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Review

The influence of exercise on brain aging and dementia ☆

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ABSTRACT

Physical activity has been recognized as an important protective factor reducing disability and mortality and therefore it is focus of many health promotion activities at all ages. More recently a growing body of literature is focusing whether physical activity could also have a positive impact on brain aging with exploring healthy brain aging as well as on cognitive impairment and dementia. An increasing number of prospective studies and randomized controlled trials involving humans take place both with older adults with normal cognition as well as with mild cognitive impairment or dementia. However, the body of evidence is still sparse and many methodological issues make comparisons across studies challenging. Increasingly research into underlying mechanisms in relation to physical activity and brain aging identify biomarker candidates with especially neuroimaging measurements being more used in trials with humans. Whilst the evidence base is slowly growing more detailed research is needed to address methodological issues to finally achieve clinical relevance. This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

1. Introduction

There is clear evidence that physical activity (PA), if performed safely, can contribute to healthy aging and reduce morbidity and mortality rates [1,2]. Even when performed in old age it has multiple health benefits [3]. Accordingly, PA is seen as an important modifiable behavioral factor and is often the focus of health promotion initiatives. More recently, researchers have begun to focus on whether PA could also contribute to healthy brain aging and this has prompted calls that it should be investigated more closely as a potential protective factor against cognitive decline and dementia. Despite warnings that more research evidence is needed [4], consumer organizations such as Alzheimer Associations in many countries specifically recommend PA as an activity that might help prevent cognitive decline and dementia. This is understandable in light of the rising incidence of cognitive impairment and dementia around the globe. In 2006, the estimated number of people suffering from Alzheimer's Disease (AD), the most common neurodegenerative form of dementia, was 26.6 million worldwide with an estimated increase to 106.8 million by 2050 [5].

It is now commonly accepted that older adults who develop AD experience a transitional phase between normal cognition and their clinical diagnosis of AD, where they experience some form of cognitive impairment which is too mild to fulfill current dementia criteria [6]. In a recent American population-based study, it was estimated that approximately 22% of Americans aged 71 years and older experience what is called cognitive impairment no dementia (CIND). CIND includes many underlying causes and not all need to lead to progressive cognitive decline.

However, 43.2% of those experiencing CIND were categorized as suffering from prodromal AD (defined as CIND with a clinical presentation and test results suggesting the presence of AD pathology in the absence of other conditions). In comparison, only 4% were labeled as having amnestic Mild Cognitive impairment (MCI) which is associated with an increased risk of developing AD in the future [7]. In the same study, follow-up data available for an average of 17 months revealed an annualized conversion rate to dementia of 11.7% for CIND and of 20.1% for prodromal AD. These figures indicate that a substantial number of the aging global population is experiencing some form of cognitive impairment and therefore investigating potential protective modifiable factors which could help to slow down or prevent cognitive decline, such as PA, is of significant relevance. Given that currently no specific medication is available that convincingly reduces AD risk, despite intense research activities in the drug development field, this makes the case for investigating modifiable environmental factors such as PA even more salient and in urgent need of investigation. In this context, primary (older adults with normal cognition), secondary (older

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adults with CIND or MCI) and tertiary (older adults with dementia) prevention strategies in relation to PA are of interest. This review aims to give an overview on recent evidence from prospective studies, and randomized controlled trials (RCT) on physical activity and the aging brain. We will discuss the three prevention categories in more detail and will highlight questions for future research.

2. Overall health benefits of physical activity

Physical inactivity is an independent factor contributing to mortality and disability with estimates of 5–10% deaths worldwide being due to inactivity [8]. An inverse relationship between total PA and all-cause mortality has been demonstrated for men and women [9,10].

Regular PA has been seen to be protective by reducing mortality risk even in people with chronic disease. In older adults with two or more chronic health conditions, after 42 months those who reported less than 30 min a week of PA had a mortality risk ratio of 2.82 compared with those who engaged in 30 min or more of PA a week [11]. The evidence that moderate or high levels of cardiorespiratory fitness (CRF) reduce the risk of all-cause mortality and cardiovascular disease (CVD) mortality independent of other risk factors is convincing [12–14]. For most people regular PA will improve CRF. The maintenance of increased PA or CRF reduces the risk of all-cause mortality [15,16]. The benefits of regular PA are well established and are numerous. They include reduction in the risk of CVD; hypertension; stroke; diabetes; obesity; osteoporosis; colon and breast cancer and improvements in aspects of mental health [17]. In addition, for older adults there is a growing body of evidence that PA reduces risk of falls, lessens functional limitations and prevents or delays cognitive impairment [18].

3. Prospective studies investigating PA and cognition in old age

There is a sizeable body of epidemiological literature investigating the association of PA and risk of cognitive impairment or dementia in older age. A recent systematic review [19] investigated the evidence provided by 127 observational studies between 1984 and 2009 from economically developed countries on protective as well as risk factors for cognitive decline. Selected studies had to involve 300 or more participants from the general population 50 years and older with a follow-up period of at least 12 months. Observational studies focusing on leisure activities showed that PA potentially decreased relative risk, with risk or hazard ratios in the range of 0.6 and 1.6. In the same review, PA was assigned a low quality of evidence.

Sofi et al. [20] performed a systematic review of 15 prospective studies with a combined number of 33,816 non-demented participants, aged 65 years and older who were followed between 1 and 12 years. During the follow-up period, 3210 incident cases of cognitive decline occurred. The group reports a significant protective effect of PA against cognitive decline with a hazard ratio of 0.62 (95% CI: 0.54 to 0.70; $p<0.00001$) for high level activity (38% risk reduction in cumulative analysis) and a hazard ratio of 0.65 (95% CI: 0.57 to 0.75; $p<0.00001$) for low-to-moderate level activity (35% risk reduction in cumulative analysis) compared with sedentarism. The authors flagged several limiting factors to this meta-analysis including inconsistent definitions of PA across studies and the use of cognitive assessment tools that lacked sensitivity, such as the Mini-Mental State Examination test (MMSE).

Paterson and Warburton took a different approach in their systematic review [21] of 66 prospective cohort and intervention studies by focusing on functional status, of which 34 included information on cognitive outcomes (on 19,988 participants in total). The median follow-up period was 7 years (range between 2 and 25 years). They highlighted that PA was categorized in many different ways across studies as was the outcome measure functional status (cognitive speed, visual memory, verbal memory, working memory, executive functions, visual attention and auditory attention). Level of PA was expressed several ways, including total energy expenditure, frequency and duration, and relative intensity or type of PA (walking, sports, play, recreation, household chores). Nevertheless, they attributed a 50% overall reduction in risk of functional impairment and disability to PA. The PA needed to be moderate and high levels (e.g. 30 to 60 min per day or 150 to 180 min per week). The authors concluded that light intensity PA might be ineffective. These findings related to aerobic PA. There was a positive relationship between PA and cognitive function in 71% of the studies.

However, the authors reported that the changes were mostly in only one or two cognitive tests and were usually small in magnitude. Overall, the authors assigned a Level 2, Grade A to the evidence that PA can reduce the risk of cognitive decline, but interpret the evidence for recommendation of PA for protection of cognition as being at Level 3, Grade B due to conflicting findings and enormous variability of assessments and outcomes measured.

These three recent systematic reviews are just examples of an abundant number of epidemiological studies investigating the association between PA and cognitive function or dementia with often conflicting results [22–37]. Jedrziewski et al. [38] noted that most of the negative epidemiological studies had less than 1000 participants. This team investigated the impact of PA on cognition using the data set of the National Long Term Care Survey with 3863 non-demented individuals at baseline and a follow-up period of 10 years. At baseline, participants provided information on how many minutes per session in the previous two weeks they engaged in any of 23 listed physical activities. From the 10-year data they reported a significant protective effect of the number of PA sessions with a duration of at least 20 min ($p=0.007$). The cognitive outcome measure used was the Short Portable Mental Status Questionnaire (SPMSQ). Gardening/yard work showed a significant protective effect with number of sessions of 20 min or more ($p=0.026$). Additionally, both walking ($p=0.020$) and gardening/yard work ($p=0.003$), if performed for at least 20 min per session, had a protective effect against losing independent living status in the community.

4. Clinical trials

4.1. Older adults with normal cognition

There are a number of systematic reviews on clinical RCTs with cognitively healthy older adults investigating the benefits of a PA intervention. Colcombe and Kramer [39], for example, found in their meta-analysis a relative combined effect size of 0.32 when intervention and control groups were compared. Others have found evidence of a positive effect of aerobic exercise, particularly on executive function, attention and processing speed. They also highlight the difficulties of comparing studies due to a large variation in study population selection, exercise protocol, control group design and selection of varied and often large number of cognitive tests as outcomes [40,41]. Muscari et al. [42] therefore chose to go back to basics and used as their primary cognitive outcome measure, the clinically most commonly used cognitive screening test, the Mini-Mental State Examination test (MMSE) for their RCT. This study from Northern Italy, involving 120 cognitively healthy older adults, consisted of an intervention comprising 12 months of supervised endurance exercise training (EET) (three 60 min sessions per week) in a community gym and a control group who received educational material about a healthy lifestyle. The EET included cycle ergometer, treadmill and free-body activity with the intensity individually adjusted so that 70% of maximal heart rate was achieved for at least 20 min per session. The primary outcome was change on the MMSE after one year. The control group showed a significant greater decline ($p=0.02$) on the MMSE compared to the intervention group, which experienced a very small amount of decline (control: −1.21 points; 95:% CI: −1.83 to −0.60, $p=0.0002$ versus intervention: −0.21 points; 95:% CI: −0.79 to

0.37, p = 0.47). This resulted in an odds ratio of 2.74 (95% CI: 1.16 to 6.48).

However, when physiological measures of EET were examined there was no reduction in heart rate nor was there a significant correlation between changes of fitness after one year and change in MMSE score. The authors acknowledge that a limitation of this study was the relative large amount of missing data.

Klusmann et al. [43] compared in 259 cognitively healthy women aged 70 and over, a cognitive intervention with a PA intervention and a control group. The intervention took place three times per week for 1.5 h in groups of 12 and lasted for 6 months. The participating women had to be computer illiterate and also exercised less than 1 hour per week. The PA intervention included aerobic, strength, balance, coordination and flexibility components. The cognitive training intervention was a computer course. The outcome measure was a cognitive test battery. Both intervention groups showed a significant improvement ($p<0.001$) on delayed story recall compared to the control group (40% improvement for the PA group and 35% for the cognitive intervention group). There were no significant differences between the two intervention groups. The authors acknowledged that one limitation of their approach was using a variety of cognitive outcomes and also questioned to what extent the social component of the two interventions contributed to the finding.

Finally, Baker et al. [44] investigated the impact of a 6-month aerobic exercise program compared to a stretching control group on cognition in 28 cognitively healthy older participants with impaired glucose tolerance. This is an interesting approach since impaired glucose intolerance is a significant risk factor for type II diabetes and diabetes has been identified as an important risk factor for cognitive decline and AD. Primary cognitive outcomes focused on executive function tests, which were significantly improved in the aerobic group ($p = 0.04$).

The aerobic group also experienced improved cardiorespiratory fitness ($p = 0.03$) as well as insulin sensitivity ($p = 0.05$). Interestingly there was also a trend of a reduction of the AD biomarker Aβ42 plasma levels in the aerobic group ($p = 0.07$).

4.2. Older adults with cognitive impairment without dementia

The previously mentioned recent systematic review by Plassman et al. [19] investigated 22 RCTs with at least 50 participants with CIND and a trial duration of at least 12 months. They only reported one RCT on PA which fulfilled their criteria and was published in the search period (1984–2009). The Fitness for the Aging Brain Study (FABS), a single-site RCT, was conducted in Western Australia [45] with 170 community-dwelling volunteers, 50 years and older, with subjective memory complaints or MCI. The 24-week home-based intervention with a target of at least 150 min PA per week was individually tailored with a focus on walking, but also allowed other modes of PA depending on preference and co-morbidity. A modified behavioral approach based on social cognitive theory [46] was chosen to enhance compliance and adherence via a workshop, manual, newsletters and regular phone calls. Participants were re-assessed at the end of the active intervention period. They then were encouraged to continue with their PA program, but without any further structured support from the research team, and were re-assessed after 12 and 18 months. The primary outcome measure was the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog). At the end of the intervention at 24 weeks, there was an absolute difference of –1.3 points on the ADAS-cog (95% CI: −2.38 to −0.22 points), which was significant.

Interestingly, the significant difference was not lost 12 months after completion of the active intervention. At 18 months, the intervention group showed an improvement on the ADAS-cog (scale of 70 points) of 0.73 points (95% CI: −1.27 to 0.03 points) compared to a 0.04 point improvement (95% CI: −0.46 to 0.88; $p = 0.04$) in the control group. Whilst this finding is encouraging, it is unclear whether it has any clinical relevance.

With PA interventions the greatest health benefits are seen with individuals who are sedentary. A beneficial effect on cognition was demonstrated by Baker et al. [47] in a study with 33 previously sedentary (defined as less than 30 min of PA fewer than three times a week in the past six months) older adults with MCI. The participants were randomly assigned to either six months of aerobic training or a control group that did flexibility exercises. The results showed a gender-specific effect with women in the aerobic group demonstrating improved executive function as well as some interesting changes in biological variables such as an increased glucose disposal and reduced fasting plasma levels of insulin, cortisol and brain-derived neurotrophic factor. On the other hand male participants improved on the Trails B test and had increased plasma levels of insulin-like growth factor 1. The authors suggested that these findings might be due to gender-specific differences in certain metabolic systems.

In a Hong Kong-based study [48], 389 non-demented adults, 65 years or older with either a diagnosis of amnestic MCI or a Clinical Dementia Rating (CDR) score of 0.5, both indicating an increased risk for future cognitive decline, were recruited from 19 social centers or residential homes for elders. The participating centers were cluster randomized either to an intervention or control group.

The intervention group trained for 12 months in 24 forms of simplified Tai Chi with the target to exercise at least three times per week for no less than 30 min per session. In the induction phase (first 8 to 12 weeks) the participants learnt the correct techniques from Tai Chi masters and then received a training video or DVD for the maintenance phase. The control group practiced stretching exercises which were conducted by trained allied health staff and varied from centre to centre. Two months after completion of the induction phase, both groups showed significant improvement regarding their subjective cognitive complaints (measured with the Memory Inventory for the Chinese (MIC)) and cognitive performance (measured with the ADAS-cog, MMSE, delayed recall, Trail A, verbal fluency test) ($p<0.05$). The intervention group showed additional improvement on a balance test (Berg Balance Scale), in visual attention and on the CDR sum of boxes score. Logistic regression demonstrated that the baseline ADAS-cog score and the word fluency tests significantly predicted the development of dementia at 12 months. Participation in the intervention group showed an independent association with a stable CDR score at follow-up (OR = 0.14; 95% CI: 0.03 to 0.71, $p = 0.02$). The authors conclude that the improvement in visual attention in the intervention group might be related to the specific demands of Tai Chi with a focus on posture and motor sequence. This raises the interesting question as to whether physical activities which have an integral cognitive component, such as having to remember the motor sequences of Tai Chi or having to remember the step sequences while dancing, might have more of a protective effect due to the additional cognitive activity.

Liu-Ambrose et al.[49] recently published a study protocol for a 12-month RCT with the novel approach of focusing on older adults who have mild sub-cortical Ischaemic Vascular Cognitive Impairment (SIVCI). They made the important point that cerebrovascular disease contributes to the second most common cause of dementia, vascular dementia (VD). It is now increasingly accepted that vascular risk factors such as hypertension, obesity, hypercholestorelaemia, diabetes mellitus, smoking and heart disease also increase the risk not only of stroke, cerebrovascular disease and VD, but also AD [50] and that both cerebrovascular disease and AD seldom appear in isolation [51]. The authors report that their study aims to recruit 60 non-demented participants with SIVCI and randomize them either to aerobic PA training or a usual care control group. The intervention will be group based and last for six months. Outcome parameters will be cognition, biomarkers, physical function and fall risk, quality of life and health resource utilization.

4.3. Older adults with dementia

A recent systematic review by Blankevoort and colleagues [52], including 16 clinical trials on PA interventions in patients with dementia, concluded that PA can improve physical functioning at almost every stage of dementia. They reported that a combination of different types of PA (e.g. endurance, strength and balance training) led to greater improvement of physical function than progressive resistance training alone, suggesting that a multi-component PA intervention may be more effective. The high drop-out rate of 20–25% was expected, but it was remarkable that no participant had to withdraw due to adverse effects of the intervention. The authors concluded that the higher training volumes resulted in larger improvements in physical functioning. However, they note that the number of included studies was small, the differences between the PA programs (range of duration varied between three weeks to four years) were large and that there was a lack of high-quality methodological approaches. Only four studies included measurements of basic activities of daily living and the results were inconsistent.

Based on the results, Blankenvoort and colleagues [52] recommend that future clinical trials should have an intervention duration of at least 12 weeks with a training frequency and duration of three times a week for 45 to 60 min. Despite the limitations of this review, these findings suggest that PA programs for older adults with dementia are of benefit for physical function. But can improvement or a slowing down of deterioration also be achieved for cognitive function, behavioral and psychological symptoms and quality of life? A few systematic reviews have provided an encouraging indication that PA interventions for older adults with dementia might be of significant benefit for cognition and behavior [53,54], however they pointed out that more clinical trials are needed.

Recently, a French research team [55] conducted a small RCT with participants with AD residing in nursing homes. Participants needed to be able to walk at least 10 meters without technical assistance. Thirty-one out of 38 participants were able to complete the study. The intervention consisted of 15 weeks of three 60-minute PA sessions per week focusing on walking, stamina and equilibrium. Cognitive outcome was the French ERFC (Rapid Evaluation of Cognitive Function) which includes 12 sub-tests covering various cognitive functions. Participants in the intervention group improved their ERFC score significantly ($p<0.01$) whereas participants in the control group experienced a deterioration of their score. The authors found a significant correlation between the improvement on the ERFC and the walking speed ($p<0.01$), stride length ($p<0.01$) and double limb support time ($p<0.01$) in the intervention group. Participants in the control group deteriorated in walking speed and stride length. The authors acknowledged that limitations of their trial include the small sample size as well as not being able to rule out that an increase in contact time might have contributed to the cognitive improvement rather than the PA alone.

They also provided no information on medications and co-morbidities. The authors concluded that their findings are consistent with a small number of previous studies [56–58].

Another small RCT with 27 patients with AD [59] also reported some positive findings. The participants were randomized either to a six-week PA intervention or a standard care control group. Participants were recruited from the National Health Service Memory Clinic in the United Kingdom and had to have a MMSE score of at least 12 points. The intervention followed the Brain Gym ® Programme[60] and spanned 15 exercises focusing on fine motor involvement, balance and hand–eye coordination. The cognitive outcome measure was the Cambridge Neuropsychological Test Automated Battery (CANTAB)-Expedio. Participants in the intervention group experienced significant improvements in attention and visual memory whereas the control group deteriorated in attention. The authors pointed out that their trial was a pilot study with a small sample size and results were not adjusted for the use of psychotropic or cognitive enhancing medication.

There are also three recent interesting RCTs underway with this population. Cerga-Pashoja at al. [61] aim to recruit 146 community-dwelling participants with dementia and their carers to investigate the effectiveness of planned walking on behavioral and psychological symptoms of dementia (BPSD). Most patients with dementia experience BPSD at some stage of their disease, which can include for example depression, psychosis, anxiety, agitation, aggression, apathy, disinhibition and wandering. BPSD are associated with increased carer burden, reduced quality of life, increased costs for care and institutionalization [62]. The 12-week intervention consists of individual walking sessions of 20–30 min for the patient and carer in the area around their home.

Initially, the sessions are supervised by qualified exercise therapists, and then continued independently at least five times per week. The primary outcome of interest is the Neuropsychiatric Inventory (NPI) which is a standardized carer interview to measure the presence of BPSD.

An Australian group [63] published a study protocol for a 12-month RCT with 230 community-dwelling participants with AD and their carers. The 6-month intervention is based on a previous RCT with older adults with subjective memory complaints and MCI [45] and focuses on a home-based walking program which includes a behavioral intervention based on the stages of change model modified for PA [64]. A carer is enrolled as a "coach" to encourage the patient to perform the PA. The control group comprises standard care and both groups receive educational material on healthy lifestyle and dementia. Outcomes include cognition, BPSD, quality of life of the patient and carer, carer burden, functional level and global clinical impression.

Finally Pitkala et al. [65] published a study protocol for a Finnish RCT aiming to recruit 210 community-dwelling participants with AD and their carers. The RCT has three arms with a home-based PA intervention, a group-based PA intervention in a rehabilitation centre and a control group with usual care and information on exercise and nutrition. The intervention period will be 12 months and outcomes will include physical function, mobility, cognition, BPSD, carer burden and quality of life. Interestingly, this trial aims to perform a follow-up after 24 months to measure the rate of institutionalization and additional outcome related to health economics. These ongoing RCTs should generate interesting data which will hopefully provide further evidence of the benefits of PA programs for older adults with dementia.

5. Underlying basic mechanisms

5.1. Studies with animals

Animal research investigating the impact of PA on the aging brain, both involving experiments with healthy aging animals as well as for models of AD, is invaluable to advance our knowledge of the complexity of underlying biological mechanisms driving the effect of PA on the brain. In a recent review paper Lazarov et al. [66] investigated whether neurogenesis enhancing activities could counteract age-related cognitive impairment and even AD symptomatology. Lazarov et al. pointed out that age-dependent reduction of neurogenesis can be minimized [67] and even better can be partially reversed [68] when rodents have the opportunity to exercise. However there seems to be an age limit to this effect. Eighteen-month old mice that were exposed to a running wheel showed benefit, however this did not occur when the exercise was introduced to very old mice (22 months old) [69]. Lazarov explains further that in AD rodent models results in relation to PA are more inconsistent, showing benefit on cognition and neurogenesis in some models [70,71], but not in others [72–75]. Remarkably, PA was shown to impact directly on AD pathology via reducing amyloid deposition [76,71] and suppressing Aβ dependent neuronal cell death in the hippocampus [77]. Other neurobiological effects proposed to contribute to the cognitive benefits of PA are angiogenesis, synaptogenesis, increase in cerebral blood flow, reduced inflammation and changes to neurotransmitter balance to name just a few. Lista and Sorrentino [78] recently

summarized the effect of PA on a number of these supramolecular and molecular mechanisms.

In a recent animal study with female cynomolgus monkeys [79] a five-month intervention of treadmill running (for 1 h per day for 5 days for 5 months) was compared to a sedentary lifestyle. Middle-aged (10–12 years) and mature (15–17 years) monkeys in the intervention group showed improved cognitive performance ($p = 0.05$) as well as an increase in their vascular volume fraction in the motor cortex ($p = 0.029$) compared to the control group. However, this increase could not be maintained when the animals returned after completion of the intervention to a sedentary lifestyle for another three months.

Nakajima et al. [80] investigated whether PA could protect again the negative effects of chronic stress on the brain. One of the main underlying mechanisms of how chronic stress harms the brain is an increase of oxidative stress with an increase of lipid peroxide which subsequently impairs hippocampal neurogenesis. A chronic restraint stress (CRS) model exposed mice for eight weeks to 12 h of immobilization daily and being housed in a small cage. Mice in the intervention group were allowed free access to running wheels during the 12 h of exposure to CRS. The access to exercise reduced CRS induced cognitive impairment and improved cell proliferation in the dentate gyrus, possibly via increase of insulin-like growth factor 1 (IGF-1) and increased activity of glutathione s-transferases (GST). Herring et al. [81] also investigated the impact of PA on AD related oxidative damage in an AD mouse model. From day 30 until 5 months, mice were either house in standard housing or in an enriched environment which also allowed opportunity for voluntary PA. They report that the enriched environment triggered anti-oxidative defense mechanisms in the brain via several mechanisms such as reduction of oxidative stress biomarkers and down-regulation of pro-inflammatory and pro-oxidative mediators amongst others. This is an encouraging finding as it indicates that PA may reduce the damage caused by inflammatory reactions to AD pathology.

Berchthold and colleagues [82] were interested in the time-dependent relationship between benefits of PA on cognition of mice in relation to biological markers. They investigated brain-derived neurotrophic factor (BDNF) levels immediately after completion of a three-week running period compared to a one and a two weeks delay after completion of the exercise period. They report significant elevations of BDNF (186% of sedentary levels) immediately after completion of the exercise and at one and two weeks after completion with the BDNF levels returning to pre-exercise levels by three to four weeks. The BDNF increase also correlated with cognitive improvements in the radial water maze at day 4. This is a relevant finding as it indicates that benefits on brain plasticity do continue for a certain amount of time after completion of the physical active period. This might be one biological mechanism contributing to the continuing cognitive benefit of PA in human trials after completion of the intervention, as has been shown for example in the FABS trial (participants had subjective memory complaints or MCI) where cognitive performance was still significantly improved 12 months after the completion of the intervention [45].

5.2. Studies with humans

Whilst there are an increasing number of cross-sectional studies investigating the relationship between PA and cognition is increasing, prospective studies or clinical trials with human participants that have investigated the underlying biological mechanisms of the effect of PA on the brain are still relatively sparse. However, this is not surprising considering how recent the increase in interest is in this research area. The evidence from animal research is gradually making an impact on the study design of trials for human participants.

Neuroimaging which has been widely used in basic science research is the fastest emerging area to be taken up and used in prospective studies and RCTs to date.

In a population-based longitudinal study with a follow-up period of 9 years, Erickson and colleagues [83] investigated the association between PA and grey matter volume measured on MRI. The 299 participants, aged 65 and older, who were part of the Pittsburgh component of the Cardiovascular Health Cognition Study (CHS-CS) and PA were assessed at baseline with the modified Minnesota Leisure-Time Activities Questionnaire. The main PA measure was total number of blocks walked over one week. Brain volume was measured with voxel-based morphometry (VBM) approximately 9 years after baseline in conjunction with an assessment for cognitive impairment and dementia. The results showed that self-reported walking distance at baseline significantly predicted the grey matter volumes of frontal, occipital, enthorinal and hippocampal regions 9 years later. However, this effect was only significant for participants within the highest quartile of PA suggesting that a threshold of walking 72 blocks per week was necessary to achieve this effect. This increased gray matter volume was associated with a two-fold reduction in risk for cognitive impairment. Recently in a RCT by the same group [84] in120 community-dwelling non-demented sedentary older adults (aged between 55 and 80 years) showed that aerobic PA can increase the size of the anterior hippocampus which was correlated with improved spatial memory. The 12-month aerobic exercise program with a focus on walking was compared to a stretching and toning control group. The authors reported that the aerobic PA related 2% gain in hippocampus volume would be equivalent to reversing the age-related atrophy by one to two years. This volume gain was also associated with increase serum levels of BDNF. The control group experienced a hippocampus volume decline of 1.43%.

Burdette and colleagues [85] investigated exercise induced changes in cerebral blood flow and connectivity in the hippocampus of older adults. They used a subgroup of community-dwelling participants from the SHARP-P study (Seniors Health and Activity Research Program Pilot trial) who were considered at risk for cognitive decline as they were aged between 70 and 85 years and reported subjective memory loss. Individuals with dementia, MCI or depression were excluded. The subgroup was composed of 6 participants from the PA intervention group and 5 from the control group. The 4-month PA intervention utilized walking with a target of at least 150 min per week to improve cardiovascular fitness and consisted of educational lectures and light stretching sessions. MRI scans to determine resting brain blood flow and connectivity were performed within 1 month after completion of the intervention. Hippocampal blood flow was significantly increased in the intervention group compared to the control group (54 ml/100 g/min versus 38 ml/100 g/min; $p < 0.0002$) which also corresponded with a greater connectivity. Furthermore, the hippocampus and the anterior cingulate were highly interconnected only in the intervention group. The authors suggested that the increased connectivity could explain how PA can lead to increased blood flow and neurogenesis. This finding therefore contributes important results. Despite some limitations of this study such as the small sample size and the difference in contact time between the intervention and the control group these findings contribute important insights into the potential mechanisms by which PA may affect the brain.

In a RCT with 155 community-dwelling cognitively healthy older women [86] a 12-month resistance training intervention (using leg press and weights, once or twice weekly) reduced whole-brain volume of participants compared to a balance and tone training program.

The resistance training group improved significantly on the Stroop test compared to the balance and tone training group ($p \leq 0.03$). Whilst this reverse brain volume finding is puzzling it is interesting that resistance training and not only aerobic training can improve executive function in older adults.

Finally, an interesting RCT by Voss et al. [87] randomized 75 non-demented older adults (55 to 80 years) to either an aerobic walking group or stretching and toning control group. The walking program was supervised and walking duration was gradually increased to

40 min per session. The control group exercises were also supervised. Both interventions lasted 12 months. Results on functional MRI (fMRI) showed increased functional connectivity between the frontal, posterior and temporal cortices which reached significance after 12 months, but not at 6 months. The improvement produced connectivity levels more typical of those for younger people. These imaging findings were associated with improved executive functions. Interestingly both intervention groups showed increased connectivity, but not for exactly the same systems in the brain. The authors interpret the time-dependent finding as possibly indicating exercise triggered changes to brain plasticity need a minimum of time to develop.

6. Discussion

Whilst the reviewed selected literature highlights that there has been an exciting increase in knowledge in recent years, numerous questions remain when exploring the impact of PA on the aging brain. Table 1 summarizes the most relevant future considerations in the context of designing clinical trials.

In addition to more refined basic science approaches, the many remaining questions may in part be addressed by better coordination of the emerging evidence across countries and research teams. Plassman et al. [19], for example, suggested in their review that a more optimal standardization of assessment tools, interventions and outcomes between studies is needed to be better able to pool and compare data. They acknowledge that this effort needs to be balanced with innovative ideas to allow progress.

Like others before them they highlight the importance of timing in relation to the PA exposure or intervention. Not enough is known about how the impact of a potentially protective factor such as PA might vary between age groups which is obviously related to the question of when is the best time window in life for a protective factor to be effective. Further, how long does the exposure need to last and is there an age limit beyond which the exposure loses relevance due to increasing pathology in the brain and overall frailty? Others mention factors most likely to increase the complexity of interaction levels such as type of PA or combinations of different types of PA, the presence of other medical illnesses in older age and genetic influences [88,20]. The FABS trial for example showed in a post-hoc analysis that there was a differential effect of PA on the ADAS-cog scores according to APOE e4 status with APOE e4 non-carrier participants in the intervention group showing significantly better improvement of their ADAS-cog scores [45]. Another challenge is the difference between statistical significance and how relevant this finding is to the target group in their daily lives, e.g. will the intervention improve daily function to a level where it is noticeable. Paterson and Warburton [21] discuss the importance of not underestimating older adults by starting at a too low intensity and going too slow and thus risking drop out due to the participants missing out on the subjective feelings of "improvements". They point out that older adults can adapt physiologically to PA in the same time frame as younger adults.

Equally as important as the optimal selection of type and dosage of PA is the question of how to motivate older adults to embrace PA. Programs being developed to initiate physical activity in older populations will have to incorporate strategies that include the particular psychological and social elements that have been shown to be associated with higher PA.

In a review of best practice for PA programs for older adults, Cress et al. [89] recommended that interventions combine the established principles of behavior change such as social support, self-efficacy, active choices, health contracts, assurances of safety and positive reinforcement. Many of the interventions developed to change behavior and increase PA involve counseling and cognitive processes in their strategy to affect the mediators of that behavior change. For example, one theory often used as the basis of PA interventions is the stage of change theory (SOC) [64]. The elements hypothesized to mediate change in PA are change in self-efficacy, decisional balance and cognitive and behavioral processes of change. When these psychosocial aspects were investigated in sedentary adults aged 35–75 years without cognitive impairment in a 24-month trial that used three interventions to increase PA only the changes in behavioral processes of change mediated the relationship between the active interventions and improvements in PA and fitness [90]. The behavioral processes of change involve the more practical aspects of motivating increased PA such as using social support, personal rewards, personal commitment and substituting alternatives. Whereas the cognitive processes require activities such as comprehension of the benefits, increasing knowledge, finding healthy alternatives, warnings of risk and care about consequences. Given that those with cognitive impairment and dementia will be limited in their ability to deal with the more complex elements of behavior change, it would seem prudent to focus on the behavioral and more practical aspects when promoting physical activity in adults with cognitive impairment and dementia.

In the meantime, until more research evidence is gathered, there is the question of what should clinicians recommend to older adults?

The American College of Sports Medicine (ACSM) and the American Heart Association have reviewed the evidence for the health benefits of PA and based on this evidence they have developed recommendations for physical activity for older adults [18]. The recommendation is for older adults to do moderate-intensity aerobic physical activity for a minimum of 30 min on 5 days each week or vigorous- intensity aerobic activity for a minimum of 20 min on 3 days each week. In addition, they should include muscle strengthening, flexibility and balance exercises [18]. The ACSM recommendations also highlight the need for older adults to have an activity plan that integrates preventative and therapy recommendations.

When it come to older adults who already experience cognitive impairment, like CIND and MCI, clinical management often is complex and due to the prognostic uncertainty clear guidelines for management have not been developed. This applies also to advice on modifiable risk and protective factors for cognitive decline for this clinical group, but PA is now regularly mentioned as a topic when educating the patients and their families [91,92]. A recent paper which reported on a survey of 420 neurology service providers (members of the American Academy of Neurology) in the US [93] found that 93.7% of the surveyed clinicians gave their patients with MCI or CIND advice on the benefits of physical

Table 1
Suggestions for the design of clinical research into physical activity and the aging brain.

Area	Specific suggestions
Methodology	Standardize study protocols across studies
	Aim for longer observation periods and larger participant numbers
	Investigate clinical relevance next to statistical significance
	Ask trial participants/carers regarding effects on daily life
	Investigate clinical subgroups with targeted intervention programs
	Include biomarkers that are hypothesis driven
	Include health economic analyses
Physical activity	Consider timing of intervention (what age, for how long)
	Compare different types of physical activity
	Investigate the duration, frequency and intensity of physical activity
	Investigate physical activity with additional cognitive components
	Avoid too careful interventions in older adults (risk of missing reward)
	Focus on self-efficacy to achieve maintenance of physical activity
	Consider other psychosocial aspects of motivating increased physical activity

activity. This finding is interesting considering the limited evidence base to date, but probably demonstrates that most clinicians view PA as a healthy lifestyle option. If correctly performed, has enough health benefits to justify recommending it while we wait for more evidence to be gathered to enable clear recommendations to be made for the optimal PA for the healthy aging brain.

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