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Review

Beneficial effects of physical exercise on neuroplasticity and cognition

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ABSTRACT

The human brain adapts to changing demands by altering its functional and structural properties ("neuroplasticity") which results in learning and acquiring skills. Convergent evidence from both human and animal studies suggests that physical activity facilitates neuroplasticity of certain brain structures and as a result cognitive functions. Animal studies have identified an enhancement of neurogenesis, synaptogenesis, angiogenesis and the release of neurotrophins as neural mechanisms mediating beneficial cognitive effects of physical exercise.

This review summarizes behavioral consequences and neural correlates at the system level following physical exercise interventions in humans of different ages. The results suggest that physical exercise may trigger processes facilitating neuroplasticity and, thereby, enhances an individual's capacity to respond to new demands with behavioral adaptations. Indeed, some 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.

Contents

1. Introduction

Until the 1960s it was common textbook knowledge in neuropsychology that the adult nervous system is rather hard-wired and had probably a rather limited capacity to change (Grossman, 1967). Although the idea that the central nervous system is able to change its organization dates back to the times of William James

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(James, 1890) and Santiago Ramón y Cajal (Ramon y Cajal, 1895), empirical research supporting these theories did not start before the 1940s (Hebb, 1949). Today we know from both animal and human studies that the adult mammalian brain is continuously shaped by environmental input (for a review see Pascual-Leone et al., 2005). The capacity of the nervous system to modify its organization to altered demands and environments has been termed "neuroplasticity" (Bavelier and Neville, 2002). Neuroplasticity occurs when, for example, acquiring new skills, after damage to the nervous system and as a result of sensory deprivation (Bavelier and Neville, 2002). Neuroplasticity has been studied at different organizational levels of the nervous system, ranging from ion channels, to synapses, neurons, neuronal columns, cortical maps and behavior. These levels are, however, highly interlinked and interdependent. Associative learning, for example, induces changes in the release of neurotransmitters, which then may trigger a cascade of neurochemical events resulting in structural changes in the cerebral cortex such as the formation of new synapses or the reorganization of synaptic connections (Rosenzweig et al., 2002). For instance, these structural changes could sometimes lead to an expansion of cortical maps (Weinberger, 2004). Reorganizations of sensory cortical maps have been linked to changes in perceptual abilities measured at the behavioral level (Recanzone et al., 1991).

Behavioral correlates of neuroplasticity might be adaptive. For example, interpreters who underwent an intense training procedure to learn a new language have been shown to develop larger gray matter volume in the hippocampus and to increase cortical thickness of the left middle frontal gyrus, inferior frontal gyrus and superior temporal gyrus (Martensson et al., 2012). The increase of gray matter in the hippocampus and in the superior temporal gyrus correlated positively with the interpreters' language proficiency after the training. This suggests that the observed structural changes in these brain regions contributed to the acquisition of the new language.

The hippocampus is known for its prominent role in spatial navigation and spatial memory (Bird and Burgess, 2008). This can be observed in the changes of the human hippocampus after a four-month spatial navigation training in a virtual environment: young and old men showed less hippocampal volume loss and had improved their spatial navigation skills after their training period, compared to the control group who did the same amount of walking, but did not receive a spatial navigation training (Lövden et al., 2012). Moreover, a reorganization of somatosensory and auditory cortices has been related to enhanced sensori-motor and auditory skills in professional musicians (Elbert et al., 1995; Münte et al., 2002), respectively, and to compensatory behavior in congenitally blind humans (Pascual-Leone and Torres, 1993; Pavani and Röder, 2012). Neuroplasticity mediates the behavioral recovery after brain injury and protocols known to increase cortical map plasticity have been successfully implemented into neuro-rehabilitation programs (Dancause and Nudo, 2011; Taub et al., 2002).

However, neuroplasticity may result in maladaptive behavioral consequences as well (Elbert and Heim, 2001). For instance, reorganization in frontal and hippocampal regions has been associated with the development and maintenance of addictive behavior (Eisch et al., 2008; Van den Oever et al., 2010). Moreover, agonizing phantom sensations, like phantom limb pain and tinnitus, have been attributed to cortical reorganizations of somatosensory (Flor et al., 1995) and auditory cortices (Mühlnickel et al., 1998), respectively. Focal dystonia ("musician's" or "writer's clamp") has been shown to go together with a reorganization in somatosensory (Elbert et al., 1998) and motor areas (Pujol et al., 2000). Thus, the same mechanisms that allow for adaptive changes of the nervous system and behavioral improvements sometimes result in maladaptive consequences (Nava and Röder, 2011). Maladaptive changes have been acknowledged as a "double-edged sword" of neuroplasticity and seem to be more likely in the context of atypical environments (Stevens and Neville, 2009).

Since neuroplasticity enables the adaptation to changing demands and environments, the question arises how one can enhance the mechanisms of neuroplasticity to improve learning and memory, to prevent cognitive decline across the lifespan and to enhance recovery after brain injury. In the past years, evidence from both human and animal studies has suggested that physical activity and physical exercise have a facilitating effect on neuroplasticity and often go together with improved cognitive functioning. By enhancing neuroplasticity, physical exercise may facilitate maladaptive types of learning as well, such as the acquisition of fear or undesirable habits. However, as far as we know, this has not been reported in humans yet.

As outlined in more detail below (Section 3), physical exercise seems to influence processes in the nervous systems supporting changes due to experience. Thus, additional stimulation or activity after exercising leads to neuroplasticity with a higher likelihood (Kempermann et al., 2010).

Physical activity is defined as "any bodily movement produced by skeletal muscles that requires energy expenditure" while physical exercise is "a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective" (WHO, 2010, p.52-53). The aim of this review is to give an overview of results providing evidence for beneficial consequences of both physical activity and physical exercise for cognitive processes in humans. Moreover, the neural mechanisms of plasticity mediating the influence of physical activity on cognitive variables are explored. This is done by firstly referring to results from invasive studies in animals and secondly by summarizing results from brain imaging studies in humans.

In addition to physical activity, other lifestyle factors and interventions have been considered to improve neuro-cognitive functions, including special types of nutrition (e.g. (Witte et al., 2009), pharmacological treatments (Farah et al., 2004; Sawaki et al., 2002; Walker-Batson et al., 2001), brain stimulation (Floel et al., 2008), enriched environments and cognitive stimulation (Kramer and Willis, 2002; Nyberg, 2005; van Praag et al., 2000). In this review we will focus on physical exercise interventions, including combined cognitive and physical interventions. The review will conclude with a discussion of the resulting consequences for future research and application.

2. Physical activity and cognition – studies in humans

2.1. Cross-sectional and cohort studies

During the last decades, numerous studies reporting better cognitive or academic performance in physically active people compared to sedentary individuals have been published (for reviews see Churchill et al., 2002; Etnier et al., 1997; Sibley and Etnier, 2003). However, in the cross-sectional studies, it was not possible to make any kind of inference concerning causal relationships between physical activity and cognition. For instance, the direction of the observed effects could be reversed with individuals with high cognitive abilities being more likely to engage in physical activity. Moreover, third variables such as a higher educational background and socioeconomic status, a health-conscious lifestyle and the absence of health problems could have an impact on both, cognitive variables and the likelihood to be physically active without any direct causal link between physical activity and cognitive variables.

Although cohort studies with longitudinal designs are not able to prove causal relationships either, these research designs are nevertheless more able to track the sequence of events and to check for possible confounds. Most of these studies have been conducted in middle-aged and older adults mainly with the aim to identify lifestyle factors that might reduce age-related cognitive decline and that might delay the onset of dementia. These studies assess a large number of variables, including the amount of physical activity and overall cardiovascular fitness, at one initial measurement time. Typically, the link between these variables and cognitive performance or the incidence of dementia several years later is analyzed. Follow-up time periods of these studies have varied between two years (Etgen et al., 2010) up to 31 years (Andel et al., 2008). In general, larger time periods between the first and the second assessment go together with a better control of e.g. sub-threshold cognitive impairments at baseline that might be associated with a lower level of physical activity. These studies have reported that self-reported physical activity and objectively measured cardiovascular fitness at baseline are good predictors of cognitive performance (Barnes et al., 2003; Etgen et al., 2010; van Gelder et al., 2004; Yaffe et al., 2001) and of the risk to suffer from dementia at the follow-up (Abbott et al., 2004; Andel et al., 2008; Laurin et al., 2001; Rovio et al., 2005). When taking the number of cognitive stimulating activities into account, other studies failed to observe such a relationship (Sturman et al., 2005) and have suggested that non-physical leisure time activities such as cultural, social or complimentary activities might even be more beneficial for cognitive functions than physical activity (Richards et al., 2003).

While most of the studies comprised people older than 55 years, only a few studies have investigated younger people. Richards et al. (2003) studied a cohort of 1919 middle-aged participants at three time points spanning a time period of 17 years. The authors reported that physical exercise at the age of 36 years was associated with a slower rate of memory decline between 43 and 53 years of age. Moreover, participants who stopped exercising after the age of 36 years showed a lower protection of memory functions compared to those participants who began exercising after 36 years of age. Participants who had been engaged in physical exercise at the age of 36 and at the age of 43 years had the lowest decay in memory at the age of 53 years. These results suggest that continuous exercising is necessary to maintain cognitive capacities across the lifespan. In accordance with these behavioral observations, structural brain imaging studies have demonstrated an association between physical activity at middle age and gray matter volume in later life (Rovio et al., 2010). In this prospective cohort study, people around the age of 50 were asked about their physical activities. Structural MRI scans were carried out 21 years later. Gray matter volume in frontal brain regions were found to be larger for individuals who had reported exercising at least twice a week at midlife compared to those who exercised less (Rovio et al., 2010). Other studies have provided evidence for a reduced risk of dementia at older ages when having been engaged in physical exercise at the age of 50 years (Andel et al., 2008; Rovio et al., 2005). Thus, midlife physical activity might contribute to brain health in later life.

A cohort study conducted in Sweden was able to include almost all young men born between 1950 and 1976 who were enlisted for the military service (Aberg et al., 2009). Cross-sectionally, this study confirmed previous findings of a positive correlation between cardiovascular fitness and intelligence scores after controlling for possible confounders such as parental education and assessment date. Longitudinally, better cardiovascular fitness at the age of 18 years was associated with higher academic degrees and an occupation with a higher socioeconomic index in a subgroup which was followed-up after 10 to 30 years. However, the latter finding needs to be interpreted with caution since the authors controlled for parental education only. Therefore, differences in general intelligence at the age of 18 years might account for most of the variance. Due to the large sample size at baseline, the authors were able to analyze a substantial number of data sets of brother pairs, as well as dizygous and monozygous twins. By means of a cross-twin cross-trait analyses, Aberg et al. (2009) found that non-shared environmental factors accounted for more than 80% of the covariation between cardiovascular fitness and cognitive measures suggesting that lifestyle factors (e.g. exercising) were more important than heredity in explaining the relation between physical fitness and cognition.

Taken together, cross-sectional as well as longitudinal cohort studies have provided results in favor of beneficial effects of physical activity and of cardiovascular fitness on cognitive capabilities. Moreover, being physically active in earlier life epochs is associated with preserved cognitive abilities later in life and reducing the risk for dementia as well. Most of the discussed studies controlled for possible confounders such as sex, education and health status and tried to solve the “hen and egg” problem by using a time series approach. However, these research strategies do not allow for testing of causal relations between exercising and cognitive capacities which is only possible in intervention studies with a random assignment of participants to an exercise and control group.

2.2. *Intervention studies*

There are two main types of intervention studies which address cognitive benefits of physical activities. One line of research addresses acute effects of exercising on cognitive variables. In these experiments, participants' cognitive performance is measured immediately before and after a single session of exercising with durations of a few minutes up to several hours. By contrast, another line of research addresses chronic effects of exercise programs which last for weeks or months. In chronic protocols, participants take part in regular sports activities several times a week for several months. Cognitive variables are commonly measured before the start of these training programs with either a follow-up at the end of the program or several assessments during and after the intervention period. Here, we discuss only results from studies employing a chronic exercise protocol (for reviews on cognitive variables after acute exercise see Lambourne and Tomporowski, 2010; Ratey and Loehr, 2011; Tomporowski, 2003).

Most of the studies recruited sedentary individuals and randomly assigned them to the experimental and a control group. Most published studies tested the hypothesis whether aerobic exercise, which is known to increase cardiovascular fitness, improves cognitive functions. Aerobic exercise comprises endurance programs such as running, walking, cycling and swimming (WHO, 2010). Non-endurance training programs, such as light stretching and toning programs, have often been used as a control intervention (Colcombe et al., 2004; Dustman, 1984; Kramer et al., 1999; Moul et al., 1995; Ruscheweyh et al., 2011). Other studies employed a waiting control group (Hawkins et al., 1992; Stroth et al., 2009). The interventions ranged from a few weeks (Stroth et al., 2009) up to one year (Erickson et al., 2011; Voelcker-Rehage et al., 2011).

Studies reported larger increases in executive functions (Colcombe et al., 2004; Kramer et al., 1999; Smiley-Oyen et al., 2008; Voelcker-Rehage et al., 2011), attention (Hawkins et al., 1992), memory (Stroth et al., 2009) and speed of processing (Moul et al., 1995) after an aerobic training than after a non-endurance training or in comparison to a passive control group. However, other studies failed to show an impact of aerobic exercise training on cognitive variables (Blumenthal and Madden, 1988; Madden et al., 1989; Panton et al., 1990). Some studies found beneficial effects of exercise only for a subset of the cognitive outcome measures (Hötting et al., 2012b; Kramer et al., 2001).

Angevaren and co-workers summarized randomized controlled studies which were published before 2005 that compared cognitive changes related to aerobic exercise interventions to a control intervention in older adults. They identified eleven publications from which the authors concluded that "the data are insufficient to show that the improvements in cognitive function which can be attributed to physical exercise are due to improvements in cardiovascular fitness, although the temporal association suggests that this might be the case" (Angevaren et al., 2008, p. 2).

In the following discussion we will look at three possible accounts for the partially inconsistent results found in the literature. On the one hand it has been suggested that aerobic exercise has an impact on only a few specific cognitive functions. As a consequence, only studies assessing these functions were able to demonstrate positive effects of physical exercise on cognitive functioning. The second line of reasoning to explain inconsistent results across controlled physical exercise studies criticizes the focus on cardiovascular fitness, since light physical exercise might have positive effects on cognitive variables as well. Therefore, some studies which employed a more active control group might have underestimated physical exercise related effects on neurocognitive functions. The third line of reasoning suggests that the type of exercise determines which neuronal processes and cognitive functions were modulated by physical activity.

2.2.1. Does physical activity selectively improve some cognitive functions?

The "selective improvement" hypothesis of physical exercise has first been proposed by Kramer and co-workers (Kramer et al., 1999). In a randomized intervention study, in which the effects of a six-month aerobic exercise training were compared to a stretching training, they reported an increased performance in tasks that required a high degree of executive control (e.g. response-compatibility and task switching tasks) after the aerobic training but not after the stretching training. A similar increase was not observed for trials in the same tasks that did not require executive control like compatible trials in a response-compatibility paradigm or non-switching trials in a task switching paradigm, which thereby supports the selective improvement hypothesis. Moreover, in their meta-analysis summarizing controlled intervention studies published until 2001, Colcombe and Kramer (2003) reported that the largest effect sizes were related to aerobic exercise for executive functions and tasks that required cognitive control.

Activity in frontal brain regions during executive tasks is a reoccurring finding in neuroimaging studies (Beer et al., 2004; Derrfuss et al., 2004). Moreover, lesion studies have stressed the importance of the prefrontal cortex for executive functions (Milner, 1963; Vendrell et al., 1995). Indeed, brain imaging studies in older humans (>57 years) were able to demonstrate functional brain activation changes in frontal brain regions following six months of aerobic exercise (Colcombe et al., 2004). These functional changes were accompanied by better performance in the Erickson flanker task. Moreover, an increase in gray and white matter volume in prefrontal and temporal cortices after exercising has been reported in older adults (Colcombe et al., 2006).

In a recent study (Hötting et al., 2012b), however, middle-aged adults who took part in a six-month aerobic cycling training did not show superior performance compared to a control group in a task typically used to assess executive functions (the Stroop task; Stroop, 1935). Meta-analyses have reported significant effects of aerobic exercise for a large range of other cognitive functions including auditory and visual attention, motor control, spatial cognition and cognitive speed (Angevaren et al., 2008; Colcombe and Kramer, 2003). Although effect sizes for spatial and for speeded tasks were smaller compared to executive tasks (Colcombe and Kramer, 2003), these findings argue against a strict selective improvement of executive functions after exercising.

Recently, studies on the effects of physical exercise on cognition started to focus on memory. Initial evidence that memory functions might be especially susceptible to physical exercise has been derived from animal studies. In rodents, running is known to induce structural changes (neurogenesis) especially in the hippocampus (van Praag et al., 2000) which has been associated with improvements in hippocampus-dependent learning and memory (van Praag et al., 1999a). In humans, aerobic exercise interventions seem to counteract age-related hippocampal volume loss: participants of a one-year walking training showed an increase in the anterior hippocampal volume from baseline to post-test while a decrease of gray matter in the same region was observed in the stretching control group (Erickson et al., 2011). However, corresponding differences in spatial working memory was not observed between the walking and control group. Thus, the behavioral relevance of the hippocampal volume changes has still to be demonstrated. Ruscheweyh et al. (2011) reported only a trend toward an increase in verbal memory after exercising in adults older than 50 years of age compared to a sedentary control group. There were no differences in memory between a walking and gymnastic group suggesting that any possible beneficial effect of exercising on memory was not specific for aerobic exercise. Another study in younger adults between 17 and 29 years of age found a significant increase in visuo-spatial short-term memory after 6 weeks of aerobic exercise training, compared to a waiting control group (Stroth et al., 2009).

In order to further test whether physical exercise modulates memory functions Hötting et al. (2012b) conducted a study in middle-aged (40–56 years), previously sedentary adults. Participants were randomly assigned either to a cycling training on indoor bicycles (endurance training) or a stretching/coordination training (non-endurance training). Data of both groups were compared to the results of a sedentary control group. Both, the cycling and the stretching/coordination group exercised twice a week for six months under the supervision of a qualified instructor. Significant improvements in memory were observed in both groups compared to the sedentary control group. Notably, the improvement in episodic memory correlated positively with changes in cardiovascular fitness defined as the individual VO_2peak (maximal oxygen uptake) across all participants: participants with a larger increase in cardiovascular fitness showed a larger improvement in memory. A positive association between VO_2peak and episodic memory was further supported by data collected at a follow-up assessment one year after the end of the supervised training (Hötting et al., 2012c; described in more detail in section 5 of this review). Interestingly, the correlation between cardiovascular fitness and cognitive variables was specific for episodic memory and not observed for an attention task.

Memory impairments are a core symptom of Alzheimer disease (AD) and of other types of dementia (American Psychiatric Association, 1998). Accordingly, physical activity has been recommended to prevent memory decline in patients with dementia (Intlekofer and Cotman, 2012). Physical exercise intervention studies in patients with the diagnosis of AD, however, are still rare (Palleschi et al., 1996; Vreugdenhil et al., 2012). Available results suggest that people at risk for AD might benefit from physical exercise. Lautenschlager and co-workers (2008) ran a randomized controlled trial in a large sample of older adults ($n = 170$) with either mild cognitive impairments or self-reported memory complaints. Physical activity of half of the participants was increased by a home-based aerobic and strength training (three times a week for 50 min). The other half of the participants received information about a healthy lifestyle (control group) but did not increase their physical activity. After 24 weeks, the physically active participants showed better delayed recall of word lists and less negative cognitive symptoms typically associated with dementia (like impaired naming, comprehension and orientation deficits) compared to the control group.

To sum up, although beneficial effects of physical exercise in humans have most convincingly been shown for executive functions and associated frontal brain regions, future studies need to demonstrate exactly which aspects of executive functions are affected by physical exercise. Moreover, evidence from animal studies suggests that some memory functions and underlying brain structures might be susceptible to exercise induced changes as well. The results of human studies on memory, however, are still far from being consistent. In particular, there is still a lack of convincing evidence that changes in hippocampal structures result in an improved memory performance after exercising.

2.2.2. Is an increase in cardiovascular fitness a prerequisite for positive effects of exercise on cognition?

Controlled intervention studies with a random assignment of participants to conditions have usually compared the effects of an endurance exercise program addressing cardiovascular fitness with a stretching program not affecting cardiovascular fitness (e.g. Colcombe et al., 2004; Kramer et al., 1999). This design has several advantages: it controls for social and other unspecific effects of a new leisure time activity and, thus, tries to isolate the effects of improvements in cardiovascular fitness on cognitive variables. More recent studies, however, have suggested that low intense physical exercise such as coordination and resistance training programs might have a beneficial impact on cognition as well.

Ruscheweyh et al. (2011) compared memory functions of older adults engaged either in a walking training (medium intense aerobic exercise), a gymnastic program (low-intensity aerobic exercise) or no training at all (control group). The authors reported beneficial effects of physical activity independent of the intensity of the activity: memory scores tended to be higher after the training in both the walking and the gymnastics group compared to the non-exercising control group. Moreover, changes in the self-reported overall level of the participants' physical activity correlated positively with both improvements in episodic memory and with changes in the gray matter volume of the prefrontal and cingulate cortex. These results suggest that even low levels of physical activity including daily activities might affect cognitive variables and neuroplasticity.

These findings are in line with recent results showing that both an aerobic cycling and a stretching/coordination program are capable of improving episodic memory in middle-aged adults (Hötting et al., 2012b). Such findings do, however, not necessary exclude a relation between cardiovascular fitness and cognitive variables: Hötting et al. (2012b) were able to demonstrate a positive relation between an objective measure of cardiovascular fitness (VO_2peak) and episodic memory. It has to be noted that cardiovascular fitness explained a relatively small amount of the variance in cognitive variables (8% in the study of Hötting et al.; about 8–10% in cross-sectional studies, Etnier et al., 2006; Smiley-Oyen et al., 2008). Therefore, it is necessary to identify additional factors mediating the link between physical exercise and cognitive functions. Since cardiovascular fitness seems to have effects on the central nervous system via rather diffuse mechanisms (e.g. enhancing general health, increasing general blood flow and nutrition supply; Thomas et al., 2012) as well as via direct neuronal mechanisms (e.g. enhancement of neurogenesis and synaptogenesis), future studies should assess the neural mechanisms known to be more directly linked to neuroplasticity (e.g. neurotrophins, structural brain changes; see section 3 of this review for details).

To sum up, although most intervention studies on the effects of exercising on cognition have used a cardiovascular training as the experimental condition, the increase of cardiovascular fitness explained only a small amount of variance in the cognitive variables.

2.2.3. Are cognitive effects of physical activity related to specific types of exercise?

There are only a few intervention studies employing an alternative exercise to aerobic exercise. Their results suggest that resistance training (Liu-Ambrose et al., 2010; Liu-Ambrose et al., 2012) and coordination training (Voelcker-Rehage et al., 2011) might be promising candidates to prevent cognitive decline and to enhance cognitive functioning. Moreover, different types of exercise might have differential effects on distinct neuronal processes and, thus, might affect different cognitive functions. Indeed, some of the inconsistent findings reviewed here might originate from differences in the physical exercise programs employed in the different studies.

Liu-Ambrose et al. (2010) assessed performance in the Stroop task, a frequently used test for executive functions, before and after one year of resistance training in older women (>65 years of age). They reported significant improvements in executive functions for the resistance training compared to a balance and toning program. Earlier studies had reported that resistance training improved short-term memory and attention in older individuals (Cassilhas et al., 2007). Furthermore, the authors provided evidence that these effects might be mediated by an increase in the peripheral blood level of the insulin-growth-factor-1 (IGF-1). Attempts to study the impact of resistance training on neuronal mechanisms in animals are rare so far. First results of a recent animal study (Cassilhas et al., 2012) are well in line with the results found in humans: Cassilhas et al. (2012) demonstrated that aerobic and resistance training improves spatial memory, but, importantly, via distinct mechanisms: While aerobic exercise modulated the hippocampal BDNF (brain-derived neurotrophic factor), the resistance training had more pronounced effects on central IGF-1. Therefore, it might be speculated, and has been proposed based on results of a meta-analysis (Colcombe and Kramer, 2003), that a combination of aerobic and resistance training might be particularly effective in improving cognitive variables.

Coordination training (termed motor fitness by Voelcker-Rehage et al., 2010, 2011) aims at improving the efficiency of complex body movements including eye-hand coordination, leg-arm coordination and reactions to moving objects. Generally, motor coordination training does not seem to necessarily improve cardiovascular fitness. Voelcker-Rehage et al. (2011) reported better performance in a visual search task after coordination as compared to relaxation and stretching training in older adults. Additional brain imaging data revealed functional changes in frontal and parietal brain areas during an executive task which only overlapped partially with activation changes following cardiovascular training. These data suggest that different types of exercise (e.g. strength/resistance training vs. coordination training vs. cardiovascular training) affect different neuro-cognitive networks. In line with this hypothesis an improvement of episodic memory was observed in middle-aged adults after cardiovascular training but enhanced attention scores after a combined stretching/coordination training (Hötting et al., 2012b).

Moreover, the setting in which the physical training took place must be taken into account when results of physical intervention groups are compared both within a study and across studies. Many studies employed a walking or cycling training to increase participants' cardiovascular fitness and compared their results to those of a stretching or gymnastics group or a waiting control group (Erickson et al., 2011; Hötting et al., 2012b; Ruscheweyh et al., 2011; Stroth et al., 2009; Voelcker-Rehage et al., 2011). The walking programs in some studies took place in an outdoor setting (Ruscheweyh et al., 2011; Stroth et al., 2009; Voelcker-Rehage et al., 2011) while stretching and gymnastics took place in an indoor setting. Other studies had all groups exercising indoors, for example participants walked on treadmills (Smiley-Oyen et al., 2008)

Table 1
Results of a cross-sectional study exploring the association between the amount of physical exercise and learning and attention, respectively, in middle-aged (40–59 years) and older adults (60–82 years).

		Middle-aged participants ($N = 58$)	Older participants ($N = 63$)
Face–name learning			
Physical exercise (h/week)	Standardized β	0.13	*0.23*
	p	0.27	*0.05*
	R^2	0.24	0.19
Attention			
Physical exercise (h/week)	Standardized β	0.20	**0.33**
	p	0.12	**<0.01**
	R^2	0.17	0.29

Note: Linear regression analyses with face memory score and attention score, respectively, as dependent variable and physical exercise in h/week as predictor. Results of a multiple choice vocabulary test which is sensitive to the educational background (Lehrl, 2005) and gender were included into the model to account for possible confounders.
Bold values represents $p < 0.05$.
Italic values represents $p < 0.1$.

and on indoor tracks (Erickson et al., 2011) and cycled on indoor bikes (Hötting et al., 2012b). It has to be taken into consideration that an outdoor setting might provide more sensory stimulation compared to an indoor setting and outside walking might require overall higher navigation skills as any indoor activity (Burgess et al., 2002).

Usually, sedentary participants were recruited for the intervention studies as reported in the previous paragraphs. Thus, these participants did not only start to exercise but additionally got to know new environments and made new social contacts as well. Social factors and cognitive stimulation have been shown to be important factors modulating neuroplasticity (van Praag et al., 2000). Thus, future studies must disentangle the contribution of physical activity parameters (e.g. by varying the type of physical exercise), cognitive and sensory stimulation (e.g. by varying the setting in which the physical activity takes place) and social experience associated with physical exercise programs.

In sum, beneficial effects of physical activity on cognitive variables have been shown after aerobic exercise, resistance and coordination training. First evidence suggests that different types of physical training affect different neuro-cognitive networks.

2.3. *Effects of physical activity across the lifespan*

Most of the intervention studies summarized above (Colcombe et al., 2004; Erickson et al., 2011; Kramer et al., 2006; Ruscheweyh et al., 2011; Smiley-Oyen et al., 2008; Voelcker-Rehage et al., 2011) recruited adults older than 55 years of age. There are only a few intervention studies in young (Stroth et al., 2009; Stroth et al., 2010) or middle-aged adults (Hötting et al., 2012b). The relatively large number of published studies in older adults could be mainly due to the large public interest in this age group. As industrialized societies are being faced with an aging population, identifying successful interventions to maintain and enhance cognitive functioning in older age has become a growing field of research. On the other hand, it might be hypothesized that age moderates the effect size of physical activity on cognition with older adults benefitting more than younger adults. This might especially hold for executive functions (Colcombe and Kramer, 2003). Executive functions and associated frontal lobe structures are known to be particularly affected by age-related decline (West, 1995). Moreover, frontal lobe functions are known to be particularly susceptible for change in adults (Park and Reuter-Lorenz, 2009) making them promising candidates for interventions (Hall et al., 2001; Kramer et al., 1999). Thus, it might be speculated that physical exercise affects cognitive functions during phases in life during which they undergo developmental changes, such as executive functions in old age (Colcombe and Kramer, 2003).

Interestingly, the hippocampus and memory functions are characterized by a high variability across the lifespan. In humans, shrinkage of medial temporal lobe structures has been found not only in older people, but in middle-aged adults as well (Raz et al., 2010; Scahill et al., 2003). Longitudinal studies have reported a significant decrease in episodic memory after the age of 60 years (Ronnlund et al., 2005), while some cross-sectional studies have found the decline to start as early as in the second decade of life (Park and Reuter-Lorenz, 2009). On the other side, some memory functions like learning and recognizing faces does not reach the final level before the 30s (Germine et al., 2011). These different developmental trajectories across memory functions might account for the finding that exercise modulated some memory functions in young adulthood (Stroth et al., 2009) and middle age (Hötting et al., 2012b).

In order to decide about the validity of this “age-dependence hypothesis”, more than one age group needs to be included in the same study. Therefore, we recently recruited middle-aged (40–59 years of age) and older adults (60–82 years of age) for a cross-sectional study (see supplementary material for methods). Physical exercise was assessed with a questionnaire (Frey et al., 1999). Participants were asked whether they went swimming, took part in any physical exercise sessions, and if they went bowling or dancing during the last month. Moreover, they specified the time they spent with each activity during the last month. In addition, participants took part in two cognitive tests, an associative face-name learning paradigm and a selective attention task (Brickenkamp, 2002). As expected, the middle-aged group showed better learning ($t(119) = 6.06$, $p < 0.01$) and higher attention scores ($t(119) = 3.03$, $p < 0.01$) compared to the older group. Learning face-name pairs and attention scores positively correlated with the amount of self-reported physical exercise, but only in the group of participants older than 60 years (Table 1). Since the middle-aged group did not perform at ceiling, the lack of a significant correlation between cognitive variables and physical exercise could not be explained by a ceiling effect in this group compared to the older group. These data support the hypothesis that physical exercise is associated with cognitive functions mainly at ages at which these functions are subject of decline. This correlation data need to be confirmed by randomized intervention studies.

Exercising in children has become a focus of recent research (Singh et al., 2012). Most studies used a cross-sectional design (Sibley and Etnier, 2003). Interestingly, associations between both physical activity and physical exercise, and especially executive functions, have been reported in children as well (Barenberg et al., 2011; Best, 2010). Moreover, particularly strong associations have been shown between cardiovascular fitness and tasks that require a high amount of cognitive control rather than for less demanding tasks (Chaddock et al., 2012; Kramer et al., 1999;

Pontifex et al., 2011). The few existing randomized controlled trials have reported a more general improvement in academic achievement (Donnelly et al., 2009; Coe et al., 2006) and creativity (Tuckman and Hinkle, 1986). Davis et al. (2011) systematically tested cognitive subfunctions after 13 weeks of aerobic exercise in overweight children between 7 and 11 years of age. The children were randomly assigned to either 40 min/day aerobic exercise (high dose), 20 min/day aerobic exercise (low dose) and a no exercise control group. After the intervention, both exercise groups outperformed the control group in a test of planning abilities; these improvements were increasing the more the children exercised.

Executive functions critically depend on frontal lobe structures (Beer et al., 2004), which mature late in adolescence (Best and Miller, 2010; Gogtay et al., 2004). The immature neuronal circuitry might be especially sensitive to experiences and, thus, might be more easily affected by physical exercise compared to mature structures (Best, 2010). As suggested above, age-related decline in frontal lobe structures might explain the robust beneficial effect of exercising on executive functions in old age. Although the developmental changes in frontal lobe structures in childhood and adolescence clearly differ from those in old age, beneficial effects in children and adolescents in the same functional domain might be due to the high plasticity of these functions in the respective age groups.

To sum up, effects of exercise on cognition have been shown across the lifespan from childhood to old age. Comparing the results across studies suggests that the functions undergoing developmental changes (e.g. executive functions in childhood and old age) and functions which show a high intraindividual variability across the lifespan (e.g. memory) might benefit most from changes in the central nervous system induced by exercising.

3. Neural mechanisms underlying the link between physical activity and cognitive variables

3.1. Animal studies

Voluntary wheel running in rodents is a well-established animal model to study behavioral benefits and neural changes induced by exercising. One of the most often reported structural change after exercising in rodents is an increase in the rate of neurogenesis within the dentate gyrus of the hippocampus (Brown et al., 2003; van Praag et al., 1999a; van Praag et al., 1999b). The hippocampus is known to be important for spatial learning and memory. Accordingly, animals that showed an increase in neurogenesis after wheel running were found to improve in spatial learning tasks (Uysal et al., 2005) as well and additionally showed better consolidation of contextual memories (Kohman et al., 2012). Abolishing neurogenesis was observed to impair hippocampus-dependent learning (Imayoshi et al., 2008; Saxe et al., 2006), suggesting a functional role of adult neurogenesis in learning and memory. Moreover, neurogenesis continues throughout life, albeit the level of neurogenesis decreases considerably with age (Kuhn et al., 1996). Nevertheless, physical exercise seems to increase cell proliferation rates even in older animals (Kronenberg et al., 2006).

The facilitating effect of physical exercise on associative learning and neurogenesis is demonstrated by a study of Mustroph et al. (2011) as well. They showed that when mice were engaged in exercising prior to a drug conditioning procedure, they developed a stronger, that is less easy to extinguish, addiction. Thus, these data suggest that, theoretically, exercise could facilitate maladaptive forms of learning as well. By contrast, when physical exercise was administered after the drug conditioning procedure, extinguishing was facilitated and the animals showed reduced addiction compared to a drug conditioning procedure without additional exercising (Mustroph et al., 2011).

Post-mortem studies have provided evidence for adult neurogenesis in the human hippocampus as well (Bhardwaj et al., 2006; Eriksson et al., 1998). Nevertheless, it has not been possible to study an activity-dependent regulation of adult neurogenesis in humans yet. Given the relatively small number of newborn neurons compared to the total number of neurons in the adult dentate gyrus, some authors have suggested that adult neurogenesis does most likely not essentially contribute to structural changes as assessed by brain imaging techniques in humans (Zatorre et al., 2012). Moreover, neurogenesis is known to be limited to the dentate gyrus and the olfactory bulb in adult individuals (Gross, 2000), suggesting that neurogenesis plays only a minor role for the structural plasticity in neocortical regions which was observed in humans after exercising (Zatorre et al., 2012).

Despite neurogenesis, animal research has suggested that physical exercise induces a cascade of partially interdependent functional and structural changes in the nervous system. These changes included an increase in angiogenesis (Black et al., 1990; Rhyu et al., 2010) and in dendritic spine density (Stranahan et al., 2007), an enhanced long-term potentiation (van Praag et al., 1999a) and an augmented release of growth factors like the brain-derived neurotrophic factor (BDNF; Lafenetre et al., 2010; Vaynman et al., 2004) and the insulin-like growth factor-1 (IGF-1; Trejo et al., 2001). Furthermore, physical exercise has been shown to affect neurotransmitter systems, for example by increasing levels of serotonin, noradrenalin and acetylcholine (Lista and Sorrentino, 2010), or by enhancing cortical choline uptake and dopamine receptor density (Fordyce and Farrar, 1991). These factors all play important roles in inducing neuroplasticity.

3.2. Studies in humans

3.2.1. Structural and functional changes as assessed with brain imaging techniques

In humans, non-invasive brain imaging techniques have been employed to uncover the mechanisms of physical exercise induced neuroplasticity in humans. It needs to be taken into account that these techniques commonly detect changes at higher organization levels than invasive functional and structural techniques used in animal research. Moreover, the exact underlying mechanisms at the neuronal level that contribute to signal changes particular in human fMRI studies are not fully understood yet (Kelly and Garavan, 2005).

Aerobic exercise might induce beneficial effects on brain functions by changes in blood flow and vascularization which would lead to an overall better oxygen and nutrition supply. For example, physically active older adults have been found to display a higher number of small cerebral vessels than physically less active older adults (Bullitt et al., 2009).

More direct effects on the neuronal tissue were studied by Erickson and co-workers (Erickson et al., 2012). They measured N-acetylaspartate (NAA) levels in the frontal cortex of healthy, older adults using magnetic resonance spectroscopy. The authors reported a positive correlation between NAA levels and cardiovascular fitness and working memory, respectively. When dividing the participants into a young-old group (58–65 years) and an old-old group (66–80 years), a difference between low- and high-fit adults with respect to NAA levels was observed only in the old–old group. NAA is found only in neuronal tissue and plays an important role in enhancing mitochondrial energy production (Moffett et al., 2007). Therefore, it has been recognized as a marker of neuronal health, viability and number in human magnetic resonance spectroscopy (Moffett et al., 2007). Thus, Erickson et al. (2012) speculated that aerobic fitness in humans might slow down age-related decline in neuronal tissue that goes beyond vascular effects.

As summarized above, studies using magnetic resonance imaging (MRI) to track structural changes after physical exercise interventions in humans have reported increases in gray matter in frontal brain regions (Colcombe et al., 2006) and of the hippocampus (Erickson et al., 2011; Pajonk et al., 2010). Results of functional MRI studies (fMRI) have been interpreted as evidence for an increased neuronal efficiency during executive (Colcombe et al., 2004; Voelcker-Rehage et al., 2011) and memory tasks (Holzschneider et al., 2012). After six months of aerobic exercise vs. a stretching control training in older adults, Colcombe et al. (2004) observed a greater task-related activity in prefrontal and parietal areas in the aerobic group compared to the control group. In contrast, the anterior cingulate cortex (ACC) showed a reduction in activity after aerobic exercise. Reduced ACC activity was interpreted as better conflict monitoring and thus, enhanced executive functions in the aerobic group after the training. The pattern of fMRI signals with increases in frontal brain areas and a decrease in the ACC argues against the assumption that fMRI results after aerobic exercise merely reflect a global increase in blood flow rather than changes directly linked to cognitive functions (Colcombe et al., 2004). In line with these findings Holzschneider et al. (2012) reported a correlation of training induced changes in cardiovascular fitness and changes in the fMRI signal in the medial frontal gyrus and cuneus. These authors had investigated spatial learning before and after six months of regular exercising. The association between brain activation changes and cardiovascular fitness was specific for the spatial learning condition, but, however, a similar correlation was not found in a non-spatial control condition. These results provide evidence for the assumption that cardiovascular fitness specifically affects neuronal processing in task-relevant brain areas (Holzschneider et al., 2012).

Changes in task-related fMRT signals might be due to increased neuronal efficiency within the respective region, but might be influenced by changes in functional connectivity between brain regions as well. Recent studies provide first evidence that exercising may increase the functional connectivity between brain areas in humans, especially the connection between the hippocampus and the ACC (Burdette et al., 2010). Moreover, a stronger connectivity within the default mode network and the frontal executive network (Voss et al., 2010) has been observed after physical exercise. Future studies must investigate the relation between local activity changes and changes in connectivity.

One might ask whether changes in functional MRI studies observed after exercising were related to structural changes. Although the exact mechanisms are yet unknown, it has been suggested that experience-related structural changes have a direct effect on the fMRI signal (Poldrack, 2000). A change in the functional activation pattern, however, does not necessarily indicate structural changes. Thus, future studies would benefit from a parallel assessment of functional and structural changes.

3.2.2. *Neurotrophins*

Analogous to animal studies, levels of neurotrophins, such as IGF-1 and BDNF have been measured after exercising in humans. For example, it has been found that the peripheral BDNF level increases in humans after an acute bout of physical exercise and returns to baseline within a few minutes to several hours (Gold et al., 2003; Winter et al., 2007; for a review see Knaepen et al., 2010). A few studies have reported changes in the BDNF level after an endurance training that lasted for a few months (Seifert et al., 2010; Zoladz et al., 2008). However, other authors failed to observe changes in BDNF levels after chronic exercising (Ruscheweyh et al., 2011; Schulz et al., 2004). The data on acute exercise effects on peripheral IGF-1 levels in humans are similarly inconsistent (Nindl and Pierce, 2010): while a few studies reported an increase in IGF-1 after exercising (Rojas Vega et al., 2010), others failed to find similar effects (Stokes et al., 2010). Chronic exercise interventions, and especially resistance training regimes have, however, been found to augment the IGF-1 level (Cassilhas et al., 2007; Koziris et al., 1999; Sillanpaa et al., 2010).

Since neurotrophic factors can only be assessed in the peripheral blood in humans, the validity of this approach has been questioned (Knaepen et al., 2010). BDNF, for example, is produced by peripheral non-neuronal and neuronal tissue as well as by central neurons (Huang and Reichardt, 2001). The contribution from peripheral vs. central sources relating to the increase in circulating BDNF after exercising is not yet known (Zoladz and Pilc, 2010). Moreover, it has been disputed whether BDNF crosses the blood-brain barrier (Zoladz and Pilc, 2010). Thus, it remains to be shown that an increase in the peripheral neurotrophic factors correlates with an increase in the central nervous system.

3.2.3. *Indirect effects of physical activity on brain health*

Besides these direct effects of physical exercise on neuronal processes, regular physical activity is known to reduce the risk of chronic diseases, including cardiovascular diseases, stroke, hypertension or type 2 diabetes mellitus (Haskell et al., 2007). These diseases are associated with a higher risk of dementia (Haan and Wallace, 2004). Moreover, the endocrine effects of the metabolic syndrome, a constellation of metabolic disturbances that comprises risk factors for diabetes and cardiovascular diseases, have been shown to alter neuronal functioning and to accelerate cognitive decline in aging humans (Stranahan and Mattson, 2012). There is evidence that the metabolic syndrome can be reduced or even reversed by regular physical activity (Eckel et al., 2005). Some protective effects of physical exercise on cognitive aging might therefore be due to an attenuation of risk factors associated with the metabolic syndrome (Cotman et al., 2007; McAuley et al., 2004). In sum, data from animal studies provide convincing evidence that physical exercise up-regulates brain processes associated with neuroplasticity, especially in the hippocampus. First results suggest that exercise induces functional and structural changes in the central nervous system in humans as well. The exact mechanisms, however, are not yet known. Moreover, indirect beneficial effects of exercising on cognition might be mediated by reducing risk factors for cognitive decline.

4. Combining physical exercise with cognitive challenges

Animal research has suggested that the hippocampus and spatial learning abilities are not only susceptible to physical exercise, but can also be affected by cognitive stimulation. In rodents, both wheel running and practicing hippocampus-dependent learning tasks have been shown to enhance neurogenesis (Gould et al., 1999; van Praag et al., 1999a), to increase the release of neurotrophins (Kesslak et al., 1998; Vaynman et al., 2004) and to improve spatial memory (Uysal et al., 2005; van Praag et al., 2005). The neural mechanisms mediating physical exercise and cognitive stimulation induced cognitive effects, however, were successfully separated at the cellular level in animal models. Physical exercise increases the proliferation of precursor cells in the subgranular zone of the dentate gyrus (Kempermann et al., 2010). Running, at least over shorter periods of time, seems to be insufficient to promote the survival and integration of these new cells into functional networks (Kronenberg et al., 2006). Environmental enrichment and complex learning tasks, on the other hand, do not affect the proliferation of precursor cells to the same degree as running but rather promote the survival of new neurons (Kempermann et al., 2010). These findings suggest that a combination of physical activity with cognitive challenge might be particularly effective in inducing beneficial prevailing effects on the brain's structure and function (Kempermann, 2002). Indeed, this hypothesis has been supported by animal research: when mice were engaged in voluntary wheel running before they were exposed to an enriched environment, they showed a more pronounced increase in neurogenesis compared to animals exposed to only physical exercise or only to an enriched environment (Fabel et al., 2009).

There are a large number of studies which reported beneficial effects of either physical exercise (Hillman et al., 2008) or cognitive training (Lövden et al., 2012; Stine-Morrow, 2011) on the functional or structural organization of the human brain. However, hardly any study has combined both interventions. At the behavioral level, Fabre et al. (2002) provided first evidence that a combination of an aerobic endurance training and a cognitive training targeting various cognitive functions (e.g. memory, attention, spatial skills) might be more effective in improving cognition in older adults than any of the interventions alone or no training at all. Recently, Holzschneider et al. (2012) combined a physical exercise and spatial memory training and tested effects on spatial memory functions both at the behavioral and neural level. Forty to fifty-five years old, sedentary adults were randomly assigned to either a six-month long aerobic endurance training ('cycling') or a non-endurance control training (stretching/coordination) of the same duration. In the last month of the physical training participants took part in six additional cognitive training sessions; either a spatial training ('spatial training') or a non-spatial visual-perceptual control training ('perceptual training'). Spatial learning skills and functional brain activation (*f*MRI) were measured during a spatial maze learning task before and after the interventions. After the physical and the cognitive intervention, participants of the spatial learning groups showed a larger improvement in the maze task than the perceptual learning groups, irrespectively of the type of previous physical training (Holzschneider et al., 2012). Moreover, at post-test, participants of the spatial training group activated a network of regions associated with spatial learning, including the hippocampus and the parahippocampal gyrus, to a lower degree compared to the perceptual training group (Hötting et al., 2012a).

In participants who had received both, a cardiovascular training *and* a spatial cognitive training, a positive correlation between the brain activation level associated with the spatial task and the level of cardiovascular fitness (VO_2peak values) was observed (Holzschneider et al., 2012). This correlation was found mainly for the medial frontal gyrus and the cuneus (Fig. 1). These results provide first evidence in humans that a physical training (over six months) alone might not be sufficient to induce significant functional changes in brain networks of spatial learning. Rather these data suggest in accord with results from animal research (Fabel et al., 2009) that physical and cognitive stimulation might provide complementary contributions necessary for improving brain functions. Interestingly, the effects of cognitive training were more pronounced than effects of physical exercise (Holzschneider et al., 2012). Therefore, it might be speculated that cognitive stimulation such as spatial learning, addresses associated functional networks in a more specific manner than physical exercise interventions. This hypothesis is in line with results from cognitive training studies in humans, demonstrating effects in specific functional networks rather than overall changes in brain functioning, e.g. in the hippocampus after language learning (Martensson et al., 2012), in visual-motion areas after juggling (Draganski et al., 2004) or in auditory and motor areas after musical training (Hyde et al., 2009). By contrast, physical exercise might have stronger overall facilitating effects on learning, such as an increase in angiogenesis and in the availability of certain neurotrophins, which are prerequisites of neuroplasticity.

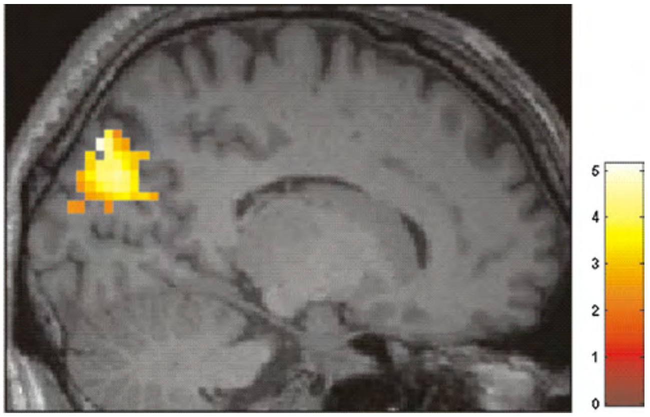

Fig. 1. Results of a combined physical exercise and spatial training. FMRI data showing the activation difference (pretest vs. post-test) in the cuneus correlating positively with the changes in VO_2peak in a group of participants that received a spatial training in addition to physical exercise (FDR-corrected, $p < 0.05$, > 4 voxel per cluster; derived from a ROI analysis of the cuneus. $x = 15$, $y = -81$, $z = 24$). The activations are superimposed on a normalized T1 image of one participant. Color scale indicates *T*-Scores.

Source: Adapted from Holzschneider et al. (2012).

In sum, physical exercise may prepare the brain to respond to cognitive stimulation (Kempermann, 2008). A cognitive training then induces neuronal changes in specific networks associated with the trained skill. This does not rule out the possibility that certain brain regions are more susceptible to physical exercise than others, and that physical exercise training alone can have effects on cognition and neuroplasticity under some circumstances. As discussed above (Section 2.3), during epochs of enhanced neuroplasticity (as in childhood and adolescence) or neuronal decline (as in aging populations) the changes induced by physical exercise might sometimes be sufficient to induce behavioral relevant changes. Nevertheless, we put forward the hypothesis that these changes might be potentiated by a combined physical and cognitive stimulation, as has been shown in animals (Fabel et al., 2009).

5. Long-term effects of exercise

As outlined in this review so far, data from intervention studies have provided convincing evidence that a few months of regular physical exercise have positive effects on cognitive functioning. However, little is known about the sustainability of exercise induced effects on cognitive functions; that is whether or how long gains prevail and under which conditions they prevail. Follow-up data one or more years after the end of an intervention would not only inform about a possible causal relationship between physical fitness and cognitive capabilities but would have consequences for the design of public health programs as well.

Rhyu et al. (2010) studied angiogenesis in monkeys immediately and three months after an aerobic exercise program which had lasted for five months. An increased angiogenesis compared to sedentary control animals was observed only immediately after the training, but not three months later, suggesting that effects of physical exercise on brain vasculature were only transient. Additional results from enrichment studies in rodents have suggested that environmental effects on neuroplasticity disappear after the enrichment ended (Green and Greenough, 1986). Importantly, however, prolonged exposure to an enriched environment for several months might have a longer lasting effect (van Praag et al., 2000).

In humans, follow-up data after exercise interventions have been rare so far. One study in older adults at risk for dementia reported beneficial effects on cognitive variables up to one

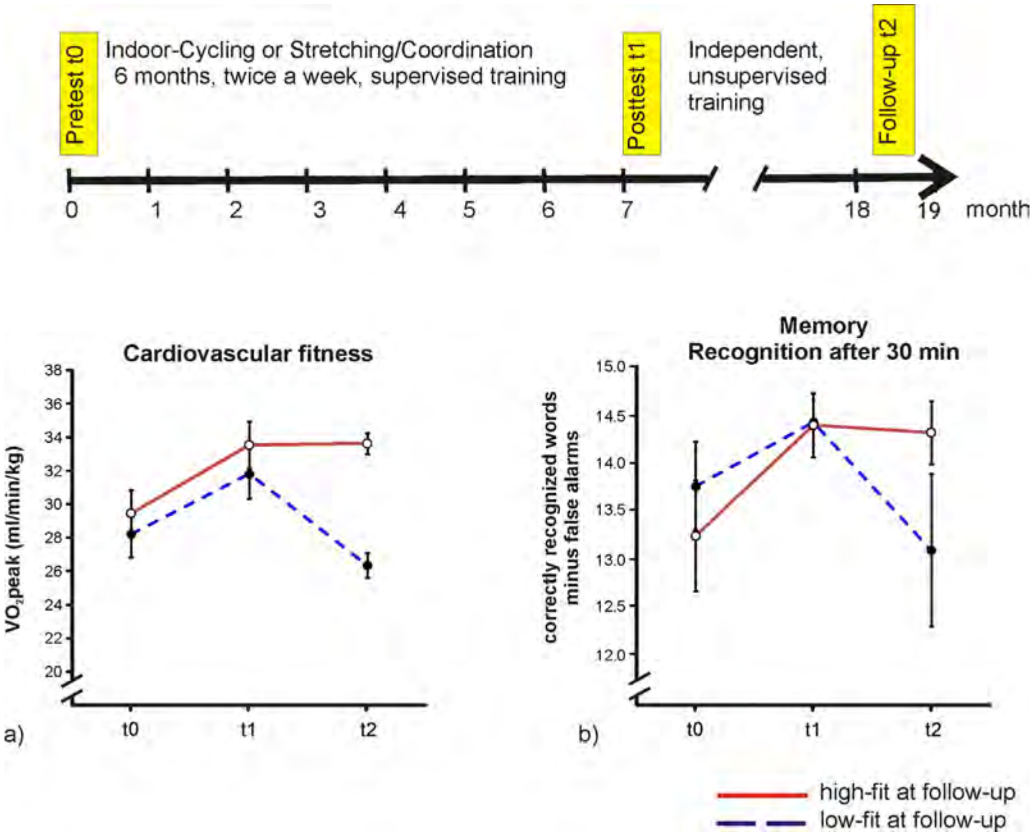

Fig. 2. Study design (top) and results (bottom) of a physical exercise intervention study with a follow-up assessment of learning and memory one year after the end of the supervised training. Cardiovascular fitness and cognitive variables were assessed before the start of either a cycling or a stretching/coordination training (*t*0), after six months of taking part in the assigned intervention (*t*1) and again one year after the end of the intervention (*t*2). Cognitive data at *t*2 was analyzed with respect to participants' cardiovascular fitness at *t*2. Cardiovascular fitness (a) and memory (b), recognition score 30 min. after learning of a list of words) were depicted separately for participants with high fitness (red, solid line) vs. low fitness (blue, dashed line) at follow-up. Group means with standard error bars (for interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

Source: Adapted from Hötting et al. (2012c).

year after the end of a home-based program of physical activities (Lautenschlager et al., 2008) suggesting that such programs have sustainable effects on cognitive outcomes. Although physical activity in this study decreased after the end of the six-month program, participants' average physical activity was still above the pre-intervention baseline level. Unfortunately, Lautenschlager and co-workers did not analyze a possible correlation between the amount of physical activity and cognitive variables at follow-up.

Hötting et al. (2012c) were able to follow-up participants one year after they finished a supervised exercise intervention. During the intervention, participants took part twice a week in either an aerobic exercise training (cycling) or a non-endurance training (stretching/coordination) for a period of six months (summarized in Section 2.2). At the end of the intervention participants were encouraged to continue exercising and were informed about sports facilities in their neighborhood. Nevertheless, they were not specifically instructed how to continue (Fig. 2). One year after the end of the supervised training, participants were invited for a follow-up assessment to test whether post-intervention variance in cardiovascular fitness was related to cognitive functions. Based on their VO_2peak value at follow-up, participants were divided into a low- vs. high-fit group, irrespective of their group assignment during the intervention phase. As seen in Fig. 2, cardiovascular fitness remained stable in the high-fit group from post-training to follow-up, while VO_2peak values decreased in the low-fit group. The high vs. low fit groups, however, did not differ with respect to VO_2peak or any cognitive variables, neither at baseline nor after the end of the six months lasting training. Importantly, changes in cardiovascular fitness during the one year follow-up were mirrored by changes in episodic memory: the group of participants with higher cardiovascular fitness at follow-up performed at a similar high level in a memory task one year after the end of the intervention as immediately after the intervention. By contrast, participants with lower cardiovascular fitness lost in memory. These results suggest that an active maintenance of cardiovascular fitness might be necessary to keep cognitive capabilities at a higher level.

Although there is converging evidence that regular physical exercise across the lifespan has beneficial effects on cognition and contributes to the prevention of many diseases (Haskell et al., 2007), a rather physically inactive lifestyle is common in industrialized societies. Survey data from the United States and Germany have found that less than half of the American and German adults meet the exercise recommendations of the American College of Sports Medicine and the American Heart Association (Haskell et al., 2007; Mensink, 2003). For the study reported above (Hötting et al., 2012b; Hötting et al., 2012c), we had recruited sedentary participants. On average, they had reported exercising 0.25 h/week at baseline and thus, did not meet these recommendations either. During the intervention phase, participants exercised two hours/week. On average, they were able to maintain this amount of activities one year later and most of the participants met common exercise recommendations at follow-up (Haskell et al., 2007). Thus, one might ask which factors determine whether or not an individual establishes a physically active lifestyle after an exercise intervention. Strategies to implement behavior changes and to improve health behavior have been the subject of psychological

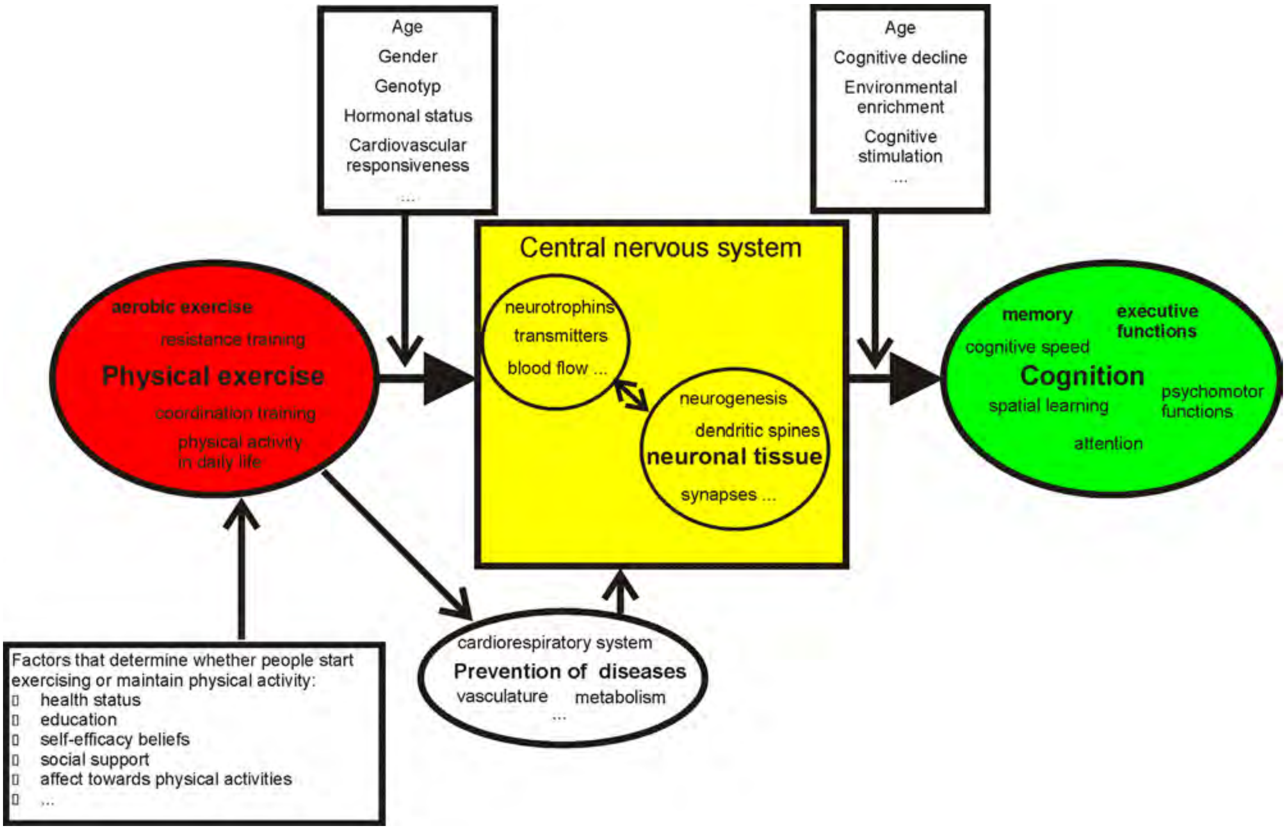

Fig. 3. Summary of the possible relationship between physical exercise, neuroplasticity and cognition with possible moderator variables which might influence exercise behavior, the impact of exercising on the central nervous system and whether changes in the nervous system translate into measurable changes in cognitive variable. This schematic summary is far from being complete and neglects possible reciprocal connections between the variables which have rarely been studied so far.

research for decades (Oettingen, 2012). It is, however, beyond the scope of this paper, to summarize the findings of this research. Here we would like to demonstrate with one example, how psychological factors modulate the outcome of physical exercise studies.

In social cognitive theory, efficacy beliefs (peoples' belief in their capacities to execute an action) play a central role in predicting how long people sustain an action despite obstacles and failures (Bandura, 2001). For example, it has been reported that self-efficacy beliefs in older adults predicted whether or not people continue physical exercise up to 18 months after a physical exercise intervention (Litt et al., 2002; McAuley et al., 2003). In accordance with these reports, Hötting et al. (2012c) found that middle-aged adults that reported high self-efficacy beliefs at follow-up, had engaged in sports activities for more hours after the end of the supervised intervention than those who reported low self-efficacy beliefs.

In addition to psychological factors, other variables seem to influence the effectiveness of physical training interventions. For example participants differ in their responsiveness to aerobic exercise (Bouchard and Rankinen, 2001). Indeed, Hötting et al. (2012b) observed an increase in the variance of the VO_2peak among participants after the intervention. The cardiovascular fitness was a better predictor for cognitive changes than the type of intervention, suggesting that individual differences in the responsiveness to exercise must be taken into account when analyzing relationships between exercising and cognitive variables. However, as mentioned above, no more than eight percent of the variance in memory scores was explained by cardiovascular fitness. Thus, future studies must address additional moderator variables influencing the effects of physical and cognitive exercising on neural and cognitive processes. Results of recent studies suggest that variables like gender (Colcombe and Kramer, 2003), hormonal status (e.g. estrogen replacement therapy in postmenopausal women; Erickson et al., 2007), genotype (Rovio et al., 2005; Stroth et al., 2010), social support (Litt et al., 2002) and affects toward exercising (McAuley et al., 2003) might be additional moderator variables (see Fig. 3 for a summary).

The currently available literature strongly supports the assumption that physical exercise does have beneficial effects on cognition by enhancing neuroplasticity and preventing diseases associated with cognitive decline. The interaction between cognitive and physical interventions is not yet known, and has to be addressed in future studies as well as the modulating influence of additional psychological and physical constitution variables.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2013.04.005.

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