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The impact of exercise on Alzheimer's disease progression

Thierry Paillard^a, Hubert Blain^b, Pierre Louis Bernard^c

- a. Département STAPS, Tarbes, Université de Pau & Pays de l'Adour; Laboratoire Mouvement, Equilibre, Performance et Santé (EA 4445),
- b. Pole de Gérontologie Antonin Balmes, CHU de Montpellier; EuroMov Digital Health in Motion. Univ Montpellier, IMT Mines Ales
- c. UFR STAPS, EuroMov Digital Health in Motion, Université de Montpellier, IMT Mines Ales.

Thierry Paillard
Laboratoire Mouvement, Equilibre, Performance et Santé
Université de Pau et des Pays de l'Adour
Département STAPS
ZA Bastillac Sud
11 rue Morane Saulnier
65000 Tarbes
France
Tel: + 33 (0)562566100
Fax: +33 (0)562566110
Email: thierry.paillard@univ-pau.fr

ABSTRACT

Introduction: Preventive effects of chronic physical exercise (CPE) on Alzheimer's disease (AD) are now admitted by the scientific community. Curative effects of CPE are more disputed, but they deserve to be investigated, since CPE is a natural non-pharmacological alternative for the treatment of AD.

Areas covered: Evidence suggests that CPE slows AD progression by inducing neurotrophic effects. Aerobic exercise promotes angiogenesis and the release of neurotrophic factors (e.g., IGF-1, BDNF, VEGF) linked to increased cerebral blood flow, which in turn promotes cerebral plasticity. In addition, neurotrophic factors such as IGF-1 are thought to facilitate the clearance of beta-amyloid and reduce the hyperphosphorylation of tau proteins that are key features of AD.

Expert opinion: Aerobic exercise alone is probably not the unique solution and needs to be complemented by other exercises (physical activities) in order to optimize the slowing down of AD. Anaerobic, muscle strength and power, balance/coordination and meditative exercises may also help to slow down the AD progression. However, the scientific evidence does not allow a precise description of the best training program for patients with AD. Influential environmental conditions (e.g., social relations, outdoor or indoor exercise) should also be studied in order to optimize training programs aimed at slowing down the AD progression.

Key Words Alzheimer's disease, exercise, physical activity, slowing-down effects, Alzheimer's disease progression, cognitive function, activity of daily living

Article highlights

- Evidence suggests that chronic physical exercise (CPE) slows down the progression of AD by inducing neurotrophic effects.
- Aerobic exercise promotes angiogenesis and the release of neurotrophic factors (e.g., IGF-1, BDNF, VEGF) linked to increased cerebral blood flow, which in turn promotes cerebral plasticity.
- Neurotrophic factors such as IGF-1 are thought to facilitate the clearance of beta-amyloid and reduce the hyperphosphorylation of tau protein that are key features of AD.
- Anaerobic, muscle strength and power, balance/coordination and meditative exercises may also help to slow down the progression of AD.
- CPE could contribute to increase cognitive reserve (along with nutrition, level of education, social relations and mental activity), which is the most promising way of preventing and combating AD.

1. Introduction

Compared with the resting state, acute physical exercise (APE) involves increased oxygen and energy requirements, which are met by a cascade of physiological reactions/responses of a metabolic and energetic nature, enabling the organism to adapt to effort. These physiological responses, regularly triggered as part of chronic physical exercise (CPE), generate lasting and beneficial structural and functional physiological adaptations to metabolic and energy functions (e.g. cardiovascular, pulmonary, muscular and endocrine).

CPE increases *i*) exercise tolerance (due to increased cardiac and skeletal muscle strength and improved maximum oxygen consumption, combined with a more extensive capillary network); *ii*) insulin sensitivity in adipose tissue and skeletal muscle (which reduces the risk of systemic insulin resistance); *iii*) regulates body weight (due to increased catabolism in muscle and adipose tissue) and blood pressure (due to increased vascular density of arterioles and a reduction in systemic vascular resistance caused by increased release of nitric oxide (NO) which facilitates vasodilation from the vascular endothelium); *iv*) protects against adverse effects of cholesterol (increase high density lipoprotein -HDL- and decrease low and very lipoprotein -LDL and VLDL respectively); and *v*) improves immune system responses by delaying the onset of immunescence and reducing systemic inflammation (e.g., reducing blood levels of inflammatory cytokines, increasing the phagocytic activity of neutrophils and improving the cytotoxic activity of natural killer cells) [1-3]. Hence, CPE has been recognized as being good for human health, reasonably protecting these different functions against various diseases [4].

More recently, it has even been suggested that CPE has beneficial effects on brain function in animals [5] and humans [6]. CPE indeed engenders structural and

functional brain adaptations facilitating neuroprotective processes [7,8] that may prevent the development of neurodegenerative diseases in the brain [9]. The prevalence of the most widespread of neurodegenerative diseases, being Alzheimer's disease (AD), has evidently been the subject of numerous studies in the context of CPE. AD is characterized by progressive neuronal loss and cerebral atrophy as well as neuronal and synaptic impairments in the cortical and subcortical structures linked to the accumulation of the fragment of beta-amyloid protein (beta-amyloid plaques) and abnormal intracellular accumulation of tau proteins [e.g.,10]. AD alters cortical functions, clinically leading to progressive deterioration in memory, cognitive dysfunctions, and a series of non-cognitive deficits including affective manifestations and personality, psychological, and behavioral changes, as well as impaired motor function [11]. These cerebral and behavioral involutions could be prevented or limited by the implementation of CPE [12]. Given that the current pharmacological treatments (cholinesterase inhibitors and memantine) have moderate effects on AD progression [13], CPE could contribute to an increase in cognitive reserve (along with nutrition, level of education, social relations and mental activity), which is the most promising way of preventing and combating AD.

APE increases cardiac output, leading to increased cerebral blood flow, which triggers various neurobiological mechanisms in the brain tissues. Repeated increases in cerebral blood flow in a context of CPE facilitate angiogenesis, neurogenesis, synaptogenesis, dendritogenesis, and neurotransmitter synthesis in the different cerebral areas [14-16].

The beneficial effects of CPE on the brain are globally mediated by its influence on multiple systems, including the immune system, the cerebrovascular system, the neuroendocrine system and neurotrophic response [17-19]. Hence, it has been

suggested that CPE can not only protect against the development of AD [12,20,21] but also slow the progression of AD once it has been diagnosed [22]. A large number of recent systemic reviews and/or meta-analyses support this precept with regard to cognitive function and activities of daily living through regular aerobic and/or combination exercise [e.g., 11,18 23-35]. Nevertheless, it has also been reported that CPE has positive effects on brain structures and functions in people with mild cognitive impairment (or MCI which can be due to Alzheimer, but also vascular or depressive causes), while these effects would be limited in people with AD [36]. CPE is thought to have a preventive effect against the development of AD in healthy persons but no curative effect in AD patients [19], although the relationship between CPE and a reduction in the risk of developing AD still needs to be refined [37] and the dose-response association remains unclear [38].

Overall, while the neuroprotective role of CPE in the primary prevention of AD is clearly recognized and rarely questioned, its role in combating the progression of AD remains to be substantiated. The aim of this opinion article is therefore to take stock of the current state of scientific knowledge concerning the effects of CPE on the progression of AD.

2. Methodology

An exhaustive search for articles dealing with the effects of CPE on the progression of AD was completed on the basis of keywords “Alzheimer’s disease”, “exercise”, “physical activity”, “Alzheimer’s disease progression” using the electronic databases PubMed, ScienceDirect and Google Scholar. The complexity and wide variety of experimental protocols undertaken (the lack of standardization of protocols), led us to carry out a descriptive and theoretical analysis (i.e., a narrative review as an opinion

article; not a systematic review) in order to provide a comprehensive review of the literature.

3. Neuroprotective mechanisms of CPE in people with AD

Human and animal studies confirm that various mechanisms linked to the increase in blood flow induced by exercise help to improve metabolic and cognitive functions [e.g., 39]. In the long term, CPE attenuates expression of pro-inflammatory factors [40] and enhances the actions of anti-inflammatory factors [19,41].

3.1. Human studies

Based on imaging technologies, evidence suggests that CPE engenders beneficial effects on brain function. For instance, basic exercises such as ergocycle, treadmill, or stair-climbing for 40 min regularly practiced (4 weekly sessions, 12 weeks) augmented the cerebral blood flow of the hippocampus (dentate gyrus), which may increase neurogenesis [42]. One year of aerobic exercise at moderate intensity [60–75% of the maximum heart rate reserve (HRR), 40 min, 3 sessions a week] developed the hippocampal volume by 2% and increased the plasmatic concentration of the brain-derived neurotrophic factor (BDNF) in healthy old people [43]. There is a correlation between the level of plasma BDNF and the level of CPE performed by AD patients [44]. Moreover, aerobic CPE (60 min, 3 sessions a week, 6 months) is also likely to develop the volumes of cortical matters (gray and white) at the prefrontal and temporal level in people aged from 60 to 79 years [45]. However, the same cortical adaptations were not observed in people (of the same age) who performed stretching and toning exercises [45]. Although the studies mentioned above were carried out on healthy people, the evidence suggests that CPE engenders beneficial adaptations in brain function. In AD patients, if aerobic exercise does not increase cortical volume after

aerobic CPE, it can at least slow the progression of white matter hyperintensity in AD [46].

The relationship between AD and vascular risk factors has been highlighted as has the influence of endothelial and cerebrovascular dysfunction on the pathophysiology of AD [47]. The positive effects of CPE on the vasculature from a view point of molecular mechanisms have been described by Lange-Asschenfeldt and Kojda [47] in particular the activation of the vascular nitric oxide (NO)/endothelial NO synthase (eNOS) pathway (Figure 1). CPE engenders upregulation of vascular endothelial growth factor (VEGF) and other growth factors, which have angiogenic and neuroprotective roles [48]. Overall, CPE by creating a vascular reserve and facilitating neuronal plasticity, may counteract the pathophysiology of AD.

Regarding circulating growth factors, it is known that AD patients display a tendency to have lower circulating insulin-like growth factor-1 (IGF-1) levels compared with older adults without dementia [49]. These authors reported that AD patients increase circulating IGF-1 levels after an acute bout of aerobic exercise while IGF-1 levels in older adults without dementia remain similar. CPE would thus be particularly relevant for people with AD since, on the one hand, increased IGF-1 is associated with improvement of cognitive function in response to exercise, and on the other hand, IGF-1 is thought to facilitate the clearance of beta-amyloid and reduce the hyperphosphorylation of tau protein in AD [49].

Because of the difference between oxygen requirements and oxygen supplied, intense APE generates lactate, which is transported throughout the entire body and constitutes an essential source of energy for the muscles and brain especially at rest after effort. The lactate-mediated interplay between astrocytes and neurons, where lactate produced by astrocytes is taken up and used by neurons, is thought to be essential for

synaptic plasticity and memory modulation [50]. Lactate is positively linked to both BDNF and VEGF levels following exercise and contributes to the mediation of BDNF levels in response to exercise [51]. Hence, the increase in lactate with high-intensity exercise may enhance hippocampal mitochondrial biogenesis and function and promote cerebral VEGF and BDNF levels, stimulating hippocampal angiogenesis and neurogenesis [50]. This is particularly interesting for participants with AD since their brain displays a clear signature of glucose hypo-metabolism [51] even though CPE is already independently associated with improvements in glucose metabolism [52]. However, this data on the effects of lactate needs to be confirmed for people with AD.

3.2. Animal studies

On the basis of animal models artificially affected by AD features (increased number of beta-amyloid plaques and the presence of neurofibrillary tangles), protective mechanisms induced by CPE have been identified. The findings thus far suggest that CPE reduces the noxious effects of oxidative stress, the production of total cholesterol, insulin resistance, and pro-inflammatory factors [e.g., interleukin1(IL1), tumor necrosis factor- α (TNF- α)], increases vascularization and anti-inflammatory factors and also improves energy metabolism (e.g., glucose metabolism) [16,22,40,41,53-55,47,56]. CPE activates angiogenesis and neurotrophic functions, generating synaptogenesis and neurogenesis, which improve cognitive functions and memory (Figure 1) [16,26,40,41,47,54,56,57].

On the one hand, moderate-to-vigorous CPE stimulates the production of beneficial biological agents such as antioxidant enzymes (for example, superoxide dismutase), eNOS, VEGF, IGF-1, nerve growth factor (NFG), and BDNF [58]. On the other hand, CPE lowers the production of deleterious biological agents such as free radicals (for example, reactive oxygen species) and reduces the concentration of amyloid plaques

in the hippocampus, which is particularly involved in the memory (Figure 1) [16,18,40,47,50,59,60]. Overall, CPE facilitates brain plasticity. A running training program in mice with AD (60 min, 5 sessions a week, 16 weeks) increased the hippocampal volume [$F(3,31)=4.577$; $p=0.009$] more than in control non-trained subjects [61]. On the basis of old trained and non-trained mice, it has been observed that the hippocampal neurogenesis is associated with synaptogenesis [5]. These two factors being necessary to improve learning ability (spatial memory), the hippocampal adaptations related to CPE turn out to be fundamental for combating AD [5].

Another running program (16 weeks) in mice with AD reduced their level of β -amyloid precursor protein (β -APP or $A\beta$ peptide) compared with control non-trained subjects [55]. The surface area of the $A\beta$ -plaques of mice with AD decreased in the frontal cortex (38%; $p=0.018$), the cortex at the level of hippocampus (53%; $p=0.0003$) and the hippocampus (40%; $p=0.06$) after 5 months of training aerobic [62]. This decrease was associated with a reduction in the proteolytic fragments of β -APP. CPE may contribute to both reduced production and increased clearance of cortical $A\beta$ [17,18,23]. Changes in neuronal metabolism induced by CPE may counteract APP processing regardless mRNA/protein changes in insulin-degrading enzyme and neprilysin. Hence, the memory and learning capacities of mice with AD improved [62]. Nevertheless, an improvement of these capacities is not systematically associated with a decrease in $A\beta$ -plaques [63]. Mice with AD indeed improved their spatial memory after a training program (11 months) in a condition of environmental enrichment (well-equipped and spacious cage) while the concentration of $A\beta$ -plaques did not reduce in hippocampal and cortical structures. Only mice that had benefited from environmental enrichment showed cognitive enhancements through increases in BDNF, hippocampal neurotrophin, and activation of hippocampal neurogenesis compared with control mice

(identical training) did not benefit from environmental enrichment [63]. In this way, the effects of CPE can be optimized under favorable (stimulating) environmental conditions by generating a neuronal reserve in mice with AD.

Moreover, CPE may facilitate the prevention of neurofibrillary degeneration. The hippocampal concentration of tau protein was reduced in mice with AD after a 9-month training program [64]. CPE may also reduce the neuroinflammatory responses resulting from increased tau proteins in cerebral tissue [65] as well as the expression of choline acetyltransferase [64]. Cholinesterase enzyme inhibitors (anti-cholinesterase drugs) are currently the main treatment (along with memantine) used to combat AD.

3.3. Genetic aspects

Knowledge of the effect of CPE on the neuroprotective mechanisms of people with AD has progressed well over the last twenty years. Out of over 250 treatments, three datasets for exercise were identified as the top theoretical treatments for AD via reversal of large-scale gene expression patterns [66]. These authors specified that CPE reversed expression patterns of hundreds of AD genes across multiple categories, including cytoskeleton, blood vessel development, mitochondrion, and interferon-stimulated related genes. However, the prescription of an optimal training program remains to be clarified.

4. What and how to exercise for people with AD?

It is now well known that CPE is an efficient technique for slowing the decline in cognitive and physical function in AD patients [57,67-73] and reducing the depressive symptoms related to this disease [74-76] and mortality [77]. The various exercises and, above all, their application contexts still need to be fully explored.

4.1. Effects of different types of CPE for people with AD

It is well known that the different natures (e.g., aerobic and anaerobic, muscular strength and power, stretching, postural balance and coordination), durations (e.g., from 10 minutes to over an hour), intensities (e.g., high, moderate, low) and frequencies (e.g., from twice a week to once a day) of the exercises and program lengths (number of weeks) differently influence their physiological effects. Although it has been reported that chronic exercise in different forms, in terms of intensity and duration, for the same exercise such as aerobic exercise, can promote the reduction of β -amyloid levels [41], the search for optimal CPE (the right combination of exercises and the right dosage) has only just begun in order to combat the progression of AD.

There is currently no consensus on the best CPE regimen to improve clinical outcomes in patients with AD. Aerobic CPE is natural, practical and easy to implement for people with AD [78] - except in advanced forms of AD where it is difficult for patients to understand the instructions - and has been shown in numerous studies to be associated with improved cognitive function [54,57,79-82]. Changes in VO_2 peak are associated with changes in cognition and neuropsychiatric symptoms after 16 weeks (60-min sessions 3 times weekly) of supervised moderate-to-high intensity aerobic exercise [83]. Aerobic CPE may inhibit or delay the emergence of more severe neuropsychiatric symptoms with disease progression [84]. For example, an CPE as simple and natural as walking reduced the decline in cognitive performance (as assessed on the mini mental state examination - MMSE - score) in AD people [85,86]. Walking is also proving effective in improving the postural and motor skills of people with AD.

As AD is associated with a reduction in muscle mass and strength [87], training muscle strength and power can be very beneficial for patients with AD. Indeed, strength

training can not only compensate for the loss of skeletal muscle mass and strength (i.e., sarcopenic profil), but also improve cognitive decline and memory [56,88,89]. An increase in muscle strength is associated with a slower rate of global cognitive decline [90]. Strength training may indeed promote neurogenesis by elevating the levels of BDNF and IGF-1 [36,41,91].

Balance training has been reported to improve the balance and postural capabilities of patients with moderate to severe AD, thereby reducing the risk of falls at a more advanced stage of the disease [92]. Meditative exercises (e.g., yoga, Tai chi, and qi gong) can also be considered for slowing down the progression of AD [11]. Given that different types of exercise are likely to slow the AD progression, the effects of multimodal training are worth considering.

4.2. Multimodal CPE: the optimal solution

Multi-component or combined physical training programs - including muscle strengthening, aerobic (usually walking) and balance exercises - turn out to be significantly efficient in improving postural and motor functions and reducing the risk of falls in AD patients [93-95]. Although the best CPE regime for pathological subjects with AD has not yet been established, there is growing evidence that multi-component/combined training programs have significant positive effects on the health of these patients. For instance, the combination of aerobic and strength training can modulate genes related to hippocampal neuroplasticity and neurogenesis, thereby delaying the symptoms of AD [91]. The combining of aerobic and muscle strengthening exercises can also improve some markers of cognitive function [96].

Among the able-bodied, numerous studies have highlighted the effects of a specific exercise on a specific function, while the combination of various types of exercise have demonstrated their influences on functional capacities [97,98]. The multimodal

program, while presenting advantages, also questions the notion of the "concurrent effect" of practice content [99,100]. Today, the search for programs adapted to AD patients needs to take into account these methodological issues.

4.3. Influence of socio-environmental and temporal conditions

The data suggest that environmental conditions should be taken into account as they have a positive impact on the effects of CPE. Research carried out on AD patients has revealed that walking with conversation has a greater preventive effect than walking alone [101], which means that the "socialization effect" of CPE is crucial for these patients. Walking has also been reported to improve sleep, particularly when combined with exposure to bright light in community-dwelling Alzheimer's patients [102]. Moreover, there are associations between temporally local distributional aspects of exercise across the day and clinical cognitive scales impacted in early AD, especially, attention [103]. For example, AD patients are more likely to fall in the evening than in the morning during physical activity [104]. In addition, the time of day that people exercise can potentially influence the efficiency of exercises for fall prevention in older adults [105]. Finally, according to Wang et al. [32] exercising outdoors in a natural setting can be energising, reduce stress, anger and depression, and increase energy levels compared to exercising indoors in AD subjects.

In animal models, the conditions under which CPE is performed also have an impact on neurobiological adaptations. For example, the concentration of amyloid plaques in the brains of mice and the impairment of their memory capacity decreased more when they ran freely in a wheel (i.e. without a predefined speed of rotation) than when they ran at a predefined speed (i.e. at a forced speed) [61]. This means that the beneficial

effects of CPE on brain function are not only generated by cardiovascular adaptations, but are also regulated by other factors such as motivation (for example).

4.4. Inter-individual differences

The effects of CPE on cognitive function may vary according to the cognitive status of patients. Based on the meta-analysis by Zhang et al. [32], a worse basal cognitive status contributes to more significant improvements in cognitive function under the effects of CPE (MMSE score). Moreover, Pisani et al. [106] reported that although physical exercise improved MMSE scores in subjects with AD and MCI, exercise appeared to have a stronger effect for those with lower MMSE scores at baseline in the subjects with MCI. There may therefore be a relationship between basic cognitive state and the capability to slow down AD progression under the effect of CPE, but this relationship is not clear and needs to be explored further.

4.5. Optimal workloads

The main characteristics defined in the literature are the intensity, duration and frequency of effort prescribed with regards to aerobic exercises. Low and moderate-to high intensity training seems safe and feasible to apply in an interventional study in mild AD [107]. Although higher intensity is more beneficial, Frederiksen et al. [107] reported beneficial effects on anti and pro inflammatory cytokines (increase and decrease respectively) for AD patients on the basis of low and moderate-to high intensity training (14 supervised weeks, 60-min sessions 3 times a week). Furthermore, according to the systematic review by Ayari et al. [41] the effects of low-to-moderate intensity aerobic exercise (< 70 % HRR) or high-intensity aerobic exercise (> 70 %HRR) showed positive effects by reducing circulating interleukin.

There is a reverse relationship between intensity and finding the intervention enriching and fun [107]. However, based on the systematic review by Huang et al. [36] only moderate-to-high intensity aerobic exercise that more significantly improves cardiorespiratory function promotes an increase in hippocampal volume and brain activation and is likely to stop hippocampus atrophy. Studies in humans have shown that an acute bout of high intensity exercise elicits larger increases in BDNF than a bout of lower intensity exercise, and the benefits seemed to be dependent on lactate production [108]. Moreover, many moderate physical activities (e.g., dancing, mowing the lawn, and heavy cleaning) may be both more physically demanding and more cognitively complex than lower-intensity physical activities (e.g., sweeping and watering plants) and thus may be more challenging for individuals with mild AD [109]. Therefore, even though high intensity exercise is more beneficial than low intensity exercise, physical activity interventions across intensities may help slow the disease course and preserve independent function among AD patients [109]. The exercise intensity should be adapted to the ability of each AD patient in order to be as beneficial as possible.

Overall, the meta-analyses by Zhang et al. [34] and Zhou et al. [35] suggest that training 3 to 4 times a week for 30 to 45 minutes for more than 12 weeks (e.g., walking, bicycling, running and swimming) has a relatively significant effect on improving global cognition in AD patients.

As far as resistance training is concerned, the workloads must be significantly intense (impossible to repeat the movement more than 15 times with at least 6-8 sets) and sufficiently long (2-3 times a week) to stimulate the production of IGF-1 and BDNF, thus exerting positive effects on cognitive function. Regarding postural balance training, postural tasks should be sufficiently difficult (e.g., proactive and reactive

exercises in static and dynamic conditions on stable and unstable supports, in the sagittal and frontal planes, with eyes open and closed, in different postures; 2-3 times a week) in order to generate adaptations of central and peripheral components of the postural and balance function and reduce the risk of falling in AD patients while concomitantly stimulating cognitive function [110,111].

5. Impact of CPE on the non-cognitive behavior of people with AD

Activities of daily living (ADL) are improved by CPE through aerobic and anaerobic exercise [35,112,113]. Stretching tonic is less efficient than aerobic exercise to improve ADL [114]. This means that exercise requires minimal metabolic and energy activation and relatively dynamic movement to improve ADL in people with AD. In addition, CPE reduces the production of cortisol, i.e., the “stress hormone”, and adrenalin, which can cause anxiety [32]. CPE leads to greater happiness in both the short and long term, and increased physical activity can even improve mood [75] by producing serotonin that may make people with AD feel good [32]. A relationship between the serotonergic system and BDNF has been suggested, implying that development of depressive symptoms may be associated with a decrease in BDNF [30]. BDNF promotes regulation of brain plasticity in neural networks, which play important roles in depression. Thus, the contribution of BDNF to prevention of late-onset depression, which is directly associated with the etiology of AD, can be highlighted. Finally, another recently suggested association revealed is the improvement in mood and anxiety linked to the increase in IGF levels [30]. CPE could contribute to treatment of depression in nursing home residents with severe AD [74].

Overall, the positive effects of CPE on ADL, mood and behavioural and psychological symptoms of dementia have been reported as mentioned above, but still need to be confirmed (or refuted) by further studies.

6. Optimal effects of CPE: combination with other non-pharmacological approaches

The effects of CPE could be maximized by combining it with other non-pharmacological approaches (independently of the level of education, social relation and mental activity of AD patients as indicated above). Indeed, the clinical impact and translational value of, for example, certain dietary compounds [115], non-invasive brain stimulation [116], sleep homeostasis and plasticity-induced interventions [117], and certain complementary/alternative therapies [118] are also likely to optimize the fight against the progression of AD.

7. Conclusion

Current knowledge supports CPE as a viable and natural non-pharmacological alternative for the treatment of AD. Evidence suggests that CPE slows AD progression by inducing neurotrophic effects. Aerobic exercise promotes angiogenesis and the release of neurotrophic factors (e.g., IGF-1, BDNF, VEGF) linked to increased cerebral blood flow, which in turn promotes cerebral plasticity. In addition, neurotrophic factors, such as IGF-1 are thought to facilitate the clearance of beta-amyloid and reduce the hyperphosphorylation of tau proteins in AD. However, aerobic exercise and activity alone cannot stop or prevent the multiple pathophysiological causes of AD. Muscle strength and power training, anaerobic exercises, meditative exercises (e.g., yoga, Tai chi, and qi gong), balance/coordination exercises, and other types of CPE also

probably contribute to the slowing down of AD progression (even if the scientific evidence has yet to be established). Multimodal training is presumed to be a better exercise regime than aerobic training alone.

8. Expert opinion

Although the literature is informative and unambiguous regarding the relationship between CPE and AD onset, data regarding the relationship between CPE and AD progression is also informative but less precise and formal. Furthermore, among the studies published on the relationship between CPE and AD progression, certain experimental protocols merit greater methodological rigor and certain interpretations of results still lack strong evidence. Despite this, the current literature based on solid experimental protocols and reliable data addressing the impact of CPE on AD progression allows us to be optimistic about its potential beneficial effects.

Faced with the ever-increasing population of people affected by Alzheimer's disease in the world, research into the impact of exercise on AD is essential in terms of both public health and financial cost. Not only exercise is likely to slow the progression of AD but it is also a non-pharmacological and ecological technique with no side effects which can be practiced at low cost (or even free of charge) for the patient suffering from this disease. Hence, the possible curative effects of CPE should be widely investigated in future studies on the best types/modalities of exercise accompanied by the best environmental conditions for different AD patient profiles. If the curative effects of exercise were scientifically and definitively proven, exercise should be generalized to all populations through new public policies aimed at combating the disease. Someday maybe, in the best-case scenario, CPE could be considered not as a

technique for slowing the progression of AD, but as a technique for tackling/reversing the mechanistic causes (i.e., neurodegenerative) of the disease.

To date, while awaiting the most optimistic scientific discoveries, the current scientific evidence is still lacking to allow a precise description of the best exercise regimen for patients with AD. Only future studies based on blinded control trials of the effects of CPE on AD patients (despite the difficulty of setting them up), randomising subjects between different exercise regimes and sedentary behaviour, would certainly provide reliable informative data on the most relevant exercises. The optimal parameters for different exercises in terms of intensity, duration, and frequency and the best combination of different exercises still remain to be established. Moreover, the best prescription for one AD patient would systematically not be the best prescription for another AD patient, as there are inter-individual differences between different AD patients in terms of how they respond to exercise. The environmental conditions (e.g., social relation, exercising outdoors versus indoors) are also likely to influence the impact of exercise on AD progression. In addition to the positive effects on AD, the effects of CPE on maintaining or even improving functional abilities in order to promote autonomy in the acts of daily living are fundamental to a person's quality of life. However, the effects of CPE on the behavioral activities of AD patients remain to be confirmed (or refuted) by future studies. Prescription of CPE specifically related to cognitive impairments in AD patients also remain to be discovered. At last, independently of physical exercise, it has also been reported that mental activity increases a person's cognitive reserve and encourages the formation of new communications between brain cells, which helps slow down the progression of AD.

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Declaration of interest

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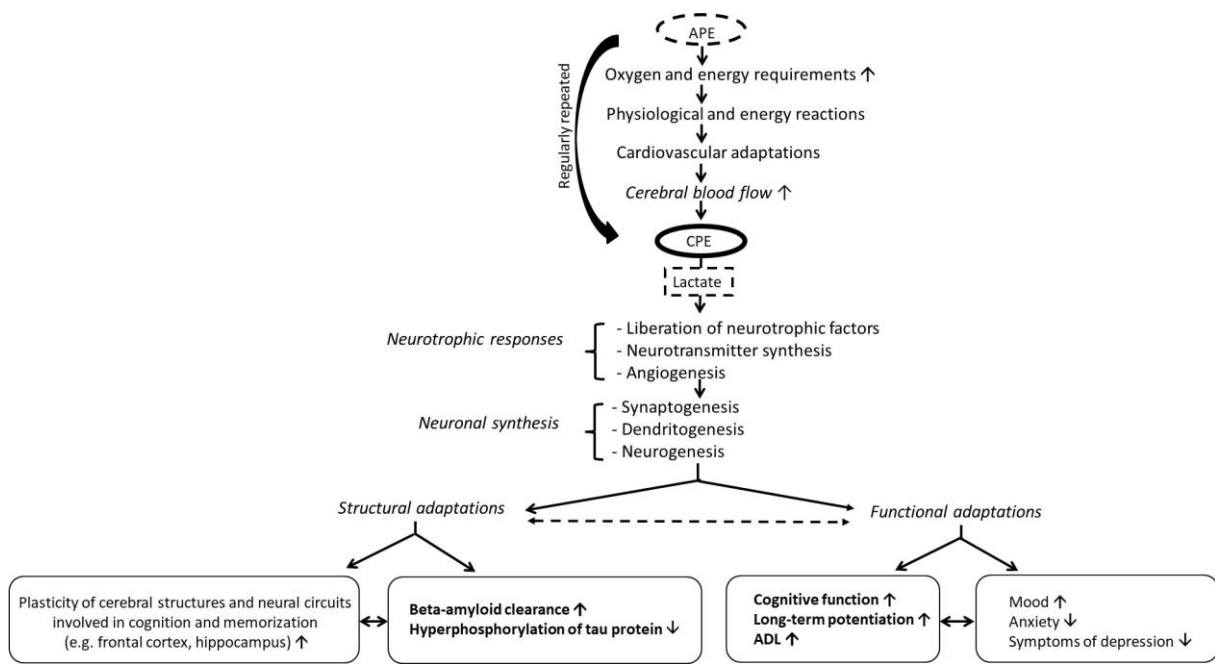
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APE: acute physical exercise; CPE: chronic physical exercise; ADL: Activities of daily living; ↑: increase or improvement; ↓: decrease or impairment.

Figure 1: The impact of chronic physical exercise on Alzheimer's disease progression