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Review

Exercise benefits on Alzheimer's disease: State-of-the-science

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ABSTRACT

Although there is no unanimity, growing evidence supports the value of regular physical exercise to prevent Alzheimer's disease as well as cognitive decline in affected patients. Together with an introductory summary on epidemiological evidence, the aim of this review is to summarize the current knowledge on the potential biological mechanisms underlying exercise benefits in this condition. Regular physical exercise has proven to be beneficial for traditional cardiovascular risk factors (*e.g.*, reduced vascular flow, diabetes) involved in the pathogenesis of Alzheimer's disease. Exercise also promotes neurogenesis *via* increases in exercise-induced metabolic factors (*e.g.*, ketone bodies, lactate) and muscle-derived myokines (cathepsin-B, irisin), which in turn stimulate the production of neurotrophins such as brain-derived neurotrophic factor. Finally, regular exercise exerts anti-inflammatory effects and improves the brain redox status, thereby ameliorating the pathophysiological hallmarks of Alzheimer's disease (*e.g.*, amyloid-β deposition). In summary, physical exercise might provide numerous benefits through different pathways that might, in turn, help prevent risk and progression of Alzheimer's disease. More evidence is needed, however, based on human studies.

1. Introduction – epidemiological evidence

Alzheimer's disease (AD) is the most common type of dementia, and although research in this field is extensive, the prevalence of AD continues to increase worldwide (Scheltens et al., 2016). It has long been recognized that regular physical activity (PA) is beneficial for health, and is proven to decrease the risk of major non-communicable diseases (notably, cardiovascular conditions, diabetes, chronic respiratory diseases, and a variety of cancers) (Booth et al., 2012; Pedersen and Saltin, 2015). There is also growing evidence to support the salutary effects of PA on neurodegenerative diseases such as AD. Of note, PA is any bodily movement produced by skeletal muscles that requires energy expenditure whereas exercise is a subset of PA that is planned, structured and repetitive, and that has a final or an intermediate objective of improving or maintaining physical fitness. The epidemiological evidence regarding the risk of AD mainly refers to regular PA (usually self-reported, through questionnaires). In turn, regular exercise or 'exercise training' is a proxy but not a perfect surrogate for PA and is thought to induce more profound molecular adaptations in the different body systems than PA.

Recent meta-analytical evidence has demonstrated that regular exercise or PA has positive effects on hippocampal volume in humans, preventing the volumetric decreases that occur over time (Firth et al., 2018). As the hippocampus is one of the major brain sites of neuroplasticity, these promising findings suggest the need for implementing PA interventions to attenuate age-related neurological decline. There is, indeed, robust evidence supporting the beneficial role of regular PA against cognitive decline. Physically active individuals have a 35–38 % lower risk of cognitive decline than their sedentary counterparts, as confirmed by a meta-analysis of prospective studies (Sofi et al., 2011). Further, a recent meta-analysis from our group showed that adherence to minimum international PA recommendations (*i.e.*, ≥150 min/week

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of moderate-vigorous PA) is associated with a remarkable (40 %) reduction in the risk of AD (Santos-Lozano et al., 2016). Beyond its benefits on physical function (cardiorespiratory fitness, muscle strength, functional ability) (Heyn et al., 2004; Pitkälä et al., 2013), recent meta-analyses have concluded that regular exercise (particularly aerobic exercise) might be a potential strategy to improve cognitive function – or at least attenuate cognitive decline – in individuals who are at risk for AD as well as in affected patients (Du et al., 2018; Jia et al., 2019; Panza et al., 2018)

It must be noted, however, that there is no unanimity among studies, with some authors reporting that greater PA levels are not associated to a lower AD risk in people aged > 65 years (Ravaglia et al., 2008; Verghese et al., 2003; Wilson et al., 2002). On the other hand, PA effects are not everlasting. A study conducted in more than 4000 older adults found that those with higher PA levels at baseline had a lower risk of dementia – including AD – during the following four years, but not in a subsequent follow-up up to 14 years (De Bruijn et al., 2013). The latter was attributed to potential changes in PA levels but also to the detrimental – and eventually unavoidable – effects of aging. In addition, although PA might also reduce the levels of AD-associated biomarkers (*e.g.*, Pittsburgh compound-B, tau, phosphorylated tau) in the cerebrospinal fluid of cognitively normal older adults (Liang et al., 2010) – with a recent longitudinal study showing that high PA levels attenuated the relationship between amyloid beta (Aβ) deposition and cognitive decline/neurodegeneration during a ~6-year follow-up in this population (Rabin et al., 2019) – the potential benefits of PA/exercise on AD-related biomarkers have not been consistently replicated, as confirmed by recent systematic reviews (Frederiksen et al., 2019a, 2018). Indeed, exercise interventions have not proven to be overall effective to improve AD-related biomarkers in already demented patients (Brown et al., 2017; Frederiksen et al., 2019b; Tarumi et al., 2019), although some benefits have been reported (*i.e.*, reduced hippocampal atrophy and amyloid load) in those who were Aβ positive (Brown et al., 2017; Tarumi et al., 2019).

The aim of this review is to summarize the current knowledge on the biological mechanisms that might underlie the potential protective effects of PA in AD, as well as to propose areas for future research on this topic.

2. Biological mechanisms

2.1. Exercise and neurogenesis

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that promotes neuronal survival and synaptic integrity, and is crucial for brain plasticity and regulation of memory function (Loprinzi and Frith, 2019). Patients with AD have low blood and brain BDNF levels from the early stages of the disease, and BDNF levels are positively correlated with cognitive function (Peng et al., 2005; Qin et al., 2017). In this respect, even a single bout of acute physical exercise is a powerful stimulus for BDNF production in both healthy adults (Dinoff et al., 2017) and elderly individuals with AD (Coelho et al., 2014; Kwak, 2015). A recent report showed that six months of aerobic exercise increased hippocampal volume in patients with AD (Vieira de Ligo Teixeira et al., 2017). A recent pre-clinical study found that inducing hippocampal neurogenesis *per se* (*e.g.*, pharmacologically or genetically) failed to confer any benefit on cognition in a transgenic mouse model of AD (the 5× Familial Alzheimer's disease [FAD] mouse, which expresses human Aβ precursor protein [*APP*] and presenilin 1 [*PSEN1*] transgenes with a total of five FAD-linked mutations: the Swedish [K670 N/M671 L], Florida [I716 V], and London [V717I] mutations in *APP*, and the M146 L and L286 V mutations in *PSEN1*) (Choi et al., 2018). By contrast, improvements in memory were observed when hippocampal neurogenesis was accompanied by an elevation in the levels of different exercise-induced proteins such as BDNF, interleukin (IL)-6, or fibronectin type III domain-containing protein 5 (FNDC5, *see below for details*), which suggests that hippocampal neurogenesis might benefit cognition in AD but only in the presence of an optimal environment for the production of neurotrophic factors such as BDNF (Choi et al., 2018). For this reason, exercise-induced neurotrophins – and particularly BDNF – have emerged as key mediators of the potential cognition benefits of exercise on AD (Wang and Holsinger, 2018).

How exercise stimulates the production of BDNF in the brain is unknown. Rasmussen and colleagues collected blood samples from the radial artery and the internal jugular vein of subjects performing aerobic exercise and observed that BDNF levels increased remarkably (by ~3-fold) as compared with resting conditions, contributing to approximately 70–80 % of circulating BDNF levels (Rasmussen et al., 2009). The same authors confirmed that aerobic exercise increases BDNF mRNA levels in the brain hippocampus and cortex in mice submitted to treadmill exercise (Rasmussen et al., 2009). On the other hand, growing evidence supports the existence of cross-talk between the muscle tissue and several other organs, with contracting muscles producing a myriad of *myokines* – defined as cytokines or other small peptides released into the bloodstream that can reach several tissues, including the brain, and induce beneficial effects at the multi-systemic level (Delezie and Handschin, 2018). BDNF mRNA and protein expression were shown to be elevated in human skeletal muscle after exercise, but muscle-derived BDNF was not released into the circulation (Matthews et al., 2009). However, more recent evidence has shown that muscle contractions evoked *via* electrical stimulation can increase plasma BDNF levels (Miyamoto et al., 2018). Thus, the link between muscle-derived BDNF and the increased presence of this neurotrophic factor in the brain remains elusive.

The levels of a recently discovered myokine, cathepsin B (CTSB), were reported to increase in plasma in response to exercise in human and animals models (including mice and monkeys), and CTSB could cross the blood-brain barrier (BBB) to bolster the expression of BDNF in the hippocampus in response to exercise (Fig. 1) (Moon et al., 2016). Supporting a role for this myokine in muscle-brain cross-talk, the authors observed that wild-type mice but not their *Ctsb*-deficient littermates showed enhanced neurogenesis and improved memory with exercise training (Moon et al., 2016).

Irisin is another myokine that has been shown to cross the BBB and stimulate hippocampal neurogenesis *via* increased BDNF expression (Fig. 1). Exercise stimulates the muscle expression of peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α), a major regulator of mitochondrial biogenesis (Irrcher et al., 2003). Wrann and colleagues reported that exercise training (30 days of voluntary running-wheel exercise) induced increases in the expression of PGC-1α and FNDC5, a membrane-bound precursor of irisin (the cleaved version of this protein) in the hippocampus of mice, which increased the expression of *Bdnf* and other neuroprotective genes (Wrann et al., 2013). Indeed, the authors observed that PGC-1α-deficient mice had reduced *Fndc5* expression in the hippocampus, and that the peripheral delivery of FNDC5 (*via* adenoviral vectors) increased *Bdnf* expression in this brain site (Wrann et al., 2013). Further support of the potential role of irisin in mediating exercise-induced cognitive benefits comes from the finding that the levels of this myokine are reduced in the hippocampus of patients with AD, and that knock-down and overexpression of brain irisin impairs and enhances, respectively, exercise-induced benefits on memory function in AD mouse models (Lourenco et al., 2019).

Lactate, a by-product of glycolysis, is another relevant exercise-related molecule because of its potential role in cognition (Fig. 2). Lactate is released from contracting muscles to the bloodstream during high-intensity exercise and can cross the BBB *via* endothelial monocarboxylate transporters (MCTs) (Pierre and Pellerin, 2005). Lactate import into neurons is necessary for long-term memory formation and, indeed, both the disruption of MCT expression in astrocytes (preventing lactate transport into these cells) and the inhibition of astrocyte glycogenolysis (curbing lactate formation) results in impaired memory (Newman et al., 2011; Suzuki et al., 2011). Moreover, a recent study in

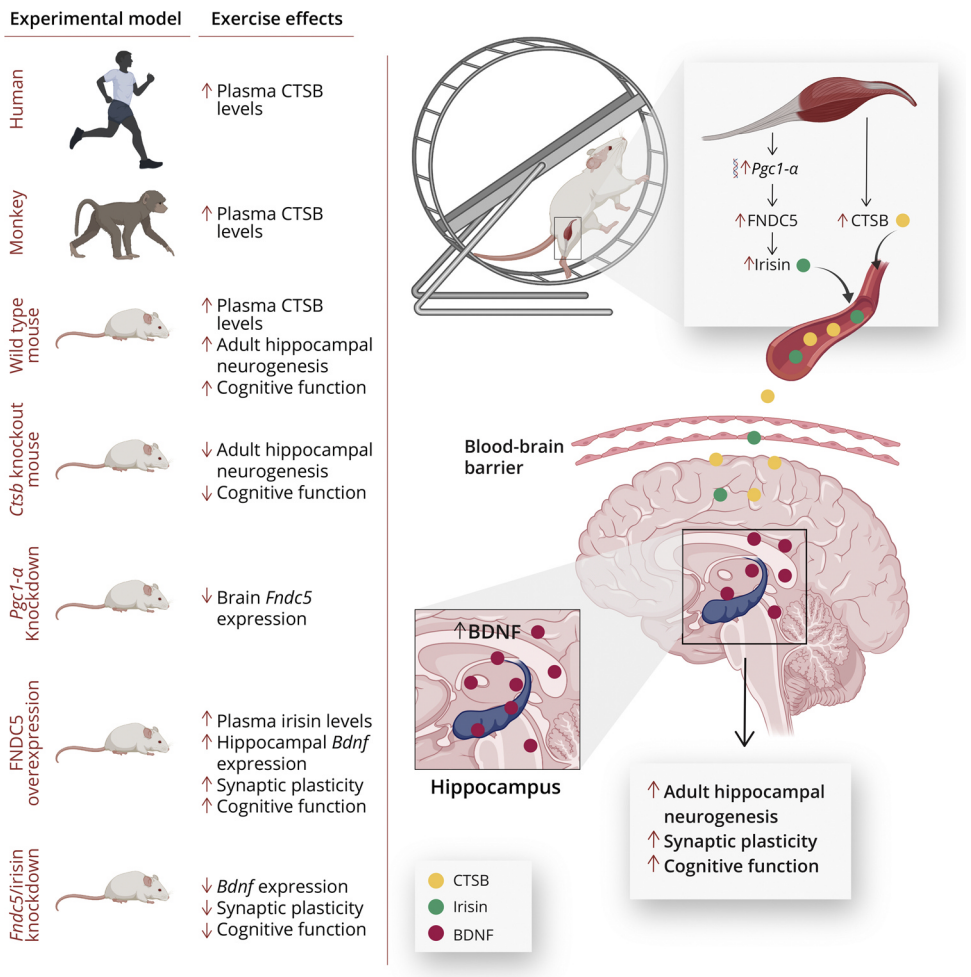

Fig. 1. Existing evidence for a role for exercise-induced myokines in the prevention of Alzheimer's disease. Abbreviations: BDNF, brain-derived neurotrophic factor; CTSB, cathepsin B; FNDC5, fibronectin type III domain-containing protein 5; Pgc1α, peroxisome proliferator-activated receptor alpha.

mice found that voluntary aerobic exercise (30 days of wheel running) leads to the accumulation of lactate in the hippocampus, where it promotes an improvement of cognitive function (learning and memory) *via* increased *Bdnf* expression (El Hayek et al., 2019). Confirming these findings, the inhibition of lactate transport in the brain resulted in a lower expression of *Bdnf* in response to exercise, and the intraperitoneal administration of lactate increased *Bdnf* expression and signaling in the mouse hippocampus together with an increase in cognitive function (El Hayek et al., 2019). It has also been reported that the treatment of primary hippocampal and cortical neurons *in vitro* with lactate induces the expression of *Bdnf* and of genes involved in neural excitability and synaptic plasticity (El Hayek et al., 2019; Margineanu et al., 2018). Moreover, a recent study observed that lactate induced neurogenesis in rat brains through the activation of the nuclear factor-kappaB (NF-κB) signaling pathway (Zhou et al., 2018), and another study reported that lactate induced the expression of genes (*e.g.*, early growth response 1, CCAAT/enhancer binding protein, and proto-oncogene c-Fos) associated with neural plasticity both *in vitro* (primary neuron cultures) and *in vivo* (sensory-motor cortex of mice), which seemed to be mediated by the activation of the ionotropic glutamate receptor N-methyl-D-aspartate (and its downstream extracellular signal-regulated kinase [Erk]1/2 signaling cascade) and changes in redox cellular state (Yang et al., 2014). The link between lactate and BDNF has also been observed in humans, where an intravenous infusion of lactate elevates the circulating levels of BDNF (Schiffer et al., 2011). In line with these findings, an acute bout of high-intensity exercise (90 % of maximal work rate) results in higher blood lactate values than does moderate-intensity exercise (70 % of maximal work rate), coupled with a higher concentration of plasma BDNF (Saucedo Marquez et al., 2015). It has been suggested that the relationship between lactate and BDNF might be mediated by the PGC1α/FNDC5 pathway, which is supported by the finding that elevated levels of lactate (through intraperitoneal injection or induced by exercise) increase PGC1α levels and *Fndc5* mRNA expression and protein levels in the hippocampus of wild-type mice (El Hayek et al., 2019).

Finally, recent evidence shows that prolonged aerobic exercise – or other conditions in which body glycogen stores are reduced, such as fasting or the so-called ketogenic diets – induces the production of ketone bodies (*e.g.*, β-hydroxybutyrate [BHB] and acetoacetate). In turn, ketone bodies released into the bloodstream cross the BBB and stimulate the production of BDNF at the brain level (Fig. 2) (Hu et al., 2018; Sleiman et al., 2016). Sleiman and colleagues observed that the exercise-induced benefits on BDNF hippocampal expression in response to voluntary running during 30 days occurred concomitantly with higher levels of BHB, and confirmed both *in vitro* (cortical neurons treated with BHB) and *in vivo* (ventricular injection of BHB) that BHB induced the expression of *Bdnf* in the hippocampus of mice (Sleiman et al., 2016). Recent findings also suggest that an increase in blood ketone levels (*i.e.*, ketosis) with ketone ester supplementation improves cognitive function in healthy rats (Hernandez et al., 2018; Murray et al., 2016). In the same line, ketosis – whether induced by a ketogenic diet or ketone supplementation – can promote brain network stability in humans, with this effect associated with higher brain activity and cognitive acuity (Mujica-Parodi et al., 2020).

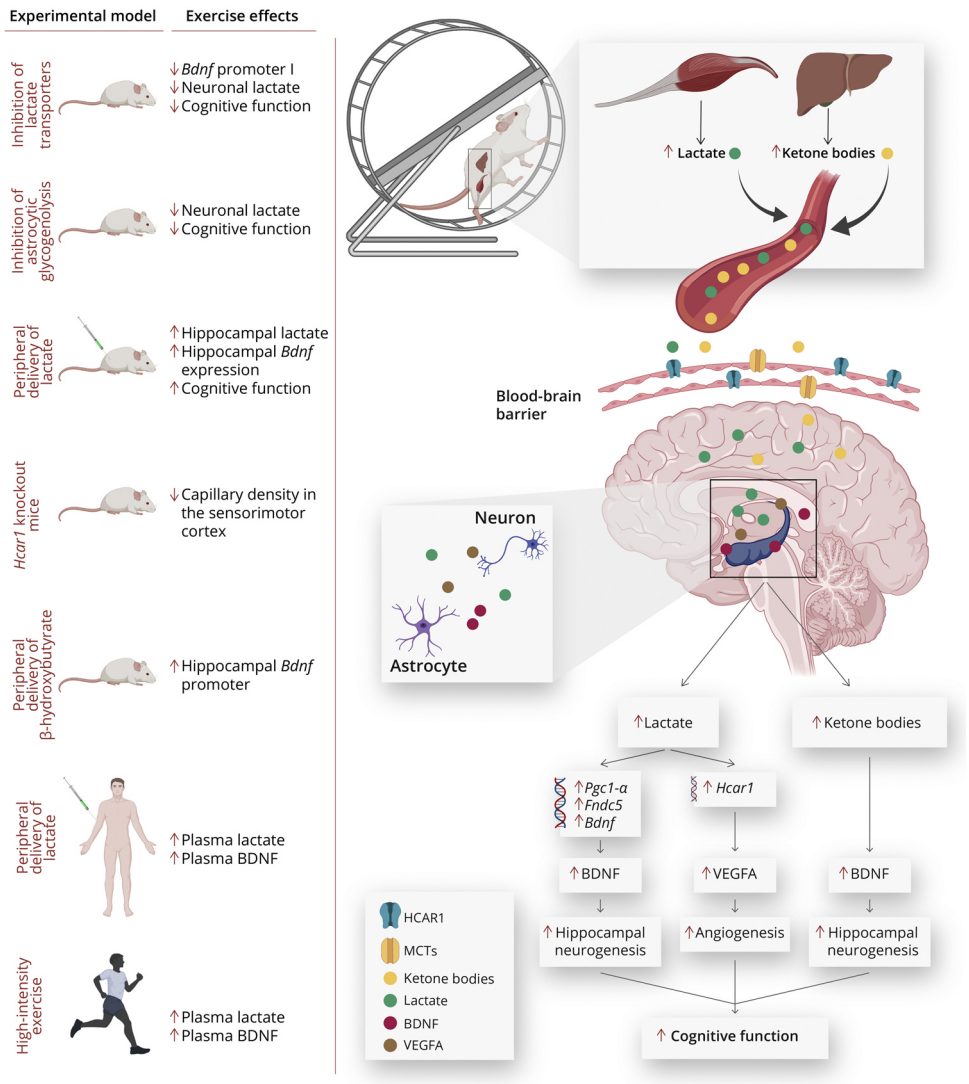

Fig. 2. Existing evidence for a role for exercise-induced metabolic changes (*i.e.*, production of lactate and ketone bodies) in the prevention of Alzheimer's disease. Abbreviations: Hcar1, hydroxycarboxylic acid receptor 1; BDNF, brain-derived neurotrophic factor; FNDC5, fibronectin type III domain-containing protein 5; MCTs, monocarboxylate transporters; Pgc1α, peroxisome proliferator-activated receptor alpha; VEGFA, vascular endothelial growth factor A.

2.2. Exercise and cardiovascular risk factors

AD shares common pathophysiological mechanisms with cardiovascular disease (CVD) (Santos et al., 2017). Indeed, the presence of CVD risk factors, such as hypercholesterolemia, hypertension, diabetes or smoking (known together as the Framingham Stroke Risk Profile) is associated with a greater cognitive decline in individuals with or without AD (Jefferson et al., 2015; Viticchi et al., 2015). In large community-dwelling populations across middle and older age (UK Biobank), the presence of multiple CVD risk factors, notably hypertension, diabetes and smoking, was recently shown to be related to multiple regional magnetic resonance imaging (MRI) hallmarks associated with dementia risk: lower frontal and temporal cortical volumes, lower subcortical volumes, higher white matter hyperintensity volumes, and poorer white matter microstructure in association and thalamic pathways (Cox et al., 2019).

The mechanisms associating CVD and AD are still uncertain; however, there is indication that cerebral blood flow (CBF) might play a relevant role. Reduced CBF, commonly associated with the presence of CVD risk factors such as vascular endothelial dysfunction and hypertension, has been identified as a major contributor to cognitive decline and AD (Leeuwis et al., 2017; Wolters et al., 2017). Indeed, a recent study observed that a higher carotid stiffness, which can be considered reflective of local cerebral arterial stiffness and has therefore a major role on CBF, was associated with a greater brain Aβ burden in adults with mild cognitive impairment (MCI) (Pasha et al., 2020). AD patients show significant decreases in CBF in the frontal, temporal, and parietal lobes of the brain (Johnson et al., 1987), with reduced local or whole CBF being associated with impairment of multiple cognitive domains in these patients (Leeuwis et al., 2017) as well as with faster cognitive decline (Benedictus et al., 2017). Furthermore, the presence of low CBF in the temporal parietal lobes is connected to intensified Aβ burden, which potentially explains the substantial involvement of these areas in AD pathology (Mattsson et al., 2014).

Regular endurance ('aerobic') exercise can impact age-associated decline in CBF and thus potentially protect the brain against AD development. A study demonstrated a ~10-year decrease in CBF "aging" (measured as blood flow velocity in the middle cerebral artery) in endurance-trained men aged 18–79 years *versus* their age-matched, healthy sedentary peers (Ainslie et al., 2008). In a cross-sectional study investigating the potential benefits of life-long aerobic exercise on cerebrovascular function, higher CBF in posterior cingulate cortex (PPC)/precuneus – which are key regions of the default mode network (DMN) that are highly sensitive to age and neurodegeneration and

display irregular activity in AD (Greicius et al., 2004) – was found in a group of master endurance athletes (aged ~75 years on average) compared to their age-matched sedentary controls (Thomas et al., 2013). Moreover, six months of aerobic exercise have recently been shown to improve CBF in sedentary older adults in the preclinical stage of AD (Dougherty et al., 2017). Similarly, a 12-month exercise intervention improved CBF in older adults with MCI, with the magnitude of improvement of this marker – particularly in the anterior cingulate cortex and adjacent prefrontal cortex – correlated with the improvement in memory function (Thomas et al., 2020). Besides its effects on CBF, exercise could be beneficial to brain health by decreasing arterial hypertension, a condition that is associated with AD risk, mainly in midlife (Launer et al., 2000; Shah et al., 2012). However, even though hypertension is a risk factor for CVD and AD with regular exercise helping to lower blood pressure, the primary mechanisms are still hypothetical, and therefore studies in animal models revealing the responsible mechanisms are needed (McGurran et al., 2019).

Other traditional CVD risk factors, notably obesity, have also been linked to an increased risk of AD (Alford et al., 2018), with a recent study showing an association between higher adiposity and lower grey matter volume in humans (Hamer and Batty, 2019). Diabetes might also be associated with a higher risk of dementia (Chatterjee et al., 2016), and this association likely has a multifactorial pathophysiology, including hyperglycemic toxicity, pro-inflammatory processes, and vascular deterioration (Ninomiya, 2014). In this respect, PA significantly attenuates CVD risk, increases vascular health (*i.e.*, through improvements in endothelial function and angiogenesis) and glucose homeostasis, and decreases obesity (Fiuza-Luces et al., 2018).

The beneficial effects of exercise on vascular health are partly explained by its angiogenic effects, as it increases the mRNA and protein levels of vascular endothelial growth factor (VEGF) in both young and elderly individuals (Gavin et al., 2007). Aerobic exercise also improves endothelial function through the activation of peroxisome proliferator activated receptor gamma (Butcher et al., 2008; Thomas et al., 2012), which promotes the storage of fatty acids in adipose tissue thereby reducing their release into the blood (Cheang et al., 2015), and consequently protecting against atherosclerosis and vascular aging (Cannon, 1998). Of note, lactate was recently shown to stimulate the lactate receptor hydroxycarboxylic acid receptor 1 and to enhance cerebral angiogenesis *via* increases in VEGF-A levels in the brain (Fig. 2) (Morland et al., 2017). In line with these findings, three months of aerobic exercise (running) have been reported to normalize hippocampal vascular morphology and to reduce cerebral amyloid angiopathy – together with improvements in spatial memory and neurogenesis – in a mouse model of AD amyloidosis (TgCRND8, *i.e.,* hemizygous mice carrying and overexpressing a double-mutant human APP 695 transgene [hAPP1/2] harboring the “Swedish” and “Indiana” mutations KM670/671 N L & V717 F) (Maliszewska-Cyna et al., 2016).

2.3. Exercise and oxidative stress

Oxidative damage is a hallmark of AD pathogenesis (Rottkamp et al., 2000), with patients showing low antioxidant capacity and high levels of oxidative stress biomarkers from the early stages of the disease (Kim et al., 2006; Padurariu et al., 2010; Schrag et al., 2013; Sultana et al., 2011). Although the generation of moderate amounts of reactive oxygen species (ROS) is necessary for optimal cell function, abnormally high levels have been linked to DNA damage and neurodegeneration, increasing the production and accumulation of Aβ and inducing the overexpression of hyperphosphorylated and aggregated Tau proteins, which in turn leads to mitochondrial dysfunction and further ROS production in a vicious cycle (Chen and Zhong, 2014; Tönnies and Trushina, 2017). Oxidative stress has also been identified as one of the signals that up- or down-regulate the levels of microRNAs proposed to be involved in the pathogenesis of AD (Prasad, 2017). Moreover, a recent study confirmed that brain Aβ levels are associated with a higher likelihood of cognitive decline from preclinical stages (Donohue et al., 2017). Accordingly, mitochondrial dysfunction and subsequent ROS production – which contribute to the accumulation of Aβ – play major roles in the onset of AD (Cheng and Bai, 2018).

Exercise training has been proven to improve redox status (*i.e.*, increased antioxidant status and decreased presence of pro-inflammatory markers) irrespective of the population studied (de Sousa et al., 2017d; Simioni et al., 2018). Moreover, it enhances antioxidant capacity specifically in the brain, as confirmed in rodent models of different ages (Camiletti-Moirón et al., 2013). Pre-clinical studies using a transgenic mouse model (3×Tg-AD; homozygous for the *Psen1* mutation and homozygous for the co-injected APPSwe and tauP301 L transgenes [Tg (APPSwe,tauP301 L)1Lfa]) that mimics the major hallmarks of AD neuropathology (*e.g.*, increased oxidative stress, Aβ and tau pathologies, and impaired learning and memory) have demonstrated that oxidative stress levels are associated with the severity of AD, and physical exercise improves redox status, reduces Aβ and tau pathology, and enhances memory function (García-Mesa et al., 2016, 2011). Indeed, higher levels of exercise are related to lower levels of plasma and brain Aβ in AD patients (Brown et al., 2017, 2013; Liang et al., 2010). Overall, exercise training appears as a potentially effective strategy for improving mitochondrial function and redox homeostasis with subsequent attenuation of AD progression (Bernardo et al., 2016; Radak et al., 2010).

2.4. Exercise and inflammation

Traditionally, the pathogenesis and the pathophysiology of AD were accounted for by the amyloid hypothesis, which postulates that the accumulation of the Aβ peptide, followed by the deposition of neurofibrillary tangles, is the leading cause of AD (Heppner et al., 2015). AD-associated neuroinflammation was thought to be a secondary response to pathophysiological events related to the disease; however, more recent evidence supports a direct role of inflammation as a key contributor to the disease (Heppner et al., 2015).

Chronic inflammation has been identified as one of the causes of neurodegeneration, possibly by influencing the levels of microRNAs involved in AD (Prasad, 2017). Also, numerous pro-inflammatory factors, such as tumor necrosis factor (TNF)-α, caspase-1 or IL-1β, have been linked to AD-related neurodegeneration (Heneka et al., 2015); for example, individuals with MCI and patients with AD show increased levels of active caspase-1 in the brain (Heneka et al., 2013). Moreover, caspase-1-deficient murine models are protected from AD-associated memory loss and are characterized by enhanced Aβ clearance (Heneka et al., 2013).

Microglia seems to play a pivotal role in the link between inflammation and neurodegenerative diseases (Fig. 3). The function of these cells is mainly determined by their phenotype, with M1 and M2 phenotypes being involved in pro-inflammatory and anti-inflammatory processes, respectively (Hopperton et al., 2018; Sica and Mantovani, 2012; Svensson et al., 2015). The pro-inflammatory ‘microenvironment’ of AD has been shown to drive microglia towards an M1 phenotype, which is a determinant factor for neurodegeneration (Clayton et al., 2017; Franco and Fernández-Suárez, 2015; Halle et al., 2008; Li and Barres, 2017). Indeed, recent evidence from post-mortem brain samples shows that AD patients present with high and low levels of M1 and M2 microglia, respectively (Hopperton et al., 2018).

Physical exercise has been reported to promote a phenotypic conversion of M1 to M2 microglia in different rodent models (He et al., 2017; Jiang et al., 2017; Kohman et al., 2013), including the hippocampal microglia of a rat model of AD (*via* injection of streptozotocin) (Lu et al., 2017). Of note, this polarization of microglia to an M2 phenotype was accompanied by a switch to an anti-inflammatory phenotype in the hippocampus (*i.e.*, increased expression of anti-inflammatory cytokines such as IL-4β and IL-10β, and reduction of pro-inflammatory cytokines such as TNF-α and IL-1β) (Lu et al., 2017).

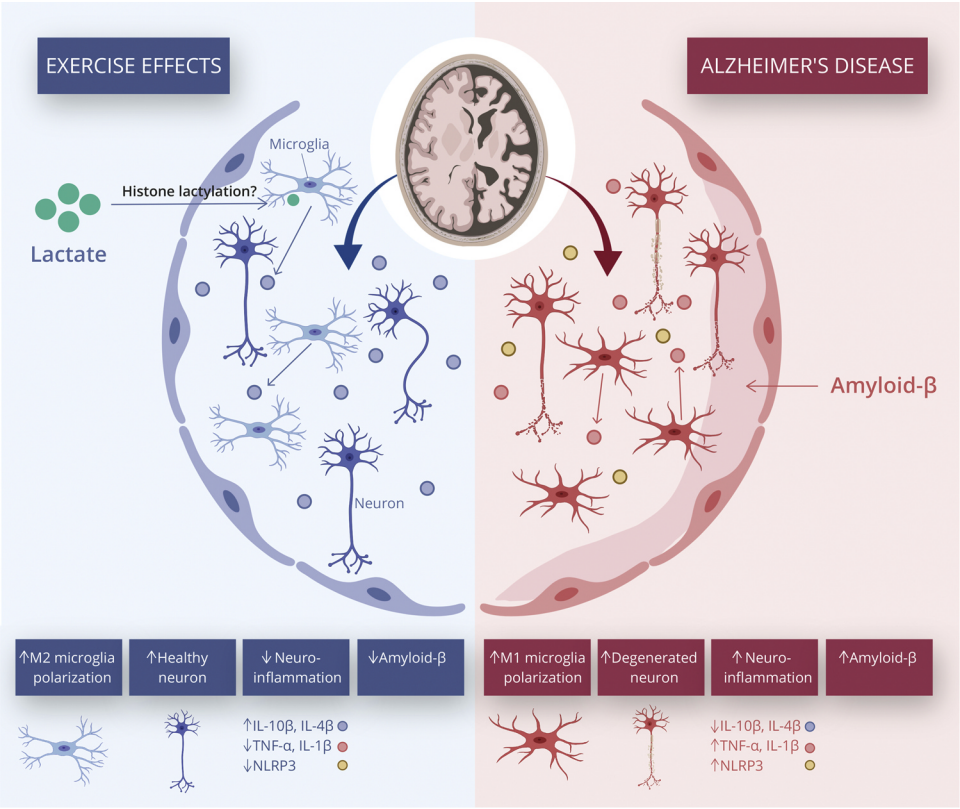

Fig. 3. Physical exercise effects on microglia status and inflammation, and its relationship with Alzheimer's disease progression. Abbreviations: IL, interleukin; NLRP3, NOD-like receptor family, pyrin domain containing 3; TNFα, tumor necrosis factor alpha.

Therefore, exercise seems to be effective in modulating microglia phenotypes, inducing anti-inflammatory effects and ultimately improving cognitive function (Fig. 3) (He et al., 2017; Jiang et al., 2017; Lu et al., 2017).

The inflammasome is a cytosolic multiprotein complex of the innate immune system that detects pathogenic microorganisms and sterile stressors and is responsible for the activation of highly pro-inflammatory cytokines such as IL-1 β and IL-18. An inflammasome component, the NOD-like receptor family, pyrin domain containing 3 (NLRP3), plays a major role in the pathogenesis of AD (Olsen and Singhrao, 2016). Research has shown that Aβ-induced NLRP3 activation promotes AD progression through chronic inflammation. In turn, the lack of NLRP3 inflammasome in a knockout mouse model of AD resulted in a lower pro-inflammatory status – as reflected by reduced brain levels of caspase-1 and IL-1β, and a conversion of microglia towards M2 phenotype – as well as in a lower Aβ deposition and an enhanced cognitive function and hippocampal synaptic plasticity (Heneka et al., 2013). In this regard, exercise might be a potentially effective strategy to lower the activity of the inflammasome. Preliminary evidence indicated that four weeks of exercise training reduced the hippocampal levels of inflammatory markers (IL-1β and IL-18) and NLRP3 activation in mice showing an increased pro-inflammatory status due to ovariectomy-induced depression (Wang et al., 2016). Also supporting the potential benefits of exercise, β-hydroxybutyrate (which, as mentioned above, can be produced during prolonged aerobic exercise) has been reported to suppress activation of NLRP3 inflammasome (Youm et al., 2015). To the best of our knowledge, the aforementioned exercise effects have not been confirmed in AD models, but there is recent evidence of exercise benefits on the NLRP3 inflammasome of humans: both moderate-intensity aerobic exercise training and resistance training result in a reduced NLRP3 expression and lower serum levels of pro-inflammatory markers (IL-1β, IL-18, caspase-1/procaspase-1 ratio) (Abkenar et al., 2019; Mejías-Peña et al., 2017). It must be noted, however, that the opposite trend was observed when exercise was performed at high-intensity, which suggests that high-intensity training might not be so beneficial regarding its effects on the inflammatory status (Abkenar et al., 2019).

Supporting the overall anti-inflammatory effects of exercise (at least up to moderate intensities), recent preliminary evidence suggests that the infusion of plasma containing exercise-induced factors (obtained from mice that performed voluntary physical exercise during 28 days) to sedentary mice resulted in a downregulation of hippocampal neuroinflammatory processes, which seemed to be mainly mediated by changes in plasma proteins within the complement system and particularly of clusterin (*see below for more information on this protein*) (de Miguel et al., 2019d). Of note, exercise-induced increases in the plasma levels of clusterin and a reduction of the complement pathway (*e.g.*, complement factor 3) were also observed in response to long-term (6 months) exercise training in humans (de Miguel et al., 2019d). Also confirming the overall potential beneficial effects of exercise on inflammatory status, it must be noted that although acute unaccustomed or exhaustive exercise might result in an increased production of ROS, regular exercise training has been proven to decrease biomarkers of inflammation (*e.g.*, IL-6, C-reactive protein) in the elderly (Monteiro Junior et al., 2018) and in individuals with cognitive impairments (Nascimento et al., 2015), thereby promoting brain health (Cotman et al., 2007).

3. Perspectives and guidelines for future research

Although exercise seems to be a potentially effective strategy to improve cognition and potentially prevent the onset of AD (see Fig. 4 for a summary), a vast amount of research still needs to be implemented not only to shed more light on the cognitive effects of exercise but also to disentangle pathophysiological underpinnings. Despite the numerous mechanisms proposed in preclinical research as underlying pathways of

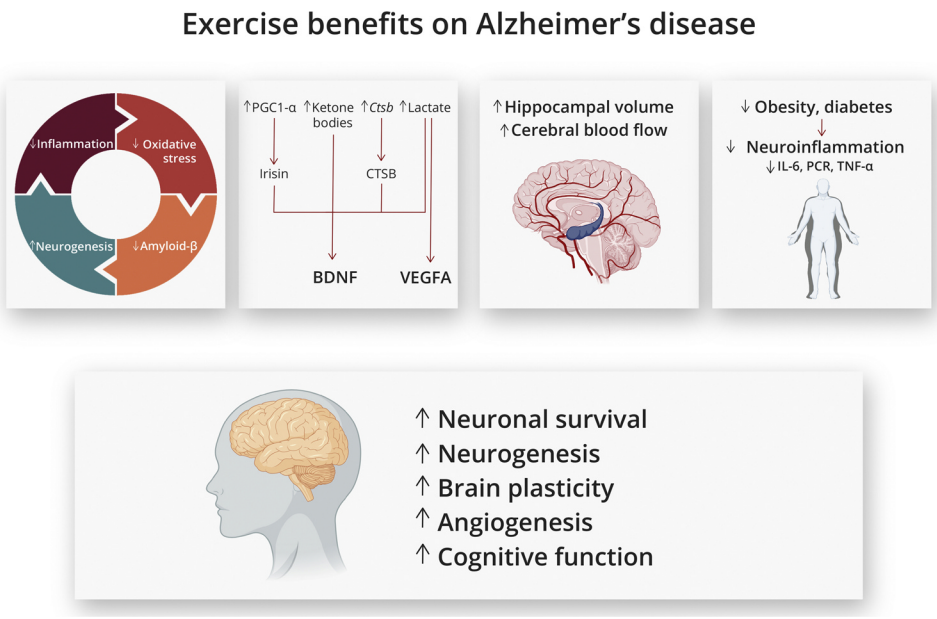

Fig. 4. Summary of exercise benefits on Alzheimer's disease. Abbreviations: BDNF, brain-derived neurotrophic factor; CTSB, cathepsin B; *Ctsb*, gene encoding CTSB; IL6, interleukin-6; PGC1α, peroxisome proliferator-activated receptor alpha; TNFα, tumor necrosis factor alpha; VEGFA, vascular endothelial growth factor A.

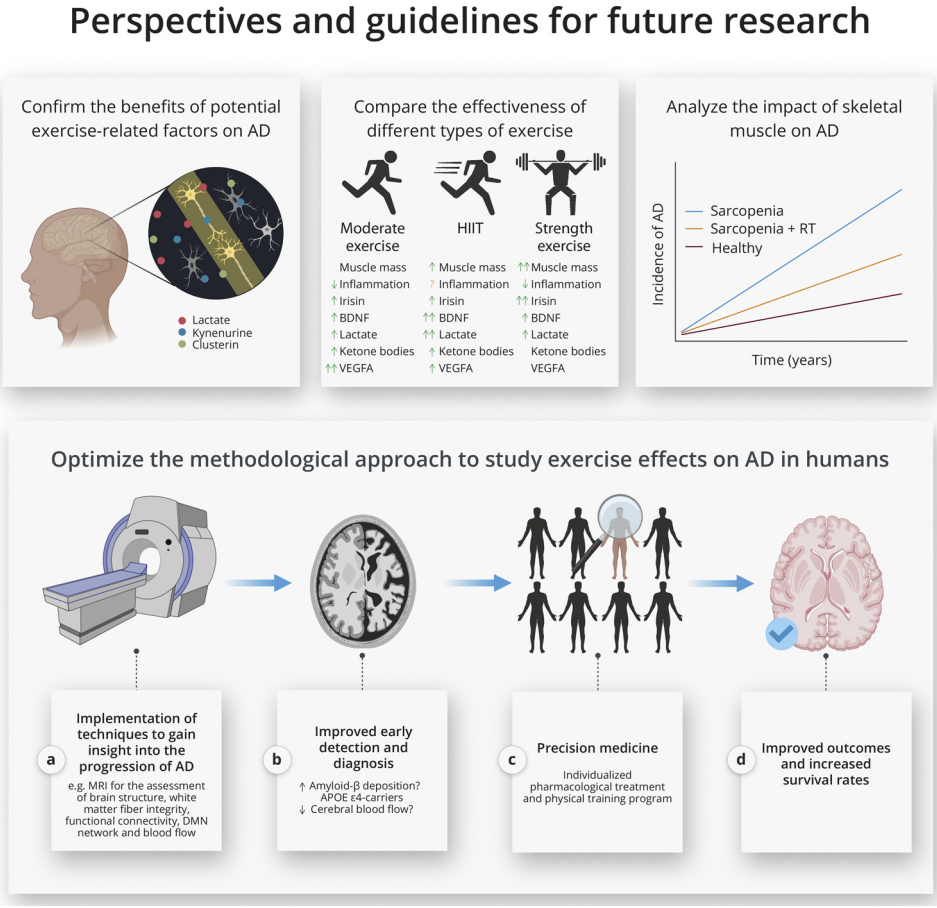

Fig. 5. Summary of potential avenues for further research on exercise and Alzheimer's disease (AD). Abbreviations: BDNF, brain-derived neurotrophic factor; HIIT, high-intensity interval training; RT, resistance (strength) training; VEGFA, vascular endothelial growth factor A.

exercise benefits on AD, the evidence supporting an actual role of these pathways in humans is scarce. In this section, we summarize potential avenues for further research and suggest testable protocols on how to investigate the main open issues (see also Fig. 5).

3.1. The search for novel candidate mediators of exercise benefits on brain health

While there are several provocative hypotheses to explain the

benefits of exercise against AD risk, more research is needed to unveil the biological underpinnings of such benefits, including identification of novel myokines or exercise-induced factors in general with potential neurotrophic effects. Indeed, in addition to irisin and CTSB, several myokines are potential candidates to cross the BBB and exert an effect in the brain tissue.

3.1.1. Kynurenine

Kynurenine is a metabolite of the amino acid L-tryptophan that can readily cross the BBB to promote neuroinflammation and neuronal cell death (Cervenka et al., 2017), and alterations in its plasma levels have been strongly correlated with depression (Ogyu et al., 2018). Agudelo et al. (Agudelo et al., 2014) demonstrated that overexpression of PGC1α – which, as explained above, can be induced by physical exercise – might increase the expression of kynurenine aminotransferases at the muscle level, thereby enhancing the conversion of kynurenine into a metabolite unable to cross the BBB, kynurenic acid. According to the authors, this study opened therapeutic avenues for the treatment of depression by targeting the PGC-1α pathway in skeletal muscle, without the need to cross the BBB. The question as to whether the beneficial effects of exercise on AD might also be mediated, at least partly, by an enhanced exercise-elicited muscle conversion of kynurenine into kynurenic acid remains open.

3.1.2. Lactate

Other potential candidate to mediate exercise benefits on AD is lactate. Apart from the aforementioned role of lactate on the promotion of angiogenesis and hippocampal neurogenesis, this metabolite could also mediate exercise benefits on AD-related neuroinflammation. The mechanisms and signaling pathways that govern the exercise-induced modulation of microglia towards an M2 anti-inflammatory phenotype remain to be elucidated. In this respect, tumor-derived lactic acid can induce the polarization of tumor-associated macrophages towards an M2 phenotype (Colegio et al., 2014), and lactic acid (or lactate) modulates the phenotype of macrophages in general towards an M2 phenotype in both a Gi protein-coupled receptor 81 (a lactate receptor)-dependent (Hoque et al., 2014) and independent manner (Errea et al., 2016). Moreover, a recent study reported that lactate-induced histone lactylation (*i.e.*, the addition of a lactyl group to the lysine amino-acid residues in the tails of histone proteins) might act as an epigenetic mechanism stimulating the expression of M2-like genes in M1 macrophages (Zhang et al., 2019). Accordingly, future research might determine whether lactate is also responsible for a healthy anti-inflammatory *milieu* in the microglia.

3.1.3. Clusterin

Clusterin (also known as apoJ) is a multifunctional heterodimeric protein that acts as a natural chaperone. In AD brains, apoJ is co-deposited with fibrillar Aβ in cerebrovascular and parenchymal lesions (Howlett et al., 2013; Matsubara et al., 1995), and an association has been reported between clusterin levels and the severity and progression of AD (Thambisetty et al., 2010). However, the increased clusterin levels found in AD patients could actually represent a compensatory – and in fact beneficial – mechanism, through the modulation of different pathways including Aβ aggregation and neuroinflammation (Yu and Tan, 2012). Indeed, clusterin might play a major role in Aβ clearance through the BBB (Bell et al., 2007; Merino-Zamorano et al., 2016), and a recent study observed that the peripheral administration of human recombinant clusterin reduced Aβ accumulation in amyloid precursor protein transgenic mice (APP23), a preclinical model of cerebral β-amyloidosis (Fernández de Retana et al., 2019). A recent study showed that the infusion of plasma from exercised mice – which contained high clusterin levels – to sedentary mice resulted in an attenuation of brain inflammatory processes and improvements in neurogenesis and cognitive function (de Miguel et al., 2019d). Of note, exercise-induced increases in the plasma levels of clusterin have also been observed in response to exercise training in humans, and these increases were related to the magnitude of improvement in inflammatory markers and physical fitness (de Miguel et al., 2019d). More research is thus needed to elucidate the relationship between clusterin and neurodegeneration (Foster et al., 2019), and to confirm the potential modulatory effects of exercise in this relationship.

3.2. Intense vs. moderate exercise. Which is best?

Exercise rehabilitation programs for adults are traditionally based on moderate-intensity continuous exercise training (MICT) protocols sustained for ~20–30 min per session. In line with the potential role of lactate in the benefits of exercise against AD, intense exercise sessions (*i.e.,* relying mainly on aerobic/anaerobic glycolysis, and thus resulting in higher lactate levels than MICT sessions) might be a suitable type of exercise against AD risk, not only in middle-aged adults but also in older people. Studies in humans have shown that an acute bout of high-intensity exercise elicits larger increases in BDNF than a bout of lower intensity, and the benefits seemed to be dependent on lactate production (Antunes et al., 2019; Boyne et al., 2019; Saucedo Marquez et al., 2015). Moreover, 6 weeks of 'high-intensity interval training' (HIIT, which is a type of exercise that typically involves repeated bouts of intense exercise interspersed with short periods of recovery) have been reported to elicit greater long-term increases in BDNF than MICT in rats (Afzalpour et al., 2015). Recent evidence also suggests that HIIT is more beneficial than MICT for the prevention of some risk factors of AD such as obesity (Türk et al., 2017) or high blood pressure (Way et al., 2019). In addition, HIIT might be a more effective strategy – or at least, a more efficient one – for the improvement of cardiorespiratory fitness – usually expressed as peak oxygen uptake (VO_{2peak})- (Helgerud et al., 2007; Williams et al., 2019), which is of major importance given that the gains in VO_{2peak} observed after an exercise intervention have been recently reported to be correlated with the improvements in white matter tract integrity of the prefrontal cortex in individuals with MCI (Tarumi et al., 2020). It must be noted, however, that training continuously (*i.e.*, during a 3-month intervention) at high intensity has been reported to result in a pro-inflammatory status compared to moderate-intensity exercise training (Abkenar et al., 2019), and indeed acute bouts of intense unaccustomed physical exercise can result in an increased production of ROS and pro-inflammatory markers (Abkenar et al., 2019). Thus, it might be interesting to compare the effects of MICT (*e.g.,* walking or brisk walking) *versus* HIIT on AD development.

3.3. Resistance (strength) exercise: are its effects comparable to endurance training?

Resistance (strength) exercise (*e.g.,* weight lifting), which unfortunately remains largely overlooked despite its tremendous therapeutic potential in older adults, notably against CVD risk (Fiuza-Luces et al., 2018), can influence AD risk and cognitive function in general (*e.g.,* through myokine release). Whereas strong evidence supports the benefits of endurance exercise for improving cognitive in AD patients, the effects of resistance exercise are still unclear (Herold et al., 2019; Panza et al., 2018). In this regard, a recent study reported that 6 months of resistance training improved cognition and protected from the structural and functional degeneration of hippocampal subfields in the long-term (12 months after training cessation) in individuals with MCI (Broadhouse et al., 2020).

Resistance exercise has been reported to result in greater acute and long term (*i.e.*, after 8 weeks of training) increases in irisin concentration than endurance exercise in humans (Kim et al., 2016; Tsuchiya et al., 2015), which given the role of irisin on brain health (see above), suggests the potential effectiveness of resistance exercise training for the prevention of AD and for the improvement of cognition in already affected patients. Moreover, resistance training has been reported to prevent NLRP3 inflammasome activation in cognitively healthy older

adults (Mejías-Peña et al., 2017), with the latter playing a key role in AD pathogenesis (*see above,* Section 2.4). A prospective study in individuals without dementia at baseline observed that muscle strength was inversely associated with cognitive decline and AD risk during the follow-up (Boyle et al., 2009). In line with these data, a lower muscle mass has been related to brain atrophy and an increased risk of AD (Burns et al., 2010; Kim et al., 2019). Meta-analytical evidence shows that sarcopenia (*i.e.*, excessive loss of muscle mass and function with aging) is associated with a greater cognitive impairment (Chang et al., 2016). Moreover, the incidence of sarcopenia has been reported to increase since the early stages of AD, becoming more prevalent as the stage of the disease increases (from 11 to 13 % in individuals with normal cognition, to 36–41 %, 45–47 % and 47–60 % in those with early, mild, and moderate AD, respectively) (Ogawa et al., 2018). Future longitudinal studies should confirm the link between skeletal muscle mass/function and AD risk, and research is also needed to analyze if the prevention of sarcopenia through interventional exercise strategies (notably, those focused on resistance training) might attenuate the incidence or progression of AD.

3.4. Can exercise have an effect on neuroimaging biomarkers of AD?

There is a need for more studies on the human nervous system, especially on the hippocampal region, to understand why and how exercise can reduce the risk of developing AD. Preliminary evidence suggests that physical exercise can induce structural and functional brain changes in patients with MCI and AD, but results are still inconclusive (Haeger et al., 2019). Exercise effects can be investigated in relation to neuroimaging biomarkers of AD, including *1)* Aβ deposition, as assessed by brain positron emission tomography (PET) (Grothe et al., 2017), *2)* focal changes in the grey matter and structural information on the hippocampus by MRI, followed by voxel-based analysis and statistical parametric mapping (Ridgway et al., 2008), and *3)* changes in functional connectivity and CBF by functional MRI (Preti et al., 2017).

3.4.1. Aβ deposition

Recent studies have shown a potential beneficial effect of exercise/PA, which might reduce Aβ deposition in the brain, a key biomarker of AD pathology (Brown et al., 2013). For instance, a cross-sectional study of 201 cognitively normal individuals found a novel interaction between apolipoprotein E (*APOE)* gene *ε4*-allele status (with *ε4*-carriage being a significant risk factor for AD) and exercise engagement for [^{11}C]-Pittsburgh Compound-B (PiB)-PET binding (amyloid imaging), such that a more sedentary lifestyle was significantly associated with higher [^{11}C]PiB binding for carriers of the ε4 'risk' allele (Head et al., 2012). Another cross-sectional analysis of 116 cognitively normal adults (aged 60–95 years) reported the association of greater levels of PA with decreased brain Aβ loads in *APOE ε4*-carriers (Brown et al., 2013). However, a 16-week exercise intervention with moderate- to high-intensity aerobic exercise was not able to affect the extent of cortical Aβ deposition, as assessed by amyloid PET, in a cohort of patients with mild AD (Frederiksen et al., 2019b) from the ADEX Study (Sobol et al., 2016) – a multicenter, single-blinded randomized controlled trial (RCT) of physical exercise (NCT01681602). Notably, there is the trend toward trials exploring exercise interventions at the earliest stages of AD pathology. In this regard, one exercise study, NCT02000583, is ongoing. The aim is to examine the potential benefits of aerobic exercise in monitoring or decreasing the amount of brain Aβ, decreasing brain structure alterations responsible for AD, and increasing cognitive ability in participants at risk to develop AD displaying Aβ deposits (https://clinicaltrials.gov/ct2/show/NCT02000583).

3.4.2. Structural magnetic resonance imaging

Several studies have analyzed the possible effect of PA/exercise on brain structures' volumes in both cognitively normal older adults and AD patients. Cross-sectional studies of older adults have shown that higher levels of aerobic fitness or PA are linked to: greater white matter tract integrity in the frontal and temporal lobes as well as in the uncinate fasciculus and cingulum (Marks et al., 2007; Voss et al., 2013); increased gray matter volumes in temporal, parietal, and inferior frontal areas (Bugg and Head, 2011; Flöel et al., 2010; Gordon et al., 2008); and larger cortical, hippocampal, and whole-brain volumes (Burns et al., 2008; Erickson et al., 2007). An analysis from the Cardiovascular Health Cognition Study reported that increased PA was a predictor of greater volumes of frontal, occipital, entorhinal, and hippocampal areas over a 9-year follow-up (Erickson et al., 2010). An RCT performed in older individuals showed that aerobic exercise training enlarged the volume of the anterior hippocampus, resulting in progresses in spatial memory (Erickson et al., 2011). In particular, the hippocampal volume was increased by 2 % and age-related volume loss was reversed over one to two-year follow-up. In turn, the exercise-induced increase in hippocampal volume was related to higher serum BDNF concentrations (Erickson et al., 2011). On the other hand, in people with early AD higher levels of cardiorespiratory fitness are negatively associated with brain atrophy (Burns et al., 2008) and positively associated with regional brain volumes in the medial-temporal and parietal cortices (Honea et al., 2009).

Deep/machine learning approaches using MRI data are being used to accurately predict the conversion from moderate cognitive impairment to AD (Lin et al., 2018; Spasov et al., 2019; Tam et al., 2019). In this context, a recent study observed a significant association between cardiorespiratory fitness and MRI-measured white matter fiber integrity, which was in turn associated to some aspects of executive function in patients with MCI (Ding et al., 2018). Thus, research (ideally using RCT designs) could analyze if mid- or longer term (~3 or more months) exercise interventions are able to modify the MRI signatures that differentiate 'converters' from 'non-converters' *versus* a control group. Ideally, the effects of MCIT, HIIT and resistance training should also be compared.

3.4.3. Functional magnetic resonance imaging

In general, the literature points to the consistent effectiveness of PA as a means to preserve or reinforce connectivity in large-scale brain networks disrupted in both normal and pathological aging (Stillman et al., 2019). Notably, during both MCI and AD, the connectivity patterns of the DMN become inefficient (Zhou et al., 2015), and PCC/precuneus is a hub of the DMN that is susceptible to functional connectivity disruption in MCI and AD, with reduced connectivity of this hub representing a potential a biomarker to detect cognitive impairment prior to AD clinical signs. In this context, cardiorespiratory fitness has been shown to be associated with DMN connectivity (Voss et al., 2010). In addition, another study showed higher functional connectivity of the PCC/precuneus in subjects with MCI after 12 weeks of moderate-intensity walking (Chirles et al., 2017). Hence, DMN network seems to be a suitable outcome for interventions during aging, MCI, and AD (Huang et al., 2016). Despite recent advances, this field is still in its beginning. Indeed, some aspects of the intervention (type and dosage of exercise) needed to optimize effects on the integrity of functional networks are currently unclear. Moreover – since one study has described a bidirectional link between exercise and functional connectivity (Baniqued et al., 2018), indicating that functional connectivity patterns may predict successive responsiveness to exercise interventions – using the brain itself as "predictor" might be useful to develop individualized therapies. In fact, this strategy may facilitate the identification of individuals that gain maximum benefit from exercise interventions and the detection of obstacles to exercise adherence (Stillman and Erickson, 2018).

3.5. Towards systems biology and precision medicine

The pathophysiology of AD is complex and involves a multifaceted combination of genomic/epigenomic, interactomic, and environmental factors. Moreover, AD is currently considered the result of altered networks affecting crucial modules and interactomes, characterized by a constant interaction between impaired cellular/molecular networks and mechanisms protecting homeostasis (Castrillo and Oliver, 2016). Systems biology is a hypothesis-free, integrative, and holistic approach (Hood, 2003; Ideker et al., 2001; Kitano, 2002) aimed at exploring how AD and other polygenic, multifactorial diseases originate from "altered network states". Systems biology is grounded on the use of integrative, systems-level methods, both at the experimental and computational level (Castrillo et al., 2018). The ultimate goal of systems biology is to disclose and characterize mechanism-based molecular signatures of AD that allow the introduction of tailored interventions under the precision medicine framework (Hampel et al., 2018, 2017, 2016).

In general, precision medicine aims at matching diagnostic and treatment approaches to the specific needs of the individual patient (Hampel et al., 2019). Precision medicine therefore represents a paradigm shift from the outdated "one-treatment-fits-all" construct in drug discovery toward biomarker-guided "tailored" therapies. The application of this paradigm has been extensively advocated for AD (Hampel et al., 2018, 2017, 2016). Systems biology is also increasingly used to interpret physiological adaptations to exercise (Hittel et al., 2007)–ultimately allowing the charting of biological networks that underlie its systemic health benefits (Hoffman, 2017). Moreover, the call for precision medicine is entirely applicable not only to AD, but also in the exercise setting (DiMenna and Arad, 2018).

4. Conclusions

Physical exercise provides a myriad of benefits that might affect AD through different pathways which range from the prevention of associated risk factors (*e.g.*, vascular dysfunction, obesity, diabetes) to the promotion of brain health, notably through a muscle-brain connection. Based on the available evidence, it is conceivable that physical exercise-based interventions may be helpful for preventing AD or attenuating – at least partly – its progression in affected individuals. However, despite the numerous mechanisms proposed in preclinical research as potential mediators of exercise benefits on AD, evidence is still lacking from research conducted with human subjects. More research is therefore needed to elucidate the exact biological underpinnings supporting exercise benefits, to confirm if these benefits apply to all populations (*e.g.*, particularly to older adults who already have AD), and to determine the most beneficial interventions. After reviewing the current literature, we have provided practical, testable hypotheses for future research in the field–with a special focus on key questions that still remain unanswered.

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He is co-inventor in the following patents as a scientific expert and has received no royalties:

- *In Vitro* Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Patent Number: 8916388
- *In Vitro* Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases Patent Number: 8298784
- Neurodegenerative Markers for Psychiatric Conditions Publication Number: 20120196300
- *In Vitro* Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Publication Number: 20100062463
- *In Vitro* Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Publication Number: 20100035286
- *In Vitro* Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases Publication Number: 20090263822
- *In Vitro* Method for The Diagnosis of Neurodegenerative Diseases Patent Number: 7547553
- CSF Diagnostic in vitro Method for Diagnosis of Dementias and Neuroinflammatory Diseases Publication Number: 20080206797
- *In Vitro* Method for The Diagnosis of Neurodegenerative Diseases Publication Number: 20080199966
- Neurodegenerative Markers for Psychiatric Conditions Publication Number: 20080131921

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