characterized by a high task variability that do not target specific processing demands affected in aging and cognitive decline, which show small effects on unspecific cognitive abilities; process-based novelty interventions which are introduced to overcome the aforementioned difficulties and are hoped to provide enhanced effects on specific cognitive functions; and finally, physically demanding novelty interventions, by combining cognitively with physically challenging tasks in an attempt to induce multi-mechanistic effects, which might even interact positively as explained above and which are believed to have enhanced effects on unspecific cognitive abilities.

However, still today, the exact interaction between cognitive and physical interventions is not yet known, and has to be addressed (Park and Bischof, 2013). Undoubtedly, a few more results are expected in this direction from funded projects that have recently been completed (see for example the LLM project: www.longlastingmemories.eu) where games combining physical and cognitive exercises have been exploited (Bamidis et al., 2011). However, future studies should also examine the modulating influence of additional social, psychological and physical constitution variables (Hötting and Röder, 2013). We postulate that these studies should certainly be multi-modal, but also multi-disciplinary in nature and go hand-in-hand with advanced neuroscientific research and innovations in technology as applied to healthy aging interventions. To this front, conclusions from a recent technical neuroscience workshop are essential, in which three grand challenges were identified, including high spatiotemporal resolution neuroimaging, perturbation-based neuroimaging, and neuroimaging in naturalistic environments (He et al., 2013). The latter requires the development of new noninvasive methods to image the human brain while it is interacting with its natural environment, e.g. while exercise takes place, or right before and after each training session, preferably in-home with low-cost portable technologies for extracting all required information. However, so far, such brain monitoring applications have been primarily limited to low-level neural signals for use in entertainment devices, such as game playing. To this extent, as He et al. (2013) suggest, wearable technology has the potential to provide increasingly rich information within the context of the users, especially if it is combined with immersive brain monitoring systems suitable for *natural* dynamic settings. Fissler et al. (2013) argue that future training designs should not only be multimodal (i.e. combined physical and cognitive exercises) but also attempt to induce a mismatch of supply and demand, have a high task variability but a low variability in targeted processes, fulfill basic individual senior needs while be engaging and conducted in a personally meaningful environment which is deemed necessary for long-term adherence. If these are wed with contemporary exergaming systems and novel analytical approaches for characterizing how neural signals co-vary with *environmental dynamics* while physical/cognitive training is conducted, then one has a powerful tool to tackle the research questions underlined above. Such facilities could help understand predictive changes in brain dynamics that could be used for providing elderly patients suggestions on changing interventions pertaining to cognitive impairment/decline, thereby personalizing the training in a neuroscientifically validated way. Evidence to this end stems from recent reports (e.g. Anderson-Hanley et al., 2012) where the added value of modern exergaming facilities like cybercycling was shown in older adults who achieved better cognitive function than traditional exercisers, and therefore, indicated the great potential of these technologies for preventing cognitive decline. In Fig. 2 we illustrate these ideas in view of envisaged future neuroscientific research and technological advances.

Such technological achievements would drive further success in developing models and theories and would ultimately enable the

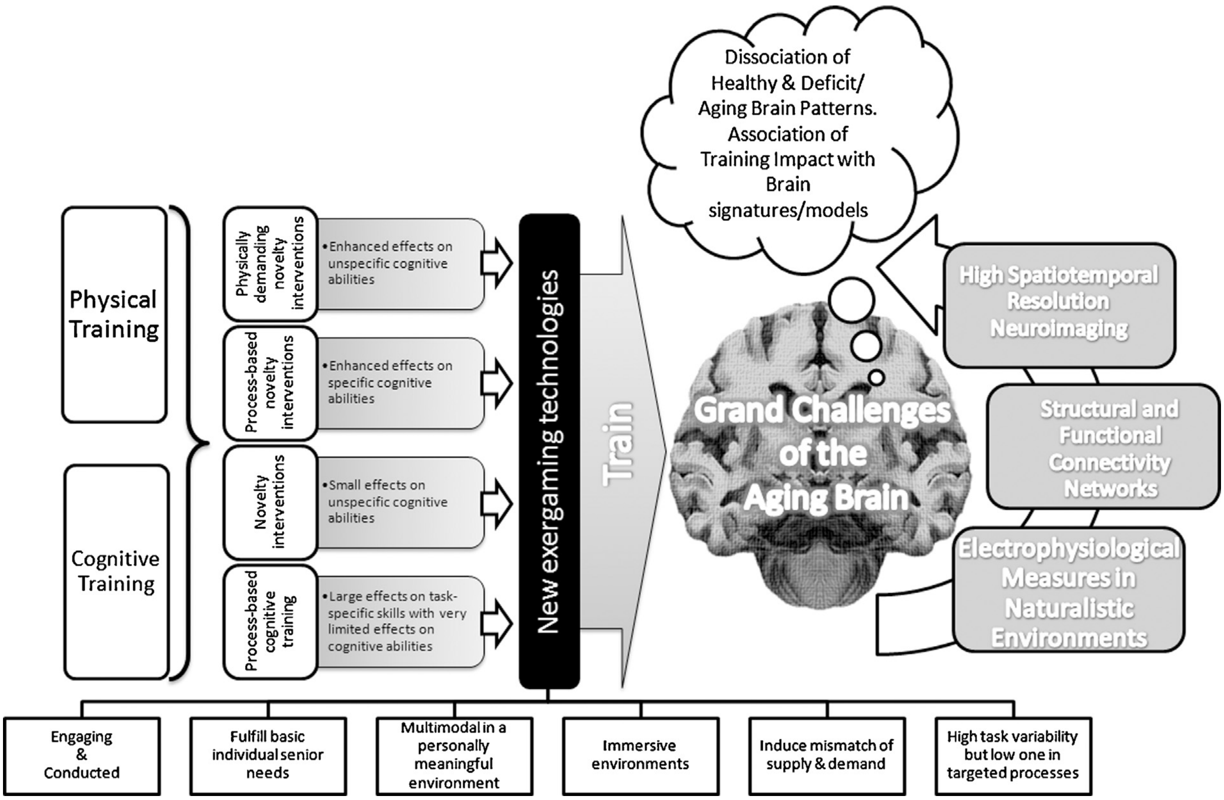

Fig. 2. Challenges in studying the aging brain. Evidence is for combining cognitive and physical training in view of new exergaming design strategies (see also Fissler et al., 2013). Electrophysiological. structural, functional, connectivity and spatiotemporal brain dynamics studies are pivotal for future brain health research.

development of synthetic brain-based cognitive systems. This is a direction where the contribution and importance of this review becomes clear. Functional mapping and connectivity techniques can be used to discern both the origin, as well as the direction, of information propagation within the aging brain and can facilitate the analysis and understanding of the complex pattern of interconnected neuronal networks associated with the aging process or the intervention attempted. Characterizing these neural circuits will enable a much deeper understanding of the mechanisms by which the brain operates or declines cognitively, thereby leading not only to improved diagnoses for associated neuropathology, but also to their better management through the personalization capacity mentioned above. Needless to mention that gender related effects and studies are necessary prerequisites. In this way one might also guide or abet interventions, based on objective metrics of brain health which is recognized as foremost to the field of active and healthy aging. Quite certainly, model-based procedures and algorithms are needed that can distil succinct, predictive, descriptions of the aging brain physiology (He et al., 2013; Smith, 2013). To this respect, vital contributions from animal research should not be ignored. This is admitted in the recent launch of the giant Human Brain Project funded by the European Commission, where it is recognized that “modeling the mouse and later the human brain will require huge volumes of standardized, curated data on the brain’s different levels of organization”. It is hoped that as this project drives international efforts to develop neuroscience ontologies, brain atlases, model descriptions and data sharing, thereby playing an important role in coordinating international neuroscience research, part of the emphasis will be devoted to understanding the brain mechanisms of the aging process so as to facilitate healthy aging through the design and adoption of suitable (multimodal) interventions based on objective criteria and standardized knowledge.

Acknowledgments

This work has been partially funded by the European community’s 7th framework programme (USEFIL, project no. 223920), the CIP-PSP program (LongLastingMemories, project no. 238904; and DISCOVER, project no. 297268). Authors would like to thank: P. Fissler and I T. Kollassa of Clinical and Biological Psychology, Institute of Psychology & Education, University of Ulm, Germany; F. Thurm of Lifespan Developmental Neuroscience Group, Department of Psychology, Technical University of Dresden, Germany; and A. Ladas from Cognitive Psychology and Neuropsychology Lab, Department of Psychology, The University of Sheffield International Faculty, City College, Greece, for enlightening discussions and comments on the manuscript.

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